Mucopolysaccharidosis Type III Panel: Sequencing and CNV Analysis

Condition Description

Mucopolysaccharidosis type III (MPS III, Sanfilippo syndrome), is a member of a group of inherited metabolic disorders collectively termed mucopolysaccharidoses (MPS's). The MPS's 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 MPS's 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 III are similar to other MPS's 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 III is caused by a deficiency of any of four lysosomal membrane enzymes, which leads to impaired degradation of heparan sulfate. The forms of MPS III are clinically indistinguishable each other and are caused by mutations in distinct genes. All four forms of MPS III result in buildup of the same GAG, heparin sulfate.

- MPS IIIA is caused by deficiency of the enzyme heperealpha-glucosaminidase encoded by the gene NAGLU.
- MPS IIIB is caused by deficiency of the enzyme heparin-alpha-glucosaminide N-acetylttransferase (N-acetylttransferase), encoded by the gene HGSNAT.
- MPS IIID is caused by deficiency of the enzyme alpha-N-acetylglucosaminidase, encoded by the gene SGSH.
- MPS IIIE is caused by deficiency of the enzyme N-acetylglucosamine 6-sulfatase (N-acetylttransferase), encoded by the gene GNS.

Diagnostic sequencing analysis of the panel of genes associated with MPS III is available for patients with a clinical diagnosis who have not had a fibroblast enzyme study to identify the specific subtype (FQ). For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (HV). For questions about testing for MPS III, 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, HGSNAT, NAGLU, SGSH

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of MPS III when enzyme activity studies have not been obtained to identify the specific subtype.
- Carrier testing in adults with a family history of MPS III

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 intended 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.

Copy Number Analysis: Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

Detection

Next Generation Sequencing: Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory elements, and some mutations of unknown clinical significance cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical presentation.
clinical/biochemical phenotype.

Analytical sensitivity for sequence variant detection is ~99%.

**Copy Number Analysis:** The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (< 500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

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**Specimen Requirements**

**Submit only 1 of the following specimen types**

**Type: DNA, Isolated**

**Specimen Requirements:**

- Microtainer
- 8µg

Isolation using the Perkin Elmer™Chemagen™ 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: Saliva**

**Specimen Requirements:**

- Oragene™ Saliva Collection Kit

Orangene™ 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: 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 72 hours of collection. Do not 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 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 a specific MPS III gene when enzyme activity studies have identified the subtype.
- Known mutation analysis (Custom Diagnostics) is available to test family members if mutations are identified by sequencing
- For comprehensive testing a deletion/duplication assay is available separately. This test is indicated 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.