Tay-Sachs Disease Testing

Tay-Sachs disease is a genetic disorder that causes deficiency of the hexosaminidase A (HEX A) enzyme. Patients with Sandhoff disease also lack HEX A activity, together with hexosaminidase B (HEX B) activity. Screening for Tay-Sachs carrier status should be performed for individuals from high-risk populations, especially individuals of Ashkenazi Jewish or French Canadian descent. HEX A enzymatic activity is the initial test to suggest a diagnosis in symptomatic individuals or to determine carrier status. Genetic testing can identify causative HEXA gene variant(s) in individuals with abnormal HEX A activity.1,2

Testing Strategy

- HEX A enzymatic activity:
  - Initial test to evaluate symptomatic individuals
  - First-tier test to determine carrier status
  - Leukocytes specimen appropriate for individuals who are pregnant, use oral contraceptives, have severe liver or autoimmune disease, or have a previous inconclusive result with different specimen type
  - Plasma or serum specimen appropriate for all other individuals
- Molecular testing of HEXA gene:
  - Identify pathogenic variant(s) when HEX A enzyme activity is abnormal
  - Distinguish pseudodeficiency alleles from pathogenic variants
  - HEXA common variants panel is recommended for individuals of Ashkenazi Jewish ethnicity
  - Tay-Sachs disease sequencing and deletion is recommended for all other ethnicities

Disease Overview

Incidence

Varies by ethnicity:

- 1/3,000 in individuals of Ashkenazi Jewish, French Canadian, and Cajun descent2
- 1/300,000 for the general population2
Diagnostic Issues

- Affected individuals have absent or extremely low HEX A enzymatic activity
- Enzymatic testing cannot predict disease severity
- Milder variant forms of Tay-Sachs disease, such as the B1 variant, may not be identified by enzymatic assay

Screening Issues

Pseudodeficiency alleles: clinically benign variants that have reduced HEX A enzyme activity toward synthetic substrates but have normal activity in vivo

- Heterozygotes have HEX A activity level in the carrier range
- Molecular testing is necessary to distinguish pathogenic variants from pseudodeficiency alleles
- Common pseudodeficiency alleles:
  - c.739C>T (p.R247W)
  - c.745C>T (p.R249W)

Genetics

Gene

HEXA

Inheritance

Autosomal recessive

Variants

- >130 HEXA variants have been identified
  - Majority are null alleles that result in no HEX A enzymatic activity
  - 7.6kb deletion is the only recurring large deletion
- Commonly detected variants vary by ethnicity
  - Individuals of Ashkenazi Jewish descent:
    - c.1274_1277dupTATC severe variant accounts for 80% of all pathogenic HEXA variants
    - c.805G>A (p.G269S) variant is typically associated with adult-onset HEX A deficiency
    - ~2% of individuals with enzyme level in the carrier range have pseudodeficiency alleles
  - Individuals of French Canadian descent: 7.6kb deletion is the most common pathogenic variant

Related Tests

Tay-Sachs Disease (HEXA), 7 Variants 0051428

Method: Polymerase Chain Reaction/Fluorescence Monitoring

- Confirm common pathogenic and pseudodeficiency HEXA gene variants in individuals of Ashkenazi Jewish or French Canadian descent with abnormal levels of HEX A enzyme
- Included in a panel of tests for common disorders/variants for screening individuals of Ashkenazi Jewish descent
Test Interpretation

Tay-Sachs Disease (HEXA) Sequencing and 7.6kb Deletion

Sensitivity/Specificity

- Clinical: 99%
- Analytical: >99%

Results

<table>
<thead>
<tr>
<th>Result</th>
<th>Variant(s) detected</th>
<th>Interpretation</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Heterozygous: one pathogenic HEXA gene variant detected</td>
<td>Individual is at least a carrier of HEX A deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Homozygous: more than one pathogenic HEXA gene variants detected</td>
<td>Diagnosis of HEX A deficiency confirmed</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>No pathogenic HEXA gene variant detected</td>
<td>Greatly decreased probability that the individual is affected with, or a carrier of, HEX A deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pseudodeficiency alleles will be reported but are considered clinically insignificant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconclusive</td>
<td>Sequence variant(s) of uncertain clinical significance identified</td>
<td>Unknown clinical significance</td>
<td></td>
</tr>
</tbody>
</table>

Limitations

- Regulatory region and deep intronic variants will not be detected
- Large deletions/duplications in HEXA other than the 7.6kb deletion 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