SGSH, NAGLU, HGSNAT, and GNS Gene Analysis in Sanfilippo Syndrome A, B, C, and D (Mucopolysaccharidosis III; MPS IIIA, IIIB, IIIC, and IIID)

Clinical Features:
Sanfilippo syndrome (Mucopolysaccharidosis III; MPS III) 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.

Inheritance Pattern/Genetics:
Autosomal Recessive

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-acetylg glucosaminidase (MPS IIIB), heparan sulfate acetyl-CoA: α-glucosaminide N-acetyltransferase (MPS IIIC) and N-acetylg glucosamine 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, has 8 coding exons, and 502 amino acids.¹ The NAGLU gene is located on chromosome 17q21, has 6 exons, and encodes a protein of 743 amino acids. The HGSNAT gene is located on chromosome 8p11.1, has 18 exons, and encodes a protein of 635 amino acids. The GNS gene is located on chromosome 12q14.3, has 14 exons and encodes a protein of 552 amino acids. 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
Test Methods:
Variant analysis of the SGSH, NAGLU, and HGSNAT genes is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the SGSH, NAGLU, and HGSNAT genes in a proband, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of that gene. For the GNS gene only, sequencing of GNS is performed concurrently with targeted deletion/duplication testing of this gene (ExonArrayDx). Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis or another appropriate method.

Test Sensitivity:
In one large study of 44 patients with MPS IIIA, SSCP with subsequent sequencing of fragments showing a mobility shift in addition to SGSH common variant (p.R245H) testing identified approximately 74% of mutant alleles.¹ In several large studies including 14-22 patients with MPS IIIB, sequence analysis of the NAGLU gene detected 82-100% of mutant alleles.³,⁵,⁶ Sequence analysis of the HGSNAT gene detected 89% of variants in a cohort study of 30 patients with MPS IIIC from Europe, North America and North Africa.⁷ Variant analysis of the GNS gene in 23 unrelated MPS IIID patients diagnosed with isolated GNS enzyme deficiency identified variants on 26/26 alleles.⁸

References: