

Selenoprotein N, 1 (*SEPN1*) Gene Sequencing (Test #330)

Brief Description of Clinical Features: Mutations in the *SEPN1* gene (OMIM 606210) cause a clinically heterogeneous group of myopathic conditions in which muscle fibers show areas of diminished oxidative staining due to lack of mitochondria (minicores), or fiber-type disproportion in which type 1 muscle fibers are smaller than type 2 fibers. Both minicores and fiber-type disproportion can be observed in the muscle of the same patient (Tajsharghi et al. *Neuromuscul Disord* 15:299-302, 2005). Approximately 75% of all cases of multimincore disease (MmD) fall into the classic form with onset at birth or in early childhood (Beggs and Agrawal *GeneReviews*, 2008). Clinical findings include hypotonia, delayed motor development and axial and proximal weakness. Severe, life threatening scoliosis and respiratory complications develop secondary to axial weakness. Cardiomyopathy and right ventricular failure often develop following respiratory symptoms. Ambulation is seen in classic MmD patients because limb muscles are spared. It is now established that rigid spine muscular dystrophy (RSMD1; OMIM 602771, Moghadaszadeh et al. *Nature Genet* 29:17-18, 2001) and severe classic form of MmD are the same entity (Ferreiro et al. *Am J Hum Genet* 71:739-749, 2002). Other forms of MmD are the moderate form with hand involvement, the antenatal form with arthrogryposis multiplex congenital (OMIM 607552), and the ophthalmologic form (OMIM 255320), which resembles the classic form but has external ophthalmoplegia. Each of these forms represents less than 10% of the total number of cases of MmD. There is evidence that some cases of the mild form with hand involvement result from *RYR1* gene mutations (Ferreiro et al. *Ann Neurol* 51:750-759, 2002). Congenital fiber-type disproportion (CFTD, OMIM 255310) is a genetically heterogeneous congenital myopathy sometimes caused by *SEPN1* mutations (Taylor-DeChene et al. *GeneReviews*, 2008). Clinical features of CFTD are similar to rigid spine muscular dystrophy (Clarke et al. *Ann Neurol* 59:546-552, 2006).

Genetics: *SEPN1* codes for selenoprotein N, 1, a selenocysteine-containing protein involved in selenium metabolism. The *SEPN1*-related disorders are inherited as autosomal recessive conditions. Mutations are distributed throughout the gene with most causing amino acid substitutions. Other forms of mutations include nonsense, splicing, frame-shifting, and gross deletions (www.dmd.nl). One patient with rigid spine muscular dystrophy has been reported with a homozygous mutation of the selenocysteine insertion sequence located in the 3' UTR (Allamand et al. *EMBO Rep* 7:450-454, 2006).

Description of This Particular Test: The 13 *SEPN1* coding exons and ~50 bp of adjacent noncoding sequence as well as the conserved 3' UTR selenocysteine insertion sequence are amplified from genomic DNA. Sequencing is accomplished using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

Reference Sequences: Genomic: NC_000001.10 mRNA: NM_020451.2
 Protein: NP_065184.2 mRNA and Protein: CCDS 41282.1

Indications for Testing: Individuals with clinical symptoms consistent with MmD or RSMD1 with minicores in a large proportion of muscle fibers, and stable or slowly progressive weakness. Patients with congenital myopathy with fiber-type disproportion who have had *TPM3*, *ACTA1* and *RYR1* mutations ruled-out.

Sensitivity of Test: *SEPN1* mutations account for approximately 30% of all MmD and 40% of rigid spine muscular dystrophy. Mild cases of MmD with hand involvement may have *RYR1* gene mutations. Evaluation of other genes associated with congenital fiber-type disproportion (*TPM3*, *ACTA1*, *RYR1*, *TPM2*) may increase the overall clinical sensitivity.

Turnaround 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 *SEPN1* \$ 740

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x16	83898	\$220	Sequencing x16	83904	\$310
Separation	83894	\$ 50	Interpretation/Report	83912	\$ 90

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

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