Ashkenazi Jewish Diseases (*BLM, ASPA, IKBKAP, FANCC, GBA, MCOLN1, SMPD1, HEXA*)

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

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 mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, Bloom syndrome, and Gaucher disease to Ashkenazi Jewish individuals.
- Approximately 25 percent of Ashkenazi Jewish individuals carry a gene mutation for any one of these disorders
- DNA-based carrier screening for the above conditions in Ashkenazi Jewish individuals is possible due to a relatively small number of common mutations in this population.

Epidemiology

The following table applies only to individuals of Ashkenazi descent. The incidence and carrier rate is mostly unknown 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
Mucolipidosis 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

The eight 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(C>A), E285A, A305E, 433(-2)A>G Polymorphism: Y231Y (C>T)	99%	55%
Familial dysautonomia	*IKBKAP*	R696P, IVS20(+6)T>C	99%	Unknown
Fanconi anemia group C	*FANCC*	322delG, IVS4(+4)A>T	99%	Unknown
Gaucher disease	*GBA*	84G>GG, IVS2(+1)G>A, N370S, L444P, Delta55bp, V394L, D409H, R496H	90%	55%
Mucolipidosis IV	*MCOLN1*	Delta6.4kb, IVS3(-2)A>G	95%	Unknown
Niemann-Pick disease type A	*SMPD1*	L302P, 1bp del P330fs, R496L, Delta R608	95%	Unknown
Tay-Sachs disease	*HEXA*	Delta7.6kb, G269S, IVS9(+)1G>A, 1278insTATC, IVS12(+1)G>C Pseudodeficiency alleles: R247W, R249W	92%	Unknown

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Pathophysiology

- Bloom syndrome is caused by a deficiency of a DNA helicase, leading to pre- and postnatal growth deficiency, sparse subcutaneous tissue, sunsensitive 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 3–5 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.
- Mucolipodosis 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 3–6 months of age that progresses to blindness, seizures, and total incapacitation and death by age 4.

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

- Cystic fibrosis (CF) carrier testing is NOT included as part of this panel. Please order Cystic Fibrosis (CFTR) 32 Mutations (ARUP test #2001933) to assess CF carrier status.
- 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.
- 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.

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(C>A), E285A, A305E, 433(-2)A>G Polymorphism: Y231Y(C>T)	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
Gaucher disease	*GBA*	84G>GG, IVS2(+1)G>A, N370S, L444P, Delta55bp, V394L, D409H, R496H	90%	1/900	1/15	1/140
Mucolipidosis IV	*MCOLN1*	Delta6.4kb, IVS3(-2)A>G	95%	1/63,000	1/127	1/2,500
Niemann-Pick disease type A	*SMPD1*	L302P, 1bp del P330fs, R496L, Delta R608	95%	1/32,000	1/90	1/1,780
Tay-Sachs disease	*HEXA*	Delta7.6kb, G269S, IVS9(+)1G>A, 1278insTATC, IVS12(+1)G>C Pseudodeficiency alleles: R247W, R249W	92%	1/3,000	1/30	1/480

Methodology

The assay is designed to detect 28 deleterious mutations, two pseudodeficiency alleles, 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

- Cystic Fibrosis (*CFTR*) 32 Mutations (2001933)
- Each test on the Ashkenazi Jewish Disease panel can be ordered as a stand-alone test.
  - Bloom Syndrome (*BLM*) 2281del6/ins7 Mutation (0051433)
  - Canavan Disease (*ASPA)* 4 Mutations (0051453)
  - Dysautonomia, Familial (*IKBKAP*) 2 Mutations (0051463)
  - Fanconi Anemia Group C, (*FANCC)* 2 Mutations (0051468)
  - Gaucher (*GBA)* 8 Mutations (0051438)
  - Mucolipidosis, Type IV (*MCOLN1)* 2 Mutations (0051448)
  - Niemann-Pick, Type A (*SMPD1)* 4 Mutations (0051458)
  - Tay-Sachs Disease (*HEXA)* 7 Mutations (0051428)

References

1. ACOG committee opinion no. 298. Prenatal and preconceptual carrier screening for genetic diseases in individuals of Eastern European Jewish descent. *Ob Gyn* 2004;298;425–8.
2. Gross SJ, et al. ACMG practice guidelines: carrier screening in individuals of Ashkenazi Jewish descent. *Gen Med* 2008;10:54–6.
3. Leib J, et al. Carrier screening panels for Ashkenazi Jews: is more better? *Gen Med* 2005; 7;3:185–9.
4. Online GeneTests. www.genetests.org (accessed on October 1, 2008).
5. Online Mendelian Inheritance in Man. www.ncbi.nlm.nih.gov (accessed on October 1, 2008).

Test Information

0051415 Ashkenazi Jewish Diseases (*BLM, ASPA, IKBKAP, FANCC, GBA, MCOLN1, SMPD1, HEXA*)

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.