IDUA Gene Analysis in Mucopolysaccharidosis Type I (MPSI)

Clinical Features:
Mucopolysaccharidosis type I (MPS I) is a progressive and multisystemic lysosomal storage disorder. The prevalence of MPS I is estimated to be 1 in 35,000 newborns, based on newborn screening data.\(^1\) Patients with MPS I have historically been classified as having either Hurler syndrome, Hurler-Scheie syndrome, or Scheie syndrome, based on severity of clinical features; however, due to clinical overlap, these designations have now been replaced with severe and attenuated MPS I.\(^2\) Onset of symptoms before 24 months typically corresponds with severe MPS I, whereas onset between 3-10 years typically corresponds with attenuated MPS I. Common clinical findings include coarse facial features, gibbus deformity, hepatosplenomegaly, limited joint mobility, and corneal clouding. Severe cases are characterized by profound central nervous system involvement and a significantly shortened lifespan.\(^2\) The diagnosis of MPS I is established based on clinical features and enzyme analysis demonstrating deficient activity of α-L-iduronidase.\(^2\)

Inheritance Pattern:
Autosomal recessive

Genetics:
MPS I is caused by pathogenic variants in the \textit{IDUA} gene, which contains 14 exons and is located at 4p16.3. \textit{IDUA} encodes alpha-L-iduronidase, an enzyme involved in the hydrolysis of terminal alpha-L-iduronic acid residues of the glycosaminoglycans dermatan sulfate and heparan sulfate. Pathogenic variants in \textit{IDUA} result in the buildup of dermatan sulfate and of heparan sulfate in lysosomes.\(^2\)

The majority of pathogenic variants in the \textit{IDUA} gene are missense variants, however nonsense, and small insertions/deletions have also been reported.\(^3\) Exonic deletions are rare but have been reported.\(^4\) Recurrent and ethnic-specific pathogenic variants have been described,\(^5\) as well as a pseudodeficiency allele.\(^2\) Complete loss of IDUA enzyme activity is typically associated with severe truncating variants; however, genotype-phenotype correlations have not been fully elucidated and is limited by the frequency of private and non-recurrent variants.\(^2,5\)

Test Methods:
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the \textit{IDUA} gene 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 the reference sequence 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.

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.

Test Sensitivity:
In patients with biochemically confirmed MPS I, sequence analysis is expected to identify a pathogenic variant in greater than 95%-97% of alleles.6,7

References: