

Mucopolysaccharidosis Type VII/Sly Syndrome via *GUSB* Gene Sequencing --Test #457

Brief Description of Disorder: The mucopolysaccharidoses (MPS) are a group of inherited disorders caused by defects in lysosomal enzymes responsible for degradation of glycosaminoglycans (GAGs). 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 VII** (Sly syndrome, OMIM 253220), is caused by deficiency in beta-glucuronidase enzyme and subsequent intralysosomal accumulation and excessive urinary excretion of dermatan and heparan sulfates. The most severe and common form of MPS VII is characterized by neonatal onset, hydrops fetalis, dysostosis multiplex, dysmorphic features and death within one year of age. A milder form is characterized by variable age of onset and clinical severity with normal intelligence and survival to the fifth decade of life. Symptoms include umbilical hernias, hepatosplenomegaly, skeletal abnormalities, short stature, developmental delay, corneal clouding, and vertebral deformation (Neufeld and Muenzer In Scriver eds, 8th ed: 3421-3452, 2001). Beta-glucuronidase enzyme deficiency may be associated with increased risk for spontaneous abortions (Vervoort et al. Am J Hum Genet 58:457-471, 1996).

Genetics: MPS VII is inherited with an autosomal recessive manner, and results from mutations in the *GUSB* gene (Fukuda et al. J Inherit Metab Dis 14:800-804, 1991). Over 50 mutations, mostly missense, have been reported in patients from various ethnic populations. A few nonsense, small deletions and splicing mutations were also reported (Tomatsu et al. Hum Mutat 30:511-519, 2009). Most mutations were private, and the few mutations detected in more than one family do not appear to be identical by descent (Vervoort et al. 1996). Some mutations were detected in specific populations only. For example, two mutations in the same allele, c.1222C>T (p.P408S) and c.1244C>T (p.P415L), were reported in Mexican patients (Islam et al. Hum Genet 98:281-284, 1996); while the mutation c.1856C>T (p.A619V) was reported in Japanese (Fukuda et al. 1991).

Description of This Particular Test: The *GUSB* gene encodes the beta-glucuronidase enzyme, which is involved in the degradation of glucuronic acid-containing glycosaminoglycans. This test involves bidirectional DNA sequencing of all 12 exons and splice sites of the *GUSB* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. As indicated, we will also sequence one (Test #100) or two (Test #200) exons in family members of patients with known mutations or to confirm research results (\$190-340).

Reference Sequences: Genomic: NC_000007.12 mRNA: NM_000181.2 Protein: NP_000172.1 (CCDS 5530.1)

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

Sensitivity of Test: This Test is expected to detect > 90% of all *GUSB* mutations (Tomatsu et al. 2009).

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 *GUSB* Gene: \$660

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x10	83898 \$ 190	Sequencing x 10	83904 \$ 280
Separation x1	83894 \$ 40	Interpretation/Report x1	83912 \$ 80

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

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