



PREDICTIVE

PREVENTATIVE

PERSONALIZED

SPINAL MUSCULAR ATROPHY (SMA)

GENE: SMN1 (survival of motor neuron 1, telomeric)

CHROMOSOMAL LOCATION: 5q13.2

MODE OF INHERITANCE: autosomal recessive

Spinal muscular atrophy (SMA) is a genetic disorder which causes degeneration and loss of the anterior horn cells (motor neurons) of the brain stem and spinal cord, resulting in progressive muscle weakness and loss of motor control. Common complications include failure to thrive, scoliosis, joint contractures, respiratory issues, and sleeping difficulties. Severity and age of onset are variable. Children with SMA type I (Werdnig-Hoffman) have severe weakness before six months of age, do not achieve any motor milestones, have trouble eating and breathing, and have a significantly decreased life expectancy. Individuals with SMA type II (Dubowitz) have onset of muscle weakness between 6 and 18 months, and gain only the ability to sit independently (typically lost by adolescence). Individuals with SMA type III (Kugelberg-Welander) have onset of muscle weakness after one year of age and are typically able to walk independently until their 30s-40s, though they may have frequent falls or trouble with stairs. Individuals with SMA type IV have onset of muscle weakness in adulthood (usually 20s – 30s) with decreased ambulation.



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Niemann-Pick Disease

Gene: SMPD1

Chromosomal location: 11

Mode of Inheritance: autosomal recessive

A recessive genetic condition in which there exists an error in the breakdown of the sphingomyolipids in the WBCs, resulting in what is commonly known as “foamy cells”.

Symptoms include the enlargement of the liver and spleen (hepatosplenomegaly), reduced appetite, abdominal pain.

Accumulation of sphingomyelin in the central nervous system results in unsteady gait (ataxia), slurring of speech, and difficulty in swallowing. Basal ganglia dysfunction causes abnormal posturing of the limbs, trunk, and face. In the upper brainstem disease results in impaired voluntary rapid eye movement. More widespread disease involving the cerebral cortex and subcortical structures causes gradual loss of intellectual abilities, causing dementia and seizures.

There is currently no cure for Niemann-Pick disease, with most patients surviving only until 18 months of age.



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## FRAGILE X SYNDROME

GENE: FMR1 (fragile X mental retardation 1)

CHROMOSOMAL LOCATION: Xq27.3

INCIDENCE: 1.6-4 in 10,000 affected males; 0.8-2.2 in 10,000 affected females; 1 in 250 carrier females

MODE OF INHERITANCE: X-linked recessive with anticipation

Fragile X syndrome is characterized by moderate intellectual disability in affected males and mild intellectual disability in affected females. Males may have a characteristic appearance (large head, long face, prominent forehead and chin, protruding ears), connective tissue findings (joint laxity), and large testes (postpubertally). Behavioral abnormalities, sometimes including autism spectrum disorder, are also common. In at least 96% of cases of Fragile-X syndrome there is a trinucleotide repeat expansion (CGG). About 1 in 250 females are premutation carriers and are at increased risk to develop premature ovarian failure. Male and female premutation carriers are also at risk to develop the Fragile-X Tremor Ataxia Syndrome (FXTAS).



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## TAY-SACHS DISEASE

GENE: HEXA (beta-hexosaminidase alpha chain)

CHROMOSOMAL LOCATION: 15q23-q24

MUTATIONS ANALYZED: 1277insTATC, IVS12+1(G->C), IVS 7+1(G->A)/G269S, and 7.6kb del

CARRIER FREQUENCY: 1 in 30 (Ashkenazi Jewish or French Canadian); 1 in 256 (Other) Carrier frequency in Cajun and Old Order Amish populations may be higher

MODE OF INHERITANCE: autosomal recessive

Classic Tay-Sachs disease (TSD) is a progressive neurodegenerative condition with typical onset between 3-6 months of age. There are also juvenile and adult forms of TSD. In almost all cases of Tay-Sachs disease there is a mutation in the HEXA gene, which can be detected using a panel of 5 mutations. Specifically, 98% of mutations in the Ashkenazi Jewish population are detected by this screen; 80-85% of mutations in the French Canadian population; and 38% of mutations in individuals who are neither of Ashkenazi Jewish nor French Canadian ancestry. The American College of Obstetrics & Gynecology (ACOG) recommends carrier screening for couples in which at least one person is of Ashkenazi Jewish or French Canadian ancestry.



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## CYSTIC FIBROSIS

GENE: CFTR (cystic fibrosis transmembrane conductance regulator)

CHROMOSOMAL LOCATION: 7q31

CARRIER FREQUENCY: 1 in 25

MODE OF INHERITANCE: autosomal recessive

Cystic fibrosis affects epithelia of the respiratory tract, exocrine pancreas, intestine, male genital tract, hepatobiliary system, and exocrine sweat glands, resulting in complex multisystem disease. Pulmonary disease is the major cause of morbidity and mortality in CF. The majority of cases of cystic fibrosis have a demonstrable mutation in the CFTR gene. The American College of Obstetrics & Gynecology (ACOG) recommends CF carrier screening to all couples in which at least one person is Caucasian.



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## FAMILIAL DYSAUTONOMIA

GENE: IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B cells, kinase complex-associated protein) / IKAP (IKK complex-associated protein)

CHROMOSOMAL LOCATION: 9q31

MUTATIONS ANALYZED: IVS20(+6T->C) and R696P

CARRIER FREQUENCY: 1 in 32 (Ashkenazi Jewish); <1 in 150 (Other) MODE OF INHERITANCE: autosomal recessive

Familial dysautonomia is a progressive neurodegenerative condition that is typically present at birth. Individuals with this condition may have a variety of sensory/neuronal disturbances and a decreased life expectancy.

## FAMILIAL DYSAUTONOMIA (2 MUTATIONS)



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## GAUCHER DISEASE

GENE: GBA (acid-beta glucosidase/glucoocerebrosidase)

CHROMOSOMAL LOCATION: 1q21-31

MUTATIONS ANALYZED: N370S, 84GG, and L444P

CARRIER FREQUENCY: 1 in 13 (Ashkenazi Jewish); 1 in 150 (Other)

MODE OF INHERITANCE: autosomal recessive

Gaucher disease consists of several subtypes of varying severity that may involve the skeletal, CNS, and cardiopulmonary systems. In almost all cases of Gaucher disease there is a mutation in the gene for glucocerebrosidase. Although over 150 mutations have been identified, three common GD mutations detect approximately 92% of the mutations in the Ashkenazi Jewish population and 55% of the mutations in persons of Non-Ashkenazi Jewish ancestry. The American College of Obstetrics & Gynecology (ACOG) recommends carrier screening for couples in which at least one person is of Ashkenazi Jewish ancestry.



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MUCOLIPIDOSIS TYPE IV

GENE: MCOLN1 (mucolin-1)

CHROMOSOMAL LOCATION: 19p13.3-p13.2

MUTATIONS ANALYZED: IVS3-2 A>G, Deletion exons 1-7

CARRIER FREQUENCY: 1 in 122 (Ashkenazi Jewish)

MODE OF INHERITANCE: autosomal recessive

Mucopolipidosis type IV is a neurodegenerative lysosomal storage disorder characterized clinically by severe psychomotor impairment and ophthalmologic abnormalities. The splice mutation and partial gene deletion account for approximately 95% of mutations in individuals with Ashkenazi Jewish descent.

MUCOLIPIDOSIS TYPE IV (MCOLN1)



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## CANAVAN DISEASE

GENE: ASPA (Aspartoacylase)

CHROMOSOMAL LOCATION: 17pter-p13

MUTATIONS ANALYZED: E285A, Y231X, and A305E

CARRIER FREQUENCY: 1 in 40 (Ashkenazi Jewish)

MODE OF INHERITANCE: autosomal recessive

Canavan Disease is a severe progressive genetic disorder of the CNS that occurs most frequently in children of Ashkenazi (European) Jewish ancestry. Symptoms appear after the first few months and may include macrocephaly, hypotonia, and poor head control. The disease typically progresses with lack of muscle development, seizures, optic atrophy, and feeding problems. The large majority of children with Canavan Disease die before age five. The American College of Obstetrics & Gynecology (ACOG) recommends carrier screening for couples in which at least one person is of Ashkenazi Jewish ancestry.



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## PROTHROMBIN

GENE: F2 (coagulation factor II)

CHROMOSOMAL LOCATION: 11p11-q12

INCIDENCE: 1-2% of the Caucasian population

MODE OF INHERITANCE: autosomal dominant

Prothrombin is the precursor of thrombin (the activated form of factor II) in the clotting cascade. A mutation in the gene for prothrombin causes an elevation of the level of functional prothrombin in plasma, which is associated with an increased risk of thrombosis. Persons who are at risk to carry the prothrombin mutation are those with a family history of early onset stroke, deep vein thrombosis, thromboembolism, pregnancy associated with thrombosis/embolism, hyperhomocystinemia, and multiple miscarriage. Individuals with the mutation are at increased risk of thrombosis in the setting of oral contraceptive use, trauma, and surgery.



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## FACTOR V LEIDEN

GENE: F5 (coagulation factor V)

CHROMOSOMAL LOCATION: 1q21-25

INCIDENCE: 2-8% of the Caucasian population

MODE OF INHERITANCE: autosomal dominant

The most common hereditary blood clotting disorder is due to a specific mutation in the gene for factor V called the Leiden mutation (Arg506Gln). Persons who are heterozygous for the Leiden mutation have a 7-fold increased risk for thrombosis, and those who are homozygous have an 80-fold increased risk for thrombosis. Persons who are at risk to carry the factor V mutation are those with a family history of early onset stroke, deep vein thrombosis, thromboembolism, pregnancy associated with thrombosis/embolism, hyperhomocystinemia, and multiple miscarriage. Individuals with the mutation are at increased risk of thrombosis in the setting of oral contraceptive use, trauma, and surgery.



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METHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR)

GENE: MTHFR (methylenetetrahydrofolate reductase; c.665C>T and c.1286A>C)

CHROMOSOMAL LOCATION: 1p36.3

MODE OF INHERITANCE: autosomal recessive

Genetic risk factors are involved in the predisposition of individuals to venous thrombosis. These include increased plasma homocysteine levels, which are associated with a nucleotide variant in the methylenetetrahydrofolate reductase (MTHFR) gene. The MTHFR 665C>T (previously 677C>T) thermolabile variant results in a decreased utilization of folate, which is a cofactor required for homocysteine remethylation. Homozygosity for the MTHFR 665C>T variant or compound heterozygosity (665C>T/1286A>C) is associated with mild to moderate hyperhomocysteinemia with an increased risk for premature cardiovascular disease.



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## WILSON DISEASE

GENE: ATP7B (Copper-transporting ATPase 2)

CHROMOSOMAL LOCATION: 13q14.3-q21.1

MODE OF INHERITANCE: autosomal recessive

Wilson disease is a disorder of copper metabolism that can present with hepatic, neurologic, or psychiatric disturbances, or a combination of these. Copper accumulation in tissues and organs can lead to liver disease, neurological symptoms including movement disorders, dysarthria, dystonia, migraines and seizures; and psychiatric symptoms including depression, personality changes and psychoses. The age of onset can be from childhood to adulthood; signs and symptoms are rarely observed in children under 3 years of age. Children tend to present with liver disease as their primary symptom, whereas most neurological and psychiatric symptoms tend to arise in adulthood.



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## BLOOM SYNDROME

GENE: BLM (DNA helicase Rec Q protein-like 3)

CHROMOSOMAL LOCATION: 15q26.1

MUTATION ANALYZED: 2281del6bp/ins7bp

CARRIER FREQUENCY: 1 in 111 (Ashkenazi Jewish)

MODE OF INHERITANCE: autosomal recessive

Individuals with Bloom syndrome typically have short stature, pigmentation abnormalities, and an increased susceptibility to infections, respiratory illnesses, and certain malignancies, such as leukemia. Bloom syndrome causes chromosomal instability and sister chromatid exchange. The 2281del6bp/ins7bp is present in at least 98% of affected individuals.



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## 21 hydroxylase

Congenital adrenal hyperplasia (CAH), with an incidence rate of 1 in 10,000 to 18,000 live births, is one of the most common inherited syndromes. The condition is characterized by impaired cortisol production due to inherited defects in steroid biosynthesis. The clinical consequences of CAH, besides diminished cortisol production, depend on which enzyme is affected and whether the loss of function is partial or complete.

In >90% of CAH cases, the affected enzyme is 21-steroid hydroxylase, encoded by the CYP21A2 gene located on chromosome 6 within the highly recombinant human histocompatibility complex locus. Since sex steroid production pathways branch off proximal to this enzymatic step, affected individuals will have increased sex steroid levels, resulting in virilization of female infants. If there is some residual enzyme activity, a nonclassical phenotype results, with variable degrees of masculinization starting in later childhood or adolescence. On the other end of the severity spectrum are patients with complete loss of **21-hydroxylase** function. This leads to both cortisol and mineral corticosteroid deficiency and is rapidly fatal if untreated due to loss of vascular tone and salt wasting.

Because of its high incidence rate, 21-hydroxylase deficiency is screened for in most United States newborn screening programs, typically by measuring 17-hydroxyprogesterone concentrations in blood spots by immunoassay. Confirmation by other testing strategies (eg, LC-MS/MS, CAHBS / Congenital Adrenal Hyperplasia [CAH] Newborn Screening, Blood Spot), or retesting after several weeks, is required for most positive screens because of the high false-positive rates of the immunoassays (due to physiological elevations of 17-hydroxyprogesterone in premature babies and immunoassay cross-reactivity with other steroids). In a small percentage of cases, additional testing will fail to provide a definitive diagnosis. In addition, screening strategies can miss many nonclassical cases, which may present later in childhood or adolescence and require more extensive steroid hormone profiling, including testing before and after adrenal stimulation with adrenocorticotrophic hormone (ACTH)-1-24.



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For these reasons, genetic diagnosis plays an important ancillary role in both classical and nonclassical cases. In addition, the high carrier frequency (approximately 1 in 50) for CYP21A2 mutations makes genetic diagnosis important for genetic counseling. Genetic testing plays a role in prenatal diagnosis of 21-hydroxylase deficiency. However, accurate genetic diagnosis continues to be a challenge because most of the mutations arise from recombination events between CYP21A2 and its highly homologous pseudogene, CYP21A1P (transcriptionally inactive). In particular, partial or complex rearrangements (with or without accompanying gene duplication events), which lead to reciprocal exchanges between gene and pseudogene, can present severe diagnostic challenges. Comprehensive genetic testing strategies must therefore allow accurate assessment of most, or all, known rearrangements and mutations, as well as unequivocal determination of whether the observed changes are located within a potentially transcriptionally active genetic segment.



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ALPHA-THALASSEMIA INTELLECTUAL DISABILITY SYNDROME (Chudley-Lowry Syndrome, XLMR-Hypotonic Facies Syndrome, Smith-Fineman-Myers MR Syndrome)

**GENE: ATRX (transcriptional regulator ATRX)**

CHROMOSOMAL LOCATION: Xq13

MODE OF INHERITANCE: X-linked

Alpha-thalassemia X-linked intellectual disability (ATRX) syndrome is characterized by distinctive craniofacial features, genital anomalies, and severe developmental delays with hypotonia and intellectual disability.



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## Alpha Thalassemia (HBA1 and HBA2) 7 Deletions

Characteristics: Alpha (+) thalassemia (silent carrier): Mutation of a single alpha2 globin gene ( $-\alpha/\alpha$ ); asymptomatic. Alpha (0) thalassemia (trait): Mutation of both alpha2 globin genes, or deletion of alpha1 and alpha2 globin genes in cis ( $-\alpha/-\alpha; --/\alpha\alpha$ ); mild microcytic anemia possible. Hemoglobin H disease: Mutation of three alpha globin genes ( $--/-\alpha$ ); hemolysis with Heinz bodies, moderate anemia, and splenomegaly. Hb Bart Hydrops Fetalis Syndrome: Mutation of four alpha globin genes ( $---/---$ ); lethal in fetal or early neonatal period.

Incidence: Carrier frequency in Mediterranean (1:30-50), Middle Eastern, Southeast Asian (1:20), African, African-American (1:3).

Inheritance: Autosomal recessive.

Cause: Mutations in the alpha globin gene cluster; 95 percent are deletions.

Mutations Tested:  $-\alpha 3.7, -\alpha 4.2, -(\alpha) 20.5, --SEA, --MED, --FIL, --THAI$



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## HEREDITARY HEMOCHROMATOSIS

GENE: HFE

CHROMOSOMAL LOCATION: 6p21.3

INCIDENCE: 1 in 200 to 1 in 400

CARRIER FREQUENCY: 1/7 to 1/10 Caucasians

MODE OF INHERITANCE: autosomal recessive

Hemochromatosis is characterized by inappropriately high absorption of iron by the gastrointestinal mucosa, resulting in excessive storage of iron, particularly in the liver, skin, pancreas, heart, joints, and testes. Abdominal pain, weakness, lethargy, and weight loss are early symptoms. One mutation (C282Y) and two polymorphisms (H63D, S65C) account for approximately 95% of all hemochromatosis alleles. Early detection and presymptomatic diagnosis is important for therapeutic intervention to prevent multi-organ damage from iron overload.