Sandhoff Disease: HEXB Gene Deletion/Duplication

**Condition Description**

Sandhoff disease is an autosomal recessive lysosomal storage disorder caused by deficiency of two components of the hexosaminidase enzyme, called beta-hexosaminidase-A (HEX A) and beta-hexosaminidase B (HEX B). When functioning normally, this complex is responsible for breaking down a fatty substance in the lysosomes called GM2 ganglioside. Deficiency of this complex causes accumulation the GM2 ganglioside substance in the lysosomes, particularly in the brain. Symptoms become evident in the first 6 months of life and include progressive neurodegeneration, early blindness, mental and motor deterioration, doll-like face, cherry red spots on the retina and macrocephaly. Death typically occurs between 2-4 years of age. A variant form of Sandhoff disease, characterized by a later age of onset and milder clinical progression, is associated with residual enzymatic activity and can be caused by a variety of mutations[1].

There are three protein components to the hexosaminidase complexes: the alpha subunit, the beta subunit and the GM2 ganglioside activator protein. Deficiency of the alpha subunit, due to mutations in the HEXA gene, results in deficiency of the hexosaminidase A complex and causes Tay-Sachs disease. Deficiency of the beta subunit, due to mutations in the HEXB gene, results in deficiency of both the beta-hexosaminidase A and B complexes and causes Sandhoff disease. Deficiency of the GM2 ganglioside activator protein, due to mutation in the GM2A gene, is associated with the rare AB variant form of GM2 gangliosidosis. Enzymatic analysis can distinguish between the GM2 gangliosidoses. Clinically, these diseases are indistinguishable.

Mutations in the HEXB gene cause Sandhoff disease. There have been more than 25 different mutations identified in the HEXB gene[2]. Diagnostic sequencing analysis of the HEXB gene coding region is available for patients with Sandhoff disease and their at-risk relatives on a clinical basis.

For questions about testing for Sandhoff disease, call EGL Genetics at 470-378-2200 or 855-831-7447.

For further clinical information about lysosomal storage diseases, including management and treatment, call the Emory Lysosomal Storage Disease Center at (404) 778-8565 or (800) 200-1524.

**References:**
2). www.hexdb.mcgill.ca/Topic=HEXBdb

**Genes**

- **HEXB**

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of Sandhoff disease in individuals who have tested negative for sequence analysis
- Carrier testing in adults with a family history of Sandhoff disease who have tested negative for sequence analysis

**Methodology**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a "backbone" of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

Detection is limited to duplications and deletions. Array CGH will not detect point mutations or intronic mutations.

Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**
Specimen Requirements:

In EDTA (purple top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Please submit copies of diagnostic biochemical test results with the sample. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition. Contact the laboratory if further information is needed.

**Related Tests**

- Sequence analysis of the HEXB gene is available and is required before deletion/duplication analysis.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.