HEXB Gene Analysis in Sandhoff Disease

CLINICAL FEATURES

Sandhoff disease is a lysosomal storage disorder with a wide range of symptoms that are virtually indistinguishable from those seen in patients with Tay-Sachs disease. Patients are usually classified as having infantile, juvenile or adult forms depending upon the age of onset. The infantile form is the most severe with onset by 6 months of age and death typically before 4 years. Infants generally appear normal at birth; at 3-6 months of age motor weakness, hypotonia and an exaggerated startle reaction are usually the presenting features followed by developmental retardation and regression, loss of vision and eventually blindness, spasticity, disordered swallowing and seizures. A “cherry-red” spot on the retina is a typical funduscopic finding. Macrocephaly appears by about 18 months, with death by the second or third year, often due to aspiration pneumonia.[1] In Sandhoff disease organomegaly and bony abnormalities are rarely observed.[1] The late infantile and juvenile forms present at about 2 to 10 years of age with ataxia, incoordination and dysarthria, followed by progressive psychomotor deterioration, spasticity and seizures. Cherry red spots may not be present.[1] The chronic and adult forms may show variable presentations with pyramidal and extrapyramidal signs, movement disorders, psychosis, lower motor neuron and spinocerebellar dysfunction, autonomic dysfunction or spinocerebellar degeneration.1 Several geographically isolated populations have a high incidence of Sandhoff disease, including an inbred community of Metis Indians in northern Saskatchewan and individuals from the northwestern region of the province of Córdoba and the central southern region of the province of La Roija in Argentina where the carrier frequency is estimated to be 1 in every 16-29 persons.[4] In the general population, the incidence of Sandhoff disease is estimated at 1 in 300,000 births.[4]

GENETICS

Sandhoff disesase is caused by pathogenic variants in the *HEXB* gene encoding the β-subunit of the hexosaminidase A (Hex A) and the hexosaminidase B (Hex B) isoenzymes. Since hexosaminidase A and hexosaminidase B both contain the β-subunit, both isoenzymes are deficient in Sandhoff disease. Hex A binds the GM2 activator/ GM2 ganglioside complex and hydrolyzes GM2 to GM3. Patients with Sandhoff disease have absent to near-absent Hex A enzyme activity in serum, white blood cells or other tissues resulting in the intralysosomal storage of GM2 ganglioside in neurons of the central nervous system. The Hex B enzyme hydrolyses glycoproteins and glycolipids but not GM2 ganglioside. The *HEXB* gene is located on chromosome 5q13 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 *HEXB* 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.

VARITANT SPECTRUM

Variants reported in the *HEXB* gene include missense, nonsense, splice site, small deletions/insertions and large deletions. A 16-kb deletion that includes the *HEXB* promoter and exons 1- 5 that accounts for approximately 30% of pathogenic alleles in patients of different ethnic groups.3Recurrent variants have also been described in specific populations including the p.R284X variant found on 29% of *HEXB* alleles in Italian patients and the IVS2+1 G>A described in the Argentine population.[2,3] A genotype-phenotype correlation has been identified.[2]

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