

# ASHKENAZI JEWISH SCREENING PANEL

The Ashkenazi Jewish screening panel currently consists of testing for seven diseases common in the Ashkenazi Jewish population: Bloom syndrome (BLM), Canavan disease (CVN), Familial dysautonomia (FD), Fanconi anemia group C (FA-C), Mucopolysaccharidosis type IV (MLP4), Niemann-Pick disease type A & B (NP) and Tay-Sachs disease (TSD). Although these conditions have been reported in individuals of various ethnic backgrounds, these diseases occur most frequently in people of Ashkenazi Jewish ancestry.

## GENETICS

These conditions present when a child receives two copies of an altered gene, one from each parent. Any person with one copy of an altered gene is a carrier of that disease. Carriers are not affected themselves and will not develop the disease. However, if their partner is also a carrier for the same disease, there is a one in four chance (25%) that their baby will be born with the disease condition. There is a three in four chance (75%) that their baby will not have the disease condition.

## WHO SHOULD BE TESTED?

- Individuals at elevated risk of being carriers of BLM, CVN, FD, FA-C, MLP4, NP or TSD
- Individuals of Ashkenazi Jewish descent

## TEST METHODS

- Direct mutation detection assay to test for mutations causing BLM, CVN, FD, FA-C, MLP4, NP and TSD common in the Ashkenazi Jewish population.

## TEST SENSITIVITY

In the Ashkenazi Jewish population approximately 95-99% of patients will have mutations detectable by this test (see chart). The detection rate in other ethnic populations is not well known. As prior carrier risk varies by ethnic origin, individual risk reductions are not provided for non-Ashkenazi Jewish individuals.

| Disease Indication                | Carrier frequency in AJ pop'n | Gene          | Mutation (cDNA, aa)   | Detection rate in the AJ pop'n |
|-----------------------------------|-------------------------------|---------------|---|--------------------------------|
| Bloom Syndrome                    | ~1 in 102                     | <i>BLM</i>    | 2281del6ins7, 2281del6, 2407dupT  | 98%                            |
| Canavan Disease                   | ~ 1 in 57                     | <i>ASPA</i>   | 433-2A>G, Y231X, E285A, A305E, Y288C  | 98%                            |
| Familial dysautonomia             | ~ 1 in 30                     | <i>IKBKAP</i> | R696P, R696Q, IVS20+6T>C  | 99%                            |
| Fanconi Anemia, Group C           | ~1 in 89                      | <i>FANCC</i>  | 322delG, IVS4+A>T   | 99%                            |
| Mucopolysaccharidosis IV          | ~1 in 100                     | <i>MCOLN1</i> | IVS3-2A>G, Delta6.4kb   | 95%                            |
| Niemann Pick Disease (type A & B) | ~1 in 90                      | <i>SMPD1</i>  | DeltaR608, R496L, F333fs(fs330), L302P  | 95%                            |
| Tay-Sachs disease                 | ~ 1 in 29                     | <i>HEXA</i>   | R178H, R178L, G250D, G269S, 1278dupTATC, IVS12+1G>C, G250S**, delta7.6kb**, IVS9+1G>A**, R247W*, R249W* | 99%                            |

\*Non-disease-causing pseudodeficiency alleles. Individuals that have a pseudodeficiency allele are not affected by Tay-Sachs disease, and are not carriers of the disease.

\*\*Reported in non-Ashkenazi Jewish chromosomes. Tay Sachs disease is seen at an increased frequency in the French Canadian and Cajun populations.

### For More Information

The National Foundation for Jewish Genetic Diseases [www.nfjgd.org](http://www.nfjgd.org)

Online Mendelian Inheritance in Man <http://www.ncbi.nlm.gov/omim>

- BLM #210900
- CVN #272800
- FD #223900
- FA-C #227650
- NP#257200
- MLP4 #252650
- TSD #271900

To locate a genetics center near you, please visit the Canadian Association of Genetic Counsellors website at [www.caqc-acccg.ca](http://www.caqc-acccg.ca) or the National Society of Genetic Counsellors website at [www.nsgc.org](http://www.nsgc.org)



1. Current molecular testing will not detect all possible mutations in these genes. A negative result does not rule out the possibility that the individual carries a rare mutation not included in the assay.

2. Test results should be interpreted in the context of clinical findings, family history, ethnic background and other laboratory data.

3. The test sensitivity and specificity is different in individuals who are not of Ashkenazi Jewish ancestry.

4. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.

## ASHKENAZI JEWISH SCREENING PANEL

**BLOOM SYNDROME** (BLM) is characterized by short stature, sun-sensitive facial erythema, and immunodeficiency. Individuals with BLM are at increased risk for the development of cancer and diabetes. BLM is an autosomal recessive (AR) condition caused by the lack of RecQ DNA helicase, an enzyme involved in DNA repair. The BLM gene which codes for RecQ DNA helicase located at 15q26.1.

**CANAVAN DISEASE** Patients with Canavan disease (CVN) exhibit progressive mental delay, atonia of neck muscles, macrocephaly, hyperextension of legs, flexion of arms and blindness. Although survival rates vary, the majority of patients with CVN die in childhood. CVN is an AR disorder caused by a deficiency of the enzyme aspartoacylase, which breaks down N-acetylaspartic acid (NAA). The gene for aspartoacylase (*ASPA*) has been localized to chromosome 17p13-*pter*.

**FAMILIAL DYSAUTONOMIA** (FD) is a progressive degenerative disorder affecting the autonomic and sensory nervous systems. Some common features of FD include a decreased ability to feel pain or temperature sensations, blood pressure and body temperature fluctuations, difficulties feeding and swallowing, gastrointestinal motility problems, developmental delay, recurrent pneumonias and decreased stature. FD is an AR disorder caused by a mutation in the *IKBKAP* gene, located on chromosome 9 (9q31).

**FANCONI ANEMIA** (FA) is a clinically and genetically heterogeneous condition. Both interfamilial and intrafamilial clinical heterogeneity has been reported. Clinical findings in individuals with FA include: anemia, progressive pancytopenia; abnormal skin pigmentation; short stature; and/or multiple malformations of the skeletal and organ systems. Individuals with FA are at increased risk for leukemias and solid tumours. Fancioni anemia group C (FA-C) is the most common form of FA seen in the AJ population. FA-C is an AR disorder caused by mutations in the *FANCC* gene, located on chromosome 9 (9q22.3).

**MUCOLIPIDOSIS IV** Mucopolipidosis IV (MLP4) is a neurodegenerative lysosomal storage disorder characterized by severe psychomotor retardation, ophthalmological abnormalities including corneal clouding, retinal degeneration and strabismus, elevated blood gastrin and iron deficiency. Most patients present at 2-3 years of age and remain in an apparent steady-state for the next 2-3 decades. MLP4 is an AR disorder caused by mutations in the *MCOLN1* gene, located on chromosome 19 (19p13.3).

**NIEMANN-PICK DISEASE (TYPE A&B)** (NP) are lysosomal storage disorders resulting from the accumulation of sphingomyelin, cholesterol and other lipids in the cells of affected individuals due to a deficiency of sphingomyelinase activity. Niemann-Pick type A (NPA) presents in infancy with organomegaly and rapid neurodegeneration leading to death by ~3 years of age. Niemann-Pick type B (NPB) is clinically heterogeneous and individuals can present with multiple findings including hepatosplenomegaly, growth delay, frequent respiratory infections, fatigue and hematologic abnormalities. Individuals with NPB usually survive into adulthood. DNA testing for three mutations common in the Ashkenazi Jewish population for NPA and one mutation in NPB is performed. NP is an AR disorder caused by mutations in the *SMPD1* gene, located on chromosome 11 (11p15.4).

**TAY-SACHS DISEASE** (TSD) is characterized by progressive weakness and loss of motor skills beginning between three and six months of age. Over time, signs of progressive neurodegeneration occur, such as seizures, blindness, and paralysis, usually leading to death before the age of four. TSD is caused by a deficiency of the enzyme hexosaminidase-A (Hex-A). Deficiency of the Hex-A enzyme can also be identified by biochemical enzyme tests. TSD is an AR disorder caused by mutations in the *HEXA* gene, located on chromosome 15 (15q23-q24). The benign pseudodeficiency alleles [R247W & R249W] do not increase the risk for Tay-Sachs disease.

TSD is also seen at a comparable frequency in other ethnic groups including French Canadians and Cajuns. Two mutations that are seen more frequently in the French Canadian population are also screened for as part of this panel.