

Mucopolysaccharidosis Type I via *IDUA* Gene Sequencing --Test #452

Brief Description of Disorder: The mucopolysaccharidoses (MPS) are a group of inherited disorders caused by defects in lysosomal enzymes responsible for glycosaminoglycans (GAGs) degradation. Each enzyme deficiency results in progressive storage of distinct GAGs in multiple organ systems and subsequent abnormalities. Although MPS share several symptoms, including physical and mental developmental abnormalities, they may differ even within the same enzyme deficiency. MPS are classified in seven groups on the basis of the clinical symptoms (Types I, II, III, IV, VI, VII, and IX). Defects in eleven different enzymes have been associated with the various MPS. **MPS Type I** is caused by deficiency in the alpha-L-iduronidase enzyme and subsequent systemic accumulation of dermatan and heparan sulfates. Three clinical subtypes are recognized on the basis of the age of onset, severity and disease course: **1)** Hurler syndrome (OMIM 607014) is the most severe and frequent form of MPS type I. It is characterized by onset in infancy and death by the first decade of life, as the result of heart or lung failure. Symptoms include coarse facial features, corneal clouding, hydrocephalus, heart disease, respiratory difficulties, hepatosplenomegaly, joint stiffness, learning disabilities, and mental retardation. **2)** Hurler-Scheie syndrome (OMIM 607015) is characterized by onset in childhood and intermediate severity with normal intelligence and survival to adulthood. **3)** Scheie syndrome (OMIM 607016) is the mildest form with normal life span. Symptoms include stiff joint and heart disease (Neufeld and Muenzer In Scriver eds, 8th ed:3421-3452, 2001). See also Clarke (GeneReviews, 2007, www.genetests.org) and the National MPS Society at (www.mpssociety.org).

Genetics: The three MPS I variants are inherited in an autosomal recessive manner, and result from mutations in the *IDUA* gene (Scott et al. Hum Mutat 1:103-108, 1992; Lee-Chen et al. Clin Genet 56:66-70, 1999; Moskowitz et al. Hum Mutat 2:141-144, 1993). Over 110 mutations have been reported in patients with MPS I from various ethnic populations, and include missense, nonsense, splicing, and small insertions or deletions. Gross deletions and complex rearrangements are rare. Patients with two nonsense (or other premature termination) mutations typically develop a more severe phenotype (Terlato and Cox Genet Med 5:286-294, 2003).

Description of This Particular Test: The *IDUA* gene encodes the alpha-L-iduronidase enzyme, which catalyzes the hydrolysis of dermatan and heparan sulfates. This test involves bidirectional DNA sequencing of all 14 exons and splice sites of the *IDUA* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. As indicated, we will sequence one (Test #100) or two (Test #200) exons in family members of patients with known mutations or to confirm previous results.

Reference Sequences: Genomic: NC_000004.10 mRNA: NM_000203.3 Protein: NP_000194.2 (CCDS 3343.1)

Indications for Test: Patients with symptoms suggestive of MPS, increased dermatan and heparan sulfate excretion in urine, and reduced alpha-L-iduronidase enzyme activity; and potential heterozygous carriers.

Sensitivity of Test: This Test is expected to detect nearly all *IDUA* mutations (Clarke, 2007).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 20-30 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price:	Sequencing of all coding exons of the <i>IDUA</i> Gene:	\$840
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x14	83898 \$ 250	Sequencing x14 83904 \$ 370
Separation x1	83894 \$ 60	Interpretation/Report x1 83912 \$ 90

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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