

Mucopolysaccharidosis Type II via *IDS* Gene Sequencing --Test #453

Brief Description of Disorder: The mucopolysaccharidoses (MPS) are a group of inherited disorders caused by defects in lysosomal enzymes responsible for glycosaminoglycans degradation. 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 II (MPS II), also called Hunter syndrome (OMIM 309900), is caused by deficiency in the iduronate-2 sulfatase (I2S) enzyme and subsequent accumulation of dermatan and heparin sulfates in several organ systems, resulting in a wide range of symptoms. MPS II is an X-linked recessive disease characterized by a great heterogeneity in regard to age of onset, severity and clinical course. Typical symptoms include coarse facial features, short stature, stiff joint, thick bones, skeletal deformities, claw-hand deformity, skin lesions, airway obstruction, hearing loss, hepatosplenomegaly, cardiomyopathy, learning difficulties, and neurological decline. In contrast to MPS I, there is no corneal clouding in MPS II (Neufeld and Muenzer In Scriver eds, 8th ed:3421-3452, 2001). MPS II is the most common MPS. It occurs in diverse ethnic groups throughout the world, with an estimate incidence of 1.3 in 100,000 males (Baehner et al. J Inher Metab Dis 28:1011-1017, 2005). See also Martin (GeneReviews, 2007, www.genetests.org).

Genetics: Mutations in the *IDS* gene (which is located on the X chromosome) are responsible for the I2S enzyme deficiency and subsequent development of MPS II (Mossman et al. Arch Dis Child 58:911-915, 1983). More than 350 mutations have been reported. All types of mutations have been reported, including *de novo* mutations in sporadic male patients (Froissart et al. Clin Genet 53:362-368, 1998). Total or partial deletions of the *IDS* gene represent ~8% of the mutations (<http://www.biobase-international.com>) and appear to result in a severe phenotype (Froissart, 1998). Point mutations may result in a wide range of phenotypes, with the same mutation leading to different phenotypes even among siblings, making genotype-phenotype correlations difficult. Hunter disease has been reported in rare female cases as the result of skewed X-chromosome inactivation alone (Sukegawa et al. Clin Genet 53:96-101, 1998) or in combination with *de novo* mutations on the paternal chromosome, or as the result of a homozygous mutation that led to mildly affected, undiagnosed male patients in consanguineous families (Cudry et al. J Med Genet 37:E29, 2000). Heterozygous female carriers are usually asymptomatic.

Description of This Particular Test: The *IDS* gene encodes the I2S enzyme, which catalyzes the first step of the degradation of dermatan and heparan sulfates. This test involves bidirectional DNA sequencing of all 9 exons and splice sites of the *IDS* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. As indicated, we will sequence any single (Test #100) or double (Test #200) exons in family members of patients with known mutations or to confirm previous results.

Reference Sequences: Genomic: NC_000023.9 mRNA: NM_000202.4 Protein: NP_000193.1 (CCDS 14685.1)

Indications for Test: Patients, including males and rare females (Tuschl et al. Pediatr Neurol 32:270-272, 2005), with symptoms suggestive of MPS, increased dermatan and heparan sulfate excretion in urine, and deficiency of I2S activity.

Sensitivity of Test: This Test is expected to detect mutations in ~ 82% of MPS II patients (Martin, 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 *IDS* Gene: \$670

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x10	83898 \$ 180	Sequencing x10	83904 \$ 280
Separation x1	83894 \$ 50	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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