

Myofibrillar Myopathy via *LDB3* (*ZASP*) Gene Sequencing (Test #365)

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. Patients with *LDB3*-related MFM (OMIM #609452) demonstrate distal more than proximal weakness, peripheral neuropathy, and sometimes cardiac involvement (Selcen and Engel *Ann Neurol* 57:269-276, 2005).

Genetics: Myofibrillar myopathy and dilated cardiomyopathy related to *LDB3* are inherited as autosomal dominant disorders. The LIM domain-binding protein-3, or *Zasp*, interacts with alpha-actinin and protein kinase C, and is an integral component of the Z-disc. All mutations thus far reported cause amino acid substitutions. Other genes involved with MFM include *DES*, *MYOT*, *FLNC*, *CRYAB*, and *BAG3*.

Description of This Particular Test: The LIM domain-binding protein-3 is coded by exons 1 - 16 of the *LDB3* gene on chromosome 10q23. Four isoforms result from alternative splicing of the 16 exons. 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. As indicated, we will also sequence any single exon (Test #100, \$190) in family members of patients with known mutations or to confirm research results.

Reference Sequences:

	Isoform 1	Isoform 2	Isoform 3	Isoform 4
Genomic: NC_	000010.9	000010.9	000010.9	000010.9
mRNA: NM_	007078.2	00108114.1	001080115.1	001080116.1
Protein: NP_	009009.1	001073583.1	001073584.1	001073585.1
mRNA and Protein: CCDS	7377.1	41544.1	44450.1	41545.1

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. Individuals with idiopathic cardiomyopathy.

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, *GeneReviews* 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. In a study of 100 probands with dilated cardiomyopathy, six patients were found to have *LDB3* mutations (Vatta et al. *J Amer Coll Cardiol* 42:2014-2027, 2003).

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 *LDB3* Gene Exons 1-16 \$ 940

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x17	83898 \$ 280	Sequencing x17	83904 \$ 410
Separation x1	83894 \$ 60	Interpretation/Report x1	83912 \$ 120

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

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