

Sandhoff Disease via *HEXB* Gene Sequencing --Test # 476

Brief Description of Clinical Features: Sandhoff disease (OMIM 268800), also called GM2 Gangliosidosis (Type II; O-Variant), is a neurodegenerative lysosomal storage disorder due to deficiency in both beta-Hexosaminidase A and B isoenzymes. It is characterized by the accumulation of GM2 ganglioside, particularly in the brain and by elevation of other uncharged glycolipids in the brain and in visceral organs (Sandhoff et al. Neurochem 18:2469-2489, 1971). Three clinical forms have been reported: **1)** Infantile Sandhoff disease, like Infantile Tay-Sachs disease, is characterized by onset before the age of 6 months, rapid progression and death by 4 years of age. Symptoms begin with decline of physical and mental abilities and progress to blindness, deafness, paralysis and difficulty to swallowing. In addition, organomegaly and slight bone deformation may occur. **2)** Juvenile Sandhoff disease is characterized by onset between 3-10 years of age, slurred speech, cerebellar ataxia, psychomotor retardation, and progressive spasticity. The vision is spared. **3)** Adult Sandhoff disease is characterized by unsteady gait and slow neurological progression with cognitive loss and accumulation of uncharged enzyme substrate (Kolter and Sandhoff Biochim Biophys Acta 1758:2057-2079, 2006). Unlike Tay-Sachs disease, Sandhoff disease is relatively rare in Jewish populations (Cantor et al. Am J Hum Genet 41:16-26, 1987). See also the National Tay-Sachs and Allied Diseases Association at <http://www.ntsad.org/>.

Genetics: Sandhoff disease is inherited with an autosomal recessive manner and results from mutations in the *HEXB* gene (Bikker et al. Hum Genet 81:287-288, 1989; Nakano and Suzuki J Biol Chem 264:5155-5158, 1989). At least 40 mutations have been detected in patients with Sandhoff disease and include missense (13), nonsense (2), splicing (11), small insertions/deletions (9) and large deletions (5). *HEXB* mutations occur throughout the gene. They have been identified in homozygous and compound heterozygous form in patients from various populations.

Description of This Particular Test: The *HEXB* gene encodes the beta-subunit of beta-hexosaminidase A and B isoenzymes, which catalyze the biodegradation of GM2 gangliosides. This test involves bidirectional DNA sequencing of all 14 exons and splice sites of the *HEXB* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. We will sequence any single or double exons in family members of patients with known mutation or to confirm previous results.

Reference Sequences: Genomic: NC_000005.9 mRNA and Protein: CCDS 4022.1

Indications for Test: Patients with symptoms suggestive of Sandhoff disease and heterozygous carrier relatives.

Sensitivity of Test: Unknown

Turn Around Time: Maximum of 40 calendar days, although many tests are completed in 20-30 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of all coding exons of the *HEXB* Gene: \$840

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x15	83898	\$ 250	Sequencing x15	83904	\$ 370
Separation x1	83894	\$ 70	Interpretation/Report x1	83912	\$ 80

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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