Mucolipidosis Type III Gamma: \textit{GNPTG} Gene Deletion/Duplication

\textbf{Test Code: DGNPT}
\textbf{Turnaround time: 2 weeks}
\textbf{CPT Codes: 81228 x1}

\textbf{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, \(\gamma\) and \(\beta\) encoded by the gene \textit{GNPTAB}, and \(\delta\), encoded by the gene \textit{GNPTG}. Pathogenic variants in the \textit{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: \textit{GNPTG} gene

\textbf{Genes}

\textit{GNPTG}

\textbf{Indications}

This test is indicated for:

- Confirmation of a clinical diagnosis of ML IIIC in an individual in whom sequence analysis was negative.
- Carrier testing in adults with a family history of ML IIIC in whom sequence analysis was negative.

\textbf{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.

\textbf{Detection}

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

\textbf{Specimen Requirements}

\textbf{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.

\textbf{Type: Saliva}
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**

- Sequence analysis of the GNPTG gene is available and is required before deletion/duplication analysis.
- Sequencing and deletion/duplication analysis is available for ML IIIA.
- Custom diagnostic analysis for deletions or duplications (test code: DKMDD) is available to family members if deletions or duplications are identified.
- 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.