EMORY UNIVERSITY SCHOOL OF MEDICINE

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Ashkenazi Jewish Comprehensive Carrier Screening

(Tay Sachs, Canavan Disease, Familial Dysautonomia, Cystic Fibrosis, Bloom, Fanconi Anemia, Gaucher, Mucolopidosis IV, Niemann Pick A)

Ashkenazi Ancestry: Having relatives from Eastern or Central Europe who practiced the Jewish faith, regardless of an individual's current religion or residence.

Sephardic Ancestry: Having relatives from Mediterranean areas (Greece, Spain, etc.) who practiced the Jewish faith, regardless of an individual's current religion or residence.

Autosomal Recessive (AR): A genetic condition caused by inheritance of an abnormal gene from two carrier parents. The chance of an affected child is 1 in 4 or 25% for each pregnancy of two carrier parents.

Inheritance: All of the conditions included in this screening panel are inherited in an autosomal recessive manner.

The following conditions are more prevalent among individuals of Ashkenazi Jewish ancestry than in the general population:

Tay Sachs Disease is fatal in children (usually by age 5) and involves progressive degeneration of the central nervous system. Absence of an enzyme called *hexosaminidase* A (or hex A) causes a fatty substance to build up in the brain and spine. The process begins in the fetus prenatally, but is not evident until the child is several months old. To date, there is no cure for Tay Sachs disease.

Canavan Disease is similar to Tay Sachs in that it also involves progressive degeneration of the central nervous system and is fatal in early childhood. The condition is caused by the absence of an enzyme called *aspartoacylase* (ASPA). To date there is no cure for Canavan disease.

Familial Dysautonomia (FD) is a rare genetic condition involving deficiency of the enzyme *beta hydroxylase*. The sensory and autonomic nerves (those controlling involuntary functions) are affected, resulting in problems with blood pressure control, temperature regulation, feeding, growth, sensitivity to pain, and others. Early diagnosis and treatment improves prognosis and survival, but there is no cure for the disease.

Cystic Fibrosis (CF) is a condition with a range of clinical severity. People with classic CF secrete abnormally thick body fluids, especially in their lungs. The mucus interferes with normal body functions and leads to chronic infections. Classic CF also involves the pancreas, resulting in decreased absorption of nutrients. Survival rates have improved, but death ultimately occurs from respiratory failure. Some variant forms of CF may have *only* lung involvement, pancreatitis, sinusitis, or infertility.

Bloom syndrome is caused by a gene defect that results in an increased number of chromosomal breaks. Affected persons generally have short stature, skin color changes and rashes (especially after sunlight exposure), and increased susceptibility to infections and cancer. Mental retardation occurs in some affected individuals. Fertility problems are common in both sexes. While there is no cure for Bloom syndrome, treatment is geared toward prevention of symptoms.

Fanconi anemia, type C is also caused by a gene defect that results in an increased number of chromosomal breaks. This leads to decreased production of blood cells, skeletal abnormalities, and an increased risk of cancer. Onset is usually in childhood, with survival into the late teens or early twenties. Mental retardation, gastrointestinal problems and cardiac abnormalities are seen in some affected individuals. In rare cases, diagnosis is in adulthood, generally because of atypical cancers. Treatment is primarily preventative and includes frequent screenings and avoidance of the sun and agents that cause chromosomal damage.

Gaucher disease, Type 1 is caused by deficiency of the enzyme *glucocerebrosidase* which results in storage of a fatty substance called glucocerebroside in the spleen, liver, bone marrow and other systems. Onset may be early in life or delayed until adulthood. Symptoms include easy bruising and bleeding, anemia, chronic fatigue, liver and spleen enlargement, bone pain and bone fractures. Highly effective enzyme replacement therapy is available, but there is no cure at this time.

Mucolipidosis, type IV (ML4) is caused by a gene defect that leads to abnormalities of the nervous system and the eyes. The earliest sign of ML4 may be clouding of the corneas in the first year of life, along with delayed motor milestones, mental retardation and slowly progressive neurological deterioration. Affected persons have lived into their mid 40s. Treatment includes supportive care, such as occupational or physical therapy. There is no cure for ML4.

Niemann Pick Disease, type A is caused by lack of the enzyme *acid sphingomylinase* (ASM), resulting in accumulation of a fatty substance called sphingomyelin, and leading to severe damage to the central nervous system, liver, and lungs. Symptoms beginning in infancy include loss of previously achieved milestones, blindness, progressive spasticity, enlargement of the liver and spleen, and a "cherry red spot" in the back of the eye. There is currently no cure, and death usually occurs by age 2-3.

Disease	Gene/Enzyme	Carrier Rate	Methodology	Detection Rate
Tay Sachs	*Hex A* Hexosaminidase A	1 in 30 Ashkenazi 1 in 30 French Canadian/Cajun 1 in 300 other ancestries	Analysis for 7 common gene mutations	Over 92%
Canavan Disease	*ASPA* Aspartoacylase	1 in 36 Ashkenazi 1 in 360 other ancestries	Analysis for 4 common gene mutations	Over 98%
Familial Dysautonomia	*IKBKAP* Beta-hydroxylase	1 in 30 Ashkenazi	Analysis for 2 common gene mutations	Over 99%
Cystic Fibrosis	*CFTR* CF Transmembrane Conductance Regulator	1 in 29 Ashkenazi 1 in 29 Caucasians 1 in 46 Hispanics 1 in 60-65 African Americans 1 in 90 Asians	Analysis for 32 common gene mutations	94% Ashkenazi 88% Caucasians 72% Hispanics 65% African Americans 49% Asians
Bloom syndrome	*BLM*	1 in 100 Ashkenazi	Analysis for 1 common gene mutation	Over 97%
Fanconi Anemia, type C	*FANCC*	1 in 89 Ashkenazi	Analysis for 2 common gene mutations	Over 99%
Gaucher, type1	*GBA* Glucocerebrosidase	1 in 15 Ashkenazi	Analysis for 8 common gene mutations	Over 97%
Mucolipidosis, type IV	*MCOLN1* Mucolipin 1	1 in 127 Ashkenazi	Analysis for 2 common gene mutations	Over 96%
Niemann Pick, type A	*ASM* Spingomylinase	1 in 90 Ashkenazi	Analysis for 4 common gene mutations	Over 95%

If you have any questions about this information, please call Emory Genetics at 1-800-366-1502 and ask to speak with the Genetic Counselor on-call.