

Mucopolipidosis Type II: *GNPTAB* Gene Sequencing

Test Code: BK

Turnaround time: 4 weeks

CPT Codes: 81479 x1

Condition Description

Mucopolipidosis II (ML II or I-cell disease) is described as a Hurler-like lysosomal storage disorder with severe clinical and radiologic features. Leroy et al. (1970) first described this condition and named it I-cell disease, for inclusion cell disease, reflecting the buildup or inclusions noticeable in the lysosomes. 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 I-cell disease is due to the lack of the enzyme (abbreviated GlcNAc-1-P) involved in the addition of the mannose-6-phosphate residue.

Clinical symptoms may be noticeable from infancy and may include: congenital dislocation of the hip, thoracic deformities, hernia, and hyperplastic gums which are evident soon after birth. Other symptoms may include delayed psychomotor development, clear corneas, and restricted joint mobility.

Mutations in the *GNPTAB* gene cause a deficiency of the enzyme GlcNAc-1-P. Diagnostic sequencing analysis of the *GNPTAB* gene coding region is available for mucopolipidosis II 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 (LJ).

For questions about testing for ML II, 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:

1. Leroy JG, Spranger JW. I-cell disease. *N Engl J Med.* 1970 Sep 10;283(11):598-9.
2. Kudo M, Brem MS, Canfield WM: Mucopolipidosis II (I-cell disease) and mucopolipidosis IIIA (classical pseudo-Hurler polydystrophy) are caused by mutations in the GlcNAc-phosphotransferase alpha/beta-subunits precursor gene. *Am. J. Hum. Genet.* 78: 451-463, 2006.
3. Olkkonen VM, Ikonen E. Genetic defects of intracellular-membrane transport. *New Eng. J. Med.* 343: 1095-1104, 2000.
4. Tiede S, Storch S, Lubke T, Henrissat B, Bargal R, Raas-Rothschild A, Braulke T. Mucopolipidosis II is caused by mutations in *GNPTA* encoding the alpha/beta GlcNAc-1-phosphotransferase. *Nature Med.* 11: 1109-1112, 2005.
5. Paik, K. H.; Song, S. M.; Ki, C. S.; Yu, H.-W.; Kim, J. S.; Min, K. H.; Chang, S. H.; Yoo, E. J.; Lee, I. J.; Kwan, E. K.; Han, S. J.; Jin, D.-K. Identification of mutations in the *GNPTA* (MGC4170) gene coding for GlcNAc-phosphotransferase alpha/beta subunits in Korean patients with mucopolipidosis type II or type IIIA. *Hum. Mutat.* 26: 308-314, 2005.

Genes

[GNPTAB](#)

Indications

- Confirmation of clinical diagnosis of ML II 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 meant 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: In 3 unrelated Korean girls with type II mucopolipidosis, compound heterozygosity for 5 different mutations was detected in the *GNPTAB* gene [4]. In 6 patients with clinically and biochemically diagnosed mucopolipidosis II, homozygosity or compound heterozygosity was identified for 7 mutations in the *GNPTAB* gene [5].

Analytical Sensitivity: ~99%

Prevalence: The estimated prevalence of all lysosomal storage disorders is 2-5 per 100,000. The prevalence of ML II is not specifically known, but is likely to be rare and may vary by ethnicity.

Specimen Requirements

Submit only 1 of the following specimen types

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 72 hours of collection. Do not freeze.

Type: DNA, Isolated**Specimen Requirements:**

Microtainer
8µg
Isolation using the Perkin Elmer™ Chemagen™ 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.

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.

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 (KM) is available to test family members.
- 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.
- 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.