SGSH, NAGLU, HGSNAT, and GNS Gene Analysis in Mucopolysaccharidosis III (Sanfilippo Syndrome A, B, C, and D)

Clinical Features:
Mucopolysaccharidosis III (MPS III, Sanfilippo syndrome) is an inherited lysosomal storage disorder caused by an inability to degrade heparan sulfate. There are 4 types of MPS III that are distinguished by the specific enzyme defect. Generally, all types of MPS have similar clinical manifestations although MPS IIIA has been reported to be more severe. Patients usually present in infancy or early childhood with developmental delay, delayed speech, difficulty in feeding, hyperactivity or sleep disturbances. Additional clinical symptoms include intellectual disability, progressive neurologic symptoms including aggressive behavior, poor coordination, seizures and hearing loss. Coarse facies, mild dysostosis multiplex, hepatosplenomegaly and joint contractures may also be present. There is considerable variation in onset and severity of the clinical phenotype even within a sibship. Death usually occurs by the third decade, often due to respiratory complications. The incidence of MPS III ranges from 1:20,000 in Germany to 1:324,000 in British Columbia.1 MPS IIIA is the most common subtype in Northern Europe.1 MPS IIIB is more common in Greece and Italy.1 There is a very high prevalence of this disorder in the Netherlands (1/24,000) and the Cayman Islands. MPS III is more rarely caused by variants in the GNS gene (MPS IIID). The incidence of MPS IIID is less than 1,000,000.2

Genetics:
MPS IIIA, IIIB, IIIC, and IIID are caused by variants in the SGSH, NAGLU, HGSNAT and GNS genes, respectively. These genes encode enzymes required for the degradation of heparan sulfate: heparan N-sulfatase (MPS IIIA), α-N-acetylglucosaminidase (MPS IIIB), heparan sulfate acetyl-CoA: α-glucosaminide N-acetyltransferase (MPS IIIC) and N-acetylglucosamine 6-sulfatase (MPS IIID). Each of these enzyme deficiencies lead to the storage of heparan sulfate in the lysosomes. The SGSH gene is located on chromosome 17q25.3 and has 8 coding exons.1 The NAGLU gene is located on chromosome 17q21 and has 6 exons. The HGSNAT gene is located on chromosome 8p11.1 and has 18 exons. The GNS gene is located on chromosome 12q14.3 and has 14 exons.

Inheritance Pattern:
Autosomal recessive

Test Methods:
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the SGSH, NAGLU, HGSNAT, and/or GNS genes are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene
specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request. Testing for the SGSH, NAGLU, HGSNAT, and GNS genes can be ordered individually or sequentially if specifically requested, or all 4 genes can be analyzed simultaneously if a more rapid turnaround time is needed.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

References: