

Spinal Muscular Atrophy with Respiratory Distress Type 1 via *IGHMBP2* Gene Sequencing (Test #339)

Brief Description of Clinical Features: Spinal muscular atrophy with respiratory distress type 1 (SMARD1; OMIM 604320) is a disease of the anterior horn cell which most often presents before 6 months of age with intrauterine growth retardation, foot deformities, distal muscle weakness, and respiratory failure due to diaphragmatic eventration and paralysis (Grohmann et al. *Nat Genet* 29:75-77, 2001). Muscle weakness is progressive and predominately affects the lower distal extremities. Motor nerve conduction velocities, particularly in the legs, are very slow (Pitt et al. *Brain* 126:2682-2692, 2003). Among a cohort of twenty-nine infants with mutation-confirmed SMARD1, Grohmann et al. (*Ann Neurol* 54:719-724, 2003) found that three-fourths of the patients had IUGR and more than a third were affected by prematurity. The most prominent feature was life-threatening respiratory distress, with stridor and/or a weak cry being the most common presenting signs. Nearly all patients developed eventration resulting in diaphragmatic paralysis. Muscle weakness was first evident in the lower distal muscles, however upper limbs were subsequently affected leading to paralysis of the trunk and limb muscles. Muscle biopsies showed neurogenic changes with myofiber hypertrophy and atrophy.

Genetics: Spinal muscular atrophy with respiratory distress type 1 is inherited as an autosomal recessive disorder due to mutations in the *IGHMBP2* gene. *IGHMBP2* encodes the immunoglobulin μ -binding protein 2, an ATP-dependent helicase which localizes to neuronal and non neuronal cells and associates with ribosomes (Guenther et al. *Hum Mol Genet* 18:1288-1300, 2009). Degeneration of α -motor neurons from the anterior horn is likely related to disruption of protein translation (Guenther et al. 2009). Missense mutations appear to be concentrated in the predicted helicase domains (Grohmann et al. *Ann Neurol* 54:719-724, 2003) while nonsense mutations occur throughout the protein. Small deletions and splice site mutations are also documented.

Description of This Particular Test: The immunoglobulin μ -binding protein 1 is coded by the *IGHMBP2* gene (OMIM #600502) located on chr 11q13. Testing is accomplished by amplifying the 15 coding exons and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

Reference Sequences: Genomic: NC_000011.9 mRNA: NM_002180.2 Protein: NP_002171.2 (CCDS 8187.1)

Indication for Testing: Infants with distal limb weakness and respiratory distress secondary to diaphragmatic paralysis. It is recommended that consanguineous parents of a child with sudden infant death syndrome consider carrier testing (Grohmann et al. *Ann Neurol* 54:719-724, 2003).

Sensitivity of Test: Respiratory failure between ages 6 weeks and 6 months along with diaphragmatic eventration or, alternatively pre-term birth, is a highly sensitive predictor of *IGHMBP2* involvement (Guenther et al. *Hum Mutat* 28:808-815, 2007).

Turn Around Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price:	Sequencing of <i>IGHMBP2</i>	Exons 1-15	\$ 910
CPT Codes:			
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x16	83898 \$270	Sequencing x16	83904 \$ 400
Separation x1	83894 \$ 70	Interpretation/Report x1	83912 \$ 100

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

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