Mucolipidosis Type III Gamma: GNPTG Gene Sequencing

**Test Code:** SGNPT

**Turnaround time:** 6 weeks

**CPT Codes:** 81479 x1

### Condition Description

Mucolipidosis III gamma (ML IIIC or variant pseudo-Hurler polydystrophy) is an autosomal recessive lysosomal storage disorder that is related to mucolipidosis II and (ML II) and mucolipidosis IIIA/B (ML IIIA/B). These three disorders are caused by the alteration of activity of the enzyme, N-acetylglucosamine-1-phosphotransferase (GlcNAc-1-PT or GNPT). The GNPT enzyme has three subunits, ?, and ?, encoded by the gene GNPTAB, and ?, encoded by the gene GNPTG. Pathogenic variants in the GNPTG gene (16p13.3) cause ML IIIC.

ML IIIC, which is clinically indistinguishable from ML IIIA, is characterized by short stature, skeletal abnormalities (mild to moderate dysostosis multiplex, joint stiffness), cardiomegaly, mild coarsening of facial features and developmental delay. In patients with ML IIIC, the activity of nearly all lysosomal hydrolases is up to tenfold higher in plasma and other body fluids than in normal controls due to inadequate targeting of GlcNAc-1-PT to lysosomes.

For patients with suspected ML IIIC, sequence analysis is recommended as the first step in pathogenic variant identification. For patients in whom pathogenic variants are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

### References:

- GeneReviews
- OMIM #252605: Mucolipidosis III gamma
- OMIM #607838: GNPTG gene

### Genes

**GNPTG**

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of ML IIIC.
- Carrier testing in adults with a family history of ML IIIC.

### Methodology

PCR amplification of 11 exons contained in the GNPTG 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 dideoxy 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: Sequencing can detect approximately 95% of cases. Pathogenic variants in the promoter region, some pathogenic variants in the introns and other regulatory element pathogenic variants 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

#### 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

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Specimen Requirements:

OrageneTM Saliva Collection kit (available through EGL) used according to manufacturer instructions.

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

**Special Instructions**

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.

**Related Tests**

- Deletion/duplication analysis of the GNPTG gene by CGH array is available for those individuals in whom sequence analysis is negative.
- Sequencing and deletion/duplication analysis is available for ML IIIA.
- Custom diagnostic analysis for pathogenic variants or variants of unknown clinical significance (test code: KM) is available to family members if pathogenic variants or variants of unknown clinical significance are identified by targeted testing or sequencing analysis.
- Prenatal testing is available only for known familial pathogenic variants to individuals who are confirmed carriers of pathogenic variants. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.