Sandhoff Disease: **HEXB Gene Sequencing**

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<th>Test Code: DA</th>
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<td>Turnaround time: 4 weeks</td>
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<td>CPT Codes: 81479 x1</td>
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### 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]. The most common mutation deletes a large segment of DNA near the beginning of the **HEXB** gene, which results in a total loss of enzyme activity. Diagnostic sequencing analysis of the **HEXB** gene coding region in addition to analysis for the common 16kb deletion is available for patients with Sandhoff disease and their at-risk relatives on a clinical basis.

For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array NG.

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

### Methodology

PCR amplification of 14 exons contained in the **HEXB** gene coding region will performed on patient genomic DNA. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence dideoxy sequencing methods. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. Allele-specific PCR analysis is used to detect the 16kb deletion in the **HEXB** gene. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements. Large deletions, other than the common 16kb deletion, are not detected by this analysis. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

### Detection

Clinical Sensitivity: More than 30 mutations have been described in the literature for the **HEXB** gene. However, no systematic analysis of the **HEXB** gene has been performed in a cohort of individuals with a biochemical analysis of the disease which would allow calculation of a detection rate.

Analytical Sensitivity: ~99%

Prevalence: The estimated prevalence of all lysosomal storage disorders is 2-5 per 100,000. The prevalence of Sandhoff is not specifically known, but is likely to be rare and may vary by ethnicity.

### Specimen Requirements

Submit only 1 of the following specimen types

**Disclaimer:** This information is confidential and subject to change without notice. It may not be reproduced in whole or part unless authorized in writing by an authorized EGL representative.
* 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**

- Sequencing of HEXA Gene (DD).
- Lysosomal Enzyme Screening Panel (LS).
- Custom Diagnostics Known Mutation Analysis (KM) is available to test family members.
- Sandhoff Disease Gene Deletion/Duplication Assay (NG) is available separately for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.
- 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.