

Dysferlin (*DYSF*) Gene Sequencing (Test #342)

Brief Description of Clinical Features: The dysferlinopathies encompass two primary phenotypes. Limb girdle muscular dystrophy type 2B (LGMD2B; OMIM 253601) is characterized by atrophy and weakness of proximal muscles with onset in adolescence or young adulthood. Miyoshi myopathy (MM; OMIM 254130) affects distal leg muscles initially with atrophy and weakness spreading to the thighs and gluteal muscles (Miyoshi et al. *Brain* 109:31-54, 1986). Marked inflammatory changes are sometimes seen in muscle biopsies from MM patients. Age of onset of MM is late teens (Aoki et al. *Neurology* 57:271-278, 2001) and, as in LGMD2B, progression is slow. Both phenotypes exhibit massive elevations of serum CpK. Distal myopathy with anterior tibial onset (DMAT; OMIM 606768) is a third *DYSF* association. This phenotype has been described in a single Spanish family (Illa et al. *Ann Neurol* 49:130-134, 2001). It should be noted that intrafamilial variability spanning all three phenotypes has been reported (Weiler et al. *Am. J Hum Genet* 59:872-878, 1996; Liu et al. *Nat Genet* 20:31-36, 1998). Approximately half of a cohort of forty dysferlinopathy patients reviewed by Nguyen et al. (*Arch Neurol* 64:1176-1182, 2007) had MM or LGMD2B. Another one-third of the cohort had atypical phenotypes with mixed proximal and distal weakness. Distal painful leg swelling without muscle weakness occurred in 10%. The same study reported that 25% of the patients were initially misdiagnosed as having polymyositis.

Genetics: Dysferlin-related disorders are inherited in an autosomal recessive manner. Mutations are distributed throughout the gene (<http://www.dmd.nl/>). Nonsense, missense, small insertions and deletions and splice site mutations have been reported. Dysferlin appears to function in calcium-dependent membrane repair of skeletal muscle fibers (Bansal and Campbell *Trends Cell Biol* 14:206-213, 2004). Evaluation of muscle biopsies shows that most dysferlinopathy patients have complete deficiency of the protein although individuals with partial dysferlin deficiency have been reported (Piccolo et al. *Ann Neurol* 48:902-912, 2000). Dysferlin deficiency can also occur secondary to mutations in the genes for caveolin-3 or calpain-3. Patients with MM who have negative *DYSF* tests may have mutations in the *ANO5* gene (Bolduc et al. *Am J Hum Genet* 86:213-221, 2010).

Description of This Particular Test: Dysferlin is encoded by exons 1 – 56 of the *DYSF* gene located on chromosome 2p13. Testing is accomplished by amplifying all 56 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_000002.11 **mRNA:** NM_001130978.1
 Protein: NP_001124450.1 **mRNA and Protein:** CCDS 46326.1

Indication for Testing: Individuals with clinical symptoms consistent with LGMD, MM or DMAT. Individuals with absent staining of dysferlin in muscle or peripheral blood monocytes.

Sensitivity of test: Nguyen et al. (*Hum Mutat* 26:165-175, 2005) found two *DYSF* mutations in 23 of 34 dysferlinopathy patients and one mutation in the remaining 11 patients. The patients were from various ethnic backgrounds and unrelated to one another. In a large cohort of North American LGMD patients Moore et al. (*J Neuropathol Exp Neurol* 65:995-1003) made a diagnosis of dysferlinopathy in 18% of the cohort using a combined immuno and molecular approach, making *DYSF* the most common cause of LGMD in this mixed population. Dysferlinopathy is also prevalent in certain ethnic groups. For example, a c.1624delG mutation underlies the high (1:1,300) prevalence for LGMD2B in Libyan Jews (Argov et al. *Brain* 123:1229-1237, 2000) and in Sueca, Spain a founder mutation has been found in 2% of the population (Vilchez et al. *Arch Neurol* 62:1256-1259, 2005). In 20 of 25 Japanese patients with a clinical diagnosis of MM, 6 different *DYSF* mutations were identified (Takahashi et al. *Neurology* 60:1799-1804, 2003).

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 <i>DYSF</i>	\$ 2490			
CPT Codes:					
Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x51	83898	\$ 850	Sequencing x51	83904	\$1270
Separation	83894	\$ 170	Interpretation/Report	83912	\$ 130

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

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