Ashkenazi Jewish Genetic Diseases

Indications for Ordering

Carrier screening for 16 disorders in individuals of Ashkenazi Jewish descent who are
- Planning a pregnancy
- Currently pregnant

Test Description

Polymerase chain reaction and fluorescence monitoring

Tests to Consider

Primary tests

Ashkenazi Jewish Diseases, 16 Genes 0051415
- Preferred gene panel for carrier screening for individuals of Ashkenazi Jewish descent
- Detects 51 variants associated with 16 disorders common in Ashkenazi Jews

Cystic Fibrosis (*CFTR*) 165 Pathogenic Variants 2013661
- Carrier screening for expectant individuals and those planning a pregnancy AND diagnostic testing for individuals with symptoms of classic CF
- Not included in prenatal screening panel for Ashkenazi Jews

Related tests

Assess gene variant(s) associated with a specific disorder
- *ABCC8*-Related Hyperinsulinism, 3 Variants 2013725
- Bloom Syndrome (*BLM*), 1 Variant 0051433
- Canavan Disease (*ASPA*), 4 Variants 0051453
- Dysautonomia, Familial (*IKBKAP*), 2 Variants 0051463
- Fanconi Anemia, Group C (*FANCC*), 2 Variants 0051468
- Gaucher Disease (*GBA*), 8 Variants 0051438
- Glycogen Storage Disease, Type 1A (*G6PC*), 9 Variants 2013740
- Joubert Syndrome Type 2 (*TMEM216*), 1 Variant 2013909
- Lipoamide Dehydrogenase Deficiency (*DLD*), 2 Variants 2013735
- Maple Syrup Urine Disease, Type 1B (*BCKDHB*), 3 Variants 2013730
- Mucolipidosis Type IV (*MCOLN1*), 2 Variants 0051448
- *NEB*-Related Nemaline Myopathy, 1 Variant 2013745
- Niemann-Pick Type A (*SMPD1*), 4 Variants 0051458
- Tay-Sachs Disease (*HEXA*), 7 Variants 0051428
- Usher Syndrome, Types 1F and 3 (*PCDH15* and *CLRN1*), 2 Variants 2013750

Disease Overview

Symptoms – see Table 1

Incidence and carrier frequency
- See Table 1 for incidence and carrier frequency in Ashkenazi Jews
- Largely unknown in non-Ashkenazi Jews

Screening
- Routine preconception or prenatal carrier screening for genetic diseases common in Ashkenazi Jews is recommended by
  - American Congress of Obstetrics and Gynecology (ACOG) for the following conditions (ACOG Committee on Genetics, 2009)
    - Canavan disease
    - Cystic fibrosis
    - Familial dysautonomia
    - Tay-Sachs disease
  - American College of Medical Genetics (ACMG) for the following conditions (Gross, 2008)
    - Four disorders recommended by ACOG listed above in addition to
      - Bloom syndrome
      - Fanconi anemia group C
      - Gaucher disease
      - Mucolipidosis type IV
      - Niemann-Pick disease type A
- Screening for a specific disorder may be offered to non-Jewish individuals
  - With relatives who carry one or more variants included in the test
  - Whose partners are carriers of one of the panel disorders, although detection rate for non-Jews is variable by disorder and largely unknown

Genetics

Genes/variants – see Table 2

Inheritance – autosomal recessive

Test Interpretation

Sensitivity/specificity
- Clinical sensitivity/specificity – see Table 2
- Analytical sensitivity/specificity – 99%

Results

- Positive
  - One pathogenic variant detected
    - Individual is a carrier of the associated disease
    - Screening for that disease should be offered to the individual's reproductive partner
    - Genetic counseling is recommended
- Negative
  - No targeted pathogenic variants identified
  - For residual risk estimates, see Table 2

Limitations

- Variants other than those tested on this panel will not be detected
- Diagnostic errors can occur due to rare sequence variations

References

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Table 1

Disease (*Gene*)	Disease Incidence in Ashkenazi Jews	Carrier Frequency in Ashkenazi Jews	Type of Disorder/Symptoms
ABCC8-related hyperinsulinism (*ABCC8*)	1/10,800	1/52	• Hypoglycemia that varies from mild to severe neonatal onset • With proper management, life span is normal
Bloom syndrome (*BLM*)	1/40,000	1/100	• Pre- and postnatal growth deficiency • Sun sensitive skin lesions appear at 1-2 years of age • Benign and malignant tumors in childhood • Telangiectatic hypo- and hyperpigmented skin lesions • Male sterility • Life expectancy is decreased due to malignancy

Disease (*Gene*)	Disease Incidence in Ashkenazi Jews	Carrier Frequency in Ashkenazi Jews	Type of Disorder/Symptoms
Canavan disease (*ASPA*)	1/10,000	1/50	• Macrocephaly • Loss of motor control beginning at 3-5 months of age • Failure to sit, stand, or ambulate • Survival usually until childhood or teenage years
Familial dysautonomia (*IKBKAP*)	1/3,600	1/32	• Delayed motor milestones in infants and progressive deterioration of gait throughout life • Gastrointestinal dysfunction with emesis • Altered sensitivity to pain and temperature • Cardiovascular instability • Survival typically until 30s
Fanconi anemia group C (*FANCC*)	1/32,000	1/89	• Progressive bone marrow failure during first decade of life • Increased risk of malignancy (hematological in ~20%, nonhematological in ~30%) • Physical malformations may include short stature, abnormal skin pigmentation or malformations of the eyes, ears, heart, forearms, thumbs, kidneys • Survival usually until childhood or teenage years
Gaucher disease (*GBA*)	1/900	1/15	• Type 1 (most prevalent type among Ashkenazi Jews) o Bone disease o Hepatosplenomegaly o Anemia, thrombocytopenia o Lung disease o No primary central nervous system (CNS) disease • Type 2 o CNS degeneration by age 2 years, with a rapidly progressive course; survival until age 4 years • Type 3 o Slowly progressive CNS degeneration; survival until 20s
Glycogen storage disease type 1A (*G6PC*)	1/20, 000	1/71	• Hepatomegaly • Growth delay/short stature • Hypoglycemia, lactic acidosis, hyperuricemia, hyperlipidemia • Additional long-term complications include osteoporosis, delayed puberty, renal disease, systemic hypertension, hepatic adenomas with potential for malignant transformation • With treatment, individuals live into adulthood
Joubert syndrome type 2 (*TMEM216*)	1/34,000	1/92	• "Molar tooth sign" cerebellar and brain stem malformation • Hypotonia • Developmental delay/intellectual disability • Individuals typically have a normal lifespan, but a minority may have a shortened lifespan depending on severity
Lipoamide dehydrogenase deficiency (*DLD*)	1/35,000	1/94	• Early onset disease presents in infancy o Hypotonia, lethargy, and vomiting with progressive encephalopathy o Survival usually until 1-2 years of life • Primarily hepatic disease has variable onset from infancy to 30s o Liver injury/failure, usually preceded by nausea/vomiting o Typically normal intellect with no neurological findings o Life span varies depending on the severity of the condition
Maple syrup urine disease type 1B (*BCKDHB*)	1/50,000	1/113	• Maple syrup odor in urine • Classically affected individuals present within the first few days of life with o Irritability o Poor feeding and lethargy o Intermittent apnea • Progresses to coma and death within 7-10 days if untreated
Mucolipidosis type IV (*MCOLN1*)	1/63,000	1/127	• Severe psychomotor delay • Progressive visual impairment due to retinal degeneration and corneal clouding • Neurological state o Static until age 30 in most affected individuals o Neurological degeneration in ~15% • Variable life expectancy, most individuals live into adulthood
NEB-related nemaline myopathy (*NEB*)	1/47,000	1/108	• Presents in the first year of life with o Muscle weakness of the face, neck, arms, and legs, which is static or very slowly progressive o Hypotonia o Feeding difficulties • Individuals typically have a normal lifespan and have an active, independent life
Niemann-Pick disease type A (*SMPD1*)	1/32,000	1/90	• Hepatosplenomegaly • Developmental delay and severe neurodegeneration • Progressive hypotonia and rigidity • Cherry-red spot on the macula of the retina • Survival until 3-5 years of age

Disease (*Gene*)	Disease Incidence in Ashkenazi Jews	Carrier Frequency in Ashkenazi Jews	Type of Disorder/Symptoms
Tay-Sachs disease (*HEXA*)	1/3,000	1/30	• Progressive loss of motor skills beginning at 3–6 months of age • Progressive neurodegeneration resulting in blindness, seizures, and eventually total incapacitation • Survival until 4-6 years of age
Usher syndrome type 1F (*PCDH15*)	1/20,500	1/72	• Congenital, bilateral, profound sensorineural hearing loss • Adolescent-onset retinitis pigmentosa • Loss of vestibular function
Usher syndrome type 3 (*CLRN1*)	1/82,000	1/143	• Postlingual, progressive hearing loss • Late-onset progressive loss of vision due to retinitis pigmentosa • Variable loss of vestibular function

Table 2

Disease (*Gene*)	Variants Tested (HGVS Nomenclature)	Variants Tested (Legacy Nomenclature)	Clinical Sensitivity in Ashkenazi Jews	Clinical Sensitivity in Non-Ashkenazi Jews	Carrier Risk for Ashkenazi Jews After Negative Test
ABCC8-related hyperinsulinism (*ABCC8*)	p.F1388del (c.4163_4165del) p.V187D (c.560T>A) c.3992-9G>A		97% (Glaser, 2011)	Unknown	1/1,700
Bloom syndrome (*BLM*)	p.Y736Lfs (c.2207_2212delinsTAGATTC)	2281del6/ins7	97% (German, 2007)	~3%	1/3,300
Canavan disease (*ASPA*)	c.433-2A>G p.Y231X (c.693C>A) p.E285A (c.854A>C) p.A305E (c.914C>A)		99% (Matalon, 2011)	55%	1/4,900
Familial dysautonomia (*IKBKAP*)	p.R696P (c.2087G>C) c.2204+6T>C	IVS20+6T>C	99% (Gross, 2008)	Unknown	1/3,100
Fanconi anemia group C (*FANCC*)	p.D23Ifs (c.67delG) c.456+4A>T	322delG IVS4+4A>T	99% (Gross, 2008)	Unknown	1/8,800
Gaucher disease (*GBA*)	p.L29Afs (c.84dupG) c.115+1G>A p.N409S (c.1226A>G) c.1263_1317del55 p.V433L (c.1297G>T) p.D448H (c.1342G>C) p.L483P (c.1448T>C) p.R535H (c.1604G>A)	84G>GG IVS2+1G>A N370S del55bp V394L D409H L444P R496H	90% (Pastores, 2000)	55%	1/140
Glycogen storage disease type 1A (*G6PC*)	p.Q27Rfs (c.79delC) p.Y128Tfs (c.379_380dupTA) p.R83H (c.248G>A) p.R83C (c.247C>T) p.G188R (c.562G>C) p.Q242X (c.724C>T) p.Q347X (c.1039C>T) p.G270V (c.809G>T) p.F327del (c.979_981delTTC)		99% (Ekstein, 2004)	Varies by ethnicity	1/7,000
Joubert syndrome type 2 (*TMEM216*)	p.R73L (c.218G>T)		99% (Edvardson, 2010)	Unknown	1/9,100
Lipoamide dehydrogenase deficiency (*DLD*)	p.Y35X (c.104dupA) p.G229C (c.685G>T)		99% (Shaag, 1999)	Unknown	1/9,300
Maple syrup urine disease type 1B (*BCKDHB*)	p.R183P (c.548G>C) p.G278S (c.832G>A) p.E372X (c.1114G>T)		99% (Edelmann, 2001)	Unknown	1/11,000

Disease (*Gene*)	Variants Tested (HGVS Nomenclature)	Variants Tested (Legacy Nomenclature)	Clinical Sensitivity in Ashkenazi Jews	Clinical Sensitivity in Non-Ashkenazi Jews	Carrier Risk for Ashkenazi Jews After Negative Test
Mucolipidosis type IV (*MCOLN1*)	c.406-2A>G g.511_6493del	IVS3-2A>G del6.4kb	95% (Schiffmann, 2005)	6-10%	1/2,500
NEB-related nemaline myopathy (*NEB*)	exon 55 del (p.R2478_D2512del)		99% (Anderson, 2004)	Unknown	1/10,700
Niemann-Pick disease type A (*SMPD1*)	p.L304P (c.911T>C) p.F333Sfs (c.996delC) p.R498L (c.1493G>T) p.R610del (c.1829_1831delGCC)	L302P fsP330 R496L R608del	90% (Wasserstein, 2006)	Varies by ethnicity	1/900
Tay-Sachs disease (*HEXA*)	7.6 kb del p.G269S (c.805G>A) c.1073+1G>A p.Y427Ifs (c.1274_1277dup TATC) c.1421+1G>C Pseudodeficiency alleles: p.R247W (c.739C>T) p.R249W (c.745C>T)	 IVS9+1G>A 1278dupTATC IVS12+1G>C	94% (Kaback, 1993)	59%	1/480
Usher syndrome type 1F (*PCDH15*)	p.R245X (c.733C>T)		62% (Ben-Yosef, 2003)	Unknown	1/190
Usher syndrome type 3 (*CLRN1*)	p.N48K (c.144T>G)		98% (Fields, 2002; Ness, 2003)	Unknown	1/7,000