PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

CLIA #: 52D1027685 ● CAP #: 7185561
AU ID: 1407125 ● NPI: 1114140571
3700 Downwind Drive
Marshfield, WI 54449 USA
Phone: 715-387-0484 Fax: 715-384-3661

Myofibrillar Myopathy via *DES* Gene Sequencing (Test #363)

Brief Description of Clinical Features: Myofibrillar myopathy (MFM) refers to a genetically heterogeneous group of disorders sharing a homogeneous morphological pattern and, most often, onset of clinical symptoms in adulthood. Stained with trichome, abnormal muscle fibers are seen containing hyaline structures and vacuoles containing membrane fragments from disintegrated sarcomeric Z disc and myofibrils (Selcen et al. *Brain* 127:439-451, 2004). With electron microscopy, affected muscle fibers reveal progressive degeneration of myofibrils beginning at the Z-disk. Immunohistochemical staining of the structurally abnormal fibers reveals abnormal expression and accumulation of several proteins, including myotilin, desmin, alpha-B crystalline, dystrophin and β-amyloid precursor protein (Selcen et al. 2004). Clinically, patients present in adulthood with proximal and distal weakness and in some cases with cardiomyopathy. Dilated cardiomyopathy is present in 15%-30% of desmin-related MFM (Selcen and Engel, *GeneReview* 2010). Cardiac manifestations include conduction blocks, arrhythmias and restrictive heart failure (Li et al. *Circulation* 100:461-464, 1999; Goldfarb et al. *Nat Genet* 19:402-403, 1998; Dalakas et al. *N Eng J Med* 342:770-780, 2000).

Genetics: Desmin, a cytoskeletal protein that functions as an attachment between the terminal Z disc and membrane-associated proteins (Tidball, *Exp Cell Res* 199:206-212, 1992), is expressed in smooth, cardiac, and heart muscles. Desmin-related myofibrillar myopathy (OMIM #601419) is inherited as an autosomal dominant disorder. Approximately 25% of affected individuals have an affected parent, but the proportion of *de novo* mutations is unknown (Selcen and Engel, 2010). Other genes involved with MFM include *MYOT*, *FLNC*, *LDB3*, *CRYAB*, and *BAG3*.

Description of This Particular Test: The desmin protein is coded by exons 1 - 9 of the *DES* gene on chromosome 2q35. Testing is accomplished by amplifying each coding exon 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_001927.3**
Protein: NP_001918.3 **mRNA and Protein: CCDS 33383.1**

Indications for Testing: Patients with clinical features consistent with myofribillar myopathy, demonstrated autosomal dominant inheritance, and a muscle biopsy with characteristic immunohistochemical and ultrastructural features. Individuals with idiopathic cardiomyopathy.

Sensitivity of test: Among a cohort of 80 MFM patients diagnosed at the Mayo Clinic, only 46% were found to have mutations in one of the six known causative genes (Selcen and Engel, 2010). The relative frequencies of mutations found in the Mayo Clinic cohort was *LDB3* (14%), *MYOT* (13%), *DES* (8%), *FLNC* (4%), *BAG3* (4%), and *CRYAB* (3%). Among eight other families with dominantly inherited MFM and two patients with sporadic disease, Dalakas et al. (2000) found mutations in four of the families and in one of the sporadic cases. Of the twelve total affected individuals with *DES* mutations in this study, seven had cardiomyopathy. MFM appears to be a genetically heterogeneous disorder, and the clinical sensitivity for testing any of the known genes is likely low.

Turnaround Time: Maximum of 40 days, although many tests are completed in 2 – 3 weeks.

Specimen Requirements: See page 4 of Requisition Form.

Price: **Sequencing of *DES* Gene** **Exons 1-9** **$ 670**

CPT Codes:

Sample Ascertainment x1	83890	$ 30	DNA Isolation x1	83891	$ 40
Amplification x9	83898	$ 180	Sequencing x9	83904	$ 280
Separation x1	83894	$ 60	Interpretation/Report x1	83912	$ 80

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

Contact: Thomas L. Winder, PhD, FACMG, tom.winder@preventiongenetics.com, www.preventiongenetics.com