Comprehensive Jewish Panel (96 disorders)

Ashkenazi Jewish Disorders (48)

. Abetalipoproteinemia *(MTTP)*
. Alport Syndrome *(COL4A3)*
. Arthrogryposis, Mental Retardation, and Seizures *(SLC35A3)*
. Bardet-Biedl Syndrome *(BSS2)*
. Bloom Syndrome *(BLM)*
. Canavan Disease *(ASPA)*
. Carnitine Palmitoyltransferase II Deficiency *(CPTII)*
. Choreoacanthocytosis *(VPS13A)*
. Congenital AmegakaryocyticThrombocytopenia *(MPL)*
. Congenital Disorder of Glycosylation Type Ia *(PMM2)*
. Deafness, Autosomal Recessive 77 *(LOXHD1)*
. Dyskeratosis Congenita *(RTEL1)*
. Ehlers-Danlos Type VIIC *(ADAMTS2)*
. Enhanced S-Cone Syndrome *(NR2E3)*
. Factor XI Deficiency *(F11)*
. Familial Dysautonomia *(IKBKAP)*
. Familial Hypercholesterolemia *(LDLR)*
. Familial Hyperinsulinism *(ABCC8)*
. Fanconi Anemia Group C *(FANCC)*
. Galactosemia *(GALT)*
. Gaucher Disease *(GBA)*
. Glycogen Storage Disease Type Ia *(G6PC)*
. Glycogen Storage Disease Type IV Adult Polyglucosan Body Disease *(GBE1)*
. Glycogen Storage Disease Type VII *(PFKM)*
. Hermansky-Pudlak Syndrome 3 *(HPS3)*
. Joubert Syndrome 2 *(TMEM216)*
. Lipoamide Dehydrogenase Deficiency *(DLD)*
. Maple Syrup Urine Disease Type 1b *(BCKDHB)*
. Mitochondrial Complex 1 Deficiency *(NDUFAF5)*
. Mucolipidosis Type IV *(MCOLN1)*
. Multiple Sulfatase Deficiency *(SUMF1)*
. Nemaline Myopathy *(NEB)*
. Niemann-Pick Disease, Type A&B *(SMPD1)*
. Non-Syndromic Hearing Loss *(GJB2)*
. Osteopetrosis 1 *(PKHD1)*
. 3-Phosphoglycerate Dehydrogenase Deficiency *(PHGDH)*
. Polycystic Kidney Disease, Autosomal Recessive *(PKHD1)*
. Pontocerebellar Hypoplasia Type 1A *(VRK1)*
. Primary Ciliary Dyskinesia *(DNAH5)*
. Primary Ciliary Dyskinesia *(DNAI1)*
. Primary Ciliary Dyskinesia *(DNAI2)*
. Primary Hyperoxaluria Type 3 *(HOGA1)*
. Retinitis Pigmentosa 59 *(DHDDS)*
. Tyrosinemia Type I *(FAH)*
. Usher Syndrome Type IF *(PCDH15)*
. Usher Syndrome Type III *(CLRN1)*
. Walker-Warburg Syndrome and Other *FKTN*-Related Dystrophies *(FKTN)*
. Zellweger Syndrome Spectrum *(PEX2)*

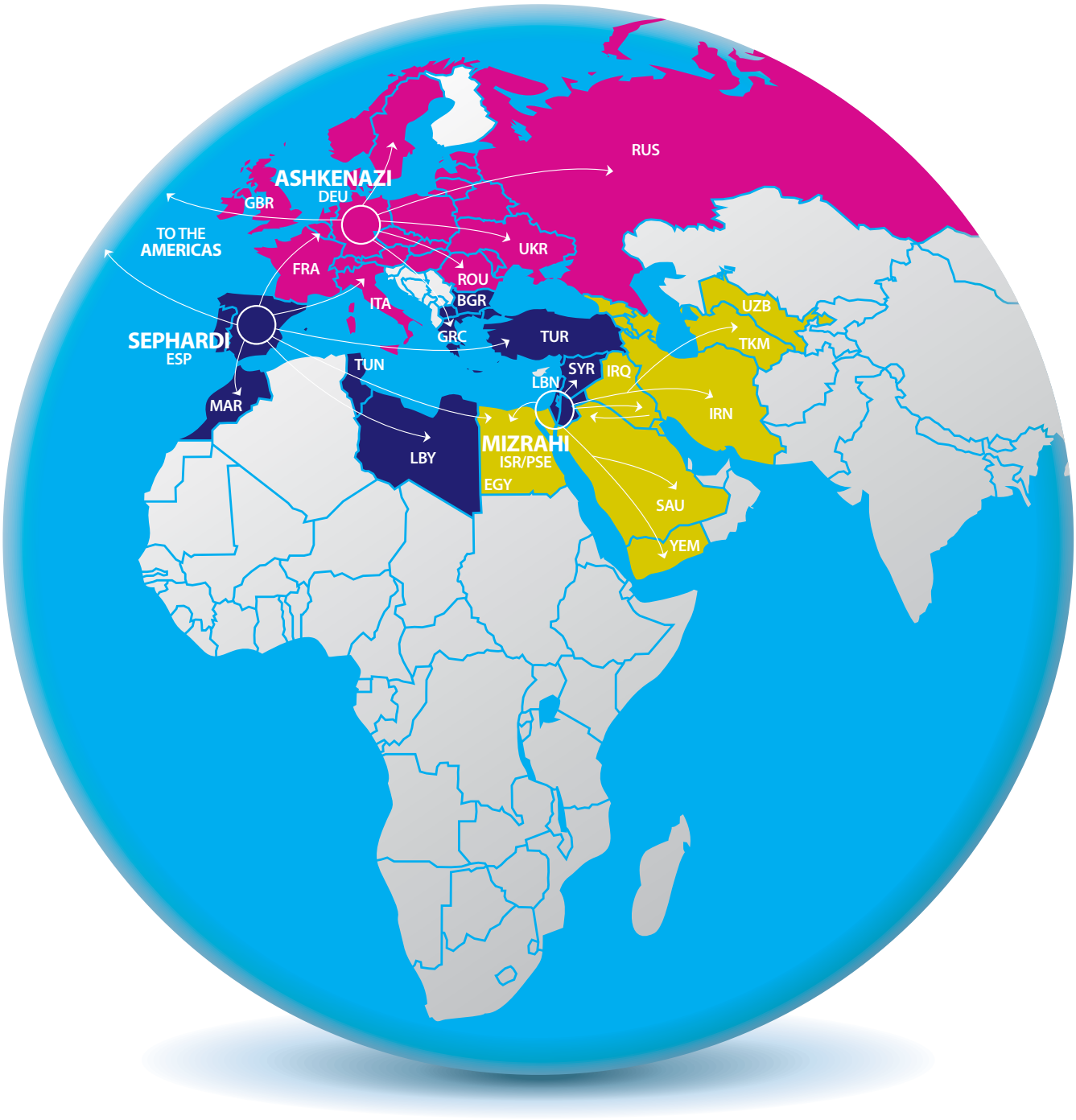
Diseases common to all Jewish groups (10)

. Cystic Fibrosis *(CFTR)*
. Familial Mediterranean Fever *(MEFV)*
. Fragile X Syndrome *(FMR1)*
. Glycogen Storage Disease Type II *(GAA)*
. Phenylalanine Hydroxylase Deficiency *(PAH)*
. Retinitis Pigmentosa 28 *(FAM161A)*
. Smith-Lemli-Opitz Syndrome *(DHCR7)*
. Spinal Muscular Atrophy *(SMN1)*
. Tay-Sachs Disease *(HEXA)*
. Wilson Disease *(ATP7B)*

Sephardi-Mizrahi Disorders (38)

. Acute Infantile Liver Failure *(TRMU)*
. Adrenoleukodystrophy, X-Linked *(ABCD1)*
. Asparagine Synthetase Deficiency *(ASNS)*
. Ataxia-Telangiectasia *(ATM)*
. Beta-Globin-Related Hemoglobinopathies *(HBB)*
. Cerebrotendinous Xanthomatosis *(CYP27A1)*
. Chronic Granulomatous Disease *(CYBA)*
. Congenital Insensitivity to Pain with Anhidrosis *(NTRK1)*
. Congenital Myasthenic Syndrome *(RAPSN)*
. Corticosterone Methyloxidase Deficiency *(CYP11B2)*
. Cystinosis *(CTNS)*
. Fanconi Anemia, Group A *(FANCA)*
. Glycogen Storage Disease Type III *(AGL)*
. Glycogen Storage Disease Type V *(PYGM)*
. Hereditary Spastic Paraparesis, Type 49 *(TECPR2)*
. Homocystinuria due to *MTHFR* Deficiency *(MTHFR)*
. Inclusion Body Myopathy 2 *(GNE)*
. Infantile Cerebral and Cerebellar Atrophy *(MED17)*
. Leber Congenital Amaurosis 2, Retinitis Pigmentosa 20 *(RPE65)*
. Limb Girdle Muscular Dystrophy Type 2B *(DYSF)*
. Megalencephalic Leukoencephalopathy with Subcortical Cysts *(MLC1)*
. Metachromatic Leukodystrophy *(ARSA)*
. 3-Methylglutaconic Aciduria, Type III / Optic Atrophy3, with Cataract *(OPA3)*
. Microphthalmia / Anophthalmia *(VSX2)*
. Mitochondrial Complex I Deficiency *(NDUFS6)*
. Mitochondrial Myopathy and Sideroblastic Anemia 1 *(PUS1)*
. Myoneurogastrointestinal Encephalopathy *(TYMP)*
. Omenn Syndrome *(RAG2)*
. Ornithine Aminotransferase Deficiency *(OAT)*
. Polyglandular Autoimmune Syndrome Type 1 *(AIRE)*
. Pontocerebellar Hypoplasia, Type 6 *(RARS2)*
. Progressive Cerebello-Cerebral Atrophy *(SEPSECS)*
. Renal Tubular Acidosis and Deafness *(ATP6V1B1)*
. Retinitis Pigmentosa 25 *(EYS)*
. Retinitis Pigmentosa 26 *(CERKL)*
. Usher Syndrome Type IIA *(USH2A)*
. Wolman Disease / Cholesteryl Ester Storage Disease *(LIPA)*
. Zellweger Syndrome Spectrum *(PEX6)*

Jewish Migration Map



Comprehensive Jewish Panel (96 Disorders)

Abetalipoproteinemia [*MTTP*]: Severe malabsorption of dietary fats and fat-soluble vitamins causing failure to thrive, diarrhea, blood abnormalities (acanthocytosis), and stool abnormalities (steatorrhea). Symptoms arising later in childhood include poor muscle coordination, ataxia, and retinitis pigmentosa.

Acute Infantile Liver Failure [*TRMU*]: Protein involved in mitochondrial tRNA modification, and is thus important for mitochondrial translation and has been associated with transient infantile liver failure.

Adrenoleukodystrophy, X-linked [*ABCD1*]: A peroxisomal disorder characterized by impaired peroxisomal betaoxidation of very-long-chain fatty acids (VLCFAs) resulting in demyelination of the nervous system and adrenocortical insufficiency.

Alport Syndrome [*COL4A3*]: Progressive loss of kidney function (hematuria, proteinuria) resulting in end-stage renal disease, sensorineural hearing loss, and eye abnormalities such as anterior lenticonus.

Arthrogryposis, Mental Retardation and Seizures [*SLC35A3*]: Arthrogryposis, mental retardation, autism spectrum disorder, epilepsy, microcephaly, and hypotonia.

Asparagine Synthetase Deficiency [*ASNS*]: Enzyme that catalyzes the transfer of ammonia from glutamine to aspartic acid to form asparagine. Phenotyope characterized by congenital microcephaly, intellectual disability, progressive cerebral atrophy, and intractable seizures.

Ataxia Telangiectasia [*ATM*]: Autosomal recessive disorder characterized by cerebellar ataxia, telangiectases, immune defects, and a predisposition to malignancy. Patients present in early childhood with progressive cerebellar ataxia and later develop conjunctival telangiectases, other progressive neurologic degeneration, sinopulmonary infection, and malignancies.

Bardet-Biedl Syndrome [*BBS2*]: Features include retinitis pigmentosa, obesity, polydactyly, intellectual disability/developmental delay, renal problems, anosmia, genital abnormalities, and male infertility. Other affected organs include the heart, liver and digestive system. There is variable age of onset and severity of symptoms.

Beta-globin-related Hemoglobinopathies [*HBB*]: A group of disorders involving the quantity and/or quality of the beta-globin protein. Deficient or abnormal beta-globin results in a deficiency in hemoglobin which leads to abnormalities of the red blood cells' ability to properly transfer oxygen throughout the body. Affected individuals are at risk for poor growth, organ damage (generalized, or specified to the spleen), episodes of pain, and anemia.

Bloom Syndrome [*BLM*]: Poor growth, frequent infections, learning disabilities, predisposition to common cancers such as breast cancer, colon cancer and leukemia.

Canavan Disease [*ASPA*]: Progressive disease of the central nervous system presenting with poor head control, generalized weakness, macrocephaly, seizures, regression of early developmental milestones, and severe mental retardation.

Carnitine Palmitoyltransferase II Deficiency [*CPT2*]: Characterized by recurrent episodes of myalgia and rhabdomyolysis causing myoglobinuria which may be triggered by exercise, stress, exposure to extreme temperatures, infections, or fasting. The first episode usually occurs during childhood or adolescence. Episodes can damage the kidneys, in some cases leading to life-threatening kidney failure.

Cerebrotendinous Xanthomatosis [*CYP27A1*]: An inherited lipid-storage disease characterized clinically by progressive neurologic dysfunction (cerebellar ataxia beginning after puberty, systemic spinal cord involvement and a pseudobulbar phase leading to death), premature atherosclerosis, and cataracts. Large deposits of cholesterol and cholestanol are found in virtually every tissue, particularly the Achilles tendons, brain, and lungs.

Choreoacanthocytosis [*VPS13A*]: Progressive neurological disorder resulting in movement disorders (affecting gait, speech/feeding, as well as control of arms and legs), psychiatric manifestations and cognitive disturbances that begins in late teen/early adulthood.

Chronic Granulomatous Disease [*CYBA*]: A genetically heterogeneous immunodeficiency disorder resulting from an inability of phagocytes to kill ingested microbes. This impairment in killing is caused by any of several defects in the NADPH oxidase enzyme complex which generates the microbicidal 'respiratory burst'.

Congenital Amegakaryocytic Thrombocytopenia [*MPL*]: Pancytopenia, decreased bone marrow activity, and very low platelet counts.

Congenital Disorder of Glycosylation Ia [*PMM2*]: Hypotonia, abnormal fat distribution, strabismus, developmental delay, and failure to thrive appear in infancy. Other symptoms include elevated liver function tests, seizures, and pericardial effusion that could lead to death under 1 year of life due to multiple organ failure. Affected individuals who survive infancy may have intellectual disability, lethargy, temporary paralysis, neuropathy, kyphoscoliosis, ataxia, contractures and retinitis pigmentosa.

Congenital Insensitivity to Pain with Anhidrosis [*NTRK1*]: Congenital insensivity to pain with anhidrosis, also known as hereditary sensory and autonomic neuropathy type IV, belongs to a group of rare autosomal recessive peripheral sensory neuropathies. Clinical features may include loss of pain sensation that leads to fractures, skin lacerations with complications such as infections and Charcot joints, moderate to severe mental retardation which when in combination with insensitivity to pain leads to self-mutilation or autoamputation, and anihidrosis that is often associated with recurrent episodes of unexplained fever that can be fatal.

Congenital Myasthenic Syndrome [*RAPSN*]: A reduction in a normal protein essential to muscle movement triggering. Features include early infancy onset of muscle weakness, respiratory insufficiency, feeding difficulty, and delayed milestones.

Corticosterone Methyloxidase Deficiency [*CYP11B2*]: *CYP11B2* mutations lead to insufficient production of aldosterone leading to salt imbalances in the body. Affected individuals have failure to thrive (as infants), nausea, vomiting, dehydration, low blood pressure, fatigue, and muscle weakness. Additional features can include life-threatening seizures and coma. Individuals who survive infancy usually have diminished symptoms and can have a normal life expectancy.

Cystic Fibrosis [*CFTR*]: Thick mucus accumulation in the lungs leading to breathing difficulty and infection, poor digestion, male infertility, average life expectancy into the 30s.

Cystinosis [*CTNS*]: Cysteine transport defect leading to progressive renal failure. It is a lysosomal storage disorder on the basis of cytologic and other evidence pointing to the intralysosomal localization of stored cystine. The basic defect in cystinosis is impaired cystine transport across the lysosomal membrane. The features resulting from accumulation of cystine in the kidney are those of the Fanconi syndrome.

Deafness, Autosomal Recessive 77 [*LOXHD1*]: Mild- to moderate- hearing loss that onsets during childhood which could progress into moderate- or severe- hearing loss during adulthood.

Dyskeratosis Congenita, Autosomal Recessive [*RTEL1*]: Abnormal growth of fingernails and toenails, pigmentary changes on neck and chest. Symptoms include bone marrow failure, aplastic anemia and increased risk for leukemia. Increased risk for cancers of the head, neck, anus, or genitals. Other features include pulmonary fibrosis, hair loss, osteoporosis, avascular necrosis of the joints, liver disease and short stature.

Ehlers-Danlos VIIC [*ADAMTS2*]: Extremely fragile skin, hypermobility, easy bruising, and blue sclera.

Enhanced S-Cone Syndrome [*NR2E3*]: Childhood onset of vision loss beginning with night blindness and loss of peripheral vision. Vision loss is progressive, but there is some potential improvement with new treatment medications.

Factor XI Deficiency [*F11*]: A condition that can cause uncontrolled bleeding after surgery or injury because of a decrease in production of protein, Factor XI, which contributes to proper clot formation. Expression of the disease (severity/frequency of bleeding) varies from person to person, even within families.

Familial Dysautonomia [*IKBKAP*]: Severe disease of the autonomic nervous system, severe gastrointestinal problems and pulmonary complications such as pneumonia.

Familial Hypercholesterolemia [*LDLR*]: Abnormal low-density lipoprotein receptors caused by mutations in the *LDLR* gene effectively remove cholesterol from the bloodstream primarily into the liver; therefore leaving an excess amount of cholesterol in the blood to be stored in inappropriate places. High cholesterol levels in the bloodstream and other relevant tissues such as the heart can cause serious health conditions (such as early heart disease and even a heart attack).

Familial Hyperinsulinism [*ABCC8*]: Insulin dysregulation, hypoglycemia, seizures, hypotonia, poor feeding, apnea, and low blood sugar in the newborn period or during childhood with variable phenotypes.

Familial Mediterranean Fever [*MEFV*]: A disorder characterized by recurrent attacks of fever and inflammation in the peritoneum, synovium, or pleura, accompanied by pain. Amyloidosis with renal failure is a complication and may develop without overt crises.

Fanconi Anemia, Group A [*FANCA*]: A disorder characterized by developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. The cellular hallmark of FA is hypersensitivity to DNA crosslinking agents and high frequency of chromosomal aberrations pointing to a defect in DNA repair.

Fanconi Anemia Group C [*FANCC*]: Short stature, bone marrow failure, congenital malformations and a predisposition to leukemia, learning disabilities or mental retardation.

Fragile X Syndrome [*FMR1*]: X-linked condition - features include mental retardation, behavioral problems (autistic-like features, etc), and characteristic facial features in affected males. Affected females may also have milder clinical manifestations. Premutation carrier females are at increased risk for premature ovarian insufficiency; whereas premutation carrier males are at increased risk for Fragile X-associated tremor/ataxia syndrome.

Galactosemia [*GALT*]: Feeding difficulties, lethargy, failure to thrive, jaundice, and bleeding within a few days after birth. Increased risk for sepsis and shock, developmental delay/intellectual disability, and cataracts. Managed by dietary restrictions.

Gaucher Disease [*GBA*]: Enlargement of spleen and liver, blood abnormalities (anemia, easy bruising, impaired clotting, etc), and bone problems (joint pain, bone fractures, etc). Variable age of onset and severity of symptoms. Successful enzyme replacement therapy exists, reducing or reversing symptoms.

Glycogen Storage Disease Ia [*G6PC*]: Biochemical abnormalities such as very low glucose level leading to delayed growth/development presenting in infancy. Symptoms include enlarged spleen, gastrointestinal problems, recurrent infection, and pancreatitis. Managed by dietary restrictions.

Glycogen Storage Disease Type II [*GAA*]: A malfunction in the enzyme acid alpha-glucosidase resulting in toxic sugar buildup. There are 3 types of Pompe disease: classic infantile-onset (symptoms include: muscle weakness, poor muscle tone, failure to thrive, heart defects leading to death in the first year of life), non-classic infantile-onset (the following symptoms are usually apparent in the first year of life: delayed motor milestones, progressive muscle weakness, serious breathing problems, leading to death in early childhood), and late-onset (progressive muscle weakness onsetting in adolescence or adulthood, especially in the legs and the trunk, breathing problems that can lead to respiratory failure).

Glycogen Storage Disease Type III [*AGL*]: An autosomal recessive metabolic disorder caused by deficiency of the glycogen debrancher enzyme and associated with an accumulation of abnormal glycogen with short outer chains. Most patients are enzyme-deficient in both liver and muscle (IIIa), but about 15% are enzyme-deficient in liver only (IIIb). Clinically, patients with GSD III present in infancy or early childhood with hepatomegaly, hypoglycemia, and growth retardation. Muscle weakness in those with IIIa is minimal in childhood but can become more severe in adults; some patients develop cardiomyopathy.

Glycogen Storage Disease Type IV / Adult Polyglucosan Body Disease [*GBE1*]: An adult-onset neurological disorder resulting in reduced sensation and progressive muscle weakness. Other features include dementia and poor bladder control.

Glycogen Storage Disease Type V [*PYGM*]: A disorder of muscular glycogen metabolism characterized by exercise intolerance, muscle pain and stiffness on exertion. An autosomal recessive metabolic disorder characterized by onset of exercise intolerance and muscle cramps in childhood or adolescence. Transient myoglobinuria may occur after exercise, due to rhabdomyolysis. Severe myoglobinuria may lead to acute renal failure. Patients may report muscle weakness, myalgia, and lack of endurance since childhood or adolescence. Later in adult life, there is persistent and progressive muscle weakness and atrophy with fatty replacement. McArdle disease is a relatively benign disorder, except for possible renal failure as a complication of myoglobinuria.

Glycogen Storage Disease Type VII [*PFKM*]: *PFKM* mutations lead to the inability of muscles to properly use glycogen, resulting in muscle weakness and eventual breakdown. There are 4 types of GSDVII: classical form of GSDVII (childhood onset muscle pain and cramps, nausea and vomiting after strenuous exercise, myoglobinuria that can damage the kidneys and lead to kidney failure); severe infantile form (leading to jaundice, hypotonia, weakened and enlarged heart and difficulty breathing normally leading to death in the first year of life); late-onset form (myopathy, generally affecting proximal muscles); hemolytic form (hemolytic anemia without muscle pain or weakness).

Hereditary Spastic Paraparesis 49 [*TECPR2*]: A complicated form of spastic paraplegia, a neurodegenerative disorder of the corticospinal tracts. It is characterized by delayed psychomotor development, mental retardation, and onset of spastic paraplegia in the first decade. Affected individuals also have dysmorphic features, thin corpus callosum on brain imaging, and episodes of central apnea, which may be fatal.

Hermansky-Pudlak Syndrome 3 [*HPS3*]: A mild form of oculocutaneous albinism (fair skin, light-colored hair and eyes, and poor vision). Mutations in the *HPS3* gene disrupt the normal function of lysosome-related organelles in melanocytes, impairing proper production and distribution of melanin. Affected individuals are also at increased risk for improper clot formation and bleeding problems.

Homocystinuria due to *MTHFR* Deficiency [*MTHFR*]: A common inborn error of folate metabolism. The phenotypic spectrum ranges from severe neurologic deterioration and early death to asymptomatic adults. In the classic form, both thermostable and thermolabile enzyme variants have been identified.

Inclusion Body Myopathy 2 [*GNE*]: In this adult onset disease decreased production of sialic acid results in progressive proximal and distal muscle weakness. Additionally, there is muscle wasting of the upper and lower limbs with sparing of the quadriceps muscles leading to severe incapacitation within 10 to 20 years.

Infantile Cerebral and Cerebellar Atrophy [*MED17*]: A neurologic disease characterized by postnatal progressive microcephaly, seizures, and brain atrophy.

Joubert Syndrome Type 2 [*TMEM216*]: Neurological disorder associated with a specific brain malformation, developmental delay, mental retardation, breathing difficulties, ataxia, failure to thrive, retinal degeneration and renal dysfunction.

Leber Congenital Amaurosis 2, Retinitis Pigmentosa 20 [*RPE65*]: Visual impairment beginning early in life that could lead to total blindness.

Limb Girdle Muscular Dystrophy Type 2B [*DYSF*]: Part of a group of diseases that cause weakness and wasting of the muscles in the arms and legs. It is characterized by early weakness and atrophy of the pelvic and shoulder girdle muscles in adolescence or young adulthood, with slow progression.

Lipoamide Dehydrogenase Deficiency [*DLD*]: Variable age of onset and severity of symptoms including fatigue, episodes of decompensation, severe neurological decline and sometimes death. Managed by dietary restrictions.

Maple Syrup Urine Disease Ib [*BCKDHB*]: Severe neurological complications including poor suck, irritability, lethargy, coma, death if untreated; even when treated, may result in impaired intellectual development or neurological complications.

Megalencephalic Leukoencephalopathy with Subcortical Cysts [*MLC1*]: A leukodystrophy characterized by early-onset macrocephaly and delayed-onset neurologic deterioration, including cerebellar ataxia, spasticity, epilepsy, and mild cognitive decline.

Metachromatic Leukodystrophy [*ARSA*]: A lysosomal storage disease in which the deficiency of the hydrolase aryl sulfatase A leads to a progressive degenerative disease of the nervous system. The deterioration of the nervous system leads first to deficits in motor function and later to deficits in mental abilities. In most cases the affected child falls into a vegetative state by the age of 3-5 and dies shortly afterward.

3-Methylglutaconic Aciduria, Type III / Optic Atrophy 3, with Cataract [*OPA3*]: Type III 3-methylglutaconic aciduria is a neuro-ophthalmologic syndrome consisting of early-onset bilateral optic atrophy and later-onset spasticity, extrapyramidal dysfunction, and cognitive deficit. Urinary excretion of 3-methylglutaconic acid and of 3-methylglutaric acid is increased.

Microphthalmia / Anophthalmia [*VSX2*]: Microphthalmia / Anophthalmia is a clinically heterogeneous disorder of eye formation ranging from small size of a single eye to the complete absence of ocular tissues. The disorder may be unilateral or bilateral and may present with or without coloboma.

Mitochondrial Complex 1 Deficiency [*NDUFAF5*]: This disease has a wide range of severity from lethal neonatal disease to adult-onset neurodegenerative disease. Features of the disease include macrocephaly with progressive leukodystrophy, encephalopathy, cardiomyopathy, myopathy, liver disease, Leigh syndrome (brain malformations leading to neuromuscular abnormalities, seizures, and eye abnormalities), and Leber hereditary optic neuropathy.

Mitochondrial Complex I Deficiency [*NDUFS6*]: A mitochondrial disease that causes a wide range of clinical disorders, ranging from lethal neonatal disease to adult-onset neurodegenerative disorders. Phenotypes include macrocephaly with progressive leukodystrophy, nonspecific encephalopathy, hypertrophic cardiomyopathy, myopathy, liver disease, Leigh syndrome, Leber hereditary optic neuropathy, and some forms of Parkinson disease.

Mitochondrial Myopathy and Sideroblastic Anemia [*PUS1*]: An oxidative phosphorylation disorder specific to skeletal muscle and bone marrow. Features include myopathy, lactic acidosis, and sideroblastic anemia with ringed sideroblasts.

Mucolipidosis IV [*MCOLN1*]: Severe neurodegenerative condition characterized by a variable degree of growth and psychomotor retardation, abnormalities of the cornea and retina, and inability to speak or walk.

Multiple Sulphatase Deficiency [*SUMF1*]: Accumulation of sulfatides, sulfated glycosaminoglycans, sphingolipids, and steroid sulfates causing neurologic deterioration with mental retardation, skeletal anomalies, organomegaly, and ichthyosis.

Myoneurogastrointestinal Encephalopathy [*TYMP*]: Mitochondrial DNA depletion syndrome-1 (MTDPS1) is an autosomal recessive progressive multisystem disorder clinically characterized by onset between the second and fifth decades of life of ptosis, progressive external ophthalmoplegia (PEO), gastrointestinal dysmotility (often pseudo-obstruction), cachexia, diffuse leukoencephalopathy, peripheral neuropathy, and mitochondrial dysfunction.

Nemaline Myopathy 2 [*NEB*]: Slowly progressive onset of muscle weakness, particularly involving the tone of muscles in the face, neck, upper limbs, and respiratory tract, difficulties with feeding and respiration, and delayed motor development.

Niemann-Pick Type A / B [*SMPD1*]: Severe neurodegenerative condition, loss of brain function and enlargement of the liver and spleen, average life expectancy 2–3 years of age.

Nonsyndromic Hearing Loss [*GJB2*]: Hearing loss ranging from mild to severe that onsets during childhood. Treatment can include hearing aids and/or cochlear implant. This disorder is isolated to an acoustic impairment and does not affect any other organ systems.

Omenn Syndrome [*RAG2*]: A severe form of immunodeficiency characterized by T-cell infiltration of skin, gut, liver, and spleen, leading to diffuse erythroderma, protracted diarrhea, failure to thrive, and hepatosplenomegaly.

Ornithine Aminotransferase Deficiency [*OAT*]: Gyrate atrophy of the choroid and retina due to deficiency of ornithine aminotransferase is clinically characterized by a triad of progressive chorioretinal degeneration, early cataract formation, and type II muscle fiber atrophy. Characteristic chorioretinal atrophy with progressive constriction of the visual fields leads to blindness at the latest during the sixth decade of life. Patients generally have normal intelligence.

Osteopetrosis 1 [*TCIRG1*]: Features of the disorder include macrocephaly, progressive deafness and blindness, hepatosplenomegaly, and severe anemia beginning in early infancy. Deafness and blindness are generally thought to represent effects of pressure on nerves - all features are related to abnormal bone formation.

Phenylalanine Hydroxylase Deficiency [*PAH*]: Inability to tolerate phenylalanine, commonly found in everyday foods. If not managed properly, affected individuals can display microcephaly, epilepsy, decreased skin and hair pigmentation, eczema, severe intellectual disability, and behavior problems. Management includes dietary restrictions and other treatment medications.

3-Phosphoglycerate Dehydrogenase Deficiency [*PHGDH*]: Microcephaly, psychomotor retardation, and seizures.

Polycystic Kidney Disease, Autosomal Recessive [*PKHD1*]: Cyst development in the kidneys causes kidney enlargement and can lead to kidney failure. Symptoms include cysts in the liver, hypertension, hematuria, recurrent urinary tract infections, kidney stones, and an increased risk for aneurysms. This condition is often lethal early in life.

Polyglandular Autoimmune Syndrome, Type I [*AIRE*]: A disease characterized by the presence of 2 of 3 major clinical symptoms: Addison disease, hypoparathyroidism, and/or chronic mucocutaneous candidiasis.

Pontocerebellar Hypoplasia Type 1A [*VRK1*]: Brain development abnormalities that lead to developmental delay, problems with movement, and intellectual disability.

Pontocerebellar Hypoplasia, Type 6 [*RARS2*]: A heterogeneous group of disorders characterized by an abnormally small cerebellum and brainstem and associated with severe developmental delay.

Primary Ciliary Dyskinesia [*DNAH5*]: Abnormal cilia formation leads to respiratory problems such as chronic infection (due to improper clearing of the lungs), infertility in males (due to abnormal sperm tails), and possible situs invertus (organs forming on the opposite side of the body).

Primary Ciliary Dyskinesia [*DNAI1*]: Abnormal cilia formation leads to respiratory problems such as chronic infection (due to improper clearing of the lungs), infertility in males (due to abnormal sperm tails), and possible situs invertus (organs forming on the opposite side of the body).

Primary Ciliary Dyskinesia [*DNAI2*]: Mutations in *DNAI2* cause abnormal cilia formation leading to respiratory problems such as chronic infection (due to improper clearing of the lungs), infertility in males (due to abnormal sperm tails), and possible situs invertus (organs forming on the opposite side of the body).

Primary Hyperoxaluria Type 3 [*HOGA1*]: Affected individuals may have repeated kidney stone malformation; however, many can live through life completely asymptomatic.

Progressive Cerebello-Cerebral Atrophy [*SEPSECS*]: A disease characterized by progressive microcephaly, postnatal onset of progressive atrophy of the cerebrum and cerebellum, profound mental retardation, spasticity, and variable seizures.

Renal Tubular Acidosis and Deafness [*ATP6V1B1*]: This gene encodes a component of vacuolar ATPase (V-ATPase), a multisubunit enzyme that mediates acidification of intracellular organelles and has been shown to lead to renal tubular acidosis and progressive sensorineural hearing deficit.

Retinitis Pigmentosa 25 [*EYS*]: An inherited ocular disease that results in a progressive retinal degeneration. Symptoms include night blindness, the development of tunnel vision, and slowly progressive decreased central vision starting at approximately 20 years of age.

Retinitis Pigmentosa 26 [*CERKL*]: An inherited ocular disease that results in a progressive retinal degeneration. Symptoms include night blindness, the development of tunnel vision, and slowly progressive decreased central vision starting at approximately 20 years of age.

Retinitis Pigmentosa 28 [*FAM161A*]: An inherited ocular disease that results in a progressive retinal degeneration. Symptoms include night blindness, the development of tunnel vision, and slowly progressive decreased central vision starting at approximately 20 years of age.

Retinitis Pigmentosa 59 [*DHDDS*]: Childhood loss of night vision developing into peripheral blind spots and, later, leading to tunnel vision and blindness.

Smith-Lemli-Opitz Syndrome [*DHCR7*]: Characteristic facial features, microcephaly, intellectual disability, and behavioral problems (e.g. autism). Abnormalities of the heart, lungs, kidneys, gastrointestinal tract, fingers/toes and genitalia are also common. Variable severity of symptoms.

Spinal Muscular Atrophy [*SMN1*]: Severe and progressive weakness of the voluntary muscles affecting breathing, swallowing, head/neck control, walking and crawling. Variable onset and severity, with shortened lifespan for those with onset in infancy.

Tay-Sachs Disease [*HEXA*]: A progressive neurodegenerative disorder which is characterized by the onset in infancy of developmental retardation, followed by paralysis, dementia and blindness, with death in the second or third year of life. A gray-white area around the retinal fovea centralis, due to lipid-laden ganglion cells, leaving a central 'cherry-red' spot is a typical funduscopic finding. Pathologic verification is provided by the finding of the typically ballooned neurons in the central nervous system. An early and persistent extension response to sound ('startle reaction') is useful for recognizing the disorder.

Tyrosinemia, Type I [*FAH*]: Tyrosine aminotransferase deficiency that can affect the eyes, skin, and mental development. Symptoms include photophobia, painful skin lesions on the palms and soles, and intellectual disability.

Usher Syndrome, Type IF [*PCDH15*]: Profound hearing loss and prepubertal onset of retinitis pigmentosa with progressive degeneration of the cells in the retina.

Usher Syndrome, Type IIA [*USH2A*]: A clinically and genetically heterogeneous autosomal recessive disorder characterized by sensorineural hearing deficiencies at birth and later development of progressive retinitis pigmentosa. It is the most frequent cause of combined deafness and blindness in adults and affects 3 to 6% of children born with hearing impairment. In brief, patients with Usher syndrome type II have mild hearing impairment with normal vestibular responses.

Usher Syndrome, Type III [*CLRN1*]: Postlingual onset of moderate to severe hearing loss and variable onset and severity of retinitis pigmentosa.

Walker Warburg Syndrome and Other *FKTN*-Related Dystrophies [*FKTN*]: Muscle weakness, feeding difficulties, seizures, blindness, brain malformations and developmental delay with mental retardation, life expectancy less than 3 years.

Wilson Disease [*ATP7B*]: A disease characterized by dramatic build-up of intracellular hepatic copper with subsequent hepatic and neurologic abnormalities.

Wolman Disease / Cholesteryl Ester Storage Disease [*LIPA*]: An early-onset fulminant disorder of infancy with massive infiltration of the liver, spleen, and other organs by macrophages filled with cholesteryl esters and triglycerides. Death occurs early in life.

Zellweger Syndrome Spectrum [*PEX2*]: Demyelination of white matter causing hypotonia, feeding problems, hearing loss, vision loss, and seizures. Other affected organs include the liver, heart, kidneys, and bones. Life expectancy is shortened.

Zellweger Syndrome Spectrum [*PEX6*]: A disorder characterized by absence of morphologically identifiable peroxisomes and deficiency of multiple peroxisomal metabolic functions. PBDs are multisystem disorders manifesting with craniofacial dysmorphism, hypotonicity, seizures, psychomotor retardation, vision and hearing impairment, and skeletal, renal, hepatic, and gastrointestinal disease.