GM2-Gangliosidosis AB Variant: GM2A Gene Sequencing

**Condition Description**

The GM2 gangliosidoses (Tay Sachs, Sandhoff, and GM2 gangliosidosis AB variant) are a clinically indistinguishable group of neurodegenerative diseases caused by accumulation of a fatty substance, glycosphingolipid GM2 ganglioside, in the lysosomes. The GM2 gangliosides are normally broken down, in the lysosomes, by the enzyme β-hexosaminidase A, which is made up of an alpha and a beta subunit, with the help of a cofactor, the GM2 activator protein. The alpha and beta subunits are coded by the genes, HEXA, and HEXB, respectively and the GM2 activator protein is coded by the GM2A gene.

Mutations in the HEXA and HEXB genes cause Tay Sachs disease and Sandhoff disease, respectively. These two diseases are distinguished biochemically by enzymatic analysis of β-hexosaminidase A (a heterodimer of the alpha and beta subunits), that is deficient in Tay Sachs and β-hexosaminidase B (a homodimer of two beta subunits), that is deficient in Sandhoff’s disease. β-hexosaminidase A and β-hexosaminidase B enzyme activities are normal in GM2 gangliosidosis AB variant.

Mutations in the GM2A gene (5q33.1) cause the rare GM2 gangliosidosis AB variant (GM2 AB variant) due to the deficiency of the GM2 activator protein and are inherited in an autosomal recessive manner. The clinical course of GM2 AB variant is similar to that of a patient with classic Tay Sachs disease. Disease onset usually occurs after five or six months of age and follows a neurodegenerative course with features including delayed motor milestones, hypotonia, macular cherry red spots, and abnormal MRI findings.

Sequence analysis of the entire GM2A gene coding region is available for individuals suspected of having GM2 AB variant and their at-risk relatives on a clinical basis.

**References:**

- Chen et al. (1999), Am J Hum Genet, 65:77-87.
- OMIM #272750: GM2-gangliosidosis AB variant
- OMIM #613109: GM2A gene

**Genes**

**GM2A**

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of GM2-gangliosidosis AB variant.
- Carrier testing in adults with a family history of GM2-gangliosidosis AB variant.

**Methodology**

PCR amplification of 4 exons contained in the GM2A gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence deoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are 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, and does not detect large deletions.

**Detection**

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%

**Specimen Requirements**

*Submit only 1 of the following specimen types*

**Type: Saliva**

**Specimen Requirements:**

Oragene™ Saliva Collection Kit

Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot
provide a blood sample.

**Specimen Collection and Shipping:**
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

**Type: Whole Blood (EDTA)**

**Specimen Requirements:**
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old): 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

**Specimen Collection and Shipping:**
Ship sample at room temperature for receipt at EGL within 24 hours of collection. Do not refrigerate or freeze.

**Type: DNA, Isolated**

**Specimen Requirements:**
Microtainer
8µg
Isolation using the Perkin Elmer™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

### Special Instructions
Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

### Related Tests
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.
- For confirmation purposes, if two mutations or variants of unknown clinical significance are identified, glycolipids in CSF can be performed on a research basis.