

# Jewish Genetic Disease Panel

*TO DETERMINE CARRIER STATUS FOR EIGHT DISEASES COMMON TO ASHKENAZI JEWISH INDIVIDUALS*

## Clinical Background

- Disease Overview
  - In 2004, the American College of OB/GYN (ACOG) recommended routine preconceptual or prenatal carrier screening for Canavan disease, cystic fibrosis, familial dysautonomia, and Tay-Sachs disease in individuals of Eastern European Jewish (Ashkenazi) descent.
  - ACOG also indicated carrier screening should be made available for mucopolipidosis IV, Niemann-Pick disease Type A, Fanconi anemia group C, Bloom syndrome, and Gaucher disease to Ashkenazi Jewish individuals. DNA-based carrier screening for the above conditions in this ethnic group is possible due to a relatively small number of common mutations.
- Epidemiology
 

The following table applies only to individuals of Ashkenazi descent. The incidence and carrier rate is mostly not known in non-Ashkenazi individuals.

Disease	Average Age of Death	Disease Incidence in Ashkenazi Jewish	Carrier Rate in Ashkenazi Jewish
Bloom syndrome	Variable	1/40,000	1/100
Canavan disease	Teens	1/10,000	1/50
Familial dysautonomia	60% survive until 20s	1/3,600	1/32
Fanconi anemia Group C	8 to 12 years	1/32,000	1/89
Gaucher disease	Highly variable (infancy to adulthood)	1/900	1/15
Mucopolipidosis IV	Variable childhood to adulthood	1/63,000	1/127
Niemann-Pick disease Type A	3 years	1/32,000	1/90
Tay-Sachs disease	3 to 4 years	1/3,000	1/30

- Genetics
 

Disorders tested by this assay are inherited in an autosomal recessive fashion.

Disease	Gene Symbol	Mutation(s) Screened	Detection in Ashkenazi Jewish	Detection in Non-Ashkenazi Jewish
Bloom syndrome	BLM	2281del6/ins7	95%	Unknown
Canavan disease	ASPA	Y231X, E285A, A305E, 433(-2)A>G	99%	55%
Familial dysautonomia	IKBKAP	R696P, IVS20(+6)T>C	99%	Unknown
Fanconi anemia Group C	FANCC	322delG, IVS4(+4)A>T	99%	Unknown

Disease	Gene Symbol	Mutation(s) Screened	Detection in Ashkenazi Jewish	Detection in Non-Ashkenazi Jewish
Gaucher disease	GBA	84G>GG, IVS2(+1)G>A, N370S, Delta55bp, V394L, D409H, L444P, R496H	90%	55%
Mucopolipidosis IV	MCOLN1	Delta6.4kb, IVS3(-2)A>G	95%	Unknown
Niemann-Pick disease Type A	SMPD1	L302P, 1BP DEL fsP330, R496L, Delta R608	95%	Unknown
Tay-Sachs disease	HEXA	Delta7.6kb, R247W, R249W, G269S, IVS9(+1G>A), 1278insTATC, IVS12(+1)G>C	92%	Unknown

- Pathophysiology
  - Bloom syndrome is caused by a deficiency of a DNA helicase, leading to pre- and postnatal growth deficiency, sparse subcutaneous tissue, sun-sensitive telangiectatic hypo- and hyperpigmented skin lesions, chromosome instability causing benign and malignant tumors early in life, and male sterility.
  - Canavan disease is a neurodegenerative brain disorder, resulting in macrocephaly and lack of head control by 3 to 5 months of age. This progresses to a failure to achieve sitting, ambulation, or speech and leads to death, typically in early childhood to teen years.
  - Familial dysautonomia is caused by abnormal development and survival of sensory, sympathetic, and parasympathetic neurons. This leads to a debilitating disease of gastrointestinal dysfunction, vomiting and autonomic crises, recurrent pneumonia, altered sensitivity to pain and temperature, scoliosis, and cardiovascular instability. Other characteristics include: infantile hypotonia, a broad based ataxic gait that deteriorates, and decreased life expectancy.
  - Fanconi anemia group C is caused by a deficiency of FANCC, resulting in short stature, abnormal skin pigmentation, and multiple malformations including: eyes, ears, heart, oral cavity, thumbs, forearms, kidneys, urinary tract, hearing loss, hypogonadism, and developmental delay. Progressive bone marrow failure occurs during the first decade of life. Hematologic and nonhematologic malignancies occur in ~20 percent and ~30 percent of those affected, respectively.
  - Gaucher is a lysosomal storage disease with extreme variability from perinatal lethality to individuals who are asymptomatic. Three subtypes have been described based on their characteristics. Type one has bone disease, hepatosplenomegaly, anemia, thrombocytopenia, and lung disease but no primary CNS disease. Type two has CNS onset before age 2 and progresses rapidly to death by age 4. Type three may have onset by age 2, but is slowly progressive, resulting in death, usually in one's 20s or 30s.

- Mucopolipidosis IV is a lysosomal storage disorder, leading to early onset severe psychomotor delay and progressive visual impairment from corneal clouding and retinal degeneration. Although most affected individuals' neurological state remains static until age 30, about 15 percent of those affected will have neurological degeneration. Affected persons may occasionally learn to say a few words or to walk independently.
- Niemann-Pick disease Type A is a lysosomal storage disease resulting in the accumulation of lipid in CNS ganglion cells, leading to cell death. Symptoms include: hepatosplenomegaly, delayed physical and mental growth, hypotonia, rigidity, mental retardation, and death by age 3.
- Tay-Sachs disease is a lysosomal storage disease caused by accumulation of glycosphingolipid (GM2) ganglioside. This leads to loss of motor skills beginning at 3 to 6 months of age that progresses to blindness, seizures, and total incapacitation and death by 4 years of age.

### Indications for Ordering

- Carrier screening  
All persons of Ashkenazi descent who are planning a pregnancy or are currently pregnant.
- Contraindications for ordering
  - Non-Jewish individuals who have relatives who carry or are affected with one of the panel disorders should only be tested for the specific disorder in the family.
  - Non-Jewish individuals whose partners are carriers should only be tested for the specific disorder their partner carries.
  - Individuals of French-Canadian and Cajun descent should only undergo Tay-Sachs screening, as they are not known to be at increased risk for the other disorders in this panel.
- Additional Ordering Notes  
Please provide information about whether the individual being tested is of Ashkenazi descent, any family history of the above disorders, and specific familial mutations, if known.

### Interpretation

- If no mutations are identified in any of the common Ashkenazi Jewish disorders screened by this panel, the results are reported as negative. If the patient is of Ashkenazi Jewish descent and has no family history of these diseases, he/she may use the table below to review the reduced carrier risk for each disorder. If the patient is not of Ashkenazi Jewish descent or has a positive family history, the figures in the table do not apply.

Disease	Gene Symbol	Mutation(s) Screened	Clinical Sensitivity in Ashkenazi	Disease Incidence in Ashkenazi	Carrier Rate Before Test in Ashkenazi	Carrier Rate After Test in Ashkenazi
Bloom syndrome	BLM	2281del6/ins7	95%	1/40,000	1/100	1/1,980
Canavan disease	ASPA	Y231X, E285A, A305E, 433(-2)A>G	99%	1/10,000	1/50	1/4,900
Familial dysautonomia	IKBKAP	R696P, IVS20(+6)T>C	99%	1/3,600	1/32	1/3,100
Fanconi anemia Group C	FANCC	322delG, IVS4(+4)A>T	99%	1/32,000	1/89	1/8,800

Disease	Gene Symbol	Mutation(s) Screened	Clinical Sensitivity in Ashkenazi	Disease Incidence in Ashkenazi	Carrier Rate Before Test in Ashkenazi	Carrier Rate After Test in Ashkenazi
Gaucher disease	GBA	84G>GG, IVS2(+1)G>A, N370S, Delta55bp, V394L, D409H, L444P, R496H	90%	1/900	1/15	1/140
Mucopolipidosis IV	MCOLN1	Delta6.4kb, IVS3(-2)A>G	95%	1/63,000	1/127	1/2,500
Niemann-Pick disease Type A	SMPD1	L302P, IBP DEL, f8P330, R496L, Delta R608	95%	1/32,000	1/90	1/1,780
Tay-Sachs disease	HEXA	Delta7.6kb, R247W, R249W, G269S, IVS9(+1)G>A, 1278insTATC, IVS12(+1)G>C	92%	1/3,000	1/30	1/480

- If one mutation is detected for one of these genes, the report identifies the patient as a carrier of that disease, and genetic counseling and screening for that disease in the patient's reproductive partner are recommended. If the patient is of Ashkenazi Jewish descent and has no family history of these diseases, he/she may use the table above to review the reduced carrier risk for the other disorders. If the patient is not of Ashkenazi Jewish descent or has a positive family history, the figures in the table do not apply.

### Methodology

The assay is designed to detect the 30 mutations and one polymorphism involved in eight different diseases using polymerase chain reaction (PCR), multiplexed allele-specific primer extension (ASPE) via bead array, and fluorescent detection.

### Related Tests

- Each test on the Ashkenazi Jewish Panel can be ordered as a stand-alone test.
- Blood Syndrome (BLM), (0051433)
- Canavan (ASPA), (0051453)
- Familial dysautonomia (IKBKAP), (0051463)
- Fanconi anemia Group C (FANCC), (0051468)
- Gaucher disease (GBA), (0051438)
- Mucopolipidosis IV (MCOLN1), (0051448)
- Niemann-Pick disease Type A (SMPD1), (0051458)
- Tay-Sachs disease (HEXA), (0051428)

### References

1. ACOG Committee Opinion No. 298 Prenatal and Preconceptional Carrier Screening for Genetic Diseases in Individuals of Eastern European Jewish Descent. *Ob Gyn* 2004;298:425-8.
2. Leib, Jennifer, et al. Carrier screening panels for Ashkenazi Jews: Is more better? *Gen Med* 2005;7;3:185-89.
3. Online Genetests at [www.genetests.org](http://www.genetests.org).
4. Online Mendelian Inheritance in Man at [www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov).

**The Molecular Genetic DNA Test Request Form has been updated to include the Ashkenazi Jewish Panel, as well as each of its individual components. Fetal Molecular Genetic DNA testing has been moved to a separate form. Please call Client Services at (800) 522-2787 to order updated forms.**

## Test Information

**0051415**      **Ashkenazi Jewish Panel**  
**0051416**      **Ashkenazi Jewish Panel, Fetal**

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).