The Myriad Foresight® Carrier Screen

myriad®
WOMEN'S HEALTH

180 Kimball Way | South San Francisco, CA 94080
www.myriadwomenshealth.com | prenatalsupport@myriad.com | (888) 268-6795

The Myriad Foresight® Carrier Screen - Disease Reference Book

Test Methodologies

SEQUENCING WITH COPY NUMBER ANALYSIS (V4.1)

Hybridization capture-based target enrichment, high-throughput sequencing, and read-depth-based copy number analysis are used to analyze the genes listed in the Conditions Tested section of the report. Except where otherwise noted, the region of interest (ROI) comprises the indicated coding regions and 20 non-coding bases flanking each region. The ROI is sequenced to a minimum acceptable read depth, and the sequences are compared to a reference genomic sequence (Genome Reference Consortium Human Build 37 [GRCh37]/hg19). On average, 99% of all bases in the ROI are sequenced at a read depth that is greater than the minimum read depth. Sequence variants may not be detected in areas of lower sequence coverage. Insertions and deletions may not be detected as accurately as single-nucleotide variants. Select genes or regions for which pseudogenes or other types of genomic features (e.g., homology or homopolymers) impede reliable variant detection may be assayed using alternate technology, have reduced sensitivity, or be excluded from the ROI. *CFTR* and *DMD* testing includes analysis for full exon-level deletions and duplications with a sensitivity of ~99%. Only full exon-level deletions and larger are assayed for other genes on the panel with a sensitivity of ≥75%. Partial exon and single or multi-exon deletions in regions of genomic or assay complexity may have reduced sensitivity or may be excluded from the ROI. Selected founder deletions may be detected at higher sensitivity. Affected exons and/or breakpoints of copy number variants are estimated from tiled regions and, when available, using junction reads. Only exons included in the region affected by the copy number variant (CNV) are included in the variant nomenclature. In some cases, the copy number variant may be larger or smaller than indicated. If *GJB2* is in the ordered ROI, large upstream deletions involving the *GJB6* and/or *CRYL1* genes that may affect the expression of *GJB2* are also analyzed. If in the ordered ROI, the following are not assessed: CCG trinucleotide repeat expansions in *AFF2*; polyalanine expansions in exon 2 of *ARX*; variants in the *ORF15* region of *RPGR*.

SEQUENCING ANALYSIS (V4.1)

Hybridization capture-based target enrichment and high-throughput sequencing are used to analyze the genes listed in the Conditions Tested section of the report. Except where otherwise noted, the region of interest (ROI) comprises the indicated coding regions and 20 non-coding bases flanking each region. The ROI is sequenced to a minimum acceptable read depth, and the sequences are compared to a reference genomic sequence (Genome Reference Consortium Human Build 37 [GRCh37]/hg19). On average, 99% of all bases in the ROI are sequenced at a read depth that is greater than the minimum read depth. Sequence variants may not be detected in areas of lower sequence coverage. Insertions and deletions may not be detected as accurately as single-nucleotide variants. Select genes or regions for which pseudogenes or other types of genomic features (e.g., homology or homopolymers) impede reliable variant detection may be assayed using alternate technology, have reduced sensitivity, or be excluded from the ROI.

TARGETED GENOTYPING (V1.0)

Targeted DNA analysis via high-throughput sequencing is used to determine the genotypes of the variants listed in the Conditions Tested section of the report. The region of interest (ROI) is sequenced to a minimum acceptable read depth, and the sequences are compared to a reference genomic sequence (GRCh37/hg19). On average, 99% of all bases in the ROI are sequenced at a read depth that is greater than the minimum read depth. Sequence variants may not be detected in areas of lower sequence coverage. Insertions and deletions may not be detected as accurately as single-nucleotide variants.

TRIPLET REPEAT DETECTION (V1.0)

Polymerase chain reaction (PCR) with fluorescently labeled primers is used to amplify the CGG repeat region in the 5' UTR of *FMR1* (NM_002024.4: c.1-131CGG[1_n]), and PCR products are sized using capillary electrophoresis. Reported sizes are accurate to ±1 repeat for normal or intermediate alleles and ± two repeats for premutation alleles. Alleles above 200 CGG repeats (full mutations), while identified, are not specifically sized and will be reported as ">200" CGG repeats. In an unknown number of cases, other genetic variation may interfere with CGG repeat analysis. Other *FMR1* pathogenic variation will not be detected. *FMR1* promoter methylation is not analyzed. Allele size mosaicism may not be detected, as the test has been calibrated to yield results that are equivalent to the results from Southern blot. Opt-in testing of *FMR1* AGG interruptions is available for results showing between 50 and 54 CGG repeats. Automatic reflex testing of AGG interruptions is performed for results showing between 55 and 90 CGG repeats. AGG interruption analysis is performed by a reference laboratory, and methods are provided in the appended report, when applicable. This assay is designed to detect germline (constitutional) variation of the CGG repeat in the 5' UTR of *FMR1*; gonadal mosaicism will not be detected. Results assume a normal karyotype. Sex chromosome variations and aneuploidies may affect the accuracy of this assay.

SPINAL MUSCULAR ATROPHY (V4.0)

Targeted copy number analysis via hybridization capture-based target enrichment and high-throughput sequencing is used to determine the copy number of exon 7 of the *SMN1* gene. In an unknown number of cases, other genetic variation may interfere with this analysis. Some individuals with two copies of *SMN1* are "silent" carriers with both *SMN1* genes on one chromosome and no copies of the gene on the other chromosome. This is more likely in individuals who have two copies of the *SMN1* gene and are positive for the g.27134T>G single-nucleotide polymorphism (SNP) (PMID: 9199562, 23788250, and 28676062), which affects the reported residual risk. Ashkenazi Jewish or Asian patients with this genotype have a high post-test likelihood of being carriers for SMA and are reported as carriers. The g.27134T>G SNP is only reported in individuals who have two apparent copies of *SMN1*. Further, individuals who are negative for the g.27134T>G SNP, and who are reported as having two copies of the *SMN1* gene may have additional *SMN1* gene copies. If additional unreported *SMN1* copies are present, the reported residual risk for these individuals may be overestimated. Other rare carrier states, where complex exchanges exist between gene copies or chromosomes, may not be detected by the assay.

ANALYSIS OF HOMOLOGOUS REGIONS (V4.0)

Hybridization capture-based target enrichment, high-throughput sequencing, targeted genotyping, and read-depth-based copy number analysis are used to determine the number of functional gene copies and/or the presence of selected variants in genes that have significant homology to other genomic regions. The precise breakpoints of large deletions in these genes cannot be determined but are instead estimated from copy number analysis. Pseudogenes may interfere with this analysis, especially when many pseudogene copies are present. In some instances, additional unreported pseudogene-derived variants may be present in the same gene copy as the reported variant (e.g. chimeric alleles). The ability of other assays to detect this complex genotype is dependent on the specific test methodology utilized.

If *CYP21A2* is tested, patients who have one or more additional copies of the *CYP21A2* gene and a pathogenic variant may or may not be a carrier of 21-hydroxylase deficient congenital adrenal hyperplasia (CAH), depending on the chromosomal location of the variants (i.e., phase). Benign *CYP21A2* gene duplications and/or triplications will only be reported in this context. Some individuals with two functional *CYP21A2* gene copies may be "silent" carriers, with two gene copies resulting from a duplication on one chromosome and a gene deletion on the other chromosome. This and other rare carrier states, where complementary changes exist between gene copies or chromosomes, may not be detected by the assay. If the 30kb deletion (aka *CYP21A2* deletion) is reported, the extent of impacted gene sequence can vary and in some instances may extend through the end of the gene (i.e. full gene deletion). If further testing is pursued for the 30kb deletion, the methodology should accommodate deletions of variable size. Given that the true incidence of non-classic CAH is unknown, the residual carrier and reproductive risk estimates on the report are based on the published incidence for classic CAH. However, the published prevalence of non-classic CAH is highest in individuals of Ashkenazi Jewish, Hispanic, Italian, and Yugoslav descent. Therefore, the residual and reproductive risks are likely an underestimate for CAH, especially in the aforementioned populations, as they do not account for non-classic CAH.

ALPHA THALASSEMIA (HBA1/HBA2) SEQUENCING WITH TARGETED COPY NUMBER ANALYSIS (V4.0)

Hybridization capture-based target enrichment, high-throughput sequencing, and copy number analysis are used to identify sequence variation and functional gene copies within the region of interest (ROI) of *HBA1* and *HBA2*, which includes the exons listed in the assay specifications plus 20 intronic flanking bases. In a minority of cases where genomic features (e.g., homopolymers) compromise calling fidelity, the affected intronic bases are not included in the ROI. The ROI is sequenced to a minimum acceptable read depth, and the sequences are compared to a reference genomic sequence (Genome Reference Consortium Human Build 37 [GRCh37]/hg19). On average, 99% of all bases in the ROI are sequenced at a read depth that is greater than the minimum read depth. Sequence variants may not be detected in areas of lower sequence coverage. Insertions and deletions may not be detected as accurately as single-nucleotide variants. For large deletions or duplications in these genes, the precise breakpoints cannot be determined but are instead estimated from copy number analysis. This assay has been validated to detect up to two additional copies of each alpha globin gene. In rare instances, more than two additional copies of either gene may be present but will not be reported. Extensive sequence homology exists between *HBA1* and *HBA2*. This sequence homology can prevent certain variants from being localized to one gene over the other. In these instances, variant nomenclature will be provided for both genes. If follow-up testing is indicated for patients with the nomenclature provided for both genes, both *HBA1* and *HBA2* should be tested. Some individuals with four functional alpha globin gene copies may be "silent" carriers, with three gene copies resulting from triplication on one chromosome and a single gene deletion on the other chromosome. This and other rare carrier states, where complementary changes exist between gene copies or chromosomes, may not be detected by the assay.

INTERPRETATION OF REPORTED VARIANTS (V4.0)

The interpretation and classification of variants reflect the current state of Myriad's scientific understanding based on information available at the time of variant assessment. Variants are classified according to internally defined criteria, which are compatible with the ACMG Standards and Guidelines for the Interpretation of Sequence Variants (PMID: 25741868). Variants that have been determined by Myriad to be disease-causing or likely disease-causing (i.e., pathogenic or likely pathogenic) are reported. Benign variants, likely benign variants, variants of uncertain clinical significance (VUS), and variants not directly associated with the specified disease phenotype(s) are not reported. Variants and/or haplotypes associated with a non-Mendelian risk for disease are only reported on request. Variant classification and interpretation may change over time for a variety of reasons, including but not limited to, improvements to classification techniques, availability of additional scientific information, and observation of a variant in additional individuals. If the classification of one or more variants identified in this patient changes, an updated report reflecting the new classification generally will not be issued. If a report is updated or re-issued for other reasons, the variants reported may change based on their classification at the time of re-issue. This can include changes to the variants displayed in gene-specific 'variants tested' sections. Healthcare providers may contact Myriad directly to request updated variant classification information specific to this test result.

3-methylcrotonyl-CoA Carboxylase Deficiency, MCCC2-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MCCC2.
Exons Sequenced: NM_022132:1-17.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is 3-methylcrotonyl-CoA Carboxylase Deficiency, MCCC2-related?

3-methylcrotonyl-CoA carboxylase deficiency, or 3-MCCD, is an inherited condition caused by an inability to break down the amino acid leucine. Amino acids are essential for proper growth and development. Two genes cause the condition. 3-methylcrotonyl-CoA carboxylase deficiency, MCCC2-related, is caused by harmful genetic changes (variants) in the *MCCC2* gene.

Symptoms for individuals affected with 3-MCCD are highly variable. The first symptom is usually an episode known as a "metabolic crisis." During these episodes, individuals have low blood sugar, vomiting, lack of energy, difficulty feeding, irritability, and weak muscles (hypotonia). These episodes can be triggered by infections, not eating for long stretches (fasting), or a protein-rich diet. In some cases, the episodes may cause neurological abnormalities such as metabolic stroke, weakness or inability to move on one side of the body (hemiparesis), and decreased blood flow or oxygen to the brain (encephalopathy). Some individuals may experience developmental delays. Symptoms can appear as early as infancy or early childhood, but many individuals do not develop symptoms until adulthood or may live their entire lives without any apparent symptoms.

How common is 3-methylcrotonyl-CoA Carboxylase Deficiency, MCCC2-related?

3-methylcrotonyl-CoA carboxylase deficiency has an incidence of approximately 1 in 36,000 births.

How is 3-methylcrotonyl-CoA carboxylase deficiency treated?

There is no cure for 3-methylcrotonyl-CoA carboxylase deficiency. Treatment for the condition is directed at managing an individual's specific symptoms. Many asymptomatic individuals will never require any treatment. Common treatments include a low-leucine diet with limited protein and/or oral L-carnitine supplementation. Individuals are advised to avoid fasting, particularly for infants and young children. A leucine-free medical formula may be recommended for some infants to help prevent metabolic crises. During times of significant illness, an emergency regimen of IV glucose may be used.

What is the prognosis for an individual with 3-methylcrotonyl-CoA carboxylase deficiency?

The prognosis depends on the severity of the symptoms but is generally good. For the most severely affected, without treatment for metabolic crises, the condition can lead to developmental delay, seizures, coma, or even death. Treatment is often unnecessary for those who are asymptomatic, and the prognosis may be no different than somebody who does not have the condition.

6-pyruvoyl-tetrahydropterin Synthase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PTS.
Exons Sequenced: NM_000317:1-6.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is 6-Pyruvoyl-Tetrahydropterin Synthase Deficiency?

6-pyruvoyl-tetrahydropterin synthase (PTPS) is a rare disorder caused by harmful genetic changes (mutations) in the *PTS* gene. The *PTS* gene is required to make tetrahydrobiopterin (BH4). Low levels of BH4 result in a condition called hyperphenylalaninemia, caused by toxic levels of the amino acid phenylalanine. Additionally, BH4 deficiency results in very low levels of chemicals that transmit impulses from one nerve cell to another in the brain (neurotransmitters).

Individuals with PTPS deficiency can have a variety of symptoms including neurological abnormalities (seizures and swallowing problems); low muscle tone (hypotonia); excess muscle tone (rigidity) in the arms and legs; loss of coordination or delayed motor development; delayed intellectual development; and temperature regulation problems. Infants with PTPS deficiency are often healthy at birth but quickly begin to show signs that they are not growing (failure to thrive). Additional symptoms generally appear within the first four to six months of life. A small head size (microcephaly) may develop in early infancy.

The symptoms of PTPS deficiency can vary widely and range from mild to severe. Twenty percent of individuals have the mild or atypical form. Individuals with the mild or atypical form of PTPS deficiency have moderate or momentary alterations in phenylalanine levels and normal levels of neurotransmitters.

How common is 6-Pyruvoyl-Tetrahydropterin Synthase Deficiency?

Several genes are known to cause tetrahydrobiopterin deficiency, which has an incidence of 1 in 1,000,000 births. PTPS is responsible for approximately 60% of tetrahydrobiopterin deficiency cases. The incidence of PTPS is more common among individuals of East Asian descent.

How is 6-Pyruvoyl-Tetrahydropterin Synthase Deficiency treated?

There is no cure for PTPS deficiency. Treatment will generally focus on reducing high phenylalanine levels through a specialized diet. Affected individuals may also need to take BH4 supplements and other medications that help restore neurotransmitter levels. All individuals with PTPS deficiency will be followed by a metabolic specialist.

What is the prognosis for an individual with 6-Pyruvoyl-Tetrahydropterin Synthase Deficiency?

Early treatment of PTPS deficiency is important in reducing severe, irreversible damage to the brain. With treatment, some individuals may have healthy growth and development. However, affected individuals can still have symptoms such as seizures, developmental delay, and intellectual disability even with proper diet and medications.

Abetalipoproteinemia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MTTP.
Exons Sequenced: NM_000253:2-19.

Detection Rate	Population
99%	African American
99%	Ashkenazi Jewish
99%	Eastern Asia
99%	Finland
99%	French Canadian or Cajun
99%	Hispanic
99%	Middle East
99%	Native American
99%	Northwestern Europe
99%	Oceania
99%	South Asia
99%	Southeast Asia
99%	Southern Europe
99%	Worldwide

What is Abetalipoproteinemia?

Abetalipoproteinemia is a disease of fat metabolism. Individuals with abetalipoproteinemia cannot absorb fats, fat-soluble vitamins, and cholesterol due to the loss of protein needed to transfer fats throughout the body. This can lead to diarrhea, poor growth, vision loss, an inability to coordinate muscle movements (ataxia), abnormal red blood cells, and liver complications. Without treatment, life expectancy is expected to be reduced. Abetalipoproteinemia is caused by harmful genetic changes (variants) in the *MTTP* gene.

The first symptoms often seen with abetalipoproteinemia are diarrhea and poor growth due to the inability to absorb fats. As patients age, they develop vision and neurological problems caused by severe vitamin deficiencies.

Patients often develop a vision disorder called retinitis pigmentosa. Retinitis pigmentosa causes night blindness, color blindness, and a loss of peripheral vision. Eventually, complete vision loss can occur. Rarely, other eye problems such as rapid involuntary eye movements, droopy upper eyelids, or weakness of the eye muscles can occur.

Patients with abetalipoproteinemia also develop neurological problems. These problems include difficulty walking and controlling body movements (ataxia). These symptoms often appear in the first or second decade of life and increase in severity. Some patients also develop loss of reflexes and balance.

Abnormal red blood cells are found in patients with abetalipoproteinemia. These cells have a spiked or spur-like shape when observed through a microscope. A low red blood cell level (anemia) is sometimes seen in patients with the condition. In addition, some patients may develop fatty liver disease, leading to liver damage.

How common is Abetalipoproteinemia?

Abetalipoproteinemia is a rare condition and has an estimated incidence of less than 1 in 1,000,000. The condition may be more common in individuals of Ashkenazi Jewish descent.

How is Abetalipoproteinemia treated?

There is no cure for abetalipoproteinemia. Treatment is based on an individual's symptoms and may involve a team of specialists, including an ophthalmologist, neurologist, and gastroenterologist. Common treatment includes a low-fat diet and high doses of fat-soluble vitamins. Prescribed supplements of Vitamins A, E, D and K have been shown to reduce or prevent some of the neurological and eye symptoms associated with the condition.

What is the prognosis for a person with Abetalipoproteinemia?

Generally, prognosis depends on how early the condition is diagnosed and how well treatment is followed. Without treatment, lifespan is significantly reduced. With treatment, patients have been reported to live into their 50's. Women with abetalipoproteinemia have had successful pregnancies.

Achromatopsia, CNGB3-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CNGB3.
Exons Sequenced: NM_019098:1-18.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Achromatopsia, CNGB3-related?

Achromatopsia, CNGB3-related is an inherited disease that causes poor vision, sensitivity to bright light (photophobia), the inability to see color, and occasionally a vibration or rapid movement in the field of vision (pendular nystagmus). It is also common for individuals to have blurry vision with up close objects (farsightedness).

In individuals with achromatopsia, certain cells in the eye do not function properly, making it difficult for them to see well in bright light. Individuals with achromatopsia will also be colorblind and will not perceive detail well. Most individuals with the disease have 20/200 vision or poorer without correction, and color detection is completely lacking. Some individuals with the disease have incomplete achromatopsia and may be able to see some colors and typically have vision of 20/80 or poorer without correction. In general, symptoms of achromatopsia do not typically result in complete blindness.

Several genes can cause achromatopsia, although harmful genetic changes of the *CNGB3* gene are the most common cause of the disorder. Changes in the *CNGB3* gene have also been observed in a small number (approximately 5%) of patients with progressive cone dystrophy. Unlike achromatopsia (also known as stationary cone dystrophy because symptoms do not worsen over time), individuals with progressive cone dystrophy develop similar symptoms to those with achromatopsia, but with a worsening of vision over time. Progression usually occurs gradually over several years and is variable in severity and age of onset.

How common is Achromatopsia, CNGB3-related?

Several genes are known to cause achromatopsia, which has an incidence of 1 in 30,000 births. Approximately 50% of achromatopsia is caused by *CNGB3*. The incidence of achromatopsia, CNGB3-related is more common among individuals of Pingelap in Pohnpei, part of the Federated States of Micronesia.

How is Achromatopsia, CNGB3-related treated?

There is no cure for achromatopsia, but there are methods to help adapt to vision changes. Many individuals with achromatopsia have found that dark brown-, red-, or gray-tinted glasses help them see outdoors during the day or in bright indoor spaces. Tinted contact lenses may also be beneficial. Other low-vision aids such as large-type books or magnifiers may be helpful. Parents of children with the disease should work with their child's school to make any necessary modifications to their learning environment. Routine ophthalmologic evaluations are recommended.

What is the prognosis for an individual with Achromatopsia, CNGB3-related?

Achromatopsia does not affect lifespan, nor does it affect any other system of the body. While individuals will have poor eyesight, particularly in bright light, the disease is not progressive and will not lead to blindness. However, a small number of harmful genetic changes in *CNGB3* are associated with a different disease known as progressive cone dystrophy. This disease will cause an individual's eyesight to worsen over time.

Acute Liver Failure, TRMU-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: TRMU.
Exons Sequenced: NM_018006:1-11.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Acute Liver Failure, TRMU-related?

Acute liver failure (ALF), TRMU-related, is an inherited condition that causes the liver to stop working suddenly. Acute liver failure has numerous causes, including infections, certain medications, and immune-related conditions. ALF, TRMU-related, is caused by harmful genetic changes (variants) in the *TRMU* gene. This specific form of ALF affects an important part of the body's cells needed to generate energy (mitochondria).

The symptoms of ALF, TRMU-related, are typically seen by six months of age and include yellowing of the skin (jaundice), vomiting or diarrhea, poor feeding, enlarged liver, liver failure, and poor muscle tone (hypotonia). These symptoms are life-threatening and require admission to a hospital for intensive care. Some individuals may experience developmental delay.

How common is Acute Liver Failure, TRMU-related?

ALF, TRMU-related, is a rare condition. The overall frequency of cases is estimated to be less than one in one million individuals.

How is Acute Liver Failure, TRMU-related, treated?

There is no cure for ALF, TRMU-related, and treatment is generally supportive. Supplementation with cysteine has been reported to improve outcomes. Some patients have also required a liver transplant. Individuals with developmental delays may benefit from early intervention and educational support.

What is the prognosis for a person with Acute Liver Failure, TRMU-related?

ALF, TRMU-related, is a life-threatening condition. Up to one-third of individuals may die in infancy. However, many patients survive the initial crisis, and symptoms tend to resolve in two to three weeks. Liver size can take years to return to normal. Developmental delay may improve with intervention.

Adenosine Deaminase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ADA.
Exons Sequenced: NM_000022:1-12.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Adenosine Deaminase Deficiency?

Adenosine deaminase (ADA) deficiency, caused by harmful genetic changes (mutations) in the *ADA* gene, is a metabolic disease that affects lymphocytes, components of blood that play an important role in the immune system. ADA is an enzyme produced by the body that breaks down a toxic substance that results from natural processes in the cells. When there is a deficiency of ADA, the toxic substance builds up in the body and destroys lymphocytes. As a result, people with ADA deficiency can have higher risks for infections.

ADA deficiency is separated into different forms based on the age of onset and severity of symptoms.

ADA-DEFICIENT SEVERE COMBINED IMMUNODEFICIENCY DISEASE (ADA-SCID)

ADA-SCID is the most severe form of this condition and usually appears in the first six to twelve months of life. Infants may fall behind in growth (weight and height) and have a high chance of infection. Lung infections are common at this early age, and these and other infections can cause severe diarrhea, skin rashes, or other severe symptoms. Some individuals with ADA deficiency have skeletal (abnormal rib shape), liver, and neurological problems (cognition, behavior, and/or deafness).

DELAYED/LATE-ONSET ADA DEFICIENCY

About 15% of people with ADA deficiency first develop symptoms after six months of age. Usually symptoms will present within the first few years of life, but a small number of people do not have symptoms until their teens or adulthood. Effects of infections on individuals with delayed/late-onset ADA deficiency are usually less severe than those observed in people with ADA-SCID. These effects often include ear, nose, and throat infections and the appearance of warts on the hands and feet. Eventually, many develop chronic breathing problems and anemia.

PARTIAL ADA DEFICIENCY

Partial ADA deficiency does not typically result in symptoms or require treatment. Low levels of ADA enzymes that are present in this type function well enough to prevent symptoms. Thus, this form of the condition is generally recognized only by enzyme-based blood tests, though it may be predicted to some extent based on one's genetic test results.

How common is Adenosine Deaminase Deficiency?

The worldwide frequency of ADA deficiency in the general population has not been established. Where estimates have been made, the number of individuals affected with the condition each year ranges from 1 in 200,000 to 1 in 1,000,000 and the number of people affected with the condition each year in the US is approximately 1 in 600,000.

How is Adenosine Deaminase Deficiency treated?

Following a diagnosis of ADA deficiency, short-term treatment goals are focused on strengthening the immune system. This is often accomplished with various medications and infusions to help prevent or fight infections. The long-term treatment goal is to restore the function of the immune system through hematopoietic stem-cell transplant (HSCT). If a transplant is not possible or if the associated risks are too high, enzyme-replacement therapy is possible through intra-muscular injections. Researchers have also been experimenting with gene therapy for many years with some success. However, studies about long-term outcomes are still lacking.

What is the prognosis for an individual with Adenosine Deaminase Deficiency?

Without treatment, a child with ADA-SCID can die in the first two years of life. When treated with a transplant from a matched sibling or family member, up to 90% will survive for at least one year, with potentially higher success rates if this treatment is done within the first few months of life. Some have been found to restore immune systems even 10 years after transplant. The survival rate for transplants from unrelated donors is lower (up to 70%). There appears to be a higher chance of cognitive and behavioral abnormalities, in addition to hearing loss, associated with HSCT. When treated with enzyme-replacement therapy, the survival rates are similar to those for individuals who received transplants from an unrelated individual, but some have lived 8 to 10 years or more. Gene therapy, though still in the experimental stages, appears to be a promising option.

Aicardi-Goutières Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: RNASEH2B.
Exons Sequenced: NM_024570:1-11.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Aicardi-Goutières syndrome?

Aicardi-Goutières syndrome (AGS) is an inherited condition that affects the brain, immune system, and skin. It is caused by harmful genetic changes (variants) in the *RNASEH2B* gene. Early onset brain disease (encephalopathy) is a common feature that often causes intellectual and developmental disability. Other symptoms of the condition typically present within the first few weeks of life and can include a small head size (microcephaly), neurologic problems, enlarged liver and spleen (hepatosplenomegaly), fevers (sterile pyrexias), and a shortage of blood cells called platelets (thrombocytopenia). Some individuals will develop painful, itchy skin lesions, called chilblains, on the fingers, toes, and ears.

How common is Aicardi-Goutières syndrome?

The exact incidence of Aicardi-Goutières syndrome is unknown. Approximately 120 individuals have been diagnosed worldwide.

How is Aicardi-Goutières syndrome treated?

There is no cure for Aicardi-Goutières syndrome. Treatment for the condition is directed at managing an individual's specific symptoms. Individuals diagnosed with Aicardi-Goutières syndrome will often benefit from receiving early intervention and other supportive services beginning at a young age. Common interventions may include treating breathing problems, managing feeding problems by focusing on diet to ensure adequate caloric intake and managing seizures. This often means receiving care through a team of specialists, including physicians, speech therapists, occupational therapists, physical therapists, and social workers.

What is the prognosis for an individual with Aicardi-Goutières syndrome?

Infants who experience brain disease (encephalopathy) often have severe intellectual and physical disabilities. Approximately 80% of individuals with the severe form will die within the first ten years of life; however, longer survival has been reported in individuals affected with milder and later-onset forms.

Aldosterone Synthase Deficiency

Available Methodologies: targeted genotyping (v1.0) and interpretation of reported variants (v4.0).
Gene: CYP11B2.
Variants Genotyped (3): R181W, V386A, V35Afs*3.

Detection Rate	Population
32%	African American
32%	Ashkenazi Jewish
32%	Eastern Asia
32%	Finland
32%	French Canadian or Cajun
32%	Hispanic
>99%	Middle East
32%	Native American
32%	Northwestern Europe
32%	Oceania
32%	South Asia
32%	Southeast Asia
32%	Southern Europe
32%	Worldwide

What is Aldosterone Synthase Deficiency?

Aldosterone synthase deficiency (ASD), also known as corticosterone methyloxidase deficiency, is a condition characterized by an imbalance of a specific of minerals (electrolytes) in the blood and other body fluids. It is caused by harmful genetic changes (variants) in the *CYP11B2* gene. Individuals with ASD do not produce enough of a hormone called aldosterone. Because of this, their kidneys are unable to correctly regulate amount of sodium, potassium, and water in the body, which causes the symptoms of the condition.

Common symptoms of ASD include nausea, drowsiness, muscle weakness, dehydration, low blood pressure, and growth issues. Blood tests show a high level of potassium (hyperkalemia) and a low level of sodium (hyponatremia). In severe cases, seizures may occur. Symptoms usually develop within the first few days or weeks of life.

How common is Aldosterone Synthase Deficiency?

The incidence of ASD in the population is thought to be less than 1 in 1,000,000 births. The incidence of ASD is more common among individuals of Amish and Persian (Iranian) Jewish descent.

How is Aldosterone Synthase Deficiency treated?

There is no cure for aldosterone synthase deficiency, but it can be treated with sodium supplements as well as a medication called fludrocortisone. This type of treatment has been successful in preventing symptoms in infants and restoring normal growth and development.

What is the prognosis for an individual with Aldosterone Synthase Deficiency?

Generally, symptoms resolve with treatment. As an individual ages, their body's ability to regulate electrolytes improves. Children typically have stable levels of sodium and potassium by age 4, and adults are usually free from symptoms of the disease. However, without treatment, early death may occur as a result of vomiting and dehydration that leads to low blood pressure, rapid heart rate, and too much acid in the body fluids (acidosis), resulting in circulatory system failure.

Alkaptonuria

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: HGD.
Exons Sequenced: NM_000187:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Alkaptonuria?

Alkaptonuria, caused by harmful genetic changes in the *HGD* gene, is an inherited condition that causes the urine and skin to have a dark color.

Alkaptonuria is caused when the body does not make enough of a particular substance called homogentisate 1,2-dioxygenase (HGD) that is responsible for breaking down a toxic chemical called homogentisic acid (HGA). Excess HGA in the body causes the symptoms of alkaptonuria. The most common symptoms include joint pain (arthritis), urine that turns a brownish-black color when exposed to air, and darkening of skin and cartilage (ochronosis). Other symptoms include kidney stones, prostate stones, and heart problems. Most of the symptoms of alkaptonuria do not occur until the late twenties or early thirties.

Not all patients with alkaptonuria will have the same symptoms. Joint pain often begins in the spine or major joints like the hips and knees. Generally, the joint pain begins between 30 and 40 years of age. In one large study of individuals with alkaptonuria, roughly half reported lower back pain in their thirties, and 94% reported the symptom by age 40. Hips, knees, and shoulders are frequently affected by alkaptonuria, though smaller joints are not.

Many individuals with alkaptonuria will have dark-colored urine. Sometimes the darker color can only be observed after the urine undergoes prolonged exposure to air, so many patients may never be aware of this symptom. Many patients will notice a bluish-black color in certain connective tissue such as the whites of the eyes, the cartilage of the ears, and the tendons of the hands. Alkaptonuria can also cause an individual's sweat to be darker, which can stain clothing.

By their mid-sixties, half of the patients with alkaptonuria will have experienced kidney stones. Some males with alkaptonuria may also experience painful prostate stones. After the age of 60, individuals with the disease frequently experience hardening, thickening, and/or narrowing of the heart valves. The coronary arteries of the heart may also harden.

The symptoms of alkaptonuria generally become worse as individuals age and may lead to significant disability over time.

How common is Alkaptonuria?

The incidence of alkaptonuria in the population is 1 in 250,000 to 1 in 1,000,000 births. The incidence of alkaptonuria is more common among individuals descending from the Dominican Republic and certain parts of Slovakia.

How is Alkaptonuria treated?

There is no prevention or cure for the symptoms of alkaptonuria. Treatment for the condition is directed at managing the specific symptoms an individual has. This often means receiving care through a team of specialists that may include physicians, occupational therapists, and physical therapists. Routine monitoring for cardiac and urology complications is recommended.

Physical and occupational therapy can help individuals maintain muscle strength and flexibility. Nearly all patients will need long-term pain management for their joint pain. Non-weight-bearing exercises, such as swimming, may be beneficial. Patients should avoid putting physical stress on their spine and major joints. For this reason, heavy manual labor and high-impact sports are not recommended at any age.

Studies indicate that 50% of individuals with alkaptonuria will require at least one joint replacement by the age of 50. Surgery may also be needed for elimination of kidney or prostate stones. A small number of patients may need surgery to replace valves in the heart.

Ongoing clinical trials are analyzing the use of a drug called nitisinone to treat alkaptonuria. While nitisinone is currently approved for treatment of alkaptonuria by the European Medicines Agency, it has not yet been approved in the United States.

What is the prognosis for an individual with Alkaptonuria?

All individuals with alkaptonuria will experience chronic joint pain, usually beginning in their thirties. This disease does not usually reduce an individual's lifespan, but can lead to significant disability as one gets older.

Alpha Thalassemia, HBA1/HBA2-related

Available Methodologies: alpha thalassemia (HBA1/HBA2) sequencing with targeted copy number analysis (v4.0) and interpretation of reported variants (v4.0).
Genes: HBA1, HBA2.
Exons Sequenced: NM_000517:1-3; NM_000558:1-3.
The HS-40 enhancer region is also analyzed.

What is Alpha Thalassemia, HBA1/HBA2-related?

Alpha thalassemia is an inherited blood disorder that affects hemoglobin. Hemoglobin is a protein found in red blood cells (RBCs) that makes it possible for RBCs to bind and carry oxygen throughout the body. Hemoglobin is made up of two different protein chains, which are referred to as alpha and beta chains (or alpha and beta globin). Alpha thalassemia is caused by harmful genetic changes (variants) in the *HBA1* and *HBA2* genes. These genes work together to make the alpha globin protein.

Most individuals inherit two normal copies of the *HBA1* gene (one from each parent) and two normal copies of the *HBA2* gene. This means that everyone has four gene copies that make up the alpha chain of their hemoglobin (two *HBA1* and two *HBA2*). Individuals can inherit a harmful change in one, two, three, or all four gene copies. There are also different types of changes within the *HBA1* and *HBA2* genes. Larger changes that remove most or all of the gene are called "deletional," while smaller changes are called "non-deletional."

The symptoms associated with alpha thalassemia can range from a reduced number of RBCs (anemia) to fetal death. The different forms of alpha thalassemia are described below. Because there are several forms of alpha thalassemia and the risk for disease depends on a variety of factors, individuals with variants in *HBA1* and *HBA2* should consult a genetics professional to determine both their personal risk for disease and their reproductive risk.

SILENT CARRIER

Silent carriers of alpha thalassemia have a change in just one of the four alpha globin genes. Individuals with this finding are known as silent carriers because they typically do not have any disease symptoms or visible abnormalities in their RBCs.

ALPHA THALASSEMIA-TRAIT (CARRIER)

Carriers of alpha thalassemia have a change in two of the four alpha globin genes. Individuals with this finding generally have RBCs that are pale (hypochromic) and small (microcytic) when visualized. They may also have a mild decrease in the amount of RBCs (mild anemia). Symptoms of anemia can include tiredness, shortness of breath, lightheadedness, or dizziness. Individuals with only two functional alpha globin genes normally do not require treatment, as they generally do not exhibit symptoms of disease. However, there are reports of individuals with two non-deletional changes who have a diagnosis of a more severe form of the disease called hemoglobin H (HbH) (see below). One example of this is when individuals have two copies of the hemoglobin Constant Spring variant, which is common in the Southeast Asian population.

HEMOGLOBIN H DISEASE

HbH disease is typically the result of changes in three of the four alpha globin genes. This form is highly variable, and symptoms depend on the type of changes present in an individual. Some individuals with HbH do not have any symptoms, while some may have mild to moderate anemia. Other symptoms of HbH can include yellowing of the skin or eyes (jaundice), enlargement of the spleen, and other rarer complications. Although the severity of symptoms can vary, individuals with HbH disease are still considered affected with alpha thalassemia and treatment is often required.

HEMOGLOBIN BART SYNDROME

Hemoglobin Bart (Hb Bart) syndrome is typically the result of changes in all four of the alpha globin genes. Hb Bart is generally associated with fetal death due to the buildup of excess fluid in the body and tissues (hydrops fetalis). Most babies with this condition are stillborn or die soon after birth. Signs and symptoms in the newborn period can include severe anemia, enlargement of the liver and

spleen, and birth defects of the heart, urinary system, and genitals. When fetal blood transfusions are successful, survival is possible; however, there is a high risk for intellectual and physical disability in these survivors.

DELETIONAL VS. NON-DELETIONAL VARIANTS

Historically, the predicted severity of alpha thalassemia was based on how many *HBA1* and *HBA2* genes were impacted. In general, individuals with changes in more of their alpha globin genes typically have more severe symptoms (i.e. variants in three or four genes result in more clinical features than variants in only one or two genes). However, research has shown that both the number *and* the type of changes determine the severity of an individual's symptoms. Larger changes that remove most or all of the gene are called "deletional," while smaller changes are called "non-deletional." Some non-deletional changes are associated with a higher risk for severe symptoms than deletional changes. Thus, the severity of an individual's condition can vary based on the combination of deletional and non-deletional changes they have. Given the many different factors that can influence an individual's personal and reproductive risk for alpha thalassemia, a consult with a genetics professional may be recommended.

How common is Alpha Thalassemia, HBA1/HBA2-related?

The incidence of alpha thalassemia in the population is approximately 1 in 10,000 births. However, the incidence of Hb Bart and HbH is much higher among individuals of Southeast Asian, Mediterranean, and Middle Eastern descent. Southeast Asia has the highest documented incidence, with estimates around 1 in 400 affected births.

How is Alpha Thalassemia, HBA1/HBA2-related treated?

Treatment for HbH disease varies based on the severity of the symptoms. Many individuals will need a blood transfusion during times of severe illness (crises). This is usually a rare occurrence, and it can be caused by environmental stressors such as fever or exposure to specific medications. Individuals with more severe symptoms may require regular blood transfusions, folic acid supplementation, antibiotics during certain procedures, removal of excess iron from the body (iron chelation therapy), removal of the spleen, and possibly therapies to increase fetal hemoglobin levels.

Rare cases of survivors with Hb Bart syndrome have been reported when fetal blood transfusions were given, followed by regular treatments similar to those given to individuals with HbH disease. Treatment or surgical correction of birth defects may also be possible. There is a high risk for intellectual and physical disability in these survivors. These individuals may be candidates for hematopoietic stem cell transplantation.

What is the prognosis for an individual with Alpha Thalassemia, HBA1/HBA2-related?

The long-term outcome of HbH ultimately depends on the severity of the disease. Mild disease may be manageable with little effect on daily life. However, more severe disease will require frequent and regular therapy and may be associated with a shortened lifespan. When treated, individuals with HbH disease can have a near-normal lifespan.

Hb Bart syndrome is the most severe clinical condition related to alpha thalassemia, and death may occur during pregnancy (*in utero*) or in the newborn period. There may also be maternal complications during pregnancy if the fetus has Hb Bart syndrome. These complications include high blood pressure with fluid buildup and protein in the urine (preeclampsia); excessive amniotic fluid (polyhydramnios) or reduced amniotic fluid (oligohydramnios); hemorrhage; and premature delivery. When fetal blood transfusions are successful, survival is possible. However, there is a high risk for intellectual and physical disability in survivors.

Alpha-1 Antitrypsin Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SERPINA1.
Exons Sequenced: NM_000295:2-5.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Alpha-1 Antitrypsin Deficiency?

Alpha-1 Antitrypsin Deficiency (AATD), caused by mutations in the *SERPINA1* gene, is an inherited condition that can cause lung and liver disease. The symptoms of AATD vary greatly from individual to individual, even among those in the same family. Knowing which mutations a child inherits can serve as a guide to how severe his or her symptoms might be. The primary mutation that causes symptoms is called the "Z allele."

As the name indicates, AATD is caused by a deficiency in a protein called alpha-1 antitrypsin. This protein protects the body from neutrophil elastase, an enzyme which normally fights infection in a helpful way. Without sufficient levels of alpha-1 antitrypsin, neutrophil elastase can attack and harm healthy tissue in the lungs. Abnormally formed alpha-1 antitrypsin can also build up in the liver and cause damage.

Ninety-five percent of AATD is caused by the presence of two Z alleles. Individuals who inherit two copies of the Z allele ("ZZ") are most likely to have the severe symptoms of the disease. Smokers with the disease are much more likely to develop symptoms than non-smokers. Secondhand smoke, particularly from one's parents, can also increase the chances of developing symptoms.

Emphysema, a chronic disease in which air sacs in the lungs lose their normal ability to expand and contract, is the most common symptom of AATD. Emphysema causes a progressive difficulty in breathing and a hacking cough. It can severely limit physical activity. The first signs of emphysema, shortness of breath and wheezing, often appear between the ages of 40 and 50 in smokers with the disease. Non-smokers with AATD typically develop emphysema symptoms later, even after the age of 60.

Liver disease is another possible symptom of AATD. About 2.5% of children with AATD will develop severe liver complications. Common symptoms of these early liver problems include a swollen abdomen, swollen feet or legs, abnormal liver enzyme activity, and a yellowing of the skin or whites of the eyes (jaundice).

Overall, 15 to 19% of adults over the age of 50 with two Z alleles develop a build-up of scar tissue in the liver (cirrhosis). This symptom can develop at any age, with a greater risk of cirrhosis later in life. When liver disease associated with AATD begins later in life, destruction of the liver tissue can be rapid.

Higher risk for a particular type of liver cancer has been reported among individuals with AATD, notably in men.

Individuals with only one copy of the Z allele (called carriers) have a slightly elevated risk for lung or liver problems. One study placed this risk at 8%, versus 2 to 4% for the general population. Smokers who are carriers of the Z allele are more likely to develop lung problems such as emphysema, while non-smoking carriers rarely do.

Individuals with AATD may rarely experience inflammation of the skin (panniculitis) or of the blood vessels (vasculitis). These symptoms are much less common than lung or liver complications, with panniculitis estimated to occur in 0.1% and vasculitis estimated to occur in 2% of patients with AATD.

How Common Is Alpha-1 Antitrypsin Deficiency?

In North America, AATD affects 1 in 5,000 to 7,000 individuals. In a study of 75,000 Europeans, researchers estimated that 1 in 4,700 were affected by AATD. The Z allele is most common among individuals of Northwestern European, French Canadian, Cajun, Ashkenazi Jewish, and Middle Eastern ancestry, where up to 1 in 32 individuals are carriers.

AATD is rare in Asian and African populations, except in populations that are racially heterogeneous. For example, African-Americans in the United States have a higher rate of AATD than populations in Africa.

Researchers believe that AATD is often diagnosed as chronic obstructive pulmonary disease (COPD), a relatively common disease, without the realization that AATD is the cause of the COPD. For this reason, the disease may be more common than prevalence numbers indicate.

How Is Alpha-1 Antitrypsin Deficiency Treated?

Individuals with AATD should not smoke. Smokers are more likely to develop symptoms of AATD. In smokers, symptoms tend to develop at an earlier age and progress at a faster rate. Individuals with the disease should also avoid exposure to secondhand smoke, pollution, mineral dust, gas, and chemical fumes. Regular exercise and good nutrition are beneficial for people with AATD.

Carriers of the Z allele should also avoid smoking, as it can increase the risk for health problems related to the Z allele such as COPD or emphysema.

Patients who have moderate lung damage are recommended to have infusions of purified human alpha-1 antitrypsin via intravenous injections. This treatment is considered most effective among individuals with moderate lung damage. This type of treatment is not recommended for patients with AATD who have very little or no lung damage.

In individuals with severe liver or lung disease, transplantation of the failing organ may be an option. Liver transplants can "cure" the disease, because the donor liver will produce the alpha-1 antitrypsin protein.

What Is the Prognosis for an Individual with Alpha-1 Antitrypsin Deficiency?

The prognosis, or outcome, for patients with AATD depends on the type and severity of symptoms they have. In some patients the disease can shorten lifespan, while in others it allows for a normal lifespan. Roughly 2.5% of children with two copies of the Z allele develop severe liver disease and may need a liver transplant.

Overall, smokers show much more severe and rapid lung damage beginning earlier in life than non-smokers, and those with one or more copies of the Z allele are more likely to develop symptoms. In non-smokers who develop lung complications after their 60th birthday, lifespan may be normal.

Alpha-mannosidosis

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MAN2B1.
Exons Sequenced: NM_000528:1-23.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Alpha-Mannosidosis?

Alpha-mannosidosis is an inherited disease that can cause intellectual disability, skeletal abnormalities, hearing loss, muscle weakness, coarse facial features, increased susceptibility to infection, and problems with controlling body movement. This disease, caused by mutations in the *MAN2B1* gene, blocks an enzyme that breaks down the sugar mannose, leading to abnormal accumulation of specific compounds called glycoproteins. The accumulation of sugar-binding glycoproteins results in organ and tissue damage, and the symptoms associated with alpha-mannosidosis.

The severity of symptoms can vary widely among individuals with the disease. However, there are three main types:

TYPE 1

The mildest form, type 1, appears after the age of ten. Individuals with type 1 typically do not have skeletal abnormalities but do show muscle weakness. Their symptoms may be so mild as to be barely detectable. Symptoms tend to progress slowly.

TYPE 2

In the moderate form, type 2, symptoms appear before the age of ten. This form of the disease causes skeletal abnormalities and muscle weakness, but symptoms often progress slowly.

TYPE 3

In the severe form, type 3, the disease is usually fatal in childhood; some affected fetuses even die before birth. The symptoms appear early in infancy and progress rapidly.

While most individuals who are affected with alpha-mannosidosis fall into the moderate category, it may not be possible to predict which form of the disease a person will have based on their specific genetic mutations. Even siblings with the same genetic mutations may have symptoms that vary in severity.

All forms of alpha-mannosidosis involve some degree of intellectual disability, ranging from mild or moderate in type 1 to severe in type 3. Individuals may also demonstrate hearing loss and speech delay. People with alpha-mannosidosis often experience a lack of muscle coordination (ataxia) and general muscle weakness (myopathy) which can translate into individuals learning to walk later than other children and the appearance of clumsiness.

Many individuals with alpha-mannosidosis have a reduced immune response that leads to frequent infection, particularly of the lungs, ears, and digestive system. These infections are most frequent in childhood. Those with type 2 and 3 alpha-mannosidosis experience skeletal abnormalities that may include a reduction in bone density, a deformed spine, bowed legs, and a deterioration of the bones and joints.

Some individuals with the disease experience a buildup of fluid around the brain (hydrocephaly). Some also have an enlargement of the liver and spleen, although this is not thought to cause health problems. Individuals with alpha-mannosidosis may also experience vision problems.

Individuals with this condition share certain facial characteristics, regardless of race. They have prominent foreheads, flattened nasal bridges, broad mouths, and protruding jaws. About 25% of individuals with the disease experience psychiatric problems, often beginning in late puberty or early adolescence. These psychiatric issues have included depression, confusion, anxiety, and hallucinations.

How Common Is Alpha-Mannosidosis?

Alpha-mannosidosis can affect individuals from any race or ethnic group. The prevalence of alpha-mannosidosis is estimated at 1 in 500,000 people worldwide. However, there is currently insufficient information on the prevalence of alpha-mannosidosis in distinct populations.

How Is Alpha-Mannosidosis Treated?

There is no treatment for the underlying cause of alpha-mannosidosis, but physicians can treat symptoms that arise to prevent complications or to enhance an individual's quality of life. Treatments may include the following: antibiotics to reduce bacterial infections; hearing aids and/or tubes to drain fluid from the middle ear; physical therapy to aid in movement; speech therapy and special-education classes to facilitate learning and speech; the use of wheelchairs and other orthopedic aids to improve mobility; and the placement of an implanted shunt near the brain to help drain fluid buildup.

Additional treatments may include treatment for bone disorders such as osteoporosis and vision correction for vision problems. Bone-marrow and stem-cell transplants may improve some symptoms but can carry their own risk for complications.

What Is the Prognosis for an Individual with Alpha-Mannosidosis?

Individuals with milder forms of alpha-mannosidosis typically live until adulthood, with many living into their fifties. Those with the most severe forms, however, usually die before birth or in childhood. Infections are common during childhood but become less frequent when an individual reaches their 20s and 30s, when bone and muscle problems are more of a concern.

Insufficient information on life expectancy, the primary causes of death, and the factors determining disease severity limit the accuracy of prognoses for individuals with alpha-mannosidosis.

Alpha-sarcoglycanopathy

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SGCA.
Exons Sequenced: NM_000023:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Alpha-Sarcoglycanopathy?

Alpha-sarcoglycanopathy, also known as limb-girdle muscular dystrophy type 2D (LGMD2D), causes muscle weakness as a result of a deficiency or abnormality of alpha-sarcoglycan, an important protein in muscle. The condition is caused by mutations in the *SGCA* gene. The symptoms of alpha-sarcoglycanopathy can vary greatly from person to person, even within the same family. Some individuals with the disease may experience only mild muscle weakness, while others may have severe symptoms that can be fatal. The age at which symptoms first develop is also variable, although the condition typically presents in childhood.

The most common symptom of alpha-sarcoglycanopathy is a progressive weakening of muscles in the hips, shoulders, and abdomen (the proximal muscles). The rate at which the muscles weaken can vary, but many experience progressive weakness to a point where a wheelchair becomes necessary. Other symptoms individuals may experience include enlarged calf muscles (calf hypertrophy), contractures, scapular winging (prominence of the shoulder blades), and scoliosis. Respiratory and/or heart complications are also possible, although involvement of the heart muscles is less common in alpha-sarcoglycanophathy compared to other types of limb-girdle muscular dystrophy. Alpha-sarcoglycanopathy does not affect intelligence or cognitive function.

How Common Is Alpha-Sarcoglycanopathy?

There are numerous types of limb-girdle muscular dystrophy. The estimated prevalence of all types of limb-girdle muscular dystrophy is 1 in 15,000 individuals. The exact proportion of cases that have alpha-sarcoglycanopathy is unknown. However, it is reported to be most common in Europe, the United States, and Brazil.

How Is Alpha-Sarcoglycanopathy Treated?

There is no cure for alpha-sarcoglycanopathy and there are few effective treatments. Physical therapy is often recommended to retain muscle strength and mobility for as long as possible. Stretching, mechanical aids, or surgery may also aid in that goal. As muscles deteriorate, a ventilator may be required to help with breathing. Cardiac surveillance is recommended, and those who develop heart problems should consult with a cardiologist for appropriate treatment.

What Is the Prognosis for an Individual with Alpha-Sarcoglycanopathy?

The outlook for an individual with alpha-sarcoglycanopathy varies. Generally speaking, the earlier the symptoms begin, the faster they progress. However, because symptoms and onset can be variable, the prognosis can be variable. Individuals with more severe symptoms often become wheelchair-bound in their early teens and die in early adulthood, with death often the result of respiratory failure. Individuals with mild symptoms may remain able to walk for 30 or more years after symptoms appear and may have a normal lifespan.

Alport Syndrome, COL4A3-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: COL4A3.
Exons Sequenced: NM_000091:1-52.

Detection Rate	Population
94%	African American
94%	Ashkenazi Jewish
94%	Eastern Asia
94%	Finland
94%	French Canadian or Cajun
94%	Hispanic
94%	Middle East
94%	Native American
94%	Northwestern Europe
94%	Oceania
94%	South Asia
94%	Southeast Asia
94%	Southern Europe
94%	Worldwide

What is Alport syndrome, COL4A3-related?

Alport syndrome is an inherited connective-tissue disorder that can cause progressive kidney disease, abnormalities affecting the eyes, and hearing loss. There are three genes associated with Alport syndrome, and Alport syndrome, COL4A3-related, is caused by harmful genetic changes in the *COL4A3* gene. Alport syndrome can be inherited in an X-linked or autosomal-recessive manner. Alport syndrome, COL4A3-related, is inherited in an autosomal-recessive manner.

The presentation of Alport syndrome is variable in severity. Some individuals have a milder disease course, while others develop more severe symptoms. Males and females with Alport syndrome, COL4A3-related, have similar disease severity. Although the data are somewhat limited, recent studies have shown that some individuals with Alport syndrome may have a harmful genetic change in *COL4A3* and another gene (suggesting digenic inheritance).

The first symptom of Alport syndrome is typically blood in the urine (hematuria) from kidney disease, which usually presents during childhood. This is usually not detectable by the naked eye, but it may be visible during periods of illness. Individuals also develop protein in the urine (proteinuria) during childhood. Kidney disease often progresses to kidney failure by early adulthood. This kidney failure is associated with various symptoms, including high blood pressure, fatigue, poor appetite, swelling of legs and feet, and frequent urination. Medications may delay the progression of kidney failure, but typically, a kidney transplant and/or dialysis will eventually be necessary.

Alport syndrome is associated with varying degrees of progressive hearing loss and eye abnormalities. The onset and severity of hearing loss are variable, but it is not uncommon for some degree of hearing loss to develop by adolescence. Eye abnormalities, including those affecting the outer protective layer of the eye (the cornea), the transparent tissue behind the iris (the lens), and the light-sensitive tissue in the back of the eye (the retina), are the most common. These abnormalities may result in light sensitivity, clouding of the lens of the eye (cataracts), and blurred vision. Glasses are sometimes required to correct vision.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Approximately two-thirds of all carriers of a harmful change in *COL4A3* will have small amounts of blood in their urine (hematuria). Some carriers may develop other symptoms of Alport syndrome over their lifetime, including high blood pressure, protein in the urine, or poor kidney function. Carriers should not be kidney donors because this could increase their chance of developing kidney disease. Carriers of harmful genetic changes in *COL4A3* should have routine physical exams and speak with their healthcare provider about the risk of developing kidney disease. Genetic counseling is recommended.

How common is Alport syndrome, COL4A3-related?

All forms of Alport syndrome are estimated to occur in approximately 1 in 50,000 live births. The two genes associated with the recessive form of Alport syndrome, *COL4A3* and *COL4A4*, are responsible for about 20% of all cases. Alport syndrome occurs at a similar frequency amongst all ethnicities. Alport syndrome, COL4A3-related, is more common in certain populations, such as individuals of Ashkenazi Jewish descent.

How is Alport syndrome, COL4A3-related, treated?

Currently, there is no cure for Alport syndrome. However, treatments are available to address many of the associated symptoms. Medications are used to treat high blood pressure, reduce protein in the urine, and slow the progression of kidney disease. However, kidney failure will eventually develop. Because the onset of kidney failure is variable, transplantation or dialysis may be required as early as the teenage years in some individuals but is most often necessary by adulthood. Hearing aids may be required to manage hearing loss. Additionally, ophthalmologic intervention, such as cataract surgery, may be required for some affected individuals. A multidisciplinary team of physicians, including nephrologists, audiologists, ophthalmologists, and other healthcare professionals, will need to be involved in the ongoing treatment and management of individuals with Alport syndrome.

What is the prognosis for an individual with Alport syndrome, COL4A3-related?

While the prognosis of Alport syndrome is variable, most affected individuals develop kidney failure by 40 years of age. Renal transplantation and/or dialysis are typically successful as patients approach kidney failure. Complications from kidney disease may still result in a shortened life span. In addition, hearing loss typically develops in most individuals by 40 years of age. Often, the eye complications do not cause any severe visual abnormalities, although cataract surgery and/or corrective lenses may be required.

Alport Syndrome, COL4A4-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: COL4A4.
Exons Sequenced: NM_000092:2-48.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Alport syndrome, COL4A4-related?

Alport syndrome is an inherited connective-tissue disorder that can cause progressive kidney disease, abnormalities affecting the eyes, and hearing loss. There are three genes associated with Alport syndrome, and Alport syndrome, COL4A4-related, is caused by harmful genetic changes in the *COL4A4* gene. Alport syndrome can be inherited in an X-linked or autosomal-recessive manner. Alport syndrome, COL4A4-related, is inherited in an autosomal-recessive manner.

The presentation of Alport syndrome is variable in severity. Some individuals have a milder disease course, while others develop more severe symptoms. Males and females with Alport syndrome, COL4A4-related, have similar disease severity. Although the data are somewhat limited, recent studies have shown that some individuals with Alport syndrome may have a harmful genetic change in *COL4A4* and another gene (suggesting digenic inheritance).

The first symptom of Alport syndrome is typically blood in the urine (hematuria) from kidney disease, which usually presents during childhood. This is usually not detectable by the naked eye, but it may be visible during periods of illness. Individuals also develop protein in the urine (proteinuria) during childhood. Kidney disease often progresses to kidney failure by early adulthood. This kidney failure is associated with various symptoms, including high blood pressure, fatigue, poor appetite, swelling of legs and feet, and frequent urination. Medications may delay the progression of kidney failure, but typically, a kidney transplant and/or dialysis will eventually be necessary.

Alport syndrome is associated with varying degrees of progressive hearing loss and eye abnormalities. The onset and severity of hearing loss are variable, but it is not uncommon for some degree of hearing loss to develop by adolescence. Eye abnormalities, including those affecting the outer protective layer of the eye (the cornea), the transparent tissue behind the iris (the lens), and the light-sensitive tissue in the back of the eye (the retina), are the most common. These abnormalities may result in light sensitivity, clouding of the lens of the eye (cataracts), and blurred vision. Glasses are sometimes required to correct vision.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Approximately two-thirds of all carriers of a harmful change in *COL4A4* will have small amounts of blood in their urine (hematuria). Some carriers may develop other symptoms of Alport syndrome over their lifetime, including high blood pressure, protein in the urine, or poor kidney function. Carriers should not be kidney donors because this could increase their chance of developing kidney disease. Carriers of harmful genetic changes in *COL4A4* should have routine physical exams and speak with their healthcare provider about the risk of developing kidney disease. Genetic counseling is recommended.

How common is Alport syndrome, COL4A4-related?

All forms of Alport syndrome are estimated to occur in approximately 1 in 50,000 live births. The two genes associated with the recessive form of Alport syndrome, *COL4A3* and *COL4A4*, are responsible for about 20% of all cases. Alport syndrome occurs at a similar frequency amongst all ethnicities. Alport syndrome, COL4A4-related, is more common in certain populations, such as individuals of Ashkenazi Jewish descent.

How is Alport syndrome, COL4A4-related, treated?

Currently, there is no cure for Alport syndrome. However, treatments are available to address many of the associated symptoms. Medications are used to treat high blood pressure, reduce protein in the urine, and slow the progression of kidney disease. However, kidney failure will eventually develop. Because the onset of kidney failure is variable, transplantation or dialysis may be required as early as the teenage years in some individuals but is most often necessary by adulthood. Hearing aids may be required to manage hearing loss. Additionally, ophthalmologic intervention, such as cataract surgery, may be required for some affected individuals. A multidisciplinary team of physicians, including nephrologists, audiologists, ophthalmologists, and other healthcare professionals, will need to be involved in the ongoing treatment and management of individuals with Alport syndrome.

What is the prognosis for an individual with Alport syndrome, COL4A4-related?

While the prognosis of Alport syndrome is variable, most affected individuals develop kidney failure by 40 years of age. Renal transplantation and/or dialysis are typically successful as patients approach kidney failure. Complications from kidney disease may still result in a shortened life span. In addition, hearing loss typically develops in most individuals by 40 years of age. Often, the eye complications do not cause any severe visual abnormalities, although cataract surgery and/or corrective lenses may be required.

Alstrom Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ALMS1.
Exons Sequenced: NM_015120:1-23.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Alstrom Syndrome?

Alstrom syndrome, caused by harmful genetic changes (mutations) in the *ALMS1* gene, is an inherited condition that affects fat cells and tiny hair-like parts of a cell called cilia. The *ALMS1* gene produces a protein that is thought to be involved in movement of various molecules inside and outside of the cell, cell division, the proper function of the cilia, and gene regulation. The ALMS1 protein is found in most tissues in the body, and impairment of the protein function results in a range of symptoms. Although severity of symptoms can vary from person to person, even among those in the same family, most individuals develop heart disease, obesity, diabetes, and progressive vision and hearing loss. Most individuals with Alstrom syndrome have normal intelligence, but may have delayed developmental milestones.

Vision loss, caused by progressive retinal dystrophy, begins in infancy and worsens over time, with most individuals eventually losing all ability to see. Eighty-five percent of individuals with the disease will develop hearing loss in both ears that progresses over time. Nearly all individuals with the disease have high fat (lipid) levels which can lead to obesity. Insulin resistance begins in childhood which can result in individuals developing type 2 diabetes mellitus in adolescence. Two-thirds of individuals with Alstrom syndrome also develop a heart disease called dilated cardiomyopathy which causes the heart muscle to enlarge and weaken. Some individuals with Alstrom syndrome may develop liver or kidney disease. Chronic respiratory infections can begin early in childhood and eventually cause various types of lung illnesses. Other symptoms include short stature, curvature of the spine (scoliosis or kyphosis), extra, missing, or mislocated teeth, seizures, and urinary problems.

Alstrom syndrome can also affect sexual development and fertility. Approximately 80% of males with Alstrom syndrome do not produce enough testosterone (male sex hormone) leading to small external genitalia and degeneration of the testes. Females with Alstrom syndrome may begin puberty early, and their menstruation may be abnormal or absent. Females may also have abnormal hair growth, abnormal growth of uterine tissue (endometriosis), or polycystic ovaries. Most individuals with Alstrom syndrome cannot have biological children.

How common is Alstrom Syndrome?

The exact frequency of Alstrom syndrome in the general population is unknown, though estimates range from 1 in 100,000 to less than 1 in 1,000,000. Only about 950 people have been diagnosed worldwide. The frequency is higher in isolated populations or those where marriage between blood relatives (consanguinity) is common.

How is Alstrom Syndrome treated?

There is no cure for Alstrom syndrome, but careful monitoring of vision, hearing, liver, heart, thyroid, and kidney function is important for detecting and treating symptoms early. Young children benefit from red-tinted prescription glasses, development of non-visual language skills, and hearing aids. Cardiac function should be routinely monitored, and patients who develop cardiomyopathy need to take angiotensin-converting enzyme (ACE) inhibitors. Physical exercise is important for weight management. Some patients require insulin, insulin-sensitizing agents, or thiazolidinediones. Patients may also need hormone replacement therapy. Intermittent self-catheterization can help with bladder control. Some patients may need specific medications and treatments to help with liver and kidney problems. Patients and their families benefit greatly from seeking social and emotional support to cope with the isolation that may come with living with a rare and complicated disorder.

What is the prognosis for an individual with Alstrom Syndrome?

Prognosis is highly variable due to the range of disease presentations. Alstrom syndrome is associated with a number of chronic, life-threatening issues, such as congestive heart failure and end-stage renal disease, which are also the two major causes of death. Life expectancy is reduced with this condition and patients rarely live past 40 years of age.

Andermann Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SLC12A6.
Exons Sequenced: NM_133647:1-25.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Andermann Syndrome?

Andermann syndrome, also called agenesis of corpus callosum with peripheral neuropathy, is an inherited disease that causes progressive damage to the nervous system. Andermann syndrome is caused by mutations in the *SLC12A6* gene. Its symptoms appear early in life and include intellectual and developmental disabilities, delayed motor skills, overall muscle weakness, curvature of the spine, and dysfunction in the nerves of the hands and feet resulting in numbness, pain, and muscle weakness. These symptoms are progressive and will worsen over time.

Motor and sensory skills are impaired from infancy and individuals with the condition also share certain physical features including a small head, long asymmetric face, small upper jaw, large ears, and a large distance between the eyes.

Two-thirds of individuals with the condition are missing the corpus callosum, a structure that connects the right and left sides of the brain, while the remaining individuals have a partially formed corpus callosum. Individuals with the disease learn to walk later than normal, often around the age of three, and progressively lose the ability to walk in their early teens. They may also experience seizures.

In their twenties, individuals with Andermann syndrome often develop hallucinations and psychosis. The disease is typically fatal before the age of 40.

How Common Is Andermann Syndrome?

Andermann syndrome is seen almost exclusively in individuals from the Saguenay–Lac-Saint-Jean region of Québec, Canada where it affects 1 in 2,117 births. Andermann syndrome has only been reported in other populations on rare occasions, and the worldwide prevalence is unknown.

How Is Andermann Syndrome Treated?

There is no cure for Andermann syndrome, and there are few effective treatments for its symptoms. Physical therapy may be useful to maintain movement as long as possible. Surgery may also be recommended to straighten the spine.

What Is the Prognosis for an Individual with Andermann Syndrome?

Andermann syndrome is a progressive disease that impairs a patient's motor functions and causes intellectual and developmental disabilities. All individuals with the disease will eventually be wheelchair bound. Individuals with Andermann syndrome typically develop severe neurological problems in their twenties and the disease is usually fatal before the age of 40.

Argininemia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ARG1.
Exons Sequenced: NM_000045:1-8.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe
97%	Worldwide

What is Argininemia?

Argininemia is a urea cycle disorder caused by harmful genetic changes (mutations) in the *ARG1* gene. Individuals with argininemia have arginase deficiency, which leads to toxic levels of arginine and ammonia in the body. Symptoms typically include poor growth, stiff muscles (spasticity), seizures, loss of skills (developmental regression), and intellectual disability. Some individuals may also have a small head size (microcephaly), scarring of the liver (cirrhosis), problems with balance and coordination, or episodes of high levels of ammonia (hyperammonemia) in the blood. Hyperammonemia may cause additional complications like lack of energy (lethargy) or vomiting. Most affected individuals present with symptoms between the ages of one and three years, although cases of earlier onset have been reported.

How common is Argininemia?

The incidence of argininemia in the population is 1 in 350,000 to 1 in 1,000,000 births.

How is Argininemia treated?

There is no cure for argininemia. Treatment for argininemia is dietary, through restriction of dietary protein and by taking necessary amino acids. Additionally, medications called nitrogen-scavenging drugs may help maintain lower amounts of ammonia in the body. Seizures can be treated with medication, but valproic acid should be avoided. In individuals where ammonia levels cannot be managed, a liver transplant may be considered. Acute episodes of hyperammonemia (hyperammonemic crisis) are treated in a hospital to quickly reduce ammonia levels in the blood, to prevent brain damage. All individuals with argininemia will be followed by a metabolic specialist.

What is the prognosis for an individual with Argininemia?

Without treatment, individuals will experience poor growth, stiff muscles, developmental delay, and intellectual disability. Lifespan is normal in most affected individuals, but some may die early from complications of extremely high ammonia (hyperammonemic crisis). With treatment, some neurological symptoms may be stabilized and the risk of hyperammonemic crises may be reduced over the course of the individual's life.

Argininosuccinic Aciduria

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ASL.
Exons Sequenced: NM_001024943:1-16.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Argininosuccinic Aciduria?

Argininosuccinic aciduria (ASL deficiency) is a urea cycle disorder caused by harmful genetic changes (mutations) in the *ASL* gene. Mutations in *ASL* cause deficiency of argininosuccinate lyase, which results in the build-up of argininosuccinic acid, citrulline, and toxic ammonia in the body (hyperammonemia). There are two forms of the disease: neonatal-onset form and late-onset form.

NEONATAL-ONSET FORM

The neonatal-onset form is severe. It presents within the first few days of life with symptoms such as vomiting, excessive sleepiness (lethargy), low body temperature (hypothermia), poor feeding, and rapid breathing (tachypnea). Other early symptoms may include brittle hair and an enlarged liver. If left untreated, symptoms will progress and eventually lead to seizures, coma, and death.

LATE-ONSET FORM

The late onset form can have a wide range of symptoms. Symptoms may include developmental delay, intellectual disability, behavioral abnormalities and episodic increases in ammonia levels.

How common is Argininosuccinic Aciduria?

The incidence of argininosuccinic aciduria in the population is 1 in 70,000 births. Argininosuccinic aciduria is more common among individuals of Saudi Arabia and the Druze community.

How is Argininosuccinic Aciduria treated?

Treatment for argininosuccinic aciduria is dietary, through restriction of dietary protein and the taking of arginine supplements. Additionally, medication called nitrogen-scavenging drugs may help maintain lower amounts of ammonia in the body. In individuals whose ammonia levels cannot be managed, or in those with liver cirrhosis, a liver transplant may be considered.

Acute episodes of excess ammonia are treated in a hospital. Though intravenous (IV) supplements and nitrogen-scavenging drugs can help lower the amount of ammonia in the body, filtering the ammonia from the blood directly (hemodialysis) may be necessary if these measures are ineffective.

What is the prognosis for an individual with Argininosuccinic Aciduria?

There is no cure for argininosuccinic aciduria, and the prognosis depends upon the severity of the symptoms. Individuals who have milder symptoms and are provided with early dietary and therapeutic interventions will have a more favorable outcome. However, they will still require long-term management to prevent neurologic and liver damage. Those who have more severe symptoms could experience seizures, coma, and early death. Treatments to reduce ammonia levels in the body do not prevent intellectual disability, liver disease, and brittle hair.

Arthrogryposis, Impaired Intellectual Development, and Seizures

Available Methodologies: targeted genotyping (v1.0) and interpretation of reported variants (v4.0).
Gene: SLC35A3.
Variant Genotyped (1): Q214*.

What is Arthrogryposis, Impaired Intellectual Development, and Seizures?

Arthrogryposis, impaired intellectual development, and seizures is a combination of symptoms observed in individuals with harmful genetic changes (variants) in the *SLC35A3* gene. Only a few individuals with these harmful changes are described in the medical literature. Reported symptoms include seizures that can start in early infancy, malformed bones (skeletal defects), and small head size (microcephaly). Stiff and contracted joints (arthrogryposis) has also been reported. All individuals with harmful changes in the *SLC35A3* gene have some level of intellectual disability. Autism spectrum disorders have also been observed.

How common is Arthrogryposis, Impaired Intellectual Development, and Seizures?

The incidence of arthrogryposis, impaired intellectual development, and seizures is unknown. Only a few cases have been reported in the literature.

How is Arthrogryposis, Impaired Intellectual Development, and Seizures treated?

There is no cure for arthrogryposis, impaired intellectual development, and seizures. Treatment should be directed at an individual's specific symptoms and may include a variety of healthcare providers.

What is the prognosis for a person with Arthrogryposis, Impaired Intellectual Development, and Seizures?

Since the condition is so rare, the prognosis for individuals with arthrogryposis, impaired intellectual development, and seizures is not well known. Of the few cases reported, the prognosis has generally been poor. Individuals who survive the neonatal period will have some level of intellectual disability.

ARX-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ARX.
Exons Sequenced: NM_139058:1-5.

Detection Rate	Population
31%	African American
31%	Ashkenazi Jewish
31%	Eastern Asia
31%	Finland
31%	French Canadian or Cajun
31%	Hispanic
31%	Middle East
31%	Native American
31%	Northwestern Europe
31%	Oceania
31%	South Asia
31%	Southeast Asia
31%	Southern Europe
31%	Worldwide

What are ARX-related disorders?

ARX-related disorders are a spectrum of diseases that can cause various conditions that impair brain function and are largely associated with intellectual disability. The conditions are caused by harmful genetic changes (variants) in the *ARX* gene. ARX-related disorders are inherited in an X-linked manner, meaning that people assigned male at birth (XY) usually have symptoms, while those assigned female (XX) at birth typically do not. ARX-related disorders can be classified into different syndromes (as detailed below). There is wide variability in the symptoms of ARX-related disorders and even people in the same family can have different forms.

DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY-1 (DEE1)

The primary symptom of DEE1 is seizures that cause sudden tension or stiffness (tonic seizures). These seizures can happen repeatedly and usually start within the first year of life. Intellectual disability is common in individuals with DEE1, and some infants may lose previously acquired skills, such as sitting or rolling over.

X-LINKED LISSENCEPHALY-2 (LISX2)

LISX2 is a disorder primarily affecting the development of the brain and the genitals. The condition is sometimes called "X-linked lissencephaly with abnormal genitalia" or XLAG. The distinguishing characteristics of this condition include a smooth appearance of the brain (lissencephaly) and abnormal development of the genitals. This may include a small penis (micropenis), undescended testes (cryptorchidism), or genitalia that do not externally appear either male or female (ambiguous genitalia). Intellectual disability and seizures are often present in LISX2. This condition is often fatal for XY individuals within the first few days or months of life. XX individuals are considered carriers and are usually either unaffected or have mild symptoms.

PARTINGTON SYNDROME

Partington syndrome is characterized by mild to moderate intellectual disability, speech difficulties (dysarthria), and involuntary hand movements (dystonia). Recurrent seizures and behavioral problems may also be present. Some affected individuals have characteristic facial features. The onset of symptoms is usually in infancy or early childhood.

PROUD SYNDROME

Proud syndrome is characterized by severe intellectual disability, seizures, and a birth defect in the brain called agenesis of the corpus callosum. Other symptoms may include urologic abnormalities such as undescended testes (cryptorchidism), opening of the penis on the underside of the organ (hypospadias), and underdeveloped kidneys (renal dysplasia).

X-LINKED INTELLECTUAL DEVELOPMENTAL DISORDER

Some individuals whose symptoms do not fit one of the categories listed above may be given a diagnosis of "X-linked intellectual developmental disorder."

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Female (XX) individuals who are carriers of ARX-related disorders usually do not have symptoms, however, it is possible for them to have some mild symptoms.

How common are ARX-related disorders?

The exact incidence of ARX-related disorders is unknown. At least 20 Partington syndrome and 30 cases of LISX2 have been reported.

How are ARX-related disorders treated?

There is no cure for ARX-related disorders. Treatment for these conditions is directed at managing an individual's specific symptoms. The goal of treatment is to optimize the individual's abilities. Children with the condition will often benefit from receiving early intervention and other supportive services beginning at a young age. Many of the seizures associated with ARX-related disorders tend to be difficult to treat.

What is the prognosis for an individual with ARX-related disorders?

The prognosis for males with ARX-related disorders is not well understood but is generally considered poor. The prognosis will depend on the severity of symptoms. Males affected with LISX2 will often die within the first days or months of life, whereas some children with DEE1 survive into childhood. Female (XX) carriers of ARX-related disorders may or may not be symptomatic, though symptoms are often milder than those for male (XY) individuals.

Asparagine Synthetase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ASNS.
Exons Sequenced: NM_001673:3-13.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Asparagine Synthetase Deficiency?

Asparagine synthetase deficiency, caused by harmful genetic changes in the *ASNS* gene, is a severe neurological disorder. Symptoms begin during pregnancy or at birth and include a small head (microcephaly), severe developmental delay, degeneration of the brain (atrophy), and seizures. Individuals also experience low muscle tone (hypotonia) that eventually progresses to muscle weakness and stiffness (spastic quadriplegia). Blindness has been reported in some cases.

How common is Asparagine Synthetase Deficiency?

The exact incidence of asparagine synthetase deficiency is unknown. More than 20 individuals have been diagnosed worldwide.

How is Asparagine Synthetase Deficiency treated?

There is currently no cure for this disorder. Treatment for the condition is directed at managing the specific symptoms an individual has. This often means receiving care through a team of specialists that may include physicians, therapists, and social workers. Dietary supplementation with asparagine has been suggested but it is not clear if this would alleviate any of the symptoms of the disease. Some families may opt to pursue palliative care, which focuses on improving quality of life and may have limited medical intervention.

What is the prognosis for an individual with Asparagine Synthetase Deficiency?

Individuals with asparagine synthetase deficiency typically do not live past the first year of life. Individuals who live beyond this are not expected to obtain developmental skills (such as walking, talking, or communicating) and will have profound intellectual disability. If any developmental milestones are achieved, individuals typically lose these abilities over time (developmental regression).

Aspartylglucosaminuria

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: AGA.
Exons Sequenced: NM_000027:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Aspartylglucosaminuria?

Aspartylglucosaminuria (AGU) is an inherited condition caused by mutations in the *AGA* gene in which the body lacks an enzyme called aspartylglucosaminidase. A deficiency of the aspartylglucosaminidase enzyme impairs the body's ability to break down large molecules called glycoasparagines, resulting in their buildup in the fluid and tissues of the body.

AGU is progressive, with affected individuals typically appearing normal at birth. Subsequently, children with AGU experience developmental delays and are often characterized as having attention problems and restlessness. Speech delays are often the first symptom recognized, usually around the age of two or three. Speech difficulties, slow learning, and lack of coordination are typical. With time, intellectual disability worsens and some skills and abilities may be lost. Affected adults exhibit profound intellectual impairment and eventually lose the ability to speak. Adolescents and adults with the condition may also experience epileptic seizures and may have the need for a wheelchair later in life.

Individuals with AGU share certain physical features, including widely spaced eyes, a broad nose and face, full lips, and small ears. Their facial features tend to coarsen over time, and connective tissue problems or weakened bones (osteoporosis) may develop. Individuals may also have spinal and skeletal deformities such as a curvature of the spine. While children with AGU tend to be taller than their peers, affected adults often have short stature due to the lack of a growth spurt during puberty. Affected individuals also tend to have more-frequent infections of the skin and respiratory system.

How Common Is Aspartylglucosaminuria?

The prevalence of AGU in the general population is unknown. The condition is most common in individuals of Finnish decent. The prevalence of AGU in Finland is 1.7 in 100,000 to 5 in 100,000 live births.

How Is Aspartylglucosaminuria Treated?

Currently, there is no cure for AGU. Medical professionals can only treat symptoms as they arise. These treatments may include, but are not limited to, special education, anti-seizure medication, and orthopedic aids to help in movement.

What Is the Prognosis for an Individual with Aspartylglucosaminuria?

Individuals with AGU experience a progressive decline in abilities, with most affected adults having profound intellectual impairment and loss of speech. Lifespan is decreased, with death typically occurring between 35 and 50 years of age. The most-common cause of death is severe respiratory infection.

Ataxia with Vitamin E Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: TTPA.
Exons Sequenced: NM_000370:1-5.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Ataxia With Vitamin E Deficiency?

Ataxia with vitamin E deficiency (AVED) is an inherited disease that causes the nervous system to degenerate, leading to a progressive inability to control one's voluntary movements (ataxia). If treated early and consistently with vitamin E, symptoms of the disease can be avoided.

If untreated with vitamin E, other symptoms of the disease can include difficulty speaking, loss of sensation in the arms and legs, and loss of some visual acuity. In some people, intellectual decline and mental problems can occur. Other people with AVED have experienced heart problems as well.

In people with the disease who remain untreated, movement problems often begin between the ages of 4 and 18 and worsen over time. Early symptoms often include clumsiness of the hands, problems with handwriting, and reduced awareness of how one's body is positioned. These people will lose tendon reflexes in the arms and legs.

The type and severity of symptoms will vary from person to person, even among those in the same family.

How common is Ataxia With Vitamin E Deficiency?

AVED is rare, but its exact prevalence is unknown. It may be more common in people of Mediterranean or North African descent.

How is Ataxia With Vitamin E Deficiency treated?

AVED is treatable with high doses of vitamin E taken regularly throughout life. If taken before symptoms begin, vitamin E can prevent symptoms from occurring at all. If symptoms have already begun, vitamin E may prevent them from worsening and in some people, symptoms have been reversed to some degree. Unsteadiness walking, however, often cannot be reversed.

People with AVED should not smoke, as this can reduce the amount of vitamin E in the body. They also should not undertake jobs that require quick responses or good balance. Before learning to drive a car, their abilities should be assessed to determine whether driving is safe.

What is the prognosis for a person with Ataxia With Vitamin E Deficiency?

If treated with vitamin E before symptoms start, people with AVED can lead normal lives. Without treatment, people with AVED will become wheelchair-reliant between the ages of 11 and 50, and may develop significant physical and mental problems.

Ataxia-telangiectasia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ATM.
Exons Sequenced: NM_000051:2-63.

Detection Rate	Population
96%	African American
96%	Ashkenazi Jewish
96%	Eastern Asia
96%	Finland
96%	French Canadian or Cajun
96%	Hispanic
96%	Middle East
96%	Native American
96%	Northwestern Europe
96%	Oceania
96%	South Asia
96%	Southeast Asia
96%	Southern Europe
96%	Worldwide

What is Ataxia-Telangiectasia?

Ataxia-telangiectasia (A-T) is an inherited disease characterized by the loss of one's ability to coordinate movement (ataxia), a weakening of the immune system, and an increased risk for cancer. It is also typically characterized by small, red, spider-like blood vessels (telangiectasia) in the eyes and on the skin. A-T is caused by harmful genetic changes, or mutations, in the *ATM* gene, which is involved in the control of cell growth, cell division, and the repair of damaged DNA.

In most cases, A-T presents in early childhood. Children with the condition will begin to wobble or stagger and have poor balance. Children affected with A-T may exhibit delayed motor skills and slurred speech. They may also lose the ability to follow objects with their eyes. By the age of 7 or 8, children with the disease often lose the muscle control necessary to write, and most individuals require the use of a wheelchair by the age of 10. While neurological problems may impair their ability to communicate, those with A-T are usually of average or above-average intelligence.

Most individuals with A-T also have weakened immune systems, leaving them prone to infection, particularly in the lungs. Also, they are at an increased risk of developing cancers at an early age, particularly cancers of the blood (leukemia) or the immune system (lymphoma). These individuals are also hypersensitive to the type of radiation found in X-rays and used in cancer therapy and typically must avoid it.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

While carriers of A-T do not show symptoms of the disease, studies have shown that they do have an increased risk of developing cancer. Female carriers have an increased risk of developing breast cancer. Therefore, starting at age 40 or earlier, female carriers are recommended to have an annual mammogram and consider breast MRI to screen for cancer. Both male and female carriers may have an increased risk of developing pancreatic cancer. The exact risks for cancer depend on personal and family history, so carriers of *ATM* mutations should consider genetic counseling to determine the most appropriate screening recommendations.

How common is Ataxia-Telangiectasia?

The estimated prevalence of A-T is 1 in 40,000 to 1 in 100,000 individuals worldwide.

How is Ataxia-Telangiectasia treated?

While there is no cure for A-T, the symptoms of the disease may be addressed. Injections of gamma globulin may be prescribed to help boost the immune system. High-dose vitamins may also be recommended. Antibiotics are typically used for infections, and vaccines for influenza and pneumonia may be recommended, as these infections can be devastating to those with A-T. Physical, occupational, and speech therapies may also be useful and recommended.

What is the prognosis for an individual with Ataxia-Telangiectasia?

Nearly all children with A-T are wheelchair-bound by the age of 10, and teenagers and adults with the disease require help with everyday tasks, including dressing, eating, washing, and using the bathroom. Life expectancy for individuals with the condition is shortened, with death often occurring in early adulthood. A small number of affected individuals have survived into their forties or fifties. The most common causes of death from A-T are cancer, lung infection, or lung failure. Because their intelligence remains normal, many individuals with A-T graduate high school and college.

ATP7A-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ATP7A.
Exons Sequenced: NM_000052:2-23.

Detection Rate	Population
90%	African American
90%	Ashkenazi Jewish
90%	Eastern Asia
90%	Finland
90%	French Canadian or Cajun
90%	Hispanic
90%	Middle East
90%	Native American
90%	Northwestern Europe
90%	Oceania
90%	South Asia
90%	Southeast Asia
90%	Southern Europe
90%	Worldwide

What are ATP7A-related Disorders?

ATP7A-related disorders are a group of diseases characterized by the body's inability to control the amount of copper in its organs and tissues. These disorders are caused by harmful genetic changes (mutations) in a gene called *ATP7A*. The *ATP7A* gene moves copper across the barriers that separate cells (cell membranes), so that the correct amount of copper is present in different areas of the body. Deficient *ATP7A* function causes individuals to have abnormal copper levels, which leads to organ damage. These disorders generally occur in males, while females do not usually have symptoms.

CLASSIC MENKES DISEASE

Menkes disease, the most common ATP7A-related disorder, is associated with low or absent copper levels in the blood. Boys with Menkes disease usually start to show symptoms at a few months of age. Symptoms include delayed development and/or loss of milestones, low muscle tone, poor growth, seizures, and out-pouching of the bladder (diverticula). Differences in an individual's appearance may also be noticeable at a few months of age. These differences include hair with lighter color, a coarse texture, and a flat, twisted shape of the hair shaft (*pili torti*); and sagging in the face.

MILD MENKES DISEASE

Boys with mild Menkes disease develop symptoms at an older age than those with the classic form. Many of the symptoms of mild Menkes disease are related to the connective tissues (which connect and protect the organs and other tissue types in the body) and include loose skin, unstable joints, and unique facial features. In addition, boys typically have learning difficulties (mild intellectual disability), issues with balance (ataxia) and speech (dysarthria), and *pili torti*.

OCCIPITAL HORN SYNDROME (OHS)

OHS is a milder copper transport disorder, with boys not showing symptoms until they are several years old. Many of the symptoms of OHS are related to the connective tissues. Symptoms of OHS typically include loose skin, unstable joints, *pili torti*, and wedge-shaped calcium deposits at the base of the skull (occipital horns), which give the condition its name.

DISTAL MOTOR NEUROPATHY

In rare cases, *ATP7A* mutations can lead to a variable condition that causes weakness in the hands and feet and some absent reflexes. Individuals may also have trouble lifting the front of the foot (foot drop), which can affect walking. It has been reported in early childhood to late adulthood, but most individuals develop symptoms between ages 20 and 40.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

ATP7A-related disorders are X-linked diseases. This means that the *ATP7A* gene is on the X chromosome. Males have just one copy of the X chromosome and the *ATP7A* gene, while females have two copies. Because of this, ATP7A-related disorders primarily affect males. It is possible for some females with a mutation in the *ATP7A* gene (known as carrier females) to have some symptoms. About half of carrier females have *pili torti*.

How common are ATP7A-related Disorders?

The incidence of Menkes disease is estimated to be between 1 in 100,000 and 1 in 250,000 births worldwide and is reported to be significantly higher in Australia. The exact incidence of OHS is unknown. At least 34 individuals have been reported with OHS worldwide. The exact incidence of distal motor neuropathy due to an *ATP7A* mutation is also unknown. Only a few families with this disorder have been reported.

Approximately one out of three males with an ATP7A-related disorder has a brand new *ATP7A* mutation that was not inherited from his parent (known as a "*de novo*" mutation).

How are ATP7A-related Disorders treated?

These conditions are treated by providing the body with extra copper by an injection (copper supplementation). Early supplementation (within the first few weeks of life) may improve outcomes and increase life expectancy for some children with Menkes disease, though less is known about the effects for OHS and distal motor neuropathy.

In individuals where symptoms have already developed, treatment is aimed at helping manage those symptoms. For example, a feeding tube may be given to ensure proper nutrition. Early intervention may assist with developmental issues, and physical or occupational therapy and orthopedic aids may improve symptoms caused by connective-tissue problems.

What is the prognosis for an individual with an ATP7A-related Disorder?

Without treatment, children with classic Menkes disease do not typically survive more than three years. Early treatment of Menkes disease with copper supplementation can improve outcomes and increase life expectancy in some cases. Individuals with OHS can live into mid-adulthood. Little is known about the success of copper supplementation in OHS. Life expectancy is thought to be unaffected by distal motor neuropathy, but only a few cases with this condition have been identified, and long-term outcomes are unknown.

Atransferrinemia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: TF.
Exons Sequenced: NM_001063:1-17.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Atransferrinemia?

Atransferrinemia, also known as congenital atransferrinemia, is a blood disorder that causes too little hemoglobin in the red blood cells (microcytic anemia). Atransferrinemia is caused by harmful genetic changes (variants) in the *TF* gene. Symptoms of the condition typically include tiredness, slow growth, recurrent infections, enlarged liver (hepatomegaly), and heart problems. Symptoms typically begin in infancy or childhood. Not everyone with atransferrinemia will have the same symptoms.

How common is Atransferrinemia?

Atransferrinemia is an extremely rare condition. Approximately 16 individuals have been diagnosed worldwide, but the exact incidence is unknown.

How is Atransferrinemia treated?

There is no cure for atransferrinemia, but the condition can be treated. One common treatment is receiving plasma or a medication called apotransferrin through an IV (transfusions) every month. Some individuals may need blood removed (phlebotomy) or have extra iron removed (iron chelation therapy) if iron levels are too high.

What is the prognosis for an individual with Atransferrinemia?

The prognosis for individuals with atransferrinemia is good with treatment. Since the condition is so rare, there is not enough data to know long-term outcomes. Without treatment, this condition can be fatal due to heart problems or serious lung infections (pneumonia).

Autoimmune Polyglandular Syndrome Type 1

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: AIRE.
Exons Sequenced: NM_000383:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Autoimmune Polyglandular Syndrome Type 1?

Autoimmune polyglandular syndrome type 1 (APS1), caused by mutations in the *AIRE* gene, is an inherited disease in which the body's immune system mistakenly attacks healthy cells, especially those of the glands that produce the body's hormones. Individuals with APS1 have at least two of the disease's main symptoms: fungal infections of the skin and mucous membranes (chronic mucocutaneous candidiasis), decreased function in the parathyroid glands (hypoparathyroidism), and decreased function in the adrenal glands (Addison's disease). Many individuals with the disease have all three main symptoms. The disturbance in hormone production may also lead to a variety of other symptoms.

In the majority of individuals with APS1, the first symptom to appear is recurrent and persistent fungal infections of the skin and mucous membranes, such as in the lining of the nose, mouth, and esophagus. These infections typically begin before age 5.

Individuals with APS1 typically develop an underactive parathyroid gland (hypoparathyroidism) by age 10. An underactive parathyroid gland can cause numerous symptoms including tingling in the lips, fingers, and toes; muscle cramps; pain in the abdomen, face, legs, and feet; weakness or fatigue; and dry hair and skin.

APS1 will usually lead to under-active adrenal glands by age 15. Since the adrenal glands are not secreting enough hormones, individuals with APS1 can experience fatigue, muscle weakness, weight loss, low blood pressure, and changes in skin coloration.

There are numerous other symptoms which can also occur in individuals with APS1 including but not limited to: chronic liver disease, extreme fatigue, skin disease, hair loss, under-active pituitary gland, abnormalities in the ovaries and testes, diarrhea, digestive issues, and eye problems. The severity and exact symptoms can vary from individual to individual.

How Common Is Autoimmune Polyglandular Syndrome Type 1?

APS1 affects approximately 1 in 145,000 individuals worldwide. The incidence of APS1 is more common among certain ethnic groups. The incidence of APS1 in Iranian Jewish individuals is 1 in 6,500 to 1 in 9,000, in Sardinian individuals, it is 1 in 14,000, in Finnish individuals, it is 1 in 25,000, in Slovenian individuals, it is 1 in 43,000, and in Norwegian individuals, it is 1 in 80,000.

How Is Autoimmune Polyglandular Syndrome Type 1 Treated?

There is no cure for APS1. Each symptom is treated as it arises, and lifelong regular checkups are necessary to look for any new symptoms. It is important to discover and treat new symptoms as soon as possible, to prevent permanent damage to the body. Physicians often prescribe drugs to help replenish the hormones that are deficient in individuals with APS1. Calcium and vitamin D are often helpful to treat an underactive parathyroid gland. Fungal infections can be treated with medication.

Other symptoms are treated as they appear. For example, individuals with APS1 who develop diabetes can take insulin and monitor their diet.

What Is the Prognosis for an Individual with Autoimmune Polyglandular Syndrome Type 1?

The prognosis for an individual with APS1 varies depending on the number and severity of his or her symptoms. Most individuals with APS1 will have at least two of the three main symptoms of the disease: fungal infections of the skin and mucous membranes, decreased function in the parathyroid glands, and decreased function in the adrenal glands. Early detection and treatment of the disease are important for achieving the best quality of life possible. Life expectancy may be shortened by complications from various symptoms.

Autosomal Recessive Osteopetrosis Type 1

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: TCIRG1.
Exons Sequenced: NM_006019:2-20.

Detection Rate	Population
96%	African American
96%	Ashkenazi Jewish
96%	Eastern Asia
96%	Finland
96%	French Canadian or Cajun
96%	Hispanic
96%	Middle East
96%	Native American
96%	Northwestern Europe
96%	Oceania
96%	South Asia
96%	Southeast Asia
96%	Southern Europe
96%	Worldwide

What is Autosomal Recessive Osteopetrosis Type 1?

Autosomal recessive osteopetrosis type 1 (ARO1), caused by harmful genetic changes (mutations) in the *TCIRG1* gene, is a disorder that causes abnormal bone formation. In most cases, symptoms of the condition first appear in infancy. Characteristic features include unusually dense bones; a high risk of bone fractures; a large head size (macrocephaly) with a prominent forehead (frontal bossing); growth deficiency; and dental problems. The abnormal bone present in the skull may also lead to compression of nerves in the face and head, resulting in vision impairment or blindness, hearing loss, and paralysis of the facial muscles. In addition, breathing and feeding difficulties may result from narrowing of the passageways connecting the nose and throat.

The abnormal bone formation in ARO1 also affects the bone marrow, which is important for blood cell formation and immune system function. Consequently, children with ARO1 may have a shortage of red blood cells (anemia); problems with immune system function that lead to an increased risk for infections; and enlargement of the liver and spleen (hepatosplenomegaly). In addition, some affected individuals may have seizures due to low blood calcium levels. Intellectual disability (usually mild to moderate) may result from recurrent seizures and/or brain abnormalities that may occur in some individuals with ARO1.

How common is Autosomal Recessive Osteopetrosis Type 1?

The incidence of autosomal recessive osteopetrosis (ARO) is 1 in 250,000 individuals. About 50 percent of ARO cases are attributed to ARO1. ARO is more common in certain populations, including the Chuvash and Mari populations of Russia (1 in 3,500 and 1 in 14,000 individuals, respectively), the Middle East, the Swedish province of Västerbotten, and Costa Rica.

How is Autosomal Recessive Osteopetrosis Type 1 treated?

The treatment for ARO1 is primarily supportive. Patients are monitored, and symptoms are treated as they arise. Medical management typically includes blood transfusions and the treatment of fractures, infections, vision and hearing problems, and seizures if they develop. In addition, certain medications may slow the progression of the disease in some individuals. The only known cure for ARO1 is a bone marrow transplant early in life.

What is the prognosis for an individual with Autosomal Recessive Osteopetrosis Type 1?

Generally, the prognosis for children with ARO1 is poor. Most children with the condition die within the first decade of life, although early bone marrow transplants can be curative if they are successful.

Autosomal Recessive Polycystic Kidney Disease, PKHD1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PKHD1.
Exons Sequenced: NM_138694:2-67.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Autosomal Recessive Polycystic Kidney Disease, PKHD1-Related?

Autosomal recessive polycystic kidney disease (ARPKD), is an inherited condition caused by mutations in the *PKHD1* gene in which clusters of fluid-filled sacs (cysts) form in the kidneys, often leading to kidney failure by the age of 10 and a reduced lifespan. Children with ARPKD may have underdeveloped lungs, leading to breathing problems or lung infections. Without treatment, 30% of children with ARPKD die within the first year of life. However, with treatments to aid breathing and/or kidney transplantation, about 80% of infants will survive.

The majority of infants with ARPKD show enlarged, cyst-filled kidneys within the first month of life. These cysts will impair the kidneys' ability to filter waste from the body. About 50% of infants with ARPKD will also have an enlarged liver. These anomalies are often detectable through an ultrasound before the child is born. More than half of the children will develop kidney failure by the age of 10. Without dialysis or transplantation, the disease is often fatal.

Extremely high blood pressure is common in people with ARPKD. They are also prone to urinary tract infections, frequent urination, low blood-cell counts, pain in the back or the sides, varicose veins, and hemorrhoids. Many affected individuals are also smaller in stature than normal.

A minority of people with ARPKD do not show symptoms of the disease until later in childhood or early in adulthood, with liver disease being the dominant symptom. In these people, the kidney disease is often mild.

How Common Is Autosomal Recessive Polycystic Kidney Disease, PKHD1-Related?

The prevalence of ARPKD is 1 in 10,000 to 1 in 40,000 infants. However, the disease may actually be more common than these estimates suggest because people with milder forms of the disease may not be diagnosed without genetic testing. Mutations in the *PKHD1* gene account for about 75% of ARPKD cases.

How Is Autosomal Recessive Polycystic Kidney Disease, PKHD1-Related Treated?

The initial concern with infants who have ARPKD is to protect their ability to breathe. Stabilizing respiratory function through mechanical ventilation may be required. Eating a nutritious diet can aid growth, and in some cases, growth hormones are recommended. Infants and children may require feeding tubes in order to ensure proper growth.

If faced with kidney failure, people with ARPKD frequently undergo dialysis (a "cleansing" of the blood through a machine that removes waste) or kidney transplantation. If the liver is extremely damaged, transplantation of this organ may also be recommended. Some individuals with ARPKD must undergo dialysis or kidney transplantation in infancy. Treatments to minimize dehydration and medications to lower blood pressure and to treat urinary tract infections may also be necessary.

What Is the Prognosis for a Person with Autosomal Recessive Polycystic Kidney Disease, PKHD1-Related?

Without treatment, approximately 30% of infants with ARPKD die within the first year of life due to breathing difficulties or lung infections. However, with treatments to aid breathing and/or kidney transplantation, about 80% of affected individuals will survive past infancy. Of those who survive infancy, about 82% survive to age 10, and 73% live past the age of 15. In one study, 58% of individuals required dialysis or kidney transplantation by age 20. As transplantation methods improve, it is expected that people with ARPKD will live longer lives.

Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SACS.
Exons Sequenced: NM_014363:2-10.

Detection Rate	Population
99%	African American
99%	Ashkenazi Jewish
99%	Eastern Asia
99%	Finland
99%	French Canadian or Cajun
99%	Hispanic
99%	Middle East
99%	Native American
99%	Northwestern Europe
99%	Oceania
99%	South Asia
99%	Southeast Asia
99%	Southern Europe
99%	Worldwide

What Is Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay?

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a progressive inherited condition that affects the body's ability to create a protein called sacsin, normally found in the brain, skin, and muscles. ARSACS is caused by mutations in the *SACS* gene.

The first symptom, unsteady gait, typically appears between 12 and 18 months of age, as toddlers begin to walk. Children also develop speech problems due to weak neck and facial muscles. The condition becomes increasingly worse over time, with muscle tension and spasms, difficulty coordinating movements, involuntary eye movements, and muscle wasting. Some people with ARSACS also lose sensation in their arms and legs as the nerves degenerate.

Other symptoms include incontinence, deformities of the fingers and feet, and buildup of fatty tissue on the retina leading to vision problems. Occasionally, the disease also causes leaks in one of the valves that control blood flow through the heart.

Most people with the condition are of normal intelligence and are able to live independently well into adulthood, although they eventually lose the ability to walk.

How Common Is Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay?

The majority of people with ARSACS have ancestry in the Charlevoix-Saguenay region of Quebec, Canada, where the condition affects approximately 1 in 1,500 to 2,000 people. While patients with ARSACS have been reported in other populations, the worldwide incidence is unknown.

How Is Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay Treated?

There is no cure for ARSACS. Treatment focuses on easing the symptoms and postponing major functional disabilities. Physical therapy and anti-spasmodic oral medications can help control muscle spasms, prevent joint and tendon deformities, and preserve muscle function for some time. Low doses of medication can control incontinence. Occupational therapy and adaptive tools such as leg braces can support people with ARSACS in daily tasks such as driving. As the disease progresses, however, people with ARSACS typically lose the ability to perform these tasks. Children with the condition may benefit from speech therapy and other forms of support in school.

What Is the Prognosis for a Person with Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay?

People with ARSACS become wheelchair-bound at an average age of 41 and commonly die in their fifties.

Bardet-Biedl Syndrome, BBS1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: BBS1.
Exons Sequenced: NM_024649:1-17.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Bardet-Biedl Syndrome, BBS1-Related?

Bardet-Biedl Syndrome (BBS), BBS1-Related is an inherited disease that affects many different parts of the body. This condition generally causes vision problems, mild obesity, extra fingers or toes, genital and kidney abnormalities, and learning difficulties. Vision problems result from degeneration of the cone cells of the retina. In approximately 90% of individuals, the vision loss begins as night blindness in childhood and progresses to a loss of peripheral vision and eventual blindness by adolescence. Abnormal weight gain begins in early childhood and continues throughout adulthood. As a result, obesity-related diabetes, high blood pressure, and high cholesterol may also develop.

Kidney abnormalities range from a few functional problems to life-threatening kidney failure. Approximately 50% of individuals with the disease have developmental disabilities, which can range from delayed emotional development or mild learning difficulties to more severe intellectual disability. In some cases, these delays are due in part to vision loss, while in other cases they are a direct result of the condition.

Other features of BBS include liver disease, poor balance and coordination, behavioral issues, characteristic physical features (facial features and dental irregularities), and hearing loss. BBS can also affect the heart and reproductive system. These features tend to vary by the BBS type. Some secondary features reported in BBS type 1 are liver disease, diabetes, characteristic facial features, heart defects, dental anomalies, hearing loss, and short fingers that may be webbed or joined together.

There are at least 19 genes that are associated with BBS.

How Common Is Bardet-Biedl Syndrome, BBS1-Related?

The prevalence of BBS in North American and European populations is 1 in 100,000 to 1 in 160,000. Approximately 20% of BBS is caused by mutations in *BBS1*. However, the incidence varies greatly by region, especially in small, possibly isolated populations. The prevalence

of BBS is up to 1 in 13,500 in Kuwaiti Bedouins, up to 1 in 87,000 in Tunisians, and up to 1 in 17,000 in Canadians from Newfoundland. Incidence information specific to BBS type 1 is lacking for these populations. However, BBS associated with *BBS1* has been reported in both the Newfoundland and Faroe Islands populations.

How Is Bardet-Biedl Syndrome, BBS1-Related Treated?

There is no cure for BBS. Regular monitoring of vision; weight; blood pressure; thyroid, kidney, and liver function; and development are recommended. Visual aids and education can help with impaired vision. Proper diet and exercise can help with obesity. Behavioral, speech, and educational therapies are also beneficial.

Kidney issues are managed in a standard way, but if they become life-threatening, dialysis or transplantation may be necessary. Surgery can correct some birth defects (extra digits may be removed in childhood and heart or vaginal malformation may be corrected), and an orthodontist may assist with correction of dental anomalies. While hormone therapy can aid sexual development, males can still have fertility issues.

What Is the Prognosis for an Individual with Bardet-Biedl Syndrome, BBS1-Related?

Predicting symptoms and the course of the disease for individuals with BBS can be difficult due to the variable nature of the condition. Symptoms vary, even within families. One of the most consistent features is progressive vision loss, which leads to blindness in about 90% of cases. Kidney disease is also frequent, with about a third of individuals developing kidney failure and about 10% requiring dialysis or transplantation. Kidney failure is a major cause of early death for those with BBS, although complications of obesity, heart disease, and diabetes have also been reported as causes of death. With proper treatment and monitoring, a majority of individuals may have a normal or near-normal life expectancy.

Bardet-Biedl Syndrome, BBS10-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: BBS10.
Exons Sequenced: NM_024685:1-2.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Bardet-Biedl syndrome, BBS10-related?

Bardet-Biedl syndrome (BBS), BBS10-related, is an inherited disease that causes a variety of symptoms including vision problems, obesity, extra fingers or toes (polydactyly), genital and kidney problems, and learning difficulties. The condition is caused by harmful genetic changes (variants) in the *BBS10* gene.

A hallmark of BBS is vision loss caused by retina degeneration (rod-cone dystrophy). It begins as night blindness in childhood and progresses to a loss of peripheral vision. Individuals with BBS can also lose central vision during childhood or adolescence. The mean age at which individuals become legally blind is 15.5 years. By early adulthood, affected individuals are severely visually impaired.

Kidney problems are present in most individuals with BBS and can range from a few functional problems to life-threatening kidney failure. Many affected individuals have developmental disabilities. This can range from mild learning disabilities or delayed emotional development to more severe symptoms. In some individuals, these delays are partly due to vision loss, while in other cases, they directly result from the disease.

Rarer features include liver disease, diabetes, neurological issues such as poor balance and coordination, behavioral issues, characteristic physical features, high blood pressure, defects of the heart or reproductive system, and hearing loss. These features vary between individuals.

More than 20 genes are associated with BBS, some associated with other syndromes such as Laurence-Moon syndrome, retinitis pigmentosa, and Meckel-Gruber syndrome. It is unclear if these represent a spectrum of diseases or if BBS is distinct from the other associated syndromes. A few reports identified harmful changes in the *BBS10* in individuals with Meckel-like syndrome, which has features that include kidney disease, extra fingers or toes, and brain malformations.

How common is Bardet-Biedl syndrome, BBS10-related?

Harmful changes in the *BBS10* gene account for approximately 15% of BBS cases. The number of individuals affected with BBS ranges from 1 in 100,000 to 1 in 160,000. BBS is more common in Kuwaiti Bedouins (1 in 13,500) and individuals from Newfoundland (1 in 17,500). It is also reported to be more common in individuals from South Africa.

How is Bardet-Biedl syndrome, BBS10-related, treated?

There is no cure for BBS. A team of specialists must manage the associated symptoms. A geneticist is typically involved in diagnosing and managing an affected child. Treatment may include monitoring, provision of aids and therapies, or surgery. Patients are recommended to undergo regular monitoring of vision, weight, and blood pressure, as well as thyroid, kidney, and liver function. An ophthalmologist will manage vision issues; vision aids can help improve quality of life. The FDA has approved at least one medication, setmelanotide (Imcivree), for the treatment of obesity in individuals with BBS. Medications can help treat high blood pressure. An endocrinologist may be consulted for diabetes, thyroid disease, and proper pubertal development. Kidney issues are managed in a standard fashion, but if they become life-threatening, dialysis or transplantation may be necessary. Surgery can correct some birth defects (extra digits may be removed in childhood, or heart and vaginal malformation may be corrected), and an orthodontist may assist with correction of dental anomalies. Early intervention and therapies may assist with learning difficulties.

What is the prognosis for an individual with Bardet-Biedl Syndrome, BBS10-related?

Predicting symptoms and the course of the disease for individuals with BBS can be difficult due to the variable nature of the condition, even within families. One of the most consistent features is progressive vision loss, frequently leading to blindness. Kidney disease is also frequent and is a cause of early death for individuals with BBS. Complications of obesity, heart disease, and diabetes have also been reported as causes of early death. However, with treatment, many individuals have a normal or near-normal life expectancy with some impairments.

Bardet-Biedl Syndrome, BBS12-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: BBS12.
Exon Sequenced: NM_152618:2.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Bardet-Biedl Syndrome, BBS12-related?

Bardet-Biedl syndrome (BBS), caused by harmful genetic changes (mutations) in the *BBS12* gene, is an inherited disease that causes vision problems; mild obesity; extra fingers or toes (polydactyly); genital and kidney problems; and learning difficulties.

A hallmark of BBS is vision loss caused by degeneration of the retina (rod-cone dystrophy). It begins as night blindness in childhood and progresses to a loss of peripheral vision. Individuals with BBS can also lose central vision during childhood or adolescence. The mean age at which individuals become legally blind is 15.5 years. By early adulthood, affected individuals are severely visually impaired.

Kidney problems are present in most individuals with BBS and can range from few functional problems to life-threatening kidney failure. Many affected individuals have developmental disabilities. This can range from mild learning disabilities or delayed emotional development to more severe symptoms. In some individuals these delays are due in part to vision loss, while in other cases they are a direct result of the disease.

Rarer features include liver disease; diabetes; neurological issues such as poor balance and coordination; behavioral issues; characteristic physical features (facial features and dental irregularities); high blood pressure; defects of the heart or reproductive system; and hearing loss, among others. These features may vary according to the type of the disease. Some secondary features reported in BBS, BBS12-related are diabetes, dental irregularities, heart disease, and behavioral issues.

There are at least 19 genes associated with BBS, and some of these genes have been associated with other syndromes (e.g., Laurence-Moon syndrome, retinitis pigmentosa, and Meckel-Gruber syndrome). It is unclear whether these represent a spectrum of disease or whether BBS is distinct from the other associated syndromes. A few reports identified *BBS12* mutations in individuals with retinitis pigmentosa (vision loss only).

How common is Bardet-Biedl Syndrome, BBS12-related?

Mutations in *BBS12* account for approximately 11% of BBS cases. The number of individuals affected with BBS ranges from 1 in 100,000 individuals in North America to 1 in 160,000 in Europe. Disease frequency also varies by population, being higher in populations where marriage between blood relatives (consanguinity) is common or the population was isolated. Populations with higher frequencies *BBS12*-related cases of BBS are the Romani and Iranian populations.

How is Bardet-Biedl Syndrome, BBS12-related treated?

There is no cure for BBS, and a team of specialists must manage the associated symptoms. A geneticist is typically involved in the diagnosis and centralized management of an affected child. Management may include monitoring; provision of aids and therapies; or surgery. Patients are recommended to undergo regular monitoring of vision; weight; blood pressure; thyroid, kidney, and liver function; and development. An ophthalmologist will manage vision issues, and there may be aids that help improve quality of life. A registered dietician may help with managing weight, and medications may help with high blood pressure. An endocrinologist may be consulted for diabetes, thyroid disease, and proper pubertal development. Kidney issues are managed in a standard fashion, but if they become life-threatening, dialysis or transplantation may be necessary. Surgery can correct some birth defects (extra digits may be removed in childhood, or heart and vaginal malformation may be corrected), and an orthodontist may assist with correction of dental anomalies. Early intervention and therapies may assist with learning difficulties, and a pediatric neurologist may help monitor the progression of development, if necessary.

What is the prognosis for an individual with Bardet-Biedl Syndrome, BBS12-related?

Predicting symptoms and the course of the disease for individuals with BBS can be difficult due to the variable nature of the condition, even within families. One of the most consistent features is progressive vision loss, which frequently leads to blindness. Kidney disease is also frequent and is a major cause of early death for individuals with BBS, though complications of obesity, heart disease, and diabetes have also been reported as causes of death. However, a majority of individuals may have a normal or near-normal life expectancy, though with various impairments.

Bardet-Biedl Syndrome, BBS2-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: BBS2.
Exons Sequenced: NM_031885:1-17.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Bardet-Biedl Syndrome, BBS2-related?

Bardet-Biedl syndrome (BBS), caused by harmful genetic changes (mutations) in the *BBS2* gene, is an inherited disease that causes vision problems; mild obesity; extra fingers or toes (polydactyly); genital and kidney problems; and learning difficulties.

A hallmark of BBS is vision loss caused by degeneration of the retina (rod-cone dystrophy). It begins as night blindness in childhood and progresses to a loss of peripheral vision. Individuals with BBS can also lose central vision during childhood or adolescence. The mean age at which individuals become legally blind is 15.5 years. By early adulthood, affected individuals are severely visually impaired.

Kidney problems are present in most individuals with BBS and can range from few functional problems to life-threatening kidney failure. Many affected individuals have developmental disabilities. This can range from mild learning disabilities or delayed emotional development to more severe symptoms. In some individuals these delays are due in part to vision loss, while in other cases they are a direct result of the disease.

Rarer features include liver disease; diabetes; neurological issues such as poor balance and coordination; behavioral issues; characteristic physical features (facial features and dental irregularities); high blood pressure; defects of the heart or reproductive system; and hearing loss, among others. These features may vary according to the type of the disease. Some secondary features reported in BBS, BBS2-related are characteristic facial features, heart defects, and short fingers that may be webbed or joined together.

There are at least 19 genes associated with BBS, and some of these genes have been associated with other syndromes (e.g., Laurence-Moon syndrome, retinitis pigmentosa, and Meckel-Gruber syndrome). It is unclear whether these represent a spectrum of disease or whether BBS is distinct from the other associated syndromes. A few reports identified *BBS2* mutations in individuals with retinitis pigmentosa (vision loss only) and Meckel-Gruber syndrome (typical features include kidney disease, extra fingers or toes, and brain malformations).

How common is Bardet-Biedl Syndrome, BBS2-related?

Mutations in *BBS2* account for approximately 8% of BBS cases. The number of individuals affected with BBS ranges from 1 in 100,000 individuals in North America to 1 in 160,000 in Europe. Disease frequency also varies by population, being higher in populations where marriage between blood relatives (consanguinity) is common or the population was isolated. Populations with higher frequencies of BBS include Kuwaiti Bedouins (1 in 13,500), individuals from Newfoundland (1 in 17,500), individuals from Tunisia, a Hutterite population from South Dakota, and the Ashkenazi Jewish.

How is Bardet-Biedl Syndrome, BBS2-related treated?

There is no cure for BBS, and a team of specialists must manage the associated symptoms. A geneticist is typically involved in the diagnosis and centralized management of an affected child. Management may include monitoring; provision of aids and therapies; or surgery. Patients are recommended to undergo regular monitoring of vision; weight; blood pressure; thyroid, kidney, and liver function; and development. An ophthalmologist will manage vision issues, and there may be aids that help improve quality of life. A registered dietician may help with managing weight, and medications may help with high blood pressure. An endocrinologist may be consulted for diabetes, thyroid disease, and proper pubertal development. Kidney issues are managed in a standard fashion, but if they become life-threatening, dialysis or transplantation may be necessary. Surgery can correct some birth defects (extra digits may be removed in childhood, or heart and vaginal malformation may be corrected), and an orthodontist may assist with correction of dental anomalies. Early intervention and therapies may assist with learning difficulties, and a pediatric neurologist may help monitor the progression of development, if necessary.

What is the prognosis for an individual with Bardet-Biedl Syndrome, BBS2-related?

Predicting symptoms and the course of the disease for individuals with BBS can be difficult due to the variable nature of the condition, even within families. One of the most consistent features is progressive vision loss, which frequently leads to blindness. Kidney disease is also frequent and is a major cause of early death for individuals with BBS, though complications of obesity, heart disease, and diabetes have also been reported as causes of death. However, a majority of individuals may have a normal or near-normal life expectancy, though with various impairments.

BCS1L-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: BCS1L.
Exons Sequenced: NM_004328:3-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Are BCS1L-Related Disorders?

BCS1L-related disorders are a group of autosomal recessive disorders caused by mutations in the *BCS1L* gene. This gene is important for the energy-generating structures (mitochondria) in our cells to work properly. Since many cells in different parts of the body need energy to work properly, individuals with BCS1L-related disorders may have problems in many different parts of the body. BCS1L-related disorders are comprised of three different conditions described below.

GRACILE SYNDROME

GRACILE syndrome is the most severe of the BCS1L-related disorders. "GRACILE" is an acronym which stands for the disease's main symptoms:

Growth retardation - Newborns have trouble growing and are usually smaller than average.

Aminoaciduria - There are increased levels of amino acids in the urine.

Cholestasis - Newborns have trouble making digestive fluid (bile) or transporting it to the right place, which can lead to liver damage.

Iron overload - The body is unable to break down iron properly leading to high levels of iron in the liver.

Lactic acidosis - There is too much lactic acid in the blood.

Early death - Newborns with GRACILE syndrome usually pass away within the first few months of life.

COMPLEX III DEFICIENCY

Complex III deficiency can be relatively mild or can cause death in childhood. Individuals with complex III deficiency often feel weak and tired and can sometimes have problems with their liver, kidney, and brain. If the brain is affected, there can be issues with learning,

movement, and muscle weakness. Some patients may also have a defect in their heart muscles (cardiomyopathy) which can cause heart failure. Hearing impairment or deafness can occur. Individuals with complex III deficiency can also have high levels of lactic acid (lactic acidosis), ketones (ketoacidosis), or sugar (hyperglycemia).

BJÖRNSTAD SYNDROME

Björnstad syndrome is characterized by hearing loss (sensorineural deafness) and dry, brittle hair (pili torti). Children with Björnstad syndrome usually have mild to severe hearing loss within the first two years of life. There can be hair loss (alopecia) due to their abnormally fragile hair, usually on the head, eyebrows, and eyelashes. Björnstad syndrome is the mildest BCS1L-related disorder.

How Common Are BCS1L-Related Disorders?

The prevalence of GRACILE syndrome is approximately 1 in 47,000 babies in Finland. GRACILE syndrome is very rare outside of Finland.

The prevalence of complex III deficiency is unknown.

Björnstad syndrome is estimated to affect 1 in 1,000,000 individuals in the world.

How Are BCS1L-Related Disorders Treated?

Most treatments for GRACILE syndrome are aimed at making infants comfortable until they pass away. There is no known treatment for GRACILE syndrome that extends lifespan.

Complex III deficiency syndrome treatment generally focuses on managing symptoms and slowing down the progression of the disease. There is no cure for complex III deficiency.

Individuals with Björnstad syndrome may use hearing aids or cochlear implants to improve their hearing. Otherwise, Björnstad syndrome does not usually require medical treatment.

What Is the Prognosis for Individuals with a BCS1L-Related Disorder?

Even with the best possible treatment, most babies with GRACILE syndrome will die within four months of birth.

Severe cases of complex III deficiency can be fatal in childhood while individuals with milder symptoms of complex III deficiency can survive into adolescence or adulthood.

Björnstad syndrome usually does not affect lifespan.

Beta Globin-related Hemoglobinopathy (Including Beta Thalassemia and Sickle Cell Disease)

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: HBB.
Exons Sequenced: NM_000518:1-3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What are Beta Globin-related Hemoglobinopathies (Including Beta Thalassemia and Sickle Cell Disease)?

Beta globin-related hemoglobinopathies (including beta thalassemia and sickle cell disease) are a group of inherited blood disorders that affect hemoglobin, a major component of red blood cells that are responsible for carrying oxygen throughout the body. Hemoglobin is made up of two different protein chains, the alpha and beta chains. Harmful genetic changes in the *HBB* gene can result in reduced levels of beta chains (thalassemias) or the formation of structurally abnormal beta globin proteins (sickle cell disease and other hemoglobinopathies).

There are three main types of beta globin-related hemoglobinopathies: a severe form of beta thalassemia called beta thalassemia major, a milder form of beta thalassemia called beta thalassemia intermedia, and sickle cell disease. There are other types of hemoglobinopathies that can be considerably milder in presentation as well. A consultation with a hematologist is useful in predicting expression of these diseases.

Individuals with beta globin-related thalassemia produce insufficient amounts of beta globin protein and in some cases do not produce it at all, resulting in a shortage of red blood cells (anemia). Without enough properly functioning red blood cells, the tissues of the body do not receive adequate oxygen. This results in several symptoms, including poor growth, pain, and organ damage.

BETA THALASSEMIA MAJOR

In beta thalassemia major (also known as Cooley's anemia), a child will begin to show symptoms of severe anemia in the first two years of life. The lack of oxygen can cause children to be pale, tired, and irritable. The child's spleen or liver may be enlarged

(hepatosplenomegaly), which is made noticeable by a swollen abdomen and yellowing of the skin (jaundice). This condition also causes delayed growth and misshapen bones. Without frequent blood transfusions, this can be a life-threatening condition at an early age.

BETA THALASSEMIA INTERMEDIA

This is a less severe form of beta thalassemia that causes mild to moderate anemia and a wide spectrum of possible health problems. Symptoms are similar but less severe than beta thalassemia major, including bone deformities and an enlarged spleen. Individuals with thalassemia intermedia require fewer blood transfusions but may develop other symptoms such as leg ulcers and reduced bone mass leading to osteoporosis. Diagnosis of thalassemia intermedia may not be made until later in life.

SICKLE CELL DISEASE

Sickle cell disease is a type of hemoglobinopathy caused by specific harmful genetic changes in the *HBB* gene that result in abnormal beta globin protein structure. This results in red blood cells that have a stiff crescent shape resembling a sickle. The sickled blood cells die prematurely, causing anemia, repeated infections, shortness of breath, fatigue, jaundice, and bone pain starting in early childhood. These sickled cells can also cause blockages in small blood vessels, reducing blood flow and causing serious medical complications such as blood-starved organs or tissue failure. The most recognizable symptom in children is foot or hand pain, and episodes of acute back, chest, or abdominal pain are common in adults.

Individuals with sickle cell disease may also experience delayed growth, delayed puberty, gallstones, and heart disease. Blockage of blood vessels in the lung can cause acute chest syndrome, which is associated with difficulty breathing, chest pain, and fever. Acute chest syndrome is a major cause of death in sickle cell disease.

Additional Considerations For Carriers

Studies have shown that individuals that are carriers of a harmful genetic change in *HBB* may be at risk for beta thalassemia intermedia if they are also carriers of one or more extra copies of the alpha globin gene. Alpha thalassemia testing may be useful for these individuals.

How common are Beta Globin-related Hemoglobinopathies (Including Beta Thalassemia and Sickle Cell Disease)?

The incidence of beta globin-related hemoglobinopathies in the population ranges from 1 in 200 to 1 in 25,000 births. Thalassemias are most common in individuals of Mediterranean descent, especially in those from Sardinia and Cyprus, as well as individuals from the Middle East and Asia. Sickle cell disease is common in individuals from Africa, the Mediterranean, the Arabian Peninsula, India, and Central and South America.

How are Beta Globin-related Hemoglobinopathies (Including Beta Thalassemia and Sickle Cell Disease) treated?

The most common treatments for beta thalassemia are blood transfusions, which provide a temporary supply of healthy red blood cells to bring oxygen to the body. Among individuals with thalassemia major, transfusions may take place every two to three weeks. While these transfusions can be lifesaving and life-enhancing, they result in a toxic buildup of iron in the blood. To counteract this side effect, individuals with beta thalassemia require chelation therapy, which helps eliminate excess iron from the body. These individuals require frequent monitoring by a physician to assess the progress of transfusion and chelation therapy. In a small minority of individuals, a bone marrow transplant from a sibling or other suitable donor has been able to cure the disease.

The symptoms of sickle cell disease can vary in severity, depending upon the harmful *HBB* change that an individual carries. In some patients, sickle cell disease can be cured with bone marrow transplants from a sibling or other suitable donor. For patients who are not candidates for bone marrow transplantation, sickle cell disease requires lifelong care to manage and limit the frequency of crises.

Individuals with sickle cell disease, particularly children, should drink plenty of water, avoid demanding physical activity, avoid too much sun exposure, and get all appropriate vaccines and immunizations. Preventing dehydration and avoiding infection can fend off crises and may prevent the sickling of red blood cells. Nutritional therapy and pain medications are also useful.

What is the prognosis for a person with Beta Globin-related Hemoglobinopathies (Including Beta Thalassemia and Sickle Cell Disease)?

The prognosis for an individual with a beta globin-related hemoglobinopathy depends entirely on the specific type of hemoglobin disorder and the harmful genetic changes in the *HBB* gene. A shortened lifespan is possible, but lifespan varies significantly and may even be normal, depending on disease severity. Early treatment can extend a patient's average lifespan by a decade or more.

Beta-ketothiolase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ACAT1.
Exons Sequenced: NM_000019:1-12.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Beta-Ketothiolase Deficiency?

Beta-ketothiolase deficiency is an inherited disorder that causes the body to be unable to break down certain substances. The condition is caused by harmful genetic changes (variants) in the *ACAT1* gene. Individuals with beta-ketothiolase deficiency cannot break down one of the building blocks of protein (isoleucine). They are also unable to process a key source of energy (ketones) used by the body during times of fasting or illness. These deficiencies lead to a build-up of toxic substances in the body, which cause the symptoms of the disease.

The symptoms of beta-ketothiolase deficiency appear in the first decade of life, typically before the age of two. The first symptoms include vomiting, difficulty breathing, lack of energy, confusion, and may include seizures. The symptoms often appear quickly and are known as a "ketoacidotic attacks." These episodes, or crises, may be triggered by illness, infection, periods of fasting, or eating more protein-rich foods. If unrecognized and untreated with a special diet, the episodes can rapidly progress to coma and even death. Some individuals who survive one or more episodes may experience developmental delays.

How common is Beta-Ketothiolase Deficiency?

The incidence of beta-ketothiolase deficiency is estimated to be between 1 in 100,000 to 1 in 230,000.

How is Beta-Ketothiolase Deficiency treated?

There is no cure for beta-ketothiolase deficiency. Individuals with beta-ketothiolase deficiency need a special diet that is low in proteins and high-fat foods. Individuals also need to eat frequently and avoid fasting. Some individuals may need to supplement with carnitine. Individuals with beta-ketothiolase deficiency need close monitoring by a physician during illness. Symptoms such as vomiting, diarrhea, and illness with a fever require prompt treatment.

What is the prognosis for an individual with Beta-Ketothiolase Deficiency?

Without early diagnosis and treatment, beta-ketothiolase deficiency can be fatal. With early treatment, however, ketoacidotic attacks can be avoided, leading to improved growth, development, and intellectual ability. Despite treatment, some individuals may have developmental delays.

Beta-sarcoglycanopathy

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SGCB.
Exons Sequenced: NM_000232:1-6.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Beta-Sarcoglycanopathy?

Beta-sarcoglycanopathy, also known as limb-girdle muscular dystrophy type 2E (LGMD2E), causes muscle weakness as a result of a deficiency or abnormality of beta-sarcoglycan, an important protein in muscle. The condition is caused by mutations in the *SGCB* gene. The symptoms of beta-sarcoglycanopathy can vary greatly from person to person, even within the same family. Some individuals with the disease may experience only mild muscle weakness, while others may have severe symptoms that can be fatal. The age at which symptoms first develop is also variable, although the condition typically presents in childhood.

The most common symptom of beta-sarcoglycanopathy is a progressive weakening of the muscles in the hips, shoulders, and abdomen (the proximal muscles). It may also affect the muscles in the thigh and in the upper arm. The rate at which the muscles weaken can vary, but many experience severe progressive weakness that a wheelchair becomes necessary. Other symptoms of the condition include enlarged calf muscles (calf hypertrophy), contractures, scapular winging (prominence of the shoulder blades), and scoliosis. Respiratory and/or heart complications are also possible for individuals with beta-sarcoglycanopathy and may be a cause of early death. Beta-sarcoglycanopathy does not affect intelligence or cognitive function.

How Common Is Beta-Sarcoglycanopathy?

There are numerous types of limb-girdle muscular dystrophy. The estimated prevalence of all types of limb-girdle muscular dystrophy is 1 in 15,000 individuals. The exact proportion of cases that have beta-sarcoglycanopathy is unknown.

How Is Beta-Sarcoglycanopathy Treated?

There is no cure for beta-sarcoglycanopathy and there are few effective treatments. Physical therapy is often recommended to retain muscle strength and mobility for as long as possible. Stretching, mechanical aids, or surgery may also aid in that goal. As muscles

deteriorate, a ventilator may be required to help with breathing. Cardiac surveillance is recommended, and those who develop heart problems should consult with a cardiologist for appropriate treatment.

What Is the Prognosis for an Individual with Beta-Sarcoglycanopathy?

The outlook for an individual with beta-sarcoglycanopathy varies. Generally speaking, the earlier the symptoms begin, the faster they progress. However, because symptoms and onset can be variable, the prognosis can also be variable. Individuals with more severe symptoms often become wheelchair-bound in their early teens and die in early adulthood, with death usually being due to respiratory and/or cardiac complications. The lifespan in individuals with mild symptoms may not be significantly affected.

Biotin-thiamine–responsive Basal Ganglia Disease

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SLC19A3.
Exons Sequenced: NM_025243:2-6.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Biotin-Thiamine-Responsive Basal Ganglia Disease?

Biotin-thiamine-responsive basal ganglia disease, also known as BTBGD, is an inherited condition that affects an important vitamin called thiamine (vitamin B1). Thiamine is necessary for cells in the nervous system to function properly. When the amount of thiamine is decreased (often during periods of fever, illness, or stress), it can cause neurologic problems that affect movement. BTBGD is caused by harmful genetic changes (variants) in the *SLC19A3* gene. Symptoms may include involuntary tightening of the muscles, muscle weakness, or difficulty with balance and coordination (ataxia). Muscles of the face may also be affected, causing problems with chewing and swallowing, speaking, or controlling eye movements.

BTBGD is classified into three forms: classic BTBGD (or early childhood encephalopathy), early infantile Leigh-like syndrome, and adult-onset Wernicke-like encephalopathy.

CLASSIC BTBGD

The most common type of BTBGD is called the classic form. The symptoms typically involved recurring episodes of seizures, abnormal muscle movements, weakness, and confusion. Symptoms usually start between the ages of three and ten. Being sick or feeling stressed can bring on these episodes, which can be very serious. Without treatment, the episodes can lead to coma or death.

EARLY INFANTILE LEIGH-LIKE SYNDROME

This most severe form of the disease presents earlier in life, usually in the first three months. The episodes observed in this form are similar to the classic form but can cause more significant damage to the brain. Infants may have feeding difficulties, vomiting, and seizures that worsen over time.

ADULT-ONSET WERNICKE-LIKE ENCEPHALOPATHY

This is the least common form of BTBGD. The symptoms associated with adult-onset Wernicke-like encephalopathy are milder than the other forms of BTBGD. Symptoms usually start to appear in the teens or twenties and involve seizures, abnormal movements of the eye muscles, and difficulty with walking.

How common is Biotin-Thiamine-Responsive Basal Ganglia Disease?

The incidence of BTBGD in the population is approximately 1 in 215,000. It is more common among individuals of Saudi descent. This disease may be underdiagnosed because symptoms can resemble other causes of seizures and neurologic problems.

How is Biotin-Thiamine-Responsive Basal Ganglia Disease treated?

BTBGD is treated using supplements of high-dose thiamine (vitamin B1) and/or biotin (vitamin B7). Individuals experiencing severe symptoms may need to be hospitalized and treated with medication to control seizures. Fevers should be controlled with medicine as quickly as possible. Some individuals with muscle weakness or difficulty with moving or speaking may benefit from physical, occupational, and speech therapies.

What is the prognosis for an individual with Biotin-Thiamine-Responsive Basal Ganglia Disease?

The prognosis for an individual with BTBGD depends on the age of onset and how quickly treatment is initiated. For those with the classic form, symptoms may resolve completely if treatment with thiamine and biotin supplements is started promptly; however, symptoms can return if treatment is stopped. If treatment is not started promptly, changes in the brain can cause long-lasting or permanent symptoms such as difficultly walking or speaking, or even death. The prognosis is poor for individuals with the early infantile Leigh-like syndrome form of the condition, and many will pass away even with treatment.

Biotinidase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: BTD.
Exons Sequenced: NM_000060:1-4.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Biotinidase Deficiency?

Biotinidase deficiency is a highly treatable inherited disease in which the body cannot process biotin (vitamin B7), due to a deficiency in an enzyme called biotinidase. Biotinidase deficiency is caused by mutations in the *BTD* gene.

PROFOUND BIOTINIDASE DEFICIENCY

Individuals who have less than 10% of the normal amount of the enzyme biotinidase are said to have profound biotinidase deficiency. Without treatment, their symptoms tend to be significant. Individuals with biotinidase deficiency can experience seizures, poor muscle tone, difficulty with movement and balance, vision loss, hearing loss, skin rashes, breathing problems, hair loss, fungal infections, and intellectual and/or developmental delays. These symptoms often begin after the first few weeks or months of life and can be life-threatening if untreated.

PARTIAL BIOTINIDASE DEFICIENCY

Individuals who have between 10% and 30% of the normal amounts of biotinidase have a milder form of the disease known as partial biotinidase deficiency. They may experience less-severe symptoms, or they may not show any symptoms until they become ill or stressed.

How Common Is Biotinidase Deficiency?

The incidence of profound biotinidase deficiency is approximately 1 in 137,000 births. The prevalence of partial biotinidase deficiency is approximately 1 in 110,000 people. Since partial biotinidase deficiency can be mild, it is possible that the true prevalence is more common.

How Is Biotinidase Deficiency Treated?

Biotinidase deficiency is treated with a biotin pill taken daily by mouth. A physician can determine the proper dosage and adjust that dosage over time if necessary. This treatment is lifelong and highly effective. Both people with profound biotinidase deficiency and partial biotinidase deficiency should take biotin supplements.

It is important to start biotin supplementation as soon as possible. Treatment with biotin supplements can help improve some symptoms of biotinidase deficiency. If there is delayed treatment, symptoms such as vision loss, hearing loss, and developmental delay are not reversible.

For people who have vision or hearing loss, vision aids or hearing aids may be helpful. Learning specialists can help patients with intellectual delay learn as effectively as possible.

What Is the Prognosis for a Person with Biotinidase Deficiency?

With early detection and treatment, a person with biotinidase deficiency can live a completely normal life. If left untreated, the disease can cause life-threatening complications. When the disease is not detected early, patients may experience permanent damage to their hearing, vision, and intellectual ability. In cases where the disease is entirely unrecognized, it can be life-threatening.

Bloom Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: BLM.
Exons Sequenced: NM_000057:2-22.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Bloom Syndrome?

Bloom syndrome is an inherited disease that causes a person's chromosomes to break and rearrange frequently. Bloom syndrome is caused by mutations in the *BLM* gene. The chromosome instability seen in patients with Bloom syndrome causes high rates of cancer beginning in childhood or early adulthood. People with Bloom syndrome are usually smaller in stature than their peers and have a high-pitched voice. They have distinct facial features including a long, narrow face, small lower jaw, prominent nose and ears, and red lesions on the cheeks and the bridge of the nose (often described as "butterfly-shaped" lesions) which appear and worsen with sun exposure. Most people with Bloom syndrome have a normal intellectual ability, however, some will have intellectual and developmental disabilities. They may also have diabetes, chronic lung problems, and suppressed immune systems. They tend to have high rates of pneumonia and ear infections. Men with Bloom syndrome are usually infertile. Women with Bloom syndrome are fertile but often experience early menopause.

How Common Is Bloom Syndrome?

The incidence of Bloom syndrome is unknown, and fewer than 300 affected individuals have been reported. Approximately one-third of people with the disease are of Ashkenazi Jewish descent, making it more common in this population than in others. Roughly 1 in 48,000 Ashkenazi Jews is affected by the disease.

How Is Bloom Syndrome Treated?

There is no cure for Bloom syndrome. Children with Bloom syndrome need nutritional monitoring to ensure maximum growth. People with the disease are advised to stay out of the sun and wear sunscreen to prevent skin lesions, particularly during childhood. They should also make an effort to avoid infection of all kinds. In school, they may require special education classes due to learning difficulties.

People with Bloom syndrome are prone to cancer, so they should be screened regularly starting in childhood and with increasing vigilance into adulthood. Because they are particularly sensitive to radiation and DNA-damaging chemicals, standard cancer treatments often need to be modified. If diabetes is present, this condition is typically treated with diet, blood-sugar monitoring, and insulin supplements.

What Is the Prognosis for a Person with Bloom Syndrome?

Despite dealing with numerous medical problems, people with Bloom syndrome can lead productive lives. They are most often of normal or near-normal intelligence. Typically, people with Bloom syndrome lead shortened lives, although lifespan can vary greatly from person to person. The cause of death is usually cancer, which can occur in childhood, but more commonly appears in the late teens or early to mid-twenties. Early detection of cancer and appropriate treatment can help extend the lifespan of these individuals.

Calpainopathy

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CAPN3.
Exons Sequenced: NM_000070:1-24.

Detection Rate	Population
99%	African American
99%	Ashkenazi Jewish
99%	Eastern Asia
99%	Finland
99%	French Canadian or Cajun
99%	Hispanic
99%	Middle East
99%	Native American
99%	Northwestern Europe
99%	Oceania
99%	South Asia
99%	Southeast Asia
99%	Southern Europe
99%	Worldwide

What is Calpainopathy?

Calpainopathy (previously known as limb-girdle muscular dystrophy type 2A, or LGMD2A) is a spectrum of disorders that cause muscle breakdown (atrophy) and weakness. Calpainopathy is caused by harmful genetic changes (mutations) in the *CAPN3* gene. The primary symptom is worsening (progressive) muscle weakness of the hip, shoulder, and abdomen. The rate at which the muscles weaken can vary greatly, but many experience weakness to a point where a wheelchair becomes necessary. Other features include enlarged calf muscles, shortening and hardening of muscles leading to rigid joints (contractures), curvature of the spine (scoliosis), and prominence (winging) of the shoulder blades. Calpainopathy does not affect intelligence or mental function. Some individuals with the disease can have a mild course where they do not show symptoms (asymptomatic), while others may have severe symptoms that can be fatal. Failure to get enough oxygen to the lungs (respiratory failure) is the most common cause of death. The symptoms of the disease can vary greatly from person to person (even among people in the same family). The age that symptoms begin is also quite varied, with some individuals showing muscle weakness beginning in childhood. The most common age of onset is in the early teens. Genetic testing cannot predict how severe individuals will be affected.

How common is Calpainopathy?

The exact prevalence of calpainopathy is difficult to determine because of the wide range of symptoms. The estimated prevalence of calpainopathy in the population is approximately 1 in 80,000 individuals. Calpainopathy is more common among individuals of French Reunion Island and Indiana Amish descent.

How is Calpainopathy treated?

There is no cure for calpainopathy. Physical therapy helps patients to retain muscle strength and mobility for as long as possible. Mobility aids, such as walkers, canes, braces, and wheelchairs, may become necessary. If muscle weakness begins to affect the ability to breathe,

a machine that assists with breathing (a ventilator) may be needed. Cardiac surveillance is recommended, and those who develop heart problems will need to see a heart specialist (a cardiologist) for treatment. Some individuals may need surgery if they develop scoliosis or contractures.

What is the prognosis for an individual with Calpainopathy?

The outlook for a person with calpainopathy varies. Generally, the earlier symptoms begin, the faster they progress. Some people with the disease experience only mild symptoms and may have near-normal strength. Others with a mild course may remain able to walk for 30 years or more after symptoms appear. People with more severe disease typically may need to use a wheelchair as early as 10 years after their diagnosis. There is evidence that symptoms progress faster in males than in females.

Canavan Disease

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ASPA.
Exons Sequenced: NM_000049:1-6.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Canavan Disease?

Canavan disease is an inherited condition that destroys the white matter that insulates nerve cells in the brain. This impairs the ability of nerve cells to communicate with other cells. Canavan disease is caused by harmful genetic changes in the *ASPA* gene that result in deficiency of the aspartoacylase enzyme. This enzyme breaks down a material called N-acetyl-L-aspartic acid (NAA) in the brain. Without enough aspartoacylase, the NAA builds up in the brain and destroys its white matter.

NEONATAL/INFANTILE FORM

Neonatal/infantile Canavan disease is the most common form of Canavan disease. Affected children develop muscle weakness, developmental delay, and severe intellectual disability. Developmental delays typically begin at three to five months of age with poor muscle tone (hypotonia) which causes problems with an infant's ability to turn over, control head movements, and sit up. The infant's head also becomes larger (macrocephaly). Over time, children with the condition may become unable to swallow and may develop sleep disturbances, seizures, and blindness.

MILD/JUVENILE FORM

Individuals with the mild/juvenile form of Canavan disease may have mild speech or motor delays beginning in childhood. However, for some affected individuals, the delays may be so mild that they go unrecognized or so nonspecific that affected individuals may be undiagnosed.

How common is Canavan Disease?

The incidence of the neonatal/infantile form of Canavan disease in the population is 1 in 100,000 births. The incidence of the mild/juvenile form of Canavan disease is unknown. The incidence of Canavan disease is more common among individuals of Ashkenazi Jewish descent.

How is Canavan Disease treated?

Currently, there is no cure for Canavan disease. Treatment for the neonatal/infantile form of the disease focuses on keeping the affected individual comfortable with proper nutrition and hydration and controlling seizures with medication. Physical therapy can be beneficial to maximize ability and to minimize tightening of muscles. Individuals with the mild/juvenile form of Canavan disease may need speech therapy or tutoring but generally do not require special medical care.

What is the prognosis for an individual with Canavan Disease?

Most individuals with the neonatal/infantile form of Canavan disease die in childhood, although some survive into their teens or early twenties and beyond, depending on the medical care provided. Individuals with the mild/juvenile form of the disease do not typically have a shortened lifespan.

Carbamoylphosphate Synthetase I Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CPS1.
Exons Sequenced: NM_001875:1-38.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Carbamoylphosphate Synthetase I Deficiency?

Carbamoylphosphate synthetase I (CPS1) deficiency belongs to a group of disorders called urea cycle disorders. Individuals with CPS1 deficiency are missing an important liver enzyme. This leads to high ammonia levels in the blood (hyperammonemia), which can be harmful especially to the brain.

Most affected individuals will show symptoms within the first few days of life (**neonatal-onset form**), which may include unusual sleepiness, a poorly regulated breathing rate or body temperature, unwillingness to feed, vomiting after feeding, unusual body movements, seizures, or coma. Affected children who survive the newborn period may experience recurrence of these symptoms if diet is not carefully managed or if they experience infections or other stressors. They may also have delayed development and intellectual disability.

Less commonly, people with CPS1 deficiency, have moderate or mild severe symptoms that appear later during childhood or adulthood (**late-onset form**). Patients with the milder form of CPSI deficiency may still experience hyperammonemic coma and life-threatening complications.

How common is Carbamoylphosphate Synthetase I Deficiency?

The exact incidence of CPS1 deficiency is unknown, but is estimated to occur in approximately 1 in 1,300,000 infants born in the USA. Slightly higher incidences have been reported in less ethnically-diverse countries, such as Finland (1 in 539,000) and Japan (1 in 800,000).

How is Carbamoylphosphate Synthetase I Deficiency treated?

There currently is no cure for CPS1 deficiency. The treatment consists of dietary management to limit ammonia production along with medications and supplements that provide alternative pathways for the removal of ammonia from the bloodstream. Maintaining this special diet is needed to make sure that the individual gets enough calories and essential amino acids. Routine blood tests are needed to monitor the disorder and manage treatment. In some cases, transplants have been effective in reversing the symptoms.

What is the prognosis for a person with Carbamoylphosphate Synthetase I Deficiency?

CPS1 deficiency is the most severe of the urea cycle disorders. Outcomes vary, and depend on age at diagnosis and how closely the treatment plan and diet are followed. Some states screen all infants for this disease at birth. Infants who are diagnosed in the first week of life and are put on a diet immediately may reach normal brain function. Even with treatment, some individuals will experience hyperammonemic episodes leading to permanent intellectual disability and death. Without treatment, CPS1 deficiency results in death.

Carnitine Palmitoyltransferase IA Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CPT1A.
Exons Sequenced: NM_001876:2-19.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Carnitine Palmitoyltransferase IA Deficiency?

Carnitine palmitoyltransferase IA (CPT1A) deficiency, caused by mutations in the *CPT1A* gene, is an inherited disease in which the body cannot convert long-chain fatty acids into energy to fuel the body. Symptoms occur in severe episodes, often during long periods without eating (fasting) and/or during times of fever or gastrointestinal illness.

Symptoms of CPT1A deficiency usually begin in infancy. One key symptom of the disease is low blood sugar (hypoglycemia) combined with low blood levels of ketones, a byproduct of fat breakdown that can be burned for energy. Together, these symptoms are known as hypoketotic hypoglycemia. Prolonged periods of hypoketotic hypoglycemia can lead to loss of consciousness or seizures. Other symptoms of CPT1A deficiency include an enlarged liver (hepatomegaly), muscle weakness, and damage to the liver, heart, and brain due to excess fatty acid buildup. If untreated, these symptoms can be life-threatening.

Though most individuals with CPT1A deficiency will experience episodes of hypoketotic hypoglycemia in infancy or childhood, some may not begin showing symptoms until later in life.

How Common Is Carnitine Palmitoyltransferase IA Deficiency?

CPT1A deficiency is extremely rare. Fewer than 50 cases have been identified worldwide. The disease is thought to be more common among the Hutterite population in the northern United States and Canada as well as the Inuit population in northern Canada, Alaska, and Greenland.

How Is Carnitine Palmitoyltransferase IA Deficiency Treated?

A key goal of treatment is to combat low blood sugar (hypoglycemia). A physician will recommend a modified diet, typically with high-carbohydrate, low-fat foods. Infants will need to eat frequently during the day. Infants can also be given cornstarch overnight in order to provide a slow release of energy that prevents blood sugar from dipping to dangerously low levels.

Individuals with CPT1A deficiency should never go for long periods without eating. When blood sugar is low, it needs to be quickly treated with an intravenous sugar solution in order to prevent damage to the brain. Women who are carriers of CPT1A deficiency and become pregnant should undergo testing for liver-enzyme levels, especially during times of fasting or illness.

What Is the Prognosis for an Individual with Carnitine Palmitoyltransferase IA Deficiency?

After fasting or illness, individuals with CPT1A deficiency can be at risk for life-threatening liver failure. These episodes can also cause permanent damage to the brain and liver. With early diagnosis and careful management, however, individuals with CPT1A deficiency can often have normal or near-normal lives.

Additional Considerations for Carriers

Carriers of fatty-acid oxidation defects, including CPT1A deficiency, do not typically show symptoms of the disease. However, there may be an increased risk of serious pregnancy complications, particularly in the third trimester, in women carrying a fetus affected with a fatty-acid oxidation defect. A woman whose pregnancy may be affected by a fatty-acid oxidation defect, such as CPT1A deficiency, should speak with her physician for recommendations and may benefit from consultation with a high-risk physician.

Carnitine Palmitoyltransferase II Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CPT2.
Exons Sequenced: NM_000098:1-5.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Carnitine Palmitoyltransferase II Deficiency?

Carnitine Palmitoyltransferase II (CPT II) deficiency, caused by mutations in the *CPT2* gene, is an inherited disease in which the body cannot convert long-chain fatty acids into energy to fuel the body. There are three forms of the disease, and the severity and symptoms vary based on the form. In all three forms, symptoms can be triggered by periods without eating (fasting).

LETHAL NEONATAL FORM

The lethal neonatal form of CPT II deficiency is the most severe form of the disease. Symptoms begin within days of birth and include liver failure, respiratory failure, problems with the heart muscle (cardiomyopathy), irregular heartbeat (arrhythmia), kidney disease, and brain abnormalities. Affected infants tend to experience metabolic crises involving low blood sugar and low blood ketones (hypoketotic hypoglycemia). Most infants with the lethal neonatal form of CPT II will pass away within the first year.

SEVERE INFANTILE HEPATOCARDIOMUSCULAR FORM

Symptoms of the severe infantile hepatocardiomuscular form of CPT II deficiency usually begin between the ages of six months and two years. They include an enlarged liver (hepatomegaly), problems with the heart muscle, irregular heartbeat, seizures, low blood sugar, abdominal pain, headache, and muscle weakness in the arms and legs. Severe episodes of metabolic crises can be triggered by periods without eating and illness. Infants with this form of CPT II deficiency are at risk for damage to their liver and brain, and they are at risk of coma or sudden death.

MILD MYOPATHIC FORM

The mild myopathic form of CPT II deficiency is the most-common and least-severe form of the disease. Symptoms can begin in childhood or adulthood. Individuals with the mild myopathic form of CPT II deficiency will experience episodes of muscle pain (myalgia) and muscle breakdown (rhabdomyolysis) as their primary symptom. Excessive muscle breakdown can also lead to kidney damage, resulting in potential kidney failure. Symptoms can be triggered by fasting, exercise, illness, and other forms of stress. Individuals with this form of CPT II deficiency typically do not experience symptoms between these episodes, though some will experience frequent muscle pain.

The mild myopathic form of CPT II deficiency is more common in men than women. Studies have shown the ratio of symptomatic men to women to be as high as five to one. The reason for this gender differential is not well understood.

How Common Is Carnitine Palmitoyltransferase II Deficiency?

CPT II deficiency is quite rare. The lethal neonatal form of CPT II has been reported in 13 families while the severe infantile hepatocardiomuscular form has been reported in 20 families. There are more than 200 reported cases of the mild myopathic form, but scientists believe the true incidence of the mild myopathic form of CPT II deficiency may be more common, due to some individuals having minimal symptoms.

How Is Carnitine Palmitoyltransferase II Deficiency Treated?

There is no cure for CPT II deficiency, and very little can be done to help infants and children with the lethal neonatal form and severe infantile hepatocardiomusclar form of the disease other than to treat symptoms as they arise and make the patients as comfortable as possible.

Individuals with the mild myopathic form of CPT II deficiency should avoid strenuous exercise, long periods without eating, and extreme temperatures. They are recommended to eat a modified diet that consists of frequent, high-carbohydrate, low-fat meals. Some doctors also suggest using carnitine supplements. During infection, individuals with CPT II deficiency may benefit from infusions of glucose. During episodes of muscle pain and muscle breakdown, individuals should drink plenty of fluids to prevent kidney damage.

In general, individuals with CPT II deficiency should avoid taking ibuprofen, valproic acid, and diazepam in high doses. They should also notify their physician before undergoing general anesthesia, as this can provoke an episode of muscle pain and weakness.

What Is the Prognosis for an Individual with Carnitine Palmitoyltransferase II Deficiency?

Infants with the lethal neonatal form of CPT II deficiency typically die within the first year of life.

Infants and children with the severe infantile hepatocardiomuscular form are susceptible to life-threatening heart problems and typically have shortened lifespans with numerous medical issues.

Individuals with the mild myopathic form of the disease typically have normal lifespans with episodes of muscle breakdown, sometimes leading to kidney damage. This form of the disease is usually manageable and allows for a near-normal quality of life.

Additional Considerations for Carriers

Carriers of fatty-acid oxidation defects, including CPT II deficiency, do not typically show symptoms of the disease. However, there may be an increased risk of serious pregnancy complications, particularly in the third trimester, in women carrying a fetus affected with a fatty-acid oxidation defect. A woman whose pregnancy may be affected by a fatty-acid oxidation defect, such as CPT II deficiency, should speak with her physician for recommendations and may benefit from consultation with a high-risk physician.

Cartilage-hair Hypoplasia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: RMRP.
Exon Sequenced: NR_003051:1.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Cartilage-Hair Hypoplasia?

Cartilage-hair hypoplasia (CHH), caused by mutations in the *RMRP* gene, is an inherited disorder of bone growth that causes an individual to have short stature and other skeletal abnormalities. Individuals with CHH also tend to have fine, sparse hair and abnormal cartilage. Some individuals with CHH have an impaired immune system, leaving them more susceptible to infection, notably to a severe course of chicken pox. Anemia, a lowered number of red blood cells leading to fatigue and weakness, is common in children with CHH, though it usually disappears by adulthood. Some individuals may also have low levels of certain white blood cells. Individuals with CHH are at a higher risk for certain cancers, including non-Hodgkin's lymphoma and skin cancer. Symptoms and their severity vary widely among people with the disease.

How Common Is Cartilage-Hair Hypoplasia?

CHH is a rare disorder and is most common among the Amish population. One study indicated that 1 in 19 Amish were carriers of the disease and 1 in 1,340 Amish babies were born with the disease. It is also more common in the Finnish population, where 1 in 76 Finns is a carrier and 1 in 23,000 babies have the disease.

How Is Cartilage-Hair Hypoplasia Treated?

There is currently no treatment for CHH. There are drugs available that can be useful to treat chicken pox. Infections, particularly those in childhood, should be given close medical attention and those with extreme immunodeficiency may want to consider bone-marrow transplantation to ameliorate this symptom. Growth hormones can be considered for some patients.

What Is the Prognosis for an Individual with Cartilage-Hair Hypoplasia?

Individuals with CHH can live a normal lifespan. Those with severe immunodeficiency need to monitor their health more closely. Opportunistic infections can be fatal, particularly in childhood.

CC2D2A-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CC2D2A.
Exons Sequenced: NM_001080522:3-38.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
60%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What are CC2D2A-related Disorders?

CC2D2A-related disorders are inherited conditions that include a wide variety of symptoms. CC2D2A-related disorders are caused by harmful genetic changes (variants) in the *CC2D2A* gene. CC2D2A-related disorders impact part of a cell called cilia. Cilia are hair-like structures that stick out from cells and are essential for cellular movement and sensory functions. Individuals with CC2D2A-related disorders have abnormalities of the cilia, which is the cause of their symptoms.

CC2D2A-related disorders primarily include Joubert syndrome and Meckel syndrome as described below.

JOUBERT SYNDROME

Individuals with Joubert syndrome have developmental delays, low muscle tone (hypotonia), problems with balance and coordination (ataxia), and abnormal eye movements. A common feature of Joubert syndrome is a unique brain shape found using brain imaging called "molar tooth sign." Most people with Joubert syndrome have delayed milestones and may have variable degrees of intellectual disability, ranging from mild to severe. Other symptoms can include breathing issues (particularly in the newborn period), kidney disease, liver abnormalities, feeding problems, extra fingers and toes, vision loss, and behavioral disorders. Many genes can cause Joubert syndrome. Joubert syndrome caused by harmful variants in the *CC2D2A* gene is known as Joubert syndrome type 9.

MECKEL SYNDROME

Meckel syndrome (MKS), sometimes called Meckel-Gruber syndrome, is the most severe type of CC2D2A-related disorder. Individuals have birth defects, including brain, liver, and kidney abnormalities. They often have extra fingers and toes. Other symptoms can include heart defects, cleft lip and palate, underdeveloped lungs, and bone abnormalities. MKS caused by harmful variants in the *CC2D2A* gene is known as MKS type 6.

How common are CC2D2A-related Disorders?

The exact incidence of CC2D2A-related disorders is unknown. Several genes can cause Joubert syndrome, which has an incidence of 1 in 80,000 to 1 in 100,000. Approximately 8-11% of Joubert syndrome is caused by harmful variants in *CC2D2A*. Similarly, several genes can cause Meckel syndrome, which has an incidence of 1 in 13,250 to 1 in 140,000. Approximately 10-13% of Meckel syndrome is caused by harmful variants in *CC2D2A*. The incidence of CC2D2A-related disorders is more common among individuals of French Canadian descent.

How are CC2D2A-related Disorders treated?

There is no cure for CC2D2A-related disorders. Treatment for the condition is directed at managing an individual's specific symptoms. Individuals diagnosed with Joubert syndrome will often benefit from receiving early intervention and other supportive services beginning at a young age.

Management may include screening for brain, kidney, liver, and eye abnormalities. This often means receiving care through a team of specialists, including physicians (neurologists, ophthalmologists, neuropsychologists, nephrologists, etc.), speech pathologists, occupational therapists, physical therapists, and social workers. Some infants need supplemental oxygen or a breathing tube to help with breathing issues. Medications may be given to help manage symptoms such as breathing, liver, or kidney issues.

Babies with MKS are typically stillborn or die shortly after birth. Treatment for this condition is aimed at improving comfort.

What is the prognosis for an individual with CC2D2A-related Disorders?

The prognosis of CC2D2A-related disorders varies widely. Most individuals will have developmental delays and/or intellectual impairment, but this can vary from mild delay of early milestones to significant cognitive disabilities. Some individuals with Joubert syndrome will die in infancy or childhood, whereas others have a normal life expectancy. Common causes of early death in Joubert syndrome include breathing-related issues and kidney disease. Babies with MKS are typically stillborn or die shortly after birth.

CEP290-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CEP290.
Exons Sequenced: NM_025114:2-54.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
60%	Finland
60%	French Canadian or Cajun
70%	Hispanic
>99%	Middle East
>99%	Native American
60%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
60%	Southern Europe
>99%	Worldwide

What are CEP290-related disorders?

CEP290-related disorders are characterized by a wide spectrum of symptoms and severities that range from birth defects and stillbirth to isolated vision loss. They are caused by harmful genetic changes (variants) in the *CEP290* gene. Individuals with CEP290-related disorders have abnormalities in a part of a cell called cilia, which is the cause of their symptoms. Cilia are hair-like structures that stick out from cells and are essential for cellular movement and sensory functions. Individuals with CEP290-related disorders have abnormalities of the cilia, which is the cause of their symptoms.

Variants in *CEP290* cause several different disorders, including Meckel-Gruber syndrome, Joubert syndrome, and Leber congenital amaurosis. Symptoms overlap between the different forms, and it can be difficult to predict which form an individual will have based on their specific *CEP290* variants alone.

LEBER CONGENITAL AMAUROSIS

Leber congenital amaurosis (LCA) is characterized by severe vision loss that begins in infancy. Individuals may show abnormal eye movements and sensitivity to light. Multiple genes can cause LCA, and LCA due to variants in *CEP290* is known as LCA type 10. Unlike other CEP290-related disorders, LCA type 10 only affects the eyes.

JOUBERT SYNDROME

Individuals with Joubert syndrome have developmental delays, low muscle tone (hypotonia), and balance issues. A specific part of the brain, the cerebellum and brain stem, have a unique shape. When seen on a brain MRI, the shape appears somewhat like a tooth and is therefore called a “molar tooth sign.” Many newborns with Joubert syndrome have breathing issues. Other symptoms can include kidney disease, liver abnormalities, feeding problems, extra fingers and toes, vision loss, and abnormal eye movements. Most people with Joubert syndrome have intellectual disability. Many genes can cause Joubert syndrome. Joubert syndrome caused by variants in *CEP290* is known as Joubert syndrome type 5.

MECKEL-GRUBER SYNDROME

Meckel-Gruber syndrome, sometimes called Meckel syndrome, (MKS) is the most severe type of CEP290-related disorder. Individuals have birth defects including brain, liver, and kidney abnormalities. They often have extra fingers and toes. Other symptoms can include heart defects, cleft lip and palate, underdeveloped lungs, and bone abnormalities. Several genes can cause MKS. MKS caused by variants in *CEP290* is known as MKS type 4.

How common are CEP290-related disorders?

Several genes are known to cause LCA, which has an incidence of 1 in 100,000 – 1 in 300,000 births. Approximately 20% of LCA is caused by *CEP290*. Several genes are also known to cause Joubert syndrome, which has an incidence of 1 in 80,000 – 1 in 100,000 births. Approximately 10% of Joubert syndrome is caused by *CEP290*. Finally, several genes are known to cause MKS, which has an incidence of 1 in 13,250 to 1 in 140,000 births. It is unknown what proportion of MKS is caused by *CEP290*.

How are CEP290-related disorders treated?

There is no cure for CEP290-related disorders. Treatment is directed at managing the specific symptoms an individual has. Individuals with vision loss caused by either LCA or Joubert syndrome may benefit from using glasses, low-vision aids, and supportive services for those with vision impairment.

Individuals with Joubert syndrome may receive care through a team of specialists, including physicians, speech pathologists, occupational therapists, physical therapists, and social workers. Some infants need supplemental oxygen or a breathing tube to help with breathing issues. Medications may be given to help manage symptoms such as breathing, liver, or kidney issues. In some cases, surgery is required to treat certain birth defects.

Because babies with MKS are typically stillborn or die shortly after birth, treatment for this condition is usually limited and aimed at improving comfort.

What is the prognosis for a person with a CEP290-related disorder?

The prognosis of CEP290-related disorders varies widely. Individuals with LCA typically have normal lifespans. Some individuals with Joubert syndrome will die in infancy or childhood, whereas others live into adulthood. Common causes of early death in Joubert syndrome include breathing-related issues and kidney disease. Babies with MKS are typically stillborn or die shortly after birth.

Cerebrotendinous Xanthomatosis

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CYP27A1.
Exons Sequenced: NM_000784:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Cerebrotendinous Xanthomatosis?

Cerebrotendinous xanthomatosis (CTX) is a disease that leads to increased storage in the body of fats such as cholesterol. CTX is caused by harmful genetic changes (mutations) in the *CYP27A1* gene. *CYP27A1* deficiency leads to an inability to breakdown cholesterol and a toxic buildup of fats in the body.

Common features of this disorder include diarrhea that starts in infancy; clouding of the lens of the eye (cataracts); deposits of fat under the skin (xanthomas); and neurologic problems that get worse over time. For many affected individuals, chronic diarrhea beginning in infancy is the earliest symptom. Typically, sufferers develop cataracts during early childhood. Xanthomas most commonly begin appearing in adolescence and early adulthood, often on the Achilles tendon (on the back of the heel) and other tendons, though they can occur throughout the body. Most individuals with CTX have no or only mild neurologic problems before puberty. Beginning in their twenties, patients can develop neurologic symptoms such as seizures and an inability to control movements (ataxia). These symptoms will often worsen over time. Additional neurological features may include intellectual disability, dementia, and mental health problems such as depression or hallucinations. Some other reported features of CTX include weak and brittle bones (osteoporosis) and heart problems.

How common is Cerebrotendinous Xanthomatosis?

Currently, there is no consensus on the global incidence of this disorder. The condition is more common in the Druze population in Israel and in Sephardic Jews of Moroccan descent. The incidence in individuals of European descent is at least 1 in 50,000.

How is Cerebrotendinous Xanthomatosis treated?

There is no cure for CTX, but early diagnosis and treatment with chenodeoxycholic acid (CDCA) can prevent or reduce the symptoms. Other treatments are based on the presentation of the disease; for instance, medication is used for seizures and trouble controlling movements, and calcium and vitamin D are used for weak and brittle bones. Eye surgery to remove cataracts is often required in adulthood.

What is the prognosis for an individual with Cerebrotendinous Xanthomatosis?

The prognosis for CTX is greatly improved if the disease is identified and treated early. Treatment may prevent the development of some symptoms, although it may not be able to reverse all features once the disease has progressed. In addition, patients' lifespans may be normal if treatment begins early. Without treatment, the average lifespan is 50-60 years, due to progressive deterioration.

Chronic Granulomatous Disease, CYBA-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CYBA.
Exons Sequenced: NM_000101:1-6.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Chronic Granulomatous Disease, CYBA-related?

Chronic granulomatous disease (CGD), CYBA-related, is an inherited condition that causes the immune system to not work correctly (immunodeficiency). This means the body's natural defenses cannot protect it from germs. The condition is caused by harmful genetic changes (variants) in the *CYBA* gene. Symptoms include recurrent bacterial and fungal infections of the lungs, lymph nodes, liver, and skin. Individuals with this condition typically have swollen, infected nodules (granulomas) in the gastrointestinal or genitourinary tract and develop swollen areas filled with pus (abscesses), often in the liver or skin. Affected individuals may have inflammatory bowel disease (colitis), which can lead to failure to grow at the expected rate. Pneumonia is a common complication, and chronic lung disease can also occur.

Most individuals show symptoms of CGD in early childhood, although some people do not show symptoms until later.

How common is Chronic Granulomatous Disease, CYBA-related?

Several genes cause chronic granulomatous disease. Overall, the incidence of chronic granulomatous disease is about 1 in 200,000. About 7% of chronic granulomatous disease is estimated to be caused by harmful changes in the *CYBA* gene.

How is Chronic Granulomatous Disease, CYBA-related treated?

Treatment of CGD involves medications to treat ongoing infections and avoiding exposure to bacteria and fungi. In order to properly treat infections, it is usually necessary to identify the specific of the cause of the infection. Individuals may be treated with antimicrobial medications before getting an infection (prophylactically). Affected individuals should avoid exposure to decayed organic matter, such as leaf raking or other related activities, as inhalation can cause infection. Careful hygiene, including regular hand washing, can help reduce the germs an individual is exposed to. Abscesses may require drainage or removal. Affected individuals considering pregnancy may need

to discuss with their provider which antimicrobial medications should be avoided during pregnancy. Some providers may use an injection of interferon-gamma (IFN-gamma) to help boost the immune system and reduce the number of infections.

Allogeneic stem cell transplantation is the only cure for chronic granulomatous disease and typically results in excellent outcomes. Stem cell transplantation should be considered as soon as possible after diagnosis for the best results.

What is the prognosis for a person with Chronic Granulomatous Disease, CYBA-related?

Current antibacterial and antifungal medications have improved the survival rate of individuals affected with chronic granulomatous disease; however, some infections may be life-threatening. With treatment, most individuals live into adulthood; however, lifespan may be shortened due to pneumonia or other infections.

Citrullinemia Type 1

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ASS1.
Exons Sequenced: NM_000050:3-16.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
86%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Citrullinemia Type 1?

Citrullinemia type I is an inherited condition in which ammonia and other toxic substances build up in the blood, causing life-threatening complications shortly after birth. It is caused by mutations in the *ASS1* gene. Citrullinemia type I belongs to a group of diseases known as urea cycle disorders. When the body consumes protein, it also produces excess nitrogen. Under normal circumstances, the body converts that nitrogen to urea, which is then excreted in the urine. People with citrullinemia type I are deficient in an enzyme known as argininosuccinate synthase, which is needed for this vital process, leading to a buildup of ammonia and other urea cycle byproducts in the body. The excess ammonia is harmful to the nervous system, causing many of the disease's symptoms.

Infants with citrullinemia type I appear normal at birth. However, within the first week of life most will become lethargic and display poor feeding, vomiting, and seizures that often lead to unconsciousness, stroke, increased pressure around the brain, and death if untreated.

A milder form of type I citrullinemia may develop later in childhood or adulthood, but this form of the disease is less common. This later-onset form is associated with intense headaches, partial loss of vision, problems with balance and muscle coordination (ataxia), episodes of elevated ammonia that are similar to the classic form, and lethargy. Women with the later-onset form may have an onset of severe symptoms during pregnancy or postpartum.

How Common Is Citrullinemia Type 1?

Scientists estimate that 1 in 57,000 births are affected by citrullinemia type I.

How Is Citrullinemia Type 1 Treated?

The goals of treatment for citrullinemia type I are to regulate the amount of ammonia in the blood. Physicians adhere to certain protocols to control the body's ammonia levels. These protocols use medication, dialysis, and a specifically prescribed diet. Children with citrullinemia will need to be monitored closely by a physician specializing in metabolic disorders. Physicians will also monitor and attempt to relieve any excess of pressure around the brain.

Lifelong management involves strict dietary management in addition to oral administration of sodium phenylbutyrate or glycerol phenylbutyrate and L-carnitine to prevent systemic hypocarnitinemia. Liver transplantation may be warranted.

What Is the Prognosis for a Person with Citrullinemia Type 1?

The prognosis for a child with citrullinemia type I is not well established. Without treatment, the longest-known survival was 17 days. With treatment, these children can survive for an unknown period of time, but they will have significant mental and neurological impairment.

Initial neurologic findings associated with the milder, late-onset form may be more subtle than those seen in the acute neonatal form because of the older age of affected individuals.

Classical-like Ehlers-Danlos Syndrome, TNXB-related

Available Methodologies: sequencing analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: TNXB.
Exons Sequenced: NM_019105:2-20,23-31.

Detection Rate	Population
36%	African American
36%	Ashkenazi Jewish
36%	Eastern Asia
36%	Finland
36%	French Canadian or Cajun
36%	Hispanic
36%	Middle East
36%	Native American
36%	Northwestern Europe
36%	Oceania
36%	South Asia
36%	Southeast Asia
36%	Southern Europe
36%	Worldwide

What is classical-like Ehlers-Danlos syndrome, TNXB-related?

Classical-like Ehlers-Danlos syndrome, TNXB-related, also known as clEDS, TNXB-related or clEDS Type 1, is an inherited condition that causes connective tissue abnormalities. There are several types of Ehlers-Danlos syndrome that have different causes. Classical-like Ehlers-Danlos syndrome, TNXB-related is caused by harmful genetic changes (variants) in the *TNXB* gene. Most individuals with clEDS, TNXB-related, experience symptoms starting in childhood, although many are not officially diagnosed until adulthood. The most common symptoms of the condition include stretchy (hyperextensible) and soft (velvety) skin, as well as joints that have a larger-than-normal range of movement (hypermobility). Joint dislocation is frequently observed. Other symptoms of clEDS, TNXB-related, include easy bruising of the skin, hand or foot abnormalities, weak muscles, heart problems, and slipping (prolapse) of the vagina, uterus, and rectum. Many individuals with the condition experience fatigue and a loss of sensation (axonal polyneuropathy). Many people have fragile tissues that can lead to complications in the digestive system, rupture of the windpipe (trachea) if artificial breathing is required, and cartilage damage after nose blowing.

Individuals with clEDS, TNXB-related have normal intelligence.

How common is classical-like Ehlers-Danlos syndrome, TNXB-related?

The incidence of clEDS, TNXB-related is unknown. There are fewer than 100 cases reported in the published literature.

How is classical-like Ehlers-Danlos syndrome, TNXB-related, treated?

There is no cure for clEDS, TNXB-related. Treatment is intended to reduce symptoms and increase quality of life. Many individuals will require physical and occupational therapy to increase muscle strength and adaptive devices to help with movement. A foot physician (podiatrist) can assess and treat foot abnormalities, and a physician specializing in heart issues (cardiologist) can assess and treat heart problems. Individuals with clEDS, TNXB-related, should avoid sports that strain their joints and are encouraged to maintain a healthy weight.

Individuals with clEDS, TNXB-related are at a higher risk for complications during invasive gastrointestinal procedures, like a colonoscopy, therefore, all procedures should be carefully discussed with a physician who specializes in issues of the digestive system (gastroenterologist). Pregnant people with clEDS, TNXB-related, are at a higher risk for pregnancy complications and should work closely with a physician who specializes in caring for high-risk pregnancies (obstetrician/gynecologist).

What is the prognosis for an individual with classical-like Ehlers-Danlos syndrome, TNXB-related?

The prognosis for individuals with clEDS, TNXB-related, depends on the severity of their symptoms. Most individuals live well into adulthood but will require some therapy or physical support. Damage to fragile tissues, particularly of the gastrointestinal system, can be life-threatening. There are reports of pregnant individuals with clEDS, TNXB-related, successfully having a child. Although the long-term data is limited, many people with the condition can live well into their 50s and 60s.

CLN3-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CLN3.
Exons Sequenced: NM_001042432:2-16.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What are CLN3-related disorders?

CLN3-related disorders are a group of conditions that cause vision trouble (retinal degeneration) either by itself or, more commonly, with progressive loss of mental and motor skills. CLN3-related disorders are caused by harmful genetic changes in the *CLN3* gene. Symptoms result from a buildup of harmful substances in the cells, which causes damage to the nerves in an individual's brain and body. The two main conditions that make up CLN3-related disorders include neuronal ceroid lipofuscinosis and isolated retinal degeneration.

NEURONAL CEROID LIPOFUSCINOSIS, CLN3-RELATED

Neuronal ceroid lipofuscinoses (NCL) are a group of inherited diseases that affect an individual's brain and nerves. Another name for NCL is Batten disease. These conditions lead to blindness, as well as loss of cognitive, speech, and motor skills (developmental regression). There are several forms of NCL caused by harmful genetic changes in different genes.

In individuals with CLN3-related NCL, symptoms typically start between the ages of four and ten. Often, the first noticeable symptom is visual impairment that leads to complete blindness within a few years. Learning difficulties, loss of speech and motor skills, behavior problems, and seizures also develop. As individuals get older, they continue to lose skills. By the late teens, most cannot move independently and need help with basic self-care activities. They may also have other symptoms, such as difficulty eating, heart rhythm abnormalities (cardiac dysrhythmia), psychiatric issues, and difficulties with sleep. Due to the age at which symptoms begin, this form of the disorder is often referred to as juvenile NCL.

In rare instances, individuals with CLN3-related NCL may have a longer (protracted) disease course, where symptoms begin in childhood but progress at a slower rate.

ISOLATED RETINAL DEGENERATION, CLN3-RELATED

Some individuals with harmful genetic changes in *CLN3* have vision trouble without other symptoms (isolated retinal degeneration). In these individuals, the age at which the vision issues start can range from early teens into the forties. Symptoms often begin with difficulty with nighttime vision and progress to legal blindness.

How common are CLN3-related disorders?

The incidence of all forms of NCL is approximately 1 in 75,000 to 1 in 100,000 births. The exact incidence of NCL caused by CLN3 mutations is unknown, but it is more common among individuals of Scandinavian descent.

The incidence of CLN3-related isolated retinal degeneration is unknown.

How are CLN3-related disorders treated?

There is no treatment for the underlying cause of CLN3-related disorders. For individuals with CLN3-related NCL, treatment is based on the symptoms that are present. Treatment typically includes medications to control seizures and movement problems. Affected individuals may be routinely monitored for swallowing difficulties to determine if a feeding tube would be beneficial.

What is the prognosis for an individual with a CLN3-related disorder?

The symptoms in individuals with CLN3-related NCL become more severe as they age, and death usually occurs in the late teens or twenties. However, some individuals with the disease have lived into their thirties. Individuals with isolated retinal degeneration experience vision symptoms that progress to legal blindness but are expected to have an average lifespan.

CLN5-related Neuronal Ceroid Lipofuscinosis

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CLN5.
Exons Sequenced: NM_006493:1-4.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is CLN5-Related Neuronal Ceroid Lipofuscinosis?

CLN5-related neuronal ceroid lipofuscinosis (NCL) is an inherited disease that causes degeneration of the brain, leading to a progressive loss of intellectual abilities and motor skills. The condition also causes blindness and seizures and typically leads to an early death. There are several forms of NCL, largely differentiated by the gene responsible and the age at which symptoms begin. Mutations in the *CLN5* gene cause a form of NCL that is often referred to as the Finnish variant of late-infantile NCL.

Symptoms of CLN5-related NCL usually begin between the ages of 4 and 7. By the age of 10, children with the condition typically experience loss of vision and develop seizures, intellectual disability, muscle twitching, and an inability to control muscle movements (ataxia). They usually lose the ability to walk independently between 8 and 11 years of age, and will gradually lose their ability to speak and exhibit profound intellectual disability.

How Common Is CLN5-Related Neuronal Ceroid Lipofuscinosis?

NCLs are most common in Scandinavian countries but occur elsewhere as well. The worldwide prevalence of all forms of NCL is estimated to be approximately 1 in 100,000. However, the exact proportion of NCL cases that are caused by mutations in the *CLN5* gene is unknown. CLN5-related NCL is known to be most common in Finland.

How Is CLN5-Related Neuronal Ceroid Lipofuscinosis Treated?

There is no treatment for the underlying cause of CLN5-related NCL. Available treatments address the symptoms of the condition as they arise, such as with the use of medications for improving seizures and movement problems.

What Is the Prognosis for an Individual with CLN5-Related Neuronal Ceroid Lipofuscinosis?

The prognosis for an individual with NCL depends on the type of disease he or she has. Those with CLN5-related NCL experience deterioration of motor skills, deterioration of intellectual abilities, and progressive vision loss. Patients will eventually lose the ability to speak and walk independently. The average life expectancy for an individual with CLN5-related NCL typically ranges from 13 to 35 years.

CLN8-related Neuronal Ceroid Lipofuscinosis

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CLN8.
Exons Sequenced: NM_018941:2-3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is CLN8-Related Neuronal Ceroid Lipofuscinosis?

CLN8-related neuronal ceroid lipofuscinosis (NCL8) is an inherited condition that causes degeneration of the brain, leading to a progressive loss of mental and motor skills, seizures, and vision impairment in some cases. There are several forms of neuronal ceroid lipofuscinosis (NCL), largely differentiated by the gene responsible and the age at which symptoms begin. Mutations in the *CLN8* gene typically result in variant late-infantile neuronal ceroid lipofuscinosis (vLINCL) or Northern epilepsy (also know as Progressive Epilepsy with Mental Retardation, or EPMR). Northern epilepsy accounts for almost 100% of NCL8 cases in Finland but is generally rare.

Variant late-infantile neuronal ceroid lipofuscinosis The symptoms of vLINCL typically begin between 3 and 8 years of age. Early symptoms include epilepsy, vision loss, and difficulty controlling movements. Over time, motor and intellectual skills decline and epilepsy and vision loss worsens. Death occurs in late childhood or in adolescence.

Northern epilepsy Symptoms of Northern epilepsy typically begin between 5 and 10 years of age. Typical symptoms include recurrent seizures and a slow decline in mental function. The frequency of seizures decreases after puberty, and vision problems are rare. Individuals with Northern epilepsy live into late adulthood, with some living beyond age 60.

How Common Is CLN8-Related Neuronal Ceroid Lipofuscinosis?

The worldwide prevalence of NCL (all forms) is approximately 1 in 100,000. These diseases are most common in Scandinavian countries but occur elsewhere as well. Northern epilepsy occurs primarily in the Kainuu region of northern Finland, where the prevalence of the condition is approximately 1 in 10,000. The exact proportion of NCL cases that are caused by mutations in the *CLN8* gene is currently unknown.

How Is CLN8-Related Neuronal Ceroid Lipofuscinosis Treated?

There is no treatment for the underlying cause of NCL8. Seizures may be controlled with medication. However, not all individuals with NCL8 will respond to anti-seizure medications, and treatment will not slow the progression of the disease. Additional treatments address symptoms of the condition as they arise, such as medications for the various movement problems.

What Is the Prognosis for an Individual with CLN8-Related Neuronal Ceroid Lipofuscinosis?

Individuals with severe vLINCL survive into late childhood or adolescence. Individuals with Northern epilepsy often live until the fifth or sixth decade of life. However, these individuals have significant cognitive and physical impairments for much of their lives. While vision impairment may occur, significant vision loss is not as common with NCL8 as it is with other types of NCL.

Cohen Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: VPS13B.
Exons Sequenced: NM_017890:2-62.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe
97%	Worldwide

What Is Cohen Syndrome?

Cohen syndrome, caused by mutations in the *VPS13B* gene, is an inherited condition that affects motor skills, mental development, and behavior. Infants with the condition grow slowly and do not gain weight at the normal rate. They may have a smaller-than-expected head size (microcephaly) and decreased muscle tone (hypotonia) with unusually flexible joints. Infants can feel floppy, like a rag doll, when lifted, and cannot control their heads. Over time, they have difficulty learning to roll over, sit up, crawl, and walk. Beginning in late childhood, people with Cohen syndrome may begin to put on weight in the torso. Without intervention, they can become obese, although their arms and legs remain slender. Patients with Cohen syndrome have distinct facial features.

People with Cohen syndrome show moderate-to-severe intellectual and motor disability that remain constant and do not become progressively worse over time. They are prone to frequent and potentially severe infections because they have a lower-than-average level of certain infection-fighting white blood cells (neutropenia).

Cohen syndrome generally causes severe, progressive vision problems, notably extreme nearsightedness and degeneration of the retina. People with the condition often become functionally, if not entirely, blind. They also tend to be unusually friendly and cheerful, even towards strangers. As a result, parents must be extra vigilant about their child's personal safety.

How Common Is Cohen Syndrome?

The exact prevalence of Cohen syndrome is unknown. It has been reported in fewer than 1000 people worldwide, although more cases likely exist. It is most common in a small Amish community in Ohio, where it affects an estimated 1 in 500 people. It is also more common in Finland.

How Is Cohen Syndrome Treated?

There is no cure for Cohen syndrome, but early intervention with physical, occupational, and speech therapy can address symptoms like joint laxity, clumsiness, and developmental delays. Children with nearsightedness need glasses, while those with retinal degeneration benefit from training for the visually impaired.

In order to prevent recurrent infections, people with Cohen syndrome should be monitored throughout their lives for a low white blood cell count.

What Is the Prognosis for a Person with Cohen Syndrome?

The exact effect of Cohen syndrome on one's lifespan is unclear. Some people with the disease are known to be alive in their fifties.

Combined Pituitary Hormone Deficiency, PROP1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PROP1.
Exons Sequenced: NM_006261:1-3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Combined Pituitary Hormone Deficiency, PROP1-Related?

Combined pituitary hormone deficiency (CPHD), PROP1-related is an inherited disease that causes a shortage of certain hormones in the body. The severity of hormone deficiencies can vary from individual to individual, even among those who share the same disease-causing genetic mutation(s). However, the typical deficiency leaves those with the condition small in stature (a condition known as pituitary dwarfism) and deficient in the hormones required to fully undergo puberty. PROP1-related CPHD refers to those cases of CPHD caused by mutations in the *PROP1* gene.

Infants with CPHD are often born with a normal height and weight, although some may have low blood-sugar levels (hypoglycemia). At some point in late infancy or childhood they fail to grow at the expected rate due to a deficiency in growth hormone and without treatment, they will be extremely small in stature.

Individuals with CPHD also show a deficiency in additional hormones produced by the pituitary gland. Deficiencies of these hormones can lead to an under-active thyroid gland (mild hypothyroidism), delayed or absent puberty, and infertility. Untreated males usually have a small penis and testes. Women may begin to menstruate, but require hormone replacement in order to avoid early menopause. Persistent weakness, fever, abdominal pain, and weight loss have also been reported in some cases.

How Common Is Combined Pituitary Hormone Deficiency, PROP1-Related?

PROP1 is one of several genes known to be responsible for CPHD. The incidence of CPHD is 1 in 8,000 worldwide. Approximately 10% of CPHD is caused by mutations in PROP1, but this frequency varies greatly by population.

How Is Combined Pituitary Hormone Deficiency, PROP1-Related treated?

In individuals with CPHD, injections of biosynthetic growth hormone often begin at diagnosis until approximately the age of 17. The replacement of other hormones is initiated when the lack of proper hormone levels is detected. Hormone replacement can help induce puberty in both boys and girls, and some of these individuals may be fertile.

What Is the Prognosis for a Person with Combined Pituitary Hormone Deficiency, PROP1-Related?

Individuals with CPHD are typically able to live a normal lifespan.

Congenital Adrenal Hyperplasia, CYP11A1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CYP11A1.
Exons Sequenced: NM_000781:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Congenital Adrenal Hyperplasia, CYP11A1-related?

Congenital adrenal hyperplasia (CAH) is a genetic disorder that affects the body's adrenal glands. The adrenal glands regulate the production of several vital hormones. CAH occurs when the adrenal glands cannot produce these hormones properly, resulting in a hormone imbalance. There are several different types of CAH. Congenital adrenal hyperplasia, CYP11A1-related, also known as P450scc deficiency, is caused by harmful genetic changes (variants) in the *CYP11A1* gene and is one of the most severe forms of CAH. Individuals with CAH, CYP11A1-related, can have different levels of hormone deficiencies, ranging from a classic, severe form of the disease to a milder, non-classic form.

CLASSIC FORM

The severe, classic form of the condition occurs when little to no hormone is produced. Affected individuals usually experience episodes in early infancy where the body cannot retain salt, leading to dehydration and other complications that can be life-threatening (known as "salt-wasting crises"). In addition, individuals may also experience weakness, poor feeding, and/or darkened (hyperpigmented) skin. Almost all affected individuals have female genitalia regardless of biological sex. Unlike other forms of CAH, individuals with CAH, CYP11A1-related typically have normal-sized adrenal glands.

NON-CLASSIC FORM

The condition's less severe, non-classic form occurs when there is still residual hormone production. Individuals with the non-classic form typically have a later onset of symptoms. However, they may still experience salt-wasting crises. The condition has been described as a form of non-autoimmune Addison disease.

How common is Congenital Adrenal Hyperplasia, CYP11A1-related?

About 1 in 10,000 individuals worldwide are affected with some form of congenital adrenal hyperplasia. The exact incidence of CAH, CYP11A1-related, is unknown, with less than thirty individuals diagnosed worldwide.

How is Congenital Adrenal Hyperplasia, CYP11A1-related treated?

Currently, there is no cure for CAH, CYP11A1-related. Treatment for the condition is directed at managing an individual's specific symptoms. Common interventions include hormone replacement therapy for affected individuals. A multidisciplinary team of physicians, including an endocrinologist, will likely monitor the medication dosage, side effects, growth, and development of patients who continue receiving treatment. Some patients may undergo surgeries to repair genitalia and other reproductive organs.

What is the prognosis for an individual with Congenital Adrenal Hyperplasia, CYP11A1-related?

Without any interventions or treatment, CAH, CYP11A1-related, can be fatal in early infancy. However, early, consistent adherence to medication may extend the lifespan into adulthood. The overall prognosis depends on the severity of symptoms.

Congenital Adrenal Hyperplasia, CYP11B1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CYP11B1.
Exons Sequenced: NM_000497:1-9.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe
97%	Worldwide

What is Congenital Adrenal Hyperplasia, CYP11B1-related?

Congenital adrenal hyperplasia (CAH) is a group of genetic disorders that affect the body's adrenal glands. The adrenal glands regulate essential functions in the body, including the production of several important hormones. CAH occurs when the adrenal glands are unable to produce these hormones properly, resulting in a hormone imbalance.

CAH, caused by harmful genetic changes (mutations) in a gene called *CYP11B1*, is the second-most-common type of CAH. *CYP11B1* provides instructions to make 11-beta-hydroxylase. Another name for this disorder is 11-beta-hydroxylase-deficient CAH (11b-OHD CAH). When 11-beta-hydroxylase is impaired, the adrenal glands are unable to produce certain critical hormones. The body responds to this deficiency by producing an excess of male sex hormones (androgens). Collectively, the excess androgen production and hormone deficiencies lead to a variety of medical problems, which vary in severity depending on the form of CAH. There are two major forms of 11b-OHD CAH: classic and non-classic.

CLASSIC FORM

The classic form is the most severe type of 11b-OHD CAH. Female newborns often have external genitals that do not clearly appear either male or female (ambiguous genitalia), though the internal reproductive organs develop normally. Signs of early puberty and exaggerated development of male characteristics (virilization) can occur in both males and females with CAH. These symptoms may include rapid growth and development in early childhood, but shorter-than-average height in adulthood, abnormal menstruation cycles for females, excess facial hair for females, early facial-hair growth for males, severe acne, and infertility in both men and women. In addition, two out of three individuals with the classic form will develop high blood pressure (hypertension), sometimes at a very young age. Hypertension can result in significant medical complications if not treated.

NON-CLASSIC FORM

The non-classic form is the less severe type of 11b-OHD CAH. Symptoms related to excess androgen production can first appear in childhood, adolescence, or adulthood. Individuals with the non-classic form are born with genitals that appear to be normal. Both males and females may still exhibit rapid growth in childhood and shorter-than-average height in adulthood. Additionally, girls may experience symptoms of virilization, abnormal menstruation, and infertility. The non-classic form does not typically cause hypertension. Some individuals with non-classic CAH experience such mild symptoms that they do not even know that they have this condition.

How common is Congenital Adrenal Hyperplasia, CYP11B1-related?

The exact incidence of 11b-OHD CAH in the population is unknown. Some studies estimate it to be approximately 1 in 100,000 births worldwide. The incidence of 11b-OHD CAH is more common among individuals of Moroccan Jewish descent and may also be more common in other individuals of Jewish descent from North Africa and the Middle East. 11b-OHD CAH accounts for up to 8% of all CAH cases, depending on ethnic background.

How is Congenital Adrenal Hyperplasia, CYP11B1-related treated?

Currently, there is no cure for CAH; however, treatments are available to address some of the associated symptoms. Patients benefit from taking hormone-replacement medications, which work to correct the hormonal imbalances caused by CAH. Most people with the classic form will need to take hormone medications throughout their life. Those with the less severe forms of CAH are sometimes able to stop taking these medications in adulthood and are typically treated with lower doses. Some individuals with non-classic CAH do not require treatment. A team of doctors, including one who specializes in hormone conditions (an endocrinologist), will need to monitor medication dosages and side effects and the growth and sexual development of patients who receive treatment. Additionally, high blood pressure may require treatment.

Newborn females with ambiguous genitalia may need surgery to correct the function and appearance of the external genitals. Surgery, if needed, is usually performed during infancy, but can be done later in life.

Treatments provided during pregnancy may reduce the degree of virilization in female fetuses. However, because the long-term safety of prenatal treatment is unknown, these therapies are considered experimental and are not recommended by professional guidelines.

What is the prognosis for an individual with Congenital Adrenal Hyperplasia, CYP11B1-related?

With early diagnosis and proper management, most individuals with 11b-OHD CAH will have a normal life expectancy. Rarely, uncontrolled hypertension can lead to early death. Problems with growth and development, infertility, ambiguous genitalia, and virilization are monitored by physicians on an ongoing basis.

Congenital Adrenal Hyperplasia, CYP21A2-related

Available Methodologies: analysis of homologous regions (v4.0) and interpretation of reported variants (v4.0).
Gene: CYP21A2.
Variants Genotyped (13): I173N, V282L, R357W, P31L, c.293-13C>G, G111VfsX21, Q319*, L308FfsX6, CYP21A2 deletion, CYP21A2 duplication, Q319*+CYP21A2dup, [I237N;V238E;M240K], CYP21A2 triplication.

Detection Rate	Population
92%	African American
>99%	Ashkenazi Jewish
88%	Eastern Asia
89%	Finland
96%	French Canadian or Cajun
95%	Hispanic
97%	Middle East
90%	Native American
96%	Northwestern Europe
96%	Oceania
88%	South Asia
88%	Southeast Asia
96%	Southern Europe
97%	Worldwide

What Is Congenital Adrenal Hyperplasia, CYP21A2-Related?

Congenital adrenal hyperplasia (CAH) refers to a group of genetic disorders that affect the body's adrenal glands. The adrenal glands regulate essential functions in the body, including the production of several important hormones. CAH occurs when the adrenal glands are unable to produce these hormones properly, resulting in a hormone imbalance. CAH, CYP21A2-related is caused by mutations in the *CYP21A2* gene. The *CYP21A2* gene produces the 21-hydroxylase enzyme. Another name for this disorder is 21-hydroxylase-deficient CAH (21-OHD CAH).

When the 21-hydroxylase enzyme is missing or present at low levels, the adrenal glands are unable to produce two critical hormones, cortisol and aldosterone. The body responds to this deficiency by producing an excess of male sex hormones, called androgens. Collectively, the excess androgen production and hormone deficiencies can lead to a variety of medical problems, which vary in severity depending on the form of CAH. CAH associated with *CYP21A2* (21-OHD CAH) has two major forms: classic and non-classic.

CLASSIC FORM

The most severe form referred to as classic 21-OHD CAH, can be further divided into two different subtypes: salt wasting and simple virilizing (non-salt wasting) types. The classic salt-wasting type is associated with near-to-complete deficiency of the 21-hydroxylase enzyme, resulting in the complete inability to produce the hormones cortisol and aldosterone. In this type, the body cannot retain enough sodium (salt) and when too much salt is lost in the urine, it may lead to dehydration, vomiting, diarrhea, poor growth, heart-rhythm abnormalities (arrhythmias), and shock (salt wasting). If not properly treated, salt wasting can lead to death in some cases.

Additionally, female newborns often have external genitals that do not clearly appear either male or female (ambiguous genitalia), whereas male newborns may present with enlarged genitals. Signs of early puberty and the exaggerated development of male characteristics (virilization) occur in both males and females with CAH. These symptoms may include: rapid growth and development in early childhood, but shorter-than-average height in adulthood, abnormal menstruation cycles for females, excess facial hair for females,

early facial-hair growth for males, severe acne, and infertility in both men and women. Male characteristics such as muscle bulk and a deep voice can occur in females and in boys (masculinization).

The simple virilizing type of CAH is associated with partial 21-hydroxylase deficiency. Unlike the salt-wasting type, individuals with this condition typically do not experience severe and life-threatening sodium-deficiency symptoms as newborns. However, the majority of female newborns with this type will have ambiguous genitalia, and both male and female children may show signs of early puberty.

NON-CLASSIC FORM

The non-classic type (late-onset type) is the the least-severe form of 21-OHD CAH and is caused by a mild deficiency of the 21-hydroxylase enzyme. Individuals with this type may start experiencing symptoms related to excess androgen production in childhood, adolescence, or adulthood. Both males and females may exhibit rapid growth in childhood, shorter-than-average stature in adulthood, virilization, and infertility. Additionally, girls may experience symptoms of masculinization and abnormal menstruation. However, some individuals with non-classic CAH may never know they are affected because the symptoms are so mild.

How Common Is Congenital Adrenal Hyperplasia, CYP21A2-Related?

The incidence of 21-OHD CAH varies by type and ethnicity. The incidence for the classic form is approximately 1 in 15,000 births worldwide. The prevalence of the classic form varies from 1 in 300 for Yupik Eskimos in Alaska to 1 in 21,000 in Japanese. The non-classic form of 21-OHD CAH is much more common, with an incidence of approximately 1 in 1000 births. The prevalence of the non-classic form is much higher in some ethnicities, namely in the Ashkenazi Jewish (1 in 27), Hispanic (1 in 40), Slavic (1 in 50), and Italian (1 in 300) ethnicities. Mutations in *CYP21A2* account for about 90% of CAH cases.

How Is Congenital Adrenal Hyperplasia, CYP21A2-Related Treated?

Currently, there is no cure for CAH. However, treatments are available to address some of the associated symptoms. Patients benefit from taking hormone-replacement medications, which work to increase levels of deficient hormones and suppress the overproduction of male hormones. Most individuals with classic CAH will need to take hormone medications for the rest of their lives. Those with the less-severe forms of CAH are sometimes able to stop taking these medications in adulthood and are typically treated with lower doses. Some individuals with non-classic CAH do not require any treatment. A multidisciplinary team of physicians, including an endocrinologist, will need to monitor the medication dosage, medication side effects, growth, and sexual development of patients who continue to receive treatment.

Newborn females with ambiguous genitalia may need surgery to correct the function and appearance of the external genitalia. Surgery, if needed, is most often performed during infancy, but can be performed later in life. Treatments provided during pregnancy may reduce the degree of virilization in female fetuses. However, because the long-term safety of prenatal treatment is unknown, these therapies are considered experimental and are not recommended by professional guidelines.

What Is the Prognosis for an Individual with Congenital Adrenal Hyperplasia, CYP21A2-Related?

With early diagnosis and proper medication management, most individuals with 21-OHD CAH will have a normal life expectancy. Early death can occur during periods of significant sodium loss (salt crises) if medication dosage is not adequately adjusted, especially during times of illness or trauma. Problems with growth and development, ambiguous genitalia, and virilization are monitored by physicians on an ongoing basis. Females with 21-OHD CAH can become pregnant, but fertility is reduced.

Congenital Amegakaryocytic Thrombocytopenia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MPL.
Exons Sequenced: NM_005373:1-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Congenital Amegakaryocytic Thrombocytopenia?

Congenital amegakaryocytic thrombocytopenia (CAMT), caused by harmful genetic changes in the *MPL* gene, is a condition that is associated with a reduced level of platelets (thrombocytopenia) and the absence or reduction of bone marrow cells that produce platelets (megakaryocytes). Platelets are small cells in the blood that are important in binding together (clotting) to stop bleeding. The condition has also been associated with increased risks for leukemia. There are two described types of the condition:

TYPE I

Type I CAMT is associated with complete lack of the thrombopoietin receptor protein (the product that is created from the *MPL* gene), and therefore, symptoms tend to be more severe. Individuals with type I usually present in infancy, frequently in the newborn period, with bleeding that may occur from the skin, gastrointestinal system, pulmonary system, or within the brain. The condition typically progresses to bone marrow failure by the age of four.

TYPE II

Type II CAMT is associated with some activity from the thrombopoietin receptor protein, and therefore, symptoms tend to be milder. Individuals with type II may also present in infancy, though not necessarily immediately after birth. The condition may also be associated with bone marrow failure, though if it occurs, it usually is at a later age than type I (by age 10).

How common is Congenital Amegakaryocytic Thrombocytopenia?

The exact incidence of CAMT is unknown. Less than 100 individuals have been diagnosed worldwide. The incidence of CAMT may be more common among individuals of Ashkenazi Jewish descent.

How is Congenital Amegakaryocytic Thrombocytopenia treated?

Bone marrow transplantation (BMT)–also known as a stem cell transplant (SCT)–has been shown to successfully cure congenital amegakaryocytic thrombocytopenia, but there is an approximately 20% mortality rate associated with the procedure. When BMT/SCT is not performed, transient treatments (like platelet transfusion) may be helpful in the short term (though they cannot prevent all complications).

What is the prognosis for an individual with Congenital Amegakaryocytic Thrombocytopenia?

Without a successful BMT/SCT, CAMT is almost always fatal because of the development of bone marrow failure due to reduced levels of red blood cells, white blood cells, and platelets (aplastic anemia) and/or leukemia. Individuals with type I CAMT usually die in early childhood, whereas individuals with type II CAMT may survive longer without BMT/SCT.

Congenital Disorder of Glycosylation Type Ic

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ALG6.
Exons Sequenced: NM_013339:2-15.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Congenital Disorder of Glycosylation Type Ic?

Congenital disorders of glycosylation (CDG) are a group of conditions that affect glycosylation, a process that modifies proteins in the body. The CDG-I disease types are caused by defects in various steps of this process. As a result of this, a variety of symptoms may be seen in the CDG-I forms (a-z). CDG-Ic is caused by harmful genetic changes (mutations) in the *ALG6* gene, which leads to build-up of toxic proteins in the cell. CDG-Ic is the second most common CDG disorder, accounting for approximately 9% of reported CDG cases.

CDG-Ic affects many systems of the body, particularly the nervous system, resulting in poor muscle tone, developmental delay, behavioral problems, and intellectual disability in almost all cases. Brain abnormalities, impaired ability to coordinate movement, and seizures are also common. Many affected individuals have poor growth, autistic or behavioral problems, distinctive physical features, and skeletal abnormalities. Skeletal abnormalities include shortening of fingers and toes, limited joint extension, short arms, and scoliosis. Other symptoms, like bleeding problems, enlarged liver and spleen, enlarged heart, protein loss in the intestines, or pubertal abnormalities, may occur but are less typical.

How common is Congenital Disorder of Glycosylation Type Ic?

CDG-Ic has been reported in at least 89 individuals (most of Caucasian descent), but the global incidence is unknown. Milder presentations of CDG-Ic may be under-diagnosed and not yet recognized.

How is Congenital Disorder of Glycosylation Type Ic treated?

There is no cure for CDG-Ic; management of the condition involves treating symptoms of the disease. Early intervention and education planning may help improve cognition. Medications may help to control seizures. Parents of a young child with CDG-Ic should ensure the child gets the best possible nutrition to help with growth; some children will require a feeding tube. Early use of occupational, physical,

and speech therapy may be helpful in improving the child's long-term abilities in these areas. However, wheelchairs and other movement aids are often useful and become necessary. Laboratory tests are often used for monitoring of other functions in the body.

What is the prognosis for an individual with Congenital Disorder of Glycosylation Type Ic?

Some individuals with CDG-Ic die in infancy or early childhood, often due to infection, seizures, or protein loss in the intestines. Most individuals that live into adulthood will require a wheelchair. Adults are unlikely to be able to live independently, but most will be able to speak, albeit with some impairment.

Congenital Disorder of Glycosylation, MPI-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MPI.
Exons Sequenced: NM_002435:1-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Congenital Disorder of Glycosylation, MPI-Related?

Congenital disorder of glycosylation (CDG) MPI-related, caused by mutations in the *MPI* gene, is an inherited metabolic disorder that impairs the production of glycoproteins, which are proteins that have attached carbohydrates. This condition affects many systems of the body, but unlike most CDG disorders, it does not impact the nervous system. Intellect is not impacted in individuals with congenital disorder of glycosylation, MPI-related.

If left untreated, congenital disorder of glycosylation, MPI-related can cause a wide array of problems, including chronic diarrhea, failure to grow at the expected rate, loss of protein from the body, severe nausea and vomiting, low blood sugar (hypoglycemia), difficulty in forming blood clots, and liver disease. Because congenital disorder of glycosylation, MPI-related can be life-threatening, early diagnosis and treatment are important.

How Common Is Congenital Disorder of Glycosylation, MPI-Related?

CDG, MPI-related has been reported in less than 50 individuals, and its prevalence is unknown.

How Is Congenital Disorder of Glycosylation, MPI-Related Treated?

CDG, MPI-related is treated with oral supplements of mannose, a sugar. Individuals with the disease who begin mannose treatment show improvement in most of the symptoms associated with the condition. Treatment with mannose is lifelong and for some, heparin treatment can improve gastrointestinal issues that cause the body to lose protein. In some cases, liver disease worsens even with treatment, but in one case, symptom improvement was observed after a successful liver transplant.

What Is the Prognosis for an Individual with Congenital Disorder of Glycosylation, MPI-Related?

With early and regular treatment, an individual with CDG, MPI-related can live a near-normal life. Without treatment, the disease can be fatal. Generally, the prognosis varies depending on the severity of symptoms and the response to mannose treatment.

Congenital Disorder of Glycosylation, PMM2-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PMM2.
Exons Sequenced: NM_000303:1-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Congenital Disorder of Glycosylation, PMM2-related?

Congenital disorders of glycosylation (CDGs) are a group of inherited metabolic disorders caused by a disruption in the body's ability to attach sugar molecules to proteins (glycosylation) properly. There are many types of CDGs. CDG, PMM2-related is specifically caused by harmful genetic changes in the *PMM2* gene. The condition affects many parts of the body and is highly variable between individuals (even those in the same family). Some harmful changes in the *PMM2* gene are more severe and are incompatible with life, resulting in very early pregnancy loss. For infants who are born, the condition can generally be separated into three clinical phases as described below:

INFANTILE MULTISYSTEM PHASE:

Common symptoms during infancy include low muscle tone (hypotonia); slow growth; a lack of reflexes; almond-shaped, crossed eyes; and abnormal genitals. Additional features can include inverted nipples, an unusual distribution of body fat, and a large forehead. Approximately 20% of infants with the disease die within the first year of life. For those who survive the first year, many develop a particular type of limited vision that progresses to blindness (retinitis pigmentosa) and wasting away of the cerebellum.

LATE-INFANTILE AND CHILDHOOD PHASE:

This phase typically occurs between three to ten years. Symptoms include intellectual disability and delayed motor and speech development. Bone abnormalities, seizures, and stroke-like episodes may also occur.

ADULT STABLE DISABILITY PHASE:

This phase is typically between adolescence and early adulthood. Patients may develop an under-active thyroid (hypothyroidism), low blood sugar, and a decreased ability to form blood clots following an injury. Females with the disease often do not achieve sexual development. Additional features may include premature aging, enlarged liver and/or liver disease, heart problems, and kidney problems.

How common is CDG, PMM2-related?

CDG, PMM2-related, is the most common congenital disorder of glycosylation. The exact incidence is unknown but may be as common as 1 in 20,000 in some populations. It is most commonly reported in Denmark and other Scandinavian countries.

How is CDG, PMM2-related treated?

There is no cure for CDG, PMM2-related. Treatment for the condition is directed at managing the specific symptoms an individual has. This often means receiving care through a team of specialists that may include physicians, speech pathologists, occupational therapists, physical therapists, and social workers. Infants and children with CDG, PMM2-related will often benefit from receiving early intervention and other supportive services beginning at a young age. Adequate nutrition is required to assist with growth and development, and some individuals may require a feeding tube. Surgical or non-surgical measures may correct crossed eyes and ensure better vision. Medications may be prescribed to help control seizures. For individuals with an underactive thyroid gland, hormone therapy may be necessary. Wheelchairs and other movement aids can assist with mobility.

What is the prognosis for a person with CDG, PMM2-related?

Twenty percent of individuals with CDG, PMM2-related, die within the first year of life due to complications from the disease. Others may live into adulthood. Most are wheelchair-bound throughout their life. Some can speak and converse, although with some impairment. Most individuals with CDG, PMM2-related, cannot live independently but may accomplish specific tasks independently.

Congenital Hydrocephalus, CCDC88C-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CCDC88C.
Exons Sequenced: NM_001080414:1-30.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Congenital Hydrocephalus, CCDC88C-related?

Congenital hydrocephalus, CCDC88C-related, also known as congenital hydrocephalus 1 or HYC1, is a condition caused by harmful genetic changes (variants) in the *CCDC88C* gene. The condition is characterized by a build-up of fluid in the brain called hydrocephalus. Under normal circumstances, the fluid (cerebrospinal fluid) drains out of the brain down the spinal column. In congenital hydrocephalus, CCDC88C-related, the fluid does not drain properly. This causes the cavities (ventricles) of the brain to expand and can cause abnormalities in the brain to form. The other symptoms of congenital hydrocephalus, CCDC88C-related, are highly variable and include large head size (macrocephaly), seizures, mild to severe developmental delays or intellectual disability, and mild to severe motor delays. Other major organ systems are not typically affected.

A few reports in the literature suggest that carriers of a single harmful genetic change in the *CCDC88C* gene may be associated with adult-onset spinocerebellar ataxia (SCA). However, there is not enough evidence at this time to determine if all carriers are at risk for SCA.

How common is Congenital Hydrocephalus, CCDC88C-related?

The exact incidence of congenital hydrocephalus, CCDC88C-related, is unknown, but fewer than ten families have been published in the literature.

How is Congenital Hydrocephalus, CCDC88C-related, treated?

There is no cure for congenital hydrocephalus, CCDC88C-related. Treatment for the condition is directed at managing an individual's specific symptoms. Common interventions include placing a tube (shunt) in the brain that redirects cerebrospinal fluid to other parts of

the body. Seizures may be managed with medications. Early intervention and other supportive services can treat developmental and motor delays. As a result of the increased head size, many affected infants are delivered via cesarean section.

What is the prognosis for an individual with Congenital Hydrocephalus, CCDC88C-related?

Congenital hydrocephalus, CCDC88C-related, can be fatal if not treated. The prognosis depends on how severe the symptoms are. Placing a shunt as soon as possible can help increase the chances of survival and reduce the risk of more significant brain damage and physical disabilities. The prognosis will also depend on how many other brain abnormalities are present.

Congenital Insensitivity to Pain with Anhidrosis, NTRK1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: NTRK1.
Exons Sequenced: NM_002529:1-17.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Congenital Insensitivity to Pain with Anhidrosis, NTRK1-related?

Congenital insensitivity to pain with anhidrosis (CIPA), NTRK1-related, is an inherited condition that causes the inability to feel pain or sweat (anhidrosis), and intellectual disabilities. The condition is caused by harmful genetic changes (variants) in the *NTRK1* gene.

Individuals with CIPA, NTRK1-related, are unable to feel pain. This is often first noted when babies accidentally bite their tongue, lips, and fingers. Fractures, cuts, and other trauma are often not immediately noticed, increasing the risk of infection and slowing healing time. Repeated injuries can lead to scarring and nerve damage. Due to repeated injuries and lack of pain awareness, some people with CIPA, NTRK1-related, accidentally hurt themselves so severely that it can result in losing a body part (amputation). Individuals with CIPA, NTRK1-related, can also develop thick skin on the palms of their hands and feet (palmoplantar hyperkeratosis).

Individuals with CIPA, NTRK1-related, are also unable to sweat. Sweating is necessary for body temperature regulation. Without this ability, individuals can have recurrent fevers. In infants, these fevers can lead to seizures. Affected individuals are also at risk for experiencing abnormally low or high body temperatures due to poor temperature regulation.

Intellectual disabilities and behavior problems, such as hyperactivity, are common in individuals with CIPA, NTRK1-related. Young children can have weak muscles (hypotonia), which seems to improve as they age.

How common is Congenital Insensitivity to Pain with Anhidrosis, NTRK1-related?

Several genes can cause congenital insensitivity to pain, but the exact incidence is unknown. It is a rare disorder, with only a few hundred cases identified. It is thought to be more common in the Japanese and Israeli-Bedouin populations.

How is Congenital Insensitivity to Pain with Anhidrosis, NTRK1-related treated?

There is no cure for CIPA, NTRK1-related. Treatment involves minimizing the complications related to the condition. Affected individuals need close body temperature monitoring and should avoid exposure to extremely hot or cold environments. Inspections and exams for unrecognized injuries should be performed often. Individuals will need regular check-ups with their healthcare providers, including orthopedics, dentistry, pediatrics, dermatology, and ophthalmology. Children may benefit from early intervention to help with learning difficulties and emotional issues.

What is the prognosis for a person with Congenital Insensitivity to Pain with Anhidrosis, NTRK1-related?

Individuals with CIPA, NTRK1-related, require significant medical management. Their exact lifespan is unknown. However, some have survived into adulthood.

Congenital Myasthenic Syndrome, CHRNE-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CHRNE.
Exons Sequenced: NM_000080:1-12.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Congenital Myasthenic Syndrome, CHRNE-related?

Congenital myasthenic syndrome (CMS), CHRNE-related is an inherited condition that affects the ability of skeletal muscles to work correctly. Many different genes cause congenital myasthenic syndrome. CMS, CHRNE-related is caused by harmful changes (variants) in the *CHRNE* gene. Individuals with CMS, CHRNE-related, usually experience weak or underdeveloped muscles and poor muscle tone (hypotonia), typically of the muscles of the eyes and head. Common symptoms include drooping eyelids (ptosis) and paralysis or weakness of the eye muscles (ophthalmoplegia), double vision (diplopia), and trouble swallowing (dysphagia).

Many individuals with CMS, CHRNE-related, experience weakness in their arms or legs and quickly tire after exertion. The symptoms of CMS, CHRNE-related, can range from mild to severe. Some individuals may generally have mild symptoms that get suddenly worse after periods of illness or increased exertion. Some will experience changes in their muscle weakness depending on the time of day or between days. There are three subtypes of CMS, CHRNE-related. The type of CMS, CHRNE-related, is determined by the harmful changes in the *CHRNE* gene that an individual has and how those changes impact the gene. The subtypes also have different modes of inheritance. Some are caused by one harmful genetic change in the *CHRNE* gene (autosomal dominant inheritance), while the other subtypes are caused by two harmful changes in the *CHRNE* gene (autosomal recessive inheritance).

ACETYLCHOLINE RECEPTOR (ACHR) DEFICIENCY CONGENITAL MYASTHENIC SYNDROME

AChR deficiency CMS is the most common subtype of CMS. The symptoms of AChR deficiency CMS are typically present shortly after birth. Some individuals with the condition will have decreased movement in utero. Most individuals with this form of CHRNE-related CMS will have symptoms before age 2. However, a few people with the condition develop symptoms later in childhood or as adults. Infants typically have poor muscle tone, a weak ability to suck, a weak cry, and quickly get tired. Other symptoms may include distinct facial features, trouble breathing, or sleep apnea. This form of CMS, CHRNE-related, is caused by having two harmful changes in the *CHRNE* gene (autosomal recessive inheritance).

SLOW-CHANNEL CONGENITAL MYASTHENIC SYNDROME (SCCMS)

SCCMS is the least common subtype of CMS. There are only a few harmful changes that cause SCCMS. Symptoms of SCCMS are similar to those listed above. Individuals experience weakness primarily in the neck, wrist, and fingers. The onset of symptoms in SCCMS can happen at any stage of life. This form of CMS, CHRNE-related, is caused by having one harmful change in the *CHRNE* gene (autosomal dominant inheritance).

FAST-CHANNEL CONGENITAL MYASTHENIC SYNDROME (FCCMS)

The symptoms of FCCMS are nearly identical to AChR deficiency CMS. It is not possible to determine the difference between FCCMS and AChR deficiency CMS based on clinical presentation. This form of CMS, CHRNE-related, is caused by having two harmful changes in the *CHRNE* gene (autosomal recessive inheritance).

How common is Congenital Myasthenic Syndrome, CHRNE-related?

The exact incidence of congenital myasthenic syndrome is not known, but is estimated to be 1 to 9 in 1,000,000. The condition may be underdiagnosed. About fifty percent of cases of congenital myasthenic syndrome are caused by harmful changes in the *CHRNE* gene.

How is Congenital Myasthenic Syndrome, CHRNE-related treated?

Treatment for CMS, CHRNE-related is available primarily through medications. The type of medication used depends on the subtype that an individual has. Individuals with AChR deficiency CMS or FCCMS will benefit from using AChE inhibitors such as pyridostigmine or a potassium-channel blocker such as 3,4-diaminopyridine. AChE inhibitors are not effective in individuals with SCCMS. Instead, medications such as fluoxetine or quinidine are recommended for the treatment of SCCMS. Individuals who have sleep apnea may require ventilatory support at night. Depending on the symptoms an individual has, physical, occupational, or speech therapy may be helpful. Individuals may also use devices to help with movement such as orthotics or a wheelchair. Some individuals may need a tube to help with feeding. Determining an individual's subtype of CMS, CHRNE-related is not always possible based on the harmful change in the *CHRNE* gene. Individuals should speak with their healthcare provider to determine the most appropriate management.

What is the prognosis for an individual with Congenital Myasthenic Syndrome, CHRNE-related?

Individuals with CMS, CHRNE-related can live a relatively normal life with some intervention. Many patients respond very well to medications and often require no support for daily activities. Many individuals will get tired easily after physical exertion. A few individuals have difficulty walking, particularly later in life, and may need assistance.

Costeff Optic Atrophy Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: OPA3.
Exons Sequenced: NM_025136:1-2.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Costeff Optic Atrophy Syndrome?

Costeff optic atrophy syndrome (3-methylglutaconic aciduria type 3 (3-MGCA 3), caused by mutations in the *OPA3* gene, is a condition that causes individuals to experience both visual problems and involuntary spastic physical movements. These symptoms tend to worsen through childhood.

A hallmark of this condition is optic atrophy, a progressive loss of visual acuity beginning in the first few years of life. In some individuals, the eyes also show an involuntary horizontal back-and-forth movement.

The other defining symptom of this condition is chorea, a movement disorder that causes involuntary, unpredictable body movements. The onset of chorea generally begins before the age of 10. Most individuals will develop weakness and spasticity in the leg muscles along with a general lack of control of the body muscles and may have trouble maintaining their posture. Many, though not all, will need to use a wheelchair from an early age.

Some individuals with the condition may also develop mild cognitive problems between the ages of 10 and 20.

The severity of symptoms can vary from person to person, even among those in the same family.

How Common Is Costeff Optic Atrophy Syndrome?

This disease is most common in Iraqi Jews, in whom 1 in 10,000 newborns are affected by the disease. Only a few cases of the disease have been seen outside the Iraqi Jewish population.

How Is Costeff Optic Atrophy Syndrome Treated?

There is no cure for this condition. Treatments can only address symptoms as they arise and providers can attempt to maximize the patient's vision and address the movement problems. In many cases, a wheelchair will be necessary. Medical care is generally coordinated by a multidisciplinary team that includes a neurologist, an orthopedic surgeon, an ophthalmologist, a geneticist, and a physical therapist.

What Is the Prognosis for a Person with Costeff Optic Atrophy Syndrome?

While some individuals with this condition have been known to live into their thirties; life expectancy beyond that is unknown.

Creatine Transporter Deficiency

Available Methodologies: sequencing analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SLC6A8.
Exons Sequenced: NM_005629:1-13.

Detection Rate	Population
95%	African American
95%	Ashkenazi Jewish
95%	Eastern Asia
95%	Finland
95%	French Canadian or Cajun
95%	Hispanic
95%	Middle East
95%	Native American
95%	Northwestern Europe
95%	Oceania
95%	South Asia
95%	Southeast Asia
95%	Southern Europe
95%	Worldwide

What is Creatine Transporter Deficiency?

Creatine transporter deficiency (CRTR deficiency) is a condition characterized by intellectual disability. It is caused by harmful genetic changes (variants) in the *SLC6A8* gene. Individuals with this disorder have symptoms because their body cannot properly use an important substance called creatine. The body needs creatine to produce energy for the brain and muscle cells. Individuals with creatine transporter deficiency cannot move the creatine from their bloodstream into their cells. Because of this, the cells do not have enough energy to function correctly.

CRTR deficiency is an X-linked condition, meaning the *SLC6A8* gene is on the X-chromosome. Biological males have one copy of the X-chromosome (XY) and the *SLC6A8* gene, while biological females have two copies (XX). Because of this, CRTR deficiency primarily affects males, while most female carriers are unaffected. However, some females can have symptoms.

Symptoms in males with CRTR deficiency are typically noticed in infancy or early childhood. The first symptoms are typically a delay in reaching milestones, such as learning to crawl, walk, or speak. All males with this disorder have an intellectual disability. Some may have other symptoms, including behavioral issues such as autistic features or attention deficit hyperactivity disorder (ADHD), low muscle tone (hypotonia), abnormal movements, digestive problems, distinct facial features, and heart problems.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Some females with a harmful genetic change in *SLC6A8* have intellectual disability that is milder than what is seen in males. Others do not have any symptoms of the disorder. In rare cases, females have symptoms that are similar in severity to males.

How common is Creatine Transporter Deficiency?

The exact incidence of CRTR deficiency is unknown. Approximately 150 individuals have been diagnosed worldwide.

How is Creatine Transporter Deficiency treated?

There is no cure for CRTR deficiency. Individuals can take creatine and other nutritional supplements by mouth, leading to symptom improvement in some but not all people with the disorder. Other treatments are directed at managing the specific symptoms an individual has. Individuals diagnosed with CRTR deficiency will often benefit from receiving speech, physical, occupational, and behavioral therapies and other supportive services beginning at a young age. Medications may be used to manage seizures, behavioral issues, and abnormal movements.

What is the prognosis for an individual with Creatine Transporter Deficiency?

The prognosis depends on the severity of an individual's symptoms. Reports of males with CRTR living into their sixties indicate that a normal life expectancy is possible. All males with CRTR deficiency are expected to have an intellectual disability. Many cannot speak in complete sentences and need help with activities of daily living, such as dressing and feeding. They are not usually able to live independently.

Cystic Fibrosis

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CFTR.
Exons Sequenced: NM_000492:1-27.
IVS8-5T allele analysis is only reported in the presence of the R117H mutation.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Cystic Fibrosis?

Cystic Fibrosis (CF) is an inherited condition characterized by the production of abnormally thick, sticky mucus, particularly in the lungs and digestive system. It is caused by having at least two harmful genetic changes in the *CFTR* gene. Normally, the job of mucus is to protect and lubricate different organs. However, the thickened mucus produced by individuals with CF blocks and clogs various systems in the body. Individuals with CF can have a variety of symptoms ranging from mild to severe.

The severity of CF symptoms can generally be predicted by the specific genetic changes in the *CFTR* gene that an individual inherits, although the symptoms may vary somewhat from person to person (even among those with the same genetic changes). There are certain *CFTR* genetic changes that are associated with a broad spectrum of disease, which means that the symptom severity can vary significantly between individuals with the same genetic changes and is difficult to predict. Some individuals with these particular genetic changes have severe CF, while others might have mild CF, a CFTR-related disorder (CFTR-RD), or even no symptoms at all.

CYSTIC FIBROSIS

CF is usually diagnosed in infancy or early childhood. Severe forms of CF will typically involve multiple body parts including the lungs, pancreas, liver, and reproductive organs. Most individuals with CF experience breathing problems and frequent lung infections that lead to permanent lung damage such as scarring (fibrosis) and sac-like growths (cysts). The pancreas, an organ that produces important substances that help regulate blood sugar (insulin) and break down food (digestive enzymes), is often affected in individuals with severe CF. This prevents the body from digesting food properly resulting in diarrhea, malnutrition, and poor growth. Individuals with CF may develop CF-related diabetes as they age. Delayed puberty is also common among people with CF. Most men with the disorder have infertility due to congenital absence of the vas deferens (CAVD), a condition in which the vas deferens (a reproductive organ involved in sperm transport) fails to develop properly.

CFTR-RELATED DISORDERS

A few individuals with two harmful genetic changes in the *CFTR* gene have some health problems associated with CF, but are not formally diagnosed with the condition. These individuals are considered to have a CFTR-related disorder, which can include symptoms affecting only one body part (such as only the lungs or only the pancreas). Men may have CAVD causing infertility as the only symptom.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Most carriers do not experience any symptoms of CF. Rarely, carriers have symptoms of a CFTR-related disorder.

How common is Cystic Fibrosis?

The incidence of CF in the population is 1 in 3,000 births. The incidence of CF is more common among individuals of Northern European or Ashkenazi Jewish descent.

How is Cystic Fibrosis treated?

FDA approved medications are available for individuals with certain genetic changes in the *CFTR* gene. There are also many other options for treating the symptoms in everyone with CF, regardless of the genetic changes that are present. Because thick mucus can build up in the respiratory system, it is important to keep the patient's airways open to ease breathing and prevent infection. This can be accomplished with various prescription drugs as well as by physically loosening mucus by pounding on the patient's back in a specific way. This treatment, known as "postural drainage and chest percussion," can be performed by the affected person using a special vest or by someone other than the affected person, and is typically done at least once daily. As respiratory infections occur, doctors typically prescribe antibiotics.

Healthcare providers will also monitor the digestive system to ensure that the patient is getting proper nutrition. Medications such as enzymes or vitamin supplements may be prescribed. Both the respiratory and digestive systems of an individual with CF must be monitored regularly by a medical team.

Some men with CAVD may be able to have children with the use of assisted reproductive technologies.

Surgery may be needed to correct certain problems caused by CF, and lung transplant is an option for some individuals.

What is the prognosis for an individual with Cystic Fibrosis?

Individuals with CF have shortened lifespans. However, thanks to improved treatments and a better understanding of the condition, average life expectancy has been increasing over time. Many children who are born with CF today and receive proper treatment are expected to live into their fifties or sixties.

Cystinosis

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CTNS.
Exons Sequenced: NM_004937:3-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Cystinosis?

Cystinosis is an inherited disease that causes the amino acid cysteine to accumulate within body cells and form crystals which can damage the body's organs, particularly the kidneys and eyes. Without treatment, children with the condition will experience kidney failure around the age of 10.

There are three forms of cystinosis. The most severe form, nephropathic cystinosis, appears in infants. It causes poor growth and renal tubular Fanconi syndrome, a kidney disorder in which the organ eliminates certain essential nutrients and minerals. The loss of these nutrients inhibits normal body growth and may result in soft, bowed bones. Cysteine crystals also accumulate in the eyes, causing photophobia, an extreme sensitivity to light. Other symptoms may include muscle wasting, difficulty swallowing, diabetes, an underactive thyroid gland, and nervous system problems.

Less severe forms of the disease cause symptoms to begin later in life and may not affect the kidneys.

How common is Cystinosis?

Cystinosis affects approximately 1 in 200,000 people. The disease is most common in Brittany, France, where it affects 1 in 26,000.

How is Cystinosis treated?

Thanks to a drug called cysteamine, cystinosis has become easier to manage. Taken orally in capsules (brand name: Cystagon), it reduces the accumulation of cysteine crystals in the body. The drug has been shown to delay or prevent kidney failure and improve growth rates in children. Cysteamine eye drops have been successful in relieving photophobia in people with cystinosis, although they are not yet approved by the FDA for that purpose.

Nutritional monitoring is important in children with cystinosis. These children require a large amount of water to prevent dehydration. Supplements of several vitamins and minerals are also recommended for most people with the disease. Human growth hormone treatments have been shown to help people with cystinosis reach normal height.

Kidney transplants are an option for people with cystinosis. Cysteine crystals will not build up in the newly transplanted kidney, although they may still affect other organs of the body.

What is the prognosis for a person with Cystinosis?

Cystagon has extended the lifespan of people with cystinosis, but exact lifespan is not known. Some people with the disease have lived into their 50s.

D-bifunctional Protein Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: HSD17B4.
Exons Sequenced: NM_000414:1-24.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What Is D-Bifunctional Protein Deficiency?

D-bifunctional protein deficiency, also known as peroxisomal bifunctional enzyme deficiency, is an inherited disease causing severe biochemical abnormalities that are usually fatal within the first two years of life. D-bifunctional protein deficiency is the most severe among a group of diseases known as peroxisomal fatty acid oxidation disorders. Peroxisomes are structures within the cells of the body that are necessary for proper metabolism. D-bifunctional protein deficiency is caused by mutations in the *HSD17B4* gene.

Infants with D-bifunctional protein deficiency have poor muscle tone and typically experience seizures shortly after birth or within the first few months of life. They also demonstrate significant changes in brain structure, experience both vision and hearing impairment, and have severe developmental delays. Few infants with D-bifunctional protein deficiency achieve any developmental milestones. Children with D-bifunctional protein deficiency may also have enlargement of the liver and tend to share characteristic facial features.

How Common Is D-Bifunctional Protein Deficiency?

The estimated prevalence of D-bifunctional protein deficiency is 1 in 100,000 individuals.

How Is D-Bifunctional Protein Deficiency Treated?

There is no treatment for the underlying cause of D-bifunctional protein deficiency. Available treatments address the symptoms of the condition, such as the use of medications for seizures or placement of a feeding tube to ensure proper nutrition.

What Is the Prognosis for a Person with D-Bifunctional Protein Deficiency?

The prognosis for D-bifunctional protein deficiency is typically poor. Most children with the condition die within the first two years of life without achieving any developmental milestones.

Delta-sarcoglycanopathy

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SGCD.
Exons Sequenced: NM_000337:2-9.

Detection Rate	Population
96%	African American
96%	Ashkenazi Jewish
96%	Eastern Asia
96%	Finland
96%	French Canadian or Cajun
96%	Hispanic
96%	Middle East
96%	Native American
96%	Northwestern Europe
96%	Oceania
96%	South Asia
96%	Southeast Asia
96%	Southern Europe
96%	Worldwide

What is Delta-Sarcoglycanopathy?

Delta-sarcoglycanopathy, caused by harmful genetic changes (mutations) in the *SGCD* gene, is a group of disorders that typically cause muscle weakness. Symptoms of the disease vary greatly from person to person, even among individuals in the same family. Some individuals with the disease can have a mild course, where they are nearly asymptomatic, while others may have severe symptoms that can be fatal. Presentations of this condition are described below.

LIMB-GIRDLE MUSCULAR DYSTROPHY TYPE 2F

Individuals with limb-girdle muscular dystrophy type 2F (LGMD2F) develop symptoms at variable ages, though symptoms tend to present in early childhood. LGMD2F does not affect intelligence or mental function; the primary symptom is worsening (progressive) muscle weakness of the hip, shoulder, and abdomen. The rate at which the muscles weaken can vary, but often results in a wheelchair becoming necessary. Other features include enlarged calf muscles, shortening and hardening of muscles leading to rigid joints (contractures), prominence (winging) of the shoulder blades, and curvature of the spine (scoliosis). Respiratory complications (seen in ~20% of affected individuals) or heart complications (e.g., arrhythmia, cardiomyopathy) are also associated with these conditions and may lead to death.

DILATED CARDIOMYOPATHY TYPE 1L

Individuals have also been described with only weakening of the heart muscle (dilated cardiomyopathy).

How common is Delta-Sarcoglycanopathy?

The incidence of autosomal-recessive limb-girdle muscular dystrophy (LGMD) is 1 in 15,000 individuals, with LGMD2F accounting for a small subset of all cases of LGMD, though this varies by region. LGMD2F is more common in the Brazilian population.

How is Delta-Sarcoglycanopathy treated?

There is no cure for delta-sarcoglycanopathy and few effective treatments. Physical therapy helps retain muscle strength and mobility for as long as possible. Mobility aids, such as walkers, canes, braces, and wheelchairs, may become necessary. As muscles deteriorate, a machine that assists with breathing (a ventilator) may be needed. Cardiac surveillance is recommended, and individuals who develop heart problems should consult a heart specialist (cardiologist) for symptomatic treatments. Some individuals may need surgery if they develop scoliosis or contractures.

What is the prognosis for an individual with Delta-Sarcoglycanopathy?

The outlook for an individual with delta-sarcoglycanopathy varies. Generally, the earlier symptoms begin, the faster they progress. However, because symptoms and onset can be variable, prognosis can be variable. In individuals with more severe symptoms, use of a wheelchair may become necessary in their early teens and death may occur in early adulthood. Causes of early death include respiratory and cardiac complications.

Dihydrolipoamide Dehydrogenase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: DLD.
Exons Sequenced: NM_000108:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Dihydrolipoamide Dehydrogenase Deficiency (E3 Deficiency)?

Dihydrolipoamide Dehydrogenase Deficiency also known as E3 deficiency, caused by mutations in the *DLD* gene, is an inherited condition resulting in the deficiency of the enzyme dihydrolipoamide dehydrogenase, which disrupts multiple enzyme complexes that help break down substances in cells. This condition can cause metabolic abnormalities, neurological damage, poor muscle tone, developmental delay, and movement problems. Infants with E3 deficiency often appear normal until the age of eight weeks to six months, when they develop a severe buildup of lactic acid in the body (lactic acidosis) that causes vomiting, abdominal pain, and rapid breathing. If untreated, this condition can be fatal. Infants and children with the disease can have developmental delay and a progressive breakdown of their nervous system. They often have poor muscle tone (hypotonia) and abnormal movements. The disease is also called maple syrup urine disease type 3, due to the characteristic maple-syrup-like smell of their urine.

How Common Is E3 Deficiency?

The prevalence of E3 deficiency in the general population is unknown. The majority of known cases come from families of Ashkenazi Jewish background, where the prevalence is 1 in 35,000 to 1 in 48,000.

How Is E3 Deficiency Treated?

There is no established treatment for E3 deficiency. Combinations of diet, vitamins, and supplements have been tried without much success.

What Is the Prognosis for an Individual with E3 Deficiency?

While the number of known cases does not allow for a well-established prognosis, it is thought that most individuals with E3 deficiency will die during childhood.

Dihydropyrimidine Dehydrogenase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: DPYD.
Exons Sequenced: NM_000110:1-23.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Dihydropyrimidine Dehydrogenase Deficiency?

Dihydropyrimidine dehydrogenase deficiency (DPD deficiency), also known as hereditary thymine-uraciluria, is an inherited disease caused by the absence of a protein called dihydropyrimidine dehydrogenase. This protein is needed for breaking down the molecules thymine and uracil, as well as fluoropyrimidines, when present in the body. DPD deficiency is caused by harmful changes (variants) in the *DPYD* gene.

All individuals with DPD deficiency cannot properly break down a class of medications called fluoropyrimidines. Fluoropyrimidine is most commonly used as a chemotherapy agent (5-fluorouracil) but has also been used in eye treatments and as a topical agent for skin conditions. If given fluoropyrimidine, individuals will have a severe toxic reaction that could be life-threatening. Signs of this reaction include diarrhea, swelling, digestive problems, muscle weakness, and an inability to coordinate muscle movement.

Unless they receive treatment with 5-fluorouracil, most individuals with the harmful changes that cause DPD deficiency have no symptoms at any time in their lives. However, some individuals may have severe symptoms in infancy or childhood. These can include neurological symptoms, including seizures, intellectual disability, and a delay in motor skills. Less common symptoms include autism, a small head, a delay in physical growth, eye abnormalities, and speech difficulties.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Carriers of DPD deficiency are also at risk for toxicity following treatment with fluoropyrimidines.

How common is Dihydropyrimidine Dehydrogenase Deficiency?

Though the severe presentation of this disorder is thought to be rare, the incidence of this condition is unknown. Many individuals are asymptomatic. Approximately 3 - 8% of the general population is at risk for fluoropyrimidine toxicity.

How is Dihydropyrimidine Dehydrogenase Deficiency treated?

There is no cure for DPD deficiency. The symptoms can only be addressed as they arise (e.g., by medication to prevent seizures). To avoid a toxic reaction, individuals with this disease must not take fluoropyrimidine drugs.

What is the prognosis for an individual with Dihydropyrimidine Dehydrogenase Deficiency?

For those who are asymptomatic, the prognosis is very good. Their lifespan should be unaffected by the disease. For those with more severe symptoms, it is unknown how these symptoms affect lifespan.

Distal Renal Tubular Acidosis with Deafness, ATP6V1B1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ATP6V1B1.
Exons Sequenced: NM_001692:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Distal Renal Tubular Acidosis, ATP6V1B1-related?

Distal renal tubular acidosis (dRTA), ATP6V1B1-related, is an inherited condition that causes kidney problems and hearing loss. The condition is caused by harmful genetic changes (variants) in the *ATP6V1B1* gene.

One of the kidney's functions is to help maintain acid balance within the body. Individuals with dRTA, ATP6V1B1-related, cannot remove enough acidic substances through urination, leading to a high acid level in the bloodstream. The increased levels of acid in the body result in feeding difficulties, poor weight gain, growth deficiency, problems with bone development (rickets and osteomalacia), and kidney stones. Initial symptoms are observed in infancy and often include vomiting and dehydration. Progressive hearing loss often develops in infancy and results from changes within the inner ear. In most cases, hearing loss affects both ears.

How common is Distal Renal Tubular Acidosis, ATP6V1B1-related?

Distal renal tubular acidosis, ATP6V1B1-related, is considered a rare disorder. While its exact incidence is unknown, the condition is more common in certain ethnic groups, such as the North African and Mediterranean populations.

How is Distal Renal Tubular Acidosis, ATP6V1B1-related, treated?

Individuals with dRTA, ATP6V1B1-related, require treatment throughout their lifetime. Treatment involves the use of medications to balance out the high level of acids in the body and to reduce the risk of kidney stones and other complications. Some patients may also require potassium supplements. Hearing aids and cochlear implants are options for those with hearing loss.

What is the prognosis for a person with Distal Renal Tubular Acidosis, ATP6V1B1-related?

With early and consistent treatment, the prognosis is good. Symptoms related to the excess acid, such as bone problems, growth issues, and kidney stones, may be improved or prevented. However, treatment does not improve hearing. In the absence of adequate treatment, continued acidosis may eventually lead to kidney failure.

Donnai–Barrow Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: LRP2.
Exons Sequenced: NM_004525:1-79.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Donnai-Barrow syndrome?

Donnai-Barrow syndrome (DBS) is an inherited condition characterized by hearing and vision problems, issues with brain development (agenesis of the corpus callosum), kidney disease, and characteristic facial features. It is caused by harmful genetic changes (variants) in the *LRP2* gene.

The symptoms of DBS are usually present at birth. Up to 40% of infants may be born with a hole in the muscle of their chest or abdomen (diaphragmatic hernia or omphalocele). Almost all individuals with DBS may have intellectual disability and developmental delay. Many individuals have seizures and heart problems. As individuals with the condition get older, they can develop problems with their kidneys.

How common is Donnai-Barrow syndrome?

The exact incidence of Donnai-Barrow syndrome is unknown. Less than 100 individuals have been diagnosed worldwide.

How is Donnai-Barrow syndrome treated?

There is no cure for Donnai-Barrow syndrome. Treatment for the condition is directed at managing an individual's specific symptoms. Common interventions may include hearing aids or cochlear implants for hearing loss, glasses to correct vision and preventative treatments for serious eye problems. Special educational programs for the hearing impaired, vision impaired, and those with intellectual disabilities may be helpful. Seizures are addressed with medications. Surgery may address birth defects related to the heart, abdomen, and diaphragm.

What is the prognosis for an individual with Donnai-Barrow syndrome?

The prognosis for a child with Donnai-Barrow syndrome is not well known because the condition is so rare. Some individuals with Donnai-Barrow syndrome die within the first year of life due to birth defects. Individuals who survive into adolescence may experience vision and hearing loss as well as intellectual disability. Progressive kidney disease can lead to life-threatening kidney failure in adulthood.

DYNC2H1-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: DYNC2H1.
Exons Sequenced: NM_001377:1-89.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What are DYNC2H1-related Disorders?

DYNC2H1-related disorders are a group of inherited conditions that affect tiny hair-like structures that are present on some cells (cilia). Cilia play an essential role in the development of tissues including bone and cartilage as well as other organs, such as the eyes, kidneys, heart, pancreas, and intestines. DYNC2H1-related disorders belong to a larger group of diseases called skeletal ciliopathies, all of which involve problems with bone formation due to abnormal cilia. DYNC2H1-related disorders are caused by harmful genetic changes (variants) in the *DYNC2H1* gene.

DYNC2H1-related disorders can be classified into three different types: short-rib polydactyly syndrome, short-rib thoracic dysplasia (formerly known as asphyxiating thoracic dysplasia or Jeune syndrome), and chondroectodermal dysplasia (also known as Ellis-van Creveld syndrome). Although these types have many of the same features, they vary significantly in severity and prognosis.

SHORT-RIB POLYDACTYLY SYNDROME

Short-rib polydactyly syndrome (SPRS) is the most severe of the disorders caused by the *DYNC2H1* gene. Shortened ribs with a very narrow thorax prevent the lungs from fully developing, which is typically lethal in the neonatal period. Other skeletal changes include severe shortening of the bones in the arms and legs (dwarfism), short hands, and extra fingers and/or toes (polydactyly). Birth defects of the heart, brain, roof of the mouth (palate), kidneys, genitalia, and gastrointestinal tract may be present.

SHORT-RIB THORACIC DYSPLASIA

Short-rib thoracic dysplasia (formerly known as asphyxiating thoracic dysplasia or Jeune syndrome) also causes a narrow thorax due to short ribs, but the narrowing can vary from mild to severe. Shortening of the arms and legs (dwarfism) and small hands are typical features, but extra fingers are not typically present in this form. Cystic kidney disease is common in childhood, and some individuals may have complications with the liver and pancreas. Some have reduced vision or deteriorating vision due to problems with the back of the eye (retina).

CHONDROECTODERMAL DYSPLASIA

Chondroectodermal dysplasia (also known as Ellis-van Creveld syndrome) causes short ribs with a narrow thorax, variably short arms and legs, and extra fingers and toes (polydactyly). Individuals with chondroectodermal dysplasia often have heart defects, and some may also have malformed fingernails and toenails, as well as missing, small, or abnormally-shaped teeth.

How common are DYNC2H1-related Disorders?

The exact incidence of short-rib polydactyly syndrome is unknown, as it is a rare disease.

The incidence of short-rib thoracic dysplasia is approximately 1 in 100,000 to 1 in 130,000 births, and up to 50% of cases can be attributed specifically to the *DYNC2H1* gene.

The incidence of chondroectodermal dysplasia is approximately 1 in 60,000 to 1 in 200,000 births. A number of other genes are known to cause chondroectodermal dysplasia, and in some individuals the cause is unknown. Approximately 7% of chondroectodermal dysplasia cases are caused by harmful changes in *DYNC2H1*.

How are DYNC2H1-related Disorders treated?

There is no cure for DYNC2H1-related disorders. Treatment is directed at managing the specific symptoms an individual has. Many individuals with the most severe forms will pass away before birth or within the first few days of life due to lung problems. Respiratory support, such as a machine to help them breathe, may be needed for those who survive the neonatal period. Chronic lung infections can be treated with medicine. Surgery may be indicated to repair heart defects or cleft palate. Individuals with kidney, liver, pancreas, and/or eye disease may need to be seen by medical specialists. Orthopedists can monitor for skeletal complications. Physical and occupational therapy may be helpful for individuals with significant limb differences.

What is the prognosis for an individual with DYNC2H1-related Disorders?

The prognosis for individuals with DYNC2H1-related disorders depends on how much the lungs are able to develop, which is determined by the size of the ribs/thorax. Individuals with the more severe forms (specifically short-rib polydactyly syndrome) are typically stillborn or pass away within the first few days of life. Although some will pass away in infancy or within the first few years of life, some individuals with milder presentations (short-rib thoracic dysplasia or chondroectodermal dysplasia) can survive into adolescence or longer. There are limited reports about the health outcomes for affected individuals past the age of 20.

Dysferlinopathy

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: DYSF.
Exons Sequenced: NM_003494:1-55.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Dysferlinopathy?

Dysferlinopathy represents a spectrum of disorders that cause muscle weakness as a result of a deficiency of the protein, dysferlin. Symptoms of the disease vary greatly from person to person, even among people in the same family. Some people with the disease can have a mild course, while others may have severe symptoms that can be fatal. Common presentations of this condition are described below.

LIMB-GIRDLE MUSCULAR DYSTROPHY TYPE 2B

People with limb-girdle muscular dystrophy type 2B (LGMD2B) develop symptoms at variable ages. Symptoms can present at as early as 14 years of age, although onset in adulthood is possible. LGMD2B does not affect intelligence or mental function; the primary symptom is progressive muscle weakness of the hip, shoulder, and abdomen (proximal muscles). The rate at which the muscles weaken can vary greatly, but many experience progressive weakness to a point where a wheelchair becomes necessary.

Many individuals with LGMD2B live well into adulthood with respiratory failure being the most common cause of death. However, a minority of people with LGMD2B experience respiratory complications (~20%) or heart complications (~10%). Involvement of the heart muscles is less common in type 2B than in other forms of limb girdle muscular dystrophy.

MIYOSHI MUSCULAR DYSTROPHY TYPE 1

Miyoshi muscular dystrophy type 1 (MMD1) is also associated with muscle weakness, but the muscles involved are those away from the center of the body (distal muscles), such as the legs and calves. Progression tends to be slower.

OTHER

Other presentations include distal myopathy with anterior tibial onset (initially distal muscle weakness that progressives to the proximal muscles) and scapuloperoneal syndrome (distal muscle weakness with weakness in the shoulder muscles). A few case reports of congenital muscular dystrophy (severe presentation with extremely poor prognosis) have also been reported.

How common is Dysferlinopathy?

There are numerous types of limb-girdle muscular dystrophy. LGMD has an estimated prevalence of 1 in 15,000 individuals. LGMD2B is thought to account for ~5% of all cases of LGMD, though this varies by region. For example, in Japan, LGMD2B accounts for ~19% of all cases of LGMD and 75% of all cases of Miyoshi muscular dystrophy. In addition, LGMD2B is most commonly found in individuals of Libyan and Caucasus Jewish descent.

How is Dysferlinopathy treated?

There is no cure for dysferlinopathy and few effective treatments. Physical therapy is often recommended to retain muscle strength and mobility for as long as possible. Stretching, mechanical aids, or surgery may aid in that goal. As muscles deteriorate, a ventilator may be required to aid breathing. Those who develop heart problems should consult with a cardiologist for symptomatic treatments.

What is the prognosis for a person with Dysferlinopathy?

The outlook for a person with dysferlinopathy varies. Generally, the earlier symptoms begin, the faster they progress. Some people with the disease experience only mild symptoms, and may have near-normal strength. Others with a mild course may remain able to walk for 30 years or more after symptoms appear. People with more severe disease typically become wheelchair-bound approximately 20 years after their diagnosis.

Dystrophic Epidermolysis Bullosa

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: COL7A1.
Exons Sequenced: NM_000094:1-118.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Dystrophic Epidermolysis Bullosa (DEB)?

Dystrophic epidermolysis bullosa (DEB) is a condition characterized by blistering of the skin and, in some cases, other areas of the body. It is caused by harmful genetic changes (variants) in the *COL7A1 gene*.

Individuals with DEB have very fragile skin that blisters easily in response to minor trauma, such as bumps, scrapes, or rubbing. Abnormalities of the fingernails and toenails (dystrophic nails) are also present. In some cases, an individual must have two variants in *COL7A1* to develop symptoms, and this is known as "recessive DEB" (RDEB). Other individuals with only one *COL7A1* variant develop symptoms, and this is called "dominant DEB" (DDEB).

There are multiple subtypes of DEB that vary in severity and in which areas of the body the blisters occur. The most common subtypes of DEB include severe, intermediate, and localized. There are also rarer forms, including the inversa, pruriginosa, and self-improving forms. Most individuals with recessive DEB will develop either the severe or intermediate form of the condition. Individuals with dominant DEB most commonly have the intermediate or localized form of the condition, though the pruriginosa or self-improving forms can also occur.

SEVERE

The severe form occurs in individuals with recessive DEB but does not occur with dominant DEB. In this form of the condition, blisters begin developing at birth and can be found all over the skin, mouth, throat, and eyes. Blisters can become infected and, as they heal, form scars. These scars lead to other complications, such as difficulty feeding, anemia, growth issues, vision loss, kidney issues, the fusion of the fingers and toes (pseudo-syndactyly), and loss of joint mobility (joint contractures). Babies may also be born with patches of missing skin (aplasia cutis congenita). Individuals with severe DEB are at high risk of developing squamous cell carcinoma (SCC), a type of skin cancer. SCC is often diagnosed in early adulthood, and around 90% of individuals will develop SCC by age 55.

INTERMEDIATE

In this form, blistering typically begins in the newborn period but is milder than in severe DEB, and individuals are less likely to develop complications from scarring. The risk for SCC is much lower in individuals with intermediate DEB.

LOCALIZED

Individuals with the localized form of DEB have symptoms that are limited to particular areas of the body, such as blistering of hands, feet, shins, and abnormalities of the nails.

OTHER RARER FORMS

There are several rare forms of DEB. The inversa form causes blistering that is mainly on the torso, thighs, and legs beginning at birth. Individuals with the pruriginosa form have blistering that is limited to the shins, and this may not develop until childhood or even adulthood. There is also a rare self-improving form, in which the tendency to blister improves with age.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Some individuals who carry only one variant in *COL7A1* have dominant DEB (DDEB). Not everyone who carries a single variant in *COL7A1* will develop symptoms of DDEB. In some cases, it can be difficult to predict whether a particular *COL7A1* variant will cause symptoms of DDEB. Carriers of a *COL7A1* variant should speak with their healthcare provider to determine the most appropriate management options for them.

How common is Dystrophic Epidermolysis Bullosa?

The incidence of DEB in the population is between 3 in 1,000,000 – 6 in 1,000,000 births.

How is Dystrophic Epidermolysis Bullosa treated?

There is no cure for DEB. Treatment for the condition is directed at managing an individual's specific symptoms. Common interventions may include draining and bandaging blisters and giving medications to help manage pain, itching, and infections. If a fetus is known to have dystrophic epidermolysis bullosa, cesarean delivery may be recommended to avoid damage to the skin during birth. For individuals with issues related to feeding and nutrition, supplements and/or a feeding tube may be helpful.

What is the prognosis for an individual with Dystrophic Epidermolysis Bullosa?

The prognosis depends on the specific subtype and severity of DEB. Many individuals with the severe form of DEB live into young adulthood. SCC is the most common reason for early death for individuals with severe DEB. In rare cases, some infants pass away from infection. Survival is often longer for individuals with other forms of DEB, and many of those individuals have a normal life expectancy.

Dystrophinopathy (Including Duchenne/Becker Muscular Dystrophy)

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: DMD.
Exons Sequenced: NM_004006:1-79.

Detection Rate	Population
99%	African American
99%	Ashkenazi Jewish
99%	Eastern Asia
99%	Finland
99%	French Canadian or Cajun
99%	Hispanic
99%	Middle East
99%	Native American
99%	Northwestern Europe
99%	Oceania
99%	South Asia
99%	Southeast Asia
99%	Southern Europe
99%	Worldwide

What are Dystrophinopathies (including Duchenne/Becker Muscular Dystrophy)?

Dystrophinopathies are a group of conditions that generally cause muscle weakness. There are two main forms of dystrophinopathies related to the *DMD* gene: Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD). Both DMD and BMD are caused by harmful genetic changes or mutations in the *DMD* gene. DMD and BMD are X-linked conditions, which means that the *DMD* gene is on the X-chromosome. Males have one copy of the X-chromosome and the *DMD* gene, while females have two copies. Because of this, DMD and BMD primarily affect males, while most female carriers are unaffected. However, it is possible for some females with a mutation in the *DMD* gene to have symptoms.

Common presentations of DMD and BMD are described below. It is not always possible to predict, based on a genetic testing result, which of the presentations could occur in a child who has a mutation in the *DMD* gene. Additionally, there have been rare reports of males with a mutation in the *DMD* gene who do not have the characteristic symptoms described below.

DUCHENNE MUSCULAR DYSTROPHY

The primary symptoms of DMD are weakness and breakdown of muscles, which get worse over time. Symptoms typically begin in early childhood, with weakness in the muscles of the hips, pelvic region, thighs, and shoulders. This results in an abnormal way of walking (gait) and in delays to sitting up, standing, and walking (general motor skills). A small percentage of males also develop learning difficulties early in life, though the level of intellectual disability is variable. Because DMD gets worse over time, most affected individuals will need a wheelchair by 13 years of age. By the mid-teenage years, the heart muscles will weaken (this is known as dilated cardiomyopathy or DCM), as will the respiratory muscles. This weakening causes a shortened life expectancy.

BECKER MUSCULAR DYSTROPHY

BMD also causes muscle weakness and DCM. However, symptoms are much more variable in presentation, may be milder, and tend to develop later than DMD. Individuals with BMD also generally have a longer life expectancy than those with DMD.

DMD-ASSOCIATED DILATED CARDIOMYOPATHY

DMD-associated dilated cardiomyopathy (DMD-associated DCM) may occur without any muscle weakness, and both males and females are at risk of developing this condition. However, its onset is generally earlier in males than in females, and progression tends to be more rapid.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

While most individuals affected with DMD and BMD are males, females who carry mutations in the *DMD* gene may rarely experience symptoms. Less than 5% of carriers will experience muscle weakness as an adult, but the severity of symptoms depends on whether the mutations in the *DMD* gene is associated with BMD or DMD. Up to 17% of female carriers will have heart problems, including DCM.

How common are Dystrophinopathies (including Duchenne/Becker Muscular Dystrophy)?

Together, the incidence of DMD and BMD is an estimated 1 in 3,000 males. Approximately 1/3 of individuals affected by DMD or BMD do not inherit a mutation from a carrier mother (a *de novo* mutation). Note: because this is an X-linked condition, estimates of frequency generally do not include affected females.

How are Dystrophinopathies (including Duchenne/Becker Muscular Dystrophy) treated?

There is no cure for *DMD*-related dystrophinopathy; a combination of physical therapy, medication, and regular cardiac and respiratory screenings is the current standard practice for treating the condition. Carrier females are at an increased risk for DCM and should also regularly see a cardiologist.

What is the prognosis for individuals with Dystrophinopathies (including Duchenne/Becker Muscular Dystrophy)?

The prognosis for DMD is variable, but most males will be wheelchair-dependent by age 13 and die before 30 years of age due to heart or respiratory failure. Males who have BMD have a longer life expectancy, typically reaching into their forties or fifties. The prognosis in females is generally better, but those with DCM may still have a shortened lifespan. In rare cases, males with a mutation in the *DMD* gene may not experience the characteristic symptoms of dystrophinopathies.

Ehlers-Danlos Syndrome, ADAMTS2-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ADAMTS2.
Exons Sequenced: NM_014244:1-22.

Detection Rate	Population
92%	African American
92%	Ashkenazi Jewish
92%	Eastern Asia
92%	Finland
92%	French Canadian or Cajun
92%	Hispanic
92%	Middle East
92%	Native American
92%	Northwestern Europe
92%	Oceania
92%	South Asia
92%	Southeast Asia
92%	Southern Europe
92%	Worldwide

What is Ehlers-Danlos Syndrome, ADAMTS2-related?

Ehlers-Danlos syndrome, ADAMTS2-related, also known as Ehlers-Danlos syndrome type VIIC (EDS VIIC), is an inherited condition that causes connective tissue abnormalities. There are several types of Ehlers-Danlos syndrome that have different causes. Ehlers-Danlos syndrome, ADAMTS2-related, is caused by harmful genetic changes (variants) in the *ADAMTS2* gene. Typical features of all types of EDS include extremely fragile skin and extra skin that may sag. Individuals with EDS, ADAMTS2-related, are prone to bruising and scarring and have very flexible joints.

Children with EDS, ADAMTS2-related, are also often born early due to premature rupture of the amniotic sac. Some infants have skull fractures or large tears in the skin (lacerations) at birth. Fragile tissue within internal organs puts children at risk for serious complications such as bladder rupture and out-pouching of organs (hernias). Other features include short stature and missing or abnormal teeth in older children.

How common is Ehlers-Danlos Syndrome, ADAMTS2-related?

EDS, ADAMTS2-related, is a rare condition. Varied presentations of EDS, ADAMTS2-related, may not be recognized as of yet. There have been less than 100 reported cases worldwide. The global incidence is unknown.

How is Ehlers-Danlos Syndrome, ADAMTS2-related treated?

There is no cure for EDS, ADAMTS2-related. Treatment focuses on symptoms as they arise. Surgery can be performed to repair hernias or other problems but is often complicated by the fragility of the tissue. Many patients benefit from pain management treatment. Individuals with EDS, ADAMTS2-related, will need to work with a team of healthcare providers, including physical and occupational therapists, dermatologists, and surgeons.

What is the prognosis for a person with Ehlers-Danlos Syndrome, ADAMTS2-related?

Due to the rarity of the condition, the prognosis is unknown. Some infants with EDS, ADAMTS2-related, have died due to surgical complications. However, there are reports of children living into their second decade.

Enhanced S-cone Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: NR2E3.
Exons Sequenced: NM_014249:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Enhanced S-Cone Syndrome?

Enhanced S-cone syndrome (ESCS), or Goldmann-Favre syndrome, affects part of the eye (retina) and causes vision loss. ESCS is caused by harmful genetic changes (variants) in the *NR2E3* gene. The age at which vision loss starts, how quickly it gets worse, and how severe it is can vary from person to person. However, all affected individuals have a characteristic wave pattern on an electroretinogram, a diagnostic test that measures the electrical activity of the retina cells in response to light.

Symptoms can start anytime from early childhood to early adulthood. The first symptom is usually being unable to see in dim light or at night (nyctalopia). Many individuals start to squint to try and improve their vision. In the most severe form, individuals develop severe vision loss (20/200, which is considered legally blind) within the second decade of their life and often develop cataracts. Other individuals may only experience mild vision loss that requires strong reading glasses.

ESCS is typically inherited in an autosomal recessive manner, meaning an individual must have two harmful changes (one from each parent) in the *NR2E3* gene to have the symptoms. However, certain harmful genetic changes may be inherited in an autosomal dominant manner, meaning an individual only needs one harmful change in the *NR2E3* gene to have symptoms. In the dominant form of the condition, affected individuals often have one affected parent.

How common is Enhanced S-Cone Syndrome?

ECSC is rare, with an incidence of less than 1 in 1 million. Other presentations of ECSC may not be recognized as of yet.

How is Enhanced S-Cone Syndrome treated?

Currently, there is no effective treatment, but visual function can be improved with low-vision aids such as magnifying reading glasses, magnifiers, and small telescopes. Cataract surgery may be beneficial. Therapy with vitamin A palmitate may slow retinal degeneration for some individuals with retinitis pigmentosis. Individuals may also benefit from counseling and lifestyle therapy to help manage their progressive vision loss.

What is the prognosis for a person with Enhanced S-Cone Syndrome?

ESCS does not affect a person's lifespan or any other body part besides the eye. Services for those with progressive eye disorders can help increase their quality of life.

ERCC2-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ERCC2.
Exons Sequenced: NM_000400:1-23.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What are ERCC2-related Disorders?

ERCC2-related disorders are characterized by increased sensitivity to sunlight (photosensitivity), which leads to severe sunburns with minimal sun exposure. They are caused by harmful genetic changes (variants) in the *ERCC2* gene. The *ERCC2* gene plays an important role in regulating other genes in the body. It also helps repair DNA damage that regularly occurs throughout a person's life. In individuals with ERCC2-related disorders, the *ERCC2* gene cannot correctly perform these critical functions, which leads to symptoms.

ERCC2-related disorders can include several forms: Xeroderma Pigmentosum (XP), Xeroderma Pigmentosum/Cockayne syndrome complex (XP/CS complex), Trichothiodystrophy (TTD), and Cerebro-oculofacial-skeletal syndrome (COFS). It is difficult to predict which form an individual will develop based on their specific genetic changes. Some individuals have features that overlap with multiple ERCC2-related disorders.

XERODERMA PIGMENTOSUM

The name xeroderma pigmentosum (XP) comes from two of its common characteristics: dry skin (xeroderma) and skin color changes (pigmentosum). Extreme sun sensitivity is present from birth and causes people with XP to have a very high risk of skin cancer, which may arise in childhood. It may also result in eye abnormalities, such as vision loss, dry eyes, damage to the outer layer of the eye (cornea), light sensitivity (photophobia), cancerous and non-cancerous tumors, and loss of the eyelids. Individuals also have a higher than average risk of developing cancers elsewhere in the body, such as the tongue, thyroid, and nervous system. Approximately 25% of individuals with XP have neurologic issues, including learning issues, hearing loss, small head size (microcephaly), coordination issues (ataxia), and seizures. For some individuals, these neurological issues start during infancy, whereas in others, they will not develop until adulthood. Several genes can cause XP, and XP that is caused by genetic changes in the *ERCC2* gene is referred to as Xeroderma Pigmentosum type D (XPD).

XERODERMA PIGMENTOSUM/COCKAYNE SYNDROME COMPLEX

Rarely individuals can have symptoms of xeroderma pigmentosa and another disorder called Cockayne syndrome (CS). When this occurs, an individual is said to have xeroderma pigmentosum/Cockayne syndrome complex (XP/CS complex). Additional symptoms in these individuals can include distinct facial features, growth issues, intellectual disability, hearing loss, and brain abnormalities.

TRICHOTHIODYSTROPHY

Trichothiodystrophy (TTD) is characterized by brittle hair and skin abnormalities, such as dry, scaly skin and eczema. Other symptoms include distinct facial features, intellectual disability, poor growth, frequent infections, nail and eye abnormalities, tremor, and coordination issues. Babies are often born early, have low birth weight, and are small for gestational age. People with trichothiodystrophy are sensitive to the sun and may sunburn easily, but they do not have a significantly increased risk to develop skin cancer. Several genes can cause TTD. TTD caused by genetic changes in the *ERCC2* gene is referred to as TTD type 1.

CEREBRO-OCULOFACIAL-SKELETAL SYNDROME

Cerebro-oculofacial-skeletal syndrome (COFS) is the most severe ERCC2-related disorder. It is characterized by having a small head size, intellectual disability, poor growth, and abnormalities of the brain, joints, and eyes. People with COFS are sensitive to the sun and may sunburn easily, but they do not have a significantly increased risk to develop skin cancer. Several genes can cause COFS. COFS caused by genetic changes in *ERCC2* is called COFS type 2.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Carriers of ERCC2-related disorders do not typically show symptoms of the disease. However, there is an increased risk of serious pregnancy complications, particularly in the third trimester, in individuals carrying a fetus affected with trichothiodystrophy. These complications can include high blood pressure (pre-eclampsia) and HELLP syndrome. These conditions can be life-threatening and may present with symptoms such as nausea, swelling, and vision changes. An individual whose pregnancy may be affected by an ERCC2-related disorder should speak with their physician for recommendations and may benefit from a consultation with a high-risk physician.

How common are ERCC2-related Disorders?

The incidence of all ERCC2-related disorders together is unknown. Several genes are known to cause XP, which has an incidence of 1 in 430,000 births. Approximately 15% of XP is caused by *ERCC2*. The incidence of XP due to genetic changes in *ERCC2* is more common among individuals of Iraqi Jewish descent. Several genes are known to cause TTD, which has an incidence of 1 in 830,000. Between 30-60% of TTD is caused by *ERCC2*. Both XP/CS complex and COFS due to *ERCC2* have been described in only a handful of families.

How are ERCC2-related Disorders treated?

There is no cure for ERCC2-related disorders. Treatment is directed at managing the specific symptoms an individual has and can differ depending on the form and severity of the ERCC2-related disorder. Individuals with ERCC2-related disorders often require care from several specialists, such as dermatologists, neurologists, ophthalmologists, and others. They may also benefit from receiving early intervention and other supportive services beginning at a young age. Management for individuals with sun sensitivity includes strictly avoiding sun and UV light, especially to the skin and eyes. Skin-covering clothing, sunscreen, and sunglasses with UV protection are strongly recommended.

What is the prognosis for an individual with an ERCC2-related Disorder?

The prognosis for ERCC2-related disorders depends on the specific form that an individual has, though all forms are associated with a shortened lifespan. The average life expectancy of an individual with XP is in the 20s-30s. Early death typically occurs due to the increased risk of skin cancers and neurologic issues. Prognosis may be improved for some individuals who practice strict sun avoidance. Many individuals with XP-CS complex die during their childhood or teenage years. Individuals with TTD often die before adulthood,

sometimes as early as infancy, due to the high risk of developing infections. Most people with XP-CS complex and TTD have intellectual disability. Due to the severity of the condition, individuals with COFS usually die before age 5.

ERCC6-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ERCC6.
Exons Sequenced: NM_000124:2-21.

Detection Rate	Population
96%	African American
96%	Ashkenazi Jewish
96%	Eastern Asia
96%	Finland
96%	French Canadian or Cajun
96%	Hispanic
96%	Middle East
96%	Native American
96%	Northwestern Europe
96%	Oceania
96%	South Asia
96%	Southeast Asia
96%	Southern Europe
96%	Worldwide

What are ERCC6-related Disorders?

ERCC6-related disorders, caused by harmful genetic changes (mutations) in the gene *ERCC6*, are more commonly known as Cockayne syndrome type B. Cockayne syndromes are inherited disorders characterized by severe growth delay, a small head size, developmental delays, and intellectual disabilities. Other common features of the condition include an increased sensitivity to sunlight (photosensitivity), significant tooth decay, vision problems, and hearing loss. Affected individuals may also have certain facial features such as a small chin, large ears, and a slender nose, which may make them appear older than their actual age.

There are three forms of ERCC6-related disorders, called Cockayne syndrome type I, Cockayne syndrome type II, and Cockayne syndrome type III. These forms differ in the age at which symptoms first appear and how fast the symptoms progress. However, the three forms are not completely distinct, with some patients having features consistent with more than one type.

COCKAYNE SYNDROME TYPE I

This is the most common type of ERCC6-related disorder. Newborns with this type generally appear normal. However, their growth slows considerably within the first two years of life. With time, their length, weight, and head size are all significantly less than expected for their age. Affected children also develop vision and hearing problems that worsen over time, as well as neurological problems such as increased muscle tone, difficulty walking, tremors, seizures, feeding difficulties, and behavioral issues. Other possible symptoms include (but are not limited to) cataracts, frequent cavities, dry skin and hair, bone problems, and changes in the brain that can be seen on brain imaging.

COCKAYNE SYNDROME TYPE II

This form is also called cerebro-oculo-facio-skeletal [COFS] syndrome or Pena-Shokeir syndrome type II. It is the most severe form of the disease, with signs and symptoms appearing at birth or in the newborn period. Infants are small at birth and often have cataracts or other eye abnormalities. With time, they continue to have significant problems with growth and severe developmental delays. Affected children are typically unable to speak and cannot sit or walk independently.

COCKAYNE SYNDROME TYPE III

This is the mildest form of the condition, with symptoms appearing later in childhood. While affected children with this type have some of the features associated with Cockayne syndrome types I and II, their growth deficiency and developmental delays are not as severe.

How common are ERCC6-related Disorders?

The incidence of Cockayne syndrome is estimated to be 1 in 300,00 births, however the condition may be under diagnosed. Mutations in *ERCC6* account for 65% of individuals affected with Cockayne syndrome. Studies suggest the condition may be more common in certain populations, such as the Druze population in northern Israel, individuals from Reunion Island, and in individuals of French or British ancestry.

How are ERCC6-related Disorders treated?

There is no cure for ERCC6-related disorders. Treatment is focused on managing the symptoms of the condition. This may include medication for muscle stiffness, tremors, or seizures; physical therapy or assistive devices for mobility issues; educational programs for intellectual disabilities; feeding tubes for those with significant feeding difficulties; hearing aids for those with hearing loss; and standard therapies for the treatment of cataracts or other vision problems. In addition, aggressive dental care will help minimize the risk of cavities, and sun protection is necessary for managing photosensitivity, although exposure to excessive sunlight should be avoided. Metronidazole (a type of antibiotic) should also be avoided, as use of this medication can cause liver failure in individuals with Cockayne syndrome.

What is the prognosis for an individual with an ERCC6-related Disorder?

The prognosis for ERCC6-related disorders varies depending on the type of Cockayne syndrome. Most individuals with Cockayne syndrome type I die by the age of 20, with an average age at death of 12 years. However, survival past the age of 20 has been reported. For those with Cockayne syndrome type II, the most severe form of the condition, death by age 7 is typical. The average life expectancy for those with Cockayne syndrome type III is not currently known.

ERCC8-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ERCC8.
Exons Sequenced: NM_000082:1-12.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
78%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe
97%	Worldwide

What are ERCC8-related Disorders?

ERCC8-related disorders, caused by harmful genetic changes (mutations) in the gene *ERCC8*, are more commonly known as Cockayne syndrome type A. Cockayne syndromes are inherited disorders characterized by severe growth delay, a small head size, developmental delays, and intellectual disabilities. Other common features of the condition include an increased sensitivity to sunlight (photosensitivity), significant tooth decay, vision problems, and hearing loss. In addition, affected individuals may have certain facial features such a small chin, large ears, and a slender nose, which may make them appear older than their actual age.

There are three forms of ERCC8-related disorders, called Cockayne syndrome type I, Cockayne syndrome type II, and Cockayne syndrome type III. These forms differ in the age at which symptoms first appear and how fast the symptoms progress. However, the three forms are not completely distinct, with some patients having features consistent with more than one type.

COCKAYNE SYNDROME TYPE I

This is the most common type of ERCC8-related disorder. Newborns with this type generally appear normal. However, their growth slows considerably within the first two years of life. With time, their length, weight, and head size are all significantly less than expected for their age. Affected children also develop vision and hearing problems that worsen over time, as well as neurological problems such as increased muscle tone, difficulty walking, tremors, seizures, feeding difficulties, and behavioral issues. Other possible symptoms include (but are not limited to) cataracts, frequent cavities, dry skin and hair, bone problems, and changes in the brain that can be seen on brain imaging.

COCKAYNE SYNDROME TYPE II

This form is also called cerebro-oculo-facio-skeletal [COFS] syndrome or Pena-Shokeir syndrome type II. It is the severest form of the disease, with signs and symptoms appearing at birth or in the newborn period. Infants are small at birth and often have cataracts or other eye abnormalities (such as small corneas). With time, they continue to have significant problems with growth and severe developmental delays. Affected children are typically unable to speak and cannot sit or walk independently.

COCKAYNE SYNDROME TYPE III

This is the mildest form of the condition, with symptoms appearing later in childhood. While affected children with this type have some of the features associated with Cockayne syndrome types I and II, their growth deficiency and developmental delays are not as severe.

How common are ERCC8-related Disorders?

The incidence of Cockayne syndrome is estimated to be 1 in 300,00 births, however the condition may be under diagnosed. Mutations in *ERCC8* account for 35% of individuals affected with Cockayne syndrome. Studies suggest that the condition may be more common in certain populations in Northern Israel.

How are ERCC8-related Disorders treated?

There is no cure for ERCC8-related disorders. Treatment is focused on managing the symptoms of the condition. This may include medication for muscle stiffness, tremors, or seizures; physical therapy and assistive devices for mobility issues; educational programs for intellectual disabilities; feeding tubes for those with significant feeding difficulties; hearing aids for those with hearing loss; and standard therapies for the treatment of cataracts or other vision problems. In addition, aggressive dental care will help minimize the risk of cavities, and sun protection is necessary for managing photosensitivity, although exposure to excessive sunlight should be avoided. Metronidazole (a type of antibiotic) should also be avoided, as use of this medication can cause liver failure in individuals with Cockayne syndrome.

What is the prognosis for an individual with an ERCC8-related Disorder?

The prognosis for ERCC8-related disorders varies depending on the type of Cockayne syndrome. Most individuals with Cockayne syndrome type I die by the age of 20, with an average age at death of 12 years. However, survival past the age of 20 has been reported. For those with Cockayne syndrome type II, the severest form of the condition, death by the age of seven is typical. The average life expectancy for those with Cockayne syndrome type III is not currently known.

EVC-related Ellis-van Creveld Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: EVC.
Exons Sequenced: NM_153717:1-21.

Detection Rate	Population
96%	African American
96%	Ashkenazi Jewish
96%	Eastern Asia
96%	Finland
96%	French Canadian or Cajun
96%	Hispanic
96%	Middle East
96%	Native American
96%	Northwestern Europe
96%	Oceania
96%	South Asia
96%	Southeast Asia
96%	Southern Europe
96%	Worldwide

What is EVC-related Ellis-van Creveld Syndrome?

Ellis-van Creveld syndrome, caused by harmful genetic changes (mutations) in the *EVC* and *EVC2* genes, is an inherited condition that affects the formation of cartilage. EVC-related Ellis-van Creveld syndrome specifically refers to the form of the condition caused by harmful changes in the *EVC* gene. The spectrum of features seen in both EVC-related and EVC2-related Ellis-van Creveld syndrome are the same. Affected individuals typically have shortening of the arms and legs (dwarfism); a narrow chest due to shortened ribs; abnormally formed fingernails and toenails; dental abnormalities; and extra fingers (polydactyly). Approximately 60% of affected individuals are born with heart defects. Common dental problems include small teeth, missing teeth, abnormal tooth alignment, or teeth that are present at birth.

Some features of EVC-related Ellis-van Creveld syndrome may be detected before birth via ultrasound, such as extra fingers, shortening of the bones, or heart defects.

How common is EVC-related Ellis-van Creveld Syndrome?

The frequency of Ellis-van Creveld syndrome in the general population is difficult to predict. An estimated 1 in 60,000 to 1 in 200,000 individuals of various ethnicities are affected worldwide. Mutations in the *EVC* and *EVC2* genes are responsible for more than half of all reported cases of Ellis-van Creveld syndrome. It is more commonly seen among individuals in the Amish community.

How is EVC-related Ellis-van Creveld Syndrome treated?

There is no cure for the underlying cause of this condition, and treatment is based on symptoms. In the neonatal period, treatment is based on management of respiratory and cardiac symptoms. Individuals with heart defects will need to be treated by a cardiologist. Affected individuals typically require dental treatment, and infants born with teeth may require removal if the teeth affect feeding.

What is the prognosis for an individual with EVC-related Ellis-van Creveld Syndrome?

Prognosis of affected individuals may be affected by whether the size of the chest restricts breathing after birth and by the presence and severity of heart defects. Individuals who survive infancy will likely have a normal life expectancy.

EVC2-related Ellis-van Creveld Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: EVC2.
Exons Sequenced: NM_147127:1-22.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is EVC2-related Ellis-van Creveld Syndrome?

Ellis-van Creveld syndrome, caused by harmful genetic changes (mutations) in the *EVC* and *EVC2* genes, is an inherited condition that affects the formation of cartilage. EVC2-related Ellis-van Creveld syndrome specifically refers to the form of the condition caused by mutations in the *EVC2* gene. The spectrum of features seen in both EVC-related and EVC2-related Ellis-van Creveld syndrome are the same. Affected individuals typically have shortening of the arms and legs (dwarfism); a narrow chest due to shortened ribs; abnormally formed fingernails and toenails; dental abnormalities; and extra fingers (polydactyly). Approximately 60% of affected individuals are born with heart defects. Common dental problems include small teeth, missing teeth, abnormal tooth alignment, or teeth that are present at birth.

Some features of EVC2-related Ellis-van Creveld syndrome may be detected before birth via ultrasound, such as extra fingers, shortened bones, or heart defects.

How common is EVC2-related Ellis-van Creveld Syndrome?

The frequency of Ellis-van Creveld syndrome is estimated to be 1 in 60,000 to 1 in 200,000 individuals of various ethnicities worldwide. Mutations in the *EVC* and *EVC2* genes are responsible for more than half of all reported cases of Ellis-van Creveld syndrome. It is more commonly seen among individuals in the Amish community.

How is EVC2-related Ellis-van Creveld Syndrome treated?

There is no cure for the underlying cause of this condition, and treatment is based on symptoms. In the neonatal period, treatment is based on management of respiratory and cardiac symptoms. Individuals with heart defects will need to be treated by a cardiologist.

Affected individuals typically require dental treatment, and infants born with teeth may require removal if the teeth affect feeding negatively.

What is the prognosis for an individual with EVC2-related Ellis-van Creveld Syndrome?

Prognosis of affected individuals may be affected by whether the size of the chest restricts breathing after birth and by the presence and severity of heart defects. Individuals who survive infancy will likely have a normal life expectancy.

Fabry Disease

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GLA.
Exons Sequenced: NM_000169:1-7.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Fabry Disease?

Fabry disease is an inherited lysosomal storage disorder that is caused by harmful genetic changes, or mutations, in the *GLA* gene. The symptoms associated with Fabry disease are caused by a buildup of harmful substances in different organs and tissues of the body. Fabry disease is inherited in an X-linked manner, which means that the *GLA* gene is located on the X chromosome. Males typically have one copy of the X-chromosome and the *GLA* gene, while females generally have two copies. Because of this, Fabry disease primarily affects males, but carrier females can exhibit mild symptoms with a later age of onset than males. There is also both a classic and atypical form of this condition. The differences in presentation in this form are due to differences in the buildup of harmful substances in the body's tissues.

CLASSIC FORM

The classic form of Fabry disease occurs in males, with symptoms usually beginning in early childhood or adolescence. Patches of dark skin (angiokeratomas) are an early sign and most often appear on the lower half of the body. Other common symptoms include severe pain in the extremities (acroparesthesia); altered sweating (usually decreased sweating, aka hypohidrosis, but there are also reports of increased sweating, aka hyperhidrosis); and characteristic eye changes such as cloudiness in the cornea and/or lens (vision is typically not affected). Rarer symptoms include hearing loss and ringing in the ears (tinnitus); gastrointestinal issues; obstructive pulmonary disease such as chronic bronchitis or wheezing; and swelling (edema) in the lower extremities in adulthood.

Fabry disease symptoms that are a major cause of mortality are kidney disease, cardiac complications, and damage to the brain's blood vessels (cerebrovascular disease). Kidney function slowly deteriorates over time, with end-stage renal disease (ESRD) usually occurring between the ages of 30 and 50. High blood pressure is the most frequent cardiac manifestation, and this and other cardiac issues may lead to angina (chest pain), an abnormal heartbeat, heart attacks, and heart failure. Cerebrovascular disease often presents as strokes or brief episodes of blood loss to the brain (transient ischemic attacks).

ATYPICAL FORM

In the atypical form of Fabry disease, most of the classic symptoms do not manifest. The atypical form usually only causes problems of the heart or kidneys, later in life.

CARRIER FEMALES

Carrier females may be asymptomatic or may exhibit some of the symptoms of the classic disease. In most cases, symptoms are milder, with an onset later in life than for affected males. However, some female carriers have severe symptoms.

How common is Fabry Disease?

Fabry disease has an estimated pan-ethnic incidence of approximately 1 in 40,000 males, though regional incidences may vary. Because atypical forms may be unrecognized or diagnosed late in life, this incidence is likely an underestimate, and higher frequencies have been reported in both Taiwan and Italy.

How is Fabry Disease treated?

Pain may be treated with medications including diphenylhydantoin, carbamazepine, or gabapentin. Kidney disease can initially be treated with ACE inhibitors or angiotension receptor blockers to reduce protein in the urine. Late-stage renal involvement may require blood filtering (dialysis) or kidney transplantation.

There is evidence that enzyme-replacement therapy (ERT) may prevent some primary manifestations of Fabry disease, and it is typically recommended for all affected males (including children) and for some female carriers. However, because ERT may not improve symptoms of kidney, cardiac, or cerebrovascular disease, other medications may be recommended to help manage kidney disease, heart disease, and stroke.

What is the prognosis for an individual with Fabry Disease?

The majority of affected males with Fabry disease live well into adulthood, with an average life expectancy of approximately 58 years. Kidney disease and cardiac disease are the main causes of mortality. For carrier females, the prognosis is good and approaches a near-normal life span, though some individuals may be more severely affected.

Factor V Leiden Thrombophilia

Available Methodologies: targeted genotyping (v1.0) and interpretation of reported variants (v4.0).
Gene: F5.
Variant Genotyped (1): R506Q.

What Is Factor V Leiden Thrombophilia?

Factor V Leiden thrombophilia is an inherited disease that increases the chances of developing potentially dangerous blood clots. These blood clots tend to develop in the veins of the leg (deep vein thrombosis), but other types of blood clots are also possible. Factor V Leiden thrombophilia is caused by mutations in the *F5* gene.

Factor V Leiden thrombophilia is the most common cause of inherited blood clots. However, please note that most individuals who have the disease do not get abnormal blood clots. In the general population, 1 in 1000 individuals develops a blood clot each year. In individuals with one mutation for factor V Leiden thrombophilia and one normal copy of the gene, making them a carrier, that risk increases to between 4 and 8 in 1000. This is comparable to the three- to six-fold increased risk of blood clots when taking an estrogen-containing birth control pill. In individuals with two mutations causing factor V Leiden thrombophilia, the risk increases to between 18 and 80 in 1000.

Certain factors increase the risk of blood clots in individuals with factor V Leiden thrombophilia. These include smoking, advanced age, obesity, oral contraceptives, hormone replacement therapy, air travel, pregnancy, organ transplantation, surgery, cancer, and the presence of other genetic blood-clotting disorders. Children with factor V Leiden thrombophilia rarely develop abnormal blood clots. Typically if abnormal clots occur, they first appear in adulthood.

Pregnant women who have two genetic mutations that cause factor V Leiden thrombophilia are at an increased risk for certain complications including miscarriage, high blood pressure (preeclampsia), delayed physical development of the fetus, and a separation of the placenta from the uterine wall. Their risk of losing a pregnancy is two to three times greater than that of the general population. Please note however that most women with the disease will have normal pregnancies.

How Common Is Factor V Leiden Thrombophilia?

Roughly 1 in 5000 individuals in the U.S. and Europe have two copies of the mutation that causes factor V Leiden thrombophilia, putting them at higher risk for abnormal blood clots.

Having one copy of the mutation that causes factor V Leiden thrombophilia and one normal copy of the gene is fairly common in the United States and Europe. Between 3 and 8% of Caucasians have one copy of the mutation. (Please note that this causes only a slightly elevated risk for abnormal clots.)

How Is Factor V Leiden Thrombophilia Treated?

A physician with knowledge of an individual's overall health can help guide him or her in finding the appropriate treatment for factor V Leiden thrombophilia. For individuals with recurrent abnormal clots, long-term use of preventive medication that prevents blood clots may be recommended. For individuals with two factor V Leiden thrombophilia mutations who do not have a history of clotting, long-term use of medication may be recommended, although it may lead to a higher risk for excessive bleeding.

Individuals with only one copy of the factor V Leiden thrombophilia mutation and one normal gene typically do not use any preventive medications, as the risks for excessive bleeding generally outweigh the anti-clotting benefits. During short periods of higher risk, such as surgery, trauma, or pregnancy, medication may be prescribed.

When clots are discovered, they are often treated with medication according to normal medical protocols. Women with deep vein thrombosis may be asked to wear compression stockings for a period of time following the clot.

Individuals with factor V Leiden thrombophilia may want to avoid smoking, oral contraceptives, hormone replacement therapy, and obesity.

What Is the Prognosis for an Individual with Factor V Leiden Thrombophilia?

Individuals with two mutations for factor V Leiden thrombophilia have a risk of life-threatening blood clots that is 18 to 80 times greater than that of the general population. However, the majority of individuals with the condition do not experience life-threatening blood clots and will live normal lifespans.

Studies have shown that individuals with only one mutation for factor V Leiden thrombophilia have a normal lifespan.

Factor XI Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: F11.
Exons Sequenced: NM_000128:2-15.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Factor XI Deficiency?

Factor XI deficiency, also called hemophilia C, is an inherited disorder that can cause excessive bleeding. In many cases, the condition is relatively mild, and some individuals may have very few symptoms. The condition is caused by harmful genetic changes (variants) in the *F11* gene. Individuals with the condition do not have enough factor XI protein. This protein helps platelets in the blood to clot, promoting blood vessel healing following injury. In individuals with factor XI deficiency, levels of factor XI are typically lower than normal. While bleeding problems tend to occur when factor XI levels are lower than 15% of the normal level, bleeding problems can occur when levels are as high as 70%. The severity of bleeding varies widely in individuals, even among members of the same family.

In individuals with factor IX deficiency, bleeding tends to be more severe after surgery, injury, or childbirth. Bleeding can be a problem after dental, tonsil, or urinary tract surgery. Individuals with factor XI deficiency may also be prone to bruising, nosebleeds, or having blood in their urine. Rarely, biological males with the disease will bleed heavily following circumcision. More than half of individuals with factor XI deficiency who menstruate have abnormally heavy and prolonged periods (menorrhagia).

It is uncommon for individuals with factor XI deficiency to bleed spontaneously for no obvious reason. However, there may be a delay in the onset of bleeding after an injury or surgery.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Carriers of factor XI deficiency are at elevated risk for bleeding problems. Studies have suggested that 20 to 50% of carriers of the disease show "excessive bleeding," although the definition of this phrase varies. Rarely, carriers have shown major bleeding problems.

How common is Factor XI Deficiency?

The incidence of factor XI deficiency in the general population is about 1 in 1,000,000. The disease is more common among families in northwest England, where 1 in 10,000 individuals have the disease. Is it also more common in Ashkenazi Jewish individuals, with an incidence of 1 in 450.

How is Factor XI Deficiency treated?

There is no cure for factor XI deficiency. The condition can be challenging to treat because bleeding can be unpredictable. In the United States, individuals may be treated with infusions of fresh frozen blood plasma. This blood plasma contains normal quantities of factor XI, thus temporarily enhancing the body's ability to clot. However, significant amounts of plasma may be required to achieve the desired clotting effect due to the low concentration of factor XI in plasma.

In Europe, several commercially available concentrated doses of factor XI can help improve clotting. In some cases, recombinant FVIIa protein is also used to improve clotting. In the case of bleeding in the mouth, nose, intestines, or uterus, several medications may be helpful, though they are not effective for major internal bleeding and can cause clotting throughout the body. Individuals who experience heavy menstrual bleeding may use hormonal birth control pills to help control the bleeding.

What is the prognosis for an individual with Factor XI Deficiency?

Factor XI deficiency is not known to affect lifespan. In individuals who do not realize they have the disease, life-threatening bleeding is possible following surgery or injury.

Familial Dysautonomia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ELP1.
Exons Sequenced: NM_003640:2-37.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Familial Dysautonomia?

Familial dysautonomia, caused by harmful genetic changes (mutations) in the *ELP1* gene (formerly known as the *IKBKAP* gene), is an inherited condition that causes nerve cells to deteriorate. It affects the autonomic nervous system, which controls involuntary actions such as breathing, tear production, blood pressure, and body temperature. It also affects the sensory nervous system, which controls senses such as the abilities to perceive taste, pressure, pain, and temperature.

Symptoms associated with the condition may first appear in infancy. Examples of these symptoms include feeding problems, poor growth and muscle tone, lack of tears, frequent lung infections, and marked fluctuations in body temperature. Children with the condition may also hold their breath for long periods of time, which may cause fainting or make their lips or skin appear blue. This behavior usually ends by the age of six. While some children may not have any delays in development, individuals usually experience some delays in milestones such as walking and speech.

As children become older they may develop symptoms including bed-wetting, vomiting, reduced sensitivity to temperatures and pain, decreased ability to taste, poor balance, abnormal curvature of the spine, easily fractured bones, and kidney and heart problems. They can also have trouble regulating blood pressure and commonly experience a sharp drop in blood pressure when they stand up, which can cause blurred vision, dizziness, or fainting. This can also lead to episodes of high blood pressure when nervous or excited.

By adulthood, individuals with familial dysautonomia may have balance problems that prevent them from walking unaided. Other common complications include sleep apnea, lung damage due to repeated infections, poor vision as optic nerves atrophy, and kidney disease. Intellect is usually not affected in individuals with this condition.

How Common Is Familial Dysautonomia?

Familial dysautonomia is found almost exclusively in individuals of Ashkenazi Jewish descent, where it affects approximately 1 in 3,800 individuals. Roughly 1 in 31 Ashkenazi Jews is a carrier of the disease. It is extremely rare in the general population.

How Is Familial Dysautonomia Treated?

There is no cure for the cause of familial dysautonomia. Treatment focuses on relieving its symptoms.

Infants with the condition may need to be fed thickened formula to ensure adequate nutrition and prevent them from inhaling their food. Vomiting crises are treated with IV fluids and anti-nausea medication. Recurrent pneumonia caused by inhaling food or vomit requires daily chest physiotherapy. Older children who experience low blood pressure may require elastic stockings and leg exercises to improve muscle tone and prevent blood from pooling in leg veins. Corneal injuries caused by low tear production may be treated with regular eye drops, soft contact lenses, or in rare cases, surgery. Spinal fusion surgery may be necessary to correct scoliosis. Kidney disease may require dialysis. Sleep apnea is generally treated with a machine to support breathing. Many adults with the condition require walkers or wheelchairs.

What Is the Prognosis for an individual with Familial Dysautonomia?

The average lifespan of an individual with familial dysautonomia is shortened with 60% of individuals with the disease living to age 20.

Familial Hemophagocytic Lymphohistiocytosis, PRF1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PRF1.
Exons Sequenced: NM_001083116:2-3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Familial Hemophagocytic Lymphohistiocytosis, PRF1-related?

Familial hemophagocytic lymphohistiocytosis (fHLH) is a group of disorders that cause the immune system to be too active which leads to uncontrolled inflammation. Several genes are associated with fHLH. Familial hemophagocytic lymphohistiocytosis, PRF1-related, also known as FHL2, is caused by harmful genetic changes (variants) in the *PRF1* gene. This gene is important for regulating the immune system.

The first symptoms usually include high fever and infections, enlarged liver and spleen (hepatomegaly), and low blood cell counts (cytopenia). As the disease progresses, neurological symptoms may develop, including seizures, muscle problems, loss of the ability to move parts of the body (paralysis), and blindness. If left untreated, organ dysfunction and organ failure can occur. Individuals with this condition also have an increased risk of developing cancer, such as leukemia and lymphoma. Although severe symptoms often happen in the first few weeks or months of life, some individuals may experience symptoms later on.

Most individuals with FHL2 have two harmful changes in the *PRF1* gene. However, a few cases reported had one harmful change in the *PRF1* gene and one in another gene associated with familial hemophagocytic lymphohistiocytosis (digenic inheritance).

How common is Familial Hemophagocytic Lymphohistiocytosis, PRF1-related?

Familial hemophagocytic lymphohistiocytosis has an incidence of 1 in 50,000 births. Harmful genetic changes in several genes cause the condition; approximately 30%-40% of cases are caused by harmful changes in the *PRF1* gene.

How is Familial Hemophagocytic Lymphohistiocytosis, PRF1-related, treated?

Familial hemophagocytic lymphohistiocytosis can be cured by replacing the cells of the immune system with healthy ones from a donor, known as an allogeneic hematopoietic stem cell transplantation (HSCT). Patients also often require medicines to treat infections, such as antibiotics or antivirals. Some patients may need a blood transfusion. Individuals with FHL2 are best cared for through a medical team, including specialists in hematology, immunology, infectious disease, rheumatology, stem cell transplantation, neurology, and medical genetics.

What is the prognosis for an individual with Familial Hemophagocytic Lymphohistiocytosis, PRF1-related?

The prognosis for individuals with FHL2 can vary depending on several factors, including the severity of the disease at the time of diagnosis, the age of onset, treatment response, and the availability of a stem cell donor. Without treatment, individuals with FHL2 survive a few months after the onset of symptoms. Allogeneic stem cell transplantation improves survival.

Familial Hyperinsulinism, ABCC8-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ABCC8.
Exons Sequenced: NM_000352:1-39.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Familial Hyperinsulinism, ABCC8-related?

Familial hyperinsulinism, ABCC8-related is an inherited condition that causes low blood sugar levels (hypoglycemia). In a healthy individual, the pancreas secretes a hormone called insulin after eating carbohydrates in response to rising blood sugar. In familial hyperinsulinism, insulin is secreted even without carbohydrate consumption. An excess of insulin released into the blood can cause blood sugars to drop to dangerously low levels. Familial hyperinsulinism, ABCC8-related is caused by harmful genetic changes (mutations) in the *ABCC8* gene.

Infants with familial hyperinsulinism tend to have very low blood sugar within the first few days of life. These newborns are typically larger at birth and may have difficulty feeding, poor muscle tone, and breathing problems. These infants often require immediate infusions of glucose to help raise blood sugar levels and prevent seizures. Prolonged hypoglycemia can also lead to permanent brain damage. In some individuals with familial hyperinsulinism, symptoms do not appear until later in childhood. The low blood sugar associated with the condition can also range from mild to severe depending on the individual, and it can vary even among members of the same family.

There are two forms of familial hyperinsulism: the diffuse form and the focal form, each inherited in a different manner.

DIFFUSE FORM

In the diffuse form of the disease, all insulin-producing cells in the pancreas are affected. The diffuse form is typically inherited in an autosomal-recessive manner (i.e., two mutations are needed to cause the condition). In approximately 10 to 20% of cases, it is inherited an autosomal-dominant manner (i.e., only one mutation is needed to cause the condition), in which case carriers may be at risk for symptoms of hyperinsulism.

FOCAL FORM

In the focal form of the disease, only some of the insulin-producing cells of the pancreas are affected. For a child to have this form of the disease, two separate events must occur. The first is the inheritance of an *ABCC8* mutation from their father. The second is that during

fetal development a spontaneous mutation must arise in their other copy of the *ABCC8* gene. This spontaneous mutation will only occur in some of the cells, which explains the focal nature. Male carriers have a 1 in 1,200 risk of having a child affected with focal hyperinsulism.

ADDITIONAL FINDINGS

Specific mutations in the *ABCC8* gene cause neonatal diabetes. In neonatal diabetes, not enough insulin is secreted, and blood sugar increases to dangerously high levels (hyperglycemia). Infants with neonatal diabetes tend to have high blood sugar levels between birth and six months of age. These newborns are typically smaller at birth and may have difficulty feeding, severe dehydration, glucose in the urine, and excessive urination. While some with neonatal diabetes need lifelong treatment to prevent high blood sugar, others may not experience symptoms after a few weeks or months. In rare cases, some infants may also have neurological symptoms, which can include developmental delay, muscle weakness, and seizures. As in familial hyperinsulinism, symptoms of neonatal diabetes can range from mild to severe, and severity can vary among family members. In most cases, neonatal diabetes caused by *ABCC8* is inherited in an autosomal-dominant manner. Carriers may be at risk for diabetes.

How common is Familial Hyperinsulinism, ABCC8-related?

Several genes are known to cause familial hyperinsulinism, with *ABCC8* mutations accounting for approximately 45% of documented cases. The overall incidence of hyperinsulinism is approximately 1 in 50,000 individuals. The incidence of familial hyperinsulinism, ABCC8-related may be more common among individuals of Ashkenazi Jewish descent.

How is Familial Hyperinsulinism, ABCC8-related treated?

Treatment for familial hyperinsulinism includes a special diet, medications, and surgical intervention. If an infant shows symptoms of familial hyperinsulinism at birth, glucose is often given through a vein (intravenously) to raise and stabilize the blood sugar level. Infants may also need frequent feedings with large amounts of carbohydrates, even overnight. A feeding tube may be helpful to ensure that an infant receives sufficient quantities of carbohydrates.

There are also several types of medications that manage familial hyperinsulinism. Most of these medications focus on reducing the amount of insulin that is released into the body. Surgery may be needed to remove part of the pancreas if diet and medication cannot sufficiently manage a patient's blood sugar levels.

After an extended period of successful treatment, many with familial hyperinsulinism find that their symptoms become less severe or even go into remission. However, individuals with familial hyperinsulinism may find their symptoms get worse if they have a viral infections. Such individuals should manage their symptoms carefully if they become ill, even if their symptoms have gone into remission. They should also avoid long periods of time without eating.

What is the prognosis for an individual with Familial Hyperinsulinism, ABCC8-related?

The long-term outlook for an individual with familial hyperinsulinism depends upon the severity of the symptoms and how well individuals respond to treatment. Permanent brain damage can occur from episodes of low blood sugar. Even with treatment, those with the disease can develop some degree of brain damage or have learning difficulties. They also may be at an elevated risk of diabetes. In the most serious cases, when the disease is not recognized and properly treated, it can be fatal. With early diagnosis and careful treatment, individuals with familial hyperinsulinism can have normal lifespans.

Familial Hyperinsulinism, KCNJ11-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: KCNJ11.
Exon Sequenced: NM_000525:1.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Familial Hyperinsulinism, KCNJ11-related?

Familial hyperinsulinism, KCNJ11-related is an inherited condition that causes low blood sugar levels (hypoglycemia). In a healthy individual, the pancreas secretes a hormone called insulin after eating carbohydrates in response to rising blood sugar. In familial hyperinsulinism, insulin is secreted even without carbohydrate consumption. An excess of insulin released into the blood can cause blood sugars to drop to dangerously low levels. Familial hyperinsulinism, KCNJ11-related is caused by harmful genetic changes (mutations) in the *KCNJ11* gene.

Infants with familial hyperinsulinism tend to have very low blood sugar within the first few days of life. These newborns are typically larger at birth and may have difficulty feeding, poor muscle tone, and breathing problems. These infants often require immediate infusions of glucose to help raise blood sugar levels and prevent seizures. Prolonged hypoglycemia can also lead to permanent brain damage. In some individuals with familial hyperinsulinism, symptoms do not appear until later in childhood. The low blood sugar associated with the condition can also range from mild to severe depending on the individual, and it can vary even among members of the same family.

There are two forms of familial hyperinsulism: the diffuse form and the focal form, each inherited in a different manner.

DIFFUSE FORM

In the diffuse form of the disease, all insulin-producing cells in the pancreas are affected. The diffuse form is typically inherited in an autosomal-recessive manner (i.e., two mutations are needed to cause the condition). In approximately 10 to 20% of cases, it is inherited an autosomal-dominant manner (i.e., only one mutation is needed to cause the condition), in which case carriers may be at risk for symptoms of hyperinsulism.

FOCAL FORM

In the focal form of the disease, only some of the insulin-producing cells of the pancreas are affected. For a child to have this form of the disease, two separate events must occur. The first is the inheritance of an *KCNJ11* mutation from their father. The second is that during

fetal development a spontaneous mutation must arise in their other copy of the *KCNJ11* gene. This spontaneous mutation will only occur in some of the cells, which explains the focal nature. Male carriers have a 1 in 1,200 risk of having a child affected with focal hyperinsulism.

ADDITIONAL FINDINGS

Specific mutations in the *KCNJ11* gene cause neonatal diabetes. In neonatal diabetes, not enough insulin is secreted, and blood sugar increases to dangerously high levels (hyperglycemia). Infants with neonatal diabetes tend to have high blood sugar levels between birth and six months of age. These newborns are typically smaller at birth and may have difficulty feeding, severe dehydration, glucose in the urine, and excessive urination. While some with neonatal diabetes need lifelong treatment to prevent high blood sugar, others may not experience symptoms after a few weeks or months. In rare cases, some infants may also have neurological symptoms, which can include developmental delay, muscle weakness, and seizures. As in familial hyperinsulinism, symptoms of neonatal diabetes can range from mild to severe, and severity can vary among family members. In most cases, neonatal diabetes caused by *KCNJ11* is inherited in an autosomal-dominant manner. Carriers may be at risk for diabetes.

How common is Familial Hyperinsulinism, KCNJ11-related?

Several genes are known to cause familial hyperinsulinism, with *KCNJ11* mutations accounting for approximately 5% of documented cases. The overall incidence of hyperinsulinism is approximately 1 in 50,000 people. The incidence of familial hyperinsulinism, KCNJ11-related may be more common among individuals of Middle Eastern descent.

How is Familial Hyperinsulinism, KCNJ11-related treated?

Treatment for familial hyperinsulinism includes a special diet, medications, and surgical intervention. If an infant shows symptoms of familial hyperinsulinism at birth, glucose is often given through a vein (intravenously) to raise and stabilize the blood sugar level. Infants may also need frequent feedings with large amounts of carbohydrates, even overnight. A feeding tube may be helpful to ensure that an infant receives sufficient quantities of carbohydrates.

There are also several types of medications that manage familial hyperinsulinism. Most of these medications focus on reducing the amount of insulin that is released into the body. Surgery may be needed to remove part of the pancreas if diet and medication cannot sufficiently manage a patient's blood sugar levels.

After an extended period of successful treatment, many with familial hyperinsulinism find that their symptoms become less severe or even go into remission. However, individuals with familial hyperinsulinism may find their symptoms get worse if they have a viral infections. Such individuals should manage their symptoms carefully if they become ill, even if their symptoms have gone into remission. They should also avoid long periods of time without eating.

What is the prognosis for an individual with Familial Hyperinsulinism, KCNJ11-related?

The long-term outlook for an individual with familial hyperinsulinism depends upon the severity of the symptoms and how well individuals respond to treatment. Permanent brain damage can occur from episodes of low blood sugar. Even with treatment, those with the disease can develop some degree of brain damage or have learning difficulties. They also may be at an elevated risk of diabetes. In the most serious cases, when the disease is not recognized and properly treated, it can be fatal. With early diagnosis and careful treatment, individuals with familial hyperinsulinism can have normal lifespans.

Familial Mediterranean Fever

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MEFV.
Exons Sequenced: NM_000243:1-10.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Familial Mediterranean Fever?

Familial Mediterranean fever (FMF) is a condition caused by harmful genetic changes (mutations) in the *MEFV* gene. Mutations in the *MEFV* gene affect the production of a protein called pyrin, which is involved in controlling inflammation within the body. Uncontrolled inflammation can lead to repeated (recurrent) episodes (attacks) of pain and fever in patients with FMF.

Symptoms during an attack can include headache, fever, and pain, which are caused by inflammation of the membranes surrounding the abdomen (peritonitis), joints (synovitis), and lungs (pleuritis), or other organs. Some individuals also develop patches of red, tender, and swollen skin (Erysipelas-like erythema). The recurrent attacks usually last for one to three days and vary in severity. Between attacks, an affected individual typically feels normal, and these symptom-free periods can last for days or even years. Factors such as infection, hormone cycles, and stress may contribute to the timing of these episodes. In most individuals, the first attack occurs before the age of 20. Children who have FMF may experience episodic fever as the only symptom.

Some individuals with FMF develop a protein buildup (amyloidosis) in various parts of the body, notably the kidney. If left untreated, this can lead to life-threatening kidney failure. Individuals who do not experience the characteristic attacks of FMF can still develop this form of kidney failure.

Untreated FMF can also result in decreased fertility.

Some individuals with two mutations in the *MEFV* gene may never have any signs or symptoms, while some individuals with only one mutation in the *MEFV* gene may develop symptoms. Consequently, in the absence of a personal and/or family history of inflammatory disease, *MEFV* mutation status cannot be used with certainty to predict an individual's risk for symptoms.

How common is Familial Mediterranean Fever?

FMF is most common among ethnic groups from the Mediterranean region, notably individuals of Armenian, Arab, Turkish, Iraqi Jewish, and North African Jewish ancestry, in which the prevalence is approximately 1 in 200 to 1 in 1,000 individuals. In all other populations, the prevalence of FMF is lower.

How is Familial Mediterranean Fever treated?

There is no cure for FMF, but in most patients, a daily dose of the drug colchicine is effective in preventing the disease's characteristic attacks. Colchicine also prevents the dangerous buildup of proteins in the kidneys, which could otherwise lead to kidney failure.

Treatment for episodic attacks is supportive in nature, such as when medications are used to help ease pain and inflammation. Individuals who do develop serious kidney failure may require kidney transplantation.

What is the prognosis for an individual with Familial Mediterranean Fever?

With early and regular treatment, individuals with FMF can live a normal lifespan and may even be free of symptoms. The disease has the potential to be life-threatening if the patient develops kidney failure (which may result when a person is untreated or does not respond to treatment).

Fanconi Anemia Complementation Group A

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: FANCA.
Exons Sequenced: NM_000135:1-43.

Detection Rate	Population
92%	African American
92%	Ashkenazi Jewish
92%	Eastern Asia
92%	Finland
92%	French Canadian or Cajun
92%	Hispanic
92%	Middle East
92%	Native American
92%	Northwestern Europe
92%	Oceania
92%	South Asia
92%	Southeast Asia
92%	Southern Europe
92%	Worldwide

What is Fanconi Anemia Complementation Group A?

Fanconi anemia is a group of inherited disorders in which the body cannot properly produce a protein that protects DNA from damage. The defective protein results in an impaired ability of bone marrow to produce all types of blood cells. Without a sufficient number of red blood cells, the body does not receive enough oxygen, which can lead to abnormal bones and organs, as well as developmental delay. Similarly, a shortage of white blood cells makes the body more susceptible to infection and cancer, and a reduction in blood platelets make it difficult for the blood to clot when an injury arises.

Individuals with Fanconi anemia are typically born with some kind of physical abnormality with the most common being short stature, thumb or finger malformation, skin discoloration, kidney and eye anomalies, and skeletal irregularities. However, 25 to 40% of people with the condition do not have physical abnormalities. Thus, individuals may be first diagnosed in childhood with abnormally low levels of red blood cells, white blood cells, or platelets caused by bone marrow failure (because it is progressive most individuals will have some blood-related complication), hearing loss (10% of individuals), some degree of developmental delay (10% of individuals), and/or cancer.

The higher than average risk for cancer stems from the cells' inability to repair themselves when the DNA is damaged. Occasionally, the initial signs of leukemia appear in childhood as the first symptom of the disease. Other cancers may also appear at an unusually early age, particularly tumors of the head and neck, esophagus, cervix, vulva (external opening of the vagina), or liver.

How common is Fanconi Anemia Complementation Group A?

Fanconi anemia type A is the most common type of Fanconi anemia, making up between 60-70% of all cases and affecting approximately 1 in 200,000 people. However, incidence of the condition and the number of cases attributed to *FANCA* vary in certain ethnic groups due to founder effects (high frequency of disease because the group arose from a small, possibly isolated population). Founder effects have been noted in individuals of Sephardic Jewish descent (Moroccan and Indian), Tunisian descent, Afrikaners, Brazilians, Spanish Gypsies, and others.

How is Fanconi Anemia Complementation Group A treated?

There is currently no cure for Fanconi anemia type A. Treatment consists of monitoring for symptoms and treating them as they appear.

Roughly half of all people with the condition can improve their blood cell counts with medication. Over a period of years, however, people often develop resistance to the medication. Treatment with medication may also decrease the effectiveness of a later bone marrow transplant.

Bone marrow transplantation can cure leukemia associated with Fanconi anemia type A. However people with the condition are extremely sensitive to the chemotherapy and the radiation treatment necessary to prepare for transplantation, so they may not be good candidates for this surgery. A bone marrow transplant does not prevent solid tumors elsewhere in the body, which must be treated with chemotherapy and radiation.

People with Fanconi anemia type A must undergo regular blood cell count tests, bone marrow biopsies, liver scans, and gynecological, dental, and rectal exams to detect early-stage cancers so they can be removed as soon as possible.

What is the prognosis for a person with Fanconi Anemia Complementation Group A?

The prognosis for a person with the disease is dependent upon the severity of the symptoms, which will be variable from person to person.

Fanconi Anemia, FANCC-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: FANCC.
Exons Sequenced: NM_000136:2-15.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Fanconi Anemia, FANCC-Related?

Fanconi anemia is an inherited disorder in which the body cannot properly produce a protein that protects DNA from damage. This defective protein prevents the bone marrow from producing all types of blood cells. Without a sufficient number of red blood cells (anemia), the body does not receive enough oxygen, which can lead to abnormal bones and organs as well as developmental delay. A shortage of white blood cells (neutropenia) makes the body more susceptible to infection and cancer while a reduction in blood platelets (thrombocytopenia) makes it difficult for the blood to clot when an injury arises.

Fanconi anemia, FANCC-related is caused by mutations in the *FANCC* gene. There are at least 20 genes associated with Fanconi anemia.

In many cases of Fanconi anemia, the first symptoms appear in infancy as frequent nosebleeds, easy bruising, and physical abnormalities such as spotted skin or malformations of the thumbs, forearms, eyes, kidneys, gastrointestinal system, ears, or heart. Physical abnormalities can also include short stature and smaller-than-expected head size (microcephaly). However, 25 to 40% of individuals with the condition do not have physical abnormalities.

Children with the disease may also show signs of hearing loss or developmental delay and intellectual disability is observed in approximately 10% of cases. Diagnosis may first be made in childhood with abnormally low levels of red blood cells, white blood cells, or platelets. Although the bone marrow may appear normal at first, it deteriorates progressively and most children with the disease are diagnosed by age 12. Individuals with Fanconi anemia may have fertility issues and smaller-than-normal genitals.

Since Fanconi anemia prevents cells from repairing themselves when the DNA is damaged, individuals with the condition are at a higher-than-average risk of cancer. Occasionally, the initial signs of leukemia appear in childhood as the first symptom of the disease. Other cancers may also appear at an unusually early age, particularly tumors of the head and neck, esophagus, cervix, vulva, or liver. These cancers commonly develop in the patient's early twenties. Overall, about 30 to 40% of individuals with Fanconi anemia develop leukemia and/or other cancers, but the frequency of cancer rises with patient age.

How Common Is Fanconi Anemia, FANCC-Related?

The prevalence of Fanconi anemia is approximately 1 in 160,000 individuals worldwide and 1 in 130,000 individuals in the U.S. Fanconi anemia is most common in the Ashkenazi Jewish population, with a prevalence of 1 in 32,000 individuals. The *FANCC* gene accounts for about 14% of Fanconi anemia cases.

How Is Fanconi Anemia, FANCC-Related Treated?

There is currently no cure for Fanconi anemia. Treatment consists of monitoring for symptoms and treating them as they appear. About half of all individuals with the condition can improve their blood-cell counts with medication. Over a period of years, however, individuals often develop resistance to the medication. Treatment with medication may also decrease the effectiveness of a later bone marrow transplant.

Bone marrow transplantation can cure leukemia associated with Fanconi anemia. However, individuals with the condition are extremely sensitive to the chemotherapy and radiation treatments necessary to prepare for transplantation, so they may not be good candidates for this surgery. A bone-marrow transplant does not prevent solid tumors elsewhere in the body, and these must be treated with chemotherapy and radiation.

Individuals with Fanconi anemia must undergo regular blood-cell counts, bone marrow biopsies, liver scans, and gynecological, dental, and rectal exams to detect early-stage cancers so that they can be removed as soon as possible.

What Is the Prognosis for an Individual with Fanconi Anemia, FANCC-Related?

Most individuals with Fanconi anemia die before the age of 30. A bone marrow transplant can extend lifespan.

FKRP-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: FKRP.
Exon Sequenced: NM_024301:4.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What are FKRP-related Disorders?

Harmful genetic changes (mutations) in the *FKRP* gene can cause a wide spectrum of disorders known as limb-girdle muscular dystrophy-dystroglycanopathies (LGMD). The primary association of LGMD is limb-girdle muscular dystrophy R9 (LGMDR9), which causes muscle weakness as a result of fukutin-related protein (FKRP) deficiency in skeletal and cardiac muscle. Symptoms of the disease vary greatly from person to person, even among people in the same family. Some people with the disease can have a mild course where they are nearly asymptomatic, while others may have severe symptoms that can be fatal.

LIMB-GIRDLE MUSCULAR DYSTROPHY R9

Individuals with LGMDR9 develop symptoms at variable ages, although symptoms tend to present first in adolescence. LGMDR9 does not typically affect intelligence or mental function, but some studies have shown rare brain abnormalities and cognitive dysfunction in patients. The most common symptom is muscle weakness of the hip, shoulder, and abdomen that gets worse over time. The rate at which the muscles weaken can vary, but muscle weakening often results in a wheelchair becoming necessary. Other possible features include enlarged calf muscles, shortening and hardening of muscles leading to rigid joints (contractures), prominence (winging) of the shoulder blades, and curvature of the spine (scoliosis). Respiratory complications (seen in approximately 30-50% of individuals) or heart complications (seen in over 50% of individuals) are also associated with these conditions and may lead to death.

OTHER FKRP-RELATED DISORDERS

Mutations in the *FKRP* gene also cause other, more severe forms of muscular dystrophy including merosin-deficient congenital muscular dystrophy type 1C (MDC1C), muscle-eye brain disease (MEB) and Walker-Warburg syndrome (WWS). Individuals with MDC1C most often have an early age of onset (although the age of onset can vary), an inability to walk, enlarged calf muscles, and intellectual disability, and can often have brain abnormalities. Individuals with MEB and WWS are born with muscle weakness and structural abnormalities of the brain and eyes.

How common are FKRP-related Disorders?

Mutations in the *FKRP* gene are most often associated with LGMDR9. Autosomal-recessive LGMD has an estimated prevalence of 1 in 15,000 individuals. The percentage of LGMD that is attributed to LGMDR9 is approximately 10%. The mutations in the *FKRP* gene associated with other disorders, such as MDC1C, WWS, and MEB, are underrepresented in the global *FKRP* registry due to their severity and early onset. The exact contribution of *FKRP* mutations to these rarer conditions is not known.

How are FKRP-related Disorders treated?

There is no cure for any of the FKRP-related disorders, and there are few effective treatments. Physical therapy helps retain muscle strength and mobility for as long as possible. Stretching, mechanical aids, or surgery may aid in that goal. If muscle weakness begins to affect the ability to breathe, a machine that assists with breathing (a ventilator) may be needed. Cardiac surveillance is recommended, and those who develop heart problems will need to see a heart specialist (cardiologist) for treatment.

What is the prognosis for an individual with an FKRP-related Disorder?

The outlook for an individual with LGMDR9 varies. Often the earlier symptoms begin, the faster they progress; however, symptoms, onset, and prognosis can be variable. People with more severe symptoms can become wheelchair bound in their early teenage years and die in early adulthood, with death usually due to respiratory and/or cardiac complications.

Individuals with MDC1C have varied outcomes. Some die as a result of respiratory complications in the second decade of life and are never able to walk. Others retain the ability to walk into their fifth decade of life.

The prognosis for individuals with WWS/MEB is poor. Some individuals with MEB have survived into their teens, whereas individuals with WWS usually do not survive past early childhood.

FKTN-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: FKTN.
Exons Sequenced: NM_001079802:3-11.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
10%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Are FKTN-Related Disorders?

FKTN-related disorders, caused by mutations in the *FKTN* gene, include a spectrum of conditions that cause muscle weakness because of a deficiency in the fukutin (FKTN) protein. Some conditions in the spectrum have a milder course, while others may have severe symptoms and a significantly shortened lifespan. In addition, symptoms may vary greatly among individuals, even within the same family. The various conditions are described below in order of severity.

WALKER-WARBURG SYNDROME (WWS)

The most severe presentation is WWS, which is characterized by significant muscle weakness, vision problems, changes in brain structure, and severe intellectual and developmental disabilities. Impaired vision may result from a wide rage of eye problems, such as unusually small eyes, glaucoma, cataracts, and changes in the retina. Changes in the brain are significant and often include a lack of the normal folding structure resulting in a bumpy "cobblestone" appearance (cobblestone lissencephaly) or a build-up of fluid around the brain (hydrocephalus). Most children with WWS are unable to sit or walk independently, and seizures are common.

FUKUYAMA CONGENITAL MUSCULAR DYSTROPHY (FCMD)/MUSCLE-EYE-BRAIN DISEASE (MEB)

FCMD and MEB are two FKTN-related disorders with overlapping symptoms. Individuals with these conditions experience significant muscle weakness, changes in the structure of the brain, and abnormalities of the eyes that are similar to those of WWS but tend to be less severe. Rarely, individuals with these conditions learn to walk at later stages in life and may speak a few words.

LIMB GIRDLE MUSCULAR DYSTROPHY TYPE 2M (LGMD2M)

LGMD2M is the mildest presentation of FKTN-related disorders. Age of onset and severity of symptoms vary greatly among individuals. Typically, the only symptom is weakness in the muscles closest to the center of the body, specifically the muscles of the shoulders, upper arms, pelvic area, and thighs. Rarely, patients have a heart condition called dilated cardiomyopathy. The brain and eyes are not affected.

How Common Are FKTN-Related Disorders?

The overall prevalence of FKTN-related disorders has not been established. WWS is considered rare, but may be more common in the Ashkenazi Jewish population, with an estimated prevalence of 1 in 90,000. FCMD is rarely seen outside of the Japanese population, where the prevalence is approximately 1 in 140,000. The precise prevalence of MEB and LGMD2M is currently unknown.

How Are FKTN-Related Disorders Treated?

There is no treatment for the underlying cause of FKTN-related disorders. Available treatments address only the symptoms of the condition. For the more severe conditions, treatment may include medication to control seizures, surgery to reduce fluid build-up around the brain, placement of a feeding tube, and physical and occupational therapy to aid in movement. Management for LGMD2M mainly involves physical and occupational therapy, the use of assistive devices, and monitoring for heart and breathing complications.

What Is the Prognosis for an Individual with an FKTN-Related Disorder?

The prognosis depends on the severity of the condition. Individuals with WWS typically do not survive past three years of age. For those with FCMD or MEB, death typically occurs in childhood or adolescence. Those with LGMD2M generally have a normal lifespan if they do not have heart complications.

Fragile X Syndrome

Available Methodology: triplet repeat detection (v1.0).
Gene: FMR1.
Variant (1): FMR1 CGG repeat number.

What is fragile X syndrome?

Fragile X syndrome (FXS), caused by extra CGG repeats in the *FMR1* gene, is a condition that causes a variety of developmental and behavioral problems. Fragile X syndrome is an X-linked disease. This means that the *FMR1* gene is on the X-chromosome. Males have one copy of the X-chromosome, while females have two copies. Because males only have one copy, a harmful change in the *FMR1* gene typically causes more severe symptoms in males. Carrier females may be asymptomatic or may exhibit symptoms. Fragile X syndrome is the most common inherited form of intellectual disability. It is the leading single-gene cause of autism spectrum disorders.

Fragile X syndrome typically causes moderate intellectual disability (defined as an IQ below 70) in males. However, the severity of intellectual impairment varies from individual to individual. A few male patients do not have an intellectual disability. About one-third of females with fragile X syndrome have a mild intellectual disability.

As infants, children with fragile X syndrome may have weak muscles (hypotonia), stomach acid that comes up into the mouth (gastric reflux), and frequent ear infections. Their motor, mental, and speech milestones tend to be delayed. Children with fragile X syndrome often have behavioral problems such as anxiety, hyperactivity, hand flapping, biting, and temper tantrums. About one-third of males with fragile X syndrome have autism or autism-like behavior. Symptomatic females usually have milder symptoms than males. Behavioral problems in females may appear as depression, shyness, and avoidance of social situations. Some individuals with the condition have attention deficit disorder and cannot sustain focused attention on a specific task. Individuals with fragile X syndrome, particularly males, may lack impulse control, make poor eye contact, and be easily distracted.

Males with fragile X syndrome often share characteristic physical features such as a long, narrow face with a prominent jaw and forehead, a large head, flexible joints, and large ears. These features become more apparent with age. These characteristics tend to be milder or absent in females with the condition. After puberty, males with fragile X syndrome typically have enlarged testicles.

Roughly 15% of males and 5% of females with fragile X syndrome will experience seizures. While some experience heart murmurs (known as mitral valve prolapse), it is usually harmless and may not require treatment.

Effects of a premutation

Males and females with a premutation do not have fragile X syndrome but may experience specific physical symptoms. The main risks for carriers of a premutation are fragile X-associated tremor/ataxia syndrome (FXTAS), fragile X-associated premature ovarian insufficiency (FXPOI), and fragile X-associated neuropsychiatric disorders (FXAND).

Fragile X-associated tremor/ataxia syndrome (FXTAS): FXTAS causes an inability to coordinate muscle movements that worsens over time (ataxia), tremors, memory loss, impaired ability to think or remember information (dementia), a loss of feeling and weakness in the lower legs, and some mental and behavioral changes. Approximately 40% of males over 50 years of age with a fragile X premutation will develop FXTAS. Between 8-16% of females with a fragile X premutation are affected by FXTAS. Typically, symptoms of FXTAS begin around age 60 with a tremor, followed several years later by the inability to coordinate muscle movements.

Fragile X-associated primary ovarian insufficiency (FXPOI): About 20% of females with a premutation experience FXPOI. This condition causes their menstrual periods to stop before age 40. Females with FXPOI will often have difficulty getting pregnant, and many will not be able to have children. Females with a full mutation are not at increased risk for POI.

Fragile X-associated neuropsychiatric disorders (FXAND): There is an increased rate of neuropsychiatric conditions among premutation carriers. These include depression, generalized and social anxiety, and attention deficit disorder.

How is fragile X syndrome inherited?

Fragile X syndrome is inherited in an X-linked manner. The inheritance is much more complex than many other genetic diseases. A healthcare professional, such as a genetic counselor, can help answer questions about this condition and the risk of transmitting it to the next generation.

Fragile X syndrome is caused by changes in the *FMR1* gene, which is located on the X-chromosome. This gene contains a segment of DNA called the "CGG repeat." The CGG repeat in the *FMR1* gene is a pattern of DNA that repeats itself many times. By counting the number of CGG repeats in the parents, one can determine the likelihood that a child will have fragile X syndrome.

The CGG repeat in the *FMR1* gene falls into one of the following four categories:

Category	*FMR1* CGG repeat size
Normal	5 to 44 repeats
Intermediate	45 to 54 repeats
Premutation	55 to 200 repeats
Full mutation	More than 200 repeats

Normal
An *FMR1* gene with 5 to 44 CGG repeats is considered normal. Individuals with this number of *FMR1* CGG repeats do not have an increased chance of having a child with fragile X syndrome. CGG repeats in this range are considered stable because they usually pass from parent to child with the same number of repeats. For example, if a parent's gene has 30 CGG repeats, their child will likely have a gene with 30 CGG repeats.

Intermediate
An individual with 45 to 54 repeats is not expected to have an increased chance of passing on fragile X syndrome to their child, but the number of repeats transmitted to the next generation may increase slightly.

Premutation
Individuals with 55 to 200 CGG repeats have a premutation. They do not have symptoms of fragile X syndrome. However, they are at increased risk for FXTAS, FXPOI, and FXAND. Depending on which parent has the premutation, future children may be at risk of having fragile X syndrome.

Full mutation
Individuals with more than 200 CGG repeats have a non-functioning *FMR1* gene (also known as a full mutation). Males with more than 200 CGG repeats usually have symptoms of fragile X syndrome. Females with more than 200 CGG repeats may also have symptoms of fragile X syndrome and are at risk of passing the condition on to their children.

WHAT DOES IT MEAN TO HAVE AN INTERMEDIATE RESULT?

An FMR1 gene that has 45-54 repeats is considered intermediate. The number of CGG repeats is higher than normal but not large enough to be considered a premutation. Sometimes CGG repeats in the intermediate range are referred to as "gray zone" results. Individuals with an intermediate repeat do not have an increased chance of having a child with fragile X syndrome. Most intermediate genes are stable and do not significantly expand when passed on. However, repeats in the intermediate range may slightly expand when passed on to the next generation in some cases. For example, a parent with 45 CGG repeats could have a child with 50 CGG repeats. If the number of repeats continues to increase, future generations (i.e., grandchildren or great-grandchildren) may have a chance of inheriting fragile X. Expansion to a full mutation in one generation from a maternal gene with fewer than 56 repeats has not been

reported. Children of individuals with an intermediate result may consider fragile X testing to determine their CGG repeat sizes once they are adults for reproductive planning purposes.

Approximately 3% of patients undergoing fragile X carrier screening will have an intermediate result. Individuals with an intermediate repeat do NOT have an increased chance of having the physical symptoms affecting premutation carriers such as FXTAS, FXPOI, and FXAND.

WHAT DOES IT MEAN TO HAVE A PREMUTATION OR FULL MUTATION? WHAT IS THE CHANCE THAT A CHILD WILL HAVE FRAGILE X SYNDROME?

For females with a full mutation, 50% of their children will also inherit the full mutation and be at risk for symptoms of fragile X syndrome. Males who have full mutations typically do not reproduce.

Premutations are more complicated. When the parent has a premutation, the risk of a child developing fragile X syndrome depends on the answers to the following questions:

1. Which parent has the premutation?
2. Will the child inherit the premutation?
3. Will the premutation expand to a full mutation?

Which parent has the premutation?

Females that are premutation carriers are at risk of having children with fragile X syndrome. Premutations inherited from a female can be unstable and may expand to become full mutations in the child. This risk can be modified by AGG interruptions, which reduce the likelihood of expansion.

Premutations passed from a male parent may change the CGG repeat number. However, premutations do not expand to full mutations when passed from a male parent. Therefore, males with premutations are not at risk of having children with fragile X syndrome.

Will the child inherit the premutation?

Premutations are not thought to expand to full mutations when passed from a male parent to a female child. However, there can be a change in the number of CGG repeats. These female children are generally not at risk of having fragile X syndrome, but their future children (the grandchildren of the original premutation carrier) will be at risk. Male parents pass a Y chromosome to their male children instead of an X, so fragile X premutations are not passed from a male parent to a male child.

If a female parent has a premutation on one of their X chromosomes, there is a 50% chance in each pregnancy that their child will inherit the X chromosome with the premutation and a 50% chance that they will not. Only children who inherit the X chromosome with the premutation would be at risk for fragile X syndrome if it expands.

Will the premutation expand to a full mutation?

If a female parent has a gene with a premutation that gets passed to their children, there are two possibilities:

1. The premutation does not expand beyond 200 repeats and remains a premutation in the child. That child has no symptoms of fragile X syndrome but may experience FXAND and FXTAS or FXPOI as adults.
2. The premutation expands into a full mutation, causing fragile X syndrome in males and risk for fragile X syndrome in females.

Rarely, a CGG repeat may contract (or reduce in number). Therefore, there is a small possibility that a premutation could be passed on as an intermediate or normal repeat to the child.

The greater the number of CGG repeats a female has, the more unstable the gene is and the more likely it will expand to a full mutation in their children. The smallest premutation observed to expand to a full mutation in a single generation is 56 repeats.

Number of Maternal Premutation CGG Repeats	Percentage (Total Females) Which Expanded to Full Mutations
55-59	<1% (1/197)
60-64	2% (2/115)
65-69	7% (6/85)
70-74	21% (18/84)
75-79	47% (47/99)
80-84	62% (60/96)
85-90	81% (34/42)

More than 94% of genes with >90 CGGs expand to a full mutation.

Adapted from Nolin et al. (2015) and Nolin et al. (2011). These percentages typically exclude families with a family history of fragile X syndrome.

How Common Is Fragile X Syndrome?

The incidence of fragile X syndrome is estimated to be 1 in 4,000 males and 1 in 8,000 females.

How Is Fragile X Syndrome Treated?

There is no cure for fragile X syndrome, but children with the condition can be treated and supported in many ways depending on their particular symptoms and the severity of those symptoms. They may benefit from educational support like early developmental intervention, special education classes in school, speech therapy, occupational therapy, and behavioral therapies. A physician may prescribe medication for behavioral issues such as aggression, anxiety, or hyperactivity.

A small number of these children experience seizures which can be controlled with medication. While some have a heart murmur, it is usually harmless and may not require treatment.

What Is the Prognosis for an Individual with Fragile X Syndrome?

While many of the children with fragile X syndrome have learning and behavioral problems, they generally do not have major medical problems and can live a normal lifespan.

Fragile XE Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: AFF2.
Exons Sequenced: NM_002025:1-21.

Detection Rate	Population
31%	African American
31%	Ashkenazi Jewish
31%	Eastern Asia
31%	Finland
31%	French Canadian or Cajun
31%	Hispanic
31%	Middle East
31%	Native American
31%	Northwestern Europe
31%	Oceania
31%	South Asia
31%	Southeast Asia
31%	Southern Europe
31%	Worldwide

What is Fragile XE Syndrome?

Fragile XE syndrome, also known as FRAXE, is a condition that causes mild to moderate intellectual disability, developmental delays, and behavioral problems. It is caused by harmful genetic changes (variants) in the *AFF2* gene. FRAXE is an X-linked disease, meaning that people assigned male at birth (XY) usually have symptoms, while those assigned female (XX) at birth typically do not.

Some common developmental delays individuals can have include speech, reading, and writing problems. Some individuals may also have behavioral problems such as aggression, obsessive-compulsive disorder, and hyperactivity. Some individuals may experience seizures without any developmental delays. Affected individuals usually do not have characteristic physical features because of the condition.

How is Fragile XE Syndrome inherited?

The inheritance of fragile XE syndrome is more complex than many other genetic diseases. A healthcare professional, such as a genetic counselor, can help answer questions about this condition and the risk of transmitting it to the next generation.

Fragile XE syndrome is among a group of diseases called "trinucleotide repeat disorders." These diseases are caused by a DNA sequence repeated in the same gene. While everyone has these repeats, the number of times it is repeated determines if a person has the disease or can pass it on to future generations. Approximately 56% of affected individuals inherit additional repeats (triplet repeat expansions), while the rest have a different type of harmful genetic change.

The CCG repeat in the *AFF2* gene falls into one of the following four categories:

Category	*AFF2* CCG repeat size
Normal	6 to 30 repeats
Intermediate	31 to 60 repeats
Premutation	61 to 200 repeats
Full mutation	More than 200 repeats

Normal
A CCG repeat of 6 to 30 in the *AFF2* gene is considered normal. This number of repeats will not cause fragile XE syndrome when passed on to a child. A normal repeat length is stable and unlikely to change in size when passed from parent to child. For example, if the parent's gene has 15 CCG repeats, their child is also likely to have a gene with 15 CCG repeats.

Intermediate
Individuals with 31 to 60 CCG repeats are considered intermediate carriers. Intermediate carriers do not have a significant risk of passing on fragile XE syndrome to their child, but the number of repeats transmitted may vary slightly to the next generation.

Premutation
Individuals with 61 to 200 CCG repeats are considered premutation carriers. They do not have symptoms of fragile XE syndrome but are at risk of having a child with this syndrome. The CCG repeat is equally unstable when inherited from a male or a female. Each time a premutation passes from parent to child, the number of CCG repeats can increase or decrease. If the premutation increases to over 200 repeats in a child, symptoms of fragile XE syndrome will occur.

Full mutation
An individual with over 200 repeats has a non-functioning *AFF2* gene (also known as a full mutation). Many males (XY) with over 200 repeats will have symptoms of fragile XE syndrome. Most carrier females (XX) do not have symptoms.

How common is Fragile XE Syndrome?

The estimated incidence of Fragile XE syndrome is 1 in 50,000 to 1 in 100,000 males.

How is Fragile XE Syndrome treated?

There is no cure for fragile XE syndrome, but children will often benefit from receiving early intervention and other supportive services beginning at a young age. They may benefit from educational support like early developmental intervention, special education classes in school, speech therapy, occupational therapy, and behavioral therapies. A physician may also prescribe medication for behavioral issues such as aggression, anxiety, or hyperactivity.

What is the prognosis for an individual with Fragile XE Syndrome?

While many children with fragile XE syndrome have learning and behavioral problems, they generally do not have major medical problems and can live a normal lifespan.

Fraser Syndrome, GRIP1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GRIP1.
Exons Sequenced: NM_021150:1-24.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Fraser syndrome, GRIP1-related?

Fraser syndrome is an inherited disease that affects many different parts of the body. There are three different genes associated with Fraser syndrome. Fraser syndrome, GRIP1-related is caused by harmful changes in the *GRIP1* gene. The characteristic symptom of the condition is eyes that are either completely or partially covered by skin and malformed (cryptophthalmos), often leading to vision loss or impairment. Other common symptoms include fusion of the skin between the fingers and toes (cutaneous syndactyly), absence or abnormal voice box (larynx) formation, distinct facial features, and dental anomalies. Individuals may also have absent kidneys, bladder defects, abnormally formed genitals, and digestive system defects, including the anus or rectum. Many common birth defects associated with Fraser syndrome may be seen on prenatal ultrasound; however, prenatal imaging may be complex as many fetuses with Fraser syndrome, GRIP1-related, do not have enough amniotic fluid (oligohydramnios).

How common Fraser syndrome, GRIP1-related?

The incidence of Fraser syndrome caused by any gene is 1 in 200,000 births and 1 in 10,000 stillbirths. Harmful genetic changes in *GRIP1* cause less than 10% of cases of Fraser syndrome.

How is Fraser syndrome, GRIP1-related treated?

There is no cure for Fraser syndrome, GRIP1-related. Treatment is supportive based on an individual's specific symptoms. Surgery can help correct some birth defects related to the eyelids, fused skin between the fingers and toes, genitalia, and others. Surgery can be challenging for individuals with Fraser syndrome, GRIP1-related because it can be difficult to help them breathe under anesthesia. Special therapies may assist individuals with both hearing and vision loss. Other possible treatments include dental procedures, occupational therapy, and intellectual or developmental delay intervention.

What is the prognosis for an individual with Fraser syndrome, GRIP1-related?

The prognosis for individuals with Fraser syndrome, GRIP1-related, depends on the severity of their symptoms. Most individuals are stillborn or die within the first year of life, typically due to absent kidneys or a blocked larynx. Individuals who survive into adolescence may experience vision and hearing loss. While some individuals have intellectual disability and/or developmental delays, there are reports of individuals with normal intelligence.

Free Sialic Acid Storage Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SLC17A5.
Exons Sequenced: NM_012434:1-11.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
>99%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What Are Free Sialic Acid Storage Disorders?

Free sialic acid storage disorders, caused by mutations in the *SLC17A5* gene, belong to a group of diseases known as lysosomal storage disorders that affect the nervous system. There are three forms, which vary in severity: Salla disease (SD), intermediate severe SD, and infantile free sialic acid storage disease (ISSD).

SALLA DISEASE

SD is an inherited condition causing a slow, progressive decline in motor and mental skills. Children with SD appear healthy at birth but show poor muscle tone in the first year of life. Delays in their motor and mental skills become more obvious with age. They become spastic and have difficulty coordinating their voluntary movements. Loss of intellect is progressive over time, beginning in the first or second year of life. Children with SD typically have delayed language skills. By adulthood, all individuals with SD have profound intellectual and developmental disabilities, with IQs between 20 and 40. Most can speak some words in short sentences. Most will be able to walk in adulthood, though some cannot. Adults with the disease are profoundly disabled but live normal lifespans.

INTERMEDIATE SEVERE SALLA DISEASE

In a more severe form of SD, also called intermediate severe Salla disease, symptoms appear in the first six months of age. These infants have extremely poor muscle tone, have delayed growth, and may have seizures. Losses of motor and mental functions are more rapid with this form of the condition, and lifespan may be shortened.

INFANTILE FREE SIALIC ACID STORAGE DISEASE

The most severe form of this disorder is infantile free sialic acid storage disease (ISSD). Infants born with this condition do not grow at the expected rate, and they have weak muscle tone and severe developmental delay. They may have seizures, bone malformations, an enlarged liver and spleen, and an enlarged heart. Infants may have a condition called hydrops fetalis in which excess fluid accumulates in the body before birth. Individuals with ISSD usually live only into early childhood.

How Common Are Free Sialic Acid Storage Disorders?

Free sialic acid storage disorders are rare except in Northern Finland, where 1 in 50 individuals are carriers. Only 30 cases of intermediate severe SD have been documented outside of Finland.

How Are Free Sialic Acid Storage Disorders Treated?

There is no effective treatment for free sialic acid storage diseases other than to address symptoms as they arise. Special education or physical, occupational, or speech therapy may be helpful.

What Is the Prognosis for an Individual with a Free Sialic Acid Storage Disorder?

Individuals with SD have normal lifespans, but all will be profoundly disabled and will have difficulty with movement. Most will be able to walk, but some will not. Those with ISSD will have a reduced lifespan. The small number of cases known worldwide make an exact prognosis difficult. Individuals with ISSD usually live only into early childhood.

Galactokinase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GALK1.
Exons Sequenced: NM_000154:1-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Galactokinase Deficiency?

Galactokinase deficiency, also called galactosemia type II, is a treatable, inherited disease that reduces the body's ability to process a simple sugar called galactose, which is found in milk. Galactokinase deficiency is caused by harmful genetic changes (mutations) in the *GALK1* gene. The primary symptom of this condition is cataracts (clouding of the lens of the eye), which causes vision impairment. Cataracts are due to the buildup of a substance called galactitol in the lens of the eye. Cataracts usually develop in both eyes within the first few weeks or months of infancy. Galactokinase deficiency is anticipated to be milder, with better outcomes, than the more severe forms of galactosemia. Other, less common symptoms such as low blood sugar, intellectual disability, and problems with growth have been reported in a few affected individuals. However, it is unclear whether these symptoms were caused by galactokinase deficiency or other causes in these individuals.

How common is Galactokinase Deficiency?

The incidence of galactokinase deficiency is fewer than 1 in 100,000 newborns, although it is more frequent in the Romani populations across Europe. The number of affected individuals may vary across populations.

How is Galactokinase Deficiency treated?

Individuals with galactokinase deficiency should follow strict galactose- and lactose-free diets. This means avoiding any dairy products (including many "lactose-free" products, because they still contain galactose) and certain vegetables. The treatment also includes avoiding breastfeeding of a newborn and providing a galactose-free formula instead. Often, patients require calcium supplements to avoid calcium deficiency. Dietary restriction often resolves the cataracts in affected individuals.

What is the prognosis for an individual with Galactokinase Deficiency?

The prognosis of galactokinase deficiency is excellent if affected individuals continue a galactose-free diet. With treatment, cataracts can be prevented or at least partially resolved if they have started to form prior to treatment.

Galactosemia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GALT.
Exons Sequenced: NM_000155:1-11.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Galactosemia?

Galactosemia is a treatable inherited condition that reduces the body's ability to metabolize galactose, a simple sugar found in milk. It is caused by mutations in the *GALT* gene, which result in a deficiency in an enzyme called galactose-1-phosphate uridyltransferase. The classic form of galactosemia can be fatal without prompt treatment and careful management. Because milk is a staple of an infant's diet, diagnosis and treatment within the first week of life is critical to avoiding intellectual disability and life-threatening complications.

CLASSIC FORM

Classic galactosemia, the most severe form of the disease, occurs when galactose-1-phosphate uridyltransferase activity is very low or absent. After only a few days of drinking milk, including breast milk, an infant with classic galactosemia will show symptoms including loss of appetite, jaundice, vomiting, lethargy, and convulsions. Without immediate and vigilant lifelong treatment, children with the condition will experience life-threatening complications such as severe infections, cirrhosis of the liver, and intellectual disability. Even with treatment, children can still develop cataracts, speech problems, stunted growth and motor function, and learning disabilities, and most females will eventually develop menstrual irregularities and go through premature menopause.

CLINICAL VARIANT FORM

Clinical variant galactosemia occurs when occurs when galactose-1-phosphate uridyltransferase activity is approximately 10% of the normal level. People with this form of galactosemia can have some of the symptoms of classic galactosemia, such as growth problems, severe infections, cirrhosis of the liver, cataracts, and mild intellectual disability. However, females do not develop menstrual irregularities or go through premature menopause.

BIOCHEMICAL VARIANT FORM

The biochemical variant form, also called Duarte galactosemia, is a much milder form of the disease in which a person has 14 to 25% of the normal amount of galactose-1-phosphate uridyltransferase. People with Duarte galactosemia generally do not suffer any of the symptoms of classic galactosemia.

Please note that galactosemia is not the same as lactose intolerance, a more-common and less-serious condition.

How Common Is Galactosemia?

Classic galactosemia affects 1 in 30,000 to 1 in 60,000 newborns, and it is more common in individuals of Irish ancestry. The prevalence of clinical variant galactosemia is estimated to be 1 in 20,000. The prevalence of Duarte galactosemia is approximately 1 in 4,000.

How Is Galactosemia Treated?

People with classic galactosemia and clinical variant galactosemia must monitor their galactose-1-phosphate levels with regular blood tests and follow a lifelong diet free of milk, milk products, or other foods containing lactose. Infants should be fed with galactose-free formulas such as soy formula or Nutramigen, a hypoallergenic formula with no galactose, lactose, or soy. As children learn to feed themselves, parents must teach them how to read product labels so that they can avoid any food containing milk, dry milk, milk products, and other galactose-containing foods. Often they require calcium supplements to avoid calcium deficiency.

There is debate on whether people with Duarte galactosemia need to adhere to a galactose-free diet. Some medical professionals recommend modifying an affected person's diet, while others do not. The decision as to whether or not to treat a person with Duarte galactosemia may depend upon his or her level of enzyme activity.

People with galactosemia should work with a nutritionist to determine the best course of treatment.

What Is the Prognosis for a Person with Galactosemia?

Most people who are diagnosed early with classic or clinical variant galactosemia and carefully follow a galactose-free diet can have a normal lifespan. However, they are still at risk for cataracts, speech defects, poor growth, poor intellectual function, neurologic deficits, and (in women with classic galactosemia) ovarian failure. If the treatment of classic or clinical variant galactosemia is not prompt and consistent, life-threatening complications and irreversible intellectual disability can result.

Duarte galactosemia has not been associated with any long-term health problems.

Gamma-sarcoglycanopathy

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SGCG.
Exons Sequenced: NM_000231:2-8.

Detection Rate	Population
87%	African American
87%	Ashkenazi Jewish
87%	Eastern Asia
87%	Finland
87%	French Canadian or Cajun
87%	Hispanic
87%	Middle East
87%	Native American
87%	Northwestern Europe
87%	Oceania
87%	South Asia
87%	Southeast Asia
87%	Southern Europe
87%	Worldwide

What is Gamma-Sarcoglycanopathy?

Gamma-sarcoglycanopathy, also known as limb-girdle muscular dystrophy type 2C (LGMD2C), is caused by harmful genetic changes (mutations) in the *SGCG* gene and is a group of disorders that typically cause muscle weakness. Symptoms of the disease vary greatly from person to person, even among individuals in the same family. Some individuals with the disease can have a mild course, where they are nearly asymptomatic, while others may have severe symptoms that can be fatal.

Individuals with LGMD2C develop symptoms at different ages, though symptoms tend to present in early childhood. LGMD2C does not affect intelligence or mental function; the primary symptom is worsening (progressive) muscle weakness of the hip, shoulder, and abdomen. The rate at which the muscles weaken can vary, but the weakening often necessitates a wheelchair. Other features include enlarged calf muscles, shortening and hardening of muscles leading to rigid joints (contractures), prominence (winging) of the shoulder blades, and curvature of the spine (scoliosis). Respiratory complications or heart complications, such as arrhythmia or cardiomyopathy (seen in ~20% of individuals), are also associated with these conditions and may lead to death.

Individuals have also been described with only muscle pain during exercise, weak muscles close to the center of the body (proximal muscle weakness), or elevated creatine kinase levels with no known symptoms (hyperCKemia). These may not be distinct types of the condition, but instead, they represent the variable nature of the condition.

How common is Gamma-Sarcoglycanopathy?

The incidence of autosomal-recessive limb-girdle muscular dystrophy (LGMD) is 1 in 15,000 individuals. The percentage of LGMD cases attributed to LGMD2C is unknown. LGMD2C is more common in the North African and Roma populations.

How is Gamma-Sarcoglycanopathy treated?

There is no cure for gamma-sarcoglycanopathy and there are few effective treatments. Physical therapy helps retain muscle strength and mobility for as long as possible. Mobility aids, such as walkers, canes, braces, and wheelchairs, may become necessary. As muscles deteriorate, a machine that assists with breathing (a ventilator) may be needed. Cardiac surveillance is recommended, and individuals that develop heart problems should consult a heart specialist (cardiologist) for symptomatic treatments. Some individuals may need surgery if they develop scoliosis or contractures.

What is the prognosis for an individual with Gamma-Sarcoglycanopathy?

The outlook for an individual with LGMD2C varies. LGMD2C is considered one of the more severe forms of autosomal-recessive LGMD. Generally, the earlier symptoms begin, the faster they progress. However, because symptoms and onset can be variable, prognosis can be variable. In individuals with more severe symptoms, use of a wheelchair may become necessary in their early teens and death may occur in early adulthood. Causes of early death include respiratory and cardiac complications.

Gaucher Disease

Available Methodologies: analysis of homologous regions (v4.0) and interpretation of reported variants (v4.0).
Gene: GBA1.
Variants Genotyped (10): N409S, V433L, D448H, D448V, L483P, R502C, R502H, R535H, c.84dupG, c.115+1G>A.

Detection Rate	Population
60%	African American
95%	Ashkenazi Jewish
60%	Eastern Asia
60%	Finland
60%	French Canadian or Cajun
60%	Hispanic
60%	Middle East
60%	Native American
60%	Northwestern Europe
60%	Oceania
60%	South Asia
60%	Southeast Asia
60%	Southern Europe
60%	Worldwide

What is Gaucher Disease?

Gaucher disease is an inherited lysosomal storage disorder caused by harmful genetic changes in the *GBA1* gene, formerly known as the *GBA* gene. The condition develops when the body fails to properly produce a particular enzyme to break down a fatty substance called glucocerebroside. Without this enzyme, glucocerebroside and several other associated substances will build up in the body, causing a variety of symptoms.

There are five main types of Gaucher disease, each with different manifestations. These types are described below.

TYPE 1 FORM

Type 1 Gaucher disease is the most common form. It can affect individuals at any age, and its symptoms vary widely from mild to severe.

Many individuals with type 1 Gaucher disease have symptoms related to their bones. Symptoms may include bone pain, low bone mineral density, and increased fracture risk. On the mild end of the spectrum, individuals experience only slightly decreased bone mineral density. In more severe cases, the blood supply to the bones is lost, leading to permanent damage. Bone problems are often the most debilitating aspect of the disease.

Individuals with type 1 Gaucher disease often have an enlarged liver and spleen. They may also have a lowered number of red blood cells (anemia) and platelets. This typically results in patients feeling tired and weak. Fewer platelets in the blood make the individual more prone to bruising and excessive bleeding. Lung disease is another possible symptom.

Type 1 is distinct from other forms of Gaucher disease because it usually does not affect an individual's brain or spinal cord.

TYPE 2 FORM

Type 2 is the infantile or acute neuropathic form of Gaucher disease. Symptoms usually appear before age two and progress rapidly. Like individuals with type 1 Gaucher disease, children with type 2 Gaucher disease may have an enlarged liver and spleen, a lowered

number of red blood cells (anemia) leading to weakness and tiredness, a lowered number of platelets leading to bleeding and bruising, and lung disease.

While type 2 Gaucher disease does not cause bone problems, it does cause neurological problems. Neurological symptoms often include developmental delay and intellectual disability. Brainstem abnormalities can cause breathing problems and difficulty swallowing, constant arching of the back and tilting back of the head, uncontrollable tightening and releasing of the muscles, and an inability to open the mouth. As the nervous system deteriorates, children with type 2 Gaucher disease may develop dementia and the inability to coordinate their movements.

TYPE 3 FORM

Type 3 Gaucher disease is known as the juvenile or chronic neuropathic form. Symptoms often begin before age two, though this is variable. The symptoms associated with type 3 Gaucher disease usually progress more slowly than with type 2 Gaucher disease.

Like individuals with type 1 Gaucher disease, children with type 3 Gaucher disease may have an enlarged liver and spleen; lung disease; a lowered number of red blood cells (anemia) leading to weakness and tiredness; and a reduced number of platelets leading to bleeding and bruising. They may also experience bone problems, including pain, fractures, and arthritis.

As with type 2 Gaucher disease, type 3 Gaucher disease also causes neurological problems, including seizures that worsen over time, progressive cognitive issues, and difficulty controlling eye movement. Toward the end of their lives, individuals with type 3 Gaucher disease may also develop dementia.

PERINATAL-LETHAL FORM

The perinatal-lethal form is a rare but severe form of Gaucher disease. This form usually leads to death *in utero* or shortly after birth. Infants with this disease have symptoms including an enlarged liver and spleen, a lowered number of red blood cells (anemia) and platelets, neurological problems, skin abnormalities, and distinct facial features.

CARDIOVASCULAR FORM

The cardiovascular form of Gaucher disease causes symptoms involving the heart, notably a hardening of the mitral and aortic valves. If this symptom is severe, heart valve replacement may be required. Also, individuals with the cardiovascular form may have a slightly enlarged liver and spleen; bone problems including pain, fractures, and arthritis; difficulty controlling eye movement; and a clouding of the eye's cornea, which can affect vision. The cardiovascular form of the disease is sometimes called type 3C.

Additional Considerations for Carriers

Studies have shown that carriers of Gaucher disease may have an increased risk of developing Parkinson's disease, above the risks seen in the general population. This risk could be between 7 and 15% by age 80 (in comparison to the general population risk of 1 to 2%). However, most carriers of Gaucher disease never develop Parkinson's disease.

How common is Gaucher Disease?

The incidence of Gaucher disease is 1 in 40,000 to 1 in 60,000 in the general population. It is more common in people of Ashkenazi Jewish ancestry, where the incidence is approximately 1 in 800.

How is Gaucher Disease treated?

Treatment for Gaucher disease involves enzyme replacement therapy (ERT) and substrate reduction therapy. ERT is given by infusion and helps eliminate the buildup of glucocerebrosides in the body. Oral forms of ERT are also available. For many affected individuals, ERT effectively treats disease symptoms and prevents complications, particularly bone and organ damage. ERT does not improve or prevent the neurological symptoms of type 2 and type 3 Gaucher disease.

Individuals with the cardiovascular form of Gaucher disease often need heart valve replacements, after which ERT can be helpful.

Additional treatments for the symptoms of Gaucher disease include blood transfusions for tiredness and excessive bleeding, joint replacement to relieve pain and restore movement, and medication to treat bone pain.

What is the prognosis for an individual with Gaucher Disease?

Because symptoms of Gaucher disease vary widely in type and severity among individuals with the same subtype, the prognosis is also similarly varied. The prognosis for an individual with Gaucher disease depends on the type of Gaucher disease, the severity of symptoms in that particular individual, and the availability and effectiveness of treatment.

Those with a milder form of type 1 Gaucher disease are expected to have a normal lifespan, particularly if ERT is administered when necessary. Some individuals with severe cases of type 1 Gaucher disease may have debilitating symptoms that are more difficult to manage.

Those with type 2 Gaucher disease often have significant developmental delays and die between the ages of two and four. In the most severe type 2 Gaucher disease cases, death may occur before or shortly after birth.

People with type 3 Gaucher disease usually develop symptoms in childhood that slowly worsen over time. While some type 3 Gaucher disease patients have died in childhood, others have lived into their thirties and forties.

Women with milder cases of Gaucher disease can have successful pregnancies.

For those with the cardiovascular form of the disease, the prognosis depends upon the success of their valve replacement surgery.

With the perinatal-lethal form, death occurs before or shortly after birth.

Some individuals affected with Gaucher disease may also develop Parkinson's disease or Lewy body dementia, but most individuals with Gaucher disease never develop these conditions.

GJB2-related DFNB1 Nonsyndromic Hearing Loss and Deafness

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GJB2.
Exons Sequenced: NM_004004:1-2.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is GJB2-Related DFNB1 Nonsyndromic Hearing Loss and Deafness?

DFNB1 nonsyndromic hearing loss and deafness is an inherited condition in which an individual has mild to severe hearing loss, usually, from birth. It is caused by mutations in *GJB2* (which encodes the protein connexin 26) and *GJB6* (which encodes connexin 30). The condition does not typically worsen over time, but in some cases may be slowly progressive. The word "nonsyndromic" refers to the fact that there are no other symptoms or systems of the body involved with the disease. Unlike some other forms of hearing loss, DFNB1 nonsyndromic hearing loss and deafness does not affect balance or movement. The degree of hearing loss is difficult to predict based on which genetic mutation one has. Even if members of the same family are affected by DFNB1 nonsyndromic hearing loss and deafness, the degree of hearing loss may vary among them.

How Common Is GJB2-Related DFNB1 Nonsyndromic Hearing Loss and Deafness?

In the United States, the United Kingdom, France, Australia, and New Zealand, approximately 14 in 100,000 individuals have DFNB1 nonsyndromic hearing loss and deafness. This may be an underestimate as individuals with a mild presentation may not be diagnosed. Roughly 1 in 33 Caucasian individuals are carriers a the mutation that causes the condition.

While this condition is most recognized in the Caucasian population, it has also been observed in other ethnicities.

How Is GJB2-Related DFNB1 Nonsyndromic Hearing Loss and Deafness Treated?

Individuals with DFNB1 nonsyndromic hearing loss and deafness may show improvement by using hearing aids. For those with profound deafness, cochlear implants may also be helpful. They may also want to consider enrolling in an educational program for the hearing impaired.

What is the Prognosis for an Individual with GJB2-Related DFNB1 Nonsyndromic Hearing Loss and Deafness?

While an individual with GJB2-related DFNB1 nonsyndromic hearing loss and deafness will have mild to severe hearing loss, it does not affect lifespan and does not affect any other part of the body.

GLB1-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GLB1.
Exons Sequenced: NM_000404:1-16.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What are GLB1-related Disorders?

GLB1-related disorders are inherited, lysosomal storage disorders. There are two specific forms of GLB1-related disorders, GM1-gangliosidosis and mucopolysaccharidosis type IVB (MPS IVB). Both disorders are caused by harmful genetic changes (mutations) in the *GLB1* gene.

The body uses enzymes to break down fats (lipids) and sugars (carbohydrates). This process happens within the lysosome, the digestive system of the cell. When a particular enzyme is missing or not working correctly, the substance the enzyme is supposed to break down accumulates and can be harmful to the body.

Individuals with GLB1-related disorders lack an important enzyme called β-galactosidase, which is necessary for the proper function of lysosomes. This enzyme is responsible for breaking down a variety of proteins, including GM1 gangliosides and keratan sulfate.

GM1-GANGLIOSIDOSIS

GM1-gangliosidosis is a neurodegenerative condition caused by the buildup of GM1 gangliosides. This buildup is toxic and leads to the destruction of cells in many organs, particularly those in the brain. The severity of the condition varies but most individuals tend to be severely affected. GM1-gangliosidosis can be broken down into three subtypes:

Type I - Infantile Form

Type I is the most common form of GM1-gangliosidosis. Affected infants will have developmental delay followed by loss of milestones, typically before six months of age. Another characteristic finding is a cherry-red spot on the macula (portion of eye at the center of the retina) of the eye. Other findings of this form include: shortened bones, curvature of the spine (skeletal dysplasia), enlarged liver and spleen (hepatosplenomegaly), and corneal clouding. Most infants will be blind and deaf by the time they turn one. Some infants may also have heart disease (cardiomyopathy), seizures, and enlarged facial features. GM1-gangliosidosis type I progresses quickly, and most infants with this type will pass away before the age of three.

Type II - Late-Infantile and Juvenile Forms

Late-infantile form: The age of onset of this form is between one and three years of age. Children with the late-infantile form typically have motor and cognitive delay. As in the infantile form, there is progressive brain deterioration and the potential for both cardiac disease and skeletal abnormalities. Corneal clouding may also be present. Life expectancy is approximately 5 to 10 years.

Juvenile form: The age of onset of this form is between 3 and 10 years of age. Progression of symptoms is slower than the late-infantile form. These individuals do not typically have cherry-red spots in the eye, enlarged organs, or coarse facial features. Life expectancy may be into early adulthood.

Type III - Adult Form

This is the mildest subtype, and early symptoms include abnormal and involuntary muscle movement (dystonia) and speech difficulty in the second or third decade of life. Other symptoms may include heart disease, mild brain deterioration, and skeletal abnormalities. Life expectancy is variable and may be shortened.

MUCOPOLYSACCHARIDOSIS TYPE IVB

Mucopolysaccharidosis type IVB (MPS IVB) is a skeletal condition that is caused by buildup of keratan sulfate, a molecule found primarily in cartilage and bone. The excess keratan sulfate causes abnormal bone growth and development. Individuals with MPS IVB typically experience shortened bone length, abnormal spine curvature (kyphoscoliosis), deformities of the chest and rib bones (pectus carinatum), and "knocked knees." In its severe form, the age of onset is between one and three years. Some individuals have an attenuated form, with onset in late childhood or adolescence. Other features of MPS IVB include corneal clouding, abnormal or missing teeth, and cardiac disease. Intellect is generally not affected.

How common are GLB1-related Disorders?

GLB2-related disorders of all types occur in approximately 1 in 100,000 to 300,000 individuals. The disease may be more common in Brazil and in those with Roma ancestry.

How are GLB1-related Disorders treated?

There is no cure for GLB1-related disorders, and management focuses on improving quality of life for affected individuals. Physical, occupational, and speech therapies are often recommended. Individuals with GM1-gangliosidosis often need specialized strollers or wheelchairs. It is important to ensure that there is adequate hydration and caloric intake, which may require a feeding tube. Other treatment focuses on managing seizure activity and heart disease. For MPS IVB, there is no treatment, and management focuses on physical and occupational therapies. Individuals should also be monitored by pulmonologists, audiologists, ophthalmologists, and cardiologists.

What is the prognosis for an individual with a GLB1-related Disorder?

For GM1-gangliosidosis, the prognosis is poor. The infantile form of this disorder is the most common, but there is a range of severity, and some may be mildly affected. For MPS IVB, the prognosis is variable, depending on the severity of symptoms. Some may live into adulthood, but life expectancy is shortened.

Glucose-6-phosphate Dehydrogenase Deficiency

Available Methodologies: targeted genotyping (v1.0) and interpretation of reported variants (v4.0).
Gene: G6PD.
Variants Genotyped (7): V68M, S188F, R459P, R459L, A335T, G163S, V291M.

Detection Rate	Population
90%	African American
50%	Ashkenazi Jewish
30%	Eastern Asia
50%	Finland
50%	French Canadian or Cajun
90%	Hispanic
75%	Middle East
50%	Native American
50%	Northwestern Europe
50%	Oceania
50%	South Asia
80%	Southeast Asia
50%	Southern Europe
50%	Worldwide

What is Glucose-6-Phosphate Dehydrogenase Deficiency?

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, caused by harmful genetic changes in the *G6PD* gene, is an inherited disease caused by the deficiency of an enzyme called glucose-6-phosphate dehydrogenase. If the body does not have enough of this enzyme, red blood cells, which carry oxygen from the lungs to the rest of the body, are destroyed faster than the body can replace them (hemolytic anemia).

G6PD deficiency is an X-linked condition, meaning the *G6PD* gene is on the X-chromosome. Biological males have one copy of the X-chromosome (XY) and the *G6PD* gene, while biological females have two copies (XX). Because of this, G6PD deficiency primarily affects males, while most female carriers are unaffected. However, some females can have symptoms.

Individuals with G6PD deficiency are healthy most of the time but can develop bouts of fatigue and illness under certain circumstances. These episodes can be brought on by taking certain types of medication or by the physical stress of an infection. Medications known to provoke attacks of hemolytic anemia in individuals with G6PD deficiency include anti-malarial drugs, common painkillers (such as aspirin or ibuprofen), and certain antibiotics. Contact with fava beans and mothballs, even simply touching them, can also provoke attacks. Because of the connection with fava beans, G6PD deficiency is sometimes known as favism.

The symptoms of hemolytic anemia include fatigue, shortness of breath, a yellow tinge to the skin and whites of the eye (jaundice), rapid heart rate, an enlarged spleen, and overall paleness. In severe episodes, individuals can also have brown-colored urine. Occasionally, newborns show symptoms of jaundice within the first two weeks of life.

Many individuals with G6PD deficiency never develop any symptoms.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Some females with a harmful change in *G6PD* may have mild symptoms of the disease.

How common is Glucose-6-Phosphate Dehydrogenase Deficiency?

G6PD is estimated to affect 400 million individuals worldwide. G6PD deficiency is more common in African-American males, where the prevalence is 1 in 10. G6PD is also common in the Middle East (notably among Kurds and Sephardic Jews), Africa, Asia, and Papua New Guinea. G6PD deficiency is common because it offers some protection against malaria, an infectious disease carried by mosquitoes. G6PD deficiency is most common in areas where malaria is present.

How is Glucose-6-Phosphate Dehydrogenase Deficiency treated?

Under normal circumstances, individuals with G6PD deficiency do not have any symptoms and require no treatment. They should carefully avoid the medications that can cause hemolytic anemia. A healthcare provider can provide a complete list of these drugs. Individuals should also avoid eating fava beans. Infants should be monitored for jaundice in the neonatal period and treated using phototherapy.

If an episode of hemolytic anemia does occur, individuals with the disease often need bed rest, and in severe cases, they may require blood transfusions.

Once the cause of the episode is resolved (i.e., a drug is discontinued or an infection cleared up), symptoms of the disease usually subside fairly quickly, often without any treatment.

What is the prognosis for an individual with Glucose-6-Phosphate Dehydrogenase Deficiency?

Individuals with G6PD deficiency typically have no symptoms and can live a normal lifespan with a normal quality of life. In rare cases, episodes of hemolytic anemia can be fatal. Normally, individuals with G6PD deficiency who have episodes of hemolytic anemia recover quickly with minimal treatment.

Glutaric Acidemia, GCDH-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GCDH.
Exons Sequenced: NM_000159:2-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Glutaric Acidemia, GCDH-Related?

Glutaric acidemias are a group of disorders in which glutaric acid is found in high concentrations in the urine. Glutaric acidemia, GCDH-related (a.k.a. glutamic acidemia type 1, or GA I) is an inherited metabolic disease in which the body lacks an enzyme to properly break down the amino acids lysine and tryptophan. The buildup of these amino acids in the body can result in brain damage that impairs movement as well as intellectual function. GA I is caused by mutations in the *GCDH* gene.

The type and severity of symptoms in individuals with GA I can vary widely. A small number of individuals with GA I have no symptoms at all, while others have severe movement problems and/or intellectual and developmental disabilities.

About 75% of infants with GA I will have an enlarged head also known as macrocephaly, although this feature is not specific to GA I and can make diagnosis difficult. In most children, additional symptoms appear between 6 and 18 months of age typically as the result of a challenge to the body such as an illness with fevers. However, in some cases, there is no identifiable cause of symptoms. Glutaric acid accumulation in the basal ganglia of the brain can result in a severe and permanent loss of motor skills, though intellect often remains normal.

Additional symptoms typically present as a “metabolic crisis,” an episode marked by low blood sugar, excess acid levels, vomiting, lack of energy, difficulty feeding, irritability, and poor muscle tone that causes the body to seem floppy. If unrecognized and untreated with a special diet, these episodes can progress to cause spastic and jerky muscle movements, seizures, swelling and bleeding of the brain, coma, and death in some cases. Some children develop bleeding in the brain or eyes; which has been mistaken for child abuse. Other children do not experience a metabolic crisis but show a delay in motor and intellectual development. Children with these symptoms are more likely to have intellectual impairment later in life.

Early diagnosis and strict control of the child's diet can avert a metabolic crisis and significantly reduce the risk of brain damage and impaired movement ability.

How Common Is Glutaric Acidemia, GCDH-Related?

Approximately 1 in 50,000 individuals in the United States is affected by GA I. The prevalence of GA I worldwide is 1 in 100,000 individuals. It is more common in certain ethnicities and communities. Among Old Order Amish in Pennsylvania and the Ojibwa tribe in Canada, as many as 1 in 300 newborns are affected by GA I.

How Is Glutaric Acidemia, GCDH-Related Treated?

Individuals with GA I often have a specific treatment plan devised with the help of metabolic specialists. Often these plans include a low-protein diet, lysine-free formula, and carnitine supplementation. Diets will need to be carefully structured to both avoid problem foods and ensure proper nutrition.

A specialist will also devise a "sick-day plan" to use when a child shows signs of illness that could lead to a metabolic crisis. Often this involves treatment to reduce fevers, nausea, and diarrhea. Intravenous fluids and a gastric feeding tube may be used to maintain hydration and nutrition. A high-energy carbohydrate diet, removal of proteins from the diet for 24 to 48 hours, vitamins and additional supplements, and, in some cases, dialysis may also be necessary to prevent a metabolic crisis.

As children get older, the disease is often easier to manage and the risk of metabolic crises will lessen. However, many will still need lifelong dietary treatment. Physical and occupational therapy can also be useful.

What Is the Prognosis for an Individual with Glutaric Acidemia, GCDH-Related?

If the disease is identified early and treated properly, infants with GA I can have normal or near-normal motor and intellectual development. However, even with careful treatment, about 25 to 35% of individuals with GA I develop significant motor problems and other symptoms, even without a metabolic crisis.

Children who have already had a metabolic crisis are likely to develop permanent brain damage that causes severe motor difficulties and involuntary spastic movement. The disease can be fatal in children who go untreated during a metabolic crisis. The 20-year survival rate in children with severe motor and other disabilities is 50%.

Glycine Encephalopathy, AMT-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: AMT.
Exons Sequenced: NM_000481:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Glycine Encephalopathy, AMT-related?

Glycine encephalopathy (GE), AMT-related, also known as nonketotic hyperglycinemia (NKH), is a disease that impairs the body's ability to breakdown glycine, an amino acid found in proteins. It is caused by harmful genetic changes (mutations) in the *AMT* gene, which codes for the enzyme aminomethyltransferase (AMT). AMT breaks down harmful substances, such as glycine, into smaller pieces. Over time, glycine builds up to toxic levels in the brain, organs, and other body tissues. This can lead to lack of energy (lethargy), seizures, low muscle tone, breathing difficulties, coma, and often death. Individuals have intellectual disability and seizures. The majority of individuals with encephalopathy present in the newborn period, but the age at which symptoms appear can vary. There are two forms of the disease: severe and attenuated.

SEVERE FORM

Approximately 85% of those with symptoms in the newborn period and 50% of those with onset between two weeks to three months will have the severe form of GE. Individuals with the severe form will not make any developmental progress and will have seizures that are difficult to control with medications. Most affected individuals will present in the newborn period with rapidly worsening symptoms. However, individuals with the severe form can also begin to show symptoms between two weeks to three months.

ATTENUATED FORM

Approximately 20% of all children affected with GE will have less-severe symptoms (the attenuated form). Individuals who have the attenuated form will have variable progress with their development. They may have seizures, but the seizures are typically better controlled with medications. While some individuals with the attenuated form will present in the newborn period, others may not show symptoms until after three months of age.

How common is Glycine Encephalopathy, AMT-related?

Several genes are known to cause GE and approximately 15-20% of GE is caused by mutations in the *AMT* gene. The incidence of Glycine Encephalopathy, AMT-related is approximately 1/275,000.

How is Glycine Encephalopathy, AMT-related treated?

There is no cure for GE. Treatment is aimed at lowering the levels of glycine in the body and controlling seizures. Glycine can be reduced through certain medications (e.g., sodium benzoate) and a low-protein diet. Anticonvulsant medications can be used to control seizures, but they may not be completely effective for all individuals. The health of individuals with GE must usually be monitored by many different specialists.

What is the prognosis for an individual with Glycine Encephalopathy, AMT-related?

Infants with the severe form of GE will not make any progress in major developmental milestones (such holding objects, sitting, crawling, walking, or talking). However, some children may learn to smile and roll. Certain skills may be lost as the child grows (such as bottle feeding and eye contact). Seizures will develop in the first year of life and are very difficult to treat with medications. Death in the first year of life is common.

Developmental progress varies in individuals with the attenuated form. Some children may learn to sit, walk, and communicate. Communication is most often non-verbal (such as by using sign language). The majority of affected individuals will have moderate to severe intellectual disability and attend special-education classes in school. These children may develop movement disorders and behavioral problems. Individuals who have seizures typically respond to treatment. Affected individuals rarely present symptoms after one year of age. Those who do typically have milder intellectual disability, and seizures are uncommon in them.

Glycine Encephalopathy, GLDC-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GLDC.
Exons Sequenced: NM_000170:1-25.

Detection Rate	Population
94%	African American
94%	Ashkenazi Jewish
94%	Eastern Asia
94%	Finland
94%	French Canadian or Cajun
94%	Hispanic
94%	Middle East
94%	Native American
94%	Northwestern Europe
94%	Oceania
94%	South Asia
94%	Southeast Asia
94%	Southern Europe
94%	Worldwide

What is Glycine Encephalopathy, GLDC-related?

Glycine encephalopathy (GE), GLDC-related, also known as nonketotic hyperglycinemia (NKH), is a disease that impairs the body's ability to breakdown glycine, an amino acid found in proteins. Glycine encephalopathy is caused by harmful genetic changes (mutations) in the *GLDC* gene, which codes for the enzyme glycine decarboxylase (GLDC). Over time, if this enzyme is not working properly, glycine builds up to toxic levels in the brain, organs, and other body tissues. This can lead to lack of energy (lethargy), low muscle tone, breathing difficulties, coma, and often death. Individuals with GE typically have intellectual disability and seizures. The majority of individuals with encephalopathy present in the newborn period, but the age at which symptoms appear can vary. There are two forms of the disease: severe and attenuated.

SEVERE FORM

Approximately 85% of those with symptoms in the newborn period and 50% of those with onset between two weeks to three months will have the severe form of GE. Individuals with the severe form will not make any developmental progress and will have seizures that are difficult to control with medications. Most affected individuals will present in the newborn period with rapidly worsening symptoms. However, individuals with the severe form can also begin to show symptoms between two weeks to three months.

ATTENUATED FORM

Approximately 20% of all children affected with GE will have less severe symptoms (the attenuated form). Individuals who have the attenuated form will have variable progress with their development and may have seizures, but the seizures are typically more easily controlled with medications. While some individuals with the attenuated form will present in the newborn period, others may not show symptoms until after three months of age.

How common is Glycine Encephalopathy, GLDC-related?

Several genes are known to cause GE and approximately 80% of GE is caused by mutations in the *GLDC* gene. The incidence of glycine encephalopathy, GLDC-related is approximately 1/95,000, however, the incidence may be higher in certain populations, such as Finland and British Columbia.

How is Glycine Encephalopathy, GLDC-related treated?

There is no cure for GE. Treatment is aimed at lowering the levels of glycine in the body and controlling seizures. Glycine can be reduced through certain medications (e.g., sodium benzoate) and a low-protein diet. Anticonvulsant medications can be used to control seizures, but they may not be completely effective for all individuals. The health of individuals with GE is usually monitored by many different specialists.

What is the prognosis for an individual with Glycine Encephalopathy, GLDC-related?

Infants with the severe form of GE will not make any progress in major developmental milestones (such holding objects, sitting, crawling, walking, or talking). However, some children may learn to smile and roll. Certain skills may be lost as the child grows (such as bottle feeding and eye contact). Seizures will develop in the first year of life and are very difficult to treat with medications. Death in the first year of life is common.

Developmental progress varies in individuals with the attenuated form. Some children may learn to sit, walk, and communicate. Communication is most often non-verbal (such as using sign language). The majority of affected individuals will have moderate to severe intellectual disability and attend special-education classes in school. These children may develop movement disorders and behavioral problems. Individuals who have seizures typically respond to treatment. Affected individuals usually start showing symptoms before one year of age. However, for individuals who do start showing symptoms after one year of age, intellectual disability is typically milder and and seizures are uncommon.

Glycogen Storage Disease Type Ia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: G6PC1.
Exons Sequenced: NM_000151:1-5.

Detection Rate	Population
98%	African American
>99%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Glycogen Storage Disease Type Ia?

Glycogen Storage Disease Type I (GSDI), also called von Gierke disease, is an inherited disorder that impairs the body's ability to break down a stored form of sugar, called glycogen. There are two genes associated with GSDI, and harmful genetic changes (mutations) in *G6PC1* (formerly known as *G6PC*) cause GSDIa. In GSDIa, the body cannot maintain normal blood-sugar levels between meals, leading to low blood sugar (hypoglycemia). Additionally, glycogen builds up in organs, leading to an enlarged liver (hepatomegaly) and enlarged kidneys (nephromegaly).

Infants with GSDIa appear normal at birth, but usually begin to show symptoms when they start to sleep longer through the night. Low blood sugar can cause tiredness, irritability, and seizures. If not properly diagnosed, infants typically experience a medical crisis within the first few months of life.

Children diagnosed with GSDIa have swollen abdomens due to an enlarged liver, as well as delayed or stunted growth. Non-cancerous (benign) tumors in the liver are often seen around the time of puberty. Rarely, these can become cancerous. Changes in kidney function may occur as a patient reaches his or her twenties and may include kidney stones and a decreased ability to filter waste products. In advanced cases, dialysis and/or a kidney transplant may be needed. Other symptoms or complications that may develop include delayed puberty, thinning of the bones (osteoporosis), and a form of arthritis caused by uric acid crystals in joints (gout). Mental function is not affected by GSDIa.

How common is Glycogen Storage Disease Type Ia?

The incidence of glycogen storage disease type I (both Ia and Ib) is 1 in 100,000 live births. Approximately 80% of glycogen storage disease type I cases are GSDIa.

How is Glycogen Storage Disease Type Ia treated?

Individuals with GSDIa should be followed by a team of specialists who are familiar with the long-term management of glycogen storage disease to ensure appropriate monitoring and treatment for potential complications of the condition. The treatment of GSDIa involves careful monitoring of the patient's diet, both in the type of foods eaten and the frequency of meals. Individuals with GSDIa should avoid foods with sucrose (table sugar), fructose (sugar from fruits), and lactose and galactose (sugars found in milk). To maintain healthy blood sugar levels, individuals need to eat every 1-3 hours during the day and every 3-4 hours at night.

Infants and young children often need a feeding tube to tolerate frequent eating. A feeding pump may be needed at night and for emergency feedings, should their blood sugar drop to dangerously low levels. Children with GSDIa often develop problems eating and swallowing food orally and may need therapy to relearn sucking, swallowing, and sometimes speech.

Physicians recommend that individuals with GSDIa drink cornstarch mixed with water, soy formula, or soy milk. Cornstarch is digested slowly and therefore releases its glucose gradually, helping to safely extend the time between meals. Due to the restricted nature of the diet, multivitamins, calcium, and vitamin D are necessary.

What is the prognosis for an individual with Glycogen Storage Disease Type Ia?

With careful monitoring of diet and blood sugar levels, individuals with GSDIa typically have normal growth and live into adulthood. Without close monitoring of the diet, extremely low blood sugar levels can be fatal. Even with treatment, adolescence and adults may still develop kidney complications, high blood pressure, and cancerous liver tumors.

Glycogen Storage Disease Type Ib

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SLC37A4.
Exons Sequenced: NM_001164277:3-11.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Glycogen Storage Disease Type Ib?

Glycogen Storage Disease Type Ib (GSDIb), also called von Gierke disease, is an inherited disorder in which the body lacks an enzyme called glucose-6-phosphate translocase. GSDIb is caused by mutations in the *SLC37A4* gene. A deficiency of glucose-6-phosphate translocase impairs the body's ability to breakdown a stored form of sugar, called glycogen, into glucose. As a result, the body cannot maintain normal blood-sugar levels between meals, leading to low blood sugar (hypoglycemia). Also, glycogen builds up in the body and impairs the function of the liver, the kidneys, and other organs.

Children with GSDIb appear normal at birth but usually begin to show symptoms when they start to sleep longer through the night. Low blood sugar can cause tiredness, irritability, and seizures. Children with GSDIb typically have abnormal levels of certain metabolic substances, such as increased blood levels of lactic acid (lactic acidosis), fats (hyperlipidemia), and a waste product called uric acid (hyperuricemia). If not properly diagnosed, these children will likely experience a medical crisis within the first few months of life. Children with GSDIb have delayed or stunted growth and the appearance of a swollen abdomen due to an enlarged liver. Other potential symptoms or complications include delayed puberty, thinning of the bones (osteoporosis), and a form of arthritis due to uric acid crystals in joints (gout). Mental function is not affected by GSDIb. Non-cancerous (benign) tumors in the liver are often seen around the time of puberty. Rarely, these can become cancerous. Changes in kidney function may occur as the individual reaches his or her twenties, and may include kidney stones and a decreased ability to filter waste products. In advanced cases, dialysis and/or a kidney transplant may be needed.

Individuals with GSDIb are also prone to frequent bacterial and fungal infections, due to the impaired function and/or decreased levels of a type of white blood cell called neutrophils. They are also more likely to develop chronic inflammation of the pancreas, chronic inflammatory bowel disease, and Crohn's disease.

Individuals with glycogen storage disease type Ia (GSDIa) lack a different component of glucose-6-phosphatase and experience similar symptoms. For this reason, GSDIa and GSDIb are often spoken about as one disease: GSD type I.

How Common Is Glycogen Storage Disease Type Ib?

The incidence of glycogen storage disease type I (both GSDIa and GSDIb) is 1 in 100,000 live births. Approximately 20% of glycogen storage disease type I is GSDIb.

How Is Glycogen Storage Disease Type Ib Treated?

The treatment of GSDIb involves careful monitoring of the affected individual's diet, both in the frequency of meals and type of foods eaten. Individuals with GSDIb should avoid foods with sucrose (table sugar), fructose (sugar from fruits), and lactose and galactose (sugars found in milk). They need to eat around the clock, typically every one to three hours during the day and every three to four hours at night, to maintain healthy blood sugar levels.

Infants and young children often need a feeding tube in order to tolerate frequent eating. They may also need to use a feeding pump at night and for emergency feedings should their blood sugar drop dangerously low. Because they must eat so frequently, children with GSDIb frequently develop problems eating and swallowing food orally and may need therapy to re-learn sucking, swallowing, and sometimes speech.

Physicians recommend that individuals with GSDIb drink cornstarch mixed with water, soy formula, or soy milk. Cornstarch is digested slowly and therefore releases its glucose gradually, helping to safely extend the time between meals. Due to the restricted nature of the diet, multivitamins, calcium, and vitamin D are necessary.

Individuals affected by GSDIb also frequently take medication to increase the number of neutrophils, a type of white blood cell that fights infection. They must be vigilant in treating any infection in the body as it arises.

Individuals with GSDIb should be followed by a team of specialists who are familiar with the long-term management of GSD, to ensure appropriate monitoring and treatment for potential complications of the condition.

What Is the Prognosis for an Individual with Glycogen Storage Disease Type Ib?

With careful monitoring of diet and blood-sugar levels, individuals with GSDIb can improve their metabolic abnormalities and live into adulthood. Without close monitoring of the diet, however, extremely low blood sugar can be fatal. In adolescence and adulthood, individuals with GSDIb must be alert to infections, kidney complications, high blood pressure, and/or cancerous liver tumors. Long-term complications can include kidney damage, thinning bones (osteoporosis), and benign tumors of the liver (adenomas).

Glycogen Storage Disease Type III

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: AGL.
Exons Sequenced: NM_000642:2-34.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Glycogen Storage Disease Type III?

Glycogen Storage Disease Type III (GSD III), also known as Cori disease or Forbes disease, is an inherited condition in which the body lacks the glycogen debranching enzyme. GSD III is caused by mutations in the *AGL* gene. A deficiency of the glycogen debranching enzyme prevents the body from breaking down glycogen, a stored form of sugar. As a result, glycogen cannot properly be used to energize and fuel the body and glycogen molecules accumulate in the body. This results in various complications, notably involving the liver and muscles.

Symptoms of GSD III often appear in infancy or childhood. The liver is enlarged (hepatomegaly), leading to a noticeably swollen abdomen. This enlargement usually subsides with puberty, although there may be long-term liver damage. Low blood sugar (hypoglycemia) may occur. The majority of people with GSD III experience muscle weakness. This weakness can be severe at times and may worsen in adulthood. Children with the disease may experience delayed growth but usually reach normal adult height. Some people with the disease also develop an enlarged heart, though its function is usually normal.

Some individuals with GSD III do not have symptoms until adulthood. This later onset typically corresponds with milder symptoms.

How Common Is Glycogen Storage Disease Type III?

The incidence of GDS III is 1 in 100,000. This disease is more common in Sephardic Jews of North African descent and in individuals from the Faroe Islands of the North Atlantic.

How Is Glycogen Storage Disease Type III Treated?

GSD III is managed mainly by frequent, small meals and a high-protein diet with cornstarch supplementation. Cornstarch, which breaks down slowly into simple sugars, may alleviate symptoms of low blood sugar between meals. Parents of infants should be particularly careful and monitor the child's diet to avoid hypoglycemic seizures. Physicians will monitor the liver, heart, and muscles in affected individuals and recommend physical therapy when necessary to promote better movement.

What Is the Prognosis for an Individual with Glycogen Storage Disease Type III?

Among infants with GSD III, there is an increased rate of fatalities due to seizures caused by low blood sugar. While an exact lifespan is unknown, many individuals with GSD III live well into adulthood. Liver disease and muscle weakness may contribute to a cause of death in the long term.

Glycogen Storage Disease, GBE1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GBE1.
Exons Sequenced: NM_000158:1-16.

Detection Rate	Population
97%	African American
>99%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe
97%	Worldwide

What is Glycogen Storage Disease, GBE1-related?

Glycogen storage disease, GBE1-related (GSD, GBE1-related), also known as glycogen storage disease type IV (GSD IV), is characterized by variable liver, muscle, nerve, and heart symptoms. It is caused by harmful genetic changes (variants) in the *GBE1* gene. Individuals with GSD, GBE1-related, have abnormally formed sugar storage molecules (glycogen), which build up in certain tissues, resulting in various symptoms.

There are several types of GSD, GBE1-related, including a hepatic and neuromuscular form and an adult-onset form known as adult polyglucosan body disease (APBD). The severity and type of symptoms, as well as the age of onset, can vary considerably, even among individuals in the same family. Some symptoms may overlap between forms.

HEPATIC FORM

The hepatic form is the most common type of GSD, GBE1-related. In most cases, infants appear normal at birth but develop symptoms within the first few months of life. Initial symptoms include poor weight gain (failure to thrive) and enlarged liver (hepatomegaly), followed by progressive liver disease and low muscle tone (hypotonia). Some individuals may also develop an enlarged heart (dilated cardiomyopathy).

Less commonly, individuals have a milder presentation, in which symptoms do not begin until childhood, and liver disease does not worsen over time. These individuals may or may not develop symptoms affecting the muscles or heart.

NEUROMUSCULAR FORM

Most individuals with neuromuscular GSD, GBE1-related, have symptoms present at birth or develop in early infancy, such as low muscle tone, joint abnormalities (contractures), an enlarged heart, and difficulty breathing. Before birth, some will have findings on prenatal ultrasound, including decreased fetal movements (fetal akinesia), increased amniotic fluid (polyhydramnios), and a buildup of fluids in the fetal tissues and organs (fetal hydrops).

In rare cases, muscle and heart disease may present as late as the second decade and can range in severity from mild to severe.

ADULT POLYGLUCOSAN BODY DISEASE

This is an adult-onset form of GSD, GBE1-related, with symptoms typically developing after age 40. Common symptoms include weakness, difficulties with walking and bladder control, and numbness and loss of sensation in the extremities. Approximately half of individuals develop mild issues with attention and memory (cognitive decline). This condition may be mistaken for other more common neurologic conditions, such as multiple sclerosis.

How common is Glycogen Storage Disease, GBE1-related?

The incidence of GSD, GBE1-related, in the population is 1 in 600,000-800,000 births. The incidence of GSD, GBE1-related, is more common among individuals of Ashkenazi Jewish descent.

How is Glycogen Storage Disease, GBE1-related treated?

There is no cure for GSD, GBE1-related. Treatment for the condition is directed at managing an individual's specific symptoms. Individuals may benefit from receiving care through a team of specialists that may include physicians, speech, physical, and occupational therapists, and social workers. For some individuals with significant liver or heart disease, an organ transplant may be an option; however, these procedures can carry significant risks.

What is the prognosis for an individual with Glycogen Storage Disease, GBE1-related?

Prognosis is highly variable and depends on the specific form and age of symptom onset.

Individuals who present with neuromuscular GSD, GBE1-related, at birth often die as newborns or infants due to heart and breathing issues. Most individuals with hepatic GSD, GBE1-related, will die before age 5, though a liver transplant may extend the lifespan of these individuals. Individuals with milder and later-onset types of neuromuscular and hepatic GSD, GBE1-related, can live into their thirties or beyond, depending on the severity of their symptoms. Individuals with APBD typically survive into their mid-seventies.

Glycogen Storage Disease, PFKM-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PFKM.
Exons Sequenced: NM_001166686:2-25.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Glycogen Storage Disease, PFKM-related?

Glycogen storage disease, PFKM-related (GSD, PFKM-related), also known as glycogen storage disease type VII or Tarui disease, is a condition characterized by muscle issues (myopathy). It is caused by harmful genetic changes (variants) in the *PFKM* gene. Glycogen is a stored form of sugar that is normally broken down to produce energy. Individuals with GSD, PFKM-related, are unable to break down glycogen. The glycogen cannot be used as energy and instead it builds up in the muscles. This leads to many of the symptoms of the disorder.

GSD, PFKM-related, can be classified into four different forms, which vary significantly in terms of severity and age of onset.

CLASSICAL FORM

This is the most common form of GSD, PFKM-related. Beginning in childhood, individuals have symptoms that arise with physical activity, such as fatigue, muscle cramps, and weakness (exercise intolerance). They may experience nausea and vomiting with exertion. With too much exercise, they have an increased risk of excess muscle breakdown (rhabdomyolysis), which can lead to complications such as kidney damage. Individuals may also have a low number of red blood cells (hemolytic anemia).

SEVERE INFANTILE FORM

This is a rare form of GSD, PFKM-related, with only a handful of cases described. Infants with this form have severe symptoms such as low muscle tone (hypotonia), seizures, difficulty breathing, and problems with the heart (cardiomyopathy) and joints (contractures).

LATE-ONSET FORM

In this form, individuals have muscle weakness and pain that begins in adulthood, though they may have experienced some difficulty with exercise going back to childhood.

HEMOLYTIC FORM

This form of GSD, PFKM-related, is characterized by hemolytic anemia without muscle symptoms.

How common is Glycogen Storage Disease, PFKM-related?

The exact incidence of GSD, PFKM-related, is unknown. Approximately 100-200 individuals have been diagnosed worldwide. The incidence of GSD, PFKM-related, may be more common among individuals of Ashkenazi Jewish descent.

How is Glycogen Storage Disease, PFKM-related, treated?

There is no cure for GSD, PFKM-related. Treatment for the condition is directed at managing the specific symptoms an individual has. This often means receiving care through a team of specialists that may include physicians, physical therapists, and others. Regular exercise of low to moderate intensity is typically recommended to improve fitness. Individuals with symptoms of rhabdomyolysis require prompt medical attention to avoid potentially life-threatening complications such as kidney failure.

What is the prognosis for an individual with Glycogen Storage Disease, PFKM-related?

The classical, late-onset, and hemolytic forms of the disease are not known to shorten lifespan. Individuals with the rare severe infantile form of the disease typically do not survive past early childhood.

Glycogen Storage Disease, PYGM-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PYGM.
Exons Sequenced: NM_005609:1-20.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Glycogen Storage Disease, PYGM-related?

Glycogen storage disease, PYGM-related (GSD, PYGM-related), also known as McArdle disease, is a condition characterized by difficulty with exercise, such as muscle pain, cramping, and fatigue. It is caused by harmful genetic changes (variants) in the *PYGM* gene. Individuals with GSD, PYGM-related are missing an enzyme called myophosphorylase. Without this enzyme, their muscles are unable to convert a stored form of sugar called glycogen into glucose. The muscles typically use glucose as a source of fuel during physical activity, which is why individuals with GSD, PYGM-related have difficulty with exercise.

Symptoms of GSD, PYGM-related, can begin at any age, from infancy to later adulthood, but most often appear around childhood or adolescence. The severity of the symptoms can vary greatly. Some individuals have very mild symptoms, whereas others develop rapidly progressive muscle weakness shortly after birth. Individuals typically experience symptoms at the beginning of an exercise session, but their symptoms may improve if they rest for several minutes and then resume their activity (known as a "second wind"). Some people have muscle weakness when they are not exercising.

How common is Glycogen Storage Disease, PYGM-related?

The prevalence of GSD, PYGM-related, is estimated to be 1 in 100,000 in the United States; however, this may be an underestimate since some individuals with GSD have mild symptoms that may go unrecognized.

How is Glycogen Storage Disease, PYGM-related treated?

A carefully supervised moderate-intensity exercise training program can improve exercise tolerance, while inactivity can decondition the body and result in a worsening of symptoms. Generally, it is recommended that individuals with GSD, PYGM-related avoid certain high-intensity exercises that can cause the breakdown of muscle and potentially result in kidney damage.

What is the prognosis for an individual with Glycogen Storage Disease, PYGM-related?

If an individual with GSD, PYGM-related, properly manages their physical activity the disease should not significantly affect their lifespan.

GNE Myopathy

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GNE.
Exons Sequenced: NM_001128227:1-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is GNE Myopathy?

GNE myopathy, caused by mutations in the *GNE* gene, is an inherited disease that disrupts a specific enzyme involved in the production of sialic acid. Without appropriate amounts of sialic acid, cells cannot move, attach to one another, or signal each other properly.

Individuals with GNE myopathy have a progressive weakening of the legs and arms, typically beginning in the late teens or early twenties and almost always before the age of 40. Typically individuals with the disease lose the ability to walk 20 years after symptoms appear. The muscles of the lower leg are typically affected first. As these muscles slowly weaken, walking becomes more difficult and the patient's gait changes. The weakness will spread to the thighs, hand muscles, and certain muscles of the shoulder and neck. A small number of individuals will also have weakness in the facial muscles. Often the large thigh muscles (quadriceps) are unaffected until late in the course of the disease.

For reasons not well understood, a small number of individuals with *GNE* mutations do not have symptoms of the disease.

How Common Is GNE Myopathy?

Roughly 220 individuals with GNE myopathy have been reported in medical literature. GNE myopathy is most common among Middle-Eastern Jews, particularly of Iranian descent. The disease has also been found in small numbers of non-Jews, both within and outside of the Middle East. Studies estimate that among Iranian Jewish communities in Israel and Los Angeles, 1 in every 500 to 1000 are affected by GNE myopathy.

How Is GNE Myopathy Treated?

There is no cure or treatment for GNE myopathy that can reverse or delay the progression of muscle weakness. Neurologists, rehabilitation specialists, and physical and occupational therapists can aid in relieving symptoms as they appear.

What Is the Prognosis for an Individual with GNE Myopathy?

The disease often does not cause noticeable symptoms until the late teens or early twenties, when muscle weakness begins. Movement of the arms and legs will become progressively impaired, and typically people with GNE myopathy are wheelchair-bound 20 years after symptoms begin. The disease's effect on lifespan is not well studied.

GNPTAB-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GNPTAB.
Exons Sequenced: NM_024312:1-21.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
92%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What are GNPTAB-related Disorders?

GNPTAB-related disorders are inherited, lysosomal storage disorders caused by harmful genetic changes (mutations) in the *GNPTAB* gene. There are two specific forms of GNPTAB-related disorders, mucolipidosis II and mucolipidosis III alpha/beta. The symptoms associated with GNPTAB-related disorders are caused by a buildup of harmful substances in the cells of the body. While the symptoms of both conditions are similar, mucolipidosis II is the more severe form of the disease. There have been patients described with intermediate forms of disease that fall between mucolipidosis II and mucolipidosis III alpha/beta.

Mucolipidosis II

Mucolipidosis II presents at birth with skeletal problems that can include internally rotated feet (clubfeet), spinal problems, dislocated hips, abnormal rib cages, and abnormal long bones. Infants are typically smaller than average and have very slow growth. Babies develop enlarged (coarse) facial features and thick gums in early infancy, which become more prominent with age. Most affected children will have joint stiffening, hernias, a small head and incomplete brain development (microcephaly), and severe learning difficulties. All affected individuals have heart abnormalities, and over time, all affected individuals develop difficulty in breathing (respiratory insufficiency). Infants with mucolipidosis II do not tend to meet any developmental milestones.

Mucolipidosis III Alpha/Beta

Mucolipidosis III alpha/beta typically does not present until late infancy or early childhood. Most affected children will have slower growth by age three, and affected individuals will usually be shorter than their unaffected family members. Affected children progressively develop coarse facial features. Heart problems are also very common. Individuals with mucolipidosis III alpha/beta are typically able to walk, though due to joint stiffening, may need to use a wheelchair by early adulthood. Intelligence and language development are typically normal, though many affected individuals still require special education due to physical limitations. Motor development is variable and may be normal or moderately delayed.

How common are GNPTAB-related Disorders?

Mucolipidosis II and mucolipidosis III alpha/beta affect approximately 1 in 160,000 individuals worldwide but may be more common in individuals from Portugal or Quebec.

How are GNPTAB-related Disorders treated?

There is no cure for mucolipidosis II or III alpha/beta. Management of symptoms may include occupational therapy, speech therapy, and low-impact physical therapy. Dental management and hearing rehabilitation may be beneficial, but surgeries should be avoided in order to prevent airway complications and adverse reactions to anesthesia. Hip replacement has been helpful for some individuals with a milder disease course. For patients with mucolipidosis III alpha/beta, intravenous pamidronate may provide relief from bone density loss, joint pain, and immobility, but it is not a cure.

What is the prognosis for an individual with a GNPTAB-related Disorder?

The prognosis for an individual with mucolipidosis II is poor, and death usually occurs in early childhood. Heart abnormalities and respiratory insufficiency are the major causes of death. Mucolipidosis III alpha/beta is more variable, and many affected individuals can survive into early or middle adulthood; however, exact life expectancy is unknown.

HADHA-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: HADHA.
Exons Sequenced: NM_000182:1-20.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What are HADHA-Related Disorders?

HADHA-related disorders result from the body lacking an enzyme called mitochondrial trifunctional protein. Without this enzyme, the body has trouble turning a specific type of fat from foods, known as long-chain fatty acids, into energy. This process, called fatty acid oxidation, normally breaks down long-chain fatty acids stepwise until they can be turned into usable energy. When mitochondrial trifunctional protein is missing, fatty acids build up in the body and cause damage to organs and tissues. HADHA-related disorders are caused by mutations in the *HADHA* gene.

LONG-CHAIN 3-HYDROXYACYL-COA DEHYDROGENASE DEFICIENCY

Individuals with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) have trouble converting long-chain fatty acids into energy, especially when they are not eating for a period of time (fasting), when they are ill, or when they do strenuous exercise. Symptoms can begin in infancy and include poor feeding, muscle weakness (hypotonia), low blood sugar (hypoglycemia), and low energy (lethargy). There can also be liver problems, vision loss due to damage to the retina, muscle breakdown, seizures, and sensory problems in the arms and legs (peripheral neuropathy). In more severe situations, individuals with LCHADD can have problems breathing and trouble with their heart muscle (cardiomyopathy) or rhythm (arrhythmia), which can lead to coma or death.

MITOCHONDRIAL TRIFUNCTIONAL PROTEIN DEFICIENCY (MTPD)

Individuals with MTPD tend to have similar symptoms to those with LCHADD, though the symptoms may be more severe. Most babies with the neonatal form of MTPD die in infancy. Children with a less-severe form of MTPD may not show symptoms until times of fasting, when they are ill, or when they do strenuous exercise. Some children may not have symptoms between these episodes, but repeated crisis events can lead to brain damage and intellectual and developmental disabilities.

How Common Are HADHA-Related Disorders?

The incidence of HADHA-related disorders in the United States is estimated at approximately 1 in 90,000 individuals. A similar carrier frequency and incidence (1 in 91,700) is seen in Estonia while the incidence in Germany and Poland ranges from 1 in 250,000 to 1 in 109,090 births with certain regions of Poland seeing a higher incidence of up to 1 in 16,900 births.

How Are HADHA-Related Disorders Treated?

The main method of management for LCHADD and MTPD is a special diet and avoidance of fasting. A physician or nutritionist will recommend a diet low in fats and high in carbohydrates, which are easier for an affected individual to break down, and a feeding schedule with frequent meals. Often it is necessary to have an additional dietary protocol in place for illness or other stressful times. A physician may also prescribe medium-chain triglyceride oil, L-carnitine, or other supplements for additional energy.

What Is the Prognosis for an Individual with a HADHA-Related Disorder?

Untreated, LCHADD and MTPD are often fatal in infancy or childhood. When symptoms appear in infancy, treatment is often not effective because the disease causes irreparable damage to the heart and leads to cognitive impairments.

For some cases of LCHADD and less-severe forms of MTPD, early detection and early treatment can prevent many of the severe complications and allow affected individuals to have typical growth and development. Even with careful treatment, there may still be some episodes of low blood sugar and damage to the heart, liver, and muscle. Recurrent acute episodes of low blood sugar can lead to cognitive impairments over time. With treatment, some individuals with LCHADD or MTPD may live into adulthood.

Individuals with later-onset disease and symptoms limited to muscle weakness and pain are typically healthy and do not have problems with the heart, liver, or changes in cognitive ability or intellect.

Additional Considerations for Carriers

Carriers of fatty-acid oxidation defects, including HADHA-related disorders, do not typically show symptoms of the disease. However, there is an increased risk of serious pregnancy complications, particularly in the third trimester, in women carrying a fetus affected with HADHA-related disorder. These complications can include HELLP syndrome and acute fatty liver of pregnancy. A woman whose pregnancy may be affected by a fatty-acid oxidation defect, such as HADHA-related disorder, should speak with her physician for recommendations and may benefit from consultation with a high-risk physician.

Hearing Loss and Deafness, LOXHD1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: LOXHD1.
Exons Sequenced: NM_144612:1-40.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Hearing Loss and Deafness, LOXHD1-related?

Hearing Loss and Deafness, LOXHD1-related, also known as DFNB77, is a condition characterized by hearing loss. It is caused by harmful genetic changes (variants) in the *LOXHD1* gene. The *LOXHD1* gene is needed for the normal function of hair cells in a part of the inner ear that is important for hearing (cochlea). Harmful changes in this gene cause abnormalities in the hair cells of the cochlea, which is why individuals with this condition experience hearing loss.

The severity of hearing loss is variable between affected individuals, even those within the same family. The majority of people with this condition have hearing loss that falls within the severe to profound range, though some are more mildly affected. Hearing loss may be progressive, meaning that it can worsen over time. The age of onset is also variable. Hearing loss typically starts before age 5, but some individuals may not experience symptoms until later childhood or even adulthood. Unlike other forms of hearing loss, hearing loss and deafness, LOXHD1-related, does not affect movement or balance.

How common is Hearing Loss and Deafness, LOXHD1-related?

The exact incidence of hearing loss and deafness, LOXHD1-related, is unknown. Over 100 individuals have been diagnosed worldwide.

How is Hearing Loss and Deafness, LOXHD1-related treated?

Depending on the degree of hearing loss, some individuals show improvement with hearing aids. Cochlear implants may be considered for individuals born with profound hearing loss or individuals whose hearing progresses to a degree to which hearing aids are not sufficient. Affected individuals may also benefit from an educational program for the hearing impaired.

What is the prognosis for an individual with Hearing Loss and Deafness, LOXHD1-related?

While a person with this condition will have hearing loss, it does not shorten lifespan and is not known to impact other systems of the body.

Hemophilia B

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: F9.
Exons Sequenced: NM_000133:1-8.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
96%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
96%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe
97%	Worldwide

What is Hemophilia B?

Hemophilia B (HEMB) is a condition that causes prolonged bleeding. It is caused by harmful changes (variants) in the *F9* gene. Individuals with HEMB do not have enough of an important protein called factor IX (nine). This protein helps to form blood clots after an injury. Individuals with the condition may experience life-threatening blood loss after an injury or medical procedures. HEMB is an X-linked disease. This means the condition is typically more severe in biological males (XY). However, biological females (XX) may also have symptoms of the condition.

HEMB has different levels of severity: severe, moderate, and mild. The severity of the condition depends on how much factor IX an individual has. The type of harmful change an individual has can help determine which severity they are at risk for. All individuals with a harmful change in *F9* should speak with a genetic counselor to understand their risks.

The symptoms of each level of severity are described below.

SEVERE HEMOPHILIA B

Individuals with severe HEMB usually have less than 1% factor IX clotting activity. These individuals often show symptoms in the first two years of life. Without ongoing treatment, they can experience excess bleeding after injury and episodes of spontaneous bleeding into muscles and joints. These episodes can lead to joint pain, swelling, and permanent damage.

MODERATE HEMOPHILIA B

Individuals with moderate HEMB usually have 1-5% factor IX clotting activity. These individuals often show symptoms in the first five to six years of life. Individuals with the moderate form also experience prolonged bleeding after injury, but they have less spontaneous bleeding than individuals with the severe form.

MILD HEMOPHILIA B

Individuals with mild HEMB usually have 6-40% factor IX clotting activity. These individuals often only experience prolonged bleeding after severe injury or surgery. These individuals may not be identified as having the condition until late childhood or adulthood. Individuals with the mild form may go years between prolonged bleeding episodes.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

About 30% of carrier females will exhibit symptoms. Most symptomatic carriers will have mild HEMB. However, there can be a wide range of severities.

How common is Hemophilia B?

The incidence of HEMB in the population is 1 in 20,000 to 1 in 30,000 male births.

How is Hemophilia B treated?

There is no cure for HEMB. Treatment for the condition is directed at replacing the missing factor IX protein in situations where the individuals need it. This is usually after an injury and before surgery or dental work. Individuals with severe disease may receive factor IX through an IV more regularly to prevent spontaneous bleeding episodes. Individuals diagnosed with hemophilia will often benefit from avoidance of high-risk activities, especially those with a high risk of head injury. Regular checkups with a physician specializing in treating hemophilia are recommended.

In addition to factor IX treatment, in 2022, the FDA approved a gene therapy treatment called etranacogene dezaparvovec–drlb (Hemgenix). This single-dose therapy is approved for use in adults with moderate to severe HEMB.

What is the prognosis for an individual with Hemophilia B?

With treatment, individuals with HEMB have a good prognosis with a normal or near-normal lifespan. Individuals with HEMB are at higher risk of early death due to bleeding in the brain.

Hereditary Fructose Intolerance

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ALDOB.
Exons Sequenced: NM_000035:2-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Hereditary Fructose Intolerance (HFI)?

Hereditary fructose intolerance (HFI)is a disorder caused by mutations in the *ALDOB* gene that is characterized by an inability to break down fructose, a common sugar found in fruit and many other foods. When an individual with HFI consumes fructose, the result is low blood sugar (hypoglycemia) and a buildup of toxic substances in the liver.

The first symptoms of HFI usually appear when a child is first introduced to formula or foods containing fructose or the related sugars sucrose and sorbitol (a sugar substitute). Symptoms that may appear include irritability, upset stomach, vomiting, sweating, and/or sleepiness. If unrecognized and untreated, children with HFI will fail to grow at a normal rate, may develop a yellowing of the skin and whites of the eyes (jaundice), and have enlargement of the liver and spleen (hepatosplenomegaly). Without treatment, HFI can eventually lead to serious liver disease, hypoglycemic shock, seizures, and kidney or liver failure. In extreme cases, it can be fatal. For this reason, early detection and treatment is critical.

Symptoms of HFI can vary from mild to severe. Individuals with HFI often show an aversion to sweets and fruit, and those with mild HFI may, therefore, be protected from some of the symptoms they would otherwise experience. In addition, those with a severe course of the disease may develop serious liver disease later in life, even with a careful diet.

How Common Is HFI?

The estimated prevalence of HFI is approximately 1 in 20,000 to 1 in 30,000 individuals worldwide. However, the condition may be more or less common among certain ethnic groups.

How Is HFI Treated?

Treatment for HFI involves strict control of diet, eliminating all foods or products (for example, medicines or vitamins) containing fructose, sucrose, or sorbitol. With a carefully managed diet, individuals with HFI can be symptom-free, although symptoms will quickly return upon consuming fructose, sucrose, or sorbitol. In cases where liver disease has progressed to a life-threatening stage, liver transplantation is possible.

What Is the Prognosis for an Individual with HFI?

Without elimination of all fructose, sucrose, and sorbitol, HFI can be life threatening. Continued consumption of these sugars can lead to hypoglycemic shock, seizures, coma, serious liver disease, liver or kidney failure, and potentially death. With a careful diet, however, individuals with HFI may be symptom-free, have normal growth and development, and have a normal life expectancy. The earlier the condition is diagnosed and the diet adjusted, the less damage is done to the liver and kidneys and the better the overall prognosis. Early detection and diet modification are also important for age-appropriate growth. In a minority of individuals who have a severe form of HFI, liver disease may still develop, despite a careful diet.

Hermansky-Pudlak Syndrome, HPS1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: HPS1.
Exons Sequenced: NM_000195:3-20.

Detection Rate	Population
94%	African American
94%	Ashkenazi Jewish
94%	Eastern Asia
94%	Finland
94%	French Canadian or Cajun
94%	Hispanic
94%	Middle East
94%	Native American
94%	Northwestern Europe
94%	Oceania
94%	South Asia
94%	Southeast Asia
94%	Southern Europe
94%	Worldwide

What is Hermansky-Pudlak syndrome, HPS1-related?

Hermansky-Pudlak syndrome, HPS1-related, also known as Hermansky-Pudlak syndrome type 1 or HPS1, is a condition characterized by light coloring of the skin, hair, and eyes (hypopigmentation). Vision problems and excess bleeding are also common. The condition is caused by harmful genetic changes (variants) in the *HPS1* gene.

Individuals with HPS1 have lighter colored skin, hair, and eyes than their family members. Affected individuals are at an increased risk for skin cancer. Over time, the skin can also become rough and thickened. Vision problems such as rapid, involuntary eye movements are often present at birth. Poor vision and sensitivity to light are also common. Generally, vision problems do not worsen after early childhood. HPS1 also causes excess bleeding and bruising. Patients with HPS1 are more prone to nosebleeds and heavy menstrual periods. Excess bleeding is also seen during tooth extraction, dental surgery, circumcision, and other surgeries. Life-threatening bleeding is rare.

Individuals with HPS1 may also develop lung disease (pulmonary fibrosis), with symptoms typically beginning in the 30s. Inflammation of the digestive tract (colitis) is also possible.

How common is Hermansky-Pudlak syndrome, HPS1-related?

The worldwide incidence of HPS1 is unknown, but it is considered rare. The condition is more common in the northwest Puerto Rican population, where 1 in 1,800 individuals are affected. It is also more common in certain Japanese, Swiss, and Indian populations.

How is Hermansky-Pudlak syndrome, HPS1-related, treated?

There is no cure for HPS1. Vision problems are treated with corrective lenses. Low vision aids such as magnifiers may also be helpful. Reduced sun exposure, sunscreen, and skin-covering clothing are recommended to reduce skin damage and skin cancer. Medication can be given before oral surgery to help reduce excess bleeding. Platelets or red cell blood transfusions can be given for excessive bleeding following major surgeries. Individuals with colitis may be treated with medication or surgery in severe cases. Some individuals with severe pulmonary fibrosis have been treated with lung transplantation.

What is the prognosis for an individual with Hermansky-Pudlak syndrome, HPS1-related?

With treatment, most individuals with HPS1 have a normal lifespan. If present, pulmonary fibrosis may be fatal within a decade unless an individual undergoes lung transplantation.

Hermansky-Pudlak Syndrome, HPS3-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: HPS3.
Exons Sequenced: NM_032383:1-17.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
94%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Hermansky-Pudlak Syndrome, HPS3-related?

Hermansky-Pudlak syndrome, HPS3-related (HPS3), is a condition characterized by light coloring of the skin, hair, and eyes (hypopigmentation). Vision problems and excess bleeding are also common. Hermansky-Pudlak has several subtypes, each caused by different genes. In the case of HPS3, it results from harmful genetic changes (variants) in the *HPS3* gene.

Individuals with HPS3 have lighter-colored skin, hair, and eyes than their family members. Affected individuals are at an increased risk for skin cancer. Over time, the skin can also become rough and thickened. Vision problems such as rapid, involuntary eye movements are often present at birth. Poor vision and sensitivity to light are also common. Generally, vision problems do not worsen after early childhood. HPS3 also causes excess bleeding and bruising. Patients with HPS3 are more prone to nosebleeds and heavy menstrual periods. Excess bleeding is also seen during tooth extraction, dental surgery, circumcision, and other surgeries. Life-threatening bleeding is rare. Inflammation of the digestive tract (colitis) is also possible.

There is wide variability in symptoms between individuals. The symptoms of HPS3 are similar to other forms of Hermansky-Pudlak syndrome but may be milder, and some individuals may not have very noticeable symptoms. Breathing problems can be common in other types of Hermansky-Pudlak syndrome but are not typically observed in individuals with HPS3.

How common is Hermansky-Pudlak Syndrome, HPS3-related?

The worldwide incidence of HPS3 is estimated to be between 1 in 500,000 to 1,000,000 individuals. The condition is most common in Puerto Ricans, with an incidence estimated to be as high as 1 in 4000, and may be more common in the Ashkenazi Jewish population.

How is Hermansky-Pudlak Syndrome, HPS3-related, treated?

There is no cure for HPS3. Vision problems are treated with corrective lenses. Low vision aids such as magnifiers may also be helpful. Reduced sun exposure, sunscreen, and skin-covering clothing are recommended to reduce skin damage and cancer. Medication can be given before oral surgery to help reduce excess bleeding. Platelets or red cell blood transfusions can be given for excessive bleeding following major surgeries.

What is the prognosis for a person with Hermansky-Pudlak Syndrome, HPS3-related?

HPS3 is not known to affect lifespan. Individuals with HPS3 will have vision impairment, increased bleeding tendency, and increased risk for skin cancer. HPS3 does not affect intelligence.

Hexosaminidase A Deficiency

INCLUDING TAY-SACHS DISEASE

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: HEXA.
Exons Sequenced: NM_000520:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Hexosaminidase A Deficiency (Tay-Sachs Disease)?

Hexosaminidase A deficiency (HEX A deficiency), also known as Tay-Sachs disease, is caused by harmful genetic changes in the *HEXA* gene. It is a condition that mainly affects the nervous system. Individuals with Tay-Sachs disease do not have enough functional beta-hexosaminidase A enzyme. The beta-hexosaminidase A enzyme normally breaks down a substance called GM2 ganglioside. Without enough functional beta-hexosaminidase A enzyme, GM2 ganglioside builds up in the brain and other nerve cells and causes them to die.

Because of the ongoing damage to the brain and nerve cells, individuals with Tay-Sachs disease experience neurological symptoms that become more severe over time. There are several forms of Tay-Sachs disease, including acute infantile (classic), subacute juvenile, and late-onset forms.

ACUTE INFANTILE (CLASSIC) FORM

Classic Tay-Sachs disease is the most common and severe form. It is a progressive condition that results in the gradual loss of movement and mental function. It is typically fatal early in childhood.

The symptoms of classic Tay-Sachs disease usually appear in infants between three and six months of age. Parents or caregivers may notice that they appear to be paying less attention with their eyes (decreased visual attentiveness) and are easily startled, and they will begin to lose the ability to turn over, sit, or crawl. As the disease progresses, infants with classic Tay-Sachs disease develop seizures, vision loss, an enlarged head size, and eventually become paralyzed. Death typically occurs by the age of four.

SUBACUTE JUVENILE FORM

Individuals with subacute juvenile Tay-Sachs disease typically begin to show symptoms between the ages of two and ten. Early signs can include weakness, clumsiness, and difficulties with speech. As the disease progresses, individuals experience a loss of their speech, motor, and cognitive skills. Other symptoms include stiff (spastic) movements, seizures, and difficulty swallowing. Death often occurs in the teenage years. There can be variability in the age of onset and symptoms experienced even among individuals from the same family.

LATE-ONSET FORM

The symptoms of late-onset Tay-Sachs disease are typically recognized in an individual's twenties or thirties, though some may have subtle features as early as childhood. Individuals may experience muscle weakness, involuntary muscle twitching, speech difficulties, altered thought processes, or severe mental disorders like psychosis or schizophrenia. Symptoms tend to progress more slowly than in other forms of Tay-Sachs disease. There is considerable variability in the age of onset and types of symptoms individuals experience with this form of the disorder, even within a single family. Symptoms of late-onset Tay-Sachs disease can appear similar to other more common diseases, which can sometimes lead to a misdiagnosis.

How common is Tay-Sachs disease?

The incidence of classic Tay-Sachs disease in the population is 1 in 320,000 births. It is more common among individuals of Ashkenazi Jewish, French-Canadian, Louisiana Cajun, and Pennsylvania Amish descent. The incidence of other forms of Tay-Sachs disease is unknown.

How is Tay-Sachs Disease treated?

At this time there is no cure for Tay-Sachs disease, and treatment largely focuses on ensuring proper nutrition and hydration, protecting the ability to breathe, managing any infections, and controlling seizures with medication.

There is also no cure for the juvenile and late-onset forms of Tay-Sachs disease. Treatment largely addresses symptoms as they arise, such as assisting mobility with mechanical aids or controlling seizures and mental disorders with medication. Because the symptoms of these forms of the disease vary widely, treatment depends on the types of symptoms and their severity.

What is the prognosis for an individual with Tay-Sachs Disease?

Even with treatment, children affected by classic Tay-Sachs disease usually die by the age of four.

The prognosis for an individual with the other forms of Tay-Sachs disease can vary, depending on both the age of onset and the severity of symptoms. Those with juvenile-onset Tay-Sachs disease typically experience progressive loss of skills between the ages of two and ten and death occurs in the teenage years. In more severe cases, those with juvenile-onset Tay-Sachs disease can die in early childhood.

The prognosis for those with the late-onset form varies even more. The lifespans of individuals with late-onset Tay-Sachs disease are not well studied and can be difficult to predict, though there are certainly examples of people with this condition who live into their sixties or seventies.

HFE-associated Hereditary Hemochromatosis

Available Methodologies: targeted genotyping (v1.0) and interpretation of reported variants (v4.0).
Gene: HFE.
Variants Genotyped (2): H63D, C282Y.

WHAT IS HFE-ASSOCIATED HEREDITARY HEMOCHROMATOSIS (HFE-HHC)?

HFE-HHC is a common and treatable inherited disease in which the body absorbs and stores too much iron, potentially damaging organs such as the liver, heart, and pancreas. If the disease is diagnosed and treated before symptoms develop, individuals with HFE-HHC typically have a normal lifespan. If the disease is untreated, however, it can lead to fatal liver and heart failure. HFE-HHC is caused by mutations in the *HFE* gene.

The most common mutations that cause HFE-HHC are C282Y and H63D. Up to 90% of individuals with HFE-HHC have two copies of the C282Y mutation, while up to 8% of patients have C282Y and H63D. Other mutations very rarely cause HFE-HHC.

For reasons not well understood, the majority of individuals with the genetic mutations that cause HFE-HHC do not develop symptoms of the disease at any point in their lives. For these individuals, simple blood tests can determine whether or not the body is storing too much iron. If iron levels are too high, beginning treatment early can leave a person virtually symptom-free for life.

Studies have found that men are more likely to develop symptoms of iron overload than women, perhaps because women's menstrual cycles regularly lower their iron levels. In men who have not been treated for HFE-HHC, the first symptoms of the disease typically begin between the ages of 30 to 50; for untreated women, symptoms usually begin later, after menopause.

Early symptoms often include weakness, abdominal pain, joint pain, weight loss, loss of interest in sex, chest pain, and a gray or bronze coloring to the skin that gets worse over time. Liver disease (either fibrosis or the more serious cirrhosis) is a common problem associated with HFE-HHC. Cirrhosis can lead to fatal liver failure and/or an increased likelihood of developing cancer of the liver.

The heart can also be affected by HFE-HHC, seen as an irregular heartbeat and/or congestive heart failure. Other problems caused by HFE-HHC can include diabetes, arthritis, impotence (in men), early menopause (in women), thyroid problems, and adrenal-gland problems.

HOW COMMON IS HFE-HHC?

HFE-HHC mutations are extremely common, particularly among Caucasians. Approximately 11% of Caucasians are carriers of the condition. In the general population, 1 in 200 to 1 in 300 has two copies of the C282Y genetic mutation. It is important to note that most individuals who have these genetic mutations do not develop the disease.

The disease is less common among Hispanics, African Americans, Asians, and Native Americans. Roughly 13% of Hispanics, 8.5% of Asians, and 6% of African Americans are carriers for the mild mutation, H63D. An additional 3% of Hispanics, 2.3% of African Americans are carriers of the potentially disease-causing C282Y mutation.

How Is HFE-HHC Treated?

Ideally HFE-HHC is treated before the organs of the body are damaged. However, not everyone who has the mutations that cause HFE-HHC develops symptoms or requires treatment. A simple blood test (serum ferritin concentration and transferrin-iron saturation levels) can determine whether the body is absorbing too much iron. When iron reaches a certain threshold, treatment is recommended. If iron levels have not reached that threshold, no treatment is necessary. Blood tests must be repeated periodically to check these iron levels. Early treatment is important to prevent long-term effects of the disease.

If a person has a high level of iron, treatment involves removing a certain quantity of blood at regular intervals. This is known as phlebotomy. Typically phlebotomy is performed frequently, perhaps weekly or twice a week, until certain iron levels are reached. After

that, it is performed less frequently, often two to four times a year, indefinitely. This treatment is simple, inexpensive, and safe. An alternative to phlebotomy is removing iron-rich red-blood cells from the blood (erythrocytapheresis) and returning other important components of the blood back to the body. This form of treatment may be helpful for patients who have side effects from phlebotomy or who have heart disease.

If a person is already suffering from symptoms of HFE-HHC, treatment can lessen or relieve some of the symptoms. However, treatment cannot reverse damage to organs such as the heart, liver, or pancreas. Cirrhosis of the liver is unlikely to improve with treatment, although treatment may slow its progression. If liver disease has reached severe levels, liver transplantation may be an option. Those who have any amount of liver damage are advised to avoid alcohol.

All individuals with symptoms of HFE-HHC are advised to avoid taking iron or vitamin C supplements. They are also advised not to eat uncooked shellfish, as they are highly susceptible to a particular kind of bacterial infection.

What Is the Prognosis for a Person with HFE-HHC?

The prognosis for a person with the genetic mutations that cause HFE-HHC is generally good, as the majority of individuals in that situation do not develop symptoms of the disease. Most will not have dangerously elevated levels of iron in their blood, and therefore will not have any iron-overload problems.

For those that do have high iron levels in their blood, beginning treatment before symptoms appear is a critical part of ensuring a long, healthy life. Nearly all symptoms of the disease can be prevented with early and ongoing treatment. If a person with HFE-HHC is treated before he or she develops cirrhosis of the liver, he or she can expect a normal lifespan. Among individuals who already have cirrhosis associated with HFE-HHC, 72% will survive at least five more years and 62% will survive at least 10 more years. Those who already have cirrhosis are at an increased risk for developing a type of liver cancer.

HMG-CoA Lyase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: HMGCL.
Exons Sequenced: NM_000191:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is HMG-CoA Lyase Deficiency?

HMG-CoA lyase deficiency, caused by harmful genetic changes (mutations) in the *HMGCL* gene, is an inherited metabolic disease that prevents the body from breaking down the amino acid leucine. Individuals with HMG-CoA lyase deficiency are also unable to produce ketones, a key source of energy used by the body during times of fasting or illness. These deficiencies lead to a build-up of toxic substances in the body, which cause the symptoms of the disease.

In most children, symptoms of HMG-CoA lyase deficiency appear before one year of age. In approximately 30% of affected individuals, symptoms begin between the second and fifth day of life. A few cases of late-onset disease, in which the disease appears during puberty or adulthood, have been reported. The first symptoms are low blood sugar, vomiting, lack of energy, difficulty feeding, irritability, and poor muscle tone that causes the body to seem floppy. The symptoms often appear quickly and are known as a "metabolic crisis." These episodes, or crises, may be triggered by illness, infection, periods of fasting, or stress. Consumption of large amounts of protein may also serve as a catalyst for metabolic crisis. If unrecognized and untreated with a special diet, the episodes can rapidly progress to permanent neurological damage, coma, and even death. Even when appropriately treated, individuals with HMG-CoA lyase deficiency are at increased risk for infections and pancreatitis, which may be fatal.

How common is HMG-CoA Lyase Deficiency?

HMG-CoA lyase deficiency has been reported in at least 150 individuals worldwide, but the global incidence is unknown. Note that less severe presentations of HMG-CoA lyase deficiency may not be recognized. It is more common among individuals of certain ethnic groups, most notably those of Saudi Arabian, Portuguese, and Spanish ancestry. However, estimates of incidence in these populations have not been published.

How is HMG-CoA Lyase Deficiency treated?

A physician specializing in metabolic diseases should help construct a treatment plan for any child with HMG-CoA lyase deficiency. Often these plans include avoidance of fasting, feeding with a low-leucine diet, medications, and prompt attention during metabolic crises. Diets will need to be carefully structured both to avoid problem foods and to ensure proper nutrition. In some cases, meals may be necessary around the clock, even overnight. A specialist will also devise a "sick-day plan" to use when a child shows signs of illness that could lead to a metabolic crisis. This typically involves frequent meals with carbohydrates and increased fluid intake, even if the child is not hungry or thirsty. During times of illness, fats and proteins should be completely eliminated from the diet.

As children get older, the disease frequently becomes easier to manage, and the risk of metabolic crisis decreases. However, many will still need lifelong dietary treatment. It is believed that those who receive treatment before their first metabolic crisis do better in the long term.

What is the prognosis for an individual with HMG-CoA Lyase Deficiency?

Prompt and careful management of symptoms is important to help reduce the long-term effects of the condition. Even with appropriate care, many individuals will experience some type of intellectual or learning disability and disordered movement. This condition can be fatal in approximately 20% of cases. Among those that survive their first incident, repeated crises may result in brain damage and significant learning and intellectual disabilities. After childhood, symptoms are often milder, but long-term effects may include recurrent seizures, muscle weakness, heart damage, vision loss, hearing loss, and intellectual disability.

Holocarboxylase Synthetase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: HLCS.
Exons Sequenced: NM_000411:4-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Holocarboxylase Synthetase Deficiency?

Holocarboxylase synthetase deficiency is a treatable inherited disease in which the body is unable to use the vitamin biotin effectively. If left untreated, the disease can cause numerous complications. The signs and symptoms of HCLSD typically appear within the first few months of life, although the age of onset can vary. Affected infants often have difficulty feeding, breathing problems, skin rash, hair loss, and a lack of energy. It can also lead to delayed development, seizures, and coma. These medical problems may be life-threatening in some cases.

How common is Holocarboxylase Synthetase Deficiency?

Holocarboxylase synthetase deficiency is estimated to affect between 1 in 87,000 to 1 in 100,000 people worldwide. The occurrence is higher for individuals of Scandinavian descent, with rates as high as 1 in 1,200 people from the Faroe Islands. Certain mutations are also believed to be relatively common among the Japanese population.

How is Holocarboxylase Synthetase Deficiency treated?

In most cases, biotin is the only required treatment for holocarboxylase synthetase deficiency, and affected individuals do not need to modify their diet or activity due to this condition. By taking daily supplements of biotin before symptoms occur, all symptoms of the disease can be avoided. If treatment begins after symptoms appear, some symptoms, such as skin problems and hair loss, will disappear; however, irreversible developmental deficits are possible and may require assistance from learning specialists.

Biotin supplements must be taken by mouth throughout life. This treatment is highly effective, provided a physician determines the proper dosage of biotin and adjusts that dosage over time if necessary.

What is the prognosis for a person with Holocarboxylase Synthetase Deficiency?

Early detection and treatment with biotin supplementation may prevent, manage, and possibly reverse symptoms. With treatment, most affected individuals are expected to have normal growth and development, although some individuals may have lifelong learning problems. Without treatment, holocarboxylase synthetase deficiency can be life-threatening.

Homocystinuria, CBS-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CBS.
Exons Sequenced: NM_000071:3-17.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Homocystinuria, CBS-Related?

Homocystinuria is an inherited metabolic condition where there is excessive homocysteine in the body. Classic homocystinuria is caused by cystathionine beta-synthase deficiency (CBS deficiency) due to a mutation in the *CBS* gene. People with classic homocystinuria are missing an enzyme called cystathionine beta-synthase which typically breaks down excessive homocysteine.

Homocystinuria can cause problems for many parts of the body. Infants with homocystinuria may have trouble growing and gaining weight. Eye problems may include nearsightedness and lens dislocation (ectopia lentis). People with homocystinuria can have skeletal problems such as curved spines (scoliosis) and fragile bones (osteoporosis). They can be taller and thinner than their siblings due to these bone changes. Homocystinuria can also cause abnormal blood clots (thromboembolisms). If these blood clots form in or travel to the heart, brain, or other vital organs, they can cause death. Some people with homocystinuria will have intellectual disability, which can range from mild to profound. About half of people who have homocystinuria will also have neurological or psychiatric problems such as seizures, behavioral disturbances, and mood problems.

Some people with homocystinuria respond to treatment with vitamin B6 (pyridoxine). These individuals usually have milder symptoms than people who do not respond to treatment with vitamin B6.

How Common Is Homocystinuria, CBS-Related?

The prevalence of homocystinuria is estimated at 1 in 250,000 people worldwide. Studies have suggested that the condition may be more common in Ireland, Germany, Norway, and Qatar. Most cases of homocystinuria are caused by mutations in *CBS*.

How Is Homocystinuria, CBS-Related Treated?

Treatment for people with homocystinuria is aimed at keeping the amount of homocysteine in the body low. Doctors will often recommend a diet low in methionine (which can turn into homocysteine in the body), which should be followed for life. Vitamin B6 can be helpful to some people with homocystinuria. A drug called betaine can also help reduce homocysteine levels. Other supplementation may include vitamin B12 (cobalamin) or vitamin B9 (folate). A person with homocystinuria will need to be in treatment for life.

In order to lower the risk of blood clots, people with the disease should avoid unnecessary surgery. Women should avoid oral contraceptives if possible. Women with the disease who become pregnant should work with their doctor to manage clotting risks associated with pregnancy. Surgery may be needed to correct dislocated eye lenses.

What Is the Prognosis for a Person with Homocystinuria, CBS-Related?

It is important that people with homocystinuria be diagnosed as soon as possible. Infants should begin treatment immediately to prevent or reduce the symptoms that occur when there are increased amounts of homocysteine in the body.

Without treatment, life expectancy for people with homocystinuria is often reduced. Blood clots are a major cause of early death in people who have homocystinuria. With lifelong treatment, the outcome for a person with homocystinuria is improved.

Homocystinuria, MTHFR-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MTHFR.
Exons Sequenced: NM_005957:2-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Homocystinuria, MTHFR-related?

Homocystinuria, MTHFR-related is an inherited condition caused by harmful genetic changes in the *MTHFR* gene. Individuals with the condition are unable to effectively process a substance in the body (homocysteine) due to reduced levels of an enzyme called methylenetetrahydrofolate reductase (MTHFR). Extremely high levels of homocysteine are toxic to the body and cause the symptoms associated with homocystinuria, MTHFR-related. Certain genetic changes in the *MTHFR* gene cause only a mild elevation of homocysteine, which results in a separate condition called MTHFR deficiency. Homocystinuria, MTHFR-related should not be confused with the common, milder MTHFR deficiency.

The symptoms and severity of homocystinuria, MTHFR-related vary widely from person to person, even within the same family. In some cases, individuals will reach adulthood before showing any symptoms. Infants may develop seizures, developmental delay, temporary pauses in breathing (apnea), weak muscle tone (hypotonia), loss of brain tissue (cerebral atrophy), small head (microcephaly), eye disorders, and decreased sucking ability. For individuals who develop symptoms later in life, symptoms may include problems with the heart (cardiovascular disease) or blood vessels (thromboembolism), progressive muscle weakness and stiffness, seizures, psychiatric symptoms, and problems with walking. These symptoms may get worse as individuals get older.

How common is Homocystinuria, MTHFR-related?

Several genes are known to cause homocystinuria, which has an incidence of 1 in 250,000 births. The exact incidence of MTHFR-related homocystinuria is unknown. There have been fewer than 200 cases reported worldwide. This condition is more common in the Amish population.

How is Homocystinuria, MTHFR-related treated?

There is no cure for homocystinuria, MTHFR-related. Treatment is aimed at keeping the amount of homocysteine in the body low and managing the specific symptoms an individual has. Doctors will often recommend a drug called betaine that can help reduce homocysteine levels, as well as certain dietary supplements (such as certain B vitamins). Severely affected individuals may need to be followed by a team of specialists that could include physicians, speech pathologists, occupational therapists, physical therapists, and social workers.

What is the prognosis for an individual with Homocystinuria, MTHFR-related?

The prognosis for an individual with homocystinuria, MTHFR-related varies significantly depending on the severity of symptoms and age of onset. Treatment often improves symptoms, but does not cure the condition. Treatment is most effective in patients who are diagnosed and treated early. In the most severe cases, death can occur in the first year of life. For those who do not develop symptoms until adulthood, the exact lifespan is unknown but thought to be shortened.

Hydrolethalus Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: HYLS1.
Exon Sequenced: NM_145014:4.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Hydrolethalus Syndrome?

Hydrolethalus syndrome is an inherited disease caused by harmful genetic changes (mutations) in the *HYSF1* gene. The *HYSF1* gene plays an important role in fetal development. Hydrolethalus syndrome causes severe brain abnormalities. These can include missing portions of the brain and extra fluid surrounding the brain (hydrocephalus). The opening at the base of the skull (foramen magnum) has an atypical key shape. Affected infants display differences in the face and skull (craniofacial malformations), including a small jaw (micrognathia) and a notched (cleft) lip and roof of mouth (palate). Other findings include extra digits of the fingers and toes (polydactyly), heart defects, narrowing of the airway, and malformation of the lungs (unilobular lungs).

The condition may be detected by an ultrasound scan around the thirteenth to fifteenth week of pregnancy due to the malformations of the brain and other organs. Extra amniotic fluid (polyhydramnios) is typically present in the later parts of the pregnancy.

How common is Hydrolethalus Syndrome?

Hydrolethalus syndrome is most common in individuals of Finnish descent, with an estimated incidence of approximately 1 in 10,000. It is extremely rare in individuals of other ethnicities.

How is Hydrolethalus Syndrome treated?

At this time, there are no cures or treatment options for individuals with hydrolethalus syndrome.

What is the prognosis for a person with Hydrolethalus Syndrome?

Unfortunately, the prognosis for an infant with hydrolethalus syndrome is poor. Most individuals are either stillborn or die shortly after birth. There have been rare cases where infants with hydrolethalus syndrome have lived for several months.

Hypophosphatasia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ALPL.
Exons Sequenced: NM_000478:2-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Hypophosphatasia?

Hypophosphatasia (HPP), caused by harmful genetic changes (mutations) in the *ALPL* gene, is an inherited disorder that disrupts the body's ability to deposit minerals like calcium and phosphorus into teeth and bones. Proper mineralization is necessary to make bones strong and rigid and to make teeth strong enough to withstand years of chewing. Symptoms can vary greatly depending upon which mutations an individual carries. Some forms of the disease are severe, while other forms are extremely mild.

The most severe form of HPP appears before birth or in early childhood. In many cases, infants are stillborn because their skeletons fail to form. Other affected infants are born with short arms and legs; an abnormally shaped chest caused by soft, weak ribs; and soft skull bones. Approximately half of the infants born with the condition die of respiratory failure in the first few weeks of life. Those who survive may have life-threatening complications such as breathing problems; seizures; or high blood-calcium levels, leading to kidney damage.

In less-severe forms, the first sign of the condition is loss of baby teeth before the age of five. As children grow, they may be below average height, and they may have abnormal curvature in their legs, large ankle and wrist joints, and an abnormally shaped skull (craniosynostosis). They are more prone to broken bones, bone pain, and arthritis. Children with HPP may also have trouble learning to walk or may develop a waddling gait. Additionally, their teeth may crack or decay more easily than normal.

The mildest form of the disorder is called odontohypophosphatasia, and it affects only the teeth. Individuals with this form of the condition have atypical tooth development and lose their teeth early, but they do not experience skeletal abnormalities.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Usually HPP is inherited in an autosomal-recessive manner, meaning both parents must carry a mutation in *ALPL* for their children to be at risk of developing HPP. In the autosomal-recessive form, carriers may experience no symptoms, or they may show mild symptoms. However, some mutations in *ALPL* cause an autosomal-dominant form of the condition, meaning symptoms will occur with only one *ALPL* mutation. In the autosomal-dominant form, a parent is affected or is at risk of developing symptoms. Generally, the symptoms in the autosomal-dominant form are milder and do not develop until middle age. The most common symptoms are early tooth loss; frequent, slow-healing stress fractures in the feet; and arthritis. Rarely, more severe symptoms develop in childhood.

How common is Hypophosphatasia?

The incidence of HPP is estimated between 1 in 100,000 to 1 in 200,000 births. The exact incidence is difficult to determine because most estimates are based on the more severe forms of disease and are, therefore, likely to be underestimates. The disease is particularly common in the Canadian Mennonite population where it affects an estimated 1 in 2,500 individuals.

How is Hypophosphatasia treated?

Enzyme replacement therapy can be used to treat individuals with the most severe and childhood forms of HPP. Individuals treated with enzyme replacement therapy have had improved survival rates and showed improvements in bone health and growth. However, the long-term effects of this treatment are not known.

Infants with the most severe form of the condition usually require mechanical help to breathe and may need surgery to release pressure within the skull. Vitamin B6 may relieve seizures. Children and adults with HPP should see a dentist every year, beginning at the age of one, to preserve teeth as long as possible. Adults will eventually need false teeth. Aspirin, ibuprofen, and other pain relievers help with bone pain and arthritis. Although preventing bone fractures is difficult, orthotics may help with common fractures in the feet.

Individuals with the condition should not take bisphosphonates, which are drugs commonly prescribed to treat other bone-loss conditions such as osteoporosis. They should also avoid excess vitamin D, which can make calcium build up in the blood.

What is the prognosis for an individual with Hypophosphatasia?

Approximately 50% of infants born with the severe form of the condition will die of respiratory failure in infancy. Exact lifespans for the remaining 50% is not known. Individuals with the milder forms of the condition have normal lifespans.

Inherited Retinal Dystrophy, RPE65-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: RPE65.
Exons Sequenced: NM_000329:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Inherited Retinal Dystrophy, RPE65-related?

Inherited retinal dystrophy, RPE65-related (IRD, RPE65-related), includes a group of conditions that affect the part of the eye called the retina. The retina contains cells that sense light (photoreceptors). When an individual has an IRD, the shape and function of their retina is altered, causing various degrees of vision loss. IRD, RPE65-related, is caused by harmful genetic changes (variants) in the *RPE65* gene. IRD, RPE65-related, can cause a range of symptoms and severities. The most severe form is known as RPE65-related Leber congenital amaurosis / early-onset severe retinal dystrophy (RPE65-LCA/EOSRD), and the less severe form is known as retinitis pigmentosa type 20 (RP20). The onset of symptoms is usually between birth and five years old, although there have been cases with later onset.

RPE65-RELATED LEBER CONGENITAL AMAUROSIS / EARLY-ONSET SEVERE RETINAL DYSTROPHY (RPE65-LCA/EOSRD)

Individuals with RPE65-LCA/EOSRD usually experience severe vision loss at birth or within the first year of life. They may have uncontrolled eye movements (nystagmus), and their pupils may not respond correctly to light. While vision remains relatively stable during childhood, it often worsens in the teen years. By the time they reach their twenties, half of the individuals with RPE65-LCA/EOSRD are legally blind. The disease typically progresses over time, and many individuals may be completely blind by the time they reach their forties. Individuals with RPE65-LCA/EOSRD generally do not have intellectual disability. However, some may struggle with learning due to vision problems. No other body systems are affected by the condition.

RETINITIS PIGMENTOSA (RP)

The type of RP associated with harmful changes in *RPE65* is often called RP20. However, the symptoms are identical to other forms of non-syndromic RP. The onset of symptoms is variable but is generally later than that observed in individuals with RPE65-LCA/EOSRD. The first sign of RP is often difficulty seeing in dim light (night blindness). As RP progresses, individuals may experience vision loss on the sides of the head (peripheral), resulting in “tunnel vision.” Eventually, individuals lose central vision. Complete blindness is uncommon but may occur. No other body system is affected in individuals with RP.

How common is Inherited Retinal Dystrophy, RPE65-related?

The exact incidence of IRD, RPE65-related, is unknown. Some estimates suggest that between 1,000 and 2,000 individuals in the United States have IRD, RPE65-related. IRD, RPE65-related contributes to 0.8–1.5% of all cases of IRD.

How is Inherited Retinal Dystrophy, RPE65-related treated?

There is no cure for RPE65-related disorders, and management is primarily supportive. Sunglasses that block harmful rays from the sun (UV-A and UV-B) are recommended. Other optical aids may increase eye comfort. Other tools include glasses, low-vision aids, and supportive services for those with vision impairment. It is also important for individuals to maintain a healthy diet that includes all recommended vitamins and minerals. Gene therapy for IRD, RPE65-related, has been approved by the FDA for individuals between 12 months and 65 years of age. Gene therapy has had mixed outcomes but has led to visual improvements.

What is the prognosis for a person with Inherited Retinal Dystrophy, RPE65-related?

While individuals with IRD, RPE65-related, may have severe vision impairment or blindness, the condition does not affect lifespan and is not expected to affect other body systems.

Isovaleric Acidemia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: IVD.
Exons Sequenced: NM_002225:1-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

WHAT IS ISOVALERIC ACIDEMIA?

Isovaleric Acidemia (IVA), caused by mutations in the *IVD* gene, is an inherited disorder in which an enzyme that breaks down the amino acid leucine does not function properly resulting in accumulation isovaleric acid in the blood. High levels of isovaleric acid in the blood can be toxic and result in damage to the brain and nervous system. IVA can result in seizures, coma, or other nervous system disorders. IVA can also be life-threatening. However, with early diagnosis and treatment, individuals with IVA are more likely to have improved growth, development, and life expectancy.

There are three forms of IVA. The severe, neonatal form has its onset during the first weeks of life. The childhood-onset form occurs episodically in childhood, in response to stress. The mild form may never result in symptoms of IVA.

NEONATAL ISOVALERIC ACIDEMIA

Symptoms of the neonatal form are often observed in the first few weeks after birth and include feeding problems, high acidity of the blood and urine, and difficulty in maintaining proper body temperature. Untreated IVA can eventually result in bleeding of the brain (cerebral hemorrhage), seizures, and death.

CHILDHOOD ISOVALERIC ACIDEMIA

Symptoms of the childhood form of IVA are often observed at about 12 months of age. These symptoms are similar to the neonatal form but are triggered by stresses such as illness, fasting, or high-protein diets. In the absence of stresses to the body, there may be no symptoms. However, children with childhood IVA may have learning problems, reduced growth, and muscle weakness.

MILD FORM

Some individuals with specific mutations in the *IVD* gene do not have symptoms of neonatal or childhood IVA. Some of these individuals do develop mild developmental delay. It is not yet clear why these changes in the *IVD* gene do not cause other IVA symptoms.

HOW COMMON IS ISOVALERIC ACIDEMIA?

The prevalence of IVA is 1 in 250,000 in the American population. The incidence of IVA is about 1 in 62,000 in the German population.

HOW IS ISOVALERIC ACIDEMIA TREATED?

Individuals with IVA need a special diet, which is low in leucine and contains proteins. For example, infants may be treated with a leucine-free formula. The supplements carnitine and glycine can reduce the toxicity of isovaleric acid and aid in its removal from the body.

Individuals with IVA need close monitoring by a physician during times of illness and may need to ensure adequate hydration and adopt a diet high in carbohydrates. Symptoms such as vomiting, diarrhea, and illness with a fever may require prompt treatment.

Frequent monitoring of individuals with IVA is important to determine that proper growth, metabolism, and development is ongoing.

WHAT IS THE PROGNOSIS FOR A PERSON WITH ISOVALERIC ACIDEMIA?

Without early diagnosis and treatment, individuals with IVA may have damage to the brain and nervous system, intellectual and developmental disability, or in severe cases, death. If a person with IVA receives treatment, they are more likely to reach normal levels of growth, development, and intellectual ability. However, some individuals may experience a reduction in growth and development, learning disabilities, or even death, due to periodic episodes of high levels of isovaleric acid, primarily in response to stress. As a person with IVA ages, the frequency of such episodes decreases.

Individuals with IVA without symptoms are more likely to live a normal lifespan.

Joubert Syndrome 2

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: TMEM216.
Exons Sequenced: NM_001173990:1-5.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Joubert Syndrome 2 (JBTS2)?

JBTS2 is an inherited condition caused by mutations in the *TMEM216* gene that lead to abnormalities in the brain structure. Symptoms include developmental delay, the inability to coordinate muscle movement, involuntary eye movements, and difficulty moving the eyes from side to side. Individuals may also exhibit intellectual disability.

At birth, children with JBTS2 have poor muscle tone. Their eyes move rapidly and involuntarily and may rotate inward. They often have difficulty eating due to problems coordinating their muscle movement, and they may have breathing problems due to structural brain abnormalities. Some children with JBTS2 have additional fingers and/or toes (polydactyly). In addition, some children with JBTS2 will have kidney problems, which may lead to kidney failure in adolescence.

Children with JBTS2 all have delayed mental and physical development. They may have mild to severe intellectual disability, though a few individuals have attended college. In the first few years of life, their eye problems often improve, leading to normal vision.

How Common Is JBTS2?

The worldwide incidence of JBTS2 is unknown. JBTS2 is common in Ashkenazi Jews, of whom 1 in 34,000 is affected.

How Is JBTS2 Treated?

There is no cure for JBTS2. A medical team can address symptoms as they arise. Regular examinations are necessary since symptoms may vary. Infants with difficulty eating should be monitored to ensure that they are receiving proper nutrition. Physical and occupational therapy may also be helpful. Children with JBTS2 should also be monitored for eye and kidney problems.

What Is the Prognosis for a Person with JBTS2?

The prognosis for a person with JBTS2 varies. Some will have milder forms of intellectual disability and mild ataxia (lack of muscle control), while others will have more severe intellectual disability and movement problems. A minority of individuals will have a shorter lifespan due to kidney or liver failure and breathing abnormalities.

Joubert Syndrome, AHI1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: AHI1.
Exons Sequenced: NM_001134831:4-29.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Joubert Syndrome, AHI1-related?

Joubert syndrome, AHI1-related, also known as Joubert syndrome type 3, is an inherited condition that causes brain structure abnormalities. There are several genes associated with Joubert syndrome. Joubert syndrome, AHI1-related is caused by harmful genetic changes (variants) in the *AHI1* gene. Individuals with Joubert syndrome, AHI1-related have problems with the structure and function of their cilia, which are finger-like projections on cells that are important for chemical signaling pathways. These malfunctioning cilia lead to physical abnormalities during development.

Individuals with Joubert syndrome, AHI1-related have low muscle tone (hypotonia), developmental delay, and a distinctive brain malformation called a "molar tooth sign" that can be seen on brain imaging (MRI). Brain imaging may also show increased folding of brain tissue in these individuals (polymicrogyria). Joubert syndrome, AHI1-related is also characterized by specific eye abnormalities such as the inability to control eye movements correctly and missing eye tissue (ocular coloboma). Approximately 80% of individuals with Joubert syndrome, AHI1-related have some disease of the retina (retinal dystrophy). Individuals with Joubert syndrome, AHI1-related often have abnormal breathing patterns and difficulty coordinating their muscle movement (ataxia), though these symptoms tend to improve over time. Some individuals with Joubert syndrome, AHI1-related have cystic kidney disease, which can progress to end-stage renal disease.

Children with Joubert syndrome, AHI1-related typically have mild to severe intellectual disability, but there are reports of individuals with average intellect. Many children also have speech and motor skills delays and exhibit behavioral issues.

How common is Joubert Syndrome, AHI1-related?

Over thirty genes are associated with Joubert syndrome. The exact incidence of Joubert syndrome has not been determined but is estimated to be about 1 in 80,000 to 1 in 100,000 births. Approximately 7-10% of Joubert syndrome is caused by harmful genetic changes in *AHI1*.

How is Joubert Syndrome, AHI1-related treated?

There is no cure for Joubert syndrome, AHI1-related. Treatment for the condition is directed at managing an individual's specific symptoms. Children with Joubert syndrome, AHI1-related should be followed by a team of specialists and monitored for eye and kidney problems. Dialysis and/or kidney transplantation may be necessary in cases of end-stage renal disease. Corrective eye interventions can be used as needed. Infants and children with breathing problems should be monitored for apnea. Common interventions for developmental delays include evaluation and care by physical therapy, speech pathology, and occupational therapy.

What is the prognosis for an individual with Joubert Syndrome, AHI1-related?

The prognosis for individuals with Joubert syndrome, AHI1-related can vary widely depending on the severity of symptoms and associated complications. Some have more severe intellectual disability, progressive retinal dystrophy, renal disease, and severe ataxia, while others have close to average intellect, mild ataxia, less severe retinal dystrophy, and no kidney involvement. Lifespan may be reduced in those with kidney failure or severe breathing abnormalities. For those with kidney involvement, end-stage renal disease typically occurs by the second decade of life.

Junctional Epidermolysis Bullosa, LAMA3-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: LAMA3.
Exons Sequenced: NM_000227:1-38.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Junctional Epidermolysis Bullosa, LAMA3-related?

Junctional epidermolysis bullosa (JEB), LAMA3-related, is an inherited disease that causes severe blistering on the skin. This condition has two subtypes: Herlitz JEB (H-JEB) and non-Herlitz JEB (NH-JEB). Both forms of JEB are caused by harmful changes (variants) in the *LAMA3* gene.

HERLITZ JUNCTIONAL EPIDERMOLYSIS BULLOSA (H-JEB)

Individuals with H-JEB lack anchors to hold the layers of their skin together. They develop large, fluid-filled blisters in response to any trauma, even something as minor as increased room temperature. Internal blistering on the lining of the nose, mouth, esophagus, trachea, rectum, stomach, intestines, and eyes is also present from birth.

Granulation tissue, a soft, pink, bumpy, moist skin, forms at blistering sites in the healing process. It is also seen around the nose, mouth, ears, fingers, and toes, as well as in areas that receive friction, such as the buttocks and back of the head. Because this tissue can chafe and wear away, it bleeds easily and can be a site of fluid loss or infection.

Other symptoms in infants and children with the disease may include a hoarse cry, cough, other breathing problems, fevers, loss of fingernails and toenails, poorly formed tooth enamel, abnormalities of the urinary tract and bladder, poor growth, electrolyte imbalance, hair loss, osteoporosis, and skin cancer.

NON-HERLITZ JUNCTIONAL EPIDERMOLYSIS BULLOSA (NH-JEB)

NH-JEB is a less severe form of JEB. Blistering occurs in fewer areas (hands, feet, knees, and elbows) and may not result in blistering of the internal organs. The onset of blistering can be later as well. Issues related to granulation tissue and complications with breathing are not common. Hair loss, improper nail formation, and poorly formed tooth enamel are observed in individuals with NH-JEB.

LARYNGO-ONYCHO-CUTANEOUS (LOC) SYNDROME

A rare subtype of JEB known as laryngo-onycho-cutaneous (LOC) syndrome is also caused by harmful genetic changes in the *LAMA3* gene. Infants with the condition have a hoarse cry due to sores (ulcers) and granulation tissue in the voicebox (larynx). The symptom that makes LOC syndrome distinct from the other forms of JEB is that the granulation tissue often grows in the eyes. Individuals with LOC syndrome often develop vision and breathing problems. Other symptoms can include missing patches of skin and abnormally developed nails and teeth.

How common is Junctional Epidermolysis Bullosa, LAMA3-related?

H-JEB is extremely rare; less than 1 in 1 million individuals are affected by H-JEB.

NH-JEB is slightly more common, with an estimated 1 in 500,000 individuals affected by the disease.

The incidence of LOC syndrome is not known.

How is Junctional Epidermolysis Bullosa, LAMA3-related, treated?

There is no cure for JEB. Symptoms are generally treated as they arise. It is best to protect children with the condition from skin damage as much as possible. For example, a cesarean section may be recommended to protect the child from the skin trauma of a vaginal birth. Affected children must avoid any movement or clothing that could damage the skin. When open wounds and blistered skin occur, they are often covered with multiple layers of non-adhesive bandages. Antibiotics and antiseptics are often prescribed to prevent and treat infections. A dietitian should be consulted for individuals with H-JEB to ensure proper nutrition. To avoid dehydration, individuals should drink plenty of fluids.

In individuals with breathing difficulty (typically those with H-JEB), an opening may be made in the neck to deliver air to the trachea (tracheostomy).

What is the prognosis for an individual with Junctional Epidermolysis Bullosa, LAMA3-related?

The prognosis for individuals with all forms of junctional epidermolysis bullosa, LAMA3-related, is poor. The disease is extremely painful, and causes of death often include impaired physical growth (failure to thrive), infection, and respiratory failure. Approximately 40-45% of individuals with either form of JEB die in the first year of life. Approximately 62% of individuals with H-JEB and 48% of individuals with NH-JEB die by age 15. The exact life expectancy for individuals with LOC is not well known, but is expected to be similar to the other forms of JEB.

Junctional Epidermolysis Bullosa, LAMB3-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: LAMB3.
Exons Sequenced: NM_000228:2-23.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Junctional Epidermolysis Bullosa, LAMB3-related?

Junctional epidermolysis bullosa (JEB), LAMB3-related, caused by mutations in the *LAMB3* gene, is an inherited disease that causes severe blistering of the skin. There are two types of this condition: generalized severe JEB (formerly JEB Herlitz) and generalized intermediate JEB (formerly JEB non-Herlitz).

GENERALIZED SEVERE JUNCTIONAL EPIDERMOLYSIS BULLOSA

Individuals with generalized severe JEB lack anchors to hold the layers of their skin together. They develop large, fluid-filled blisters in response to any trauma, even something as minor as increased room temperature. Internal blistering on the lining of the nose, mouth, esophagus, trachea, rectum, stomach, intestines, and eyes are also present from birth.

Granulation tissue, a kind of soft, pink, bumpy, moist skin, forms at blistering sites in the healing process. This tissue can also be seen around the nose, mouth, ears, fingers, and toes, as well as in areas that receive friction, such as the buttocks and back of the head. Because this tissue can chafe and wear away, it bleeds easily and can be a site of fluid loss, leaving the individual open to infection.

Other symptoms in infants and children with the disease may include a hoarse cry, cough, other breathing problems, fevers, loss of fingernails and toenails, poorly-formed tooth enamel, abnormalities of the urinary tract and bladder (which may lead to urinary-tract infections and kidney failure), poor growth, electrolyte imbalance, hair loss, osteoporosis, and skin cancer.

GENERALIZED INTERMEDIATE JUNCTIONAL EPIDERMOLYSIS BULLOSA

Generalized intermediate JEB is less severe than generalized severe JEB. Blistering occurs in fewer areas (hands, feet, knees, and elbows) and may not result in blistering of the internal organs. The onset of blistering may occur later as well. Issues related to granulation tissue and complications with breathing are not common. However, hair loss, improper nail formation, and poorly formed tooth enamel are seen.

How common is Junctional Epidermolysis Bullosa, LAMB3-related?

The incidence of JEB in the United States is approximately 1 in 275,000 to 400,000. Approximately 70% of all cases of JEB are due to mutations in the *LAMB3* gene. Exact estimates of the different subtypes of JEB are not well known, although generalized intermediate JEB seems to be more common than generalized severe JEB.

How is Junctional Epidermolysis Bullosa, LAMB3-related treated?

Treatment focuses on reducing symptoms and on protecting the child as much as possible from skin damage. For example, a cesarean section may be recommended to protect the child from the skin trauma of birth. Affected children must avoid any movement or clothing that could damage the skin. To protect open wounds and blistered skin, the affected areas are covered with multiple layers of non-adhesive bandages, and anyone handling the child must use extreme care. Affected children require frequent antibiotics for infection. An expert on nutrition (dietitian) should be consulted for proper nutrition. To avoid dehydration, affected children should drink plenty of fluids. In individuals with breathing or feeding difficulty, surgical procedures to place breathing or feeding tubes may be required.

What is the prognosis for an individual with Junctional Epidermolysis Bullosa, LAMB3-related?

The prognosis for individuals with generalized severe JEB or generalized intermediate JEB is poor. The disease is extremely painful, and causes of death often include impaired physical growth (failure to thrive), infection, and respiratory failure. Most children with generalized severe JEB do not survive past the first year of life, while roughly 48% of individuals with generalized intermediate JEB die by age 15.

Junctional Epidermolysis Bullosa, LAMC2-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: LAMC2.
Exons Sequenced: NM_005562:1-23.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Junctional Epidermolysis Bullosa, LAMC2-related?

Junctional epidermolysis bullosa (JEB), LAMC2-related is an inherited disease that causes severe blistering on the skin. There are two types of this condition: Herlitz JEB (H-JEB) and non-Herlitz JEB (NH-JEB). Both forms of JEB are caused by mutations in the *LAMC2* gene.

HERLITZ JUNCTIONAL EPIDERMOLYSIS BULLOSA

Individuals with H-JEB lack anchors to hold the layers of their skin together. They develop large, fluid-filled blisters in response to any trauma, even something as minor as increased room temperature. Internal blistering on the lining of the nose, mouth, esophagus, trachea, rectum, stomach, intestines, and eyes are also present from birth.

Granulation tissue, a kind of soft, pink, bumpy, moist skin, forms at blistering sites in the healing process. It is also seen around the nose, mouth, ears, fingers, and toes, as well as in areas that receive friction, such as the buttocks and back of the head. Because this tissue can chafe and wear away, it bleeds easily, can be a site of fluid loss, and leave the patient open to infection.

Other symptoms in infants and children with the disease may include a hoarse cry, cough, other breathing problems, fevers, loss of fingernails and toenails, poorly-formed tooth enamel, abnormalities of the urinary tract and bladder (may lead to urinary tract infections and kidney failure), poor growth, electrolyte imbalance, hair loss, osteoporosis, and skin cancer.

NON-HERLITZ JUNCTIONAL EPIDERMOLYSIS BULLOSA

NH-JEB is a less severe form of H-JEB. Blistering occurs in fewer areas (hands, feet, knees, and elbows), and may not result in blistering of the internal organs. The onset of blistering may be later as well. Issues related to granulation tissue and complications with breathing are not common. However, hair loss, improper nail formation, and poorly formed tooth enamel are seen.

How Common Is Junctional Epidermolysis Bullosa, LAMC2-related?

H-JEB is extremely rare. Overall estimates indicate that 0.37 individuals per million are affected by H-JEB.

NH-JEB is slightly more common, with overall estimates of 2 individuals per million being affected by the disease.

How Is Junctional Epidermolysis Bullosa, LAMC2-related treated?

Symptoms are generally treated as they arise. It is best to protect the child as much as possible from skin damage. For example, a cesarean section may be recommended to protect the child from the skin trauma of birth, excess movement is avoided, and clothing that may damage the skin is avoided. When open wounds and blistered skin occur, they are often covered with multiple layers of non-adhesive bandages and anyone handling the child must use extreme care.

Antibiotics are often prescribed for infection, and antiseptics are often used to prevent infection. For individuals with H-JEB, a dietitian should be consulted for an infant's proper nutrition. To avoid dehydration, these children should also drink plenty of fluids.

In individuals with breathing difficulty (more typically associated with H-JEB), an opening may be made in the neck to deliver air to the trachea. However, this may be difficult on an individual with fragile skin.

What Is the Prognosis for a Person with Junctional Epidermolysis Bullosa, LAMC2-related?

The prognosis for individuals with H-JEB or NH-JEB is poor and roughly 40-45% of individuals with either form of JEB die in the first year of life. Roughly 62% of individuals with H-JEB and 48% of individuals with NH-JEB die by age 15. This disease is extremely painful and causes of death often include impaired physical growth (failure to thrive), infection, and respiratory failure.

Krabbe Disease

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GALC.
Exons Sequenced: NM_000153:1-17.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Krabbe Disease?

Krabbe disease, also known as globoid cell leukodystrophy, is an inherited disease of the nervous system. Leukodystrophies are a group of diseases affecting the myelin sheath, a fatty covering that insulates and protects nerve cells. Individuals with Krabbe disease lack an enzyme called galactocerebrosidase. This enzyme deficiency is caused by mutations in the *GALC* gene and results in the build-up of toxic substances in the cells that produce the myelin sheath. Without this protective covering, brain cells die and nerves in the body cannot function properly.

There are two forms of the disease: infantile and late-onset.

INFANTILE FORM

The infantile form, which affects 85 to 90% of individuals with Krabbe disease, appears in the first few months of life and causes irritability, muscle weakness, unexplained fever, deafness, blindness, seizures, and slowed mental and physical development. Usually, death occurs by the age of two, often due to respiratory failure.

LATE-ONSET FORM

The late-onset form of Krabbe disease, which affects 10 to 15% of individuals with the disease, can appear at any time between the ages of six months and 50 years. These individuals slowly develop vision loss, difficulty walking, rigid muscles, and mental impairment. Symptoms among those with late-onset Krabbe disease are highly variable. The disease is often fatal 2 to 7 years after symptoms begin.

How Common Is Krabbe Disease?

The incidence of Krabbe disease is approximately 1 in 100,000 births in the United States. The condition has a higher incidence among several Druze and Muslim communities in and around Israel.

How Is Krabbe Disease Treated?

Treatment for Krabbe disease will depend on which form of the disease an individual has. Treatment options for both forms are listed below.

INFANTILE FORM

For infants with this form of Krabbe disease who have not yet started showing symptoms, treatment with umbilical-cord blood stem cells has shown promise in enabling normal or near-normal lives. This procedure can take place within weeks of birth. In many cases neural deterioration is slowed following the procedure and symptoms seem less severe.

Bone-marrow stem cells may be used in place of umbilical-cord blood stem cells, but cord blood stem cells are less particular and do not require the donor to be a perfect match. With cord blood stem cells, there is also less risk of immune-system complications.

Infants who have already started showing symptoms of the disease do not seem to benefit from this treatment. For them, the only treatment is to address symptoms as they arise.

LATE-ONSET FORM

Some individuals with late-onset Krabbe disease have benefited from treatment with umbilical-cord stem cells, although this treatment has been most successful in pre-symptomatic patients with the infantile form of the disease. In cases where the treatment has been successful, neural deterioration is slowed and symptoms are less severe.

Just as with the infantile form of the disease, bone-marrow stem cells may be used in place of umbilical-cord blood stem cells for the late-onset form, but cord blood stem cells are less particular and do not require the donor to be a perfect match. With cord blood stem cells, there is also less risk of immune-system complications.

For individuals who are not candidates for the procedure, the only treatment is to address symptoms as they arise.

What Is the Prognosis for an Individual with Krabbe Disease?

The infantile form of Krabbe disease is usually fatal before the age of two. Those infants who receive cord blood stem cells before the appearance of symptoms have longer lifespans. While their course is milder compared to untreated infants, these children still generally develop symptoms, including rigid muscles and difficulties with language and motor skills.

Those with late-onset Krabbe disease typically live between two and seven years after the onset of symptoms. The exact symptoms and rate of neurological deterioration varies greatly from among individuals, even among those in the same family who have the same genetic mutations.

L1 Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: L1CAM.
Exons Sequenced: NM_001278116:2-29.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is L1 syndrome?

L1 syndrome includes a group of inherited conditions that impact the nervous system. All conditions associated with L1 syndrome are caused by harmful genetic changes (variants) in the *L1CAM* gene. The primary symptom of L1 syndrome is excess fluid around the brain (hydrocephalus). Individuals may also have other issues like stiff and tight muscles (spasticity) in the legs, making walking hard. Other symptoms include intellectual disability, difficulty with speech, and brain abnormalities (agenesis of the corpus callosum). Some individuals may have clasped (adducted) thumbs. The symptoms of L1 syndrome can vary significantly between affected individuals, even those within the same family. L1 syndrome is an X-linked disease, meaning that people assigned male at birth (XY) usually have more severe symptoms than those assigned female (XX).

L1 syndrome is a spectrum of related disorders that are grouped into the following conditions:

X-LINKED HYDROCEPHALUS WITH STENOSIS OF THE AQUEDUCT OF SYLVIUS (HSAS)

HSAS is the most severe presentation of L1 syndrome. The symptoms are often present at or before birth. HSAS primarily affects people assigned male at birth (XY). Almost all individuals with this form will have excess fluid around the brain and brain abnormalities (agenesis of the corpus callosum). Individuals typically have clasped (adducted) thumbs and stiff and tight muscles. Severe intellectual disability is common in HSAS.

MASA SYNDROME

MASA syndrome stands for "**M**ental retardation (intellectual disability), **A**phasia (speech problems), **S**pastic paraplegia (stiffness in the legs), **A**dducted (clasped) thumbs." Many individuals will have some brain abnormalities, intellectual disability, stiff and tight muscles, and clasped thumbs, but they are usually less severely affected than individuals with HSAS.

X-LINKED COMPLICATED CORPUS CALLOSUM AGENESIS

Symptoms typically include thinning or absence of the tissue that connects the left and right side of the brain (agenesis of the corpus callosum), stiff and tight muscles of the limbs, and mild to moderate intellectual disability.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Carriers are unlikely to be affected by L1 syndrome; however, clasped thumbs and mild intellectual disability have been reported in a few female (XX) individuals with harmful changes in the *L1CAM* gene.

How common is L1 syndrome?

L1 syndrome is estimated to affect 1 in 30,000 male births.

How is L1 syndrome treated?

There is no cure for L1 syndrome. Treatment is based on the symptoms the individual is experiencing. A tube (shunt) can drain the fluid around the brain. A splint may help with clasped thumbs, and physical therapy and medications can help treat stiff and tight muscles. Individuals with intellectual disability may benefit from early intervention and educational support. All individuals with L1 syndrome will benefit from working with a team of specialists that includes surgeons, physical and occupational therapists, and neurologists.

What is the prognosis for a person with L1 syndrome?

The prognosis depends on the severity of symptoms. Severe cases of hydrocephalus may result in stillbirth or pass away shortly after birth, while less severe cases may have a normal lifespan. Intellectual disability can range from mild to severe and some individuals may need lifelong support.

Leigh Syndrome, French-Canadian Type

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: LRPPRC.
Exons Sequenced: NM_133259:1-38.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Leigh Syndrome, French-Canadian Type?

There are multiple forms of Leigh syndrome, with more than 30 causative genes identified. However, Leigh syndrome, French-Canadian type (LSFC) is exclusively caused by harmful genetic changes (mutations) in the *LRPPRC* gene. Individuals with LSFC often appear unaffected at birth, but begin to lose basic skills such as head control, sucking, walking, and talking in infancy or early childhood. They may also present with intellectual disabilities, differences in facial features, irritability, vomiting, and seizures.

The symptoms associated with this condition are the result of damage (lesions) that develop in the brain, specifically the midbrain and/or brainstem. The cells in these regions of the brain also begin to lose their protective coating (myelin sheath), which decreases the brain's ability to process information, respond to stimuli, and initiate muscle movement. In addition, LSFC often causes periods of low blood sugar and often causes the build-up of toxic substances in the blood (metabolic crisis), which can lead to vomiting, diarrhea, extreme sleepiness, irritable moods, and behavior changes. These symptoms may rapidly worsen, ultimately leading to significant breathing difficulties, heart problems, and vision loss.

How common is Leigh Syndrome, French-Canadian Type?

LSFC has never been reported outside of the French-Canadian population. Among those from the Saguenay-Lac Saint Jean region of Quebec, the disorder is observed in approximately 1 in 2,000 births.

How is Leigh Syndrome, French-Canadian Type treated?

Currently, there is no cure for LSFC, and treatment is only supportive, with the goal of alleviating symptoms as they arise. Medications may be provided for treatment of seizures, cardiac, metabolic, and respiratory issues, and for muscle and movement disorders as they develop.

What is the prognosis for an individual with Leigh Syndrome, French-Canadian Type?

Typically, symptoms of Leigh syndrome present during the first year of life and progress rapidly. The average life expectancy for children with LSFC is approximately five to six years. However, some individuals do not develop symptoms until adulthood and/or have a slowly progressing course of the disorder.

Lipoid Congenital Adrenal Hyperplasia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: STAR.
Exons Sequenced: NM_000349:1-7.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Lipoid Congenital Adrenal Hyperplasia?

Lipoid congenital adrenal hyperplasia (LCAH), caused by harmful genetic changes (mutations) in the *STAR* gene, is an inherited condition that makes the body unable to produce important hormones. Specifically, these hormones come from the gland located above the kidneys (adrenal) and testes or ovary (gonadal). LCAH is the most severe form of congenital adrenal hyperplasia. Individuals with LCAH can have different levels of hormone deficiencies, ranging from a classic, severe form of the disease to a milder, non-classic form.

CLASSIC

The severe, classic form of the condition occurs when there is little to no hormone produced. While the onset of symptoms can be variable, affected individuals usually experience episodes in early infancy where the body cannot retain salt, leading to dehydration and other complications that can be life-threatening (known as "salt-wasting crises"). In addition, individuals may also experience weakness, poor feeding, and/or darkened (hyperpigmented) skin. Almost all affected individuals have female genitalia regardless of genetic sex, and some have been described with neurological abnormalities.

NON-CLASSIC

The less severe, non-classic form of the conditions occurs when there is still residual hormone production. However, this does not prevent salt-wasting crises. Although there have only been a handful of cases, individuals with non-classic LCAH seem to present in infancy or early childhood. The condition has been described as a form of non-autoimmune Addison disease. The improper adrenal function can result in darkening of skin (hyperpigmentation), low blood sugar (hypoglycemia), vomiting, and other symptoms.

How common is Lipoid Congenital Adrenal Hyperplasia?

LCAH has been reported in many ethnic groups, but the global incidence is unknown. It has been repeatedly seen in the Japanese, Korean, Palestinian, Saudi Arabian, and Swiss populations.

How is Lipoid Congenital Adrenal Hyperplasia treated?

Currently, there is no cure for LCAH. However, hormone replacement therapy is indicated for affected individuals, and early, consistent adherence to medication may extend the lifespan into adulthood. A multidisciplinary team of physicians, including an endocrinologist, will likely monitor the medication dosage, medication side effects, growth, and development (both general and sexual) of patients who continue to receive treatment.

What is the prognosis for an individual with Lipoid Congenital Adrenal Hyperplasia?

In the absence of any interventions or treatment, LCAH is typically fatal in early infancy; however, with treatment affected individuals have survived to adulthood.

Lysosomal Acid Lipase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: LIPA.
Exons Sequenced: NM_000235:2-10.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Lysosomal Acid Lipase Deficiency?

Lysosomal acid lipase (LAL) deficiency is an inherited condition caused by harmful genetic changes (mutations) in the *LIPA* gene. Mutations in *LIPA* lead to a decrease or complete loss of acid lipase activity. Without acid lipase, the body cannot properly break down fatty substances (lipids), including cholesteryl esters (a form of cholesterol) and triglycerides (a type of fat). These lipids instead build up and damage organs such as the spleen, the liver, bone marrow, the small intestine, the gland located above the kidneys (the adrenal gland), and lymph nodes. There are two types of LAL deficiency, which are Wolman disease and cholesterol ester storage disease (CESD).

WOLMAN DISEASE

Individuals with Wolman disease typically have little to no acid lipase activity and often develop symptoms within the first few weeks of life. Symptoms include liver failure and enlargement of organs such as the liver and spleen (enlargement of the liver is called hepatomegaly, and enlargement of the spleen is called esplenomegaly). Gastrointestinal issues such as diarrhea, vomiting, swelling of the abdomen (abdominal distension) and increased fat content in the stool (steatorrhea) are common. Individuals also have severe malnutrition and poor growth (failure to thrive). Enlargement and calcification of the adrenal glands can cause a life-threatening absence of important hormones in the body (adrenal insufficiency).

CHOLESTEROL ESTER STORAGE DISEASE

Cholesterol Ester Storage Disease (CESD) is a milder disorder that progresses more slowly than Wolman disease. Individuals with CESD tend to have more remaining acid lipase activity. The age of symptom onset ranges from early childhood to adulthood. Symptoms include hepatomegaly, liver disease, gastrointestinal issues, and poor growth. Individuals have abnormal lipid levels in their blood (dyslipidemia). This can result in the early-onset formation of plaques in the arteries (coronary artery disease), which may cause complications such as heart attack or stroke.

How common is Lysosomal Acid Lipase Deficiency?

The incidence of LAL deficiency is unknown, though it has been estimated to occur in 1 in 40,000 to 1 in 300,000 individuals. It may be more frequent among certain ethnic groups, such as individuals of European, Hispanic, or Iranian Jewish descent.

How is Lysosomal Acid Lipase Deficiency treated?

Enzyme replacement therapy (ERT), which provides the acid lipase enzyme to affected individuals through an IV, has recently become available to treat both subtypes of LAL deficiency. Studies suggest that ERT increases survival in individuals with Wolman disease and reduces some of the symptoms associated with both Wolman disease and CESD. Additional research is needed to fully understand the long-term benefits and limitations of ERT for the treatment of LAL deficiency.

Procedures such as bone marrow transplant and liver transplant have been used to treat LAL. Successful bone marrow transplant has cured several cases of Wolman disease.

Other treatments focus on addressing an individual's specific symptoms. For example, treatment with medications can be used to manage abnormal lipid levels or adrenal insufficiency. A nutrition team may provide dietary recommendations to help with malnutrition and growth.

What is the prognosis for an individual with Lysosomal Acid Lipase Deficiency?

Infants with Wolman disease typically die within the first year of life due to organ damage and malnutrition. However, treatment with enzyme replacement therapy increases life expectancy for this condition. Some individuals with CESD may have a normal life span. In other cases, complications from coronary artery disease and liver disease may lead to early death. Available treatments can prolong life expectancy in many individuals with CESD.

Maple Syrup Urine Disease Type Ia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: BCKDHA.
Exons Sequenced: NM_000709:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Maple Syrup Urine Disease Type Ia?

Maple syrup urine disease (MSUD) is an inherited metabolic disorder named for the characteristic maple syrup smell of the affected individuals's urine. There are three genes that cause MSUD, but the symptoms are identical regardless of which gene is causing the disease. MSUD type Ia is caused by harmful genetic changes (mutations) in the *BCKDHA* gene. Individuals with MSUD are unable to break down substances known as branched-chain amino acids, or BCAAs. High levels of BCAAs are toxic to the body and cause the symptoms associated with MSUD. BCAAs are found in all foods containing protein.

MSUD can be classified into three general types: classic, intermediate, and intermittent. Classic MSUD is the most severe type. Individuals with other types exhibit milder symptoms, but are prone to periods of crisis in which symptoms closely resemble classic MSUD. In all types of the disease, there is a risk of intellectual and physical disability.

CLASSIC TYPE

Classic MSUD is typically observed in the first week of life. Within 12 to 24 hours of birth, the infant's urine will take on a "maple syrup" smell. Individuals who are unfamiliar with maple syrup describe the odor as similar to fenugreek. Within several days, the infant will show poor feeding; vomiting; and irritability. This is followed by symptoms including lack of energy; weight loss; seizures; a tense, arched posture; muscle tone that alternates between stiff and limp; and swelling of the brain. If untreated, life-threatening coma or respiratory failure could occur within 7 to 10 days. If untreated, classic MSUD can cause brain damage, and many untreated infants will die within the first few months. Individuals with the disease are particularly prone to crisis during illness, infection, or fasting, or after surgery. Older individuals with MSUD often experience attention-deficit/hyperactivity disorder, depression, or anxiety disorders.

INTERMEDIATE TYPE

Intermediate MSUD is similar to, but less severe than, the classic form. The age of onset varies, and individuals may not experience severe symptoms in the newborn period. Individuals with intermediate MSUD generally experience poor feeding and growth and often have developmental delay in infancy or early childhood. During times of crisis such as illness, infection, or fasting, or after surgery, the symptoms of intermediate MSUD are nearly identical to those of the classic type.

INTERMITTENT TYPE

This form of the disease is rare. Children with intermittent MSUD generally have normal feeding and growth with no developmental delays. Individuals typically only experience symptoms during illness, fasting, or periods of high protein consumption. As with the intermediate type, in times of crisis, risks and symptoms are similar to those of the classic form.

There is another type of MSUD referred to as "thiamine-responsive," where individuals are mildly affected and can be treated with high levels of thiamine to reduce or eliminate symptoms. However, this form of the condition is very rare, and it is unclear whether these individuals have a distinct form of the disease or whether they have intermediate or intermittent MSUD. Additionally, none of these individuals are treated only with thiamine, and they typically need other supplements in addition to dietary restrictions.

How common is Maple Syrup Urine Disease Type Ia?

The incidence of MSUD in the population is approximately 1 in 185,000 infants. MSUD type Ia, caused by mutations in the gene *BCKDHA*, is thought to account for approximately 45% of all diagnoses of MSUD. The incidence of MSUD type Ia is more common among individuals of Old Order Mennonite and Portuguese Gypsy descent.

How is Maple Syrup Urine Disease Type Ia treated?

MSUD is primarily controlled by diet, using foods low in protein. This often means severe restrictions on meat, fish, eggs, dairy foods, whole-grain flour, beans, and nuts. Additionally, individuals with MSUD are given prescription medical foods and a special liquid formula that supplies needed nutrients without extra proteins they cannot digest. These dietary restrictions should begin immediately upon diagnosis and must continue for the individual's entire life.

Careful management is the key to effective treatment. Protein levels should be closely monitored by a physician, and dietary adjustments should be made as needed. Blood test findings can help to calibrate the diet and are particularly important during pregnancy for a mother with MSUD. Any swelling of the brain requires immediate medical attention. Individuals with MSUD are particularly vulnerable during times of illness and should promptly consult a physician if they do not feel well. Affected individuals may need a special "sick-day diet" to avoid hospital stays. Individuals with mood, anxiety, or attention and hyperactivity disorders generally respond well to the standard medications for those conditions.

Liver transplant is an effective treatment and can often allow individuals with MSUD to have a normal diet. However, transplants cannot reverse any developmental disability or mental illness associated with the condition.

What is the prognosis for an individual with Maple Syrup Urine Disease Type Ia?

If untreated, MSUD can be fatal. With early, careful, and lifelong treatment and a low-protein diet, people with MSUD can live healthy lives into adulthood and show normal growth and mental development. Liver transplantation can reduce or eliminate the need for dietary management, but it cannot reverse any developmental delays or mood disorders. It is critical to recognize the disease as soon as symptoms appear in order to avoid brain damage and mental disability. Despite careful treatment, some people with the disease will experience periodic flare-ups, particularly during times of illness. These episodes may create learning problems or intellectual disability and can be life-threatening.

Maple Syrup Urine Disease Type Ib

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: BCKDHB.
Exons Sequenced: NM_183050:1-10.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Maple Syrup Urine Disease Type Ib?

Maple syrup urine disease (MSUD) type Ib, caused by mutations in the *BCKDHB* gene, is an inherited metabolic disorder named for the characteristic maple syrup odor of an affected individual's urine. MSUD is caused by the lack of an enzyme needed to break down three amino acids (building blocks of proteins): leucine, isoleucine, and valine, which are collectively known as branched-chain amino acids. These amino acids are found in all foods containing protein. Without the needed enzyme, known as branched-chain ketoacid dehydrogenase (BCKAD) complex, these amino acids and their byproducts accumulate and cause damage to the body.

MSUD can be classified into four general types: classic, intermediate, intermittent, and thiamine-responsive. Classic MSUD is the most severe type. Individuals with other types exhibit milder symptoms but are prone to periods of crisis in which symptoms closely resemble classic MSUD. In all types of the disease, there is a risk of intellectual and physical disability.

CLASSIC TYPE

The most common type, classic MSUD, is characterized by little or no BCKAD enzyme activity. Symptoms in infants with classic MSUD will appear in the first week of life. Within 12 to 24 hours or upon first consumption of protein, the infant's urine will take on a maple-syrup odor. Within several days, the infant will show poor feeding, vomiting, and irritability, followed by lack of energy, weight loss, seizures, muscle tone that alternates between stiff and limp, and swelling of the brain. If untreated, life-threatening coma or respiratory failure can occur within 7 to 10 days and death can occur within the first two months.

Upon any lapse of treatment, classic MSUD can cause brain damage. Individuals with the disease are particularly prone to crisis during illness, during infection, during fasting, or after surgery.

INTERMEDIATE TYPE

Individuals with intermediate MSUD have some BCKAD enzyme activity. Thus, intermediate MSUD is similar to the classic form but is less severe. Generally, individuals with this form can tolerate higher amounts of the amino acid leucine than those with the classic type. During periods of crisis, however, this tolerance drops and symptoms and risks are nearly identical to those of the classic type.

INTERMITTENT TYPE

This form of the disease is rare. In individuals with intermittent MSUD, BCKAD enzyme activity is reduced but not absent. The onset of the disease may not occur until the first or second year of life. Symptoms are often episodic and are more likely to appear during illness, fasting, or periods of high protein consumption. As with the intermediate type, in times of crisis, risks and symptoms are similar to those of the classic form.

THIAMINE-RESPONSIVE TYPE

Thiamine-responsive MSUD is distinct in that individuals with this form of the disease are expected to show a decrease in symptoms when treated with large doses of thiamine (vitamin B1). Studies suggest that this form exists; however, the evidence is not yet definitive.

How Common Is Maple Syrup Urine Disease Type Ib?

The worldwide prevalence of MSUD is estimated to be 1 in 185,000 individuals. MSUD type Ib is estimated to account for approximately 35% of all MSUD cases. It is most common among the Ashkenazi Jewish population, where the prevalence is approximately 1 in 37,000 individuals.

How Is Maple Syrup Urine Disease Type Ib Treated?

MSUD type Ib is primarily controlled by diet; patients control it primarily by eating only foods low in protein. This often means severe restrictions on meat, fish, eggs, dairy foods, whole grain flour, beans, and nuts. Often individuals with MSUD type Ib are given a special liquid formula that supplies nutrients without the amino acids they cannot digest. These dietary restrictions should begin immediately upon diagnosis and must continue for the individual's entire life.

Management is also key to proper treatment. Amino-acid levels in the blood should be monitored regularly by a physician. Blood-test findings can help to calibrate the diet and are particularly important during pregnancy for a mother with MSUD. Any swelling of the brain requires immediate medical attention. Illnesses should always prompt a consultation with a physician, as these are vulnerable periods for an individual with MSUD type Ib. He or she may need a special “sick-day diet” to avoid hospital stays.

Those with thiamine-responsive MSUD may be prescribed thiamine supplements. To date, no patients with any form of MSUD have been treated only with thiamine supplementation. Instead, a combination of thiamine supplementation and restriction of dietary protein intake has been used, which makes it difficult to determine the true impact of a thiamine-only treatment plan.

What Is the Prognosis for an Individual with Maple Syrup Urine Disease Type Ib?

If untreated, MSUD can be fatal. With early, careful, and lifelong treatment and a low-protein diet, individuals with MSUD type Ib can live healthy lives into adulthood and show normal growth and mental development. It is particularly critical to recognize the disease as soon as symptoms appear in order to avoid brain damage and mental disability. Despite careful treatment, some individuals with the disease will experience periodic flare-ups, particularly during times of illness. These episodes can lead to learning problems or intellectual disability and may be life-threatening.

Maple Syrup Urine Disease Type II

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: DBT.
Exons Sequenced: NM_001918:1-11.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe
97%	Worldwide

What is Maple Syrup Urine Disease Type II?

Maple syrup urine disease (MSUD) is an inherited metabolic disorder named for the characteristic maple-syrup smell of the affected individual's urine. There are three genes that cause MSUD, but the symptoms are identical regardless of which gene is causing the disease. MSUD type II is caused by harmful genetic changes (mutations) in the *DBT* gene. Individuals with MSUD are not able to break down substances known as branched-chain amino acids, or BCAAs. High levels of BCAAs are toxic to the body and cause the symptoms associated with MSUD. BCAAs are found in all foods containing protein.

MSUD can be classified into three general types: classic, intermediate, and intermittent. Classic MSUD is the most severe type. Individuals with other types exhibit milder symptoms but are prone to periods of crisis in which symptoms closely resemble those of classic MSUD. In all types of the disease, there is a risk of intellectual and physical disability.

CLASSIC TYPE

Classic MSUD in infants is typically observed in the first week of life. Within 12 to 24 hours of birth, the infant's urine will take on a maple-syrup smell. Individuals who are unfamiliar with maple syrup describe the odor as similar to fenugreek. Within several days, the infant will show poor feeding, vomiting, and irritability, followed by lack of energy; weight loss; seizures; a tense, arched posture; muscle tone that alternates between stiff and limp; and swelling of the brain. If the disease is untreated, life-threatening coma or respiratory failure could occur within 7 to 10 days. If untreated, classic MSUD can cause brain damage, and many untreated infants will die within the first few months. Individuals with the disease are particularly prone to crisis after surgery or during illness, infection, or fasting. Older individuals with MSUD often experience attention-deficit/hyperactivity disorder, depression, or anxiety disorders.

INTERMEDIATE TYPE

Intermediate MSUD is similar to the classic form, but less severe. The age of onset varies, and affected individuals may not experience severe symptoms in the newborn period. Individuals with intermediate MSUD generally experience poor feeding and growth and often have developmental delay in infancy or early childhood. During times of crisis such as after surgery or during illness, infection, or fasting, the symptoms of intermediate MSUD are nearly identical to those of the classic type.

INTERMITTENT TYPE

This form of the disease is rare. Children with intermittent MSUD generally have normal feeding and growth with no developmental delays. Affected individuals typically only experience symptoms during illness, fasting, or periods of high protein consumption. As with the intermediate type, in times of crisis, risks and symptoms are similar to those of the classic form.

There is another type of MSUD referred to as "thiamine-responsive," where individuals are mildly affected and can be treated with high levels of thiamine to reduce or eliminate symptoms. However, this form of the condition is very rare, and it is unclear if these individuals have a distinct form of the disease or if they actually have intermediate or intermittent MSUD. Additionally, none of these individuals are treated only with thiamine, and they typically need other supplements in addition to dietary restrictions.

How common is Maple Syrup Urine Disease Type II?

The incidence of MSUD in the population is approximately 1 in 185,000 infants. MSUD type II, caused by mutations in the *DBT* gene, is thought to account for approximately 13-27% of all diagnoses of MSUD. Type II may be more common in Filipinos and the Austronesian indigenous people of Taiwan, due to founder effects (a high frequency of the disease, because the group arose from a small, possibly isolated, population).

How is Maple Syrup Urine Disease Type II treated?

MSUD is primarily controlled by diet, using foods low in protein. This often means severe restrictions on meat, fish, eggs, dairy foods, whole-grain flour, beans, and nuts. Additionally, individuals with MSUD are given prescription medical foods and a special liquid formula that supplies needed nutrients without extra proteins they cannot digest. These dietary restrictions should begin immediately upon diagnosis and must continue for the individual's entire life.

Careful management is the key to effective treatment. Protein levels should be closely monitored by a physician, and dietary adjustments should be made as needed. Blood-test findings can help to calibrate the diet and are particularly important during pregnancy for a mother with MSUD. Any swelling of the brain requires immediate medical attention. Individuals with MSUD are particularly vulnerable during times of illness and should promptly consult a physician if they do not feel well. He or she may need a special "sick-day diet" to avoid hospital stays. Individuals with mood, anxiety, or attention and hyperactivity disorders generally respond well to the standard medications for those conditions.

Liver transplant is an effective treatment and can often allow individuals with MSUD to have a normal diet. However, transplants cannot reverse any developmental disability or mental illness associated with the condition.

What is the prognosis for an individual with Maple Syrup Urine Disease Type II?

If untreated, MSUD can be fatal. With early, careful, and lifelong treatment and a low-protein diet, people with MSUD can live healthy lives into adulthood and show normal growth and mental development. Liver transplantation can reduce or eliminate the need for dietary management, but it cannot reverse any developmental delays or mood disorders. It is critical to recognize the disease as soon as symptoms appear, in order to avoid brain damage and mental disability. Despite careful treatment, some people with the disease will experience periodic flare-ups, particularly during times of illness. These episodes may create learning problems or intellectual disability and can be life-threatening.

Medium-chain Acyl-CoA Dehydrogenase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ACADM.
Exons Sequenced: NM_000016:1-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Medium-Chain Acyl-CoA Dehydrogenase Deficiency?

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is an inherited metabolic disorder in which fats cannot be broken down into energy to fuel the body. It is part of a group of disorders called fatty acid oxidation defects and is caused by harmful genetic changes in the *ACADM* gene. These changes result in a buildup of harmful fatty acids that can accumulate in body tissues and cause damage to the brain, liver, and other organs.

For most individuals with MCAD deficiency, symptoms first appear in infancy or early childhood and can be triggered by long periods without eating (fasting) or by illness. Symptoms include vomiting, lack of energy, low blood sugar, and an enlarged liver. Without treatment, symptoms can quickly develop into life-threatening problems including seizures, breathing problems, brain damage, coma, and death. A small percentage of sudden infant death syndrome (SIDS) is likely due to undiagnosed MCAD deficiency. In some cases, symptoms may not appear until late childhood or adulthood and can be milder.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Carriers of MCAD deficiency do not typically show symptoms of the disease. However, there is increased risk of serious pregnancy complications, particularly in the third trimester, in individuals carrying a fetus affected with MCAD deficiency. These complications may include acute fatty liver disease and a life-threatening condition called HELLP syndrome which presents with headache, nausea, swelling, and chest pain. An individual whose pregnancy may be affected by MCAD deficiency should speak with their physician for recommendations and may benefit from consultation with a high-risk physician.

How common is Medium-Chain Acyl-CoA Dehydrogenase Deficiency?

The incidence of MCAD deficiency in the population is 1 in 14,000 to 1 in 25,000 births. The incidence of MCAD deficiency is more common among individuals of Northern European descent.

How is Medium-Chain Acyl-CoA Dehydrogenase Deficiency treated?

The key treatment for individuals with MCAD deficiency is to avoid fasting. Infants must be frequently fed a formula low in fat but high in carbohydrates. For children and adults, consuming cornstarch can also provide a sustained release of energy and allow for longer gaps between meals. If an individual is unable to eat or drink food on their own, it may be necessary to give them glucose by intravenous fluids.

What is the prognosis for an individual with Medium-Chain Acyl-CoA Dehydrogenase Deficiency?

Early diagnosis and dietary management are crucial for the best outcome. If dietary management starts early (especially before the onset of symptoms) and is consistent, individuals with MCAD deficiency have a good prognosis with normal or near-normal lifespan. In undiagnosed and untreated cases of MCAD deficiency, symptoms can quickly cause irreversible damage or even lead to death.

Megalencephalic Leukoencephalopathy with Subcortical Cysts

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MLC1.
Exons Sequenced: NM_015166:2-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Megalencephalic Leukoencephalopathy with Subcortical Cysts?

Megalencephalic Leukoencephalopathy with Subcortical Cysts (MLC) is an inherited disease that causes seizures and developmental delay in affected infants and children, followed by a deterioration of motor skills and intellectual abilities later in life. Additionally, individuals with MLC demonstrate changes in brain structure, including the development of cysts that are visible on brain scans. The condition is most often caused by mutations in the *MLC1* gene.

Many infants with MLC are born with disproportionately large heads, while others develop this symptom in the first year of life. After the first year, the growth of the head usually normalizes and becomes proportionate to the body. This is often accompanied by a mild delay in motor skills and the development of epileptic seizures. Most children with MLC learn to walk independently for at least several years. While some retain the ability to walk for decades, many will experience deteriorating motor skills beginning in childhood. With time, individuals with MLC may demonstrate an inability to coordinate muscle movement (ataxia) and may exhibit significant muscle stiffness (spasticity). Many will require wheelchairs or other assistive devices by their early teens or twenties. Some individuals may also experience difficulties with swallowing and speech. Decline in intellectual abilities is slower in progression and generally begins after the decline in motor skills.

How Common Is Megalencephalic Leukoencephalopathy with Subcortical Cysts?

MLC is extremely rare, although the precise prevalence of the condition in the general population is unknown. Mutations in the *MLC1* gene are estimated to account for approximately 75% of MLC cases and have been found in individuals of Middle Eastern, Turkish, Japanese, and Libyan Jewish descent, among others. In addition, it has been suggested that the condition may be more common in the Agarwali Indian and Turkish populations.

How Is Megalencephalic Leukoencephalopathy with Subcortical Cysts Treated?

There is no treatment or cure for the underlying cause of MLC. Treatments address the symptoms of the disease, such as medications to control seizures and physical therapy to improve motor skills.

What Is the Prognosis for an Individual with Megalencephalic Leukoencephalopathy with Subcortical Cysts?

MLC is slowly progressive. The majority of individuals with the condition are confined to a wheelchair in adolescence or early adulthood, although those with more severe disease may lose the ability to walk much earlier. Lifespan may be also be shortened in individuals with MLC, with death occurring as early as the late teens in some cases and as late as the forties or fifties in others.

Metachromatic Leukodystrophy

INCLUDING EARLY-ONSET FORM AND LATE-ONSET FORM

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ARSA.
Exons Sequenced: NM_000487:1-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Metachromatic Leukodystrophy (MLD)?

Metachromatic Leukodystrophy (MLD), a disease caused by mutations in the *ARSA* gene, is the most common disorder in a group of diseases known as leukodystrophies which primarily affect the nervous system. These diseases affect the myelin sheath, a fatty covering that insulates and protects nerve cells. MLD results from a deficiency in an enzyme called arylsulfatase A. The lack of this enzyme causes a fatty substance called sulfatide to build up to toxic levels in the body. This gradually destroys the myelin sheath, without which brain cells die and nerves in the body cannot function properly.

Individuals with MLD will progressively lose intellectual and motor functions. Symptoms may include stiffness and tightness of the muscles (spasticity), seizures, personality changes, and progressive dementia. As the disease progresses, the patient loses the ability to walk, talk, see, and hear, eventually leading to paralysis and unresponsiveness.

MLD can be divided into three forms: infantile (early-onset), juvenile (late-onset), and adult (late-onset). The course of the disease is similar, but the age at which symptoms appear varies, as does the rate at which symptoms progress. The age at which symptoms begin is usually similar among affected family members.

INFANTILE FORM

This is the most common form of MLD, accounting for 50 to 60% of all cases. Symptoms appear between the first and second years of life. Initially, affected children lose any language abilities they have developed and have trouble walking. Gradually their muscles waste away and become rigid. They will lose mental function and often experience seizures and loss of sensation in their limbs. By the final stages of the disease, children with infantile MLD become blind and deaf and require a feeding tube. They are unresponsive to their surroundings and eventually become paralyzed. Infantile MLD is usually fatal by the age of 10.

JUVENILE FORM

In the juvenile form of MLD, symptoms appear after the age of 3 but before adolescence. Approximately 20 to 30% of individuals with MLD have the juvenile form. Initial signs of the disease include difficulties in school and behavioral problems. Clumsiness, slurred speech, incontinence, and strange behavior often prompt parents to seek a diagnosis. As the disease continues, symptoms are similar to infantile MLD but the disease progresses more slowly in the juvenile form. The disease is usually fatal 10 to 20 years after the first symptoms appear.

ADULT FORM

In the adult form of MLD, symptoms appear after puberty and may not appear until an individual is in their forties or fifties. Roughly 15 to 20% of individuals with MLD have the adult form. Early signs of the disease often include personality changes, problems at school or work, numbness in the extremities of one's limbs, muscle weakness, loss of coordination, and psychiatric problems such as delusions, hallucinations, or drug and alcohol abuse. MLD can be initially misdiagnosed as schizophrenia, depression, or multiple sclerosis.

Over time, an affected individual's behavior will become inappropriate and he or she will have trouble making good decisions. Everyday skills become difficult, and movement will grow spastic and awkward. Eventually, an individual affected by the adult form will lose the ability to carry on a conversation. In the final stages of the disease, symptoms are similar to the infantile form: blindness, deafness, unresponsiveness, and paralysis.

This form of the disease progresses more slowly than the other forms. Affected individuals may experience periods of stability or periods of particularly rapid decline. Individuals with the adult form of MLD may live 20 to 30 years after their initial diagnosis.

How Common Is MLD?

Worldwide, the prevalence of MLD varies from 1 in 40,000 to 1 in 160,000 individuals. It is more common among Habbanite Jews in Israel, Israeli Arabs, Christian Israeli Arabs, and individuals in the western parts of the Navajo Nation.

How Is MLD Treated?

There is currently no cure for MLD. Bone-marrow transplantation may be an option for some individuals with MLD. It has shown the most promise in those who are not yet showing symptoms of MLD. At best it slows, but does not stop, the progression of the disease. This is a controversial treatment because of its substantial health risks.

Most treatments aim to manage symptoms of the disease as they arise. Seizures and muscle tightness may be treated with medication. Physical therapy may help preserve movement as long as possible. Walking aids, wheelchairs, feeding tubes, and other supportive devices may also be beneficial.

What Is the Prognosis for an Individual with MLD?

All individuals with MLD will experience mental and motor deterioration, eventually reaching a state of paralysis and unresponsiveness.

Most children with the infantile form of MLD die by the age of 10. Those with the juvenile form typically develop symptoms between the ages of 3 and 14 and can live 10 to 20 years after the onset of symptoms. The adult form of the disease is more variable, but affected adults may not develop symptoms until their forties or fifties and can live 20 to 30 years after symptoms begin. Death most commonly occurs from pneumonia or other infections.

Methylmalonic Acidemia, cblA Type

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MMAA.
Exons Sequenced: NM_172250:2-7.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Methylmalonic Acidemia, cblA Type?

Methylmalonic acidemia represents a group of disorders that affect the way a person breaks down proteins and fats. In general, symptoms of methylmalonic acidemia can occur from any time between the neonatal period and adulthood. However, the cblA type is usually associated with onset of symptoms in infancy or early childhood. Symptoms often first present as an episode due to infection or other external stressors (metabolic decompensation) and may include vomiting, dehydration, and lethargy. Long-term complications can include low muscle tone (hypotonia), developmental delay and intellectual disability, anorexia and poor growth (failure to thrive), chronic kidney disease, and pancreatitis.

How common is Methylmalonic Acidemia, cblA Type?

The estimated incidence of methylmalonic acidemia is 1 in 50,000 to 1 in 100,000 people. The portion of methylmalonic acidemia attributed to cblA Type is ~25%.

How is Methylmalonic Acidemia, cblA Type treated?

There is no cure for methylmalonic acidemia. Treatment is divided between managing an acute crisis (metabolic decompensation) and management of symptoms between crises. Metabolic crisis is managed in a hospital and involves increasing the amount of fluid in the body, ensuring proper nutrition (reduced or no protein and increased glucose-intake), and monitoring laboratory work for signs of further complications (like those related to elevated ammonia levels), which is best done by a metabolic expert. Long-term management includes a high-calorie diet that is low in protein, hydroxocobalamin (vitamin B12) intramuscular injections, carnitine and other supplements, and antibiotics. Transplant may become necessary if organ failure occurs.

What is the prognosis for a person with Methylmalonic Acidemia, cblA Type?

Methylmalonic acidemia is associated with a number of chronic issues and higher than average mortality rates. Even with treatment, the cblA type can be associated with symptoms, like intellectual disability or kidney disease. In a small percentage of cblA cases, a metabolic crisis can lead to coma and death, especially if the individual is left untreated.

Methylmalonic Acidemia, cblB Type

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MMAB.
Exons Sequenced: NM_052845:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Methylmalonic Acidemia, cblB Type?

Methylmalonic acidemia represents a group of disorders that affect the way a person breaks down proteins and fats. In general, symptoms of methylmalonic acidemia can occur at any time between the neonatal period and adulthood. The cblB type is usually associated with onset of symptoms shortly after birth. During metabolic decompensation (episodic crisis due to infection or other external stressors) symptoms include vomiting, dehydration, lethargy, seizures, metabolic acidosis (too much acid in the blood), and hyperammonemia (elevated ammonia levels). Long-term complications can include increased risk for infections, low muscle tone (hypotonia), encephalopathy (brain damage), epilepsy, developmental delay and intellectual disability, anorexia and poor growth (failure to thrive), pancreatitis, enlarged liver (hepatomegaly), and chronic kidney disease that progresses to kidney failure.

How common is Methylmalonic Acidemia, cblB Type?

The estimated incidence of methylmalonic acidemia is 1 in 50,000 to 1 in 100,000 people. The portion of methylmalonic acidemia attributed to cblB type is ~13%.

How is Methylmalonic Acidemia, cblB Type treated?

There is no cure for methylmalonic acidemia. Treatment is divided between managing an acute crisis (metabolic decompensation) and management of symptoms between crises. Metabolic crisis is managed in a hospital and involves increasing the amount of fluid in the body, ensuring proper nutrition (reduced or no protein and increased glucose-intake), and monitoring laboratory work for signs of further complications (such as those related to elevated ammonia levels), which is best done by a metabolic expert. Long-term management includes a high-calorie diet that is low in protein, carnitine and other supplements, antibiotics, and hydroxocobalamin (vitamin B12) intramuscular injections in rare cases. Transplant may become necessary if organ failure occurs.

What is the prognosis for a person with Methylmalonic Acidemia, cblB Type?

Methylmalonic acidemia is associated with a number of chronic issues and higher than average mortality rates. Even with treatment, the cblB type can be associated with symptoms, like intellectual disability or kidney failure. Metabolic crisis can lead to coma, especially if left untreated. The median age of death for patients with the cblB type is ~3 years.

Methylmalonic Acidemia, MMUT-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MMUT.
Exons Sequenced: NM_000255:2-13.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Methylmalonic Acidemia, MMUT-related?

Methylmalonic acidemia represents a group of disorders that affect the way a person breaks down proteins and fats. Methylmalonic acidemia, MMUT-related is caused by harmful genetic changes (mutations) in the *MMUT* gene (formerly known as the *MUT* gene). In general, methylmalonic acidemia may manifest any time between the neonatal period and adulthood. The most common presentation is a severe onset during infancy, referred to as the "mut0" subtype. Some individuals may present with less severe or later-onset presentations, referred to as the "mut–" subtype. Symptoms often develop as an episode due to infection or other external stressors (metabolic decompensation) and may include vomiting, dehydration, excessive tiredness (lethargy), and seizures. Long-term complications can include increased risk for infections, low muscle tone (hypotonia), brain damage (encephalopathy), developmental delay, intellectual disability, poor growth (failure to thrive), pancreatitis, enlarged liver (hepatomegaly), and chronic kidney disease that progresses to kidney failure.

How common is Methylmalonic Acidemia, MMUT-related?

The incidence of methylmalonic acidemia is estimated to be between 1 in 50,000 and 1 in 100,000 live births, but the exact incidence is unknown. Five genes are known to cause methylmalonic acidemia with approximately 60% of cases being attributed to mutations in *MMUT*.

How is Methylmalonic Acidemia, MMUT-related treated?

There is no cure for methylmalonic acidemia. Treatment involves managing acute crises (metabolic decompensation) and long-term management. Metabolic crises are managed in a hospital and involve increasing the amount of fluid in the body, ensuring proper nutrition (reduced or no protein and increased glucose-intake), and monitoring the patient for signs of further complications. Long-term

management mainly includes a high-calorie diet that is low in protein. Additional treatments may include vitamin B12 intramuscular injections, carnitine and other supplements, and antibiotics. Transplant may become necessary if organ failure occurs.

What is the prognosis for an individual with Methylmalonic Acidemia, MMUT-related?

Methylmalonic acidemia is associated with several chronic issues and higher-than-average mortality rates. Even with treatment, patients may develop intellectual disability or kidney failure. Metabolic crisis can lead to coma, especially if left untreated. For patients with early presentations, there is a significant risk of death within the first few years of life.

Methylmalonic Aciduria and Homocystinuria, cblC Type

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MMACHC.
Exons Sequenced: NM_015506:1-4.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Methylmalonic Aciduria and Homocystinuria, cblC Type?

Methylmalonic aciduria and homocystinuria, cblC type is a metabolic disorder that affects the body's ability to process a protein called cobalamin. Cobalamin is also known as vitamin B12. The most well-described form of methylmalonic aciduria and homocystinuria is type cblC, or methylmalonic aciduria and homocystinuria, cblC type; it is also the most common of these disorders.

The age of initial presentation of cblC ranges from (1) newborns who can be small for gestational age with unusually small head size; to (2) infants who can have poor feeding, failure to thrive, and neurologic/developmental abnormalities; to (3) toddlers who can have failure to thrive, poor head growth, developmental delay, low muscle tone, and seizures; and to (4) young adults/adults who may develop confusion, mental illness, cognitive decline, and anemia.

How common is Methylmalonic Aciduria and Homocystinuria, cblC Type?

The estimated incidence is estimated to be approximately 1 in 100,000 births.

How is Methylmalonic Aciduria and Homocystinuria, cblC Type treated?

Currently, there is no treatment that cures or alleviates all the symptoms of methylmalonic aciduria and homocystinuria, cblC type. Critically ill individuals must be stabilized, preferably in consultation with a metabolic specialist, by treating their metabolic disease. Dietary modifications may improve symptoms and gastrostomy tube placement for feeding is often required. Seizures are treated using standard protocols. Medications have proven effective in some cases.

During the first year of life, infants may need to be evaluated once or twice a month. Routine medical care should include special attention to growth and development; neurologic evaluation for early signs of delay, behavioral disturbances, and seizures; and ophthalmologic evaluation for retinal and optic nerve changes. Prolonged fasting and excessive dietary protein intake should be limited.

What is the prognosis for a person with Methylmalonic Aciduria and Homocystinuria, cblC Type?

Some affected individuals have early and severe symptoms, while others reach adulthood without evidence of ongoing disease progression. In some cases, severe neurologic symptoms and/or cognitive impairment persist. It is difficult to discern whether or not such impairments are due to the disease progression prior to treatment or ongoing neurological decline.

Mevalonate Kinase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MVK.
Exons Sequenced: NM_000431:2-11.

Detection Rate	Population
99%	African American
99%	Ashkenazi Jewish
99%	Eastern Asia
99%	Finland
99%	French Canadian or Cajun
99%	Hispanic
99%	Middle East
99%	Native American
99%	Northwestern Europe
99%	Oceania
99%	South Asia
99%	Southeast Asia
99%	Southern Europe
99%	Worldwide

What is Mevalonate Kinase Deficiency?

Mevalonate kinase deficiency (MKD) includes a spectrum of symptoms that are caused by harmful genetic changes (variants) in the *MVK* gene. The symptoms are caused by problems with the immune system (auto-inflammatory disease) and usually include lifelong episodes of high fevers, joint and muscle pain, swollen lymph nodes (lymphadenopathy) and stomach pain. The frequency and severity of these episodes vary from person to person, though on average, affected individuals have around twelve episodes a year. The number of episodes generally goes down as individuals get older, however, many still experience at least six episodes a year by the age of twenty. The first episode generally occurs before one year of age.

While MKD involves a spectrum of symptoms, there are two main types: hyperimmunoglobulinemia D syndrome (HIDS) and mevalonic aciduria (MVA). MVA is usually significantly more severe than HIDS.

HYPERIMMUNOGLOBULINEMIA D SYNDROME (HIDS)

Hyperimmunoglobulinemia D syndrome (HIDS) is the most common presentation of MKD. Individuals with HIDS typically experience lifelong recurrent fevers, joint and muscle pain, swollen lymph nodes, and a rash. Episodes usually occur every four to six weeks, however episodes can be triggered by stress to the immune system from illness, vaccinations, or injuries.

MEVALONIC ACIDURIA (MA)

Individuals with mevalonic aciduria (MA) have many of the same symptoms as those with HIDS, however MA is more severe. Affected infants may not grow and develop normally (failure to thrive) and may have intellectual and developmental disabilities. MA also causes problems with the nervous system that may include seizures, problems coordinating movement (ataxia), and muscle weakness. Individuals may have eye problems and often have distinctive facial features.

Some individuals with MKD may develop macrophage activation syndrome (MAS), which is a serious condition that causes very high fevers, low levels of red blood cells (cytopenia), high levels of iron in the blood (hyperferritinemia) and organ dysfunction.

How common is Mevalonate Kinase Deficiency?

The exact incidence of MKD is unknown. More than three hundred people with MKD have been reported worldwide, with most having HIDS. This number may be an underestimate as many cases are thought to be undiagnosed. The incidence of MKD is more common among individuals of Dutch descent.

How is Mevalonate Kinase Deficiency treated?

There is no cure for MKD. Treatment is targeted to the patient's symptoms and typically includes medications to help reduce the severity of attacks. One such medication, Canakinumab (Ilaris), was approved by the FDA in 2016 for treating individuals with inflammatory auto-immune diseases. Other treatments may include interventions for intellectual or developmental delays and stem cell transplantation.

What is the prognosis for an individual with Mevalonate Kinase Deficiency?

In the most common form of this condition, HIDS, lifespan is not expected to be affected. However, quality of life can be significantly impacted by the frequency and/or severity of the inflammatory episodes.

In individuals with the more severe MA, up to half of patients pass away in infancy or early childhood. Those who do survive typically have intellectual and developmental disabilities.

Microcephaly with Seizures and Brain Atrophy, MED17-related

Available Methodologies: targeted genotyping (v1.0) and interpretation of reported variants (v4.0).
Gene: MED17.
Variant Genotyped (1): L371P.

Detection Rate	Population
89%	African American
89%	Ashkenazi Jewish
Not calculated due to rarity of disease in this individual's reported ethnicity	Eastern Asia
89%	Finland
89%	French Canadian or Cajun
89%	Hispanic
89%	Middle East
89%	Native American
89%	Northwestern Europe
89%	Oceania
89%	South Asia
89%	Southeast Asia
89%	Southern Europe
89%	Worldwide

What is Microcephaly With Seizures and Brain Atrophy, MED17-related?

Microcephaly with seizures and brain atrophy, MED17-related, is an inherited condition that is associated with a small head size (microcephaly), seizures, and problems with brain development. The condition is caused by harmful genetic changes (variants) in the *MED17* gene. Newborns with the condition usually have a typical head size at birth following a normal pregnancy. Affected infants become fussy shortly after birth and have trouble eating. They develop swallowing problems as they age, fail to gain weight (failure to thrive), and cannot follow or focus on an item with their eyes (poor visual fixation). Other symptoms include seizures, muscle tightness or stiffness (muscle spasticity), and weak core muscles (truncal hypotonia). No developmental milestones are achieved after four to nine weeks of age. A small head size generally becomes evident by six months of age. Brain imaging (MRI) usually shows wasting away of parts of the brain (atrophy). All individuals with microcephaly with seizures and brain atrophy, MED17-related, have an intellectual disability. Respiratory infections are also common. Some individuals may have skeletal problems like joints that cannot bend (joint contractures), spine rotation (kyphoscoliosis), and hip dislocations.

In extremely rare cases, affected individuals may have a slightly milder disease course without evidence of seizures, microcephaly, or poor weight gain. However, these individuals are reported to have vision problems and severe developmental delays, including an inability to sit unsupported, speak, or use their hands purposefully.

How common is Microcephaly With Seizures and Brain Atrophy, MED17-related?

Microcephaly with seizures and brain atrophy, MED17-related, is extremely rare. The exact frequency of the condition in the general population is unknown, although it appears to be more common in individuals of Caucasus-Jewish ancestry.

How is Microcephaly With Seizures and Brain Atrophy, MED17-related treated?

There is no cure for microcephaly with seizures and brain atrophy, MED17-related. Treatment is based on the symptoms an individual is experiencing and is aimed at making them as comfortable as possible. Affected individuals should work with a team of healthcare providers that includes pediatrics, neurology, as well as physical and occupational therapy. Some infants may need a tube placed to help with feeding, and medications may help control seizures.

What is the prognosis for a person with Microcephaly With Seizures and Brain Atrophy, MED17-related?

To date, all individuals with postnatal progressive microcephaly with seizures and brain atrophy have moderate to profound intellectual disability and physical deficits. Because the condition is rare, the average lifespan for affected individuals is unknown. Some cases have been known to live into the teens or twenties, although many individuals die before age ten.

Microphthalmia, Anophthalmia, and Coloboma, VSX2-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: VSX2.
Exons Sequenced: NM_182894:1-5.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Microphthalmia, Anophthalmia, and Coloboma, VSX2-related?

Microphthalmia, anophthalmia, and coloboma, VSX2-related (MAC, VSX2-related), is a condition characterized by eye abnormalities. It is caused by harmful genetic changes (variants) in the *VSX2* gene. The *VSX2* gene plays an important role in the process of eye development, and variants in the gene disrupt this process, leading to the symptoms of the condition.

Common features of MAC, VSX2-related include a smaller than normal eyeball (microphthalmia) or a complete absence of the eyeball (anophthalmia), typically affecting both eyes. Individuals may also have other eye differences. These can include small missing pieces of tissue in the eye (colobomas) and clouding of the eye's lens (cataracts). Affected individuals typically have partial or complete vision loss. In most cases, symptoms of MAC, VSX2-related are limited to the eyes. In rare cases, individuals with this condition have been reported to have other symptoms, such as developmental delays or behavioral abnormalities.

How common is Microphthalmia, Anophthalmia, and Coloboma, VSX2-related?

Several genes are known to cause microphthalmia, anophthalmia, and coloboma, which has an incidence of between 1 and 4 in 10,000 births. Approximately 1.5% of microphthalmia, anophthalmia, and coloboma is caused by *VSX2*. The incidence of microphthalmia, anophthalmia, and coloboma, VSX2-related is more common among individuals of Middle Eastern descent.

How is Microphthalmia, Anophthalmia, and Coloboma, VSX2-related treated?

The structure of the eye socket is important for the development of the facial bones. Therefore, children with MAC, VSX2-related are often treated using a device to help the eye socket grow along with the rest of the facial bones. Prosthetic eyes are also used to help with the development of the facial bones, as well as for cosmetic reasons. In some cases, surgeries to treat eye abnormalities may be recommended. Additional management is typically supportive, such as the use of low vision aids and early intervention services in children with reduced vision.

What is the prognosis for an individual with Microphthalmia, Anophthalmia, and Coloboma, VSX2-related?

While a person with MAC, VSX2-related may have partial or complete vision loss, the condition does not typically affect lifespan, other body systems, or intelligence.

Mild MTHFR Deficiency

Available Methodologies: targeted genotyping (v1.0) and interpretation of reported variants (v4.0).
Gene: MTHFR.
Variant Genotyped (1): A222V.

WHAT IS MILD MTHFR DEFICIENCY?

Mild MTHFR deficiency is a condition that is associated with mildly elevated risks of fetal neural tube defects, pregnancy loss, and maternal blood clots (thromboembolism). However, it does not cause any health problems in most pregnant individuals. Mild MTHFR deficiency is caused by specific harmful changes (variants) in the *MTHFR* gene. These changes sometimes cause individuals to have slightly elevated levels of an amino acid (homocysteine) and lower levels of the vitamin folate in the body, which can increase the risk for certain pregnancy complications. Mild MTHFR deficiency should not be confused with homocystinuria, MTHFR-related, which is the result of more severe harmful changes that lead to extremely elevated levels of homocysteine and different health complications (such as seizures and developmental delay).

The vast majority of mild MTHFR deficiency cases are caused by the very common A222V (also known as C677T) change in the *MTHFR* gene. Having two copies of the A222V change is associated with an increased risk of elevated homocysteine (hyperhomocysteinemia).

Note that this condition is only significant if it raises the level of homocysteine in the blood. This does not happen to every individual who carries two copies of the A222V change.

For pregnant individuals with two copies of the A222V change *and* an elevated homocysteine level, there is an approximately 2-fold higher risk of having a child with neural tube defects (such as spina bifida). In the general population, 1 in 1,000 births are affected with a neural tube defect while individuals with two copies of the A222V change and an elevated homocysteine level have a 2 in 1,000 (0.2%) risk. There are also slightly elevated risks for pregnancy loss and maternal blood clots.

Individuals with two copies of the A222V change should speak with their physician regarding testing to measure fasting homocysteine levels. If fasting homocysteine levels are normal, no change in medical management is needed. If fasting homocysteine levels are elevated, the patient's physician may advise them to take a higher dose of folate supplements.

HOW COMMON IS MILD MTHFR DEFICIENCY?

The exact incidence of mild MTHFR deficiency is unknown, but it is considered very common. Approximately 30-40% of individuals in the general population are carriers of the A222V change and 10-15% of individuals have two copies of A222V. However, not all individuals with two copies of A222V will exhibit symptoms.

HOW IS MILD MTHFR DEFICIENCY TREATED?

Most individuals with mild MTHFR deficiency require no treatment. All pregnant individuals are already advised to take folic acid supplements before and during pregnancy to reduce the risk of birth defects by as much as 75% to 85%. Doctors may recommend higher doses of folate supplements to pregnant individuals who have an elevated homocysteine level due to mild MTHFR deficiency.

WHAT IS THE PROGNOSIS FOR AN INDIVIDUAL WITH MILD MTHFR DEFICIENCY?

Based on current scientific knowledge, most individuals with mild MTHFR deficiency will be completely unaffected. Individuals whose *MTHFR* changes result in an elevated homocysteine level have a slightly increased risk of having a child with neural tube defects (0.2-0.3% versus 0.1% in the general population). There are also mildly elevated risks for pregnancy loss and blood clots.

Mitochondrial Complex I Deficiency, NDUFAF5-related

Available Methodologies: targeted genotyping (v1.0) and interpretation of reported variants (v4.0).
Gene: NDUFAF5.
Variant Genotyped (1): G250V.

Detection Rate	Population
29%	African American
>99%	Ashkenazi Jewish
29%	Eastern Asia
29%	Finland
29%	French Canadian or Cajun
29%	Hispanic
29%	Middle East
29%	Native American
29%	Northwestern Europe
29%	Oceania
29%	South Asia
29%	Southeast Asia
29%	Southern Europe
29%	Worldwide

What is Mitochondrial Complex I Deficiency, NDUFAF5-related?

Mitochondrial complex I deficiency is a group of disorders caused by abnormalities of energy production in a cellular structure called the mitochondria. The mitochondria produce energy for the cells in the body and are critical for cellular function. There are several genes associated with mitochondrial complex I deficiency, and mitochondrial complex I deficiency, NDUFAF5-related, is caused by harmful genetic changes in the *NDUFAF5* gene.

Mitochondrial complex I deficiency can range from a very severe disease, which can be fatal in the neonatal period, to neurodegenerative disorders with onset in adulthood. Symptoms vary between affected individuals and can include progressive brain abnormalities, heart disease, muscle weakness, liver disease, vision loss, or Parkinson's disease. Symptoms in mitochondrial complex I deficiency, NDUFAF5-related typically include muscle tightness (spasticity) of the arms and legs in early childhood. Developmental delay progresses to intellectual disability in affected individuals. Abnormal muscle contractions can impact mobility as well as other functions (such as swallowing).

Some individuals with mitochondrial complex I deficiency have a condition called Leigh syndrome. Leigh syndrome is a progressive condition which impacts the central nervous system. Some symptoms of the disease are caused by tissue damage that develops in the brain. Symptoms include intellectual disability, muscle weakness, breathing problems, vision loss, hearing impairment, and heart disease. Leigh syndrome is typically progressive and affected individuals often do not survive the first two years of life.

How common is Mitochondrial Complex I Deficiency, NDUFAF5-related?

Several genes are known to cause mitochondrial complex I deficiency, which has an incidence of 1 in 8,500 births. The exact incidence of mitochondrial complex I deficiency, NDUFAF5-related is unknown.

How is Mitochondrial Complex I Deficiency, NDUFAF5-related treated?

There is no cure for mitochondrial complex I deficiency, NDUFAF5-related. Treatment for the condition is directed at managing the specific symptoms an individual has. This often means receiving care through a team of specialists that may include physicians, speech pathologists, occupational therapists, physical therapists, and social workers. Some families of severely affected infants may opt to pursue palliative care, which focuses on improving quality of life and may have limited medical intervention.

What is the prognosis for an individual with Mitochondrial Complex I Deficiency, NDUFAF5-related?

The prognosis for an individual with mitochondrial complex I deficiency, NDUFAF5-related is dependent on the symptoms and severity of disease. Severely affected individuals with neonatal onset typically do not survive the first few weeks of life. Those who develop symptoms later in infancy may pass away in early childhood. Mildly affected individuals can survive into adulthood, but have intellectual disability, developmental delay, and loss of sensory and motor control of the arms and legs.

Mitochondrial Complex I Deficiency, NDUFS4-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: NDUFS4.
Exons Sequenced: NM_002495:1-5.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe
97%	Worldwide

What is Mitochondrial complex I deficiency, NDUFS4-related?

Mitochondrial complex I deficiency is a group of disorders caused by abnormalities of energy production in a cellular structure called the mitochondria. The mitochondria produce energy for the cells in the body and are critical for cellular function. There are several genes associated with mitochondrial complex I deficiency, and Mitochondrial complex I deficiency, NDUFS4-related, is caused by harmful genetic changes in the *NDUFS4* gene.

Mitochondrial complex I deficiency can range from a very severe disease, which can be fatal in the neonatal period, to neurodegenerative disorders with onset in adulthood. Symptoms vary between affected individuals and can include progressive brain abnormalities, heart disease, muscle weakness, liver disease, vision loss, or Parkinson's disease. Most individuals affected with mitochondrial complex I deficiency, NDUFS4-related begin to display symptoms between five days and one month of age. Common symptoms include problems with low muscle tone (hypotonia), vision impairment, growth issues, feeding problems, episodes of slowed or stopped breathing (apnea), seizures, and heart problems.

Some individuals with mitochondrial complex I deficiency have a condition called Leigh syndrome. Leigh syndrome is a progressive condition which impacts the central nervous system. Some symptoms of the disease are caused by tissue damage that develops in the brain. Symptoms include intellectual disability, muscle weakness, breathing problems, vision loss, hearing impairment, and heart disease. Leigh syndrome is typically progressive and affected individuals often do not survive the first two years of life. Mitochondrial complex I deficiency, NDUFS4-related has been associated with an early onset form of Leigh syndrome.

How common is Mitochondrial complex I deficiency, NDUFS4-related?

Several genes are known to cause mitochondrial complex I deficiency, which has an incidence of 1 in 8,500 births. The exact incidence of mitochondrial complex I deficiency, NDUFS4-related is unknown. The incidence of mitochondrial complex I deficiency, NDUFS4-related may be more common among individuals of Ashkenazi Jewish descent.

How is Mitochondrial complex I deficiency, NDUFS4-related treated?

There is no cure for Mitochondrial complex I deficiency, NDUFS4-related. Treatment for the condition is directed at managing the specific symptoms an individual has. This often means receiving care through a team of specialists that may include physicians, speech pathologists, occupational therapists, physical therapists, and social workers. Some families of severely affected infants may opt to pursue palliative care, which focuses on improving quality of life and may have limited medical intervention.

What is the prognosis for an individual with Mitochondrial complex I deficiency, NDUFS4-related?

The prognosis for an individual with Mitochondrial complex I deficiency, NDUFS4-related is dependent on the symptoms and severity of disease. However, most individuals with the condition are more severely affected and do not survive past two years of age.

Mitochondrial Complex I Deficiency, NDUFS6-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: NDUFS6.
Exons Sequenced: NM_004553:1-4.

Detection Rate	Population
94%	African American
94%	Ashkenazi Jewish
94%	Eastern Asia
94%	Finland
94%	French Canadian or Cajun
94%	Hispanic
94%	Middle East
94%	Native American
94%	Northwestern Europe
94%	Oceania
94%	South Asia
94%	Southeast Asia
94%	Southern Europe
94%	Worldwide

What is Mitochondrial complex I deficiency, NDUFS6-related?

Mitochondrial complex I deficiency is a group of disorders caused by abnormalities of energy production in a cellular structure called the mitochondria. The mitochondria produce energy for the cells in the body and are critical for cellular function. There are several genes associated with mitochondrial complex I deficiency, and mitochondrial complex I deficiency, NDUFS6-related, is caused by harmful genetic changes in the *NDUFS6* gene.

Mitochondrial complex I deficiency can range from a very severe disease, which can be fatal in the neonatal period, to neurodegenerative disorders with onset in adulthood. Symptoms vary between affected individuals and can include progressive brain abnormalities, heart disease, muscle weakness, liver disease, vision loss, or Parkinson's disease. Most individuals with mitochondrial complex I deficiency, NDUFS6-related are abnormally drowsy with reduced muscle tone (hypotonia) shortly after birth. Seizures typically occur within the first few days of life. Individuals with this condition have a severe build-up of a substance called lactic acid, which can lead to breathing problems and an abnormal heartbeat. Most affected infants pass away during the neonatal period due to respiratory failure.

Some individuals with mitochondrial complex I deficiency have a condition called Leigh syndrome. Leigh syndrome is a progressive condition which impacts the central nervous system. Some symptoms of the disease are caused by tissue damage that develops in the brain. Symptoms include intellectual disability, muscle weakness, breathing problems, vision loss, hearing impairment, and heart disease. Leigh syndrome is typically progressive and affected individuals often do not survive the first two years of life.

How common is Mitochondrial complex I deficiency, NDUFS6-related?

Several genes are known to cause mitochondrial complex I deficiency, which has an incidence of 1 in 8,500 births. The exact incidence of mitochondrial complex I deficiency, NDUFS6-related is unknown.

How is Mitochondrial complex I deficiency, NDUFS6-related treated?

There is no cure for mitochondrial complex I deficiency, NDUFS6-related. Treatment for the condition is directed at managing the specific symptoms an individual has. This often means receiving care through a team of specialists that may include physicians, speech pathologists, occupational therapists, physical therapists, and social workers. Some families of severely affected infants may opt to pursue palliative care, which focuses on improving quality of life and may have limited medical intervention.

What is the prognosis for an individual with Mitochondrial complex I deficiency, NDUFS6-related?

The prognosis for an individual with mitochondrial complex I deficiency, NDUFS6-related is dependent on the symptoms and severity of disease. Most individuals are severely affected and do not survive past the first few weeks of life.

Mitochondrial Complex IV Deficiency, SCO2-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SCO2.
Exon Sequenced: NM_005138:2.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Mitochondrial Complex IV Deficiency, SCO2-related?

Mitochondrial complex IV deficiency, SCO2-related, also known as cytochrome c oxidase deficiency or Leigh syndrome, is a severe progressive neurodevelopmental regression disorder that is caused by harmful genetic changes (variants) in the *SCO2* gene. The condition typically impacts individuals within the first year of life and impacts many body organs, including the heart, brain, and skeletal muscles. Infants with the condition are noted to have difficulties with feeding and breathing, low muscle tone, abnormal brain imaging, and heart problems.

While most individuals with two harmful changes in the *SCO2* gene have the severe symptoms described above, there are a few case reports of individuals with less severe symptoms. These individuals have axonal polyneuropathy, also known as Charcot-Marie-Tooth disease type 4, which is a condition characterized by progressive weakness, typically starting in the legs. The severity and age of onset varies from person to person.

How common is Mitochondrial Complex IV Deficiency, SCO2-related?

The exact incidence of mitochondrial complex IV deficiency, SCO2-related, is unknown.

How is Mitochondrial Complex IV Deficiency, SCO2-related, treated?

There is no cure for mitochondrial complex IV deficiency, SCO2-related. Treatment for the condition is directed at managing an individual's specific symptoms. Common interventions may include therapy to help with low muscle tone, cardiomyopathy, nutrition, and

seizures. Surveillance at regular intervals with specialists is recommended to monitor the progression of disease symptoms and additional therapies as symptoms present.

What is the prognosis for an individual with Mitochondrial Complex IV Deficiency, SCO2-related?

Most infants born with mitochondrial complex IV deficiency, SCO2-related, will die of respiratory failure in infancy. Individuals with less severe axonal polyneuropathy usually live past infancy, however the outcomes for these individuals are not well known.

Mitochondrial Neurogastrointestinal Encephalopathy Disease

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: TYMP.
Exons Sequenced: NM_001257989:2-10.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Mitochondrial Neurogastrointestinal Encephalopathy Disease?

Mitochondrial Neurogastrointestinal Encephalopathy Disease (MNGIE), is a condition characterized by progressively abnormal function of the digestive and nervous systems. It is caused by harmful genetic changes (variants) in the *TYMP* gene. Individuals with MNGIE have a deficiency of an enzyme called thymidine phosphorylase. Thymidine phosphorylase plays an important role in maintaining the genetic material in a specific part of the cell called the mitochondria. The mitochondria normally provide the cells with energy. For individuals with MNGIE, thymidine phosphorylase deficiency results in damage to the genetic material of the mitochondria over time. Due to this damage, the mitochondria lose the ability to provide enough energy for the cells to function properly, which is what leads to symptoms of the disease.

MNGIE can be classified into two forms: a classic and late onset form. The two forms have similar symptoms but differ in their age of onset.

CLASSIC FORM

Individuals with classic MNGIE have symptom onset before 40 years of age. The average age at which symptoms develop is 18 years, though this can vary. There have been cases of individuals developing symptoms as young as 5 months old.

Most often, the first symptoms of MNGIE are severe digestive issues, such as diarrhea, abdominal pain, nausea/vomiting, difficulty swallowing, and abdominal cramps. These occur due to abnormalities in the way that food passes through the digestive system (gastrointestinal dysmotility). Digestive symptoms are often accompanied by severe weight loss and loss of muscle mass (cachexia). Individuals also experience progressive muscle weakness of the eyes, causing droopy eyelids (ptosis) and difficulty with eye movements (ophthalmoplegia). Nerve issues (neuropathy) may result in numbness and tingling in the hands and feet, limb weakness, and pain. Abnormalities in the white matter of the brain (leukoencephalopathy) are also characteristic of MNGIE but usually do not cause symptoms. Other features of the condition include liver disease, anemia, hearing loss, hormone issues, and dementia.

LATE ONSET FORM

This is a rare form of MNGIE in which individuals have symptoms that begin after age 40. The symptoms are similar to what is seen in the classic form.

How common is Mitochondrial Neurogastrointestinal Encephalopathy Disease?

The exact incidence of MNGIE is unknown. Over 160 individuals have been diagnosed worldwide.

How is Mitochondrial Neurogastrointestinal Encephalopathy Disease treated?

There is no cure for MNGIE. Treatment for the condition is directed at managing the specific symptoms an individual has. This often means receiving care through a team of specialists that may include physicians, speech pathologists, occupational therapists, physical therapists, and social workers. Common interventions include therapies to help with swallowing, as well as medications to manage digestive and nerve issues. A feeding tube may be necessary for adequate nutrition. Some individuals may have surgery to correct eyelid drooping and difficulties with eye movements, and physical and occupational therapy can help individuals maintain their mobility. Researchers are studying newer treatment options, such as enzyme replacement therapy, dialysis, stem cell transplant, and liver transplant. These therapies show promise; however, some are associated with a significant risk of complications.

What is the prognosis for an individual with Mitochondrial Neurogastrointestinal Encephalopathy Disease?

MNGIE disease is a progressive disease, meaning symptoms typically worsen over time. Currently, the average life expectancy people with this condition is approximately 35 years. Death typically occurs due to complications of gastrointestinal and liver disease. The prognosis for individuals with the rare late onset form of the disorder is unknown.

MKS1-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MKS1.
Exons Sequenced: NM_017777:1-18.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What are MKS1-related Disorders?

Mutations in *MKS1* can cause a spectrum of inherited disorders known as ciliopathies, which affect tiny hair-like parts of a cell (cilia).

MECKEL-GRUBER SYNDROME

Meckel-Gruber syndrome is caused by mutations in at least 13 different genes, including *MKS1*. Meckel-Gruber syndrome is an inherited genetic condition that causes central nervous system (CNS) malformations, fluid-filled sacs (cysts) in the kidney, and polydactyly (extra fingers and toes). Other birth defects, including defects of the heart, cleft lip and cleft palate, and abnormalities of the liver and genitalia, are also features of Meckel-Gruber syndrome. Due to the severity of symptoms, those affected with Meckel-Gruber syndrome are stillborn or die soon after birth. The common birth defects associated with Meckel-Gruber syndrome can often be seen on prenatal ultrasound.

BARDET-BIEDL SYNDROME 13

In some cases, mutations in this gene may cause a condition called Bardet-Biedl syndrome (BBS13). BBS13 is an inherited disease that causes vision problems, kidney abnormalities, genital anomalies, extra fingers or toes (polydactyly), and mild obesity, among other symptoms. About half of individuals with the disease have developmental delay or intellectual disability.

JOUBERT SYNDROME 28

Mutations in *MKS1* can also cause Joubert syndrome. To date, 34 genes are known to cause this disease. The defining characteristic of Joubert syndrome is a distinctive brain malformation known as the molar tooth sign. Features include intellectual disability, respiratory issues, abnormal motor function, abnormal eye movements, retinal dystrophy, and extra fingers or toes (polydactyly), among others. *MKS1* is associated specifically with Joubert syndrome 28 (JBTS28), which is a relatively mild form of the disease.

How common are MKS1-related disorders?

Meckel-Gruber syndrome affects an estimated 1 in 13,250 to 1 in 140,000 people in the general population and approximately 7% of these cases are attributed to the *MKS1* gene. It is more common in certain specific populations such as the Finnish (1 in 9,000) and Belgians (1 in 3,000).

BBS13 is rare, affecting about 1 in 100,000 in North America and 1 in 125,000 in Europe. It is more or less common in specific populations such as Kuwaiti Bedouins (1 in 13,500), residents of Newfoundland, Canada (1 in 17,500), and the Swiss (1 in 160,000). It is estimated that *MKS1* accounts for 4.5% of all BBS13 cases.

The incidence of Joubert syndrome is estimated to range from 1 in 80,000 to 1 in 100,000 live births. Approximately 2-6% of Joubert syndrome cases are caused by *MKS1*.

How are MKS1-related Disorders treated?

There is no cure for Meckel-Gruber syndrome. For those affected, treatment is supportive.

For those individuals affected with BBS13, extra fingers and toes can often be surgically removed in childhood. The vision and kidney problems associated with the disease can be treated via standard protocols by medical specialists. If kidney problems reach life-threatening levels, dialysis and/or kidney transplantation may be necessary. Diet and exercise can help control obesity. In women, vaginal malformations can be surgically corrected.

Individuals affected with Joubert syndrome should be monitored for respiratory issues, including apnea, and treated if necessary. Occupational, physical, and speech therapy may address developmental delays. Liver, kidney, and vision problems can be treated by medical specialists with surgical or other methods of intervention, including organ transplant.

What is the prognosis for an individual with an MKS1-related Disorder?

Meckel-Gruber syndrome is a lethal condition, and prognosis is poor. Those affected are either stillborn or die in the first few hours or days of life.

Kidney disease is a major cause of early death for individuals with BBS13. However, the majority of affected individuals may have a normal or near-normal life expectancy with some impairments.

The prognosis for individuals with Joubert syndrome depends on the severity of the disease. The most common causes of death are respiratory failure in young children and kidney or liver failure later in life. JBTS28 has been reported to be a milder form of Joubert syndrome.

Mucolipidosis III Gamma

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GNPTG.
Exons Sequenced: NM_032520:1-11.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Mucolipidosis III Gamma?

Mucolipidosis III gamma is an inherited, lysosomal storage disorder. Mucolipidosis III gamma is caused by harmful changes (mutations) in the *GNPTG* gene. The symptoms associated with mucolipidosis III gamma are caused by a buildup of harmful substances in the cells of the body.

Mucolipidosis III gamma is primarily associated with progressive skeletal, joint, and connective-tissue abnormalities. Symptoms typically begin in early childhood and most commonly include joint stiffness, loss of flexibility, and pain. The fingers, shoulders, and hips are particularly affected. Pain, numbness, and tingling in the hand and arm (carpal tunnel syndrome) is common in children and young adults. Other skeletal abnormalities include slow growth; short height; low bone mineral density (osteoporosis) that may cause an increased risk for fractures; curvature of the spine (scoliosis); and gradual, mild coarsening of facial features.

Additionally, symptoms may include heart-valve abnormalities; problems with the ribs, which may impact lung function; and clouding of the cornea in the eyes. Many affected individuals will develop thickened skin and facial features (broad nose, large tongue, and thick lips). The majority of affected individuals have intellectual ability within the normal range, but mild intellectual disability has been reported.

How common is Mucolipidosis III Gamma?

Mucolipidosis III gamma has been reported in fewer than 100 patients worldwide. The exact incidence is unknown.

How is Mucolipidosis III Gamma treated?

There is no cure for mucolipidosis III gamma, and there are no known treatments to slow the limitations caused by progressive stiffness of the joints. Treatment may include pain management and/or physical therapy. Surgery may be done if hip replacement or heart valve replacement is necessary.

What is the prognosis for an individual with Mucolipidosis III Gamma?

Mucolipidosis III gamma is a slowly progressive condition that causes significant joint pain and problems with mobility. Many individuals affected with mucolipidosis III gamma have survived into adulthood, but prognosis is difficult to predict due to the rarity of the condition.

Mucolipidosis IV

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MCOLN1.
Exons Sequenced: NM_020533:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Mucolipidosis IV?

Mucolipidosis IV is an inherited lysosomal storage disorder caused by mutations in the *MCOLN1* gene. Individuals with mucolipidosis IV lack an enzyme called mucolipin-1, which is important for the proper functioning of lysosomes, the digestive system of the cell, though its exact function is not fully understood.

Mucolipidosis IV affects the development of the nerves. In about 15% of cases, it also causes existing nerves to degenerate. Most infants with the condition are unable to sit up, crawl, or control their hand motions. They also chew and swallow very slowly, because the muscles of their mouth and face move slowly or not at all. Children with the condition never learn to walk independently, although a few have learned to use a walker. When they are able to speak, they tend to do so either very slowly or very quickly and slur words, mumble, or whisper. In addition, they rarely learn more than a few words, although some children with mucolipidosis IV have learned to communicate with a few dozen basic signs. In general, individuals with the disease only reach a developmental age of 12 to 15 months.

Mucolipidosis IV leads to poor vision caused by cloudy corneas (the clear front part of the eye) and degeneration of the retina (the part inside the eye which translates light into images). Individuals with the disease are also prone to dry, irritated eyes, crossed eyes, and pupils that respond slowly to changes in light levels. Although infants with the condition may be born with nearly normal vision, their vision almost always starts to deteriorate by the age of five. Almost everyone with the condition has severe visual impairments by their early teens.

About 5% of individuals with the condition have an atypical variation with less-severe movement and vision problems.

How Common Is Mucolipidosis IV?

Fewer than 100 cases of mucolipidosis IV have been reported in medical literature, and the incidence of mucolipidosis IV in the general population is unknown. Approximately 70 to 80% of those affected are of Ashkenazi Jewish background, where the incidence is 1 in 32,000.

How Is Mucolipidosis IV Treated?

Treatment for mucolipidosis IV focuses on ensuring comfort and improving function. Physical therapy, foot and ankle orthotics, walkers, and wheelchairs can help maximize mobility. Speech therapy may improve the ability to communicate. Younger children frequently develop eye irritation, which lubricating eye drops, gels, or ointments can soothe.

What Is the Prognosis for an Individual with Mucolipidosis IV?

Mucolipidosis IV typically shortens one's lifespan, but individuals with the disease commonly reach adulthood and some are known to be alive in their mid-forties.

Mucopolysaccharidosis Type I

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: IDUA.
Exons Sequenced: NM_000203:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Mucopolysaccharidosis Type I?

Mucopolysaccharidosis Type I (MPS I)is an inherited condition in which the body lacks an enzyme called alpha-L-iduronidase. Without this enzyme, the body cannot properly break down long chains of sugar molecules called glycosaminoglycans. As a result, these molecules accumulate in the body, causing numerous health problems. There are two forms of MPS I: a severe form and a milder (attenuated) form. MPS I is caused by mutations in the *IDUA* gene.

SEVERE MUCOPOLYSACCHARIDOSIS TYPE I

Children with the condition appear normal at birth but may start to develop symptoms before the age of one. Infants may develop bulging of organs or tissue (hernia) at the belly button or inner groin, coarsening of facial features (broad mouth, square jaw), spine malformations, and frequent infections in the nose, sinuses, pharynx, or larynx. Delays in development are usually present in the first year of life and progress as the child ages. By the age of three, growth slows and hearing loss is common. Enlargement of the liver and spleen may be present and heart disease (including valve problems and narrowed arteries) and lung disease frequently develop. A dangerous accumulation of fluid around the brain (hydrocephalus) can also occur. Children with this condition tend to have a shortened lifespan but may live longer with treatment.

ATTENUATED MUCOPOLYSACCHARIDOSIS TYPE I

This form of the condition is also known as Hurler-Scheie syndrome or Scheie syndrome. Children usually develop symptoms between the ages of 3 and 10 years. There is a wide range of disease severity in children with MPS I, ranging from individuals living normal lifespans to individuals having complications leading to death by the age of 20 to 30 years. Individuals with a more normal lifespan may still have significant issues from progressive joint disease (arthropathy) as well as heart and lung disease. Learning disabilities can be present, and hearing loss and cardiac valvular disease are common.

How Common Is Mucopolysaccharidosis Type I?

The prevalence of MPS I is 1 in 100,000 individuals for the severe form and 1 in 500,000 for the attenuated form. MPS I has been found in people of all ethnicities.

How Is Mucopolysaccharidosis Type I Treated?

The use of immature cells capable of developing into multiple blood cell types is the primary treatment for severe MPS I. Bone-marrow transplants can be effective in relieving physical aspects of MPS I, although it does not seem to help the bone or eye symptoms. Children who receive bone-marrow transplants early (before the age of two) tend to have better mental development, although they still have learning problems and progressive mental decline. Outcomes of the procedure do vary, but a bone-marrow transplant can prolong the lifespan of a person with MPS I, even though it will still be significantly shortened. This procedure carries a high risk of fatality.

Umbilical cord blood is a more recent treatment for MPS I, allowing for an unrelated donor and eliminating the need for total body radiation, as is the norm with a bone-marrow transplant. This treatment can prolong the lifespan of an affected child, but does not help the bone and eye issues. A cord blood transplant can help prevent a certain measure of developmental delay if it is performed before significant damage is done to the intellect, often before the age of 18 months. Like bone-marrow transplants, the procedure itself carries a high risk of fatality and can result in a variety of outcomes. For these reasons, these methods are used primarily for the severe form of MPS I.

Enzyme replacement therapy (ERT) using recombinant human alpha-L-iduronidase has also been shown to benefit individuals with MPS I, relieving many of the physical symptoms. ERT may be used alone in attenuated cases, or in tandem with the above surgical options in severe cases. The combination of these two approaches in severe MPS I may slow mental decline. Improvements in liver size, joint mobility, breathing, and liver size have been observed with ERT treatment.

It is important to note that the outcome of these treatments depends on the age of the individual and the severity of the disease. Early treatment leads to better outcomes, and less-severe disease shows the best improvement in quality of life and life expectancy. Other symptoms of the disease can be addressed as they arise. Examples of these treatments include special education for developmental delays, heart-valve replacement, shunting to remove excess fluid and relieve pressure from around the brain, sunglasses or hats to promote better vision, and physical therapy to aid in movement.

What Is the Prognosis for a Person with MPS I?

The prognosis for individuals with severe MPS I is generally poor. They need special education and assistance to perform ordinary daily functions and are often wheelchair-bound. Death usually occurs within the first ten years of life, although early treatment such as a bone-marrow transplant can extend the lifespan. Heart and breathing problems are often the cause of death among children with severe MPS I. Individuals with attenuated MPS I have a variable severity of disease and lifespan.

Mucopolysaccharidosis Type II

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: IDS.
Exons Sequenced: NM_000202:1-9.

Detection Rate	Population
89%	African American
89%	Ashkenazi Jewish
89%	Eastern Asia
89%	Finland
89%	French Canadian or Cajun
89%	Hispanic
89%	Middle East
89%	Native American
89%	Northwestern Europe
89%	Oceania
89%	South Asia
89%	Southeast Asia
89%	Southern Europe
89%	Worldwide

What is Mucopolysaccharidosis Type II?

Mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome, is an inherited lysosomal storage disorder. MPS II is caused by harmful changes (mutations) in the *IDS* gene. The symptoms associated with MPS II are caused by a buildup of harmful substances in different organs and tissues of the body. MPS II is inherited in an X-linked manner, which means that the *IDS* gene is located on the X chromosome. Males have one copy of the X-chromosome and the *IDS* gene, while females have two copies. Because of this, MPS II primarily affects males. It is rare for females to have symptoms of MPS II, and their symptoms are typically much more mild.

For males with MPS II, the onset of symptoms and disease severity can be variable. Characteristic features include coarse facial features (broad noses, large tongues, and thick lips); enlarged heads; recurrent ear infections; enlarged livers and spleens; hernias; thickened, pebbled skin; and short stature. Generally, individuals with a severe form of the condition present with symptoms between 18 months and four years of age. Approximately two-thirds of affected males will have central nervous system (CNS) involvement, leading to severe neurological decline and intellectual disability. Other major features include skeletal abnormalities (short stature, joint deformities, and limited joint mobility); hearing loss; heart abnormalities; and airway obstruction, which leads to pauses in breathing and progressive respiratory disease.

For individuals with a milder form of MPS II, the onset of non-CNS-related symptoms can occur in infancy or early childhood, although onset can also occur later than in those with a severe form of MPS II. The severity of the disease and its progression can vary significantly, but heart disease and hearing loss are still common. Individuals with a milder form of MPS II often have normal neurologic and motor development.

How common is Mucopolysaccharidosis Type II?

The frequency of MPS II in the general population varies by region but is approximately 1 in 100,000 to 1 in 170,000 males. Incidence may be higher in individuals of eastern Asian descent.

How is Mucopolysaccharidosis Type II treated?

There is no cure for MPS II. Treatment focuses on management of symptoms, for example, physical and occupational therapy for developmental delays or surgical valve replacement for heart abnormalities. Enzyme-replacement therapy (using idursulfase) is also available for treatment of non-CNS-related complications, though the success of treatment depends on the severity of disease. Treatment via bone-marrow transplant and stem-cell transplant have been attempted, though more data is needed to determine their long-term effectiveness.

What is the prognosis for an individual with Mucopolysaccharidosis Type II?

For those with severe disease, death typically occurs in the first or second decade of life. Individuals with a milder form of MPS II can have complications that lead to death in their twenties or thirties, though survival into the fifties and sixties has been reported.

Mucopolysaccharidosis Type IIIA

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SGSH.
Exons Sequenced: NM_000199:1-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Mucopolysaccharidosis Type IIIA?

Mucopolysaccharidosis type III, or Sanfilippo syndrome, consists of four disease sub-types, based on the gene that causes the disease. All sub-types of MPS III are inherited lysosomal storage disorders and have similar clinical features. Mucopolysaccharidosis type IIIA (MPS IIIA), also known as Sanfilippo syndrome Type A, is caused by harmful changes (mutations) in the *SGSH* gene. The symptoms associated with MPS IIIA are caused by a buildup of harmful substances in the central nervous system and cause progressive destruction of nerve cells. The severity of the disease can range from mild to severe, even among affected individuals in the same family.

While infants with MPS IIIA appear normal at birth, delays in speech and motor skills may begin before one year of age, and nearly all children will experience some sort of developmental delay before six years of age. Children often have recurrent ear, nose, and throat infections. Behavioral issues, such as aggressiveness, sleeplessness, and hyperactivity, typically develop in early childhood, often between the ages of three and five. Intellectual disability becomes more severe during this time period, in part because seizures frequently develop. Many children start to lose the ability to speak by age 10. Motor problems, such as difficulty swallowing and stiff or rigid muscles (spasticity), will also develop. Affected individuals may also experience recurrent diarrhea and hearing loss. Most individuals with MPS IIIA lose the ability to walk by their mid-teens. Physical features of the disease can include coarse facial features, skeletal abnormalities, a large head (macrocephaly), and thick or excess body hair (hirsutism).

How common is Mucopolysaccharidosis Type IIIA?

MPS IIIA is the most common form of Mucopolysaccharidosis type III and is observed in approximately 1 in 100,000 individuals. The disease is observed more frequently in the Cayman Islands, with some estimates as high as 1 in 400 births.

How is Mucopolysaccharidosis Type IIIA treated?

There is currently no cure for MPS IIIA. The treatment for MPS IIIA is based on the patient's particular symptoms and may include speech or occupational therapy for developmental delays, medication to treat seizures and recurrent infections, and ear tubes or hearing aids. Feeding tubes may be required in later stages of the disease. Overall, treatment is intended to relieve pain and increase the quality of life (palliative).

What is the prognosis for an individual with Mucopolysaccharidosis Type IIIA?

MPS IIIA is a progressive disease that has no cure, and individuals have a shortened lifespan. Most individuals with MPS IIIA do not survive past the second or third decade of life, with an average lifespan of approximately 15 years. However, there are rare reports of individuals with MPS IIIA who have lived into their fourth or fifth decade.

Mucopolysaccharidosis Type IIIB

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: NAGLU.
Exons Sequenced: NM_000263:1-6.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Mucopolysaccharidosis Type IIIB?

Mucopolysaccharidosis type III, or Sanfilippo syndrome, consists of four disease sub-types based on the gene that causes the disease. All sub-types of MPS III are inherited lysosomal storage disorders and have similar clinical features. Mucopolysaccharidosis type IIIB (MPS IIIB), also known as Sanfilippo syndrome Type B, is caused by harmful changes (mutations) in the *NAGLU* gene. The symptoms associated with MPS IIIB are caused by a buildup of harmful substances in the central nervous system and cause progressive destruction of nerve cells. The severity of the disease can range from mild to severe, even among affected individuals in the same family.

While infants with MPS IIIB appear normal at birth, delays in speech and motor skills may begin before one year of age, and nearly all children will experience some sort of developmental delay before six years of age. Children often have recurrent ear, nose, and throat infections. Behavioral issues, such as aggressiveness, sleeplessness, and hyperactivity, typically develop in early childhood, often between ages three and five years. Intellectual disability becomes more severe during this time period, in part because seizures frequently develop. Individuals may experience recurrent diarrhea and hearing loss. Many children start to lose the ability to speak by age 10. Motor problems, such as difficulty swallowing and stiff or rigid muscles (spasticity), will also develop. Most individuals with MPS IIIB lose the ability to walk by their mid-teens. Physical features of the disease can include coarse facial features, skeletal abnormalities, a large head (macrocephaly), and thick or excess body hair (hirsutism). Some affected individuals may develop heart problems as they get older.

How common is Mucopolysaccharidosis Type IIIB?

The incidence of MPS IIIB varies significantly by region. Where estimates have been made, the occurrence ranges from 1 in 125,000 to 1 in 500,000, with an average incidence of approximately 1 in 280,000. Incidence may be higher in individuals of southern European and Middle Eastern descent.

How is Mucopolysaccharidosis Type IIIB treated?

There is currently no cure for MPS IIIB. The treatment for MPS IIIB is based on the patient's particular symptoms and may include speech or occupational therapy for developmental delays, medication to treat seizures and recurrent infections, and ear tubes or hearing aids. Feeding tubes may be required in later stages of the disease. Overall, treatment is intended to relieve pain and increase the quality of life (palliative).

What is the prognosis for an individual with Mucopolysaccharidosis Type IIIB?

MPS IIIB is a progressive disease that has no cure, and affected individuals have a shortened lifespan. Most individuals with MPS IIIB do not survive past the second or third decade of life, with an average lifespan of approximately 15 years. However, there are rare reports of individuals with MPS IIIB who have lived into their fourth or fifth decade.

Mucopolysaccharidosis Type IIIC

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: HGSNAT.
Exons Sequenced: NM_152419:1-18.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Mucopolysaccharidosis Type IIIC?

Mucopolysaccharidosis type IIIC (MPS IIIC), also known as Sanfilippo syndrome Type C, is caused by harmful changes, or mutations, in the *HGSNAT* gene. Mucopolysaccharidosis type III, or Sanfilippo syndrome, consists of four disease sub-types, based on the gene that causes the disease and MPS IIIC is one of these sub-types. All sub-types of MPS III are inherited, lysosomal storage disorders, and they all have similar clinical features. The symptoms associated with MPS IIIC are caused by a buildup of harmful substances in the central nervous system that causes progressive destruction of nerve cells. The severity of the disease can range from mild to severe, even among affected individuals in the same family.

Infants with MPS IIIC appear normal at birth and generally do not have any delay in development for the first year of life. Delay in speech and motor skills usually begin in early childhood, and nearly all children will experience some sort of developmental delay before six years of age. Children often have recurrent ear, nose, and throat infections. Behavioral issues, such as aggressiveness, sleeplessness, and hyperactivity, typically develop in early childhood, often between ages three and five years. Intellectual disability becomes more severe during this time period, in part because seizures frequently develop. Affected individuals may experience recurrent diarrhea and hearing loss. Many individuals will lose the ability to speak in the teenage years. Motor problems, such as difficulty swallowing and stiff or rigid muscles (spasticity), will also develop. Most individuals with MPS IIIC lose the ability to walk before age 30. Physical features of the disease can include coarse facial features, skeletal abnormalities, a large head (macrocephaly), and thick or excess body hair (hirsutism). Some individuals may develop heart problems as they get older.

How common is Mucopolysaccharidosis Type IIIC?

The incidence of MPS IIIC is estimated at 1 in 1,000,000 live births.

How is Mucopolysaccharidosis Type IIIC treated?

There is currently no cure for MPS IIIC. The treatment for MPS IIIC is based on the particular symptoms, and it is generally intended to make individuals more comfortable. This can include speech or occupational therapy for developmental delays, medication to treat seizures and recurrent infections, and ear tubes or hearing aids. Feeding tubes may be required in later stages of the disease. Overall, treatment is intended to relieve pain and increase the quality of life (palliative).

What is the prognosis for an individual with Mucopolysaccharidosis Type IIIC?

MPS IIIC is a progressive disease that has no cure, and individuals have a shortened lifespan. Death typically occurs in the third or fourth decade of life, with an average lifespan of approximately 34 years. Death is often due to respiratory issues.

Multiple Sulfatase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SUMF1.
Exons Sequenced: NM_182760:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Multiple Sulfatase Deficiency?

Multiple sulfatase deficiency (MSD) is an inherited condition that affects multiple parts of the body, including the brain, skeleton, and skin. It is caused by harmful genetic changes (variants) in the *SUMF1* gene. There are three classical types of MSD.

NEONATAL MSD

The neonatal form is the most severe presentation of MSD. The symptoms begin soon after birth, and virtually all individuals with this type have died before one year of age. The most common symptoms seen in infants include too much fluid around the brain (hydrocephalus), enlarged organs, hearing loss, seizures, developmental delays, movement problems, dry/scaly skin (ichthyosis), and skeletal abnormalities.

INFANTILE MSD

Infantile MSD is the most common form. Symptoms of infantile MSD usually develop between birth and two years of age. Children with this form begin with normal development followed by a progressive loss of speech, mental and movement abilities becoming weak, and developing problems walking (ataxia). As the condition worsens, muscle tone increases to the point of rigidity (hyperreflexia). Other symptoms included skeletal changes and dry/scaly skin. Individuals with this form usually do not survive past childhood.

JUVENILE MSD

Juvenile MSD is the rarest form, and symptoms appear between the ages of two and four years. Affected individuals have normal early development but then experience loss of speech and motor skills. The juvenile form of MSD is characterized by a slower progression of symptoms than the more common infantile form of MSD.

How common is Multiple Sulfatase Deficiency?

MSD is a rare disorder, with an estimated incidence of less than 1 in 1 million births worldwide.

How is Multiple Sulfatase Deficiency treated?

There is no cure for MSD. Treatment is focused on managing specific symptoms and providing support. For example, orthopedists can provide treatment for skeletal changes such as scoliosis. Dry/scaly skin can be treated with petroleum jelly or lactate lotion.

What is the prognosis for a person with Multiple Sulfatase Deficiency?

The life expectancy for all individuals with MSD is shortened and varies depending on the severity of the condition and how quickly the neurological symptoms worsen. Most affected individuals survive only a few years after symptoms begin. It is rare for a child with MSD to survive beyond ten years of age.

Muscular Dystrophy, LAMA2-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: LAMA2.
Exons Sequenced: NM_000426:1-65.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Muscular Dystrophy, LAMA2-related?

Muscular dystrophy (MD), LAMA2-related causes significant muscle weakness and wasting (atrophy). Harmful genetic changes (mutations) in the *LAMA2* gene cause this condition. The *LAMA2* gene is important to proper functioning of the skeletal and heart (cardiac) muscles, and mutations negatively affect this function. There is both an early-onset and late-onset form of muscular dystrophy, LAMA2-related.

EARLY-ONSET MUSCULAR DYSTROPHY, LAMA2-RELATED

Early-onset MD, LAMA2-related is the most common form of this condition. It is part of a group of muscle disorders called congenital muscular dystrophies (CMD). Symptoms start at birth or within the first few months of life and include severe low muscle tone (hypotonia) and muscle weakness. Because of this, infants have delayed motor milestones. Most individuals with this condition can sit unsupported, and some may stand without assistance, but very few are ever able to walk without help. In addition, muscle weakness also causes significant breathing difficulties that may worsen with age and feeding difficulties that result in poor growth (failure to thrive). Other symptoms may include frequent chest infections, shortening and hardening of muscles leading to rigid joints (contractures), progressive curvature of the spine (scoliosis), seizures, and cardiac issues. A small percentage of individuals with this condition experience intellectual disability.

LATE-ONSET MUSCULAR DYSTROPHY, LAMA2-RELATED

The onset of symptoms in late-onset MD, LAMA2-related ranges from childhood to adulthood. This form tends to be milder than the early-onset type, and symptoms are like those of a group of muscle disorders called limb-girdle muscular dystrophies. In late-onset MD, LAMA2-related, the most affected muscles are those closest (most proximal) to the body, such as the shoulders, upper arms, pelvic area, and thighs. Individuals are usually able to walk without assistance. Other symptoms include rigidity of the back, joint contractures, and breathing problems. Seizures may occur in some individuals with this condition.

How common is Muscular Dystrophy, LAMA2-related?

The worldwide incidence of CMD is unknown, though studies of the northeastern Italian population estimate a frequency of 1 in 21,500. Mutations in *LAMA2* are the most common cause of CMD worldwide. The proportion of CMD cases due to *LAMA2* mutations varies by population, with *LAMA2* mutations responsible for 30% of CMD cases in Europe but only 6% of cases in Japan.

How is Muscular Dystrophy, LAMA2-related treated?

Treatment is focused on alleviating symptoms, with the objective of optimizing each individual's abilities. For patients with early-onset MD, LAMA2-related, treatment may include physical therapy, occupational therapy, speech therapy, and supplemental feeding. Use of a machine that helps with breathing (a ventilator) may be required. Supportive devices such as a brace or splint (orthotics) may be used for joint stiffness. Individuals with the late-onset form often need physical therapy, and some require care for breathing difficulties. Seizures are often treated with medications, if necessary. Monitoring of respiratory (lung) and cardiac function may be recommended.

What is the prognosis for an individual with Muscular Dystrophy, LAMA2-related?

Due to the serious health problems that occur in the early-onset form of the disorder, especially breathing issues, many individuals do not survive past adolescence. Those with the rarer, late-onset form have progressive muscle weakness, but life expectancy is often normal.

MYO7A-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MYO7A.
Exons Sequenced: NM_000260:2-49.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What are MYO7A-related Disorders?

MYO7A-related disorders are an inherited group of conditions associated with hearing loss with or without vision loss. This group of disorders does not affect intelligence or cause any other primary health problems. MYO7A-related disorders are caused by harmful changes, or mutations, in the *MYO7A* gene. The three main disorders that make up the MYO7A-related disorders include Usher Syndrome Type IB (USH1B), DFNB2, and DFNA11. These conditions are very similar, and the primary difference between them is the severity of the condition.

USHER SYNDROME TYPE IB

USH1B is the most common form of MYO7A-related disorders. The symptoms of USH1B include hearing loss, balance problems, and progressive vision loss. Infants with USH1B are profoundly deaf in both ears at birth. Affected individuals usually have severe balance problems, caused by abnormalities of the inner ear (vestibular system) that can lead to delays in development. In general, children with USH1B sit and walk at later ages and have difficulties sensing changes in speed or direction. In childhood or by early adolescence, individuals with USH1B develop retinitis pigmentosa, an eye disease that causes night blindness and a gradual loss of vision on the sides of the head (peripheral vision). Eventually only the central vision remains, creating "tunnel vision." This central vision can also become impaired and can lead to total blindness in a small number of individuals with the disease. In some cases, individuals with USH1B develop clouding in the lens of the eye (cataracts), which can further impair vision.

DFNB2

DFNB2 is characterized by hearing loss but no vision loss. Individuals with DFNB2 develop profound hearing loss anywhere from birth to adolescence and may also develop balance problems. Progressive vision loss is not expected in this condition, but some individuals re-evaluated later in life have developed symptoms of retinitis pigmentosa, indicating variability or overlap in the conditions associated with this gene.

DFNA11

DFNA11 is an autosomal-dominant form of nonsyndromic hearing loss and deafness. An autosomal-dominant condition is one where symptoms can be present when an individual inherits only one mutation in the associated gene. Individuals with DFNA11 seem to develop moderate to severe progressive hearing loss after learning how to talk (i.e., in late childhood or adolescence). Individuals with DFNA11 may have repetitive, uncontrolled eye movements (nystagmus) or mild balance issues. However, affected individuals typically do not have vision loss. This condition seems to be the mildest form of MYO7A-related disorders. DFNA11 is very rare, and carriers of mutations in the *MYO7A* gene do not generally experience any symptoms.

How common are MYO7A-related Disorders?

The global incidence is unknown for all MYO7A-related disorders. The incidence of USH1B is approximately 1 in 90,000 individuals. There are regions where founder effects (high frequency of the disease because the group arose from a small, possibly isolated population) occur, such as in indigenous populations in South Africa, South Asia, and the Middle East.

DFNB2 and DFNA11 are extremely rare disorders. DFNB2 has been been reported in at least three families and DFNA11 in at least five families of various ethnicities. Other presentations or variability in these two disorders may not be recognized as of yet.

How are MYO7A-related Disorders treated?

There is no cure for MYO7A-related disorders, but early treatment is important to give children with the condition the best opportunity to develop communication skills. While a child is young, his or her brain is most receptive to learning language, either spoken or signed. It is also important to take advantage of the time when the child's vision is normal. Individuals with USH1B generally do not respond to hearing aids, but cochlear implants may help regain some form of hearing. Sign language is a good option for communication. Specialists can introduce other tools and methods of instruction available to individuals with hearing loss. It is often helpful if the whole family undergoes such instruction and, as a family unit, helps the child adapt.

For those individuals that develop vision loss, visual aids and specialized instruction (for example, in tactile signing) help children adapt to their limited vision. Affected individuals can be prone to accidental injury due to their vision loss and balance problems. Well-supervised participation in sports may help an individual with Usher syndrome type 1 compensate for balance issues, but swimming may be particularly difficult, and strategies to ensure safety are needed. Use of UV-A and UV-B blocking sunglasses is recommended, and other optical aids may increase eye comfort. Therapy with vitamin A palmitate may slow retinal degeneration for some.

What is the prognosis for an individual with an MYO7A-related Disorder?

USH1B results in severe hearing and vision impairment, and DFNB2/DFNA11 results in hearing impairment only. However, none of the conditions affect one's lifespan or intelligence.

Myopathy, Lactic Acidosis, and Sideroblastic Anemia 1

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PUS1.
Exons Sequenced: NM_025215:1-6.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Myopathy, Lactic Acidosis, and Sideroblastic Anemia 1?

Myopathy, lactic acidosis, and sideroblastic anemia 1 (MLASA1) is a rare condition characterized by muscle weakness (myopathy), exercise intolerance, a buildup of lactic acid in the body (lactic acidosis), and the failure of bone marrow to produce healthy red blood cells (sideroblastic anemia). It is caused by harmful genetic changes (variants) in the *PUS1* gene. The buildup of lactate in the body can lead to deep and rapid breathing, vomiting, and abdominal pain. Individuals with MLASA1 can also have varying degrees of cognitive impairment with developmental delay of motor skills, disease of the heart muscle (cardiomyopathy), trouble swallowing, and dental and skeletal abnormalities. MLASA1 may lead to insufficient oxygen intake and/or carbon dioxide expulsion by the lungs (respiratory insufficiency) which can progress to respiratory failure and death. These symptoms typically develop in childhood, but the age of onset and progression varies.

How common is Myopathy, Lactic Acidosis, and Sideroblastic Anemia 1?

The exact incidence of MLASA1 is unknown. Less than 20 individuals have been diagnosed worldwide.

How is Myopathy, Lactic Acidosis, and Sideroblastic Anemia 1 treated?

There is no cure for MLASA1. Treatment for the condition is directed at managing the specific symptoms an individual has. For example, blood transfusion is a common treatment for anemia. Some individuals may benefit from receiving care through a team of specialists that may include multiple physicians and therapists.

What is the prognosis for an individual with Myopathy, Lactic Acidosis, and Sideroblastic Anemia 1?

The prognosis for an individual with MLASA1 varies significantly depending on the severity of symptoms and age of onset. In severe cases, death can occur in early childhood. For those who are more mildly affected, exact lifespan is unknown but may be shortened.

Myotonia Congenita

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CLCN1.
Exons Sequenced: NM_000083:1-23.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
94%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Myotonia Congenita?

Myotonia congenita, also known as congenital myotonia, is a neuromuscular condition characterized by muscle stiffness (myotonia) that prevents muscles from relaxing normally and can cause issues with movement. It is caused by harmful genetic changes (variants) in the *CLCN1* gene. Myotonia can occur in any body part, though it is most likely to occur in the legs. For some affected individuals, the muscle stiffness is mild, while for others, the muscle stiffness may be significant enough to affect activities such as walking, running, or climbing stairs. Other symptoms may include muscle cramping, increased size in muscles (hypertrophy), difficulty getting up from a seated position, difficulty releasing a grip after shaking hands, and muscle pain. Many affected individuals have also reported that symptoms tend to worsen with cold temperatures.

Myotonia congenita can be classified into two major types: Becker disease and Thomsen disease. The main differences between the two subtypes are the severity of the symptoms and how the conditions are inherited. The two subtypes are described in further detail below.

BECKER DISEASE

Becker disease is the most common type of myotonia congenita. Compared to Thomsen disease, the age of onset for Becker disease is later, with the first symptoms typically appearing between ages four and twelve. Becker disease is inherited in an autosomal recessive manner, meaning an individual must have two harmful changes (one from each parent) in the *CLCN1* gene to have the disease. The muscle stiffness seen in those with Becker disease tends to be more severe than those with Thomsen disease, particularly in individuals assigned male (XY) at birth. Affected individuals with Becker disease may also develop mild, permanent muscle weakness over time.

THOMSEN DISEASE

Thomsen disease is the less common type of myotonia congenita. The age of onset for symptoms is typically earlier than what is seen with Becker disease, with most affected individuals first showing symptoms between the first few months of life to three years of age. Thomsen disease is inherited in an autosomal dominant manner, meaning an individual only needs one harmful change in the *CLCN1* gene to have symptoms. Affected individuals often have one affected parent.

How common is Myotonia Congenita?

The incidence of myotonia congenita in the population is 1 in 100,000 births. The condition may be more common among individuals of Northern Scandinavian descent, with a prevalence of 1 in 10,000.

How is Myotonia Congenita treated?

There is no cure for myotonia congenita. Treatment for the condition is directed at managing an individual's specific symptoms. This often means receiving care through a team of specialists, including physicians, orthopedists, physical therapists, and/or other health care professionals. Common interventions may include light exercise after resting to help reduce muscle stiffness, avoidance of cold temperatures, and modifying diet to include foods that are easy to swallow to minimize choking risk. Treatment with medications is not standard, though may be used in instances of severe symptoms to help with muscle cramps and stiffness.

What is the prognosis for an individual with Myotonia Congenita?

Myotonia congenita is not thought to affect life expectancy. Most affected individuals do not experience worsening symptoms over time. Becker disease is thought to be more severe than Thomsen disease.

NAGA-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: NAGA.
Exons Sequenced: NM_000262:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What are NAGA-related Disorders?

NAGA-related disorders, also known as Schindler disease, are inherited lysosomal storage disorders caused by harmful genetic changes (variants) in the *NAGA* gene. Individuals with NAGA-related disorders are unable to break down substances known as glycoproteins and glycolipids. In individuals with NAGA-related disorders, the buildup of glycoproteins and glycolipids in the lysosomes causes cell damage in the nervous system and other parts of the body, leading to primarily neurological symptoms. There are three subtypes of NAGA-related disorders and symptoms ranging from mild to severe, even within the same family.

SCHINDLER DISEASE TYPE I

Schindler disease type I, also called infantile type, is the most severe form. Infants may appear healthy at birth, with symptoms usually developing within the first year of life. Infants may experience developmental delay and lose skills they have already gained. Additional symptoms may include weakness, low muscle tone (hypotonia), blindness, and seizures.

SCHINDLER DISEASE TYPE II

Schindler disease type II, also called Kanzaki disease, typically has milder symptoms that develop after puberty. Symptoms may include mild developmental delay, hearing loss, weakness and loss of sensation, and pain crises. A distinguishing physical trait for individuals with Schindler disease type II is the presence of hard bumps on the skin (angiokeratomas) caused by enlarged blood vessels. Individuals may also have distinct facial features.

SCHINDLER DISEASE TYPE III

The severity of Schindler disease type III lies between that of types I and II. The age of onset for symptoms may range between infancy and early childhood. Symptoms of type III may include developmental delay, seizures, enlarged liver (hepatomegaly), weakened and enlarged heart (cardiomyopathy), and features of autism spectrum disorders.

How common are NAGA-related Disorders?

The exact incidence of NAGA-related disorders is unknown. Only a few individuals have been diagnosed with each type of disorder worldwide.

How are NAGA-related Disorders treated?

There is no cure for NAGA-related disorders. Treatment is directed at managing an individual's specific symptoms and may include medications to help control seizures and ensuring proper nutrition and hydration. Some individuals may need physical or speech therapy or interventions for developmental delay.

What is the prognosis for an individual with NAGA-related Disorders?

The prognosis depends on which subtype of the condition an individual has. For individuals with Schindler disease type I, symptoms typically begin in the first year of life, and many do not survive past childhood. Individuals with Schindler disease type II will often have a later onset, with symptoms first appearing after puberty; the few individuals with this type of disease can live a relatively normal life. Schindler disease type III can present with varying ages of onset for symptoms, ranging from infancy to adulthood. The prognosis depends on the individual's symptoms.

NEB-related Nemaline Myopathy

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: NEB.
Exons Sequenced: NM_001271208:3-80,117-183.

Detection Rate	Population
92%	African American
>99%	Ashkenazi Jewish
92%	Eastern Asia
92%	Finland
92%	French Canadian or Cajun
92%	Hispanic
92%	Middle East
92%	Native American
92%	Northwestern Europe
92%	Oceania
92%	South Asia
92%	Southeast Asia
92%	Southern Europe
92%	Worldwide

What Is NEB-Related Nemaline Myopathy?

Nemaline myopathy is a genetic disease that causes muscle weakness in the face, neck, trunk, upper arms, and upper legs (that is, the muscles that are closest to the center of the body). This typically results in complications related to walking, speaking, swallowing, and breathing. There are at least six different forms of nemaline myopathy that have been described, each defined based on the age at which symptoms begin and the severity of the disease. The condition may also be caused by mutations in several different genes.

NEB-related nemaline myopathy is caused by mutations in the *NEB* gene and is most often associated with "typical" or "typical congenital" nemaline myopathy. Individuals with typical nemaline myopathy are usually born with the muscle weakness that is characteristic of the disease. They experience a delay in motor development, but most are eventually able to walk independently and lead active lives. They may have speech or swallowing difficulties, and respiratory problems are possible. Less commonly, individuals with NEB-related myopathy have a more severe form of the condition. In this case, the risk of respiratory complications is higher and is associated with a shortened lifespan. In addition, problems with mobility are more severe and may include the presence of multiple joint contractures at birth (where there is an inability to straighten the affected joints).

How Common Is NEB-Related Nemaline Myopathy?

The estimated prevalence of NEB-related nemaline myopathy is 1 in 30,000 individuals. NEB-related nemaline myopathy has also been estimated to account for up to 50% of all nemaline myopathy cases.

How Is NEB-Related Nemaline Myopathy Treated?

There is no treatment or cure for the underlying cause of nemaline myopathy. Available treatments address only the symptoms of the disease. Physical therapy may significantly improve mobility and strength, and assistive devices may benefit some individuals. In addition,

speech therapy may help those who have speech-related difficulties. It is also important to monitor all individuals with nemaline myopathy for problems with swallowing and breathing, and all respiratory infections should be treated promptly and aggressively. In cases with severe disease, a feeding tube and mechanical breathing support may be necessary.

What Is the Prognosis for an Individual with NEB-Related Nemaline Myopathy?

Individuals with typical nemaline myopathy, the form most often associated with *NEB* gene mutations, tend to have a good overall prognosis. Most are able to walk independently and have relatively active lives. However, those with more severe forms of nemaline myopathy may experience recurrent lung infections and respiratory failure, which can lead to death in early childhood.

Nephrotic Syndrome, NPHS1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: NPHS1.
Exons Sequenced: NM_004646:1-29.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Nephrotic Syndrome, NPHS1-Related?

NPHS-1 related nephrotic syndrome is an inherited condition in which the kidneys leak proteins into the urine due to an abnormality in a protein called nephrin. Symptoms of the disease begin in the first days or weeks after birth, but always before the age of three months. The disease occurs mainly in people of Finnish origin, and another name for this disease is congenital Finnish nephrosis (CNF). NPHS-1 related nephrotic syndrome is often fatal by the age of five, and many cases are fatal within the first year. If the child survives to the age of two or three, kidney transplantation may allow for a more normal lifespan. NPHS-1 related nephrotic syndrome is caused by mutations in the *NPHS1* gene.

Children with NPHS-1 related nephrotic syndrome are often born prematurely with low birth weight. Low levels of protein in the blood, combined with kidney failure, cause the whole body to swell with excess fluids (edema). These children have a poor appetite and urinate less frequently than children without the disease. Children with congenital NPHS-1 related nephrotic syndrome have difficulty getting needed nutrients and may not grow as large as they would otherwise. Fat levels in the blood may also be high.

People with nephrotic syndrome associated with loss of protein into the urine cannot retain sufficient amounts of antibodies that help the body fight infection. As a result, they are more prone to infection. They are also prone to potentially harmful blood clots.

How Common Is Nephrotic Syndrome, NPHS1-Related?

NPHS-1 related nephrotic syndrome has an incidence of 1 in 8,000 in Finland. The worldwide incidence of nephrotic syndrome is 1 to 3 in 100,000. Approximately 7% of nephrotic syndrome is caused by mutations in *NPHS1*. The incidence is 1 in 500 in children born in the Old Order Mennonite population in Lancaster County, Pennsylvania.

How Is Nephrotic Syndrome, NPHS1-Related Treated?

Because NPHS-1 related nephrotic syndrome is often fatal in infancy, early and vigilant treatment is necessary to allow the child to live until the age of two or three when a kidney transplant is feasible. This is the only hope for a normal lifespan. The disease does not affect the new kidney, but in about 20% of transplantations the body develops antibodies to the nephrin protein and high levels of protein in the blood can return.

A physician may recommend infusions of protein for children with nephrotic syndrome associated with protein loss. Diuretic drugs may be prescribed to help eliminate excess water and thus eliminate some swelling. Antibiotics will be necessary to control infection. If the disease is too severe, the child's kidneys may need to be removed before he or she is old enough for a transplant. Dialysis machines can be used as a stopgap measure to filter wastes from the child's blood until a transplant can be completed.

Some children with NPHS-1 related nephrotic syndrome have abnormal thyroid activity and may require hormone replacement. Others have a tendency towards blood clots and may benefit from a blood thinner. Good nutrition is key to growth. Those who cannot eat sufficient quantities may need a feeding tube.

What Is the Prognosis for a Person with Nephrotic Syndrome, NPHS1-Related?

Many cases of NPHS-1 related nephrotic syndrome are fatal within five years. If children with severe symptoms live until the age of two or three, an early kidney transplant may help them live a more normal lifespan. While children with NPHS-1 related nephrotic syndrome typically experience kidney failure by ages two to eight, with treatment, some may not experience kidney failure until adolescence or adulthood.

Nephrotic Syndrome, NPHS2-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: NPHS2.
Exons Sequenced: NM_014625:1-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Nephrotic Syndrome, NPHS2-Related?

Nephrotic syndrome, NPHS2-related is an inherited condition that causes issues with kidney function often leading to kidney failure. Mutations in the *NPHS2* gene cause a form of nephrotic syndrome that is unresponsive to steroid treatment known as steroid-resistant nephrotic syndrome (SRNS). Symptoms of the condition typically begin between 4 and 12 months of age, but in some cases occur later in childhood.

Symptoms of the condition include an excess of protein in the urine (proteinuria), low levels of protein in the blood, kidney failure, and swelling of the body (edema). The swelling can also cause weight gain and high blood pressure. Individuals with nephrotic syndrome are prone to infection due to their inability to retain sufficient amounts of serum antibodies. They are also prone to develop harmful blood clots. Kidney failure typically occurs before the age of 20, and kidney transplantation may allow for a more normal lifespan.

How Common Is Nephrotic Syndrome, NPHS2-Related?

The incidence of all childhood nephrotic syndrome is 2 to 16 per 100,000 individuals worldwide of which 10-20% have SRNS. Approximately 10% of individuals with SRNS carry mutations in the *NPHS2* gene.

How Is Nephrotic Syndrome, NPHS2-Related Treated?

The goal of treatment is to minimize damage to the kidneys. Medication to control blood pressure and high cholesterol may be prescribed. Often children with nephrotic syndrome with protein loss require antibiotics to control for infection. A physician may recommend infusions of protein for children with SRNS to help replace what is lost in the urine. Diuretic drugs may help eliminate excess water and thus reduce swelling while blood thinners may be required to aid in blood clotting. Typically, kidney failure will occur, and a kidney transplant will be required though symptoms of the disease can recur after transplant.

What Is the Prognosis for Nephrotic Syndrome, NPHS2-Related?

The prognosis for an individual with nephrotic syndrome, NPHS2-related varies, but with transplantation and careful medical management, affected children can live into adulthood.

Neuronal Ceroid Lipofuscinosis, CLN6-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CLN6.
Exons Sequenced: NM_017882:1-7.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Neuronal Ceroid Lipofuscinosis, CLN6-related?

Neuronal ceroid lipofuscinoses (NCL), also called Batten disease, are a group of inherited diseases that cause degeneration of the brain, leading to progressive loss of mental and motor skills. There are several forms of NCL, largely differentiated by the gene responsible and the age at which symptoms begin. NCL, CLN6-related, is caused by harmful genetic changes (mutations) in the *CLN6* gene, and it typically results in late-infantile NCL (LINCL) or adult-onset NCL.

LATE-INFANTILE NEURONAL CEROID-LIPOFUSCINOSIS

The symptoms of LINCL commonly begin between three and eight years of age. Early symptoms often include seizures, vision loss, and difficulty controlling movements. Other symptoms include jerking movements, mental decline, and speech problems. In general, most children with LINCL will lose all motor skills and vision by 4 to 10 years of age.

ADULT-ONSET NEURONAL CEROID-LIPOFUSCINOSIS

The symptoms of adult-onset NCL typically begin around the age of 30 but can appear anywhere between the second and sixth decades of life. Individuals experience worsening (progressive) seizures, have dementia, and have difficulty balancing and controlling movements. Vision is not affected in adult-onset NCL.

How common is Neuronal Ceroid Lipofuscinosis, CLN6-related?

The incidence of all forms of NCL is approximately 1 in 75,000 to 1 in 100,000 births. The exact incidence of NCL caused by *CLN6* mutations is unknown but is more common among individuals of Portuguese and Costa Rican descent.

How is Neuronal Ceroid Lipofuscinosis, CLN6-related treated?

There is no cure for NCL, CLN6-related disorders, and treatment is based on the symptoms that are present. Treatment typically includes medications to control seizures and movement problems. Affected individuals should be routinely monitored for swallowing difficulties to determine if a feeding tube would be beneficial.

What is the prognosis for an individual with Neuronal Ceroid Lipofuscinosis, CLN6-related?

The prognosis for individuals with NCL, CLN6-related disorders is poor. Individuals with LINCL generally lose their vision and all motor skills by 4 to 10 years of age. Lifespans are around 20 years of age. Individuals with adult-onset NCL generally pass away within 10 years of the onset of symptoms.

Neuronal Ceroid Lipofuscinosis, PPT1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PPT1.
Exons Sequenced: NM_000310:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Neuronal Ceroid Lipofuscinosis, PPT1-related?

Neuronal ceroid lipofuscinosis (NCL), PPT1-related, is an inherited disease that causes brain degeneration, leading to a progressive loss of intellectual abilities and motor skills. The condition also causes blindness and seizures and typically leads to early death. Several genes are associated with NCL, and the symptoms may differ depending on the gene involved. NCL, PPT1-related, is caused by harmful genetic changes (variants) in the *PPT1* gene. NCL, PPT1-related, typically results in either the infantile or juvenile form of NCL.

INFANTILE FORM

The infantile form of NCL (INCL) usually begins to cause noticeable symptoms between 6 months and 24 months of age. Initially, infants may show developmental delays, jerking movements, and/or seizures. In addition, these infants will typically have small heads. Blindness and seizures generally develop by 24 months of age, after which cognitive functions will deteriorate. The child's movement typically becomes spastic and uncontrolled, and they will experience a loss of motor skills and intellectual abilities.

JUVENILE FORM

The symptoms of juvenile NCL (JNCL), also called Batten disease, often begin between the ages of 4 and 10. The first noticeable symptom is a rapid loss of vision. Children with JNCL typically become completely blind within two years. Most develop periodic seizures, and cognitive functions decline. They often experience speech and behavioral problems in childhood. Psychiatric problems such as disturbed thoughts, attention difficulties, aggression, and dementia or memory problems often develop. Individuals with JNCL also show a decline in motor function and may have difficulty controlling body movements.

How common is Neuronal Ceroid Lipofuscinosis, PPT1-related?

The incidence of all forms of NCL is estimated to be 1 in 100,000 individuals. The exact incidence of NCL caused by harmful changes in the *PPT1* gene is unknown. All forms of NCL diseases are most common in Scandinavian countries but occur elsewhere. Harmful changes in the *PPT1* gene are most frequent among the Finnish population, where the prevalence of NCL is estimated to be 1 in 12,500.

How is Neuronal Ceroid Lipofuscinosis, PPT1-related treated?

There is no cure for NCL, PPT1-related. Treatment for the condition is based on the symptoms an individual has. Individuals with NCL, PPT1-related should work with a team of specialists including an ophthalmologist, neurologist, psychiatrist, and speech therapist to help treat symptoms. Medications manage many symptoms including seizures and psychiatric issues. Occupational and physical therapy may be helpful. In some individuals, a feeding tube can be used to ensure individuals are receiving adequate nutrition.

What is the prognosis for an individual with Neuronal Ceroid Lipofuscinosis, PPT1-related?

The prognosis for an individual with NCL depends on the disease subtype but is generally considered poor. Individuals with INCL or JNCL will become blind and experience deterioration of both motor skills and intellectual abilities. Eventually, they will be unable to do anything for themselves and will need others to care for them.

Lifespan is also shortened for individuals with NCL, PPT1-related. For those with INCL, death usually occurs in childhood. For those with JNCL, death usually occurs in the late teens, twenties, or thirties.

Niemann-Pick Disease Type C1

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: NPC1.
Exons Sequenced: NM_000271:1-25.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Niemann-Pick Disease Type C1?

Niemann-Pick disease type C (NPC) is an inherited condition in which the body cannot properly metabolize cholesterol and fats, resulting in an excess of these substances in the body. Cholesterol buildup in the liver causes severe liver disease, and fat accumulation in the brain leads to learning disabilities and progressive neurological symptoms.

Niemann-Pick disease type C can be caused by mutations in two different genes. Type C1 is caused by mutations in the *NPC1* gene, and type C2 is caused by mutations in the *NPC2* gene. Although the genes are different, the resulting symptoms are the same because *NPC1* and *NPC2* must work together to remove cholesterol and lipids from body cells. Of the known cases of Niemann-Pick disease type C, 95% have been type C1 and 5% have been C2.

The first symptoms of the disease, which can appear at any age from infancy to adulthood, are an enlarged liver, an enlarged spleen, and/or jaundice. In some cases, it is possible to detect the disease in an unborn child via ultrasound, but the disease is most commonly diagnosed in school-aged children. Symptoms may include sudden muscle problems such as seizures, clumsiness, tremors, problems walking, sudden falls, slurred speech, and trouble moving the eyes up and down. As the condition progresses, these children develop learning disabilities, psychological problems, or even dementia, and often lose the ability to speak. Eventually, individuals with Niemann-Pick disease type C lose the ability to move their facial muscles or swallow, making feeding through a stomach tube necessary.

For those diagnosed during childhood, the disease is usually fatal in the late teens or twenties due to pneumonia. Those diagnosed in adulthood generally survive 10 to 20 years after diagnosis.

How Common Is Niemann-Pick Disease Type C?

It is estimated that Niemann-Pick disease type C affects 1 in 150,000 individuals, with approximately 95% of these cases being attributed to *NPC1*. It is more common among French Acadians in Nova Scotia, people of Hispanic descent in specific parts of Colorado and New Mexico, and a small Bedouin group in Israel.

How Is Niemann-Pick Disease Type C Treated?

At this time, there is no cure for Niemann-Pick disease type C. Treatment focuses on managing symptoms with medication for seizures, sedatives for sleep disturbances, physical therapy to maintain mobility, and speech therapy to preserve communication as long as possible. Chest physiotherapy and antibiotics may help to prevent regular lung infections. Individuals with the condition need a gastronomy tube for feeding when they can no longer swallow well enough to avoid choking or malnutrition.

What Is the Prognosis for an Individual with Niemann-Pick Disease Type C?

For Niemann-Pick disease type C, an earlier age of onset is associated with a faster disease progression, while later onset is associated with slower progression and more attenuated symptoms. Individuals diagnosed in infancy rarely survive beyond 5 years. For those diagnosed during childhood, the disease is usually fatal in the late teens or twenties due to pneumonia. Those diagnosed in adulthood generally survive 10 to 20 years or more after diagnosis. Individuals presenting in adulthood are also more likely to have isolated psychiatric signs for years before developing more classic symptoms. The majority of individuals with Niemann-Pick disease type C develop symptoms in childhood.

Niemann-Pick Disease Type C2

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: NPC2.
Exons Sequenced: NM_006432:1-5.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Niemann-Pick Disease Type C2?

Niemann-Pick disease type C is an inherited lysosomal-storage disorder. Niemann-Pick disease type C is caused by harmful changes, or mutations, in two different genes, *NPC1* and *NPC2*. Individuals with Niemann-Pick disease type C cannot properly break down cholesterol and fats. In individuals with Niemann-Pick disease type C, cholesterol buildup causes severe liver disease, and fat accumulation in the brain which leads to learning disabilities and progressive neurological symptoms.

Niemann-Pick disease type C1 is caused by mutations in the *NPC1* gene, and type C2 is caused by mutations in the *NPC2* gene. Although the mutations occur in different genes, the resulting symptoms are the same, because *NPC1* and *NPC2* work together to remove cholesterol and lipids from cells. Approximately 90% of known cases of Niemann-Pick disease type C have been type C1 and 4% have been type 2.

The first symptoms of the disease, which can appear at any age from infancy to adulthood, is an enlarged liver, enlarged spleen, or jaundice. In some cases, it is possible to detect the disease in an unborn child via ultrasound, but the disease is most commonly diagnosed in school-aged children. Symptoms may include sudden muscle problems such as seizures, clumsiness, tremors, problems walking, sudden falls, slurred speech, and trouble moving the eyes up and down. As the condition progresses, affected children develop learning disabilities, psychological problems, dementia, and often lose the ability to speak. Eventually, individuals with Niemann-Pick disease type C lose the ability to move their facial muscles or swallow, making feeding through a stomach tube necessary.

How common is Niemann-Pick Disease Type C2?

The exact incidence of Niemann-Pick Disease Type C2 is unknown. It is estimated that Niemann-Pick disease type C affects 1 in 150,000 individuals, with approximately 4% of these cases attributed to mutations in the *NPC2* gene.

How is Niemann-Pick Disease Type C2 treated?

At this time, there is no cure for Niemann-Pick disease type C. Treatment focuses on managing symptoms with medication for seizures, sedatives for sleep disturbances, physical therapy to maintain mobility, and speech therapy to preserve communication as long as possible. Chest physiotherapy and antibiotics may help to prevent regular lung infections. Individuals with the condition need a gastronomy tube for feeding when they can no longer swallow well enough to avoid choking or malnutrition.

What is the prognosis for an individual with Niemann-Pick Disease Type C2?

Niemann-Pick disease type C shows variable disease advancement, with an earlier onset associated with faster disease progression. For those diagnosed during childhood, the disease is usually fatal in the late teens or twenties, due to pneumonia. Over half of those with this disease will be diagnosed by the age of 10. Individuals diagnosed in adulthood generally survive 10 to 20 years after diagnosis.

Niemann-Pick Disease, SMPD1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SMPD1.
Exons Sequenced: NM_000543:1-6.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Niemann-Pick Disease, SMPD1-Related (NPD)?

Niemann-Pick disease (NPD), SMPD1-Related is an inherited disease in which the body cannot properly metabolize a certain fatty substance called sphingomyelin due to a deficient enzyme called acid sphingomyelinase. As a result, sphingomyelin builds up in the body, causing cells to die and making it harder for certain organs to work properly. Mutations in the *SMPD1* gene can cause either the type A form or the type B form of NPD.

NIEMANN-PICK DISEASE TYPE A (NPD-A)

NPD-A causes intellectual disability, loss of motor skills, and enlargement of the liver and spleen, among other symptoms. The disease is often fatal by the age of two or three. Symptoms of NPD-A usually begin within the first few months of life. By the age of six months, infants with the disease have difficulty feeding, display an enlarged abdomen, and will begin to lose the motor skills they have developed. Seizures and spastic movement are common. Most will not learn to sit independently, crawl, or walk. They have poor muscle tone and develop cherry-red spots in their eyes. Many have a yellow tinge to the skin and whites of the eye (jaundice). Intellectual and motor skills will progressively and rapidly decline. These children may show vomiting, irritability, lung infections, and difficulty sleeping.

NIEMANN-PICK DISEASE TYPE B (NPD-B)

Unlike type A, which is fatal in early childhood, individuals with NPD-B have a less severe course of the disease and may live into adulthood. The most common symptoms include an enlargement of the liver and spleen (hepatosplenomegaly); a progressive decline in lung function and repeated respiratory infection; and poor or slower physical growth, leading to shorter stature. They typically have abnormal lipid levels in their blood, with low HDL cholesterol and high LDL and triglycerides. This can lead to coronary artery disease later in life. Individuals with NPD-B may also have a decreased number of blood platelets, which are needed to form blood clots. These symptoms are not always present at birth and may develop instead in late childhood or adolescence. Individuals with NPD-B usually do not have the nervous system complications (i.e., loss of motor skills) found in NPD-A, but some individuals with the disease develop symptoms that combine features of both NPD-A and NPD-B.

How Common Is Niemann-Pick Disease, SMPD1-Related?

The exact incidence of Niemann-Pick disease (including both NPD-A and NPD-B) is unknown but estimated to be 1 in 250,000 individuals. NPD-A is the most common form of Niemann-Pick disease, accounting for 85% of cases. NPD-A is more common in individuals of Ashkenazi Jewish descent, while NPD-B is most common in the Maghreb region of North Africa, which includes Algeria, Morocco, and Tunisia.

How Is Niemann-Pick Disease, SMPD1-Related Treated?

There are currently no effective treatments for NPD-A. Medical professionals can attempt to treat the symptoms through physical therapy, monitoring of nutrition, and medication to help sleep disorders. However, treatment cannot stop the decline caused by the disease.

There is no treatment to address the cause of NPD-B. However, individual symptoms such as high cholesterol can be addressed. Those with clotting problems may need blood transfusions, while those with breathing problems may need supplemental oxygen. Individuals with NPD-B should be monitored to ensure they are getting the proper nutrition for growth from their diet.

What Is the Prognosis for an Individual with Niemann-Pick Disease, SMPD1-Related?

The prognosis for an individual with NPD-A is poor. It is a severe disease that is typically fatal by the age of two or three. Individuals with NPD-B often survive into adulthood, but lifespan will likely be affected.

Nijmegen Breakage Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: NBN.
Exons Sequenced: NM_002485:1-16.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Nijmegen Breakage Syndrome?

Nijmegen Breakage Syndrome (NBS) is an inherited condition that increases the risk of cancer and reduces immune response. NBS is caused by harmful genetic changes, or mutations, in the *NBN* gene.

Infants with NBS are often born with small head size (microcephaly). Their physical growth is often slow, leaving them smaller than average for their age. They have characteristic features, including a sloping forehead, small chin, big ears, and a prominent nose, which become more apparent later in childhood. Many affected individuals have skeletal abnormalities of the fingers and toes.

Up to 40% of individuals with NBS will develop some sort of cancer by the age of 20. This is typically cancer of the immune system (lymphoma), but other types of cancer have been described. Individuals with NBS cannot tolerate the high doses of ionizing radiation often used to treat cancer and must find alternate treatment methods such as chemotherapy.

Individuals with NBS have a poor immune system and experience frequent infections in the lungs, ears, sinuses, and urinary tract. Recurrent pneumonia or bronchitis in those affected by NBS can be life-threatening. A patient's intellect appears to develop normally or nearly normally in early childhood but typically declines until the patient reaches mild-to-moderate levels of intellectual disability around the age of 10.

How common is Nijmegen Breakage Syndrome?

The prevalence of NBS is estimated to be 1 in 100,000 births, but there is currently insufficient population-specific prevalence information. The disease is most common in individuals of Eastern European or Slavic background, specifically those from Poland, the Czech Republic, and Ukraine.

How is Nijmegen Breakage Syndrome treated?

There is no treatment to address the underlying cause of NBS, but specific symptoms can be treated. Supplements such as vitamin E and folic acid may be helpful, and in some individuals, intravenous infusions with immunoglobulin or preventative antibiotics can be used to reduce infections. Special education and speech therapy may also address delays in development. Hormone replacement therapy may be useful for female sexual development, but most women with NBS are not fertile. Stem-cell transplantation may also be considered for treatment of NBS.

Large doses of radiation must be avoided in individuals with NBS, even before birth. Individuals with NBS should be monitored for proper growth and development, delayed onset of puberty, and early cancer signs.

What is the prognosis for an individual with Nijmegen Breakage Syndrome?

Some individuals with NBS do live into adulthood, though the lifespan does not typically extend beyond one's thirties or forties. Cancer is the most common cause of death among individuals with NBS, followed by lung infections leading to respiratory failure.

Normophosphatemic Familial Tumoral Calcinosis

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SAMD9.
Exon Sequenced: NM_017654:3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Normophosphatemic Familial Tumoral Calcinosis?

Normophosphatemic familial tumoral calcinosis (NFTC), is a condition characterized by the formation of calcium-filled masses (non-cancerous tumors) under the skin. It is caused by harmful genetic changes (variants) in the *SAMD9* gene.

In individuals with NFTC, rash-like changes in the skin and inflammation of mucous membranes typically appear within the first year of life. The skin lesions are most commonly seen on the arms and legs. Over time, these lesions become calcified masses, which leads to painful ulcers and a chalk-like discharge, as well as skin and bone infections. Most individuals with NFTC also have severe inflammation of the mucous membranes in the mouth and in the eyes.

Of note, recent studies suggests that some individuals who carry a single *SAMD9* variant may have an increased risk to develop abnormalities of blood cells and bone marrow (myelodysplasia). Further research is needed to confirm this association.

How common is Normophosphatemic Familial Tumoral Calcinosis?

The exact incidence of NFTC is unknown. At least 15 individuals/families have been diagnosed worldwide. The incidence of NFTC may be more common among individuals of Yemenite Jewish descent.

How is Normophosphatemic Familial Tumoral Calcinosis treated?

There is no cure for NFTC. Treatment may involve having surgery to remove the calcified masses.

What is the prognosis for a person with Normophosphatemic Familial Tumoral Calcinosis?

Because this condition is so rare, there is limited information about the prognosis for individuals with NFTC. Individuals with NFTC can have significant pain due to ulcers and infections caused by the calcium masses, which may be helped with surgery. Although rare, infections can become life-threatening if left untreated. However, it is not thought to significantly impact life expectancy in most cases.

Oculocutaneous Albinism, OCA2-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: OCA2.
Exons Sequenced: NM_000275:2-24.

Detection Rate	Population
82%	African American
96%	Ashkenazi Jewish
96%	Eastern Asia
96%	Finland
96%	French Canadian or Cajun
96%	Hispanic
96%	Middle East
85%	Native American
96%	Northwestern Europe
96%	Oceania
92%	South Asia
96%	Southeast Asia
96%	Southern Europe
96%	Worldwide

What is Oculocutaneous Albinism, OCA2-related?

Oculocutaneous albinism, OCA2-related, also known as OCA type 2, is an inherited condition that causes unique coloring of the skin, hair, and eyes. Several genes can cause oculocutaneous albinism and oculocutaneous albinism, OCA2-related, is caused by harmful genetic changes (variants) in the *OCA2* gene. Individuals with oculocutaneous albinism, OCA2-related, cannot produce a dark-colored pigment known as melanin. The result is that individuals with the condition have lighter-colored skin, hair, and eyes than their family members. Common features of oculocutaneous albinism, OCA2-related, include very light skin, yellow to light brown hair, and gray or tan eyes. Individuals can have vision abnormalities, including involuntary eye movements (nystagmus) and sensitivity to light (photophobia). Some individuals with oculocutaneous albinism, OCA2-related, may see increased pigmentation and/or development of freckles as they age. Individuals with oculocutaneous albinism, OCA2-related, are at high risk for sunburns and have a significantly increased risk of developing skin cancers.

How common is Oculocutaneous Albinism, OCA2-related?

The prevalence of oculocutaneous albinism, OCA2-related, varies across different ancestries. The prevalence in African populations is 1 in 10,000, with some sub-Saharan African populations having an even greater prevalence ranging from 1/1,100 to 1/3,900. The condition is also more common in specific Native American populations, with a prevalence between 1/227 to 1/2,000, depending on the tribe. The prevalence in European populations is 1 in 37,000.

How is Oculocutaneous Albinism, OCA2-related treated?

There is no cure for oculocutaneous albinism, OCA2-related. Disease management includes sunscreen and clothing to protect the individual from sunburns and reduce the risk of skin cancer. Sensitivity to light is addressed by wearing dark glasses or a wide-brimmed

hat. Contact lenses or glasses can improve vision. Regular checkups with physicians who specialize in skin disorders (dermatology) and eye disorders (ophthalmology) are recommended.

What is the prognosis for an individual with Oculocutaneous Albinism, OCA2-related?

With proper skin protection and medical care, people with oculocutaneous albinism, OCA2-related can have average lifespans. This condition does not affect an individual's development or intelligence.

Oculocutaneous Albinism, TYR-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: TYR.
Exons Sequenced: NM_000372:1-5.

Detection Rate	Population
99%	African American
99%	Ashkenazi Jewish
99%	Eastern Asia
99%	Finland
99%	French Canadian or Cajun
99%	Hispanic
99%	Middle East
99%	Native American
99%	Northwestern Europe
99%	Oceania
93%	South Asia
99%	Southeast Asia
98%	Southern Europe
99%	Worldwide

What is Oculocutaneous Albinism, TYR-related?

Oculocutaneous albinism, TYR-related, also known as OCA type 1, is an inherited condition that causes unique coloring of the skin, hair, and eyes. Several genes can cause oculocutaneous albinism and oculocutaneous albinism, TYR-related, is caused by harmful genetic changes (variants) in the *TYR* gene. Individuals with oculocutaneous albinism, TYR-related, cannot produce a dark-colored pigment known as melanin. The result is that individuals with the condition have lighter-colored skin, hair, and eyes than their family members. Common features of oculocutaneous albinism, TYR-related, include very light skin, white hair, and pink-colored eyes. Individuals may also experience involuntary eye movements (nystagmus), light sensitivity (photophobia), and poor vision. Individuals can develop some skin pigment as they get older. Individuals with oculocutaneous albinism, TYR-related, are at high risk for sunburns and have a significantly increased risk of developing skin cancers.

How common is Oculocutaneous Albinism, TYR-related?

The prevalence of oculocutaneous albinism, TYR-related, is approximately 1 in 40,000. It is the most common cause of oculocutaneous albinism in Japanese populations.

How is Oculocutaneous Albinism, TYR-related treated?

There is no cure for oculocutaneous albinism, TYR-related. Disease management includes sunscreen and clothing to protect the individual from sunburns and reduce the risk of skin cancer. Sensitivity to light is addressed by wearing dark glasses or a wide-brimmed hat. Contact lenses or glasses can improve vision. Regular checkups with physicians who specialize in skin disorders (dermatology) and eye disorders (ophthalmology) are recommended.

What is the prognosis for an individual with Oculocutaneous Albinism, TYR-related?

With proper skin protection and medical care, people with oculocutaneous albinism, TYR-related, can have average lifespans. This condition usually does not affect an individual's development or intelligence.

Opitz G/BBB Syndrome, MID1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MID1.
Exons Sequenced: NM_000381:2-10.

Detection Rate	Population
87%	African American
87%	Ashkenazi Jewish
87%	Eastern Asia
87%	Finland
87%	French Canadian or Cajun
87%	Hispanic
87%	Middle East
87%	Native American
87%	Northwestern Europe
87%	Oceania
87%	South Asia
87%	Southeast Asia
87%	Southern Europe
87%	Worldwide

What is Opitz G/BBB Syndrome, MID1-related?

Opitz G/BBB syndrome, MID1-related or MID1-OS, is an inherited disease that causes multiple birth defects and intellectual disability. The condition is caused by harmful genetic changes (variants) in the *MID1* gene. MID1-OS is an X-linked disease, meaning that people assigned male at birth (XY) typically have more severe symptoms, while those assigned female (XX) at birth typically have mild or no symptoms.

The symptoms of MID1-OS include unique facial features and birth defects involving the throat, genitals, heart, and brain. They may also have cleft lip or cleft palate. Over 30% of individuals have developmental delays or intellectual disabilities. The severity of symptoms can vary widely, even among family members. Almost all individuals with MID1-OS have facial abnormalities. Most commonly, the distance between the eyes is increased (hypertelorism). Other characteristic facial features include a wider bridge of the nose, a prominent forehead, and low-set ears.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Individuals assigned female at birth (XX) are considered carriers and usually do not have disease symptoms, but they may have increased distance between the eyes (hypertelorism) with no other symptoms.

How common is Opitz G/BBB Syndrome, MID1-related?

Opitz G/BBB syndrome, MID1-related, is thought to affect 1 in 50,000 to 1 in 100,000 males.

How is Opitz G/BBB Syndrome, MID1-related treated?

There is no cure for Opitz G/BBB syndrome, MID1-related. Treatment is directed at managing the specific symptoms an individual has. Most of the birth defects can be treated with corrective surgery. Individuals with developmental delay will benefit from early intervention and other supportive services beginning at a young age. A team of specialists, including a speech/language pathologist, surgeon, cardiologist, pulmonologist, and ophthalmologist, can help treat symptoms as needed.

What is the prognosis for a person with Opitz G/BBB Syndrome, MID1-related?

The prognosis of an individual with Opitz G/BBB syndrome, MID1-related, varies depending on the severity of the symptoms. Surgery can treat many of the symptoms of the condition. Most individuals can live a relatively normal lifespan. Some will need support throughout their entire lives.

Ornithine Aminotransferase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: OAT.
Exons Sequenced: NM_000274:2-10.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Ornithine Aminotransferase Deficiency?

Ornithine aminotransferase (OAT) deficiency, also known as gyrate atrophy of the choroid and retina (GACR), is a condition characterized by vision loss. It is caused by harmful genetic changes (variants) in the *OAT* gene. Individuals with this condition have reduced amounts of the OAT enzyme, which is responsible for breaking down a substance called ornithine. Because of the decreased amount of OAT enzyme, ornithine builds up in the body and causes damage to tissues, most notably the eyes.

Symptoms of OAT deficiency typically begin in late childhood, with difficulty seeing at night (night blindness) and reduced outer (peripheral) vision. This is followed by loss of the middle (central) vision in late childhood or early adulthood. Other symptoms may include cataracts and nearsightedness (myopia). Age of onset and rate of disease progression is somewhat variable. While most people begin developing vision issues in childhood, there have been cases where symptoms begin as early as infancy or as late as the fifth decade of life.

Typically, the symptoms of OAT deficiency are limited to vision issues. However, a minority of individuals have symptoms that impact other areas of the body. These include muscle weakness, sensory issues, and mild to moderate intellectual disability. In rare cases, newborns with OAT deficiency have higher levels of a substance called ammonia in their blood (hyperammonemia). This can lead to symptoms such as vomiting, feeding difficulties, seizures, and coma.

How common is Ornithine Aminotransferase Deficiency?

The exact incidence of OAT deficiency is unknown. At least 200 individuals have been diagnosed worldwide. The incidence of OAT deficiency is more common among individuals of Finnish descent.

How is Ornithine Aminotransferase Deficiency treated?

There is no cure for OAT deficiency. However, following a special diet that is low in protein or arginine may slow down the progression of the disease. This is because the body uses arginine, a substance found in protein, to produce ornithine. Reducing the amount of arginine that an individual consumes may therefore help reduce their level of ornithine. Additional dietary supplements, such as vitamin B6 (pyridoxine), may also be recommended in some cases. Other tools for individuals with vision impairment include low-vision aids and supportive services.

What is the prognosis for an individual with Ornithine Aminotransferase Deficiency?

Vision loss associated with OAT deficiency is progressive, meaning it worsens over time. Most people with the condition eventually become legally blind. The age at which this happens can vary, but it typically occurs between the ages of 40-60 years. Dietary changes may slow the progression of the disease. The condition is not known to impact life expectancy.

In the rare case that a newborn develops a high ammonia level, hospitalization is usually required to treat the condition. While there have not been many cases of newborns with OAT deficiency and elevated ammonia levels, symptoms of hyperammonemia generally improve with treatment.

Ornithine Transcarbamylase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: OTC.
Exons Sequenced: NM_000531:1-10.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe
97%	Worldwide

What is Ornithine Transcarbamylase Deficiency?

Ornithine transcarbamylase (OTC) deficiency is a metabolic disorder that results from problems in the urea cycle, a metabolic pathway necessary for the removal of ammonia from the body. The symptoms of OTC deficiency, which is the most common urea cycle disorder, result from elevated levels of ammonia in the blood (hyperammonemia). While ammonia is a normal byproduct of protein breakdown, it is toxic if there is too much in the body. An excess of ammonia is particularly damaging to the liver and nervous system. However, the condition is quite variable, with affected individuals presenting from birth to adulthood and with differing levels of disease severity, based on the degree of OTC enzyme deficiency. As this is an X-linked disorder (the gene that causes the condition is located on the X chromosome), OTC deficiency most often affects males, although some females may show signs of the condition.

NEONATAL ONSET FORM

This severe form of OTC deficiency, which results from absent or near-absent enzyme activity, first presents at or shortly after birth. Symptoms may include poor feeding, lethargy, low muscle tone, seizures, breathing difficulties, and potentially a hyperammonemic coma. Recurrent hyperammonemic crises (periods of high ammonia levels) lead to continued liver and brain damage and resulting complications.

LATER ONSET FORM

Partial OTC deficiency results in a later onset of symptoms (anywhere from infancy to adulthood). Individuals with this form may present with recurrent vomiting, a history of protein intolerance or avoidance, a Reye-like syndrome (with brain and liver swelling), developmental delays, intellectual disability, and/or seizures.

CARRIER FEMALES

While most carrier females (females that have one altered copy of the *OTC* gene and one copy that functions normally) show no signs of OTC deficiency, it is estimated that at least 15-20% will have a partial enzyme deficiency and may develop symptoms of the condition. It is important to know, however, that all carrier females (even those who have previously shown no signs of the condition) are more prone to experience symptoms of OTC deficiency during and just after pregnancy.

How common is Ornithine Transcarbamylase Deficiency?

It is not yet known precisely how common OTC deficiency is worldwide. While some sources estimate that OTC deficiency may occur in as many as 1 in 14,000 individuals, others estimate that it may affect approximately 1 in 50,000 to 1 in 80,000 individuals.

How is Ornithine Transcarbamylase Deficiency treated?

The treatment of OTC deficiency is focused on managing metabolic crises by reducing ammonia levels. If an infant presents with suddenly high ammonia levels, dialysis is performed, intravenous medications are given, and dietary restrictions are utilized to clear the body of problematic proteins. Liver transplantation is almost always necessary in those with the neonatal onset form, and may be considered in some cases of partial OTC deficiency. Seizures are treated with medications, while developmental delays and intellectual disabilities are managed with supportive therapies.

To avoid manifestations of OTC deficiency, affected individuals are prescribed intravenous medications, specialized formulas, and a restricted diet with less protein intake. People with OTC deficiency should also avoid exposure to valproic acid (Depakote, an anti-seizure medication), prolonged fasting or starvation, intravenous steroids, and high levels of protein or amino acids, which may trigger a metabolic crisis.

What is the prognosis for a person with Ornithine Transcarbamylase Deficiency?

The overall outcome for an individual with this condition depends on the severity of the enzyme deficiency and the extent of damage that occurs during hyperammonemic episodes. If an individual remains asymptomatic or mildly symptomatic, their prognosis may be good. However, if there is significant brain and liver damage as a result of metabolic crises, neuropsychological, gastrointestinal, and/or liver complications may occur. Adequate management of the condition during and between crises may improve prognosis, although hyperammonemic crises may lead to coma and even death, if untreated.

PCCA-related Propionic Acidemia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PCCA.
Exons Sequenced: NM_000282:1-24.

Detection Rate	Population
95%	African American
95%	Ashkenazi Jewish
95%	Eastern Asia
95%	Finland
95%	French Canadian or Cajun
95%	Hispanic
95%	Middle East
95%	Native American
95%	Northwestern Europe
95%	Oceania
95%	South Asia
95%	Southeast Asia
95%	Southern Europe
95%	Worldwide

What is PCCA-related Propionic Acidemia?

Propionic acidemia is an inherited condition caused by a deficiency in the enzyme propionyl-CoA carboxylase. This results in the body being unable to properly process certain parts of proteins and fats, causing harmful substances to build up in the the body. This build up in the blood, urine, and tissues can be toxic and cause serious health problems.

Symptoms of propionic acidemia most often begin within the first few days after birth. Initial symptoms include poor feeding, lack of energy, weak muscle tone, and vomiting. If untreated, these symptoms can progress to more serious medical complications, including organ damage, seizures, coma, and possibly death. Propionic acidemia may be associated with developmental regression, intellectual disability, frequent infection, nutritional problems, and heart problems. The severity of symptoms can be variable amongst individuals with the condition. Typically, if an individual has symptoms beginning in infancy and does not receive treatment, they do not live past the first year of life.

Less commonly, the signs and symptoms of propionic acidemia appear during childhood or later in life. In individuals with this later-onset form, symptoms may be triggered by periods of fasting, fever, or infection. In some cases, the only symptom present is thickening of the heart muscle (cardiomyopathy).

At a cellular level, propionic acidemia is caused by mutations in either the *PCCA* or *PCCB* gene. Although the genetic mutations are different, the resulting symptoms are the same because PCCA and PCCB combine together to make the enzyme propionyl-CoA carboxylase. Of the known cases of propionic acidemia, approximately 35-50% have been attributed to mutations in *PCCA*, while 50-65% have been attributed to *PCCB* mutations.

How common is PCCA-related Propionic Acidemia?

The worldwide incidence of propionic acidemia has not been estimated, but is generally accepted to be 1 in 100,000 overall. However, the incidence of this condition varies significantly across the world. Where estimates are available, the incidence is between 1 in 1,500 and 1 in 520,000. It is more common among in Japan (1 in 17,400 including an asymptomatic form identified in newborn screening), the Middle East (1 in ~27,000 in Saudi Arabia and 1 in 2000-5000 in specific tribes, 1 in 10,000 in Bahrain, and as high as 1 in 20,000 in the United Arab Emirates), and in Greenland (1 in 1600 in the Inuit population). Again, depending on region, the percent of cases attributed to the PCCA gene is between 10% and 70% with most countries showing that 40% of cases are due to *PCCA* mutations.

How is PCCA-related Propionic Acidemia treated?

At this time, there is no cure for propionic acidemia. Treatment primarily focuses on individualized dietary management to ensure proper nutrition. Dietary supplements and medication to manage medical complications may be used. Regular assessment for growth, nutritional needs, feeding, kidney function, cardiac problems, and development is recommended. Prompt identification and treatment of stressors such as fasting, fever, illness, and injury may decrease the chance of organ damage. Any time a child with propionic acidemia experiences an event causing fasting or illness, he or she needs prompt treatment, which may include a hospital visit. Liver transplant may be beneficial in some cases.

What is the prognosis for a person with PCCA-related Propionic Acidemia?

If an individual presenting with symptoms of propionic acidemia is not treated early in infancy, they do not usually live past the first year of life. If the condition is recognized promptly and treated diligently, survival and long term outcome is potentially improved. Even with treatment, affected individuals may still have significant intellectual and neurological impairment. Normal development is possible in some patients with later onset forms of the condition, with strict dietary management and close monitoring.

PCCB-related Propionic Acidemia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PCCB.
Exons Sequenced: NM_000532:1-15.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is PCCB-related Propionic Acidemia?

Propionic acidemia is an inherited condition caused by a deficiency in the enzyme propionyl-CoA carboxylase. This results in the body being unable to properly process certain parts of proteins and fats, causing harmful substances to build up in the the body. This build up in the blood, urine, and tissues can be toxic and cause serious health problems.

Symptoms of propionic acidemia most often begin within the first few days after birth. Initial symptoms include poor feeding, lack of energy, weak muscle tone, and vomiting. If untreated, these symptoms can progress to more serious medical complications, including organ damage, seizures, coma, and possibly death. Propionic acidemia may be associated with developmental regression, intellectual disability, frequent infection, nutritional problems, and heart problems. The severity of symptoms can be variable amongst individuals with the condition. Typically, if an individual has symptoms beginning in infancy and does not receive treatment, they do not live past the first year of life.

Less commonly, the signs and symptoms of propionic acidemia appear during childhood or later in life. In individuals with this later-onset form, symptoms may be triggered by periods of fasting, fever, or infection. In some cases, the only symptom present is thickening of the heart muscle (cardiomyopathy).

At a cellular level, propionic acidemia is caused by mutations in either the *PCCA* or *PCCB* gene. Although the genetic mutations are different, the resulting symptoms are the same because PCCA and PCCB combine together to make the enzyme propionyl-CoA carboxylase. Of the known cases of propionic acidemia, approximately 35-50% have been attributed to mutations in *PCCA*, while 50-65% have been attributed to *PCCB* mutations.

How common is PCCB-related Propionic Acidemia?

The worldwide incidence of propionic acidemia has not been estimated, but is generally accepted to be 1 in 100,000 overall. However, the incidence of this condition varies significantly across the world. Where estimates are available, the incidence is between 1 in 1500 and 1 in 520,000. It is more common among in Japan (1 in 17,400 including an asymptomatic form identified in newborn screening), the Middle East (1 in ~27,000 in Saudi Arabia and and 1 in 2000-5000 in specific tribes, 1 in 10,000 in Bahrain, and as high as 1 in 20,000 in the United Arab Emirates), and in Greenland (1 in 1600 in the Inuit population). Again, depending on region, the percent of cases attributed to the *PCCB* gene is between 10% and 80% with most countries showing that 60% of cases are due to *PCCB* mutations.

How is PCCB-related Propionic Acidemia treated?

At this time, there is no cure for propionic acidemia. Treatment primarily focuses on individualized dietary management to ensure proper nutrition. Dietary supplements and medication to manage medical complications may be used. Regular assessment for growth, nutritional needs, feeding, kidney function, cardiac problems, and development is recommended. Prompt identification and treatment of stressors such as fasting, fever, illness, and injury may decrease the chance of organ damage. Any time a child with propionic acidemia experiences an event causing fasting or illness, he or she needs prompt treatment, which may include a hospital visit. Liver transplant may be beneficial in some cases.

What is the prognosis for a person with PCCB-related Propionic Acidemia?

If an individual presenting with symptoms of propionic acidemia is not treated early in infancy, they do not usually live past the first year of life. If the condition is recognized promptly and treated diligently, survival and long term outcome is potentially improved. Even with treatment, affected individuals may still have significant intellectual and neurological impairment. Normal development is possible in some patients with later onset forms of the condition, with strict dietary management and close monitoring.

PCDH15-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PCDH15.
Exons Sequenced: NM_033056:2-33.

Detection Rate	Population
93%	African American
93%	Ashkenazi Jewish
93%	Eastern Asia
93%	Finland
93%	French Canadian or Cajun
93%	Hispanic
93%	Middle East
93%	Native American
93%	Northwestern Europe
93%	Oceania
93%	South Asia
93%	Southeast Asia
93%	Southern Europe
93%	Worldwide

What Are PCDH15-Related Disorders?

PCDH15-related disorders are a group of disorders associated with hearing loss, with or without vision loss. This group of disorders does not affect intelligence or cause any other primary health problems. Both Usher syndrome Type 1F (USH1F) and DFNB23 are caused by mutations in the *PCDH15* gene.

USHER SYNDROME TYPE 1F (USH1F)

USH1F is an inherited disease that causes hearing loss, balance problems, and difficulty with gaze stabilization (secondary to vestibulopathy), and progressive vision loss. Infants with USH1F are profoundly deaf in both ears, typically at birth. They have severe balance problems that can lead to delayed development (children sit and walk at later ages and have difficulties sensing changes in speed or direction). In childhood or by early adolescence, individuals with USH1F will develop retinitis pigmentosa, an eye disease which causes night blindness and a gradual loss of peripheral vision. Eventually only the central vision remains, creating a "tunnel vision" effect. Central vision can also be impaired and can lead to blindness in a small number of individuals with the disease, in part due to the occasional development of cataracts.

DFNB23

Some mutations in USH1F have been reported in recessive nonsyndromic hearing loss and deafness (isolated hearing loss), referred to as DFNB23. Individuals with DFNB23 typically have severe to profound hearing loss at birth. Unlike other forms of hearing loss, DFNB23 does not affect movement or balance.

How Common Are PCDH15-Related Disorders?

The global incidence is unknown for both conditions. The incidence and prevalence of Usher syndrome type 1 overall has been estimated in a few countries. In most countries, the frequency ranges from approximately 1 in 45,000 to approximately 1 in 65,000, with the exception of Germany, where the frequency is approximately 1 in 90,000. Approximately 7 to 12% of individuals with Usher syndrome

type I have USH1F. There are regions where founder effects (a high frequency of the disease because the group arose from a small, possibly isolated population) occur. Individuals of Ashkenazi Jewish descent have been noted to have one common mutation with an estimated carrier frequency of approximately 1 in 134 individuals. In the Hutterite population, approximately 1 in 40 individuals is a carrier of a different common mutation.

DFNB23 is a rare disorder. It has only been reported in five families, and the global incidence is unknown. Other presentations of or variability in this disorder may not be recognized yet.

How Are PCDH15-Related Disorders Treated?

There is no cure for PCDH15-related disorders, but early treatment is important, to give an affected child the best opportunity to develop communication skills. While a child is young, his or her brain is most receptive to learning language, either spoken or signed. It is also important to take advantage of the time when the child's vision is normal.

Individuals with USH1F generally do not respond to hearing aids, but cochlear implants may help regain some hearing. Sign language is a another option for communication. Specialists can introduce other tools and methods of instruction available to individuals with hearing loss and it is often helpful if the whole family undergoes such instruction and, as a family unit, helps the child adapt.

For those individuals that develop vision loss, visual aids and specialized instruction (for example in tactile signing) can help children adapt to their limited vision. Individuals can be prone to accidental injury due to their vision loss and balance problems. Well-supervised participation in sports may help an individual with Usher syndrome type 1 compensate for balance issues, but swimming may be particularly difficult and strategies to ensure safety are needed. Use of UV-A and UV-B blocking sunglasses is recommended, and other optical aids may increase eye comfort. Therapy with vitamin A palmitate may slow retinal degeneration for some.

What Is the Prognosis for a Person with a PCDH15-Related Disorder?

USH1F results in severe hearing and vision impairment and DFNB23 results in hearing impairment only. However, neither condition affects one's lifespan or intelligence.

Pendred Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SLC26A4.
Exons Sequenced: NM_000441:2-21.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Pendred Syndrome?

Pendred syndrome, caused by mutations in the *SLC26A4* gene, is an inherited condition in which the body's ability to make a protein called pendrin is impaired. Pendrin plays an essential role in normal functions of the inner ear and thyroid.

Individuals with Pendred syndrome experience profound deafness that is usually present from birth, though severity can vary. Some individuals with Pendred syndrome may lose their hearing rapidly in infancy or early childhood, while moderate hearing loss may not worsen over time in other individuals. Typical inner-ear malformations in individuals with Pendred syndrome may also affect one's balance.

Some individuals may also experience an abnormal enlargement of the thyroid (also known as a goiter) which can present itself as a large swelling at the base of the neck. This symptom is usually secondary to a diagnosis of hearing loss and can happen at any time throughout one's life. While thyroid function is usually not affected by Pendred syndrome, goiters can disrupt swallowing and breathing due to pressure placed on the esophagus and windpipe.

How Common Is Pendred Syndrome?

The frequency of Pendred syndrome is unknown, but some researchers believe it may be the cause of up to 10% of infant deafness.

How Is Pendred Syndrome Treated?

Treatment for Pendred syndrome addresses hearing loss early in life, including hearing aids for children with the condition. Cochlear implants show promise for restoring some hearing to individuals with severe to profound deafness. Children should receive special educational programs for the hearing impaired.

Breathing or swallowing difficulties caused by goiters may be treated using radioactive iodine to shrink the swelling. Surgical removal of all or part of the thyroid may also be an option.

What Is the Prognosis for an Individual with Pendred Syndrome?

Pendred syndrome causes moderate to profound hearing loss but does not affect lifespan.

Peroxisome Biogenesis Disorder Type 1

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PEX1.
Exons Sequenced: NM_000466:1-24.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Peroxisome Biogenesis Disorder Type 1?

Peroxisome biogenesis disorder type 1 (also known as PEX1-related Zellweger syndrome spectrum, ZSS) is an inherited disease that affects the functioning of the body's peroxisomes, a structure in the body's cells that normally breaks down fatty acids and other metabolic waste products. As indicated by the word "spectrum," individuals with ZSS vary widely in the type and severity of their symptoms. The disease is generally grouped into three subtypes: Zellweger syndrome (ZS, the most severe form), neonatal adrenoleukodystrophy (a form of intermediate severity), and infantile Refsum disease (the mildest form). ZSS results from mutations in the *PEX1* gene. Because mutations cannot always predict which form of the disease a person will have, families should consult a healthcare professional for more information about each form described below.

ZELLWEGER SYNDROME (ZS)

ZS is the most severe form of ZSS. Infants with ZS usually die before their first birthday without reaching any developmental milestones. Infants with ZS generally have very low muscle tone, severe developmental delay, and seizures. In some, the lack of muscle tone is so severe that the infant cannot move and may be unable to suck or swallow. Most infants with ZS have some degree of feeding and breathing difficulties. In addition, skeletal changes and liver problems are common, and episodes of spontaneous bleeding (including in the brain) are possible. Infants with ZS also tend to have characteristic facial features, including a high forehead, abnormal earlobes, a large "soft spot" on the top of their heads, and a small chin.

NEONATAL ADRENOLEUKODYSTROPHY (NALD) AND INFANTILE REFSUM DISEASE (IRD)

The symptoms of NALD and IRD are less severe than those of ZS. Symptoms in children with these conditions often begin in late infancy or early childhood and may progress more slowly than those in ZS. Infants and children with NALD or IRD typically have developmental delays and mild to severe intellectual disability. Some children with the disease learn to walk, while others lack the muscle tone needed for such movement. Similarly, many children with the disease learn to talk, while others do not. Hearing loss and vision impairment are present and typically worsen over time, potentially leading to deafness and/or blindness, respectively. Many children with NALD or IRD have liver problems and some have developed episodes of spontaneous bleeding, particularly around the brain.

How Common Is Peroxisome Biogenesis Disorder Type 1?

The estimated prevalence of peroxisomal biogenesis disorders is 1 in 50,000, with almost 70% of cases being due to mutations in the *PEX1* gene.

How Is Peroxisome Biogenesis Disorder Type 1 Treated?

There is no cure for ZSS, and there is no standard way to treat it. In children with severe forms of the disease, the main goal of treatment is to protect the child from infections and breathing problems. Physicians can also address certain symptoms as they arise, such as prescribing medication for seizures. Children with milder forms of the disease may benefit from hearing aids and glasses, as well as physical, occupational, and speech therapy. In those who reach school age, special education is likely necessary. Modifications to the child's diet may also be recommended.

What Is the Prognosis for a Person with Peroxisome Biogenesis Disorder Type 1?

Individuals with ZSS have a shortened lifespan that varies depending on the severity of the disease. The prognosis for an infant with ZS is poor. Most die within the first year of life without achieving any developmental milestones. Most children with NALD survive into childhood, while those with IRD can live into their teens or 20s, and perhaps even longer. All individuals with NALD or IRD will all have some degree of cognitive impairment.

Peroxisome Biogenesis Disorder Type 3

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PEX12.
Exons Sequenced: NM_000286:1-3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Peroxisome Biogenesis Disorder Type 3?

Peroxisome biogenesis disorder type 3 (also known as *PEX12*-related Zellweger syndrome spectrum, ZSS) is an inherited disease that stops part of the body's cells, called a peroxisome, from forming correctly. Peroxisomes normally break down waste products in a cell. Not everyone with ZSS will have the same symptoms and some may have more severe symptoms than others. The disease is generally grouped into three subtypes: Zellweger syndrome (the most severe), neonatal adrenoleukodystrophy or NALD (intermediate severity), and infantile Refsum disease or IRD (the mildest form). Individuals with ZSS usually show symptoms of the disease as newborns or as children, but some some people may not have symptoms until they are older.

ZELLWEGER SYNDROME (ZS)

ZS is the most severe form of ZSS. Infants with ZS usually die before their first birthday without reaching many mental or physical developmental milestones. Infants born with ZS have developmental delay leading to severe intellectual disability. They often have seizures and typically have facial deformities such as a high forehead, abnormal ear lobes, a large "soft spot" on the top of their heads, and a small chin. In some cases, the infant cannot move and may not be able to suck or swallow because their muscles are too weak. They often show poor feeding. Their livers are usually enlarged and their skin and the whites of their eyes may have a yellowish tinge (jaundice). Some have bleeding in their digestive tract. Abnormally shaped bones are also common.

NEONATAL ADRENOLEUKODYSTROPHY (NALD) AND INFANTILE REFSUM DISEASE (IRD)

The symptoms of NALD and IRD are less severe than those of ZS, with IRD being the mildest form of the disease. Symptoms in these children often begin in late infancy or early childhood and may progress more slowly. Infants and children with NALD or IRD may have developmental delays with mild to severe intellectual disability. Hearing loss and vision impairment typically grow worse over time and may lead to blindness and/or deafness. Many people with the disease have liver problems and some have developed episodes of spontaneous bleeding, particularly around the brain. Some children with the disease learn to walk, while others lack the muscle tone needed for such movement. Similarly many children with the disease learn to talk, though some do not.

How common is Peroxisome Biogenesis Disorder Type 3?

Peroxisomal biogenesis disorders generally affect approximately 1 in 50,000 infants, and approximately 3-9% of cases are attributed to mutations in *PEX12*. In Japan, the incidence of all peroxisomal biogenesis disorders may be lower than 1 in 500,000.

How is Peroxisome Biogenesis Disorder Type 3 treated?

There is no cure for ZSS and there is no standard way to treat it. In children with severe forms of the disease, the main goal of treatment is to protect the child from infections and breathing problems. Physicians can also address certain symptoms as they arise, such as prescribing medication for seizures. Children with milder forms of the disease may benefit from hearing aids, glasses, and/or surgery to remove cataracts. In those who reach school age, special education is likely necessary. Modifications to the child's diet may also be recommended.

What is the prognosis for a person with Peroxisome Biogenesis Disorder Type 3?

ZSS usually reduces a person's lifespan. The prognosis for an infant with ZS is poor. Most pass away within the first year of life without reaching any physical or mental developmental milestones. One study showed that children with NALD or IRD who survive the first year of life have a 77% chance of reaching school age. These children will all have some degree of intellectual disability. Most people with NALD survive into childhood while those with IRD can live into their teens or 20s, and perhaps even longer.

Peroxisome Biogenesis Disorder Type 4

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PEX6.
Exons Sequenced: NM_000287:1-17.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe
97%	Worldwide

What is Peroxisome Biogenesis Disorder Type 4?

Peroxisome biogenesis disorder type 4 (also known as *PEX6*-related Zellweger syndrome spectrum, ZSS) is an inherited disease that stops part of the body's cells, called a peroxisome, from forming correctly. Peroxisomes normally break down waste products in a cell. Not everyone with ZSS will have the same symptoms and some may have more severe symptoms than others. The disease is generally grouped into three subtypes: Zellweger syndrome (the most severe), neonatal adrenoleukodystrophy or NALD (intermediate severity), and infantile Refsum disease or IRD (the mildest form). Individuals with ZSS usually show symptoms of the disease as newborns or as children, but some some people may not have symptoms until they are older.

ZELLWEGER SYNDROME (ZS)

ZS is the most severe form of ZSS. Infants with ZS usually die before their first birthday without reaching many mental or physical developmental milestones. Infants born with ZS have developmental delay leading to severe intellectual disability. They often have seizures and typically have facial deformities such as a high forehead, abnormal ear lobes, a large "soft spot" on the top of their heads, and a small chin. In some cases, the infant cannot move and may not be able to suck or swallow because their muscles are too weak. They often show poor feeding. Their livers are usually enlarged and their skin and the whites of their eyes may have a yellowish tinge (jaundice). Some have bleeding in their digestive tract. Abnormally shaped bones are also common.

NEONATAL ADRENOLEUKODYSTROPHY (NALD) AND INFANTILE REFSUM DISEASE (IRD)

The symptoms of NALD and IRD are less severe than those of ZS, with IRD being the mildest form of the disease. Symptoms in these children often begin in late infancy or early childhood and may progress more slowly. Infants and children with NALD or IRD may have developmental delays with mild to severe intellectual disability. Hearing loss and vision impairment typically grow worse over time and may lead to blindness and/or deafness. Many people with the disease have liver problems and some have developed episodes of spontaneous bleeding, particularly around the brain. Some children with the disease learn to walk, while others lack the muscle tone needed for such movement. Similarly many children with the disease learn to talk, though some do not.

How common is Peroxisome Biogenesis Disorder Type 4?

Peroxisomal biogenesis disorders generally affect approximately 1 in 50,000 infants, and approximately 9-16% of cases are attributed to mutations in *PEX6*. In Japan, the incidence of all peroxisomal biogenesis disorders may be lower than 1 in 500,000.

How is Peroxisome Biogenesis Disorder Type 4 treated?

There is no cure for ZSS and there is no standard way to treat it. In children with severe forms of the disease, the main goal of treatment is to protect the child from infections and breathing problems. Physicians can also address certain symptoms as they arise, such as prescribing medication for seizures. Children with milder forms of the disease may benefit from hearing aids, glasses, and/or surgery to remove cataracts. In those who reach school age, special education is likely necessary. Modifications to the child's diet may also be recommended.

What is the prognosis for a person with Peroxisome Biogenesis Disorder Type 4?

ZSS usually reduces a person's lifespan. The prognosis for an infant with ZS is poor. Most pass away within the first year of life without reaching any physical or mental developmental milestones. One study showed that children with NALD or IRD who survive the first year of life have a 77% chance of reaching school age. These children will all have some degree of intellectual disability. Most people with NALD survive into childhood while those with IRD can live into their teens or 20s, and perhaps even longer.

Peroxisome Biogenesis Disorder Type 5

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PEX2.
Exon Sequenced: NM_000318:4.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Peroxisome Biogenesis Disorder Type 5?

Peroxisome biogenesis disorder type 5 (also known as *PEX2*-related Zellweger syndrome spectrum, ZSS) is an inherited disease that stops part of the body's cells, called a peroxisome, from forming correctly. Peroxisomes normally break down waste products in a cell. Not everyone with ZSS will have the same symptoms and some may have more severe symptoms than others. The disease is generally grouped into three subtypes: Zellweger syndrome (the most severe), neonatal adrenoleukodystrophy or NALD (intermediate severity), and infantile Refsum disease or IRD (the mildest form). Individuals with ZSS usually show symptoms of the disease as newborns or as children, but some some people may not have symptoms until they are older.

ZELLWEGER SYNDROME (ZS)

ZS is the most severe form of ZSS. Infants with ZS usually die before their first birthday without reaching many mental or physical developmental milestones. Infants born with ZS have developmental delay leading to severe intellectual disability. They often have seizures and typically have facial deformities such as a high forehead, abnormal ear lobes, a large "soft spot" on the top of their heads, and a small chin. In some cases, the infant cannot move and may not be able to suck or swallow because their muscles are too weak. They often show poor feeding. Their livers are usually enlarged and their skin and the whites of their eyes may have a yellowish tinge (jaundice). Some have bleeding in their digestive tract. Abnormally shaped bones are also common.

NEONATAL ADRENOLEUKODYSTROPHY (NALD) AND INFANTILE REFSUM DISEASE (IRD)

The symptoms of NALD and IRD are less severe than those of ZS, with IRD being the mildest form of the disease. Symptoms in these children often begin in late infancy or early childhood and may progress more slowly. Infants and children with NALD or IRD may have developmental delays with mild to severe intellectual disability. Hearing loss and vision impairment typically grow worse over time and may lead to blindness and/or deafness. Many people with the disease have liver problems and some have developed episodes of spontaneous bleeding, particularly around the brain. Some children with the disease learn to walk, while others lack the muscle tone needed for such movement. Similarly many children with the disease learn to talk, though some do not.

How common is Peroxisome Biogenesis Disorder Type 5?

Peroxisomal biogenesis disorders generally affect approximately 1 in 50,000 infants, and approximately 1-4% of cases are attributed to mutations in *PEX2*. However, the incidence of *PEX2*-related ZSS in the Ashkenazi Jewish population may be higher and the incidence of all peroxisomal biogenesis disorders in Japan may be lower than 1 in 500,000.

How is Peroxisome Biogenesis Disorder Type 5 treated?

There is no cure for ZSS and there is no standard way to treat it. In children with severe forms of the disease, the main goal of treatment is to protect the child from infections and breathing problems. Physicians can also address certain symptoms as they arise, such as prescribing medication for seizures. Children with milder forms of the disease may benefit from hearing aids, glasses, and/or surgery to remove cataracts. In those who reach school age, special education is likely necessary. Modifications to the child's diet may also be recommended.

What is the prognosis for a person with Peroxisome Biogenesis Disorder Type 5?

ZSS usually reduces a person's lifespan. The prognosis for an infant with ZS is poor. Most pass away within the first year of life without reaching any physical or mental developmental milestones. One study showed that children with NALD or IRD who survive the first year of life have a 77% chance of reaching school age. These children will all have some degree of intellectual disability. Most people with NALD survive into childhood while those with IRD can live into their teens or 20s, and perhaps even longer.

Peroxisome Biogenesis Disorder Type 6

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PEX10.
Exons Sequenced: NM_153818:1-6.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Peroxisome Biogenesis Disorder Type 6?

Peroxisome biogenesis disorder type 6 (also known as *PEX10*-related Zellweger syndrome spectrum, ZSS) is an inherited disease that stops part of the body's cells, called a peroxisome, from forming correctly. Peroxisomes normally break down waste products in a cell. Not everyone with ZSS will have the same symptoms and some may have more severe symptoms than others. The disease is generally grouped into three subtypes: Zellweger syndrome or ZS (the most severe), neonatal adrenoleukodystrophy or NALD (intermediate severity), and Infantile Refsum disease or IRD (the mildest form). Individuals with ZSS usually show symptoms of the disease as newborns or as children, but some people may not have symptoms until they are older.

ZELLWEGER SYNDROME (ZS)

ZS is the most severe form of ZSS. Infants with ZS usually die before their first birthday without reaching many mental or physical developmental milestones. Infants born with ZS have developmental delay leading to severe intellectual disability. They often have seizures and typically have facial deformities such as a high forehead, abnormal ear lobes, a large "soft spot" on the top of their heads, and a small chin. In some cases, the infant cannot move and may not be able to suck or swallow because their muscles are too weak. They often show poor feeding. Their livers are usually enlarged and their skin and the whites of their eyes may have a yellowish tinge (jaundice). Some have bleeding in their digestive tract. Abnormally shaped bones are also common.

NEONATAL ADRENOLEUKODYSTROPHY (NALD) AND INFANTILE REFSUM DISEASE (IRD)

The symptoms of NALD and IRD are less severe than those of ZS, with IRD being the mildest form of the disease. Symptoms in these children often begin in late infancy or early childhood and may progress more slowly. Infants and children with NALD or IRD may have developmental delays with mild to severe intellectual disability. Hearing loss and vision impairment typically grow worse over time and may lead to blindness and/or deafness. Many people with the disease have liver problems and some have developed episodes of spontaneous bleeding, particularly around the brain. Some children with the disease learn to walk, while others lack the muscle tone needed for such movement. Similarly many children with the disease learn to talk, though some do not.

How common is Peroxisome Biogenesis Disorder Type 6?

Peroxisomal biogenesis disorders generally affect approximately 1 in 50,000 infants, and approximately 3% of cases are attributed to mutations in *PEX10*. In Japan, the incidence of all peroxisomal biogenesis disorders may be lower than 1 in 500,000.

How is Peroxisome Biogenesis Disorder Type 6 treated?

There is no cure for ZSS and there is no standard way to treat it. In children with severe forms of the disease, the main goal of treatment is to protect the child from infections and breathing problems. Physicians can also address certain symptoms as they arise, such as prescribing medication for seizures. Children with milder forms of the disease may benefit from hearing aids, glasses, and/or surgery to remove cataracts. In those who reach school age, special education is likely necessary. Modifications to the child's diet may also be recommended.

What is the prognosis for a person with Peroxisome Biogenesis Disorder Type 6?

ZSS usually reduces a person's lifespan. The prognosis for an infant with ZS is poor. Most pass away within the first year of life without reaching any physical or mental developmental milestones. One study showed that children with NALD or IRD who survive the first year of life have a 77% chance of reaching school age. These children will all have some degree of intellectual disability. Most people with NALD survive into childhood while those with IRD can live into their teens or 20s, and perhaps even longer.

Phenylalanine Hydroxylase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PAH.
Exons Sequenced: NM_000277:1-13.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Phenylalanine Hydroxylase Deficiency?

Phenylalanine hydroxylase deficiency (PAH deficiency), also called phenylketonuria (PKU), is an inherited disease in which the body cannot properly process the amino acid phenylalanine due to a deficient enzyme called phenylalanine hydroxylase. It is caused by harmful genetic changes in the *PAH* gene. Phenylalanine is found in proteins and other certain foods. If individuals with PAH deficiency do not get treatment, phenylalanine can accumulate to harmful levels, which can cause irreversible intellectual disability, seizures, developmental delay, and behavioral problems.

PAH deficiency causes a spectrum of disorders ranging from severe to nearly asymptomatic. The severity depends on the level of phenylalanine in the blood. It can be difficult to predict how severely affected a child will be based on the harmful genetic changes they carry. Children with any form of PAH deficiency should be evaluated by a specialist immediately after birth.

CLASSIC FORM

Classic PAH deficiency is the most common and severe form. Individuals with classic PAH deficiency produce little to no phenylalanine hydroxylase and are at risk for accumulating high levels of phenylalanine in their blood.

If PAH deficiency is not promptly diagnosed and treated with a special diet, intellectual disability will occur, along with several other symptoms. These include a small head, seizures, behavioral problems, a "mousy" or "musty" odor, abnormal gait, low bone density, and red, itchy skin (eczema). Symptoms are avoidable if the proper diet is instituted shortly after birth and maintained throughout life.

MILD FORMS

Individuals who produce higher amounts of phenylalanine hydroxylase may have milder forms of PAH deficiency but are still at risk of developing the symptoms associated with classic PAH deficiency. Other names for the mild form include variant PKU or non-PKU hyperphenylalaninemia. Though the symptoms may be milder, there is still a risk for impaired mental development if the child's intake of phenylalanine is not monitored. Some individuals with mild PAH deficiency are able to tolerate a normal diet and do not require

treatment. This will vary from person to person and must be determined by a medical professional based on the levels of phenylalanine in the person's blood.

How common is Phenylalanine Hydroxylase Deficiency?

The prevalence of PAH deficiency is 1 in 10,000. It is more common in individuals of Turkish and Irish descent.

How is Phenylalanine Hydroxylase Deficiency treated?

The primary treatment for PAH is a low-protein diet. Given that the degree of enzyme deficiency varies among people with PAH deficiency, treatment must be individualized based on the levels of phenylalanine in the blood. An infant with any form of PAH deficiency should be evaluated immediately after birth to determine whether or not treatment is needed. A blood test can reveal the amount of functioning phenylalanine hydroxylase in the body, indicating the amount of phenylalanine the person can safely consume.

While individuals with classic PAH deficiency must adhere to a strict low-phenylalanine diet, others with milder forms can safely consume small amounts. For some, treatment may not even be necessary. Individuals on a low-protein diet must also take dietary supplements that include essential amino acids but do not include phenylalanine.

Generally speaking, a diet low in protein and free from phenylalanine is essential to preserve mental function in a person with classic PAH deficiency. Phenylalanine-free formulas are available for infants. Maintaining appropriate levels of phenylalanine in the brain can be achieved through blood testing and diet adjustment. Medical professionals must closely supervise this. In most cases, this special diet must be maintained for life.

Individuals with any form of PAH deficiency should avoid consuming aspartame, an artificial sweetener containing phenylalanine.

Women with PAH deficiency who become pregnant must be careful to maintain safe levels of phenylalanine to avoid birth defects in their children. Ideally, this begins before conception.

A few medications are available that the FDA has approved to treat patients with PAH deficiency. These medications have allowed some patients to relax their dietary restrictions. The medications do not work for all PAH patients, and some patients experience unpleasant side effects.

What is the prognosis for a person with Phenylalanine Hydroxylase Deficiency?

If an individual with PAH deficiency is treated early and consistently, the prognosis can be excellent. Many with PAH deficiency have gone on to lead normal lives with average intelligence and a normal lifespan. If treatment does not begin early or is not adequately maintained, a person with a more severe form of PAH deficiency is at risk for severe and irreversible brain damage.

Individuals with mild PAH deficiency may lead a normal life without treatment.

PLP1-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PLP1.
Exons Sequenced: NM_000533:1-7.

Detection Rate	Population
32%	African American
32%	Ashkenazi Jewish
32%	Eastern Asia
32%	Finland
32%	French Canadian or Cajun
32%	Hispanic
32%	Middle East
32%	Native American
32%	Northwestern Europe
32%	Oceania
32%	South Asia
32%	Southeast Asia
32%	Southern Europe
32%	Worldwide

What are PLP1-related Disorders?

PLP1-related disorders are inherited conditions that cause neurological symptoms and belong to a group of conditions called "leukodystrophies." The symptoms individuals with PLP1-related disorders experience are due to a problem with the body's nervous system. PLP1-related disorders are caused by harmful genetic changes (variants) in the *PLP1* gene.

PLP1-related disorders include Pelizaeus-Merzbacher disease and spastic paraplegia type 2, described below. There is wide variability in the severity of PLP1-related disorders, with individuals in the same family even having different forms of the disease.

PELIZAEUS-MERZBACHER DISEASE

The symptoms of Pelizaeus-Merzbacher disease, also called PMD, include abnormal eye movements and problems with movement. There are several forms of PMD, including connatal, classic, and null syndrome.

The connatal form is the most severe and accounts for 10-15% of cases of PMD. People often have symptoms at birth or in early infancy, including low muscle tone (hypotonia), abnormal eye movements (nystagmus), respiratory distress, feeding difficulties, and seizures. People with the connatal form of PMD have intellectual disability, motor delays, muscle stiffness (spasticity), and paralysis. Individuals have limited language abilities and typically cannot walk.

People with the classic form of PMD account for 70% of all cases and usually show symptoms within the first year of life. These include low muscle tone (hypotonia), abnormal eye movements (nystagmus), and delayed motor skills. Motor skills develop throughout childhood, but these skills are lost as the child ages. As the disease progresses, symptoms include stiff muscles (spasticity), problems with balance and coordination (ataxia), involuntary muscle tensing (dystonia), and intellectual disability. People with the classic form of PMD may learn to walk with assistance.

People with the PLP1 null syndrome show more mild symptoms of PMD. These can include mild developmental delays, mild muscle weakness or numbness (peripheral neuropathy), mild muscle stiffness (spasticity), problems with balance and coordination (ataxia), and mild intellectual disabilities.

SPASTIC PARAPLEGIA TYPE 2

The symptoms of spastic paraplegia type 2, also called SPG2, are muscle stiffness (spasticity) that gets worse over time and paralysis (paraplegia). SPG2 occurs in two forms: uncomplicated and complicated. Uncomplicated SPG2 affects the lower limbs only and does not impact cognition. Symptoms usually start between 1 and 5 years of age, but a few people may not develop symptoms until adulthood. Complicated SPG2 affects the lower limbs, upper limbs, and brain, including mild cognitive impairment and bladder control issues. Symptoms typically start between 1 and 5 years of age.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

PLP1-related disorders are X-linked diseases, meaning the *PLP1* gene is on the X chromosome. Males have just one copy of the X chromosome and the *PLP1* gene, while females have two copies. Because of this, PLP1-related disorders primarily affect males. However, some females (known as carrier females) can have symptoms. Symptoms, if they occur, usually occur in adulthood and are mild to moderate. The most common symptoms are those associated with the PLP1 null syndrome or SPG2. Rarely carrier females are diagnosed with Pelizaeus-Merzbacher disease.

How common are PLP1-related Disorders?

The incidence of Pelizaeus-Merzbacher disease is estimated to be between 1 in 200,000 to 1 in 500,000 male births in US. The exact incidence of spastic paraplegia type 2 is unknown. Approximately one hundred individuals have been diagnosed with spastic paraplegia type 2 worldwide. PLP1-related disorders may be more common in individuals from the Czech Republic.

How are PLP1-related Disorders treated?

There is no cure for PLP1-related disorders. Treatment for these conditions is directed at managing an individual's specific symptoms and typically involves a multidisciplinary team, which includes neurologists, orthopedists, respiratory medicine, and gastroenterologists. Common interventions may include medications to treat seizures or to reduce muscle stiffness, physical therapy, and devices to assist with mobility, such as a wheelchair. Speech and swallowing studies may be needed to assess swallowing difficulties, and severe symptoms may require a feeding tube.

What is the prognosis for an individual with PLP1-related Disorders?

The prognosis for people with PLP1-related disorders depends on the severity of symptoms and the specific presentation of the condition. People with the connatal form of PMD die between infancy and the third decade of life. Individuals with other forms of PMD or the complicated form of SPG2 have a shortened lifespan and may die between the third and seventh decade of life. People with uncomplicated SPG2 typically have a normal lifespan.

POLG-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: POLG.
Exons Sequenced: NM_002693:2-23.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What are POLG-related Disorders?

POLG-related disorders are a spectrum of conditions most commonly characterized by muscle weakness, seizures, and liver failure. POLG-related disorders are caused by harmful genetic changes (variants) in the *POLG* gene. The symptoms vary widely, ranging from infantile-onset seizures and liver failure to adult-onset eye weakness (ophthalmoplegia). Individuals in the same family can have different forms of POLG-related disorders. Additionally, some individuals may present with one form of POLG-related disorders and then, over time, develop symptoms of another form. The various conditions associated with the *POLG* gene are described below.

ALPERS-HUTTENLOCHER SYNDROME (AHS)

Alpers-Huttenlocher syndrome (AHS) is the most severe form of POLG-related disorders. The symptoms of AHS usually begin before age four. Individuals can have recurrent seizures that become difficult to treat over time. Progression of the condition also includes abnormal movements, loss of cognitive function, and liver disease.

CHILDHOOD MYOCEREBROHEPATOPATHY SPECTRUM (MCHS)

The symptoms of childhood myocerebrohepatopathy spectrum (MCHS) usually begin before age three. Individuals typically have developmental delays or problems with memory and thinking, liver problems, build-up of lactic acid in the body, and muscle weakness (myopathy) with failure to thrive. Individuals may also experience regular vomiting, hearing loss, problems with the pancreas, and kidney problems (renal tubular acidosis).

ATAXIA NEUROPATHY SPECTRUM (ANS)

Ataxia neuropathy spectrum (ANS) is a group of conditions that includes two specific ones: mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO). Individuals with ANS may start experiencing symptoms anywhere from early childhood to adulthood. Symptoms include problems with balance and coordination (ataxia) and problems with nerve function (neuropathy). Some individuals will have seizures and changes to their brain structure. Other possible symptoms include blindness, sudden jerking of muscles (myoclonus), liver problems, depression, and headaches.

AUTOSOMAL RECESSIVE PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA (ARPEO)

Symptoms of autosomal recessive progressive external ophthalmoplegia (arPEO) typically start in the teens or early adulthood. Symptoms include eye weakness that worsens over time and an inability to exercise for very long. Individuals with arPEO typically do not have other symptoms, but some individuals may go on to develop the ANS type of POLG-related disorders.

MYOCLONIC EPILEPSY MYOPATHY SENSORY ATAXIA (MEMSA)

Symptoms of myoclonic epilepsy myopathy sensory ataxia (MEMSA) usually start in young adulthood. MEMSA includes a spectrum of symptoms, including muscle weakness (myopathy), which may present as exercise intolerance, seizures (epilepsy), and coordination or balance difficulties (ataxia).

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Some carriers of POLG-related disorders may have symptoms of autosomal dominant progressive external ophthalmoplegia (adPEO). Symptoms usually start in adulthood and may include weakness of the eye muscles that worsens over time and exercise intolerance. Individuals may also experience hearing loss, eye problems (cataracts), muscle weakness, facial muscle weakness, changes in their balance and coordination (ataxia), Parkinsonism, depression, and nerve problems (neuropathy). A subset of carriers may additionally experience premature ovarian failure and shrinking of the testicles. The risk for symptoms may depend on the type of harmful change an individual has, but the exact risk for symptoms in carriers is not yet well understood.

Some individuals with adPEO that only have one harmful change in the *POLG* gene may have a harmful change in another gene known as *TWNK* (digenic inheritance). There have only been a few cases of digenic inheritance reported with POLG-related disorders, and more evidence is needed to know the exact risks.

How common are POLG-related Disorders?

The incidence of autosomal recessive POLG-related disorders, which includes all forms of the condition besides adPEO, may be as high as 1 in 10,000 births. The AHS form of POLG-related disorders is reported to be 1 in 51,000.

How are POLG-related Disorders treated?

There is no cure for POLG-related disorders. Treatment is directed at managing an individual's specific symptoms and supportive care. This often means receiving care through a team of specialists. Individuals with the more severe AHS may need a feeding tube, breathing assistance, and often receive palliative care to make them more comfortable. Medications to control seizures, muscle relaxants, and pain medications are often used to treat symptoms. Individuals with POLG-related disorders may need to adjust their medication dosage to avoid harmful side effects.

What is the prognosis for an individual with POLG-related Disorders?

Individuals with the AHS and MCHS forms typically have a shortened lifespan due to the severity of their symptoms.

Individuals with ANS and MEMSA have a later disease onset, and the symptoms worsen slowly over time. Because the severity and progression of symptoms vary from person to person, the impact on life expectancy is specific to each individual.

ArPEO and adPEO are generally adult-onset disorders. The impact on life expectancy depends on if other symptoms develop over time.

POMGNT1-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: POMGNT1.
Exons Sequenced: NM_017739:2-22.

Detection Rate	Population
96%	African American
96%	Ashkenazi Jewish
96%	Eastern Asia
98%	Finland
96%	French Canadian or Cajun
96%	Hispanic
96%	Middle East
96%	Native American
96%	Northwestern Europe
96%	Oceania
96%	South Asia
96%	Southeast Asia
96%	Southern Europe
96%	Worldwide

What are POMGNT1-related Disorders?

POMGNT1-related disorders include multiple conditions known as muscular dystrophy-dystroglycanopathies (MDDG). The various POMGNT1-related disorders, which are caused by mutations in the *POMGNT1* gene, are described below in the order of severity.

MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY TYPE A3 (MDDGA3)

MDDGA3 includes POMGNT1-related Walker-Warburg syndrome (WWS) and muscle-eye-brain disease (MEB). These POMGNT1-related disorders are characterized by significant and progressive muscle weakness, vision problems, changes in brain structure, and severe intellectual and developmental disabilities. In infancy, the child may feel floppy when held. In childhood, the development of motor skills is affected, with many children being unable to sit or walk independently. A wide range of eye problems may be seen in children with MDDGA3, including severe near-sightedness, glaucoma, cataracts, and changes in the retina. As a result, significant vision impairment is common. With both WWS and MEB, changes in the brain are characteristic, including a buildup of fluid around the brain (hydrocephalus) and underdevelopment of the brainstem. A hallmark of WWS, but which may also be seen in MEB, is a brain abnormality known as cobblestone lissencephaly (or type II lissencephaly), where the brain develops a bumpy “cobblestone” appearance and lacks the normal folding structure. Individuals with MDDGA3 may also experience seizures, and significant intellectual disability is expected. The severity of symptoms varies, but most individuals with MDDGA3 are severely affected and their lifespans are significantly shortened.

MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY TYPE B3 (MDDGB3)

Individuals with MDDGB3, which may also be referred to as POMGNT1-related Fukuyama congenital muscular dystrophy (FCMD), experience significant and progressive muscle weakness, although it is generally less severe than with MDDGA3. Some individuals may eventually be able to walk, while others may not. The eye problems in individuals with MDDGB3 are variable, but they also tend to be milder than seen with MDDGA3. In addition, developmental delays, moderate intellectual disability, seizures, and brain changes of variable severity are common among those with this POMGNT1-related disorder.

MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY TYPE C3 (MDDGC3)

MDDGC3 is also referred to as limb-girdle muscular dystrophy (LGMD) type 2O. LGMD2O is the mildest of the POMGNT1-related disorders, and both age of onset and severity of symptoms vary greatly among individuals with this condition. Typically, the only symptom is weakness in the muscles closest to the center of the body, specifically the muscles of the shoulders, upper arms, pelvic area, and thighs. However, the weakness is progressive and may affect mobility. The brain and eyes are not affected in those with LGMD2O, and both intelligence and lifespan are typically normal.

How common are POMGNT1-related Disorders?

The exact prevalence of POMGNT1-related disorders is unknown, although these conditions are considered rare. Certain subtypes, however, may be more common in specific populations. For example, MEB appears to be more common in the Finnish population, where the prevalence is 1 in 50,000.

How are POMGNT1-related Disorders treated?

There is no treatment for the underlying cause of POMGNT1-related disorders. Available treatments address only the symptoms of the condition, such as physical and occupational therapy to improve motor skills and mobility, vision services and glasses to treat eye problems, and the use of medication to control seizures.

What is the prognosis for a person with a POMGNT1-related Disorder?

The prognosis for an individual with a POMGNT1-related disorder varies depending on the severity of the condition. Most individuals with WWS and MEB (MDDGA3) have severe vision loss and intellectual disability, and lifespan is significantly shortened. Individuals with FCMD (MDDGB3) also tend to have significant complications that result in a shortened lifespan. In contrast, those with LGMD2O (MDDGC3) are expected to have normal intelligence and a normal lifespan.

Pompe Disease

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GAA.
Exons Sequenced: NM_000152:2-20.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
98%	Hispanic
>99%	Middle East
>99%	Native American
98%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
98%	Southern Europe
>99%	Worldwide

What Is Pompe Disease?

Pompe disease also called glycogen storage disease type II, is an inherited disorder where the body fails to produce enough alpha-glucosidase (also called maltase), an enzyme needed to break down a type of sugar called glycogen. Without adequate amounts of alpha-glucosidase, glycogen builds up in the body, particularly in the muscles, and damages cells. Pompe disease is caused by mutations in the *GAA* gene. People with Pompe disease have muscle weakness that progresses over time, mainly in the muscles used for movement and breathing. The heart may also be affected. The level of alpha-glucosidase remaining is correlated to the severity of symptoms, the age of onset, and disease progression.

Pompe disease is separated into two forms, the infantile-onset form and the late-onset form. These forms are described below.

INFANTILE-ONSET FORM

Infantile-onset Pompe disease is the most severe form because alpha-glucosidase function is entirely absent. Muscle weakness and poor muscle tone causes infants to have trouble moving, holding up their heads, and feeding. They have trouble gaining weight and grow at a slower pace. Infants also have trouble breathing, which can worsen with lung infections. They typically have enlarged hearts, livers, and tongues. Disease progression is usually rapid, and the most common causes of death are heart or lung failure.

LATE-ONSET FORM

Late-onset Pompe disease is less severe because some alpha-glucosidase is still present. Symptoms start with muscle weakness and breathing problems. Some individuals with late-onset Pompe disease have heart problems but without an enlarged heart. They may eventually lose the ability to walk and require a wheelchair, and they may need mechanical assistance to breathe. Disease progression is more gradual, and the most common cause of death is lung failure.

How Common Is Pompe Disease?

The incidence of Pompe disease is approximately 1 in 100,000. Infantile-onset Pompe disease is the most common form.

How Is Pompe Disease Treated?

The FDA has approved enzyme replacement therapy for both infantile-onset and late-onset Pompe disease. Enzyme replacement therapy can help maintain a healthy heart size and normal heart function and may also help improve muscle tone and strength. Individuals need to follow a protein-rich diet, attend physical therapy, and monitor and treat lung infections.

What Is the Prognosis for a Person with Pompe Disease?

In infantile-onset Pompe disease, symptoms may begin at birth but more often begin in the first few months of life. Patients typically die within the first year of life, although enzyme replacement therapy can now prolong life into early childhood. In late-onset Pompe disease, symptoms can begin at any age from childhood to adulthood, and the lifespan depends on how early symptoms begin. The most common cause of death in individuals with Pompe disease is lung failure.

Pontocerebellar Hypoplasia, RARS2-related

Available Methodologies: targeted genotyping (v1.0) and interpretation of reported variants (v4.0).
Gene: RARS2.
Variants Genotyped (3): Q12R, c.110+5A>G, M1?.

Detection Rate	Population
16%	African American
16%	Ashkenazi Jewish
16%	Eastern Asia
16%	Finland
16%	French Canadian or Cajun
16%	Hispanic
16%	Middle East
16%	Native American
16%	Northwestern Europe
16%	Oceania
16%	South Asia
16%	Southeast Asia
16%	Southern Europe
16%	Worldwide

What is Pontocerebellar Hypoplasia, RARS2-related?

Pontocerebellar hypoplasia (PCH), RARS2-related, also known as pontocerebellar hypoplasia type 6, is an inherited condition that causes part of the brain to not develop correctly. Several genes cause pontocerebellar hypoplasia, and PCH, RARS2-related, is caused by harmful genetic changes (variants) in the *RARS2* gene.

PCH causes underdevelopment (hypoplasia) of certain parts of the brain, including part of the brainstem (the pons) and the area of the brain that controls movement (the cerebellum). Newborns with PCH, RARS-related, generally have weak muscles (hypotonia), breathing problems, feeding difficulties, and seizures that are difficult to treat. Those who survive the newborn period have profound developmental delays and have a small head size (microcephaly) that gets worse over time.

How common is Pontocerebellar Hypoplasia, RARS2-related?

The incidence of PCH is unknown; however, it is considered a rare condition. More than 100 cases have been reported.

How is Pontocerebellar Hypoplasia, RARS2-related, treated?

There is no cure for PCH, RARS2-related. Treatment of the condition is primarily supportive and may include placement of a feeding tube, respiratory support, and medications for seizure control. However, the seizures associated with this condition often do not respond to standard therapies.

What is the prognosis for a person with Pontocerebellar Hypoplasia, RARS2-related?

The prognosis for PCH, RARS2-related, is poor. Because of the severity of the neurological symptoms, most individuals die in infancy or childhood.

Pontocerebellar Hypoplasia, SEPSECS-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SEPSECS.
Exons Sequenced: NM_016955:1-11.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Pontocerebellar Hypoplasia, SEPSECS-related?

Pontocerebellar hypoplasia (PCH), SEPSECS-related, also known as pontocerebellar hypoplasia type 2D, is an inherited condition that causes part of the brain to not develop correctly. Several genes cause pontocerebellar hypoplasia, and PCH, SEPSECS-related, is caused by harmful genetic changes (variants) in the *SEPSECS* gene.

PCH causes underdevelopment (hypoplasia) of certain parts of the brain, including part of the brainstem (the pons) and the area of the brain that controls movement (the cerebellum). The first signs of PCH, SEPSECS-related, are typically apparent at birth or early infancy and may include feeding difficulties, irritability, stiffness (spasticity), and abnormal movements. Other common symptoms include a small head size, seizures, an absence of developmental milestones such as sitting independently and speaking, and severe intellectual disability. PCH, SEPSECS-related, is a progressive disorder, meaning that different parts of the brain will deteriorate, and the symptoms will worsen over time.

How common is Pontocerebellar Hypoplasia, SEPSECS-related?

The incidence of PCH is unknown; however, it is considered a rare condition. More than 100 cases have been reported. PCH, SEPSECS-related, is thought to be more common in individuals of Moroccan or Iraqi Jewish ancestry.

How is Pontocerebellar Hypoplasia, SEPSECS-related, treated?

There is no cure for PCH, SEPSECS-related. Treatment of the condition involves the management of an affected individual's symptoms, which may include medications to control seizures or to help with movement problems or stiffness, as well as the placement of a feeding tube for those with severe feeding difficulties.

What is the prognosis for a person with Pontocerebellar Hypoplasia, SEPSECS-related?

The prognosis for PCH, SEPSECS-related is generally poor. Because of the severity of the neurological symptoms, most individuals die in infancy or childhood.

Pontocerebellar Hypoplasia, VPS53-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: VPS53.
Exons Sequenced: NM_001128159:1-22.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Pontocerebellar Hypoplasia, VPS53-related?

Pontocerebellar hypoplasia (PCH), VPS53-related, also known as pontocerebellar hypoplasia type 2D, is an inherited condition that causes part of the brain to not develop correctly. Several genes cause pontocerebellar hypoplasia, and PCH, VPS53-related, is caused by harmful genetic changes (variants) in the *VPS53* gene.

PCH causes underdevelopment (hypoplasia) of certain parts of the brain, including part of the brainstem (the pons) and the area of the brain that controls movement (the cerebellum). The first signs of PCH, VPS53-related, are typically apparent at birth or early infancy and may include feeding difficulties, irritability, stiffness (spasticity), and abnormal movements. Other common symptoms include a small head size, seizures, an absence of developmental milestones such as sitting independently and speaking, and severe intellectual disability. PCH, VPS53-related, is a progressive disorder, meaning that different parts of the brain will deteriorate, and the symptoms will worsen over time.

How common is Pontocerebellar Hypoplasia, VPS53-related?

The incidence of PCH is unknown; however, it is considered a rare condition. More than 100 cases have been reported. PCH, VPS53-related, is thought to be more common in individuals of Moroccan or Iraqi Jewish ancestry.

How is Pontocerebellar Hypoplasia, VPS53-related, treated?

There is no cure for PCH, VPS53-related. Treatment of the condition involves the management of an affected individual's symptoms, which may include medications to control seizures or to help with movement problems or stiffness, as well as the placement of a feeding tube for those with severe feeding difficulties.

What is the prognosis for a person with Pontocerebellar Hypoplasia, VPS53-related?

The prognosis for PCH, VPS53-related is generally poor. Because of the severity of the neurological symptoms, most individuals die in infancy or childhood.

Pontocerebellar Hypoplasia, VRK1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: VRK1.
Exons Sequenced: NM_003384:2-13.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Pontocerebellar Hypoplasia, VRK1-related?

Pontocerebellar hypoplasia (PCH), VRK1-related, also known as pontocerebellar hypoplasia type 1A, is an inherited condition that causes part of the brain to not develop correctly. Several genes cause pontocerebellar hypoplasia, and PCH, VRK1-related, is caused by harmful genetic changes (variants) in the *VRK1* gene.

PCH causes underdevelopment (hypoplasia) of certain parts of the brain, including part of the brainstem (the pons) and the area of the brain that controls movement (the cerebellum). The first symptoms of PCH, VRK1-related, are typically apparent at birth or early infancy and include a small head size (microcephaly), moderate to severe developmental delays, low muscle tone (hypotonia), and progressive muscle weakness similar to a more common condition known as spinal muscular atrophy. Affected individuals may also have mild to severe intellectual disability, loss of muscle tissue (atrophy), swallowing or feeding difficulties, and problems with breathing. There is a wide variability of symptoms observed in individuals with PCH.

How common is Pontocerebellar Hypoplasia, VRK1-related?

The incidence of PCH is unknown; however, it is considered a rare condition. More than 100 cases have been reported. PCH, VRK1-related, is thought to be more common in individuals of Ashkenazi Jewish or Iranian descent.

How is Pontocerebellar Hypoplasia, VRK1-related, treated?

There is no cure for PCH, VRK1-related. Treatment of the condition involves the management of an affected individual's symptoms, such as physical therapy or using assistive devices to help with mobility and placing a feeding tube for those with significant swallowing problems.

What is the prognosis for a person with Pontocerebellar Hypoplasia, VRK1-related?

Because the condition is so rare, the prognosis for PCH, VRK1-related, is unclear. While death in childhood is considered likely, survival into adulthood has been reported.

Primary Carnitine Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: SLC22A5.
Exons Sequenced: NM_003060:1-10.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Primary Carnitine Deficiency?

Primary carnitine deficiency, caused by mutations in the *SLC22A5* gene, is a condition in which the body cannot properly process fats into energy. This results in a defect in the protein that transports carnitine, a natural substance derived from an amino acid. Without early detection and treatment, the condition can cause permanent brain damage and can be fatal.

If left untreated, primary carnitine deficiency causes a weakening of the heart muscles, leading to a diminished ability to pump blood around the body, and enlargement of the heart muscles (cardiomyopathy). The liver may also become enlarged. This condition can also cause a weakness in skeletal muscles and dangerously low blood sugar (hypoglycemia) that can lead to brain damage. While this brain damage can cause irreversible learning problems or even intellectual disability, the remaining symptoms tend to disappear once an individual begins taking L-carnitine supplements.

Without supplements, an individual with primary carnitine deficiency is particularly vulnerable to "metabolic crisis" (including sleepiness, irritability, fever, nausea, vomiting, and/or low blood sugar) when they go long periods without eating (fasting) or are ill. If left untreated, the metabolic crisis can lead to seizures, swelling of the brain, and other life-threatening symptoms.

How Common Is Primary Carnitine Deficiency?

Primary carnitine deficiency affects approximately 1 in 100,000 newborns. It is more common in Japan, where the incidence is 1 in 40,000, and in the Faroe Islands, where the prevalence is 1 in 300.

How Is Primary Carnitine Deficiency Treated?

Individuals with primary carnitine deficiency will need to take supplements of L-carnitine for their entire lives. If children have begun to experience heart problems or muscle weakness, they can typically reverse those symptoms by taking L-carnitine. A physician may also recommend that individuals with primary carnitine deficiency eat more frequently, even if they do not feel hungry. This is particularly important when they are young and/or sick.

What Is the Prognosis for an Individual with Primary Carnitine Deficiency?

The prognosis for an individual with primary carnitine deficiency is very good when treatment is started at birth. These individuals can typically live normal lives. If treatment is not started early enough, children may experience permanent brain damage, leading to learning difficulties or even intellectual disability. Without any treatment, the disease causes numerous health issues and can be fatal.

Additional Considerations for Carriers

Carriers of fatty-acid oxidation defects, including primary carnitine deficiency, do not typically show symptoms of the disease. However, there may be an increased risk of serious pregnancy complications, particularly in the third trimester, in women carrying a fetus affected with a fatty-acid oxidation defect. A woman whose pregnancy may be affected by a fatty-acid oxidation defect, such as primary carnitine deficiency, should speak with her physician for recommendations and may benefit from consultation with a high-risk physician.

Primary Ciliary Dyskinesia, DNAH5-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: DNAH5.
Exons Sequenced: NM_001369:1-79.

Detection Rate	Population
99%	African American
99%	Ashkenazi Jewish
99%	Eastern Asia
99%	Finland
99%	French Canadian or Cajun
99%	Hispanic
99%	Middle East
99%	Native American
99%	Northwestern Europe
99%	Oceania
99%	South Asia
99%	Southeast Asia
99%	Southern Europe
99%	Worldwide

What is Primary Ciliary Dyskinesia, DNAH5-related?

Primary ciliary dyskinesia (PCD), DNAH5-related, is an inherited condition that causes various symptoms due to problems with cilia. Cilia are very small hair-like structures that stick out from many different cells of the body. Cilia are important for the movement of cells and help in the movement of certain fluids. In people with PCD, their cilia do not move normally, resulting in respiratory problems, infertility, and the misplacement of organs in the body. At least fifty genes are known to cause PCD. PCD, DNAH5-related, is caused by harmful genetic changes (variants) in the *DNAH5* gene.

Cilia line the respiratory tract, and their function is to keep dirt, germs, and mucus out of the lungs. When they do not function normally, it can cause inflammation and infections of the airway and a chronic cough. These symptoms can result in permanent damage to the lungs. Individuals with PCD often have ongoing nasal congestion and wheezing. Sinus infections are common. Most babies with PCD have trouble breathing and require supplemental oxygen shortly after birth. Ear infections are common in children with PCD and can result in permanent damage and hearing loss.

PCD can affect the ability to have children. People with PCD may have a hard time getting pregnant or have an increased risk for ectopic pregnancy.

Cilia play an important part in the placement of internal organs during development. Almost half of all patients with PCD have internal organs in the mirror image of where they are normally located (situs inversus totalis). For example, the heart might be on the right side of the chest rather than the left. Some patients also have abnormalities of internal organs such as the spleen or heart (heterotaxy).

How common is Primary Ciliary Dyskinesia, DNAH5-related?

The exact frequency of PCD is unknown. The estimated incidence of all forms of PCD in the United States is between 1 in 10,000 to 1 in 16,000. Harmful changes in the *DNAH5* gene account for approximately 15-29% of PCD cases.

How is Primary Ciliary Dyskinesia, DNAH5-related treated?

There is no cure for PCD. The treatment is focused on managing the symptoms of the condition. Patients must work with a team of healthcare providers, including pulmonologists, ear, nose, and throat (ENT) providers, cardiologists, fertility specialists, and others as needed. Common treatments include clearing the airways using medication and physical pounding of the chest and back. Coughing is encouraged as a way to help remove irritants in the lungs. Antibiotics are prescribed for ear and lung infections. In severe cases, removal of lung tissue or lung transplantation may be considered. Assisted reproductive technology can be helpful with infertility complications. Problems with other internal organs may not require treatment but should be assessed case-by-case. Individuals with PCD should avoid harmful substances such as smoking and maintain regular physical exercise.

What is the prognosis for a person with Primary Ciliary Dyskinesia, DNAH5-related?

Early, regular treatment can slow the progression of lung disease in PCD and may improve outcomes. The exact lifespan of patients with PCD is unknown.

Primary Ciliary Dyskinesia, DNAI1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: DNAI1.
Exons Sequenced: NM_012144:1-20.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Primary Ciliary Dyskinesia, DNAI1-related?

Primary ciliary dyskinesia (PCD), DNAI1-related, is an inherited condition that causes various symptoms due to problems with cilia. Cilia are very small hair-like structures that stick out from many different cells of the body. Cilia are important for the movement of cells and help in the movement of certain fluids. In people with PCD, their cilia do not move normally, resulting in respiratory problems, infertility, and the misplacement of organs in the body. At least fifty genes are known to cause PCD. PCD, DNAI1-related, is caused by harmful genetic changes (variants) in the *DNAI1* gene.

Cilia line the respiratory tract, and their function is to keep dirt, germs, and mucus out of the lungs. When they do not function normally, it can cause inflammation and infections of the airway and a chronic cough. These symptoms can result in permanent damage to the lungs. Individuals with PCD often have ongoing nasal congestion and wheezing. Sinus infections are common. Most babies with PCD have trouble breathing and require supplemental oxygen shortly after birth. Ear infections are common in children with PCD and can result in permanent damage and hearing loss.

PCD can affect the ability to have children. People with PCD may have a hard time getting pregnant or have an increased risk for ectopic pregnancy.

Cilia play an important part in the placement of internal organs during development. Almost half of all patients with PCD have internal organs in the mirror image of where they are normally located (situs inversus totalis). For example, the heart might be on the right side of the chest rather than the left. Some patients also have abnormalities of internal organs such as the spleen or heart (heterotaxy).

How common is Primary Ciliary Dyskinesia, DNAI1-related?

The exact frequency of PCD is unknown. The estimated incidence of all forms of PCD in the United States is between 1 in 10,000 to 1 in 16,000. Harmful changes in the *DNAI1* gene (PCD1) account for approximately 2-10% of PCD cases.

How is Primary Ciliary Dyskinesia, DNAI1-related treated?

There is no cure for PCD. The treatment is focused on managing the symptoms of the condition. Patients must work with a team of healthcare providers, including pulmonologists, ear, nose, and throat (ENT) providers, cardiologists, fertility specialists, and others as needed. Common treatments include clearing the airways using medication and physical pounding of the chest and back. Coughing is encouraged as a way to help remove irritants in the lungs. Antibiotics are prescribed for ear and lung infections. In severe cases, removal of lung tissue or lung transplantation may be considered. Assisted reproductive technology can be helpful with infertility complications. Problems with other internal organs may not require treatment but should be assessed case-by-case. Individuals with PCD should avoid harmful substances such as smoking and maintain regular physical exercise.

What is the prognosis for a person with Primary Ciliary Dyskinesia, DNAI1-related?

Early, regular treatment can slow the progression of lung disease in PCD and may improve outcomes. The exact lifespan of patients with PCD is unknown.

Primary Ciliary Dyskinesia, DNAI2-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: DNAI2.
Exons Sequenced: NM_023036:2-13.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Primary Ciliary Dyskinesia, DNAI2-related?

Primary ciliary dyskinesia (PCD), DNAI2-related, is an inherited condition that causes various symptoms due to problems with cilia. Cilia are very small hair-like structures that stick out from many different cells of the body. Cilia are important for the movement of cells and help in the movement of certain fluids. In people with PCD, their cilia do not move normally, resulting in respiratory problems, infertility, and the misplacement of organs in the body. At least fifty genes are known to cause PCD. PCD, DNAI2-related, is caused by harmful genetic changes (variants) in the *DNAI2* gene.

Cilia line the respiratory tract, and their function is to keep dirt, germs, and mucus out of the lungs. When they do not function normally, it can cause inflammation and infections of the airway and a chronic cough. These symptoms can result in permanent damage to the lungs. Individuals with PCD often have ongoing nasal congestion and wheezing. Sinus infections are common. Most babies with PCD have trouble breathing and require supplemental oxygen shortly after birth. Ear infections are common in children with PCD and can result in permanent damage and hearing loss.

PCD can affect the ability to have children. People with PCD may have a hard time getting pregnant or have an increased risk for ectopic pregnancy.

Cilia play an important part in the placement of internal organs during development. Almost half of all patients with PCD have internal organs in the mirror image of where they are normally located (situs inversus totalis). For example, the heart might be on the right side of the chest rather than the left. Some patients also have abnormalities of internal organs such as the spleen or heart (heterotaxy).

How common is Primary Ciliary Dyskinesia, DNAI2-related?

The exact frequency of PCD is unknown. The estimated incidence of all forms of PCD in the United States is between 1 in 10,000 to 1 in 16,000. Harmful changes in the *DNAI2* gene account for up to 2% of PCD cases.

How is Primary Ciliary Dyskinesia, DNAI2-related treated?

There is no cure for PCD. The treatment is focused on managing the symptoms of the condition. Patients must work with a team of healthcare providers, including pulmonologists, ear, nose, and throat (ENT) providers, cardiologists, fertility specialists, and others as needed. Common treatments include clearing the airways using medication and physical pounding of the chest and back. Coughing is encouraged as a way to help remove irritants in the lungs. Antibiotics are prescribed for ear and lung infections. In severe cases, removal of lung tissue or lung transplantation may be considered. Assisted reproductive technology can be helpful with infertility complications. Problems with other internal organs may not require treatment but should be assessed case-by-case. Individuals with PCD should avoid harmful substances such as smoking and maintain regular physical exercise.

What is the prognosis for a patient with Primary Ciliary Dyskinesia, DNAI2-related?

Early, regular treatment can slow the progression of lung disease in PCD and may improve outcomes. The exact lifespan of patients with PCD is unknown.

Primary Hyperoxaluria Type 1

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: AGXT.
Exons Sequenced: NM_000030:1-11.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Primary Hyperoxaluria Type 1?

Primary Hyperoxaluria Type 1 (PH1) is an inherited disease caused by mutations in the *AGXT* gene in which the deficiency of a particular liver enzyme causes the body to accumulate excess amounts of a substance called oxalate. Excess oxalate leads to a buildup of insoluble calcium salts in the kidneys and other organs, resulting in progressive organ damage. Accumulation of calcium oxalate in the kidneys may cause kidney stones and progressive kidney failure. Deposits in the urinary tract can lead to difficulty with urination, blood in the urine, and recurrent urinary tract infections. Insoluble calcium deposits in other body tissues can lead to bone pain; vision loss; tingling, numbness, or pain in the extremities; enlargement of the liver and spleen; and problems with the electrical system of the heart (heart block).

The majority of affected individuals develop symptoms of the condition between birth and the age of 25, although later onset is possible. In roughly 20% of affected individuals, symptoms of PH1 develop by six months of age. Patients with this severe form often develop early end-stage kidney disease, occasionally within the first year of life. More than half of individuals with PH1 have disease onset in childhood or adolescence. In those with onset in adolescence, the most common presentation is kidney stones. In contrast, those who present earlier in childhood commonly experience difficulty with urination, blood in the urine, and have recurrent urinary tract infections. Some affected individuals do not show symptoms until their forties or fifties.

How Common Is Primary Hyperoxaluria Type 1?

The overall prevalence of PH1 ranges from 1 in 1,000,000 to 3 in 1,000,000 individuals. It may be more common in Tunisia, Iran, and Israeli Arab and Druze populations.

How Is Primary Hyperoxaluria Type 1 Treated?

Treatments for PH1 are mainly aimed at preventing the formation and deposition of calcium oxalate. Increased fluid intake is extremely important. Calcium-oxalate crystallization inhibitors (i.e., potassium or sodium citrate, orthophosphate, and magnesium) and dietary interventions may be recommended. Supplementation with vitamin B6 (pyridoxine) is effective in approximately 30% of patients.

Early liver transplantation or transplantation of both the liver and kidneys is an option. Because a deficient liver enzyme leads to kidney failure, early liver transplantation may avoid the need for a kidney transplant. Kidney transplantation alone is not sufficient, as the affected liver could destroy the new kidneys as well.

Individuals with PH1 should avoid extremely large doses of vitamin C as well as foods high in oxalate, including chocolate, rhubarb, and starfruit.

What Is the Prognosis for an Individual with Primary Hyperoxaluria Type 1?

The prognosis for an individual with PH1 is variable and depends on how early the disease is detected and treated. Without treatment, PH1 leads to progressive kidney failure and eventually death. For most patients, end-stage kidney disease occurs in the third to the fifth decade. However, approximately 80% of patients with onset in infancy will be diagnosed with end-stage kidney disease by the age of 3. For those with onset in childhood, 50% will develop end-stage kidney disease by the age of 15. Death in the first decade of life is possible for those with early-onset disease.

Following organ transplant, some individuals with PH1 have lived normal or near-normal lifespans.

Primary Hyperoxaluria Type 2

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: GRHPR.
Exons Sequenced: NM_012203:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Primary Hyperoxaluria Type 2?

Primary hyperoxaluria type 2 (PH2), caused by mutations in the *GRHPR* gene, is an inherited disease in which the lack of a particular liver enzyme causes the body to accumulate excess amounts of a substance called oxalate. This oxalate leads to a buildup of insoluble calcium salts in the kidneys and other organs, resulting in progressive organ damage. The disease has similar symptoms to primary hyperoxaluria type 1 (PH1), but PH2 tends to be a less-aggressive form of the disease, even when symptoms start early in life. PH1 and PH2 are caused by different missing liver enzymes.

Symptoms of PH2 typically begin in childhood. Affected individuals are prone to recurrent kidney stones that can lead to kidney failure; however, when this occurs, it is usually later in life. Deposits in the urinary tract can lead to difficulty with urination, blood in the urine, and recurrent urinary tract infections. In addition, PH2 also leaves insoluble calcium deposits in other body tissues that may cause problems with bones, eyes, teeth, nerves, and the heart.

How Common Is Primary Hyperoxaluria Type 2?

The prevalence of PH2 is unknown.

How Is Primary Hyperoxaluria Type 2 Treated?

Treatments for PH2 are aimed at preventing the formation and deposition of calcium oxalate. Increased fluid intake is extremely important. Calcium-oxalate crystallization inhibitors (i.e., potassium or sodium citrate, orthophosphate, and magnesium) and dietary interventions may be recommended.

While individuals with PH2 are less likely to develop kidney failure than those with PH1, organ transplantation remains an option if kidney failure does occur. Because a deficient liver enzyme leads to kidney failure, early liver transplantation may avoid the need to also transplant new kidneys; however, combined liver and kidney transplantation has never yet been used for PH2. Kidney replacement alone is not a sufficient treatment, as the byproducts of the liver could destroy the new kidneys as well.

Individuals with PH2 should avoid extremely large doses of vitamin C as well as foods high in oxalate, including chocolate, rhubarb, and starfruit.

What Is the Prognosis for an Individual with Primary Hyperoxaluria Type 2?

The prognosis for an individual with PH2 is variable and depends on how early the disease is detected and treated. For some individuals with the disease, hydration and medication will be sufficient to control the disease. In other cases, affected individuals will develop kidney failure that may require kidney transplantation. As with PH1, recurrence of calcium deposits has been reported. Generally, individuals with PH2 have a better long-term outcome than those with PH1, and they require fewer surgeries.

Primary Hyperoxaluria Type 3

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: HOGA1.
Exons Sequenced: NM_138413:1-7.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Primary Hyperoxaluria Type 3?

Primary hyperoxaluria (PH) is an inherited disease in which a lack of a particular liver enzyme causes the body to accumulate a substance called oxalate. Excess oxalate leads to a buildup of insoluble calcium salts in the kidneys, which may cause kidney stones and progressive kidney damage. PH type 3 (PH3) is caused by harmful genetic changes (mutations) in the *HOGA1* gene. Approximately 10% of PH cases are of the PH3 subtype. Symptoms of PH3 are similar to those of PH1 and PH2 but are generally milder, with lower urinary oxalate excretion and the earliest onset of the three subtypes. Unlike PH1 and PH2, which can affect other organs, buildup of oxalate in PH3 is only in the kidneys.

People with PH3 are at increased risk of developing kidney stones. Symptoms can develop any time from infancy to adulthood. Approximately 50% of affected individuals develop kidney stones by five years of age, but many experience a decrease in the incidence of kidney stones by adulthood. Some individuals do not develop symptoms until adulthood. Frequent kidney stones can affect kidney function; however, individuals with PH3 rarely progress to kidney failure.

How common is Primary Hyperoxaluria Type 3?

The incidence of PH3 in the population is 1 in 165,000 births. The incidence of PH3 is more common among individuals of Ashkenazi Jewish descent.

How is Primary Hyperoxaluria Type 3 treated?

Treatments for PH3 mainly aim to prevent the formation and deposition of calcium oxalate. Individuals with the condition should drink plenty of water. Intravenous (IV) fluids may be necessary during periods of illness or times of limited fluid intake. A physician may

prescribe medication or vitamins to help lower oxalate levels and inhibit the formation of kidney stones. Dietary restriction of foods high in oxalate may be beneficial. Unlike with other types of PH, individuals with PH3 rarely require dialysis or kidney or liver transplantation.

What is the prognosis for an individual with Primary Hyperoxaluria Type 3?

Individuals with PH3 often have formation of multiple kidney stones. In many individuals with PH3, kidney stone formation decreases as they reach adulthood. Transplants are not necessary in most individuals with PH3, and there are few reports of progression to kidney failure.

Primary Microcephaly, MCPH1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MCPH1.
Exons Sequenced: NM_024596:1-14.

Detection Rate	Population
88%	African American
88%	Ashkenazi Jewish
88%	Eastern Asia
88%	Finland
88%	French Canadian or Cajun
88%	Hispanic
88%	Middle East
88%	Native American
88%	Northwestern Europe
88%	Oceania
88%	South Asia
88%	Southeast Asia
88%	Southern Europe
88%	Worldwide

What is Primary Microcephaly, MCPH1-related?

Primary microcephaly, MCPH1-related, also referred to as MCPH, is a rare condition that causes individuals to be born with a small head size (microcephaly). There are several genes that can cause small head size, however, primary microcephaly, MCPH1-related, is caused by harmful genetic changes (variants) in the *MCPH1* gene. Individuals with MCPH will have intellectual disability that can be mild or severe. They may also have developmental delays, including delayed speech and language skills. Motor skills may also be delayed. Other possible symptoms include shorter-than-average height and seizures. In general, individuals with MCPH do not have other significant birth defects or health issues.

How common is Primary Microcephaly, MCPH1-related?

The exact incidence of primary microcephaly, MCPH1-related, is unknown but is considered very rare. About 200 individuals have been reported in the literature. The condition may be more common in individuals of Pakistani descent.

How is Primary Microcephaly, MCPH1-related treated?

There is no cure for primary microcephaly, MCPH1-related. Early intervention and supportive therapies may assist with learning difficulties and motor delay.

What is the prognosis for an individual with Primary Microcephaly, MCPH1-related?

Because the condition is so rare, the estimated lifespan for individuals with MCPH is not well understood. Most individuals will have some sort of intellectual and developmental delay and may need support throughout their lives.

Primary Trimethylaminuria

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: FMO3.
Exons Sequenced: NM_001002294:2-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Primary Trimethylaminuria?

Primary trimethylaminuria (TMAU), also known as fish odor syndrome, is a condition characterized by a distinctive body odor that smells like rotten fish. It is caused by harmful genetic changes (variants) in the *FMO3* gene. Individuals with TMAU lack an enzyme that is necessary to break down numerous compounds, including trimethylamine (TMA), which has a strong odor and is most commonly found in certain foods like seafood, eggs, cabbages, and legumes.

The main feature of this condition is the strong, fishy odor released by bodily fluids. This symptom typically develops in infancy or early childhood and may worsen during puberty. Most individuals with the condition experience intermittent body odor, however some will have a strong odor all of the time. The odor may become more pronounced during physical activity or stress and is particularly apparent after consuming foods rich in choline and lecithin. The odor is often more severe during hormonal fluctuations such as when using oral contraceptives or around menstruation and menopause.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Carriers of trimethylaminuria typically do not have symptoms but may have mild episodes of fish odor, particularly after eating trigger foods.

How common is Primary Trimethylaminuria?

The exact incidence of trimethylaminuria is unknown but studies estimate the incidence between 1 in 40,000 and 1 in 200,000 individuals. Trimethylaminuria may be more common among individuals from Jordan, Ecuador and New Guinea.

How is Primary Trimethylaminuria treated?

There is no cure for trimethylaminuria. Treatment for the condition is directed at minimizing the intensity and frequency of the odor and its impact on daily life. This often includes dietary restriction of foods that contain TMA and its precursors, including choline, lecithin, and TMAO. These foods include milk, eggs, liver, kidneys, peas, beans, peanuts, soy products, brussels sprouts, broccoli, cabbage, cauliflower, fish, cephalopods, and crustaceans. However, individuals with the condition should still meet the recommended daily intake of choline and folate. Individuals with the condition should not restrict choline during pregnancy or lactation as it is important for proper brain development of the fetus.

Other treatments for trimethylaminuria include using odor-neutralizing acidic soaps and body lotions, taking vitamin B2 (riboflavin) supplements to increase enzyme activity, and supplementing with activated charcoal and copper chlorophyllin to help lower TMA levels. Low doses of antibiotics may also be prescribed to reduce gut bacteria and reduce TMA levels. Affected individuals may also want to avoid activities that induce sweating, such as heavy exercise and stressful situations.

Affected individuals may also be advised to avoid certain medications, such as clozapine, deprenyl, ranitidine, tamoxifen, benzydamine, and sulindac as these medications can worsen the condition.

What is the prognosis for an individual with Primary Trimethylaminuria?

Trimethylaminuria does not affect life expectancy, and individuals have normal, healthy lives. However, an individual's quality of life may vary depending on the intensity of their odor and the effectiveness of treatment. Children may experience bullying and/or feelings of shame and embarrassment, and adults may avoid contact with people, leading to loneliness, depression, and trouble initiating or maintaining relationships.

Prothrombin Thrombophilia

Available Methodologies: targeted genotyping (v1.0) and interpretation of reported variants (v4.0).
Gene: F2.
Variant Genotyped (1): G20210A.

What Is Prothrombin Thrombophilia?

Prothrombin thrombophilia is an inherited clotting disorder that causes an increased risk of abnormal blood clots known as venous thromboembolism (VTE). One common type of VTE is deep vein thrombosis, clots occurring most often in the legs. Clots in other locations of the body are possible but less common. These clots are caused by an overproduction of a clot-promoting protein called prothrombin. Clotting episodes can be life-threatening, but if detected they are treatable.

While prothrombin thrombophilia increases clotting risks, the effects of the disease vary greatly from individual to individual. Many individuals with the disease never develop abnormal clotting, while some experience repeated clots before the age of 30.

Individuals with prothrombin thrombophilia will be more likely to develop a clot if they also have another clotting disorder such as factor V Leiden thrombophilia, protein S deficiency, or hyperhomocysteinemia. In women, oral contraceptives, hormone replacement therapy, and pregnancy can all increase the risk of developing a VTE. Air travel or sitting for a very long time may also increase the risk for a VTE.

Prothrombin thrombophilia is caused by mutations in the *F2* gene. The most common mutation is called G20210A. The risk of developing a VTE is influenced by whether an individual is heterozygous for the condition (that is, has one copy with the G20210A mutation and one copy with no mutation) or is homozygous, meaning he or she has two mutated copies.

One copy of the mutation (heterozygous)

Overall, adults with one copy of the G20210A mutation are two to four times more likely to develop a clot than the general population. As children, their risks are three to four times greater, although most individuals with prothrombin thrombophilia will not develop abnormal clots as children.

Pregnant women with one copy of the G20210A mutation have a 3 to 15 times greater risk of developing a VTE than the general population. Some studies have indicated that pregnant women with the disease are at greater risk for pregnancy loss and other complications. However, studies on this topic have shown conflicting results. In general, this risk is very small unless the woman has other risk factors. Overall, the chances for a successful pregnancy for women with one copy of the G20210A mutation are high.

Women heterozygous for prothrombin thrombophilia who take oral contraceptives have a 16 to 59 times greater risk of developing VTE than the general population. In these women, 60% of VTEs are associated with oral contraceptive use.

Two copies of the mutation (homozygous)

In general, the VTE risks for homozygotes are presumed higher than the risks for heterozygotes (listed above), but the exact numbers are not known.

Limited studies have indicated that women who are homozygous for prothrombin thrombophilia who also take oral contraceptives have a 17 to 86 times greater risk of developing a VTE.

How Common Is Prothrombin Thrombophilia?

In the United States, 2 to 5% of the Caucasian population and 0.3% of the black population have one copy of the G20210A mutation. In Southern Europe, 3% of the population has one copy of the mutation, while in Northern Europe, that figure falls to 1.7%. The mutation is extremely rare in Asian, African, and Native American populations.

Roughly 1 in 10,000 individuals have two copies of the G20210A mutation in populations where the mutation is prevalent.

How Is Prothrombin Thrombophilia Treated?

Until an abnormal clotting incident occurs, no specific treatment is needed for individuals with prothrombin thrombophilia. Women with disease-causing mutations should avoid oral contraceptives and hormone replacement therapy. There is not yet any consensus on how pregnant women with the disease should be treated, but if a woman has had a previous abnormal clot she may be monitored closely during pregnancy.

Physicians will treat any clotting abnormality according to standard protocols, typically with anticoagulant medication such as heparin or warfarin. Individuals with more than one abnormal clot may be advised by their doctor to take these drugs preventatively, but the risk of clotting must be weighed against the risk of excessive bleeding caused by the drugs. Graduated compression stockings may also be recommended following a VTE.

A physician may recommend that someone with prothrombin thrombophilia be tested for additional clotting disorders, as these can greatly elevate the risk for abnormal clotting.

What Is the Prognosis for an Individual with Prothrombin Thrombophilia?

The prognosis for an individual with prothrombin thrombophilia is generally good. Most will not ever have a clotting episode, while those who do have one typically experience these episodes in adulthood. Clotting episodes can be life-threatening, but if detected, they are treatable.

Pseudocholinesterase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: BCHE.
Exons Sequenced: NM_000055:2-4.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Pseudocholinesterase Deficiency?

Pseudocholinesterase deficiency is a condition that causes individuals to have problems with certain anesthesia medications. It is caused by harmful genetic changes (variants) in the *BCHE* gene. Individuals with pseudocholinesterase deficiency do not have enough of an enzyme called pseudocholinesterase, which is needed to break down medications such as succinylcholine or mivacurium properly. These medications are often used during surgery to help relax muscles in the body. Individuals who have pseudocholinesterase deficiency may have muscle paralysis for a longer time than most people after surgery. They may also stop breathing after taking these medications. Individuals usually do not know that they have pseudocholinesterase deficiency until they experience symptoms after receiving anesthesia. While the condition is not inherited in an X-linked manner, biological males are more often affected than biological females.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Carriers generally do not have symptoms, but they may sometimes experience a short period of breathing paralysis following anesthesia.

How common is Pseudocholinesterase Deficiency?

The incidence of pseudocholinesterase deficiency is approximately 1 in 3,000 individuals worldwide. The condition is more common in Native Alaskans and Persian Jews.

How is Pseudocholinesterase Deficiency treated?

Individuals with pseudocholinesterase deficiency can carry a medical ID so that doctors and nurses are aware. Physicians may choose to use alternative medications during anesthesia. If someone with pseudocholinesterase deficiency receives succinylcholine or mivacurium, they will need to be carefully monitored and may need to use a breathing machine (ventilator) until they recover from paralysis.

What is the prognosis for an individual with Pseudocholinesterase Deficiency?

Individuals can live their entire lives with pseudocholinesterase deficiency without experiencing any impact on their health unless they are exposed to anesthesia. The prognosis is generally good, especially with diagnosis and careful monitoring during surgical procedures.

Pycnodysostosis

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CTSK.
Exons Sequenced: NM_000396:2-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Pycnodysostosis?

Pycnodysostosis, caused by mutations in the *CTSK* gene, is an inherited disorder that causes the bones to be abnormally dense (osteopetrosis). Individuals with this condition tend to be shorter than average and have certain bone deformities such as a curved spine (scoliosis), malformed collarbone, delayed closure of the skull plates, or shortened finger bones. The bones of individuals tend to be dense, but are brittle and can break easily while fractures of the legs, feet, jaws, and collar bones are common.

Pycnodysostosis can cause some characteristic facial features including a prominent nose, protruding forehead, prominent eyes, and small jaw. Sometimes the whites of eyes in individuals with pycnodysostosis can be tinted blue. Children with pycnodysostosis may have teeth that are late to grow, may be missing or irregular, and are prone to cavities.

How Common Is Pycnodysostosis?

Pycnodysostosis is a very rare disease. The prevalence of the disease is estimated to be rarer than 1 in 1,000,000 individuals.

How Is Pycnodysostosis Treated?

There is no treatment for the underlying cause of pycnodysostosis. Since the disease is so rare, treatments and therapies tend to be individualized. Some physicians may recommend injecting growth hormones to increase the height in individuals with pycnodysostosis. Surgery can help correct deformities of the face and jaw. Good dental hygiene and frequent visits to a dentist can be helpful as individuals with pycnodysostosis are prone to cavities and may be missing teeth. Orthodontia is also an option for improving the overall look of the teeth.

It is suggested that contact sports be avoided in order to minimize the chance of fracturing brittle bones. Exercise should be limited to low-impact sports such as swimming or cycling.

What Is the Prognosis for an Individual with Pycnodysostosis?

The prognosis for an individual with pycnodysostosis is generally good. While an individual with the condition may have a different appearance from individuals without the condition and be more prone to fractures, the lifespan is normal or near-normal with care.

Pyruvate Carboxylase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PC.
Exons Sequenced: NM_000920:3-22.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Pyruvate Carboxylase Deficiency?

Pyruvate carboxylase deficiency (PC deficiency), caused by harmful genetic changes (mutations) in the *PC* gene, is an inherited disease that leads to a buildup of toxic substances in the blood. This buildup can affect the nervous system and cause organ damage. There are three different forms of this condition.

INFANTILE FORM (TYPE A)

The infantile form of PC deficiency presents with developmental delay, failure to thrive, low muscle tone, and seizures. The build up of lactic acid (lactic acidosis) can cause vomiting and difficulty breathing, especially after illness or periods of fasting. Type A is most common in North America, specifically in those of Native American ancestry.

SEVERE NEONATAL FORM (TYPE B)

The severe neonatal form of PC deficiency presents shortly after birth with low blood sugar, severe lactic acidosis, enlarged liver, seizures, low muscle tone, and abnormal movements. Type B is most common in people of European descent, especially those originating from France, England, and Germany.

INTERMITTENT/BENIGN FORM (TYPE C)

The intermittent/benign form of PC deficiency is the mildest form of the condition. Affected individuals may have normal neurologic development or mild delays and slightly increased levels of lactic acid in the blood.

How common is Pyruvate Carboxylase Deficiency?

The overall incidence of PC deficiency is 1 in 250,000 births. The disease rate of Type A is most frequent in the Native American population (Algonquin-speaking tribes). Type C has only been reported in a small number of individuals in general.

How is Pyruvate Carboxylase Deficiency treated?

There is no cure for PC deficiency, but management involves a high-carbohydrate, high-protein diet, hydration, and correction of the biochemical abnormalities via supplementation. Fasting and a high-fat, low-carbohydrate (ketogenic) diet should be avoided, as this can worsen symptoms.

What is the prognosis for an individual with Pyruvate Carboxylase Deficiency?

Children with the infantile form of PC deficiency generally live into early childhood, while the severe neonatal form leads to death within the first few months of life. Individuals with the intermittent/benign form are expected to live a normal lifespan with limited symptoms.

RAPSN-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: RAPSN.
Exons Sequenced: NM_005055:1-8.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What are RAPSN-related Disorders?

RAPSN-related disorders are inherited disorders caused by disruption of the normal communication between nerve cells and muscle cells. They are caused by harmful genetic changes in the *RAPSN* gene.

CONGENITAL MYASTHENIC SYNDROME 11 (CMS11)

Congenital myasthenic syndrome 11 (CMS11) is the most common RAPSN-related disorder. Many children with CMS11 are diagnosed at birth or in early childhood. Affected individuals can be born with stiff joints that can be stuck in one position (arthrogryposis), poor sucking reflex, muscle weakness, a weak cry, and breathing difficulties. Infants can have feeding difficulties due to the poor sucking reflex and low muscle tone (hypotonia). They can also have difficult or labored breathing and temporary interruptions of breathing (apnea), especially if they are sick. Weak facial muscles are common and many individuals have droopy eyelids (ptosis). Delays in motor development (such as crawling and walking) are also common. The severity of symptoms can vary greatly between individuals and tends to worsen with illness or physical exertion.

FETAL AKINESIA DEFORMATION SEQUENCE (FADS)

Fetal akinesia deformation sequence (FADS) is a rarer RAPSN-related disorder. FADS causes severe prenatal restriction of movement (fetal akinesia), poor fetal growth (IUGR), underdevelopment of the lungs (pulmonary hypoplasia), limitation of joint movement (arthrogryposis) and facial differences. Many affected pregnancies result in premature delivery or stillbirth.

How common are RAPSN-related Disorders?

The exact incidence of RAPSN-related disorders is unknown. CMS11 has an estimated incidence of at least 2.5/1,000,000 individuals in the United Kingdom, but the global incidence is not known. FADS is rare and the incidence has not been reported.

How are RAPSN-related Disorders treated?

There is no cure for RAPSN-related disorders. Treatments for the conditions are directed at managing the specific symptoms an individual has. This often means receiving care through a team of specialists that may include physicians, speech pathologists, occupational therapists, physical therapists, and social workers.

In patients with CMS11, medication can often improve or stabilize the symptoms. For children who develop breathing difficulties, breathing machines and apnea monitors are often used. Stiff joints are often helped with physical therapy.

For those affected with FADS, treatment is supportive. Some families may opt to pursue palliative care, which focuses on improving quality of life and may have limited medical intervention.

What is the prognosis for an individual with RAPSN-related Disorders?

The exact lifespan of patients with CMS11 is unknown. Severe breathing problems can cause a lack of oxygen to the brain and can be life-threatening. With medication, symptoms may stabilize or improve. However, illness or physical exertion can cause exacerbations.

FADS causes stillbirth in about 30% of affected pregnancies. For surviving individuals, complications from underdevelopment of the lungs significantly shorten lifespan, with death often occurring during infancy.

Refsum Disease, PHYH-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PHYH.
Exons Sequenced: NM_006214:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Refsum Disease, PHYH-related?

Refsum disease, PHYH-related, or "classic Refsum disease," is an inherited condition that can cause vision problems, difficulty with balance and coordination, and other symptoms. The condition causes part of the body's cells (the peroxisome) not to work correctly. This causes a build-up of the fatty acid phytanic acid. This build-up can cause damage to the nerves and other parts of the body. The condition is caused by harmful genetic changes (variants) in the *PHYH* gene.

The condition is sometimes called "adult Refsum disease;" however, this is deceptive because symptoms can start anywhere between seven months of age and the fifth decade. Most individuals start having symptoms before age 20. The primary symptom is the progressive degeneration of cells in part of the eye (retina), known as retinitis pigmentosa (RP). RP initially causes night blindness and a loss of side (peripheral) vision. Over time, the field of vision narrows until only central vision remains (tunnel vision). Eventually, RP can lead to complete blindness. Affected individuals may also lose their sense of smell (anosmia) and have trouble with sensation and coordination (polyneuropathy). Other common symptoms include hearing loss, problems with balance and coordination (ataxia), dry, scaly skin (ichthyosis), shortness of certain bones in the hands and feet, and an abnormal heart rhythm (cardiac arrhythmia). Not every individual experiences all symptoms, which may vary between affected individuals, even within the same family.

How common is Refsum Disease, PHYH-related?

The incidence of Refsum disease, PHYH-related, is unknown but is considered a rare disorder. The condition may go undetected for several years before diagnosis, making it difficult to determine the exact incidence.

How is Refsum Disease, PHYH-related, treated?

There is no cure for the underlying cause of Refsum disease, PHYH-related. Treatment involves avoiding foods high in phytanic acid, such as dairy products, beef, and some seafood. Individuals must also avoid certain medications, such as ibuprofen, maintain a high-calorie diet, and avoid losing weight or going too long without eating (fasting). The phytanic acid levels of pregnant individuals with Refsum disease, PHYH-related, must be closely monitored. Some individuals may require the removal of phytanic acid in the blood by removing and replacing blood plasma (plasmapheresis). Some symptoms can improve with treatment.

What is the prognosis for a person with Refsum Disease, PHYH-related?

Most individuals can survive into the fourth or fifth decade of life or beyond with treatment. Treatment may slow progression; however, it cannot reverse the loss of hearing, vision, and sense of smell. Heart rhythm abnormalities may shorten lifespan. With strict adherence to treatment, most individuals have a good prognosis.

Retinitis Pigmentosa, CERKL-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CERKL.
Exons Sequenced: NM_001030311:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Retinitis Pigmentosa, CERKL-related?

Retinitis pigmentosa, CERKL-related (RP, CERKL-related), also known as retinitis pigmentosa type 26, is one of many described types of retinitis pigmentosa. RP, CERKL-related, is caused by harmful genetic changes (variants) in the *CERKL* gene. RP affects the part of the eye called the retina, which contains cells that sense light (photoreceptors). Individuals with RP, CERKL-related, may have onset of symptoms anywhere from childhood to adulthood. The first sign of RP is often difficulty seeing in dim light (night blindness). As RP progresses, individuals may experience vision loss on the sides of the head (peripheral), resulting in "tunnel vision." Eventually, individuals lose central vision. Complete blindness is uncommon but may occur. RP, CERKL-related, is a nonsyndromic condition, meaning there are no other symptoms or systems of the body involved beyond the retina of the eye.

How common is Retinitis Pigmentosa, CERKL-related?

RP, CERKL-related, is a rare type of retinitis pigmentosa. The prevalence of retinitis pigmentosa due to all causes is about 1 in 5000 individuals. Less than 1% of cases of RP are caused by harmful changes in the *CERKL* gene. The exact prevalence is unknown.

How is Retinitis Pigmentosa, CERKL-related treated?

There is no cure for RP, CERKL-related. Sunglasses that block harmful rays from the sun (UV-A and UV-B) are recommended. Other optical aids may increase eye comfort. Therapy with vitamin A palmitate may slow retinal degeneration for some. Individuals may also benefit from counseling and lifestyle therapy to help manage their progressive vision loss.

What is the prognosis for a person with Retinitis Pigmentosa, CERKL-related?

While people with RP, CERKL-related, have progressive vision loss, it does not affect lifespan and does not affect any other part of the body. There are state-level services for the blind or those with progressive eye disorders to help increase a person's quality of life.

Retinitis Pigmentosa, DHDDS-related

Available Methodologies: targeted genotyping (v1.0) and interpretation of reported variants (v4.0).
Gene: DHDDS.
Variant Genotyped (1): K42E.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Retinitis Pigmentosa, DHDDS-related?

Retinitis pigmentosa, DHDDS-related (RP, DHDDS-related), also known as retinitis pigmentosa type 59, is one of many described types of retinitis pigmentosa. RP, DHDDS-related, is caused by harmful genetic changes (variants) in the *DHDDS* gene. RP affects the part of the eye called the retina, which contains cells that sense light (photoreceptors). Individuals with RP, DHDDS-related, may have onset of symptoms anywhere from childhood to adulthood. However, most individuals with RP, DHDDS-related, are diagnosed after age 20. The first sign of RP is often difficulty seeing in dim light (night blindness). As RP progresses, individuals may experience vision loss on the sides of the head (peripheral), resulting in "tunnel vision." Eventually, individuals lose central vision. Complete blindness is uncommon but may occur. RP, DHDDS-related, is a nonsyndromic condition, meaning there are no other symptoms or systems of the body involved beyond the retina of the eye.

How common is Retinitis Pigmentosa, DHDDS-related?

The prevalence of RP due to all causes is about 1 in 5000 individuals worldwide. RP caused by harmful changes in the *DHDDS* gene is estimated to cause less than one percent of all cases of RP and may be more common in individuals of Ashkenazi Jewish descent.

How is Retinitis Pigmentosa, DHDDS-related, treated?

There is no cure for RP, DHDDS-related. Sunglasses that block harmful rays from the sun (UV-A and UV-B) are recommended. Other optical aids may increase eye comfort. Therapy with vitamin A palmitate may slow retinal degeneration for some. Individuals may also benefit from counseling and lifestyle therapy to help manage their progressive vision loss.

What is the prognosis for a person with Retinitis Pigmentosa, DHDDS-related?

In general, people with retinitis pigmentosa have progressive vision loss, resulting in legal blindness at the later stages of the disease. RP does not affect lifespan or any other part of the body. There are state-level services for the blind or those with progressive eye disorders to help increase a person's quality of life.

Retinitis Pigmentosa, EYS-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: EYS.
Exons Sequenced: NM_001142800:4-43.

Detection Rate	Population
96%	African American
>99%	Ashkenazi Jewish
96%	Eastern Asia
96%	Finland
96%	French Canadian or Cajun
96%	Hispanic
96%	Middle East
96%	Native American
98%	Northwestern Europe
96%	Oceania
96%	South Asia
96%	Southeast Asia
>99%	Southern Europe
96%	Worldwide

What is Retinitis Pigmentosa, EYS-related?

Retinitis pigmentosa, EYS-related (RP, EYS-related), also known as retinitis pigmentosa type 25, is one of many described types of retinitis pigmentosa. RP, EYS-related, is caused by harmful genetic changes (variants) in the *EYS* gene. RP affects the part of the eye called the retina, which contains cells that sense light (photoreceptors). Individuals with RP, EYS-related, may have onset of symptoms anywhere from childhood to adulthood. However, most individuals with RP, EYS-related, are diagnosed after age 20. The first sign of RP is often difficulty seeing in dim light (night blindness). As RP progresses, individuals may experience vision loss on the sides of the head (peripheral), resulting in "tunnel vision." Eventually, individuals lose central vision. Complete blindness is uncommon but may occur. RP, EYS-related, is a nonsyndromic condition, meaning there are no other symptoms or systems of the body involved beyond the retina of the eye.

How common is Retinitis Pigmentosa, EYS-related?

The prevalence of RP due to all causes is about 1 in 5000 individuals worldwide. Approximately 5% of cases of RP worldwide are caused by harmful changes in the *EYS* gene. However, some populations have a higher incidence of RP, EYS-related. Up to 30% of cases of RP in Spain and over 20% of cases in Japan are due to harmful changes in the *EYS* gene.

How is Retinitis Pigmentosa, EYS-related treated?

There is no cure for RP, EYS-related. Sunglasses that block harmful rays from the sun (UV-A and UV-B) are recommended. Other optical aids may increase eye comfort. Therapy with vitamin A palmitate may slow retinal degeneration for some. Individuals may also benefit from counseling and lifestyle therapy to help manage their progressive vision loss.

What is the prognosis for a person with Retinitis Pigmentosa, EYS-related?

While people with RP, EYS-related, have progressive vision loss, it does not affect lifespan and does not affect any other part of the body. There are state-level services for the blind or those with progressive eye disorders to help increase a person's quality of life.

Retinitis Pigmentosa, FAM161A-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: FAM161A.
Exons Sequenced: NM_001201543:1-7.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Retinitis Pigmentosa, FAM161A-related?

Retinitis pigmentosa, FAM161A-related (RP, FAM161A-related), also known as retinitis pigmentosa type 28, is one of many described types of retinitis pigmentosa. RP, FAM161A-related, is caused by harmful genetic changes (variants) in the *FAM161A* gene. RP affects the part of the eye called the retina, which contains cells that sense light (photoreceptors). The first sign of RP is often difficulty seeing in dim light (night blindness). As RP progresses, individuals may experience vision loss on the sides of the head (peripheral), resulting in "tunnel vision." Eventually, individuals lose central vision. Symptoms can start anywhere from childhood to adulthood, but most notice night blindness before age 20. Severe visual handicap usually occurs in the 50s, and legal blindness occurs in the 60s or 70s. Complete blindness is uncommon but may occur. RP, FAM161A-related, is a nonsyndromic condition, meaning there are no other symptoms or systems of the body involved beyond the retina of the eye.

How common is Retinitis Pigmentosa, FAM161A-related?

RP, FAM161A-related, is a rare type of retinitis pigmentosa. The prevalence of retinitis pigmentosa due to all causes is about 1 in 5000 individuals. Less than 1% of cases of RP are caused by harmful changes in the *FAM161A* gene in the general population. However, harmful changes in the *FAM161A* gene cause approximately 12% of cases of recessive RP in individuals of Israeli and Palestinian descent.

How is Retinitis Pigmentosa, FAM161A-related, treated?

There is no cure for RP, FAM161A-related. Sunglasses that block harmful rays from the sun (UV-A and UV-B) are recommended. Other optical aids may increase eye comfort. Therapy with vitamin A palmitate may slow retinal degeneration for some. Individuals may also benefit from counseling and lifestyle therapy to help manage their progressive vision loss.

What is the prognosis for a person with Retinitis Pigmentosa, FAM161A-related?

While people with RP, FAM161A-related, have progressive vision loss, it does not affect lifespan and does not affect any other part of the body. There are state-level services for the blind or those with progressive eye disorders to help increase a person's quality of life.

Rhizomelic Chondrodysplasia Punctata Type 1

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PEX7.
Exons Sequenced: NM_000288:1-10.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Rhizomelic Chondrodysplasia Punctata Type 1?

Rhizomelic chondrodysplasia punctata type 1 (RCDP1) is an inherited disease that causes small physical size, certain characteristic bone problems, mental disability, and cataracts. Most children with the classic form of RCDP1 do not live beyond the age of 10, and some will die in infancy. There is also a mild form of the disease, but it is less common.

CLASSIC FORM

Children with the classic form of RCDP1 typically have shortened arm and leg bones. They are often born smaller than average and fail to grow at the expected rate, leaving them much smaller than normal children. The cartilage in children with RCDP1 typically has round or oval areas of calcification. Affected children have stiff, painful joints which may lose the ability to bend normally. They will also have characteristic facial features.

Children with this disease are often severely mentally disabled and fail to develop skills beyond the level of a normal six month-old. The majority also develop seizures.

Other symptoms that may be seen include rough and scaly skin, a cleft palate, and malformations of the spinal column. These children usually develop cataracts early in life that obscure their vision. Most have recurrent lung infections which can be life-threatening.

MILD FORM

In the mild form of the disease, mental and growth disability are less severe. Some have shortened limbs while others do not. All children with this form of the disease have areas of calcification in their cartilage and cataracts.

How common is Rhizomelic Chondrodysplasia Punctata Type 1?

Fewer than 1 in 100,000 infants worldwide is affected by RCDP1. The disease affects children of every ethnicity, however one common mutation known as L292X is most common in Caucasians of Northern European descent.

How is Rhizomelic Chondrodysplasia Punctata Type 1 treated?

There is no cure for RCDP1. Surgery to remove cataracts can restore some vision. Physical therapy may help preserve movement. Other bone surgery may also be helpful. Many children with the disease require a feeding tube. Their lung function must be closely monitored to avoid infection and choking hazards.

Those with milder forms of the disease may benefit from a specialized diet.

What is the prognosis for a person with Rhizomelic Chondrodysplasia Punctata Type 1?

The prognosis for a child with the classic form of RCDP1 is poor. Many die in the first or second year of life, and few survive beyond the age of 10. Breathing problems are often the cause of death.

Those with milder forms of the disease may live longer, however there have been relatively few known cases with which to determine average longevity.

RTEL1-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: RTEL1.
Exons Sequenced: NM_001283009:2-34.

Detection Rate	Population
99%	African American
99%	Ashkenazi Jewish
99%	Eastern Asia
99%	Finland
99%	French Canadian or Cajun
99%	Hispanic
99%	Middle East
99%	Native American
99%	Northwestern Europe
99%	Oceania
99%	South Asia
99%	Southeast Asia
99%	Southern Europe
99%	Worldwide

What are RTEL1-related Disorders?

Harmful genetic changes (mutations) in the *RTEL1* gene are associated with two disorders called Hoyeraal-Hreidarsson syndrome (HHS) and dyskeratosis congenita (DKC). These inherited disorders impair the proper maintenance of chromosome ends (telomeres) and DNA repair, leading to a wide variety of symptoms. Most patients with mutations in the *RTEL1* gene present with HHS.

HOYERAAL-HREIDARSSON SYNDROME

HHS is associated with growth restriction *in utero* and after birth, small head size (microcephaly), a small or missing part of the brain that coordinates movement (cerebellum), severe developmental delay, and immunodeficiency as a result of bone-marrow failure. Most individuals with HHS die in childhood as a result of these symptoms.

DYSKERATOSIS CONGENITA

DKC is clinically less severe than HHS and is characterized by three main symptoms: abnormal skin coloring, specifically in the upper body; white patches on the tongue and inside of the mouth (leukoplakia); and abnormal nails of the fingers and toes (nail dystrophy). Other symptoms of DKC include short stature, dental abnormalities, thick scarring (fibrosis) in the lungs and liver, narrowing of the muscular tube connecting the throat with the stomach (esophagus), narrowing of the tube connecting the urinary bladder to the urinary opening for the removal of urine (urethra, typically only in males), weak or brittle bones (osteoporosis), progressive bone-marrow failure, and cancer (most commonly leukemia). Progressive bone-marrow failure and cancer are the most common causes of death. Most individuals with DKC have normal intelligence and development, but there are reports of individuals who are more severely affected who have varying degrees of intellectual disability or developmental delay. These symptoms are variable, as not all individuals with DKC will have the same presentation. Harmful genetic changes in *RTEL1* make up to 2-8% of all cases of DKC.

How common are RTEL1-related Disorders?

The worldwide frequency of RTEL1-related disorders in the general population is not known. RTEL1-related disorders are estimated to affect about 1 in 1,000,000 individuals. A founder effect (high frequency of disease because the group arose from a small, possibly isolated population) has been described in the Ashkenazi Jewish population, and incidence of RTEL1-related disorders may therefore be higher in this population.

How are RTEL1-related Disorders treated?

There is no cure for RTEL1-related disorders. Regular screening for bone-marrow failure and leukemia is recommended, with hematopoietic stem-cell transplantation used as a treatment option if needed. Annual pulmonary-function tests to assess for fibrosis as well as periodic follow-up with a multidisciplinary team of specialists are recommended to assess for other symptom development.

What is the prognosis for an individual with an RTEL1-related Disorder?

The prognosis for an individual with HHS is typically poor, as it often leads to early bone-marrow failure and premature death in childhood. The prognosis for an individual with DKC is variable and is dependent on the severity. Some individuals with DKC live into adulthood, while some die in childhood as a result of bone-marrow failure, lung complications, or cancer.

Additional considerations for carriers

Carriers of RTEL1-related disorders may or may not show symptoms of disease as they age. While the specific risk in carriers is uncertain, recent studies have shown that carriers of RTEL1-related disorders may be at risk of developing familial interstitial pneumonia, idiopathic pulmonary fibrosis, myelodysplastic syndrome, or other symptoms at older ages.

Sandhoff Disease

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: HEXB.
Exons Sequenced: NM_000521:1-14.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What is Sandhoff Disease?

Sandhoff disease is an inherited, lysosomal storage disorder caused by harmful genetic changes (mutations) in the *HEXB* gene. The *HEXB* gene contains instructions for an enzyme called β-hexosaminidase, which is responsible for breaking down harmful substances, primarily a fatty protein known as GM2 ganglioside. Normally, GM2 ganglioside is broken down inside cells and is harmless. In individuals with Sandhoff disease, GM2 ganglioside and other molecules do not get broken down. These molecules then build up in the brain and damage nerve cells. The disease has been broken down into three different types, based on when symptoms first appear.

INFANTILE (CLASSIC) FORM

The classic form of Sandhoff disease appears shortly after birth and is the most severe form of the disease. At around three to six months of age, affected infants start to lose milestones and their muscles will become weaker. They may not be able to roll over, sit up, or crawl. Affected infants will also have an exaggerated startle reaction to noises or touch. Over time, children with Sandhoff disease will develop seizures, vision and hearing loss, intellectual disability, and paralysis. Other symptoms include enlarged organs (organomegaly) and bone abnormalities. A red spot in the eye known as a "cherry-red spot" is characteristic of many lysosomal disorders, including Sandhoff disease.

JUVENILE-ONSET FORM

A milder, rarer form of Sandhoff disease occurs when an individual has mutations that only cause a partial enzyme deficiency. Signs and symptoms vary widely and can begin in childhood or adolescence. Affected individuals may experience muscle weakness, difficulty coordinating movement, speech problems, recurrent respiratory infections, and seizures.

LATE-ONSET FORM

The late-onset form can be difficult to diagnose. Early signs can include clumsiness and muscle weakness in the legs. Over time, people with late-onset Sandhoff disease may require mobility assistance and have difficulty with speech and swallowing. About 40% of affected adults experience mental illness, such as bipolar disorder or psychotic episodes.

How common is Sandhoff Disease?

The incidence of Sandhoff disease is estimated to be 1 in 400,000. The condition may be observed more frequently in certain populations including the Creole population of northern Argentina, the Metis Indians in Saskatchewan, Canada, and people from Lebanon.

How is Sandhoff Disease treated?

Treatment for Sandhoff disease includes supportive care for symptoms, such as medications to control seizures, assistance in getting adequate nutrition, and breathing assistance. There is no cure for the disease.

What is the prognosis for an individual with Sandhoff Disease?

Children with the severe infantile-onset form will often have recurrent seizures by age two and eventually lose muscle function, mental function, and sight, becoming mostly non-responsive to their environment. Death usually occurs by age three and is generally caused by respiratory infections. Children with juvenile-onset Sandhoff disease will show similar health problems, but at an older age, and will also progressively decline. Though challenging and debilitating, the late-onset form does not always shorten life span.

Serine Deficiency Disorder, PHGDH-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: PHGDH.
Exons Sequenced: NM_006623:1-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Serine Deficiency Disorder, PHGDH-related?

Serine deficiency disorder, PHGDH-related, or phosphoglycerate dehydrogenase deficiency (PHGDH deficiency), is an inherited condition that causes low levels of the amino acid serine. Low levels of serine lead to a wide range of symptoms. There are at least three genes that can cause serine deficiency disorder. Serine deficiency disorder, PHGDH-related, is caused by harmful genetic changes (variants) in the *PHGDH* gene.

The symptoms of serine deficiency disorder are usually first noticed shortly after birth. Babies have small heads (microcephaly), seizures, and delays in mental and motor skills (psychomotor retardation). Brain imaging (MRI) shows reduced fatty tissue covering the nerve cells (hypomyelination). Some patients have had cataracts at birth, organs that push through the muscle or tissue (hernias), low red blood cell levels (anemia), and difficulty feeding. Sometimes, symptoms begin later in childhood (juvenile onset) or adulthood. Later onset is usually associated with milder symptoms. Since this condition is rare, the full disease spectrum is not completely understood. The most severe form of the disease is known as Neu-Laxova syndrome.

NEU-LAXOVA SYNDROME

Neu-Laxova syndrome is generally associated with death in utero. Individuals with Neu-Laxova syndrome have small heads, poor growth during pregnancy, abnormal scaly skin (ichthyosis), and birth defects of the nervous system, face, and limbs. Most babies with this condition that make it to term are stillborn or die soon after birth.

How common is Serine Deficiency Disorder, PHGDH-related?

Serine deficiency disorder is extremely rare, with at least 70 cases reported to date. The global incidence is unknown, and other presentations of the condition may not be recognized yet. Of the cases reported, approximately 69% have been caused by harmful changes in the *PHGDH* gene.

How is Serine Deficiency Disorder, PHGDH-related treated?

There is no cure for serine deficiency disorder. The primary treatment is supplemental L-serine therapy and, in some cases, glycine. Many treated patients show a significant improvement after treatment. Individuals may benefit from early intervention and physical and occupational therapy to help with developmental delays. Individuals with cataracts should see an ophthalmologist for treatment, and patients taking L-serine by mouth should see a dentist regularly to treat possible dental complications.

Treatment for Neu-Laxova syndrome is not currently available.

What is the prognosis for a person with Serine Deficiency Disorder, PHGDH-related?

Due to the rarity of the condition, the prognosis for serine deficiency disorder is not clearly understood. Improvement in seizure frequency and well-being has been reported, but the long-term effects of supplemental serine are unknown.

Neu-Laxova syndrome is the most severe form of serine deficiency disorder, and death usually occurs in utero or the newborn period.

Severe Combined Immunodeficiency, RAG2-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: RAG2.
Exon Sequenced: NM_001243785:3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Severe Combined Immunodeficiency, RAG2-related?

Severe combined immunodeficiency (SCID), RAG2-related, is an inherited disorder that causes the immune system not to work correctly, making it difficult for the body to fight off infections. The condition is caused by harmful genetic changes (variants) in the *RAG2* gene. Individuals with SCID, RAG2-related, are missing essential parts of the immune system called T-cells and B-cells. Without these cells, the body cannot fight off germs. Individuals with SCID, RAG2-related, typically experience recurrent infections that can be severe. The infections typically begin in infancy and, without treatment, may lead to death in the first year of life. Additional symptoms in affected infants include poor growth and persistent diarrhea. The severity of symptoms can vary between individuals, even within the same family. Delayed-onset and atypical forms of the condition have been reported.

OMENN SYNDROME

Omenn syndrome is a specific clinical presentation that may occur in some individuals with a harmful change in the *RAG2* gene. Unlike those with typical SCID, RAG2-related, individuals with Omenn syndrome have some T-cells, however the T-cells do not function properly. As a result, individuals have recurrent infections that are typically severe. They may also have skin rashes, hair loss, enlargement of lymph nodes, persistent diarrhea, and liver and spleen enlargement.

How common is Severe Combined Immunodeficiency, RAG2-related?

There are many genes (including *RAG2*) that may be associated with SCID and Omenn syndrome. Overall, SCID is estimated to occur in approximately 1 in 58,000 births. However, the percentage of SCID cases that are due to harmful changes in the *RAG2* gene is currently unknown.

How is Severe Combined Immunodeficiency, RAG2-related, treated?

Treatment for SCID, RAG2-related, typically involves stem cell transplantation (hematopoietic stem cell transplantation or HSCT). Usually, bone marrow transplantation is performed, although cord blood transplantation may also be used. While stem cell transplantation may be effective in treating the condition, some individuals may still require treatment with infusions of antibodies (immunoglobulin therapy) after transplantation. Complications of stem cell transplants can be life-threatening. Survival rates are estimated to be highest when the transplant comes from a matched sibling of the affected individual, if available, and when performed shortly after birth. Individuals with SCID, RAG2-related should not receive immunizations with live viruses.

What is the prognosis for a person with Severe Combined Immunodeficiency, RAG2-related?

SCID, RAG2-related, can cause life-threatening infections in infancy. Without treatment, death in the first year of life is typical. However, longer survival is possible with stem cell transplantation at an early age.

Short-chain Acyl-CoA Dehydrogenase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ACADS.
Exons Sequenced: NM_000017:1-10.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Short-Chain Acyl-CoA Dehydrogenase Deficiency?

Short-Chain acyl-CoA dehydrogenase (SCAD) deficiency is an inherited disease caused by mutations in the *ACADS* gene and part of a group of disorders called fatty-acid oxidation defects. Individuals with SCAD deficiency can have trouble converting short-chain fatty acids for energy to fuel their body. Symptoms may be triggered by long periods without food (fasting), by illness, or by other stressors.

Some infants with SCAD deficiency experience episodes of metabolic crisis that can involve vomiting, low blood sugar, and fatigue. These metabolic crises can be life-threatening. Affected infants may also have difficulty feeding and failure to grow at the expected rate. Some other symptoms may include poor muscle tone, seizures, smaller head size (microcephaly), an enlarged liver, and an enlarged spleen. Untreated SCAD deficiency can lead to developmental delay and learning problems.

Some individuals with SCAD deficiency do not display any symptoms until adulthood. In these cases, the main symptom is chronic muscle weakness while some may experience periods of pain, nausea, and shortness of breath. Due to the wide variability of the disease, it is possible for individuals not to have any symptoms or to have symptoms so mild that they are never diagnosed.

How Common Is Short-Chain Acyl-CoA Dehydrogenase Deficiency?

SCAD deficiency affects 1 in 40,000 to 1 in 100,000 newborns. Researchers have hypothesized that this disease may be more common than believed because some individuals with the disease are asymptomatic or have mild symptoms.

How Is Short-Chain Acyl-CoA Dehydrogenase Deficiency Treated?

The key to managing SCAD deficiency is to avoid going for long periods of time without eating. Infants and children with SCAD deficiency may require feedings at regular intervals, including during nighttime. For children and adults, consuming cornstarch can also

provide a sustained release of energy and allow for longer gaps between meals. If an individual is unable to eat or drink food on their own, it may be necessary to give them glucose by intravenous fluids. Some physicians may recommend carnitine or riboflavin supplements as well.

What Is the Prognosis for an Individual with Short-Chain Acyl-CoA Dehydrogenase Deficiency?

Early diagnosis and dietary management are important for the best outcome. If dietary management starts early and is consistent, individuals with SCAD deficiency have a good prognosis with normal or near-normal lifespan. Some individuals with SCAD deficiency may not experience symptoms until adulthood or may only experience very mild symptoms until adulthood.

Additional Considerations for Carriers

Carriers of fatty-acid oxidation defects, including SCAD deficiency, do not typically show symptoms of the disease. However, there is an increased risk of serious pregnancy complications, particularly in the third trimester, in women carrying a fetus affected with SCAD deficiency. These complications can include HELLP syndrome and acute fatty liver of pregnancy. A woman whose pregnancy may be affected by a fatty-acid oxidation defect, such as SCAD deficiency, should speak with her physician for recommendations and may benefit from consultation with a high-risk physician.

Sjogren-Larsson Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ALDH3A2.
Exons Sequenced: NM_000382:1-10.

Detection Rate	Population
96%	African American
96%	Ashkenazi Jewish
96%	Eastern Asia
96%	Finland
96%	French Canadian or Cajun
96%	Hispanic
96%	Middle East
96%	Native American
96%	Northwestern Europe
96%	Oceania
96%	South Asia
96%	Southeast Asia
96%	Southern Europe
96%	Worldwide

What Is Sjogren-Larsson Syndrome?

Sjogren-Larsson Syndrome (SLS), caused by mutations in the *ALDH3A2* gene, is an inherited disorder caused by an inability to break down fatty alcohol molecules in the body. The buildup of these fatty alcohols leads to symptoms affecting the skin, skeleton, neurological system, and eyes.

Children with SLS are often born several weeks prematurely, and the majority will develop dry, scaling skin (ichthyosis) in the first year of life. This abnormally thick skin has a dark, scaly appearance and can be itchy but the skin of the face usually remains normal. Some individuals with SLS will also have curved spines and will have shorter than average stature.

Neurological symptoms typically begin appearing in the first two years of life in children with SLS. These symptoms may include developmental delay, speech issues, and seizures. Most individuals with SLS will have intellectual disability, which can be severe, with an IQ of below 50. Infants with SLS tend to take longer to learn how to crawl and walk, due to stiffness (spasticity) of the leg and arm muscles. Some individuals with SLS will never be able to walk. Individuals with SLS may have glistening white dots in the back of their eye (retina) that can be seen during an eye exam. SLS may also affect vision and cause sensitivity to bright lights (photophobia).

How Common Is Sjogren-Larsson Syndrome?

SLS is a rare genetic condition that affects individuals of various ethnic backgrounds. SLS is most common in Sweden, where the estimated prevalence is 1 in 250,000 individuals. In northern Sweden, the prevalence may be higher.

How Is Sjogren-Larsson Syndrome Treated?

There is no treatment for the root cause of SLS. The current treatments are aimed at alleviating the disease's symptoms.

Therapy for the scaly and tough skin include daily baths, moisturizing creams, and creams or lotions with active ingredients that scrub off dead skin cells. Drugs called retinoids may improve skin condition for adults with SLS. There are currently research trials showing that a drug called zileuton may help reduce skin itching associated with SLS, but it is not yet approved by the FDA for treating SLS. Some studies suggest that a modified diet concerning fat intake with supplementation may help with skin symptoms in some patients.

While physical therapy may help build or regain motor skills, including walking, surgery may help reduce the spastic movements of the leg. Mechanical braces or other aids may also be useful in helping individuals with SLS to walk. Anti-seizure medication can be given to help control seizures. Learning specialists may help individuals with SLS reach their learning potential.

What Is the Prognosis for an Individual with Sjogren-Larsson Syndrome?

Life expectancy is usually reduced for individuals with SLS which may be related to the neurological impact of the condition.

SLC26A2-related Disorders

INCLUDING ACHONDROGENESIS TYPE 1B, DIASTROPHIC DYSPLASIA, AND RECESSIVE MULTIPLE EPIPHYSEAL DYSPLASIA

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).

Gene: SLC26A2.

Exons Sequenced: NM_000112:2-3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Sulfate Transporter-Related Osteochondrodysplasia?

Sulfate transporter-related osteochondrodysplasias are a group of inherited diseases caused by mutations in a gene called *SLC26A2*, which plays a role in cartilage and bone formation. These diseases include achondrogenesis type Ib, diastrophic dysplasia, atelosteogenesis type II, and recessive multiple epiphyseal dysplasia.

ACHONDROGENESIS TYPE IB (ACGIB)

ACGIb is a severe skeletal disease that is fatal either before or shortly after birth. Infants born with the disease have extremely short arms, legs, fingers, and toes. The fingers and toes may be rotated inward (clubfoot). Infants with the disease also tend to have flat faces, protruding abdomens, narrow chests, and short necks that show thickening of the soft tissue. Many are born with hernias.

Fetuses with ACGIb are often in the breech position, "upside-down," with their feet toward the birth canal. Mothers of fetuses with ACGIb are prone to other pregnancy complications, like too much amniotic fluid (polyhydramnios).

DIASTROPHIC DYSPLASIA

Diastrophic dysplasia, also called diastrophic dwarfism, causes bone and joint abnormalities. It does not typically affect intelligence or mental function.

Individuals with diastrophic dysplasia have very short arms and legs (short stature, typically between 3.2 and 4.6 feet), although their skulls are often normally sized. They are often born with bone deformities such as clubfoot, cleft palate, a curved spine, and "hitchhiker thumbs" (thumbs that are bent back). The outside of the ears may also be swollen at birth which can result in abnormal-looking ears later in life. Infants may also have a small ribcage and chest with a protruding abdomen which can lead to breathing problems.

Joint abnormalities leading to pain develop at an early age, and many individuals have difficulty moving their joints, which worsens with age. This, in turn, may make walking difficult.

ATELOSTEOGENESIS TYPE II

Atelosteogenesis type II is similar to diastrophic dysplasia with the main symptoms including bone deformities, cleft palate, narrow chest with protruding abdomen, and atypical facial features. The main difference between the two diseases is that atelosteogenesis type II is much more severe, with most affected individuals being stillborn or dying from respiratory failure soon after birth.

RECESSIVE MULTIPLE EPIPHYSEAL DYSPLASIA (RMED)

rMED causes bone deformities and joint pain. Unlike individuals with the related diseases mentioned above, those with rMED typically reach normal height and live normal lifespans. Half of the individuals with rMED are born with an obvious bone abnormality such as cleft palate, clubfoot, or an inwardly-curved little finger. Some also have a mild curvature of the spine (scoliosis).

All individuals with the disease develop joint pain, often late in childhood. Pain is most common in the hips and knees but can also occur in the wrists, fingers, and elsewhere.

How Common Is Sulfate Transporter-Related Osteochondrodysplasia?

ACGIb is very rare, and its frequency is unknown. One particular mutation that causes the disease is most common in Finland, but other mutations are found globally.

Diastrophic dysplasia has been estimated to affect 1 in 100,000 people worldwide. It has been found in individuals of all ethnicities but is most common in Finland.

Atelosteogenesis type II is extremely rare, and its frequency is unknown.

rMED is also rare, but researchers believe it may be more common than realized, due to individuals with mild symptoms who go undiagnosed.

How Is Sulfate Transporter-Related Osteochondrodysplasia Treated?

There is no treatment for ACGIb or atelosteogenesis type II. Infants with either disease can only be made as comfortable as possible.

For individuals with diastrophic dysplasia, the goal of treatment is to improve and maintain mobility while relieving pain. This can be done with a combination of muscle exercises, surgery, and the use of plaster casts to hold children's joints in place. In particular, surgery can be used to correct clubfoot, to reduce compression of the spinal cord, or to correct knee joints. Surgery may need to be repeated, as bone deformities tend to re-form after surgery. It is important that individuals with diastrophic dysplasia do not become obese, as this puts harmful weight and strain on their knee and ankle joints.

rMED is usually treated through a combination of targeted muscle strengthening exercises and non-steroidal anti-inflammatory drugs (NSAIDs). Individuals with the disease should avoid sports and activities that stress their joints. Obesity can put a strain on the joints. In some circumstances, surgery may be useful.

What Is the Prognosis for an Individual with a Sulfate Transporter-Related Osteochondrodysplasia?

The prognosis for an infant with ACGIb or atelosteogenesis type II is poor. They will die before or shortly after birth.

Infants with diastrophic dysplasia rarely face life-threatening breathing problems. Most individuals with diastrophic dysplasia live into adulthood and usually have normal intelligence and mental function. All will face physical challenges with walking and other movement and may rely on various mechanical aids for mobility.

Individuals with rMED can perform most daily activities, provided these do not stress the joints. Despite joint pain and some bone and joint abnormalities, individuals with rMED can live normal, healthy lives with a normal lifespan.

Smith-Lemli-Opitz Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: DHCR7.
Exons Sequenced: NM_001360:3-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Smith-Lemli-Opitz Syndrome?

Smith-Lemli-Opitz syndrome (SLOS) is an inherited condition in which the body's ability to make cholesterol is impaired. It is caused by harmful genetic changes in the *DHCR7* gene. Cholesterol is critical for the structure of cells and the development of a baby. It also plays an important role in the production of different hormones and digestive acids. Individuals with SLOS have very low cholesterol levels, which ultimately disrupts growth and development and causes birth defects. The severity and types of symptoms can vary from individual to individual.

In children with little or no ability to make cholesterol, symptoms are severe. Common birth defects include an abnormally small head (microcephaly), an opening in the roof of the mouth (cleft palate), heart defects, and abnormal genitalia in male infants. Affected infants often have difficulty feeding because they lack the sucking reflex and have weak muscle tone (hypotonia). Some individuals have extra fingers or toes, as well as fused second and third toes on both feet (2-3 toe syndactyly). Infants with the severe form of SLOS grow slowly, and most have moderate-to-severe intellectual disability and behavioral issues. Severely affected infants may also have problems with their kidneys, which can be life-threatening. Sensitivity to sunlight (photosensitivity) is common in adults with SLOS.

Some children have a milder form of the condition in which the body can produce some cholesterol. Symptoms may include developmental delays, toe defects, slow growth, and short stature. These children generally learn to walk and talk, although most do not become independent adults.

How common is Smith-Lemli-Opitz Syndrome?

The incidence of SLOS in the population is an estimated 1 in 20,000 to 1 in 60,000 people. The incidence of SLOS is more common among individuals of European ancestry, especially in people from Slovakia and the Czech Republic. SLOS syndrome is rare among people of African and Asian descent.

How is Smith-Lemli-Opitz Syndrome treated?

There is no cure for SLOS. Treatment for the condition is directed at managing the specific symptoms an individual has. This often means receiving care from a team of specialists that may include physicians, dietitians, speech pathologists, occupational therapists, physical therapists, and social workers. The primary treatment for SLOS is to supplement the patient's diet with large amounts of cholesterol, either in the form of purified cholesterol or from high-cholesterol foods (such as egg yolks and cream). Individuals diagnosed with SLOS will often benefit from receiving early intervention and other supportive services beginning at a young age. Some birth defects may be repaired with surgery. Additional symptoms are treated as they arise.

Because the condition can cause extreme sun sensitivity, people with SLOS should try to stay out of the sun for long periods of time. Additional protective measures include wearing sunscreen, sunglasses, and appropriate clothing when outdoors.

What is the prognosis for a person with Smith-Lemli-Opitz Syndrome?

Although serious internal malformations can lead to early death, many people with SLOS can have a normal lifespan with proper nutrition and medical care.

Spastic Paraplegia Type 15

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ZFYVE26.
Exons Sequenced: NM_015346:2-42.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Spastic Paraplegia Type 15?

Hereditary spastic paraplegias are a group of disorders that cause progressive muscle stiffness (spasticity) in the lower limbs, leading to paralysis (paraplegia). Complex hereditary spastic paraplegias, such as spastic paraplegia type 15 (SPG15), affect the lower limbs and cause neurological impairment, which may include intellectual disability or dementia. Less commonly, some affected individuals have vision and hearing problems. SPG15 is caused by harmful genetic changes (mutations) in the gene *ZFYVE26*.

The onset of symptoms in SPG15 typically occurs in childhood or adolescence. Often either leg stiffness or intellectual disability is the first symptom. Neurological symptoms associated with SPG15 may include structural brain malformations, learning difficulties and intellectual disability, loss of nerve cells in different parts of the brain, involuntary movements, and dementia. These issues may be progressive. In addition, individuals may experience numbness, tingling, or pain in the arms and legs; problems with muscle movements and reflexes; and issues with bladder control. Some individuals with SPG15 also have visual impairment, due to problems with the retina in the eye. The severity of each of these symptoms is variable in affected individuals.

How common is Spastic Paraplegia Type 15?

Incidence of autosomal-recessive hereditary spastic paraplegias is approximately 1 in 50,000 births. SPG15 accounts for 3 to 15% of cases of autosomal-recessive hereditary spastic paraplegias, depending on region. In areas where relatedness between parents of offspring (consanguinity) is common, the frequency of cases is likely higher.

How is Spastic Paraplegia Type 15 treated?

There is no cure for the underlying cause of this condition. SPG15 is treated symptomatically and treatment may include physical therapy, occupational therapy, and devices to assist with walking or use of a wheelchair. Various medications may reduce muscle stiffness and pain. Patients with hearing impairment may use a hearing device.

What is the prognosis for an individual with Spastic Paraplegia Type 15?

Individuals with SPG15 typically have progressive spasticity that will often necessitate walking assistance or a wheelchair approximately 15 years after the diagnosis. Remaining outcomes will vary based on the severity of symptoms; however, this condition is not expected to shorten lifespan.

Spastic Paraplegia, TECPR2-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: TECPR2.
Exons Sequenced: NM_014844:2-20.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Spastic Paraplegia, TECPR2-related?

Spastic paraplegia, TECPR2-related, is a condition that causes stiffness (spasticity) that gets worse over time and impaired movement (paraplegia). It is caused by harmful genetic changes (variants) in the *TECPR2* gene. Spastic paraplegia, TECPR2-related, is known as a complex hereditary spastic paraplegia.

The first symptoms of spastic paraplegia, TECPR2-related, typically present in infancy or early childhood. These include low muscle tone (hypotonia), developmental delays, and feeding difficulties. Affected individuals develop weakness and stiffness of the lower limbs and may have difficulty walking independently. They often have intellectual disability and may experience vision problems and hearing loss. Seizures and changes in brain structure are also possible, including thinning the tissue connecting the brain's left and right sides (the corpus callosum). Individuals with spastic paraplegia, TECPR2-related, also tend to have characteristic facial features, such as a round face, crowding of the teeth, a low hairline, weak facial muscles, a small head, and a short, broad neck.

Some affected individuals have also been reported to have difficulty with the part of the nervous system responsible for functions that are not conscious, such as breathing and heart rate (autonomic nervous system). This may include unexplained fevers or low body temperature (hypothermia), slow heart rate, high blood pressure, a decreased sensitivity to pain, and periods in which breathing stops (apnea). Individuals may also have problems with stomach acid coming back up into their throat (gastroesophageal reflux). This can lead to a lung infection that may be life-threatening (aspiration pneumonia).

How common is Spastic Paraplegia, TECPR2-related?

Spastic Paraplegia, TECPR2-related, is rare with less than 100 cases reported. The incidence is unknown.

How is Spastic Paraplegia, TECPR2-related treated?

There is no cure for spastic paraplegia, TECPR2-related. The condition is treated based on the symptoms an individual is experiencing. Affected individuals may require physical and occupational therapies and devices to assist with walking or using a wheelchair. Medications may reduce muscle spasticity and pain associated with the condition. Standard treatments or therapies generally manage vision problems, hearing impairment, reflux, and apnea.

What is the prognosis for a person with Spastic Paraplegia, TECPR2-related?

The prognosis of spastic paraplegia, TECPR2-related, is difficult to predict due to the rarity of the condition. Apnea and aspiration may be life-threatening, and death in childhood has been reported. However, some individuals have lived to early adulthood.

Spinal Muscular Atrophy

Available Methodology: spinal muscular atrophy (v4.0).
Gene: SMN1.
Variant (1): SMN1 copy number.

Detection Rate	Population
71%	African American
94%	Ashkenazi Jewish
93%	Eastern Asia
94%	Finland
94%	French Canadian or Cajun
91%	Hispanic
92%	Middle East
93%	Native American
95%	Northwestern Europe
93%	Oceania
93%	South Asia
93%	Southeast Asia
94%	Southern Europe
91%	Worldwide

What Is Spinal Muscular Atrophy?

Spinal muscular atrophy (SMA) is a condition that causes a loss (atrophy) of motor neurons, which are specific nerves in the brain and spinal cord that control movement. It is caused by a deficiency of the SMN protein, which is most often the result of a deletion (or loss) of part of the *SMN1* gene. Without motor neurons, messages cannot be passed from the brain to the muscles of the body. In severe cases, a patient will not be able to sit independently, and their breathing and swallowing may be impaired. In the mildest cases, symptoms begin in adulthood and independent movement-such as walking-may become more difficult (but still possible). With all types of SMA, there may be difficulties with sleeping and gaining weight (failure to thrive). Frequent pneumonia is common, as is curvature of the spine (scoliosis) and stiff joints (joint contractures). Intelligence is generally unaffected in individuals with SMA. Women with the milder forms of the condition have been known to give birth to healthy children, although many of the pregnancies have complications.

There are four main subtypes of SMA, each described below. It is not always possible to predict which type of SMA an individual will have based on their genetic testing results.

TYPE 0

Type 0 is the most severe form of SMA. Symptoms can often be seen in the later stages of pregnancy, as the fetus is less active than expected. Once born, the infant will have little ability to move and may not be able to breathe and swallow independently. Infants with SMA type 0 often die before six months of age.

TYPE I, ALSO CALLED WERDNIG-HOFFMANN DISEASE

Type I is another severe form of the condition. Symptoms typically develop within the first six months of life. Infants with type I SMA often have trouble breathing and swallowing. Their muscle tone and strength are extremely poor (hypotonia and muscle weakness, respectively); they cannot sit without support and will not achieve any motor skill milestones.

TYPE II, ALSO CALLED DUBOWITZ DISEASE

In children with type II SMA, muscle weakness becomes apparent between the ages of six and twelve months. When placed in a sitting position, children with the condition can usually maintain the position without support; however, they often lose this ability by their mid-teens. Individuals with type II SMA cannot stand or walk without assistance. They have poor muscle tone and strength, and their fingers usually tremble uncontrollably.

TYPE III, ALSO CALLED KUGELBERG-WELANDER DISEASE

Type III is a milder form of the condition. Symptoms begin sometime between the age of one year and early adulthood. As young children, these individuals may fall repeatedly and have trouble walking downstairs. While their muscles are weaker than normal, individuals with type III SMA can usually stand and walk without assistance, although they may lose this ability later in life. The legs are often more severely affected than the arms.

TYPE IV

Type IV is the mildest form of SMA. With this form of the condition, muscle weakness does not begin until the twenties or thirties, or potentially even later. This weakness is often mild to moderate, and the individual is generally able to walk and move independently. They may also experience mild to moderate tremors and/or twitching of the muscles.

How Common Is Spinal Muscular Atrophy?

The incidence of SMA in the population is between 1 in every 6,000 to 10,000 individuals. The incidence of SMA is more common among individuals of Caucasian descent.

How Is Spinal Muscular Atrophy Treated?

There is no cure for SMA. Many available treatments are supportive in nature and are aimed at improving the symptoms that are present in individuals with the condition. For children with the more severe forms of SMA, mechanical breathing aids may help with sleep and prolong lifespan. In addition, placement of a feeding tube may ensure proper nutrition in those with swallowing problems or feeding difficulties. For individuals with milder forms of SMA, certain types of respiratory assistance may help with sleep problems and surgery may be used to treat orthopedic issues.

In addition to the treatments for SMA symptoms, medications are now available that have been shown to improve motor development in individuals with the condition. These medications, known as nusinersen (market name Spinraza®), onasemnogene abeparvovec (market name Zolgensma®), and risdiplam (market name Evrysdi®), have been approved in the United States for use in patients with SMA.

What Is the Prognosis for an Individual with Spinal Muscular Atrophy?

The prognosis for an individual with SMA varies greatly depending on which type they have and their treatment course.

TYPE 0

Type 0 SMA is typically fatal between two and six months of age. These infants do not develop any motor skills expected of infants their age.

TYPE I

This type of SMA is usually fatal within two years. However, children with type I SMA may live longer with the aid of mechanical breathing aids and other available therapies. There are a few known cases in which the individual survived to adolescence or early adulthood.

TYPE II

With type II SMA, 75% of those affected live to the age of 25. They are often able to sit independently when placed in a sitting position but lose this ability by their mid-teens.

TYPE III

Individuals with type III SMA may have a normal lifespan. Many learn to walk independently, although most lose the ability to do so by their thirties or forties.

TYPE IV

A normal lifespan is also possible for individuals with type IV SMA. They do not develop symptoms until their twenties or thirties and usually retain the ability to walk independently.

Spinocerebellar Ataxia, ANO10-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ANO10.
Exons Sequenced: NM_018075:2-13.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe
97%	Worldwide

What is Spinocerebellar Ataxia, ANO10-related?

Spinocerebellar ataxia, ANO10-related, also known as SCAR10 or ARCA3, is an inherited condition characterized by progressive loss of one's ability to coordinate movement (ataxia). It is caused by harmful genetic changes (variants) in the *ANO10* gene. Genetic changes in *ANO10* cause damage (atrophy) to the part of the brain that controls balance and movement (cerebellum), which is what leads to the symptoms of the disorder.

Symptoms of spinocerebellar ataxia, ANO10-related usually begin in the second to fourth decade of life with loss of balance and poor coordination of walking. While symptoms get worse over time, most people retain the ability to walk independently for up to 25 years after the start of symptoms. Other common symptoms include speech difficulties (dysarthria), abnormal eye movements, and abnormalities on brain imaging. Additional features can vary among patients but can include seizures and cognitive delays.

How common is Spinocerebellar Ataxia, ANO10-related?

There are numerous types of spinocerebellar ataxias (SCAs). The exact incidence of spinocerebellar ataxia, ANO10-related is unknown. Over 50 cases of spinocerebellar ataxia, ANO10-related have been reported worldwide.

How is Spinocerebellar Ataxia, ANO10-related treated?

While there is no cure for spinocerebellar ataxia, ANO10-related, individuals often benefit from physical therapy to help prevent loss of strength and preserve mobility. Speech therapy can help with problems speaking and eating. Occupational therapy can be beneficial to aid with strategies for everyday activities. Some individuals may show symptom improvement with coenzyme Q10 treatment.

What is the prognosis for an individual with Spinocerebellar Ataxia, ANO10-related?

The outlook for a person with spinocerebellar ataxia, ANO10-related varies, depending on the severity of symptoms. Spinocerebellar ataxia, ANO10-related has a later onset and slower progression than other SCAs so lifespan can approach normal. A wheelchair may become necessary with this condition; however, this usually occurs many years after symptoms first start.

Spondylothoracic Dysostosis

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MESP2.
Exons Sequenced: NM_001039958:1-2.

Detection Rate	Population
93%	African American
93%	Ashkenazi Jewish
93%	Eastern Asia
93%	Finland
93%	French Canadian or Cajun
93%	Hispanic
93%	Middle East
93%	Native American
93%	Northwestern Europe
93%	Oceania
93%	South Asia
93%	Southeast Asia
93%	Southern Europe
93%	Worldwide

What is Spondylothoracic Dysostosis?

Spondylothoracic dysostosis caused by harmful genetic changes, or mutations, in the *MESP2* gene, is an inherited condition characterized by skeletal abnormalities of the back bones (vertebrae) and ribs. While mutations in the *MESP2* gene typically cause spondylothoracic dysostosis, there have been very rare reports of individuals with harmful changes in the *MESP2* gene that have a similar but distinct condition called spondylocostal dystosis type 2 (SCDO2).

Individuals with spondylothoracic dysostosis typically have abnormally formed vertebrae. Additionally, the vertebrae and the ribs fuse incorrectly. This results in a shortened neck and torso, a small chest, and a "crab-like" appearance of the rib cage. Affected individuals have arms and legs of normal length, but are usually shorter than average due to their shortened torso (short-trunk dwarfism). The abnormalities of the upper body can cause severe breathing complications in infants and make individuals more likely to have lung infections. Because there is not enough room in the chest, some individuals develop hernias due to the excess pressure placed on the large muscle needed for breathing (diaphragm). Individuals typically do not have any intellectual disability.

MESP2-related SCDO2 has similar features to those of spondylothoracic dysostosis, including abnormalities of the back bones (vertebrae) and ribs, but these abnormalities are thought to be less severe than those observed in spondylothoracic dysostosis. Due to the rarity of *MESP2*-related SCDO2, the exact characteristics are unknown.

How common is Spondylothoracic Dysostosis?

The worldwide incidence of spondylothoracic dysostosis is unknown. The condition is most common in Puerto Rico, where 1 in 12,000 individuals are affected. *MESP2*-related SCDO2 is extremely rare, with only a few cases reported.

How is Spondylothoracic Dysostosis treated?

There is currently no cure for spondylothoracic dysostosis, and treatment focuses on symptoms as they arise. Infants usually require mechanical help to breathe. Surgery may be required to repair hernias and bone malformations. Lung function, heart function, and growth and development are closely monitored by physicians throughout an affected individuals' life.

What is the prognosis for an individual with Spondylothoracic Dysostosis?

The prognosis for an individual with spondylothoracic dysostosis is poor. Approximately half of all individuals die in infancy from respiratory failure. Of those who survive infancy, prognosis is good, with minimal medical complications and normal intelligence.

Surfactant Deficiency, ABCA3-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ABCA3.
Exons Sequenced: NM_001089:4-33.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Surfactant Deficiency, ABCA3-related?

Surfactant deficiency, ABCA3-related, is an inherited disease that causes individuals to have a difficult time breathing. The condition is caused by harmful genetic changes (variants) in the *ABCA3* gene. Individuals with surfactant deficiency, ABCA3-related, do not have enough of an important substance known as surfactant. Surfactant coats the lungs, allows them to expand after exhaling, and makes breathing easy. The condition typically presents shortly after birth when individuals have extreme difficulty breathing (respiratory distress syndrome). Some individuals may not become symptomatic until childhood or adolescence. Other common symptoms include rapid breathing (tachypnea), low oxygen levels in the blood, and poor weight gain (failure to thrive).

How common is Surfactant Deficiency, ABCA3-related?

The exact incidence of surfactant deficiency, ABCA3-related, is unknown.

How is Surfactant Deficiency, ABCA3-related treated?

There is no cure for surfactant deficiency, ABCA3-related. Treatment for the condition is directed at managing an individual's specific symptoms. A pulmonologist may direct care, including mechanical ventilation and inhaled nitric oxide. Many children will require a lung transplant when they are old enough.

What is the prognosis for an individual with Surfactant Deficiency, ABCA3-related?

Generally, the prognosis for individuals with surfactant deficiency, ABCA3-related, is poor. Most individuals present in infancy and die within the first year despite treatment. Some may be more mildly affected and not present with symptoms until childhood or adolescence, but life expectancy may still be shortened.

TGM1-related Autosomal Recessive Congenital Ichthyosis

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: TGM1.
Exons Sequenced: NM_000359:2-15.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is TGM1-related Autosomal Recessive Congenital Ichthyosis?

TGM1-related autosomal recessive congenital ichthyosis (ARCI) is a genetic skin condition caused by a disruption in the proper formation of proteins that are found in the outer layer of the skin (epidermis). *TGM1* accounts for 38%-55% of ARCI.

Infants with this disorder typically are born with a tight, clear covering over their skin called a collodion membrane. This membrane usually dries up and peels off in the first few weeks of life, leaving scaly skin. The eyelids and lips are turned outward (ectropion). Some newborns will have contractures of their fingers. Generally, individuals with TGM1-related ARCI have large, dark scales that cover most of their skin. Infants will commonly develop infections, and are at risk for dehydration and respiratory problems. Affected individuals may also have hair loss (alopecia), a decreased ability to sweat (hypohidrosis), increased sensitivity to heat and thick skin on their hands and feet.

How common is TGM1-related Autosomal Recessive Congenital Ichthyosis?

TGM1-related ARCI is thought to occur in less than 1 in 200,000 people worldwide. Although the data is somewhat limited, increased incidence of TGM1-related ARCI has been reported in Norway (1 in 91,000 individuals), Spain, and Southern India.

How is TGM1-related Autosomal Recessive Congenital Ichthyosis treated?

Treatment for newborns with TGM1-related ARCI generally requires a moist environment and minimizing the risk for infections and immediate treatment of infections. Topical petrolatum-based creams and ointments are used to keep the skin soft and hydrated. As affected individuals grow, daily use of petroleum or lanolin based creams, long baths to help with lubrication, and alpha-hydroxy acid treatments are required. For those with a severe form of the disease, oral retinoids may be indicated. Additionally, all affected individuals require continued surveillance for respiratory infection and dehydration.

What is the prognosis for a person with TGM1-related Autosomal Recessive Congenital Ichthyosis?

Individuals affected with TGM1-related ARCI generally have a good prognosis with early treatment. The disease will usually remain stable over the lifetime of the affected individual. In the newborn period, the risk for infection (sepsis) is great, therefore it is important that appropriate therapies be initiated immediately following delivery.

TPP1-related Neuronal Ceroid Lipofuscinosis

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: TPP1.
Exons Sequenced: NM_000391:1-13.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is TPP1-related Neuronal Ceroid Lipofuscinosis?

TPP1-related neuronal ceroid lipofuscinosis (NCL) is an inherited disease that causes degeneration of the brain leading to a progressive loss of mental and motor skills. It can also cause blindness and typically leads to an early death. In the final stages of the disease, an affected person will be in a vegetative state.

There are several forms of NCL, largely differentiated by the gene that carries the mutation and the age at which symptoms begin. Mutations in the TPP1 gene typically result in the classic late infantile form or juvenile form of NCL.

CLASSIC LATE INFANTILE FORM (LINCL)

The symptoms of classic LINCL typically begin between the ages of 2 and 4. Seizures are often the first sign, followed by a loss of the physical and mental milestones already achieved. Dementia soon follows along with a loss of motor coordination. Children with classic LINCL become blind between the ages of 4 and 6. They are often bedridden after the age of 6 and are unable to take care of themselves. Their life expectancy ranges from 6 to 40, with many succumbing to the disease by their 20s.

JUVENILE FORM (JNCL)

The symptoms of JNCL, also called Batten disease, often begin between the ages of 4 and 10. These children rapidly lose their vision, becoming completely blind within two to four years. People with JNCL often develop periodic seizures between the ages of 5 and 18.

Between the ages of 8 and 14, mental functions typically decline. Children may have difficulty with speech and show behavioral problems. Some people with JNCL also develop psychiatric problems including disturbed thoughts, attention problems, and aggression. These problems can eventually progress to dementia.

People with JNCL also show a decline in motor function and may have difficulty controlling their own movement.

How common is TPP1-related Neuronal Ceroid Lipofuscinosis?

Approximately 1 in 25,000 people globally are affected by some form of NCL. These diseases are most common in Scandinavian countries, but occur elsewhere as well. In the United States, it is estimated that 25,000 families are affected by some form of NCL.

Worldwide, 0.46 per 100,000 infants are born with TPP1-related NCL.

Mutations that cause TPP1-related NCL are more common in Iceland, Germany, and Finland than in other nations.

How is TPP1-related Neuronal Ceroid Lipofuscinosis treated?

There is no treatment for the underlying cause of TPP1-related NCL. Treatments can only address the symptoms as they arise. Various medications can be useful for treating seizures, poor muscle tone, sleep disorders, mood disorders, excessive drooling, and digestion. In some people, a feeding tube is also helpful.

What is the prognosis for a person with TPP1-related Neuronal Ceroid Lipofuscinosis?

The prognosis for people with TPP1-related NCL is generally poor. They will become blind and have severe mental deterioration. They will enter a vegetative state in childhood and become totally dependent on others to care for them. Death can occur between the ages of 6 and 40.

Tyrosine Hydroxylase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: TH.
Exons Sequenced: NM_199292:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Tyrosine Hydroxylase Deficiency?

Tyrosine hydroxylase deficiency (THD), also called dopa-responsive dystonia, is an inherited movement disorder that causes uncontrollable muscle contractions and developmental delay. Children with THD can have a range of symptoms from mild to very severe. THD is caused by mutations in the *TH* gene that result in a deficiency in an enzyme called tyrosine hydroxylase. Without it, the amino acid tyrosine cannot properly be converted to dopamine, a key neurotransmitter in the brain. Dopamine is important for many functions, including muscle control and cognition.

In the mild form of THD, symptoms typically begin in childhood, after infancy. Symptoms usually start in the feet or legs. Children develop jerky movements that quickly progress to physical rigidity. Many of the symptoms are described as "parkinsonian" and are similar to those of people who have Parkinson's disease. Children with a mild form of THD generally do not have learning disabilities. If untreated, with time, children with THD may lose the ability to walk and may require a wheelchair. Some children with THD show a diurnal pattern, meaning their symptoms tend to be less severe early in the day and more severe late in the day. With early treatment, children with THD can avoid many or all of the disease's symptoms.

The severe form of the disease will appear in infancy, usually before six months of age. Affected infants have delayed motor skills, weakness in the chest and abdomen, stiffness in the arms and legs, and tremor. Many infants with the disease will have trouble controlling eye movements. These children will eventually have learning disabilities, problems with speech, and behavioral and psychological problems. In addition, some individuals with the disease have problems with their autonomic nervous system, which regulates unconscious functions such as body temperature regulation, digestion, blood-sugar levels, and blood pressure. Treatment of the severe form of the disease may take longer to provide results. The most severe cases of the disease may have little or no success with treatment.

How Common Is Tyrosine Hydroxylase Deficiency?

The prevalence of THD is unknown, and only a small number of cases have been diagnosed globally. Cases have been reported in Japan and in the Netherlands.

How Is Tyrosine Hydroxylase Deficiency Treated?

Individuals with the mild form of THD respond well to treatment with supplements of L-dopa and carbidopa. If these are taken before symptoms appear, the symptoms may be avoided completely. Even if symptoms have already begun, children with the disease often respond extremely well to the medication. If the disease has gone untreated for some time, certain symptoms may remain, including an irregular gait and other mild movement and speech difficulties.

Treatment with L-dopa and carbidopa supplements has been less beneficial for individuals with severe THD, but this treatment may improve motor skills over time.

If symptoms have gone untreated, physical, occupational, and/or speech therapists may prove helpful.

What Is the Prognosis for an Individual with Tyrosine Hydroxylase Deficiency?

With early and consistent treatment, the prognosis for an individual with mild THD is good. Many symptoms can be reversed with treatment. If treatment is not begun early and/or the course of the disease is severe, the individual may be shorter than they would otherwise have been and may have an irregular walk and/or learning disabilities.

Tyrosinemia Type I

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: FAH.
Exons Sequenced: NM_000137:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Tyrosinemia Type I?

Tyrosinemia type I is an inherited metabolic disorder in which the body lacks an enzyme needed to break down the amino acid tyrosine, an important building block of proteins. The deficiency in this enzyme, called fumarylacetoacetate hydrolase, leads to an accumulation of tyrosine and related substances in the body which can result in damage to tissues and organs. Tyrosinemia type I is caused by mutations in the *FAH* gene.

Symptoms of the condition begin within the first few months of life and can include diarrhea, vomiting, an enlarged liver, failure to grow at a normal rate, yellowing of the skin and whites of the eyes (jaundice), a softening of the bones, irritability, and an odor like boiled cabbage or rotten mushrooms. Tyrosine can also build up in the cornea, causing itchy, irritated eyes. The liver is progressively damaged, as are the kidneys and central nervous system. If left untreated, children with tyrosinemia type I may have episodes of abdominal pain, an altered mental state, pain or numbness in the extremities, and/or respiratory failure. A mechanical ventilator may be necessary for episodes of respiratory failure, which often last between one and seven days.

How Common Is Tyrosinemia Type I?

Tyrosinemia type I affects 1 in 100,000 to 120,000 individuals worldwide. It is more common in Norway and Finland, where it affects 1 in 60,000 births and in Quebec, Canada, where it affects 1 in 16,000 individuals. In the Saguenay-Lac-Saint-Jean region of Quebec, the disease has a much higher frequency, affecting 1 in every 1,846 individuals.

How Is Tyrosinemia Type I Treated?

The drug nitisinone was FDA approved in 2002 to treat tyrosinemia type I. It prevents an accumulation of specific metabolic compounds in individuals with the disease and is typically taken as soon as the disease is diagnosed. The earlier the disease is recognized and

treated, the less damage is done to the body and the better the prognosis. It is important that individuals with tyrosinemia type I manage their diets closely in a prescribed manner to control intakes of tyrosine and another amino acid, phenylalanine. Daily nitisinone intake and careful diet monitoring will be necessary throughout the life of someone with tyrosinemia type I. Failure to comply with recommended treatments may result in the return of severe, potentially fatal symptoms and damage to the body.

Liver transplantation is an option in severe cases where an individual cannot take nitisinone or already has cancerous cells in the liver. This procedure does carry serious risks. Prior to the development of nitisinone, liver transplantation was the only treatment for tyrosinemia type I.

What Is the Prognosis for an Individual with Tyrosinemia Type I?

If not recognized and promptly treated, tyrosinemia type I is usually fatal before the age of 10 often due to liver or kidney failure, a neurological crisis, or hepatocellular carcinoma, a type of liver cancer. Some children may die within weeks of experiencing the first symptoms. However, with treatment and a managed diet, 90% of individuals with the disease will live to adulthood and experience fairly normal lives.

Tyrosinemia Type II

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: TAT.
Exons Sequenced: NM_000353:2-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Tyrosinemia Type II?

Tyrosinemia type II (TYRII) is an amino acid disorder that causes the body to have reduced production of an enzyme called hepatic tyrosine aminotransferase. Without this enzyme a protein called tyrosine builds up in the body and can cause symptoms such as pain and redness in the eye, painful skin thickening of the palms of the hand and soles of the feet, and intellectual disability. Not everyone diagnosed with TYRII will have the same symptoms and some may have more severe symptoms than others. While there are not many reported cases, available reports indicate that if a pregnant mother with TYRII is not treated it can cause growth problems or developmental delay in the unborn baby.

How common is Tyrosinemia Type II?

TYRII is reported to be rare, affecting less than 1/250,000 individuals. It has been reported in individuals of Italian, Ashkenazi Jewish, French, Scottish, Northern European, Japanese, and Middle Eastern ancestry. The diagnosis may be most common in individuals of Arab or Mediterranean ancestry, based on documented case reports.

How is Tyrosinemia Type II treated?

A low protein diet and restricting food sources of tyrosine and phenylalanine (such as artificial sweeteners) can improve symptoms associated with TYRII for some affected individuals. Beginning treatment early in life appears to reduce the severity of mental impairment, as well as the eye and skin symptoms for some individuals. There are special supplements and foods for babies and adults with TYRII. Additional medications such as oral retinoids may be useful in the treatment of the skin abnormalities.

What is the prognosis for a person with Tyrosinemia Type II?

The symptoms of an individual affected with TYRII tend to progress and persist unless the dietary restrictions are implemented. Many affected individuals see improvement in the eye and skin symptoms after removing tyrosine and phenylalanine from the diet. Infants who are diagnosed with TYRII very early and who start treatment right away can usually have a healthy and normal life. About half of individuals with TYRII have some sort of intellectual disability, but early treatment may reduce this risk.

USH1C-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: USH1C.
Exons Sequenced: NM_005709:1-21.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What are USH1C-related Disorders?

USH1C-related disorders are inherited conditions caused by harmful genetic changes (mutations) in the *USH1C* gene. USH1C-related disorders represent a group of disorders associated with hearing loss with or without vision loss. This group of disorders does not affect intelligence or cause any other primary health problems.

USHER SYNDROME TYPE IC

There are three types of Usher syndrome, identified as type I, type II, and type III. The different types of Usher syndrome are grouped by the severity of the disease and the age when symptoms appear. Usher syndrome type I has several associated genes, and the type associated with the *USH1C* gene is referred to as Usher syndrome type IC or USH1C.

USH1C is an inherited disease that causes hearing loss, balance problems, and progressive vision loss. Infants with USH1C are profoundly deaf in both ears at birth. They have severe balance problems caused by abnormalities of the inner ear (vestibular system) that can lead to delayed development. Children with USH1C sit and walk at later ages and have difficulties sensing changes in speed or direction. In childhood or by early adolescence, individuals with USH1C develop retinitis pigmentosa, an eye disease that causes night blindness and a gradual loss of peripheral or side vision. Eventually only the central vision remains, creating "tunnel vision." This central vision can also be impaired and can lead to total blindness in a small number of individuals with the disease. In some cases, individuals with Usher syndrome type 1 develop clouding of the lens of the eye (cataracts), which can further impair vision.

DFNB18A

Some mutations in *USH1C* have been reported in recessive non-syndromic hearing loss and deafness (hearing loss but no vision loss), referred to as DFNB18A. Individuals with DFNB18A typically have severe to profound hearing loss at birth. Unlike other forms of hearing loss, DFNB18A does not affect movement or balance.

How common are USH1C-related Disorders?

The global incidence is unknown for both Usher syndrome type 1 and DFNB18A. In most countries, the frequency ranges from approximately 1 in 45,000 to 1 in 65,000, except in Germany, where the frequency is 1 in 90,000. Approximately 1-15% of people with Usher syndrome type I have a harmful change in *USH1C*. Incidence for USH1C-related disorders is higher in the French Canadian population.

DFNB18A is extremely rare, having been reported in at least two families of Indian and Chinese ethnicities.

How are USH1C-related Disorders treated?

There is no cure for USH1C-related disorders, but early treatment is important to give an affected child the best opportunity to develop communication skills. While a child is young, his or her brain is most receptive to learning language, either spoken or signed. It is also important to take advantage of the time when the child's vision is normal. Individuals with Usher syndrome type 1C generally do not respond to hearing aids, but cochlear implants may help regain some form of hearing. Sign language is a good option for communication. Specialists can introduce other tools and methods of instruction available to people with hearing loss. It is often helpful if the whole family undergoes such instruction and, as a family unit, helps the child adapt.

For those individuals that develop vision loss, visual aids and specialized instruction (for example in tactile signing) help children adapt to their limited vision. Individuals can be prone to accidental injury due to their vision loss and balance problems. Well-supervised participation in sports may help an individual with Usher syndrome type 1 compensate for balance issues, but swimming may be particularly difficult, and strategies to ensure safety are needed. Use of UV-A and UV-B blocking sunglasses is recommended, and other optical aids may increase eye comfort. Therapy with vitamin A palmitate may slow retinal degeneration for some.

What is the prognosis for an individual with an USH1C-related Disorder?

Usher syndrome type IC results in severe hearing and vision impairment, and DFNB18A results in hearing impairment only. However, neither condition affects one's lifespan or intelligence.

USH2A-related Disorders

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: USH2A.
Exons Sequenced: NM_206933:2-72.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What are USH2A-related Disorders?

USH2A-related disorders are an inherited group of conditions associated with vision loss and, in many cases, hearing loss. This group of disorders does not affect intelligence or cause any other primary health problems. USH2A-related disorders are caused by harmful genetic changes (mutations) in the *USH2A* gene. *USH2A* plays an important role in the development of the inner ear and the light-sensitive tissue of the eyes (retina). The two types of USH2A-related disorders are Usher syndrome type II and retinitis pigmentosa type 39.

USHER SYNDROME TYPE II

Mutations in *USH2A* are the most common cause of Usher syndrome type II (USH2). Individuals with USH2 have mild to severe hearing loss beginning at birth (congenital). The hearing loss is usually not progressive, and it mainly affects the ability to detect high-pitched (high-frequency) sounds. Individuals with USH2 do not typically have balance issues associated with other types of Usher syndrome.

USH2 also causes vision loss, typically beginning in adolescence or early adulthood. This is due to a condition called retinitis pigmentosa (RP). RP is an eye disease that causes night blindness and a gradual loss of side vision (peripheral vision). Eventually only the central vision remains, creating "tunnel vision." This central vision can also become impaired and can lead to total blindness in a small number of individuals with the disease. In some cases, individuals with USH2 develop clouding in the lens of the eye (cataracts), which can further impair vision.

RETINITIS PIGMENTOSA 39 (RP39)

Some individuals with *USH2A* mutations have retinitis pigmentosa without hearing loss, a condition known as retinitis pigmentosa 39 (RP39).

How common are USH2A-related Disorders?

Several genes are known to cause Usher syndrome, which affects approximately 3-6 in 100,000 individuals worldwide. The proportion of Usher syndrome cases caused by *USH2A* differs significantly between ethnic groups.

The exact incidence of RP39 is not known. The prevalence of RP that occurs in the absence of other symptoms (non-syndromic RP) is approximately 1 in 3,000 and 1 in 7,000 worldwide. RP39 is thought to be the most common cause of non-syndromic RP, accounting for 10-15% of cases.

How are USH2A-related Disorders treated?

Currently there is no cure for hearing loss associated with USH2, but early treatment is important, as it provides a child the best opportunity to develop communication skills. While a child is young, his or her brain is most receptive to learning spoken language or sign language. Hearing aids can improve hearing. Some individuals with more severe hearing loss may benefit from surgical implantation of a small device that stimulates the hearing nerve (a cochlear implant). Specialists can introduce those with hearing loss to other available tools and methods of instruction. To help the child adapt, it is often helpful if the family undergoes such instruction together.

For vision loss due to RP, visual aids and specialized instruction (for example, in tactile signing) help individuals adapt to their limited vision. Use of UVA- and UVB-blocking sunglasses is recommended, and other optical aids may increase eye comfort. For some, therapy with vitamin A palmitate may slow retinal degeneration.

Research is currently being done to determine whether Usher syndrome can be treated with specific medications or gene therapy in the future.

What is the prognosis for an individual with a USH2A-related Disorder?

USH2 results in hearing and vision impairment, while RP39 results in vision impairment with normal hearing. However, neither of these conditions affect one's lifespan or intelligence.

Usher Syndrome Type 3

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CLRN1.
Exons Sequenced: NM_174878:1-3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Usher Syndrome Type 3?

Usher syndrome type 3, caused by mutations in the *CLRN1* gene, is an inherited disease that causes progressive hearing loss and vision impairment. The rate at which hearing and vision decline varies greatly from person to person, even among those in the same family. In some individuals, the hearing and/or vision loss can be profound, while in others it can be milder.

Individuals with Usher syndrome type 3 are born with normal hearing and most commonly develop hearing loss in their teenage years, requiring hearing aids by mid-to-late adulthood. By middle age, they are often completely deaf.

Usher syndrome type 3 also causes an eye disease known as retinitis pigmentosa. Often arising during puberty, this causes night blindness that progresses to blind spots in the late teens or early adult years. Peripheral (side) vision is often the first to be reduced and often, by mid-life, the person is legally blind.

Unlike other forms of the disease, Usher syndrome type 3 does not usually cause major problems with balance though some problems may arise later in life.

The disease does not affect intelligence, nor does it cause any other health problems.

How Common Is Usher Syndrome Type 3?

Usher syndrome type 3 is rare, making up just 2% of all cases of Usher syndrome. Usher syndrome type 3 is more common in Finland and among Ashkenazi Jews. One study showed that in the New York City area, 0.7% of Ashkenazi Jews are carriers of an Usher syndrome type 3-causing mutation, which would mean that 1.2 in 100,000 Ashkenazi Jewish children would be affected.

How Is Usher Syndrome Type 3 Treated?

There is no cure for Usher syndrome, but there are ways to ameliorate the vision and hearing loss it causes.

Individuals with the disease will learn to speak normally before their hearing declines. They can explore a range of options including cochlear implants, hearing aids, or sign language.

An individual with Usher syndrome will eventually require low-vision aids and specialized instructions on how to cope with their limited vision. They can be prone to accidental injury due to their vision loss and may need to devise systems to avoid such problems.

Specialists in both hearing loss and vision loss can guide individuals to the best options to fit their needs.

What Is the Prognosis for an Individual with Usher Syndrome Type 3?

Usher syndrome type 3 will cause severe hearing and vision impairment by mid-life. However, it does not affect one's lifespan or intelligence.

Very-long-chain Acyl-CoA Dehydrogenase Deficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ACADVL.
Exons Sequenced: NM_000018:1-20.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency?

Very-Long-Chain Acyl-CoA dehydrogenase (VLCAD) deficiency is an inherited metabolic disorder caused by mutations in the *ACADVL* gene. There are three different forms of VLCAD deficiency that range in severity. All three types of VLCAD deficiency are caused by an error in the production of an enzyme called very-long-chain acyl-coenzyme A dehydrogenase. This enzyme is responsible for breaking down a type of fat known as very-long-chain fatty acids and converting it into energy. Individuals with VLCAD deficiency do not have enough of this enzyme and as a result, fats are not converted into energy, leaving an individual with low blood sugar (hypoglycemia) and feelings of weakness or tiredness (lethargy). In addition, a buildup of very-long-chain fatty acids in the body can damage the heart, liver, and muscles, causing additional symptoms of the disease. The symptoms tend to appear during periods of fasting, illness, or exercise.

EARLY-ONSET FORM

Infants with the severest form of VLCAD deficiency develop symptoms within the first few months of life. This form of the disease can lead to problems with the heart muscle (cardiomyopathy) or heart rhythm (arrhythmia), which can be life-threatening. Babies with VLCAD deficiency may also have poor muscle tone (hypotonia), low blood sugar, lack of energy, and an enlarged liver (hepatomegaly). Heart problems, metabolic crises, and respiratory issues can lead to early death.

CHILDHOOD-ONSET FORM

This form of VLCAD deficiency often appears in early childhood and does not typically involve the heart. Individuals with the childhood-onset form of VLCAD deficiency typically have an enlarged liver and episodes of low blood sugar. Other liver problems may be present, and some individuals will have muscle weakness and breakdown (rhabdomyolysis).

LATE-ONSET FORM

Individuals with late-onset VLCAD deficiency typically experience mild symptoms beginning in adolescence or adulthood. Some will not experience any symptoms until periods of fasting, illness, or exercise. Late-onset VLCAD deficiency does not typically lead to heart

failure, low blood sugar, or metabolic crises. Individuals with this form of the disease may experience occasional periods of muscle cramps and muscle breakdown. This may lead to kidney damage. Symptoms usually worsen after strenuous exercise or other stress.

How Common Is Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency?

VLCAD deficiency has an estimated incidence of 1 in 30,000 to 1 in 100,000 worldwide.

How Is Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency Treated?

Individuals with VLCAD deficiency may be prescribed a special diet. For early-onset VLCAD deficiency, this often includes intravenous glucose and/or a low-fat formula designed with types of fat the individual is better able to metabolize. With early detection and proper treatment, heart issues typically associated with this form of VLCAD deficiency can be avoided. For other forms of VLCAD deficiency, foods high in fat content should be avoided if possible. It is also advisable to avoid long periods between eating (fasting) and very strenuous exercise. Individuals with VLCAD deficiency may need extra medical care during times of illness. Adults who experience muscle breakdown can try to lessen this symptom through adequate hydration and efforts to lower the acidity of the urine to protect the kidneys.

What Is the Prognosis for an Individual with Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency?

In the past, the severe heart problems in early-onset VLCAD deficiency often result in early demise. With early diagnosis and lifelong treatment, however, the prognosis for an individual with VLCAD deficiency is very good. Many are able to live without symptoms and have normal physical and mental development. In milder cases of adult-onset VLCAD deficiency, many individuals remain symptom-free for life even with minimal management.

Additional Considerations for Carriers

Carriers of fatty-acid oxidation defects, including VLCAD deficiency, do not typically show symptoms of the disease. However, there may be an increased risk of serious pregnancy complications, particularly in the third trimester, in women carrying a fetus affected with a fatty-acid oxidation defect. A woman whose pregnancy may be affected by a fatty-acid oxidation defect, such as VLCAD deficiency, should speak with her physician for recommendations and may benefit from consultation with a high-risk physician.

Vitamin D–dependent Rickets, CYP27B1-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CYP27B1.
Exons Sequenced: NM_000785:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Vitamin D–dependent Rickets, CYP27B1-related?

Vitamin D–dependent rickets, CYP27B1-related, is an inherited disease that prevents minerals from being used properly in the bones and muscles of the body. The condition is caused by harmful genetic changes (variants) in the *CYP27B1* gene. Common symptoms of the disease include delayed growth, weak muscles, curved (bowed) legs, and wider wrists and ankles. Symptoms typically appear in the first two years of life and may result in individuals walking later than their peers or needing assistance with walking. Individuals may also be more prone to bone fractures and bone pain. Some individuals also have seizures, muscle spasms, problems with their teeth, and hair loss.

How common is Vitamin D–dependent Rickets, CYP27B1-related?

The exact incidence of vitamin D-dependent rickets, CYP27B1-related, is unknown. More than 100 individuals have been diagnosed worldwide. The condition may be more common among individuals of French Canadian descent in the Saguenay region of Quebec.

How is Vitamin D–dependent Rickets, CYP27B1-related treated?

There is no cure for vitamin D-dependent rickets, CYP27B1-related. Treatment for the condition is directed at managing an individual's specific symptoms. Common interventions may include medication (calcitriol) and calcium to correct biochemical and skeletal abnormalities. Due to possible side effects of the medical intervention, regular monitoring of individuals with physical and biochemical exams, radiographs, and ultrasounds may be required.

What is the prognosis for an individual with Vitamin D–dependent Rickets, CYP27B1-related?

Most individuals will experience an improvement in the condition's symptoms after treatment. The prognosis is typically good; many individuals can live near-normal lives.

VPS13A Disease

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: VPS13A.
Exons Sequenced: NM_033305:1-72.

Detection Rate	Population
99%	African American
99%	Ashkenazi Jewish
97%	Eastern Asia
99%	Finland
99%	French Canadian or Cajun
99%	Hispanic
99%	Middle East
99%	Native American
99%	Northwestern Europe
99%	Oceania
99%	South Asia
99%	Southeast Asia
99%	Southern Europe
99%	Worldwide

What is VPS13A Disease?

VPS13A disease, also known as choreo-acanthocytosis, is a rare disorder that mainly affects the nervous system and causes abnormal movements, psychiatric symptoms, and seizures. The condition is characterized by a movement disorder that causes involuntary, jerky movements in different body areas and can impact walking (chorea). VPS13A disease is caused by harmful genetic changes (variants) in the *VPS13A* gene.

Symptoms typically begin between 20 and 40 years of age and can progress quickly. Some of the first symptoms that may appear are seizures, facial tics, behavior changes like obsessive-compulsive symptoms, personality changes, and uncontrolled movements. Psychiatric symptoms such as depression or schizophrenia-like psychosis are commonly seen in affected individuals. VPS13A disease can cause the part of the brain responsible for movement, called the basal ganglia, to look abnormal on medical imaging. Self-injuring behaviors such as tongue, lip, and finger biting are common. As the disease progresses, affected individuals also lose control over movements needed for speech and swallowing. Most individuals will eventually lose the ability to walk.

The symptoms of VPS13A disease vary significantly between individuals, even within the same family.

How common is VPS13A Disease?

VPS13A disease is a rare disorder, with an estimated incidence of 1 in 1,000,000.

How is VPS13A Disease treated?

There is no cure for VPS13A disease. Treatment usually involves managing symptoms as they arise. This can include medication to treat seizures or psychiatric symptoms, speech therapy, and assistance with feeding. Botulinum toxin may be helpful for the treatment of

abnormal movements in the mouth that interfere with eating. Movement aids such as walkers or wheelchairs can help with mobility issues. Individuals with the condition usually work with various healthcare providers, including speech and physical therapists, psychiatrists, and neurologists.

What is the prognosis for a person with VPS13A Disease?

VPS13A disease is a progressive condition that typically begins between 20 and 40 and progresses over time. Lifespan is typically shortened, and earlier death due to seizures as well as sudden unexplained death have been reported in affected individuals.

Wilson Disease

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ATP7B.
Exons Sequenced: NM_000053:1-21.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What Is Wilson Disease?

Wilson disease, caused by mutations in the *ATP7B* gene, is an inherited condition that causes the body to retain too much copper. The extra copper deposits in the liver, brain, kidneys, and eyes leading to damage and scarring in the tissues and causing the affected organs to stop working properly.

Symptoms typically first appear in childhood or early adolescence, but they can appear as early as age 3 or as late as age 70. The most common symptoms are liver disease and neurological impairment. Liver disease can first appear as fatigue, abdominal pain, or a yellowing of the skin and the whites of the eye (jaundice). Sometimes the result is liver failure, which requires a liver transplant. Neurological impairment can include tremors, clumsiness, problems walking, trouble swallowing, and impaired thinking.

Some individuals with Wilson disease also develop psychiatric problems including depression, anxiety, behavioral problems, mood changes, and difficulty with attention. Extra copper in the kidneys may also cause problems that sometimes lead to kidney failure. Individuals with Wilson disease may also have arthritis, weaker bones, heart problems, pancreatitis, and endocrine disorders. Extra copper in the eyes can cause brown circles, referred to as Kayser-Fleischer rings, around the colored part of the eyes, but this does not affect vision.

How Common Is Wilson Disease?

The prevalence of Wilson disease is approximately 1 in 30,000 individuals worldwide. In China, Japan, and Sardinia, Wilson disease is more common and may affect as many as 1 in 10,000 individuals.

How Is Wilson Disease Treated?

Wilson disease should be treated as soon as possible. Most individuals with the condition take D-penicillamine or trientine by mouth several times a day. This medicine traps (chelates) the excessive copper and helps remove it from the body through the urine. This can help prevent or reduce some of the liver, neurological, and psychiatric symptoms. People on this medication often also need to take vitamin B6 (pyridoxine) as a supplement. Treatment should continue for the whole life of the patient. Sometimes a liver transplant will still be needed. People with Wilson disease should also avoid eating food that contains a lot of copper, such as organs, chocolate, mushrooms, shellfish, and nuts.

What Is the Prognosis for an Individual with Wilson Disease?

Frequent monitoring of the blood and urine and lifelong treatment are important. Without proper treatment, an individual with Wilson disease usually suffers progressively worse liver, neurological, and psychiatric symptoms until they die from liver or neurological disease. With proper treatment, individuals with Wilson disease can often have normal lifespans.

X-linked Adrenal Hypoplasia Congenita

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: NR0B1.
Exons Sequenced: NM_000475:1-2.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe
97%	Worldwide

What is X-Linked Adrenal Hypoplasia Congenita?

X-linked adrenal hypoplasia congenita (XLAHC) is a condition caused by harmful genetic changes (mutations) in the *NR0B1* gene and primarily affects males. *NR0B1* is an important for the development of organs that are important to producing hormones. This includes parts of the brain, the glands located above each kidney (adrenal glands), the ovaries, and the testes. When these organs are unable to properly produce hormones, the body cannot retain enough salt and lacks important sex hormones for development. An inability to retain salt is commonly called "salt wasting" and leads to serious side effects, such as dehydration, vomiting, diarrhea, failure to thrive, heart rhythm abnormalities (arrhythmias), and shock. If not recognized and properly treated, a salt-wasting crisis can be fatal. Lack of sex hormones produced by the adrenal glands is called hypogonadotropic hypogonadism. The lack of sex hormones can cause males with XLAHC to have smaller than average sex organs, undescended testes, delayed or incomplete puberty, and fertility problems.

Most commonly, affected males will show signs of the disease from the first few weeks of life to early childhood, but some later-onset cases have been reported. The age of onset and severity of symptoms can be variable, even within the same family.

XLAHC is an X-linked disease which means that the *NR0B1* gene is on the X chromosome. Males have one copy of the X chromosome and the *NR0B1* gene, while females have two copies. Because of this, males with a mutation in *NR0B1* are affected by XLAHC, while most female carriers still have one working copy of the gene. While most female carriers do not have symptoms, there are rare case reports of female carriers affected by adrenal insufficiency or hypogonadotropic hypogonadism.

How common is X-Linked Adrenal Hypoplasia Congenita?

Studies estimate that between 1 in 70,000 and 1 in 600,000 males will have XLAHC, but the true global incidence is unknown. Other presentations of XLAHC may not be recognized as of yet.

How is X-Linked Adrenal Hypoplasia Congenita treated?

Currently, there is no cure for XLAHC and treatments is based on symptoms. Patients will benefit from taking hormone replacement medications to restore and maintain the right balance of hormones in the body; most patients will need to take hormone medications for the rest of their lives. A multidisciplinary team of physicians, including an endocrinologist, will need to monitor the hormone levels to determine medication dosage, medication side effects, growth, and sexual development of patients with this condition. The endocrinologist will carefully monitor sex hormones near puberty and supplement hormones if puberty is delayed or not progressing as expected. Once the condition is diagnosed, illness caused by salt wasting should be treated in a hospital, where the imbalances can be monitored and corrected.

What is the prognosis for an individual with X-Linked Adrenal Hypoplasia Congenita?

With early diagnosis and proper medication management, most individuals with XLAHC will have a normal life expectancy. Early death can occur during periods of significant salt loss (salt crises), especially during times of illness or trauma. Problems with sexual development and infertility are monitored by physicians on an ongoing basis.

X-linked Adrenoleukodystrophy

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: ABCD1.
Exons Sequenced: NM_000033:1-6.

Detection Rate	Population
77%	African American
77%	Ashkenazi Jewish
77%	Eastern Asia
77%	Finland
77%	French Canadian or Cajun
77%	Hispanic
77%	Middle East
77%	Native American
77%	Northwestern Europe
77%	Oceania
77%	South Asia
77%	Southeast Asia
77%	Southern Europe
77%	Worldwide

What is X-Linked Adrenoleukodystrophy?

X-linked adrenoleukodystrophy (X-ALD), caused by harmful changes in the *ABCD1* gene, is a genetic condition that primarily affects the nervous system and adrenal glands. Neurologic problems result from deterioration (demyelination) of the insulating covering (myelin) of the nerves in the brain and spinal cord. This causes a decline in intellectual and motor function and ultimately reduces lifespan. X-ALD is also associated with adrenal insufficiency, which results in the decreased production of certain hormones causing abnormalities in blood pressure, heart rate, and ability to have children. X-ALD is an X-linked disease. This means that the *ABCD1* gene is on the X-chromosome. Individuals assigned male at birth have one copy of the X-chromosome, while individuals assigned female at birth have two copies. Because males only have one copy of the *ABCD1* gene, a harmful change in the *ABCD1* gene typically causes more severe symptoms in males.

There are three major forms of X-ALD that occur in males:

Childhood cerebral form

The childhood form is the most severe. By age four, children will typically start to experience learning and/or behavior problems that progress over time. Symptoms include intellectual disability and problems with speech, vision, hearing, and motor function. The rate of symptom progression is variable but can result in significant disability within a few years after symptoms start.

Adrenomyeloneuropathy type (AMN)

This type of X-ALD most often presents in early adulthood. Initial symptoms may include difficulty walking, speech difficulties, loss of muscle movement coordination, impaired sexual function, and behavior changes. An absence of some hormones (adrenal insufficiency) may also lead to weakness, weight loss, skin changes, vomiting, and coma.

Addison disease only

This is the mildest form of X-ALD. Individuals with this form often present with symptoms associated with adrenal insufficiency only. The onset of this form varies but typically occurs by eight years of age. The Addison disease only form may progress into symptoms of the AMN type during adulthood. The adrenal function typically remains normal in female carriers.

X-ALD is highly variable, and different forms of X-ALD can be observed within the same family.

Female carriers

Up to 65% of females with a harmful change in *ABCD1* may develop symptoms similar to the AMN form of the condition. The onset of symptoms in females typically occurs in adulthood and has a slower progression than in males, but will typically be present by age 65.

How common is X-Linked Adrenoleukodystrophy?

Collectively, all forms of X-ALD are estimated to occur in approximately 1 in 16,800 males worldwide.

How is X-Linked Adrenoleukodystrophy treated?

Currently, there is no cure for X-ALD. However, treatments are available to address many of the symptoms. A multidisciplinary team of healthcare professionals, including neurologists, physical therapists, urologists, ophthalmologists, audiologists, endocrinologists, and other healthcare specialists, will need to be involved in the treatment and ongoing management of individuals with X-ALD. Corticosteroid replacement therapy treats symptoms caused by adrenal insufficiency but does not relieve neurologic symptoms. Hematopoietic stem cell transplantation (HSCT) is often recommended for younger males in the early stages of the disease; this treatment can often stop the progression of neurological symptoms. Recently, the FDA approved a gene therapy (elivaldogene autotemcel) for treating males ages four to seventeen. This treatment can significantly slow the progression of the disease.

What is the prognosis for a person with X-Linked Adrenoleukodystrophy?

The life expectancy of individuals with this type depends on the severity of the signs and symptoms, how quickly the disorder progresses, and how early treatment is started. Individuals with the cerebral form of X-linked adrenoleukodystrophy usually survive only a few years after symptoms begin but may survive longer with intensive medical support. The prognosis for individuals with the AMN type and Addison disease only type vary; in some cases, neurologic damage may lead to early death.

X-linked Alport Syndrome

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: COL4A5.
Exons Sequenced: NM_000495:1-51.

Detection Rate	Population
96%	African American
96%	Ashkenazi Jewish
96%	Eastern Asia
96%	Finland
96%	French Canadian or Cajun
96%	Hispanic
96%	Middle East
96%	Native American
96%	Northwestern Europe
96%	Oceania
96%	South Asia
96%	Southeast Asia
96%	Southern Europe
96%	Worldwide

What is X-Linked Alport Syndrome?

Alport syndrome is an inherited connective tissue disorder that can cause progressive kidney disease, abnormalities affecting the eyes, and hearing loss. There are three genes associated with Alport syndrome. X-linked Alport syndrome (XLAS) is caused by harmful genetic changes in the *COL4A5* gene. Alport syndrome caused by the *COL4A5* gene is inherited in an X-linked manner because the gene is located on the X chromosome. Males have one copy of the X-chromosome, while females have two copies. Because males only have one copy of the *COL4A5* gene, a harmful change in the *COL4A5* gene typically causes more severe symptoms in males.

The presentation of XLAS is variable in severity. Some individuals have a milder disease course, while others develop more severe symptoms. Although the data are somewhat limited, recent studies have shown that some individuals with Alport syndrome may have a harmful genetic change in *COL4A5* and another gene (suggesting digenic inheritance).

The first sign of the disease is often blood in the urine from kidney disease and typically presents early in life. Males with XLAS and greater than 90% of females with XLAS will have persistent blood in the urine during childhood. This is usually not detectable by the naked eye, but may be visible during periods of illness. Individuals also develop protein in the urine (proteinuria) during childhood. Kidney disease often progresses to kidney failure by early adulthood. Kidney failure is associated with various symptoms, including high blood pressure, fatigue, poor appetite, swelling of legs and feet, and frequent urination. Kidney insufficiency and associated medical complications will develop in all males with XLAS and some females with XLAS. Medications may delay the progress of kidney failure, but most often, a kidney transplant and/or dialysis will eventually be necessary.

XLAS is associated with varying degrees of progressive hearing loss and eye abnormalities. The onset and severity of hearing loss are variable, but it is not uncommon for some degree of hearing loss to develop by adolescence. Eye abnormalities, including those affecting the outer protective layer of the eye (the cornea), the transparent tissue behind the iris (the lens), and the light-sensitive tissue in the back of the eye (the retina), are the most common. These abnormalities may result in light sensitivity, clouding of the lens of the eye (cataracts), and blurred vision. Glasses are sometimes required to correct vision.

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Most carrier females exhibit symptoms of Alport syndrome, but there is a wide range of severity. A few carrier females may have no symptoms. Female carriers of XLAS typically have small amounts of blood in their urine. Some females are also affected by varying degrees of hearing loss, which tends to occur later in life. By late adulthood, up to 40% of female carriers experience kidney failure. Female carriers of XLAS should have routine physical exams and speak with their healthcare provider about the risk of developing kidney disease. Genetic counseling is recommended.

How common is X-Linked Alport Syndrome?

Collectively, all forms of Alport syndrome are estimated to occur in approximately 1 in 50,000 live births. XLAS is the most common form, accounting for about 80% of cases of Alport syndrome. XLAS occurs at a similar frequency amongst all ethnicities. Approximately 10-15% of males with X-linked Alport syndrome do not inherit a mutation from a carrier mother (*de novo* mutation).

How is X-Linked Alport Syndrome treated?

Currently, there is no cure for XLAS. However, treatments are available to address many of the associated symptoms. Medications are used to treat high blood pressure, reduce protein in the urine, and slow the progression of kidney disease. However, kidney failure will develop eventually in all males with XLAS and some females. Because the onset of kidney failure is variable, transplantation or dialysis may be required as early as the teenage years in some individuals but is most often necessary by adulthood. Hearing aids may be required to manage hearing loss. Additionally, ophthalmologic intervention such as cataract surgery may be required for some affected individuals. A multidisciplinary team of physicians, including nephrologists, audiologists, ophthalmologists, and other healthcare professionals, will need to be involved in the ongoing treatment and management of individuals with XLAS.

What is the prognosis for an individual with X-Linked Alport Syndrome?

While the prognosis of XLAS is variable, most affected individuals develop kidney failure by 40 years of age. Renal transplantation and/or dialysis are typically successful as patients approach kidney failure. Complications from kidney disease may still result in a shortened life span. Hearing loss develops in the vast majority of affected individuals by 40 years of age. Often the eye complications associated with XLAS do not cause any severe visual abnormalities, although cataract surgery and/or corrective lenses may be required.

X-linked Choroideremia

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: CHM.
Exons Sequenced: NM_000390:1-15.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe
97%	Worldwide

What is X-linked Choroideremia?

X-linked choroideremia, caused by harmful genetic changes in the *CHM* gene, is a genetic condition that results in progressive vision loss. This occurs due to the degeneration of the tissues in the back of the eye (the retina, photoreceptors, and the choroid – the network of blood vessels that lies between the retina and the white of the eye). Night blindness is usually the first symptom, followed by a loss of peripheral vision. These symptoms typically develop before the age of 20, although the rate of degeneration varies greatly from individual to individual (even among members of the same family). Eventually, the condition affects what a patient sees when looking straight ahead (central vision). Complications such as retinal detachment or cataracts may also occur in individuals with X-linked choroideremia. It does not affect any other system of the body.

X-linked choroideremia is an X-linked disease. This means that the *CHM* gene is on the X-chromosome. Males have one copy of the X-chromosome and the *CHM* gene, while females have two copies. Because of this, X-linked choroideremia primarily affects males. It is possible for some females with a harmful change in the *CHM* gene to have symptoms, such as night blindness and visual field loss later in life.

How common is X-linked Choroideremia?

The incidence of X-linked choroideremia in the population is 1 in 50,000. It is more common in males.

How is X-linked Choroideremia treated?

Treatments for X-linked choroideremia largely involve improving the patient's nutrition to support ocular health and helping the patient manage with visual impairment. Fresh fruits and vegetables, an antioxidant supplement, and omega-3 fatty acids (provided either through supplements or foods such as fish) are often recommended by physicians. Treatments for vision loss are similar to those

recommended for any person who is visually-impaired. An optometrist or another low-vision specialist may help the individual make the most of their remaining vision. Counseling may also be helpful to manage the emotional effects of living with decreased vision. For those with retinal detachment or cataracts, surgery may be necessary.

Clinical trials for gene replacement therapies are in progress, although additional research is needed at this time.

What is the prognosis for an individual with X-linked Choroideremia?

X-linked choroideremia does not affect an individual's lifespan. However, affected individuals will experience progressive vision loss, and many patients will have severe central vision loss later in life.

X-linked Juvenile Retinoschisis

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: RS1.
Exons Sequenced: NM_000330:1-6.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe
98%	Worldwide

What Is X-Linked Juvenile Retinoschisis?

X-linked juvenile retinoschisis is an inherited eye disorder that gives the inner layer of the retina a spoke-wheeled appearance, usually occurring in both eyes simultaneously. X-linked juvenile retinoschisis is caused by mutations in the *RS1* gene. This condition primarily affects males due to the x-linked pattern of inheritance.

Males with the condition may have symptoms in early childhood but are often not diagnosed until they have their first visual screening prior to starting school. They usually have a vision of 20/60 to 20/120, with tiny lesions, splits, or cysts visible on their retinas. Less than 10% of individuals with the condition experience full retinal detachment or bleeding inside the eye, both of which can cause blindness.

For boys with this condition, vision may slowly worsen through the teenage years with stabilization occurring in the twenties. When they reach their forties and fifties, their vision may start to deteriorate again and many people with the condition eventually have a vision of 20/200 or worse, making them legally blind.

How Common Is X-Linked Juvenile Retinoschisis?

X-linked juvenile retinoschisis is estimated to affect 1 in every 5000 to 1 in 25,000 males.

How Is X-Linked Juvenile Retinoschisis Treated?

In general, treatment focuses on monitoring the progression of the disease and helping affected individuals learn to cope with poor vision. For example, children can use large-text books and high-contrast reading materials while adults can purchase special magnifiers, clocks, and adaptive software to help them at home and at work.

Since X-linked juvenile retinoschisis affects only the inner layers of the retina, surgery is rarely effective in treating the disease. However, surgery may help those with complete retinal detachment.

Specialists such as optometrists can help both children and adults make the most of the vision they have. Some individuals with the condition can get restricted driver's licenses if they wear special telescopic lenses behind the wheel, however, these lenses are not legal in all states.

Children under the age of 10 should see a pediatric ophthalmologist or retina surgeon every year. Older children and adults need less-frequent monitoring.

Individuals with X-linked juvenile retinoschisis should avoid contact sports and other activities that might cause a hard blow to the head. This minimizes the risk of retinal detachment or bleeding in the eye.

What Is the Prognosis for an Individual with X-Linked Juvenile Retinoschisis?

X-linked juvenile retinoschisis does not affect lifespan but does cause progressive vision problems that can result in legal blindness after middle age.

X-linked Myotubular Myopathy

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: MTM1.
Exons Sequenced: NM_000252:2-15.

Detection Rate	Population
96%	African American
96%	Ashkenazi Jewish
96%	Eastern Asia
96%	Finland
96%	French Canadian or Cajun
96%	Hispanic
96%	Middle East
96%	Native American
96%	Northwestern Europe
96%	Oceania
96%	South Asia
96%	Southeast Asia
96%	Southern Europe
96%	Worldwide

What is X-Linked Myotubular Myopathy?

X-linked myotubular myopathy (MTMX), caused by harmful genetic changes (mutations) in the *MTM1* gene located on the X-chromosome, is a rare disorder belonging to a group of diseases known as centronuclear myopathies. Males have one copy of the X-chromosome and, therefore, one copy of the *MTM1* gene, while females have two. Because of this, MTMX primarily affects males. Presentation of the condition can vary (as described below), but MTMX almost always affects the strength of the muscles used for movement (skeletal muscles) and results in low muscle tone (hypotonia).

SEVERE X-LINKED MYOTUBULAR MYOPATHY

Most affected individuals have the severe (classic) form of the disease. Signs of this condition may present before birth with decreased fetal movement or too much amniotic fluid (polyhydramnios). At birth, babies typically have low muscle tone and develop multiple problems due to this muscle weakness, including feeding problems, delayed motor development, and respiratory failure requiring mechanical ventilator support. Some affected individuals cannot move on their own and may have absent reflexes. Many affected individuals also have weakness in the muscles that control eye movement (ophthalmoplegia) and have characteristic facial features such as large heads, narrow faces, and high, arched roofs of their mouths. Features seen less frequently may include curvature of the spine (scoliosis); liver disease; recurrent infections; seizures; or stiffening of the muscles resulting in tight joints (contractures). Affected individuals typically have some sort of intellectual disability, although this may be due to lack of oxygen in the neonatal period.

MODERATE AND MILD X-LINKED MYOTUBULAR MYOPATHY

The mild and moderate forms of MTMX are less common than the classic form. In the moderate form of the disease, developmental delay may be milder and individuals may be able to to breathe on their own or with minimal mechanical support. In the mild form of disease, individuals have less-severe muscle weakness, have near-normal motor development, and are generally able to walk. Additionally, in the mild form, ventilator support becomes unnecessary with age and affected individuals tend not to develop the characteristic facial features. It is important to note that it is usually not possible to predict the form of the disease based on the harmful genetic change carried.

Most female carriers do not have symptoms, but there are rare reports of carrier females developing mild or moderate symptoms associated with this condition.

How common is X-Linked Myotubular Myopathy?

The estimated incidence of MTMX is 1 in 40,000 male births, though this is based on limited data. Approximately 10-20% of affected males do not inherit a mutation from a carrier mother (a *de novo*, or new, mutation).

How is X-Linked Myotubular Myopathy treated?

Currently, there is no cure for MTMX. Management focuses on maximizing functional abilities and minimizing complications, using a team of specialists with expertise in the long-term care of children with neuromuscular disorders. For example, a physical therapist and/or rehabilitation medicine specialist may manage movement issues, a neurologist may assist with motor delays and seizures, a pulmonologist may manage the need for mechanical ventilation, and a surgeon may determine the need for a breathing tube (tracheostomy) and/or feeding tube. Other specialties may be involved, as needed.

What is the prognosis for an individual with X-Linked Myotubular Myopathy?

Because of severe breathing problems, 25% of male infants affected with MTMX do not survive the first year of life. Most young children who live longer than one year will need extensive support, including a breathing tube, a feeding tube, and/or a wheelchair. Individuals with the mild or moderate forms may live into childhood or adolescence, but survival into adulthood is uncommon.

X-linked Retinal Dystrophy, RPGR-related

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: RPGR.
Exons Sequenced: NM_000328:1-19.

Detection Rate	Population
38%	African American
38%	Ashkenazi Jewish
38%	Eastern Asia
38%	Finland
38%	French Canadian or Cajun
38%	Hispanic
38%	Middle East
38%	Native American
38%	Northwestern Europe
38%	Oceania
38%	South Asia
38%	Southeast Asia
38%	Southern Europe
38%	Worldwide

What is X-Linked Retinal Dystrophy, RPGR-related?

X-linked retinal dystrophy, RPGR-related, is characterized by progressive vision loss caused by harmful genetic changes (variants) in the *RPGR* gene. *RPGR* plays a role in the function of the photoreceptors. Photoreceptors are a specific type of cell in the eye that is important for vision. Variants in *RPGR* can lead to a loss of photoreceptors, which in turn causes vision issues. X-linked retinal dystrophy, RPGR-related, is an X-linked disease. This means that the *RPGR* gene is on the X-chromosome. Individuals assigned male at birth typically have one copy of the X-chromosome and the *RPGR* gene, while individuals assigned female at birth typically have two copies. Without this "backup" copy of the *RPGR* gene, biological males typically have more severe symptoms.

Most males with X-linked retinal dystrophy, RPGR-related, develop vision loss in childhood. However, some may not develop symptoms until their twenties or thirties. Individuals may experience a loss of peripheral (side) vision (also known as “tunnel vision”) and/or central vision, difficulty with color vision or seeing a night (night blindness), sensitivity to light (photophobia), and nearsightedness (myopia).

ADDITIONAL CONSIDERATIONS FOR CARRIERS

Carrier females may be asymptomatic or may have some vision issues. In most cases, vision issues are milder, with an onset later in life than in affected males. However, some female carriers have vision loss as severe as an affected male. Many females have differences in the back inner surface of the eye (fundus) that can be seen on an eye exam.

How common is X-Linked Retinal Dystrophy, RPGR-related?

Many genes are known to cause retinal dystrophy, which has an incidence of around 1 in 2000 births. Approximately 5% of all retinal dystrophy is caused by *RPGR*.

How is X-Linked Retinal Dystrophy, RPGR-related treated?

There is no cure for X-linked retinal dystrophy, RPGR-related. The use of low-vision aids, such as glasses, may increase eye comfort. UV-A and UV-B-blocking sunglasses may also be recommended. There are state-level services for those with progressive eye disorders to help increase their quality of life. Studies of more advanced treatments, including gene therapy, are ongoing.

What is the prognosis for an individual with X-Linked Retinal Dystrophy, RPGR-related?

Vision loss is progressive for those with X-linked retinal dystrophy, RPGR-related. Many males with the disorder are legally blind by their forties or fifties. Most female carriers will have normal or milder vision changes, though less commonly, a female can progress to legal blindness. The condition does not impact life expectancy.

X-linked Severe Combined Immunodeficiency

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: IL2RG.
Exons Sequenced: NM_000206:1-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is X-Linked Severe Combined Immunodeficiency?

X-linked severe combined immunodeficiency (X-SCID), caused by harmful genetic changes (mutations) in the *IL2RG* gene, is a disorder of the immune system that causes recurrent, severe infections, fevers, and skin rashes. The *IL2RG* gene gives our bodies instructions for making part of a protein called the common gamma chain, which helps our immune system function. Individuals with X-SCID are missing two important immune-system components, T lymphocytes and natural killer lymphocytes. These individuals also have B lymphocytes that do no work. Since the immune system is unable to function properly, individuals with X-SCID are unable to fight off infections.

X-SCID is an X-linked disease which means that the *IL2RG* gene is on the X chromosome. Males have one copy of the X chromosome and the *IL2RG* gene, while females have two copies. Because of this, men with a harmful change in *IL2RG* are affected by X-SCID, while most female carriers still have one working copy of the gene and do not tend to show symptoms. However, there are rare cases reports of female carriers affected by X-SCID.

Symptoms of X-SCID typically begin between three and six months of age. Most infants with untreated X-SCID will show slower than average growth, develop significant diaper and oral rashes, and will have severe, persistent infections despite active treatment. They may also have absent tonsils and lymph nodes. Babies with an atypical form of X-SCID may have immune-system dysfunction, rashes, gastrointestinal problems, and short stature.

How common is X-Linked Severe Combined Immunodeficiency?

The true incidence of X-SCID is unknown. It is thought to occur in at least 1 in 50,000 to 1 in 100,000 male births. X-SCID occurs at a similar frequency amongst all ethnicities, but X-SCID may be more prevalent in the United States due to population structure. More information about the true incidence of the condition may come as other countries adopt newborn screening and registries become more established.

How is X-Linked Severe Combined Immunodeficiency treated?

Bone-marrow transplantation is the most common form of treatment for X-SCID. Replacement of the bone marrow in a person with X-SCID with the bone marrow of a healthy individual allows the body to generate new, functional blood cells and lymphocytes. Bone-marrow transplantation has a significantly higher success rate if performed shortly after birth. Cord blood transplantation may also be an effective treatment of X-SCID. Gene therapy may also be considered for patients that are not good candidates for bone-marrow or cord blood transplantation.

What is the prognosis for an individual with X-Linked Severe Combined Immunodeficiency?

X-SCID is almost universally fatal unless a successful bone-marrow transplantation or gene therapy is completed. Approximately 90% of infants can be successfully treated with a bone-marrow transplant. For infants in which a bone-marrow transplant is not completely successful, or for those who are not candidates for a bone-marrow transplant, administration of proteins to help the immune system function may be beneficial. For infants in whom bone-marrow transplantation, gene therapy, or immunoglobulin infusion is unsuccessful, the average life expectancy is approximately one to two years.

Xeroderma Pigmentosum Group A

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: XPA.
Exons Sequenced: NM_000380:1-6.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe
>99%	Worldwide

What is Xeroderma Pigmentosum Group A?

Xeroderma pigmentosum (XP) is an inherited condition characterized by an extreme sensitivity to ultraviolet (UV) rays from sunlight. Thus, the areas of the body that are most affected by the condition are the skin and eyes. XP's name comes from two of its common characteristics: dry skin (xeroderma) and skin color changes (pigmentosum). There are multiple types of XP, some with different features that are captured by the groupings, but all types include sensitivity to UV light.

The onset of symptoms for individuals with XP group A (XPA) is usually in infancy, but some mutations have been associated with later onset. Typically, XPA is diagnosed in infants who have been sunburned after minimal time in sunlight. Affected children also develop excessive freckling on sun-exposed areas. Damage from the UV rays significantly increases the risk for skin cancer in children with XPA. The average age of onset for non-melanoma skin cancer in children with any type of XP is 9 years and for melanoma is 22 years. The eye is also susceptible to damage from UV light resulting in impaired vision due to clouding of the cornea, inflammation of the cornea, non-cancerous growths on the eye, and/or eye cancer.

Other abnormalities that occur in individuals with XPA, but are unlikely to be related to UV damage, include neurological abnormalities and internal cancers. At least 25 to 30% of individuals with XPA have progressive neurological issues that may include hearing loss, difficulty swallowing and talking, movement problems, seizures, and intellectual disability. The risk for internal cancers is thought to be linked to environmental carcinogens, like cigarette smoke and other, potentially uncontrollable, exposures.

How common is Xeroderma Pigmentosum Group A?

Worldwide, XP has been estimated to affect about 1 in 100,000 individuals. For the Caucasian population in the United States, XP is estimated to affect 1 in 250,000 individuals. In Western Europe, 1 in 1,000,000 new cases are seen annually. Of the XP cases in the United States, ~9% are XPA cases.

Higher frequency of XPA cases has been reported in other areas where marriage between blood relatives (consanguinity) is common, or where a few mutations account for the majority of cases. In Japan, ~55% of cases of XP are attributed to a few mutations in the XPA gene; thus the XPA disorder is estimated to affect approximately 1 in 40,000 Japanese individuals. Additional countries in North Africa, the Middle East, and South Asia may also have a higher frequency of XPA patients.

How is Xeroderma Pigmentosum Group A treated?

Management for all types of XP involves strictly avoiding sun and UV light especially to the skin and eyes; skin-covering clothing, sunscreen, sunglasses with UV protection are strongly recommended. Avoidance of carcinogens, like cigarette smoke, is also recommended. Treatment of individuals with XP is typically multidisciplinary. Individuals are regularly seen by dermatologists to remove skin growths, and may be prescribed high doses of a special form of vitamin D to prevent additional growths although there are many side effects. Ophthalmologists are also involved in patient care to regularly examine the eyes for damage. A neurologist and audiologist may aid in monitoring, diagnosis, and management of neurological features. Oncologists will become involved if an internal cancer is diagnosed.

What is the prognosis for a person with Xeroderma Pigmentosum Group A?

The prognosis for an individual with XPA is generally poor due to early onset of symptoms and severity of features. The life expectancy is shortened for many individuals with XPA due to the dramatically increased risk for skin cancer and risk for neurodegeneration. The average life expectancy of an individual with any type of XP with neurological features is 29 years (37 years if neurological features are not present).

Xeroderma Pigmentosum Group C

Available Methodologies: sequencing with copy number analysis (v4.1) and interpretation of reported variants (v4.0).
Gene: XPC.
Exons Sequenced: NM_004628:1-16.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe
97%	Worldwide

What is Xeroderma Pigmentosum Group C?

Xeroderma pigmentosum (XP) is an inherited condition characterized by an extreme sensitivity to ultraviolet (UV) rays from sunlight. Thus, the areas of the body that are most affected by the condition are the skin and eyes. XP's name comes from two of its common characteristics: dry skin (xeroderma) and skin color changes (pigmentosum). There are multiple types of XP, some with different features that are specific to each group, but all types include sensitivity to UV light.

XP is often diagnosed in infants who have been sunburned after minimal time in sunlight. However, not all children with XP group C (XPC) will sunburn, though they may have freckle-like changes in skin areas exposed to the sun. Damage from UV rays, regardless of the amount of sun damage observed, significantly increases the risk for skin cancer in children with XPC. The average age of onset for non-melanoma skin cancer in children with any type of XP is 9 years and for melanoma is 22 years. The eye is also susceptible to damage from UV light resulting in impaired vision or blindness in one or both eyes due to clouding of the cornea, inflammation of the cornea, non-cancerous growths on the eye, and/or eye cancer.

Other abnormalities that occur in a portion of individuals with XPC, but are unlikely to be related to UV damage, include neurological abnormalities and internal cancers. Cognitive and motor issues are less likely with XPC, but hearing loss, intellectual disability, autism, and hypoglycemia which can cause neurologic damage have been reported. Risk for internal cancers, primarily cancers of the brain, may be higher than that in other groups, even if the individual does not have any neurological abnormalities. The increased risk for internal cancers is thought to be linked to environmental carcinogens, like cigarette smoke and other, potentially uncontrollable, exposures.

How common is Xeroderma Pigmentosum Group C?

Worldwide, XP has been estimated to affect about 1 in 100,000 individuals. However, XP has been estimated to affect from as high as 1 in 5000 persons to as low as 1 in 1,400,000 individuals, depending on the population. For the Caucasian population in the United States,

XP is estimated to affect 1 in 250,000 individuals. In Western Europe, 1 case of XP is seen per 1,000,000 individuals, annually. Of the XP cases in the United States, approximately 40 to 45% are XP group C cases.

In the Japanese population, XP affects approximately 1 in 22,000 individuals, with ~3.5% being attributed to mutations in the *XPC* gene. A higher frequency of XP cases has been reported in areas where marriage between blood relatives (consanguinity) is common, or where a few mutations account for the majority of cases (founder mutations). A higher frequency of XP cases has been documented in Italy, Turkey, North Africa, and the Middle East. In the Comorian black population of Mayotte, an island off the coast of Africa, XP is found in 1 in 5000 individuals.

How is Xeroderma Pigmentosum Group C treated?

Management for all types of XP involves strictly avoiding sun and UV light especially to the skin and eyes; skin-covering clothing, sunscreen, and sunglasses with UV protection are strongly recommended. Avoidance of carcinogens, like cigarette smoke, is also recommended. Treatment of individuals with XP is typically multidisciplinary. Individuals are regularly seen by dermatologists to remove skin growths, and may be prescribed high doses of a special form of vitamin A to prevent additional growths (though there are many side effects). Ophthalmologists are also involved in patient care to regularly examine the eyes for damage. A neurologist and audiologist may aid in monitoring, diagnosis, and management of neurological features. Oncologists will become involved if an internal cancer is diagnosed.

What is the prognosis for a person with Xeroderma Pigmentosum Group C?

The prognosis for an individual without neurological features may be good and associated with a normal lifespan. However, the life expectancy is shortened for many individuals with XPC due to the dramatically increased risk for cancers. The average life expectancy of an individual with any type of XP and no neurological features is approximately 37 years (29 years if neurological features are present).