

## Myofibrillar Myopathy Test Panel - Test #595

**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  $\beta$ -amyloid precursor protein (Selcen et al. 2004). Clinically, patients present in adulthood with proximal and distal weakness and in some cases with cardiomyopathy. Unlike typical MFM, Bag3-associated MFM presents in childhood with markedly progressive limb and axial weakness, cardiomyopathy, respiratory insufficiency and variably elevated CpK levels (Selcen et al. *Ann Neurol* 65:83-89, 2009).

**Genetics:** MFM due to mutation in the *CRYAB*, *DES*, *FLNC*, *MYOT*, *LDB3* and *BAG3* genes is inherited as an autosomal dominant disorder (Selcen and Engel, *GeneReviews* 2010).

**Description of This Particular Test:** The following genes are tested in the order specified by the client. Testing is accomplished by amplifying the coding exons and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. See also the individual Test Descriptions for each gene.

### Reference Sequences:

Gene:	Genomic: NC	mRNA: NM	Protein: NP	mRNA and Protein: CCDS
<i>BAG3</i>	000010.10	004281.3	004272.2	7615.1
<i>CRYAB</i>	000011.8	001885.1	001876.1	8351.1
<i>DES</i>	000002.10	001927.3	001918.3	33383.1
<i>FLNC</i>	000007.12	001458.3	001449.3	43644.1
<i>LDB3</i> (Isoform 1)	000010.9	007078.2	009009.1	7377.1
<i>LDB3</i> (Isoform 2)	000010.9	001080114.1	001073583.1	41544.1
<i>LDB3</i> (Isoform 3)	000010.9	001080115.1	001073584.1	44450.1
<i>LDB3</i> (Isoform 4)	000010.9	001080116.1	001073585.1	41545.1
<i>MYOT</i>	000005.8	006790.1	006781.1	4194.1

**Indication for Testing:** Patients with clinical features consistent with myofibrillar myopathy, demonstrated autosomal dominant inheritance, and a muscle biopsy with characteristic immunohistochemical and ultrastructural features.

**Sensitivity of test:** Among a cohort of 80 MFM patients diagnosed at the Mayo Clinic, only 46% have been 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%). Thus, MFM appears to be a genetically heterogeneous disorder and the clinical sensitivity for testing any of the known genes is likely low.

**Turn Around Time:** Approximately 2 to 3 weeks per gene or maximum of 80 days for the panel.

**Specimen Requirements:** See page 4 of the Requisition Form.

### Price and CPT Codes: Sequencing of *BAG3*, *CRYAB*, *DES*, *FLNC*, *LDB3*, *MYOT* Genes:

CPT	<i>BAG3</i>	<i>CRYAB</i>	<i>DES</i>	<i>FLNC</i>	<i>LDB3</i>	<i>MYOT</i>	Panel
83890	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)
83891	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)
83898	\$ 180 (x10)	\$ 80 (x3)	\$ 180 (x9)	\$ 860 (x50)	\$ 270 (x17)	\$ 160 (x9)	\$ 1,660 (x98)
83904	\$ 280 (x10)	\$ 130 (x3)	\$ 280 (x9)	\$ 1,300 (x50)	\$ 400 (x17)	\$ 240 (x9)	\$ 2,500 (x98)
83894	\$ 50 (x1)	\$ 30 (x1)	\$ 60 (x1)	\$ 140 (x1)	\$ 80 (x1)	\$ 50 (x1)	\$ 290 (x1)
83912	\$ 80 (x1)	\$ 60 (x1)	\$ 80 (x1)	\$ 120 (x1)	\$ 120 (x1)	\$ 70 (x1)	\$ 340 (x1)
<b>Totals:</b>	<b>\$ 660</b>	<b>\$ 370</b>	<b>\$ 670</b>	<b>\$ 2490</b>	<b>\$ 940</b>	<b>\$ 590</b>	<b>\$ 4,860</b>

When 3 or more genes on this panel are sequentially tested, a 15% discount will apply to the sum of the prices of the individual tests.

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

**Contact:** Thomas L. Winder, PhD, FACMG, [tom.winder@preventiongenetics.com](mailto:tom.winder@preventiongenetics.com), [www.preventiongenetics.com](http://www.preventiongenetics.com)