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 disease has an autosomal pattern of inheritance. 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.

Test Methods:
Variant analysis of the HEXB gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. In addition, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed concurrently to evaluate for a deletion or duplication of one or more exons of this gene. Variants/deletions found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, quantitative PCR, oligo-array comparative genome hybridization (ExonArrayDx) or another appropriate method.

Test Sensitivity:
In one report of 12 Italian patients with Sandhoff disease, analysis of the HEXB gene identified a variant on 22 of 24 alleles (92%).[2] In a second report of patients of mixed geographic origins, variants were identified on 27/28 alleles (96%).[5]

Variant spectrum:
At this time, more than 40 variants have been identified in the HEXB gene including missense, nonsense, splicing, small deletions/insertions and large deletions including a 16-kb deletion that includes the HEXB promoter and exons 1-5 that accounts for approximately 30% of mutant alleles in patients of different ethnic groups.[3] Recurrent 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]

References:

1. Fernandes J. (2006). Inborn Metabolic Diseases. Heidelberg, Germany: Springer Medizin Verlag.
2. Zampieri et al., (2009) Neurogenetics 10:49-58.
3. Kleiman et al., (1994) Hum Genet 94:279-282.
4. Brown et al., (1992) Biochimica et Biophysica Acta 1180:91-98.
5. Zampieri et al., (2012) PLOS ONE 7 :e41516.