Mucopolysaccharidosis Type IIIC: \textit{HGSNAT} Gene Sequencing

\textbf{Test Code:} \textit{FN}  \\
\textbf{Turnaround time:} 4 weeks  \\
\textbf{CPT Codes:} 81479 x1

\textbf{Condition Description}

Mucopolysaccharidosis type IIIC (MPS IIIC, Sanfilippo syndrome type C), is a member of a group of inherited metabolic disorders collectively termed mucopolysaccharidoses (MPSs). The MPSs are caused by a deficiency of lysosomal enzymes required for the degradation of mucopolysaccharides or glycosaminoglycans (GAGs) within the lysosome [1]. When functioning normally, the lysosomal enzymes break down these GAGs, however when the enzyme is deficient, the GAGs build up in the lysosomes causing damage to the body's tissues. The MPSs share a chronic progressive course with multisystem involvement and characteristic physical features such as coarse facies, hypertelorism, and coarse hair. The MPS patients are also characterized by developmental regression, hepatosplenomegaly and characteristic laboratory and radiographic abnormalities.

Clinical features of MPS IIIC are similar to other MPSs and include hyperactivity, aggressiveness, and developmental delays in childhood. Mental abilities decline as the disease progresses. Involvement of other organ systems tends to be mild and dysmorphic features are more subtle than those observed in other type of mucopolysaccharidosis [1].

MPS IIIC is caused by a deficiency of the lysosomal membrane enzyme heparin-alpha-glucosaminide N-acetyltransferase (N-acetyltransferase), which leads to impaired degradation of heparan sulfate. MPS IIIC is caused by mutations in the \textit{HGSNAT} gene [2] (also known as the \textit{TMEM76} gene), but is clinically indistinguishable from MPS IIIA, MPS IIIB, and MPS IIID, which are caused by mutations in other genes. All four forms of MPS III result in buildup of the same GAG, heparin sulfate. Diagnostic sequencing analysis of the \textit{HGSNAT} gene coding region is available for MPS type IIIC patients and their at-risk relatives (FN). For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (HW).

For questions about testing for MPS IIIC, call EGL Genetics at 470-378-2200. 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.

Visit \url{www.ThinkGenetic.com} for patient-friendly information on mucopolysaccharidosis type III.

\textbf{References:}

\textbf{Genes}

\textit{HGSNAT}

\textbf{Indications}

This test is indicated for:
- Confirmation of a clinical diagnosis of MPS IIIC.
- Carrier testing in adults with a family history of MPS IIIC

\textbf{Methodology}

\textbf{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.

\textbf{Detection}

Full Gene Sequencing: Clinical Sensitivity: 51/60 mutations identified in 30 patients, [2], 22/24 mutations identified in 12 patients [3].
Analytical Sensitivity: >99%

Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

\textbf{Specimen Requirements}

\textit{Submit only 1 of the following specimen types}

\textbf{Type: Saliva}

\textbf{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.

Type: DNA, Isolated

Specimen Requirements:
- Microtainer
- 8 µg
- Isolation using the Perkin Elmer™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: 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 24 hours of collection. Do not refrigerate or freeze.

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 EGL Genetics, please submit a copy of the sequencing report with the test requisition.

Related Tests
- Mucopolysaccharide screen (urine GAG) (GA)
- Gene sequencing for the MPS III gene sequencing panel when enzyme testing has not been performed
- Targeted mutation analysis (Custom Diagnostics) is available to test family members.
- A deletion/duplication assay 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 before collecting a fetal sample.