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 *IDUA* gene, which contains 14 exons and is located at 4p16.3. *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 *IDUA* result in the buildup of dermatan sulfate and of heparan sulfate in lysosomes.[2]

The majority of pathogenic variants in the *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:
Variant analysis of the *IDUA* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of exons 1-14, and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *IDUA* gene, 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 this gene. 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 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:

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3. Stenson et al. (2014) Human genetics 133 (1):1-9 (PMID: 24077912)
4. Breen et al. (2016) Hum Genome Var 3 :16031 (PMID: 27766162)
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