Mucopolysaccharidosis Type IIID: GNS Gene Sequencing

**Test Code:** BH
**Turnaround time:** 4 weeks
**CPT Codes:** 81479 x1

**Condition Description**

Mucopolysaccharidosis type IIID (MPS IIID, Sanfilippo syndrome type D) 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. 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, characteristic physical features, laboratory findings, and radiographic abnormalities.

MPS IIID is an autosomal recessive disorder caused by a deficiency of the N-acetylglucosamine 6-sulfatase (GNS) enzyme and build-up of heparin sulfate. Clinical features of MPS IIID include hyperactivity, aggressiveness, and developmental delays. Mental abilities decline as the disease progresses. Involvement of other organ systems tends to be mild and dysmorphic features are subtle than those observed in other types of mucopolysaccharidosis [1]. MPS IIID is caused by mutations in the GNS gene, but the disorder is clinically indistinguishable from MPS IIIA, MPS IIIB, and MPS IIIC, 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 GNS gene coding region is available for MPS type IIID 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 (IK).

For questions about testing for MPS IIID, 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 www.ThinkGenetic.com for patient-friendly information on mucopolysaccharidosis type III.

**References:**

**Genes**

GNS

**Indications**

- Confirmation of a clinical diagnosis of MPS IIID
- Prenatal testing for known familial mutations.
- 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**

**Full Gene Sequencing:**
Clinical Sensitivity: 2/2 mutations identified in 1 patient [2], 1 mutation and an 8.7kb deletion in 1 patient [3], 2/2 mutations identified in 1 patient [4].

Analytical Sensitivity: ~99%

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

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

**Specimen Requirements**

Submit only 1 of the following specimen types
* Preferred specimen type: Whole Blood

**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.

**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 EGL Genetics, please submit a copy of the sequencing report with the test requisition. Contact the laboratory if further information is needed.

**Related Tests**

- Mucopolysaccharide screen (urine GAG) (GA)
- Gene Sequencing for MPS IIIA (AW) and MPS IIIB (BB)
- Known mutation analysis (Custom Diagnostics) is available to test family members.
- A deletion/duplication assay for the GNS gene 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 for specific requirements for prenatal testing before collecting a fetal sample.