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 descent[2]
- 1/300,000 for the general population[2]

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

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
  - Use in pregnant individuals, individuals who use oral contraceptives or hormone replacement therapy, individuals with liver or autoimmune disease, or individuals with a previous inconclusive HEX A enzyme test in plasma/serum
  - Molecular testing recommended to exclude pseudodeficiency
- Preferred test to identify carriers of Sandhoff disease

Hexosaminidase A Percent and Total Hexosaminidase in Plasma with Reflex to Hexosaminidase A Percent and Total Hexosaminidase in Leukocytes 2008129

Method: Quantitative Fluorometry

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
  - General population: ~36% of individuals with enzyme level in the carrier range have pseudodeficiency alleles

Method: Quantitative Fluorometry

- 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

Result	Variant(s) Detected	Interpretation
Positive	Heterozygous: one pathogenic *HEXA* gene variant detected	Individual is at least a carrier of HEX A deficiency
Positive	Homozygous: more than one pathogenic *HEXA* gene	Diagnosis of HEX A deficiency confirmed

	variants detected	
Negative	No pathogenic *HEXA* gene variant detected Pseudodeficiency alleles will be reported but are considered clinically insignificant	Greatly decreased probability that the individual is affected with, or a carrier of, HEX A deficiency
Inconclusive	Sequence variant(s) of uncertain clinical significance identified	Unknown clinical significance

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

1. Kaback MM, Desnick RJ. Hexosaminidase A deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2020. [Last Update: Aug 2011; Accessed: May 2020]

2. ACOG Committee on Genetics. Committee Opinion No. 690 Summary: Carrier screening in the age of genomic medicine. Obstet Gynecol. 2017;129(3):595-596. PubMed

Related Information

Ashkenazi Jewish Genetic Diseases
Ashkenazi Jewish Genetic Diseases Carrier Screening Algorithm

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