Mucopolysaccharidosis Type IIIC: *HGSNAT* Gene Sequencing

**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 *HGSNAT* gene [2] (also known as the *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 *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 the Emory Genetics Laboratory 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 [www.ThinkGenetic.com](http://www.ThinkGenetic.com) for patient-friendly information on mucopolysaccharidosis type III.

**References:**

**Genes**

*HGSNAT*

**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

**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**

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 interpreted in the context of the patients clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types

- Preferred specimen type: Whole Blood

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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

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 of Emory Genetics Laboratory, 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.