Tay-Sachs Disease: HEXA Gene Sequencing

**Test Code:** DD  
**Turnaround time:** 4 weeks  
**CPT Codes:** 81406 x1

### Condition Description

Tay-Sachs disease is an autosomal recessive lysosomal storage disorder caused by accumulation of a fatty substance, called glycosphingolipid GM2 ganglioside, in the lysosomes. The fatty GM2 ganglioside substance is normally broken down in the lysosomes, by the enzyme hexosaminidase-A (HEX A). Loss of HEX A enzyme activity results in build up of the GM2 ganglioside in lysosomes, particularly in tissues of the central nervous system. Tay Sachs disease is characterized by progressive neurodegeneration with symptoms including seizures, spasticity, and blindness as well as loss of motor skills, progressive muscle weakness, decreased attentiveness, and increased startle reflex. A significant physical finding in persons with Tay-Sachs disease is a cherry red spot on the macula of the retina. Treatment of Tay-Sachs disease is supportive only and death usually occurs by 4 years of age. Variant forms of Tay-Sachs disease include chronic, juvenile, and adult-onset. These forms of HEX A deficiency are characterized by later onset and slower progression of variable neurodegenerative symptoms.

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 HEXA gene cause Tay-Sachs disease. Targeted mutation detection can be performed to test for mutations common in the Ashkenazi Jewish population. For mutations not identified by this panel, sequencing of the HEXA gene must be performed. Diagnostic sequencing analysis of the HEXA gene coding region is available for Tay-Sachs disease patients 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 NH.

For questions about testing for Tay-Sachs 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:

### Genes

**HEXA**

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of Tay Sachs Disease.
- Follow up of individuals with a positive/borderline biochemical carrier screening test.
- Prenatal testing for known familial mutations.
- Assessment of carrier status in high risk family members with known mutation analysis.

### Methodology

PCR amplification of the 14 exons contained in the HEXA gene coding region will be performed on genomic patient 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. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements. Large deletions are not detected by this analysis.

### Detection

**Clinical Sensitivity:** 94 - 98% [1]

**Analytical Sensitivity:** ~99%

**Prevalence:** The estimated prevalence of all lysosomal storage disorders is 2-5 per 100,000. The prevalence of Tay-Sachs disease varies by ethnicity.
and is highest in the Ashkenazi Jewish population (1 in 3600), in French Canadians, in Cajuns from Louisiana, and in the Old Order Amish in Pennsylvania. The prevalence in other populations is approximately 1 in 250,000.

### 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

- **Ashkenazi Jewish Carrier Screen (AJ)** is available using targeted mutation analysis.
- **Mutation Analysis for Pseudodeficiency Allele** may be available upon request.
- **HEX A Enzyme Assay (HA)** is available to establish a biochemical diagnosis.
- **Sequencing of HEXB Gene (DA)**.
- **Lysosomal Enzyme Screening Panel (LS)**.
- **Tay Sachs Disease Deletion/Duplication Assay** 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.
- **Custom Diagnostics Known Mutation Analysis (KM)** is available to test family members.
- 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.