HEXA Gene Analysis in Tay-Sachs Disease

Clinical Features

Tay-Sachs disease (TSD) is a lysosomal storage disorder with symptoms ranging from an acute infantile form (classic TSD) to subacute juvenile and adult onset forms with later onset and slower disease progression. Infants with classic TSD generally appear normal at birth. At 3-6 months of age motor weakness, myoclonic jerks and an exaggerated startle reaction are usually the presenting features followed by developmental retardation and regression, paralysis, dementia and blindness with death by the second or third year of life. A cherry-red spot on the macula of the retina is a typical fundoscopic finding in affected infants and, histologic examination reveals the lysosomal accumulation of GM2 gangliosides represented as distended, ballooned neurons in the central nervous system. The juvenile and adult forms have more variable neurologic findings, including progressive dystonia, spinocerebellar degeneration, motor neuron disease, and in some individuals with the adult onset form, a bipolar form of psychosis.[1] The juvenile and adult onset forms differ from each other primarily by the impact of the disease on intelligence, which is minimal through much of the course of the adult form.[2] The carrier frequency in Ashkenazi Jews is approximately 1 in 30, while the carrier in Sephardic Jews and non-Jews is approximately 1 in 250 to 1 in 300.[1] Other groups that are relatively genetically isolated have also been found to have carrier frequencies similar to or higher than that observed in Ashkenazi Jews including French Canadians from eastern Quebec, Cajuns from Louisiana and the Old Order Amish in Pennsylvania.[1]

Genetics

Tay-Sachs disesase is caused by pathogenic variants in the *HEXA* gene which encodes for the beta-hexosaminidase A (Hex A) enzyme, which binds the GM2 activator/GM2 ganglioside complex and hydrolyzes GM2 to GM3. Individuals with Tay-Sachs disease have absent to near-absent Hex A enzyme activity in serum, white blood cells or other tissues, with normal Hex B levels. Deficient Hex A activity results in the intra-lysosomal storage of GM2 ganglioside in neurons of the central nervous system. The *HEXA* gene is located on chromosome 15q23 and has 14 exons.

Inheritance Pattern

Autosomal recessive

Test Methods

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the HEXA gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events.
It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

T: 1 (844) 241-1233 | **F:** 1 (201) 421-2020 | GeneDx.com
207 Perry Parkway | Gaithersburg, MD 20877

REFERENCES:

1. Toro, C. et al., (Updated [Oct 1, 2020) HEXA Disorders In: GeneReviews at Genetests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997- 2020. Available at https://www.ncbi.nlm.nih.gov/books/NBK1218/ .
2. Maegawa et al., (2006) Pediatrics 118:e1550-e1562.
3. Giraud et al., (2010) Biochem Biophys Res Commun 392:599-602.
4. Montalvo et al., (2005) Hum Mutat 26:282.
5. Park et al., (2010) Pediatr Res 67:217-20.
6. Myerowitz, R. And Hogikyan, N. (1986) Science 232:1646-1648.
7. Hechtman et al., (1992) Hum Genet 90:402-406.
8. Triggs-Raine et al., (1990) N Engl J Med 323:6-12.
9. Akerman et al., (1992) Hum Mutat 1:303-309.
10. Cao et al., (1997) J Biol Chem 272:14975-14982.
11. Braekeleer et al., (1992) Hum Genet 89:83-87

T: 1 (844) 241-1233 | **F:** 1 (201) 421-2020 | GeneDx.com
207 Perry Parkway | Gaithersburg, MD 20877