Mucolipidosis Type IIIA: GNPTAB Gene Deletion/Duplication

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-acetylgalactosamine- N-acetylgalactosamine-1-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 questions about testing for ML IIIA, 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

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

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region. Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

Detection

Detection is limited to duplications and deletions. Array CGH will not detect point mutations or intronic mutations. Results of molecular analysis must interpreted in the context of the patient's clinical and/or biochemical phenotype.

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**

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 EGL Genetics, 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.
- 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.