Myofibrillar Myopathy Panel
Sequence Analysis and Exon-Level Deletion/Duplication Testing of 8 Genes

Panel Gene List: BAG3, CRYAB, DNAJB6, DES, FHL1, FLNC, LDB3, MYOT

Clinical Features:
Myofibrillar myopathies (MFM) are a clinically heterogeneous group of slowly progressive neuromuscular disorders that are caused by disintegration of the Z-disk resulting in disruption of myofibrils. Affected individuals typically present with distal and proximal muscle weakness but may also present with muscle stiffness or cramps, peripheral neuropathy, cardiomyopathy, swallowing difficulties, respiratory restriction, lens opacities, contractures, or scoliosis.[1] Phenotypically MFM may overlap with limb-girdle muscular dystrophy (LGMD). Although MFM is usually an adult onset disorder, patients may present from early childhood to adulthood.[1] Histopathology findings include amorphous, hyaline, or granular material in muscle fibers, decreased oxidative enzyme activity in abnormal fiber regions, and small vacuoles containing membranous material in Gomori trichrome stained sections. Abnormal expression of *DES, MYOT*, or *CRYAB* proteins may be visible on immunohistochemical staining of muscle sections.[2] Electromyography findings include abnormal electrical irritability and myopathic and/or neurogenic features.[1]The overall prevalence of MFM is currently unknown.[1]

Genetics:
Myofibrillar myopathies are most often inherited in an autosomal dominant manner, however, the *CRYAB*- and *DES*-related disorders can be inherited in an autosomal dominant or autosomal recessive manner. *FHL1*-related disorders are inherited in an X-linked manner. Most of the genes on this panel encode proteins that are associated with the Z-disc of the sarcomere and lead to toxic protein accumulation when disrupted.

Test Methods:
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include

pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

References:

1. Selcen D, Engel AG. Myofibrillar Myopathy. 2005 Jan 28 [Updated 2012 Oct 29]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1499/
2. Selcen et al. (2004). Myofibrillar myopathy: clinical, morphological and genetic studies in 63 patients. Brain 127:439-51.

Myofibrillar Myopathy Panel:

Gene	Inheritance	Related Disorder(s)	Diagnostic Yield in Selected Population(s)
BAG3	AD	Myofibrillar myopathy 6	~5% of MFM[1,2,3]
CRYAB	AD/AR	Myofibrillar myopathy 2	~3% of MFM[1,3]
DES	AD/AR	Myofibrillar myopathy 1 (Limb-girdle muscular dystrophy 1D)	7% of MFM[1,3] One intronic-splice site variant has been associated with Limb-girdle muscular dystrophy (LGMD) 1D[4]
DNAJB6	AD	DNAJB6-related myofibrillar myopathy	~2% of MFM[1,5]
FHL1	XL	X-linked myopathy with reducing bodies, Emery-Dreifuss muscular dystrophy, scapuloperoneal myopathy	~3% of MFM[1]
FLNC	AD	Myofibrillar myopathy 5	~ 3% of MFM[1,3]
LDB3	AD	Myofibrillar myopathy 4	~11% of MFM[1,3]
MYOT	AD	Myofibrillar myopathy 3 (Limb-girdle muscular dystrophy 1A)	~9% of MFM[1,2,3]

References: Selcen D, Engel AG. Myofibrillar Myopathy. 2005 Jan 28 [Updated 2012 Oct 29]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1499/ 2. Hayashi, Y.K. (2011). Brain Nerve 63, 1179-1188. 3. Olivé, M., et al. (2013). Curr. Opin. Neurol. 26, 527-535. 4. Greenberg, S.A., et al. (2012). Ann. Neurol. 71, 141-145. 5.Harms, M.B., et al. (2012). Ann. Neurol. 71, 407-416.