Ashkenazi Jewish Genetic Diseases Panel

Individuals of Ashkenazi Jewish descent are at an increased risk for certain autosomal recessive genetic disorders. An estimated one in every four or five individuals of Ashkenazi Jewish descent is a carrier for one of these disorders. In combination, the Ashkenazi Jewish Disease Panel and Cystic Fibrosis 165 Pathogenic Variants tests screen for all of the disorders that the American College of Medical Genetics and Genomics (ACMG) and the American College of Obstetrics and Gynecology (ACOG) recommend testing for in individuals of Ashkenazi Jewish descent.

DISEASE OVERVIEW

Screening
- Routine preconception or prenatal carrier screening for genetic diseases common in individuals of Ashkenazi Jewish descent is recommended by:
  - ACOG
  - ABC8-related hyperinsulinemia
  - Bloom syndrome
  - Canavan disease
  - Cystic fibrosis
  - Fanconi anemia group C
  - Familial dysautonomia
  - Gaucher disease
  - Glycogen storage disease type 1A
  - Joubert syndrome type 2
  - Maple syrup urine disease type 1B
  - Mucolipidosis type IV
  - Niemann-Pick type A
  - Tay-Sachs disease
  - Usher syndrome (type 1F and type 3)
- ACMG for nine of the disorders described in the ACOG guidelines
- Screening for a specific disorder may be offered to individuals not of Ashkenazi Jewish descent, including:
  - Relatives who carry one or more variants included in the test
  - Reproductive partners who are carriers of one of the panel disorders, although detection rates for non-Ashkenazi individuals is variable by disorder and largely unknown

For additional clinical information and the carrier frequency of diseases included on the Ashkenazi Jewish Diseases, 16 Genes panel, see the Ashkenazi Jewish Genetic Diseases Consult topic.

GENETICS

Inheritance
Autosomal recessive

Genes/Variants
See Clinical Sensitivity table
<table>
<thead>
<tr>
<th>Disease (and Associated Gene)</th>
<th>Variants Tested (HGVS Nomenclature)</th>
<th>Variants Tested (Legacy Nomenclature)</th>
<th>Clinical Sensitivity in Individuals of Ashkenazi Jewish Descent</th>
<th>Clinical Sensitivity in non-Ashkenazi Jewish Individuals</th>
<th>Carrier Risk After Negative Test for Ashkenazi Jewish Individuals</th>
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</thead>
<tbody>
<tr>
<td>ABCC8-related hyperinsulinism (ABCC8)</td>
<td>p.F1388del (c.4163_4165del) p.V187D (c.560T&gt;A) c.3992-9G&gt;A</td>
<td>n/a</td>
<td>97%</td>
<td>4</td>
<td>Unknown 1/1,700</td>
</tr>
<tr>
<td>Bloom syndrome (BLM)</td>
<td>p.Y736Lfs (c.2207_2212delinsTAGATTC) 2281del6/ins7</td>
<td></td>
<td>97%</td>
<td>5</td>
<td>~3% 1/3,300</td>
</tr>
<tr>
<td>Canavan disease (ASPA)</td>
<td>c.433-2A&gt;G p.Y231X (c.693C&gt;A) p.E285A (c.854A&gt;C) p.A305E (c.914C&gt;A)</td>
<td>n/a</td>
<td>99%</td>
<td>6</td>
<td>55% 1/4,900</td>
</tr>
<tr>
<td>Familial dysautonomia (IKBKAP)</td>
<td>p.R696P (c.2087G&gt;C) c.2204+6T&gt;C</td>
<td>IVS20+6T&gt;C</td>
<td>99%</td>
<td>3</td>
<td>Unknown 1/3,100</td>
</tr>
<tr>
<td>Fanconi anemia group C (FANCC)</td>
<td>p.D231fs (c.67delG) c.456+4A&gt;T 322delG IVS4+4A&gt;T</td>
<td></td>
<td>99%</td>
<td>3</td>
<td>Unknown 1/8,800</td>
</tr>
<tr>
<td>Glycogen storage disease type 1A (G6PC)</td>
<td>p.Q27Rfs (c.79delC) p.Y128Tfs (c.379_380dupTA) p.R83H (c.248G&gt;A) p.R83C (c.247C&gt;T) p.G188R (c.562G&gt;C) p.Q242X (c.724C&gt;T) p.Q347X (c.1039C&gt;T) p.G270V (c.809G&gt;T) p.F327del (c.979_981delTTT)</td>
<td>n/a</td>
<td>99%</td>
<td>8</td>
<td>Varies by ethnicity 1/7,000</td>
</tr>
<tr>
<td>Joubert syndrome type 2 (TMEM216)</td>
<td>p.R73L (c.218G&gt;T)</td>
<td>n/a</td>
<td>99%</td>
<td>9</td>
<td>Unknown 1/9,100</td>
</tr>
<tr>
<td>Lipoamide dehydrogenase deficiency (OLD)</td>
<td>p.Y35X (c.104dupA) p.G229C (c.685G&gt;T)</td>
<td>n/a</td>
<td>99%</td>
<td>10</td>
<td>Unknown 1/9,300</td>
</tr>
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<td>Maple syrup urine disease type 1B (BCKDHB)</td>
<td>p.R183P (c.548G&gt;C) p.G278S (c.832G&gt;A) p.E372X (c.1114G&gt;T)</td>
<td>n/a</td>
<td>99%&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Unknown</td>
<td>1/11,000</td>
</tr>
<tr>
<td>Mucolipidosis type IV (MCOLN1)</td>
<td>c.406-2A&gt;G g.511_6943del</td>
<td>IVS3-2A&gt;G del6.4kb</td>
<td>95%&lt;sup&gt;12&lt;/sup&gt;</td>
<td>6-10%</td>
<td>1/2,500</td>
</tr>
<tr>
<td>NEB-related nemaline myopathy (NEB)</td>
<td>exon 55 del (p.R2478_D2512del)</td>
<td>n/a</td>
<td>99%&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Unknown</td>
<td>1/10,700</td>
</tr>
<tr>
<td>Niemann-Pick disease type A (SMPD1)</td>
<td>p.L304P (c.911T&gt;C) p.F333Sfs (c.996delC) p.R498L (c.1493G&gt;T) p.R610del (c.1829_1831delGCC)</td>
<td>L302P fsP330 R496L R608del</td>
<td>90%&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Varies by ethnicity</td>
<td>1/900</td>
</tr>
<tr>
<td>Tay-Sachs disease (HEXA)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.6 kb del p.G269S (c.805G&gt;A) c.1073+1G&gt;A p.Y427Ifs (c.1274_1277dupTATC) c.1421+1G&gt;C Pseudodeficiency alleles: p.R247W (c.739C&gt;T) p.R249W (c.745C&gt;T)</td>
<td>IVS9+1G&gt;A 1278dupTATC IVS12+1G&gt;C</td>
<td>94%&lt;sup&gt;15&lt;/sup&gt;</td>
<td>59%</td>
<td>1/480</td>
</tr>
<tr>
<td>Usher syndrome type 1F (PCDH15)</td>
<td>p.R245X (c.733C&gt;T)</td>
<td>n/a</td>
<td>62%&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Unknown</td>
<td>1/190</td>
</tr>
<tr>
<td>Usher syndrome type 3 (CLRN1)</td>
<td>p.N48K (c.144T&gt;G)</td>
<td>n/a</td>
<td>98%&lt;sup&gt;17,18&lt;/sup&gt;</td>
<td>Unknown</td>
<td>1/7,000</td>
</tr>
</tbody>
</table>

<sup>a</sup>For specific Tay-Sachs disease testing, see the Tay-Sachs Disease Testing fact sheet

For specific NEB testing, see the NEB testing fact sheet

n/a, not applicable

**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 carrier risk estimates, see the Clinical Sensitivity table

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

**REFERENCES**


RELATED INFORMATION

Ashkenazi Jewish Genetic Diseases
Ashkenazi Jewish Genetic Diseases Carrier Screening Algorithm
Cystic Fibrosis