Genetic testing of the IGHMBP2 Gene in Spinal Muscular Atrophy with Respiratory Distress Type 1

Disorder also known as: SMARD1; diaphragmatic spinal muscular atrophy; distal spinal muscular atrophy type 1; DSMA1; distal hereditary motor neuropathy type VI; dHMN-VI; severe infantile axonal neuropathy with respiratory failure

Clinical Features:
Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a rare inherited disorder characterized by distal muscle weakness and respiratory failure. It is caused by variants in the IGHMBP2 gene located on chromosome 11q13.2 and is clinically and genetically distinct from classic spinal muscular atrophy type 1 (SMA). At birth, infants with SMARD1 are often noted to have a weak cry, inspiratory stridor, feeding difficulties, and congenital contractures, especially foot deformities. Intrauterine growth retardation, premature birth, and a history of decreased fetal movements are also common. Infants with SMARD1 typically develop progressive, severe respiratory distress within the first six weeks to six months of life, resulting in the need for irreversible mechanical ventilation; however, several patients have been reported with juvenile onset of respiratory distress. The respiratory distress is due to diaphragmatic paralysis (diaphragmatic hernia observed on chest X-ray). As the disease progresses, autonomic dysfunction and tongue twitching develop, and deep tendon reflexes are absent. Cognitive abilities are reported to be age-appropriate in approximately 60% of patients, while approximately half of patients experience seizures. Electrophysiologic examinations may reveal reduced motor nerve conduction velocities. Ultrastructural studies may identify axonal and motor end-plate degeneration, and abnormal myelin formation. The muscle weakness caused by SMARD1 eventually leads to complete paralysis.

Genetics:
Spinal muscular atrophy with respiratory distress type 1 (SMARD1) has an autosomal recessive pattern of inheritance. IGHMBP2 has 15 coding exons and is ubiquitously expressed. The protein contains two nucleic acid-binding domains, in addition to an adenosine triphosphate binding motif and a helicase-like motif. The normal IGHMBP2, a multifunctional protein, is believed to be involved in recombination, replication, pre-mRNA processing, translation, and regulation of motoneuronal death. The mechanism leading to motor neuron degeneration in patients with SMARD1 is currently unknown.

Test Methods:
Analysis is performed by bi-directional sequencing of all 15 coding exons and the exon/intron splice junctions of the IGHMBP2 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:**  
IGHMBP2 is the only gene known to be associated with SMARD1 at this time. The frequency of IGHMBP2 variants in patients with early-onset severe respiratory distress and distal muscle weakness is currently not well established. The largest study to date identified IGHMBP2 variants in 29 of 65 (~45%) of patients with a SMARD-like phenotype.¹

**Variant Spectrum:**  
To date, over 80 distinct IGHMBP2 variants have been identified in patients with SMARD1. The majority of variants are missense, nonsense, or frameshift changes. Two patients have been reported with genomic rearrangements, one of which may have been due to Alu-mediated homologous recombination.³ Variants are distributed throughout the gene, although the majority are identified in exons 10 and 12.¹⁰ Most variants are private, although 9.9% of women in an isolated Muslim population in Israel were found to carry the c.114delA variant.⁹

**References:**