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.

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 descent
- 1/300,000 for the general population

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)

TESTS TO CONSIDER

Hexosaminidase A Percent and Total
Hexosaminidase, Plasma or Serum
2008121
Method: Quantitative Fluorometry
Preferred test to evaluate symptomatic patients for Tay-Sachs disease or Sandhoff disease
- Molecular testing is recommended to confirm disease status and exclude pseudodeficiency
- Can identify carriers of Tay-Sachs disease
- False positive results can be seen in serum/plasma from pregnant individuals, individuals who use oral contraceptives or hormone replacement therapy, or individuals with liver or autoimmune disease
- Molecular testing is recommended to exclude pseudodeficiency
- Can identify carriers of Sandhoff disease

Hexosaminidase A Percent and Total
Hexosaminidase in Leukocytes
2008125
Method: Quantitative Fluorometry
Evaluate symptomatic patients for Tay-Sachs disease or Sandhoff disease
- Preferred test to identify carriers of Tay-Sachs disease
- Molecular testing is recommended when HEX A enzyme activity is abnormal in plasma/serum
- 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

Hexosaminidase A Percent and Total
Hexosaminidase in Plasma with Reflex to Hexosaminidase A Percent
and Total Hexosaminidase in Leukocytes
2008129
Method: Quantitative Fluorometry
- Use in pregnant individuals, individuals who use oral contraceptives or hormone replacement therapy, or individuals with liver or autoimmune disease
- Molecular testing recommended to exclude pseudodeficiency
- Preferred test to identify carriers of Sandhoff disease

Incidence

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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)
Can be used to evaluate symptomatic patients for Tay-Sachs disease or Sandhoff disease.

Can identify carriers of Tay-Sachs disease
- Plasma/serum assayed first; reflexes to leukocytes for inconclusive/abnormal results
Can identify carriers of Sandhoff disease

**Tay-Sachs Disease (HEXA)**
*Sequencing and 7.6kb Deletion 2009298*
Method: Polymerase Chain Reaction/Sequencing/Gel Electrophoresis
Confirm pathogenic and pseudodeficiency HEXA gene variants in individuals with abnormal levels of HEX A enzyme

**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

- **Familial Mutation, Targeted Sequencing 2001961**
Method: Polymerase Chain Reaction/Sequencing
Useful when a known pathogenic familial variant has been identified by sequencing.

**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>
</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>
</tr>
<tr>
<td></td>
<td>Homozygous: more than one pathogenic HEXA gene variants detected</td>
<td>Diagnosis of HEX A deficiency confirmed</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>
</tr>
<tr>
<td></td>
<td>Pseudodeficiency alleles will be reported but are considered clinically insignificant</td>
<td></td>
</tr>
<tr>
<td>Inconclusive</td>
<td>Sequence variant(s) of uncertain clinical significance identified</td>
<td>Unknown clinical significance</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