Mucolipidosis Type IIIA: **GNPTAB** Gene Sequencing

**Condition Description**

Mucolipidosis III A (ML III, pseudo-Hurler polydystrophy) is an autosomal recessive lysosomal storage disorder characterized by short stature, skeletal dysplasia, and mild mental retardation and survival up to adulthood.

Fibroblasts from ML III patients have numerous cytoplasmic inclusion bodies. The accumulation of material in the lysosomes results from the inability of the lysosomal enzymes to enter the lysosome for normal degradation. A biochemical marker signal is required for proper trafficking of the lysosomal enzymes, from the site of production in the endoplasmic reticulum to the lysosome itself. This marker was identified as a mannose-6-phosphate residue on the lysosomal enzyme that interacts with a specific receptor on the lysosomal membrane, which then triggers entry into the lysosome. The biochemical defect in ML III disease is due to the deficiency of the enzyme UDP-N-acetylglucosamine- N-acetylglucosamine- l-phosphotransferase (abbreviated GlcNAc phosphotransferase) involved in the addition of the mannose-6-phosphate residue. The genetic defect causing this disorder results in mislocalization of the lysosomal enzymes such that they are, in part, secreted from the cell rather than transported into the lysosomes. Many lysosomal enzymes have decreased intracellular activities but increased activities in the serum and urine. The electrophoretic patterns of a number of lysosomal enzymes also are altered in ML III fibroblasts. The disorder mucolipidosis II (ML II, I-cell disease) is clinically and biochemically very similar to ML III, although with more severe characteristics leading to death by 6 years of age. Lysosomal enzyme activities also are very low in fibroblasts and have abnormal electrophoretic patterns different from ML III.

Mutations to the **GNPTAB** gene cause deficiency of this enzyme. Diagnostic sequencing analysis of the **GNPTAB** gene coding region is available for Mucolipidosis III A 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 (LK).

For questions about testing for ML IIIA, call the Emory Genetics Laboratory at (404) 778-8499 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**

**GNPTAB**

**Indications**

- Confirmation of clinical diagnosis of ML IIIA disease
- Prenatal testing for known familial mutation(s).
- Assessment of carrier status in high risk family members known mutation analysis.

**Methodology**

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient’s genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not mean to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**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 biochemical phenotype.

Analytical Sensitivity: ~99%.

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood
Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) or ACD (yellow 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

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 Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition. Contact the laboratory if further information is needed.

Related Tests

- Known mutation analysis (Custom Diagnostics) is available to test family members.
- A deletion/duplication assay for the GNPTAB gene is available separately for individuals where mutations are not identified by sequence analysis.
- Prenatal testing is available for known familial mutations only. Please call the Laboratory Genetic Counselor for specific requirements for prenatal testing before collecting a fetal sample.