Tay-Sachs Disease (HEXA) Sequencing and Deletion/Duplication

Tay-Sachs disease is a genetic disorder caused by a 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 those of Ashkenazi Jewish or French Canadian descent. Molecular testing can identify pathogenic and pseudodeficiency *HEXA* gene variant(s) in individuals with abnormal HEX A activity.[1,2]

Featured ARUP Testing

Tay-Sachs Disease (HEXA) Sequencing and Deletion/Duplication 3004486

Method: Massively Parallel Sequencing

Use to confirm pathogenic and pseudodeficiency *HEXA* gene variants in individuals with abnormal levels of HEX A enzyme, a suspected diagnosis of HEXA deficiency, and/or suspected carrier status.

Individuals of French Canadian descent may benefit from targeted Tay-Sachs screening. If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate. Refer to the Laboratory Test Directory for additional information and test options.

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]

Genetics

Gene

HEXA (NM_000520)

Variants

Over 130 *HEXA* variants have been identified. The majority are null alleles that result in no HEX A enzymatic activity. The 7.6kb deletion is the only recurring large deletion.

Commonly Detected Variant(s) by Ethnicity

Ethnicity	Variant(s)
Ashkenazi Jewish	• 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
French Canadian	7.6kb deletion is the most common pathogenic variant
General population	~36% of individuals with enzyme level in the carrier range have pseudodeficiency alleles (eg, c.739C>T [p.R247W] and c.745C>T [p.R249W])

Inheritance

Autosomal recessive

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for the detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and to confirm variant calls in certain situations.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Clinical Sensitivity

99%

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] Deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level[c] Duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by MLPA.

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; MLPA, multiplex ligation-dependent probe amplification; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Result	Variant(s) Detected	Interpretation
Positive	Heterozygous: one pathogenic *HEXA* gene variant detected	Individual is at least a carrier of HEX A deficiency
	Homozygous: more than one pathogenic *HEXA* gene variants detected	Diagnosis of HEX A deficiency confirmed
Negative	No pathogenic *HEXA* gene variant detected	Decreases the likelihood the individual is affected with, or a carrier of, HEX A deficiency

Result	Variant(s) Detected	Interpretation
	Pseudodeficiency alleles will be reported but are considered clinically insignificant	
Uncertain	Sequence variant(s) of uncertain clinical significance identified	Unknown if variant(s) are disease-causing or benign

Limitations

- A negative result does not exclude a diagnosis of Tay-Sachs disease.
- Diagnostic errors can occur due to rare sequence variants.
- Interpretation of this test may be impacted if this patient has had an allogeneic stem cell transplantation.
- This assay detects the 7.6kb deletion at a reduced sensitivity. Therefore, individuals of French Canadian descent may benefit from targeted screening; refer to the Laboratory Test Directory for available test options.
- The following will not be evaluated:
  - Variants outside the coding regions of intron-exon boundaries of the *HEXA* gene
  - Regulatory region and deep intronic variants
  - Breakpoints of large deletions/duplications
- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Large duplications less than 3 exons in size
  - Noncoding transcripts.
  - Low-level somatic variants
  - Certain other variants, due to technical limitations in the presence of pseudogenes or repetitive/homologous regions

References

1. Toro C, Shirvan L, Tifft C. HEXA disorders. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2021. [Last update: Oct 2020; Accessed: Aug 2021]

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.

Related Information

Ashkenazi Jewish Genetic Diseases
Ashkenazi Jewish Genetic Diseases Panel

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