# Neuromuscular Disorders (NMD) Panel
# Sequence Analysis and Exon-Level Deletion/Duplication* Testing of 99 Genes

**Panel Gene List:** ACTA1, ANO5, ASAH1, ATP2A1, B3GALNT2, B4GAT1*, BAG3, BICD2, BIN1, BVES, CACNA1S, CAPN3, CAV3, CCDC78, CFL2, CHKB, CLCN1, CNTN1, COL6A1, COL6A2, COL6A3, COL12A1, CRYAB, DAG1, DES, DMD, DNAJB2, DNAJB6, DNM2, DOK7, DPM1, DPM2, DPM3, DYNC1H1, DYSF, EGR2, EMD**, FHL1, FKRP, FKTN*, FLNC, GAA, GBE1, GMPPB, GNE, IGHMBP2, ISPD, ITGA7, KBTBD13, KLHL40, KLHL41, LAMA2, LAMP2, LARGE, LDB3, LMNA, LMOD3, MEGF10, MICU1, MTM1, MYH2, MYH7, MYOT, NEB, PHKA1, PLEC, PLEKHG5, POMGNT1**, POMK, POMT1, POMT2, PYGM, RYR1, SCN4A, SEPN1, SGCA, SGCB, SGCD, SGCG, SIL1, SLC52A2, SLC52A3, SYNE1, TCAP, TMEM5, TNNI2**, TNNT1**, TNPO3, TOR1AIP1, TPM2, TPM3, TRAPPC11, TRIM32, TRIP4, TRPV4, TTN, UBA1, VCP, VRK1

* Sequence analysis only of B4GAT1 and FKRP genes.

** Only whole gene deletions or duplications may be detected for EMD, POMGNT1, TNNI2, TNNT1 genes.

**Clinical Features:**

Disorders of the neuromuscular system are clinically and genetically heterogeneous, but generally impair the function of the musculoskeletal or peripheral nervous systems, leading to progressive muscle weakness. Neuromuscular disorders (NMDs) are classified into distinct clinical categories, and the diagnosis is based on clinical presentation, genetic testing, electromyography (EMG), muscle biopsy histopathology, biochemical testing and other ancillary testing.[1] The age-of-onset of clinical symptoms depends on the specific disease and can range from the neonatal period to adulthood. Most NMDs have a genetic cause, although some NMDs are acquired or pharmaceutical-induced.[2] The prevalence of the hereditary neuromuscular disorders has been reported to be 1 in 3,500.[3]

Genes on this panel cause muscular dystrophies, myopathies, spinal muscular atrophies, and myotonias. The muscular dystrophies are caused by the destruction of muscle fibers, leading to progressive muscle weakness and wasting. The clinical features are variable depending on the specific diagnosis but often include elevated creatine kinase (CPK) levels, cardiomyopathy, joint contractures, respiratory complications, developmental delay, and rarely brain and eye abnormalities. Examples of muscular dystrophies with a known genetic etiology include Duchenne and Becker muscular dystrophy, Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, congenital muscular dystrophy, and Myofibrillar myopathy.[4,5,6] The congenital myopathies are characterized by a reduced ability of the muscles to contract, resulting in muscle weakness and decreased muscle tone with onset in early childhood. Examples of myopathies include nemaline myopathy, central core disease, multiminicore

disease, and centronuclear myopathy.[7,8] Spinal muscular atrophies are characterized by the degeneration of the antenatal anterior horn cells, leading to progressive muscle weakness and wasting often associated with respiratory problems. The nondystrophic myotonias are caused by functional defects in chloride or sodium channels and are often referred to as channelopathies. Examples include paramyotonia congenita and hypokalemic periodic paralysis, which manifest as attacks of transient weakness and reversible flaccid paralysis and result in muscle stiffness, fatigue, and pain.[9,10] Individuals with channelopathies and some other forms of NMDs are at increased risk for intraoperative complications such as malignant hyperthermia, rhabdomyolysis, and hyperkalemia when exposed to anesthetics commonly used during surgery.[11,12] The NMD Panel can assist in the diagnosis of neuromuscular disorders without requiring invasive diagnostic testing such as muscle biopsy. Confirmation of a clinical diagnosis allows for development of a comprehensive medical management plan, including monitoring for cardiac and respiratory complications.

**Genetics:**
The neuromuscular disorders included on this panel are inherited in either an autosomal dominant, autosomal recessive, or X-linked manner or they may be the result of a *de novo* variant.

**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). For FKTN, nucleotides surrounding the insertion site of an ALU-based founder mutation in the 3' UTR are also captured to determine if the insertion is present or absent. Presence of an insertion is confirmed using multiplex PCR, followed by gel electrophoresis. 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; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. 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. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: B4GAT1 and FKRP genes, no copy number testing; EMD, POMGNT1, TNNI2, and TNNT1 genes, only whole gene deletions or duplications may be detected. Missense variants in regions of high homology in the TTN gene may not be reliably identified due to inherent properties of the DNA.

## References:

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## Neuromuscular Disorders Panel - 99 Genes

| Gene | Inheritance | Disease Associations | Diagnostic Yield in Selected Population(s) |
|---|---|---|---|
| *ACTA1* | AD | Congenital fiber-type disproportion myopathy /Nemaline myopathy (NM) | 15-25% of NM is attributed to mutations in *ACTA1* [1] |
| *ANO5* | AR | Limb-girdle muscular dystrophy (LGMD) type 2L; Miyoshi MD | Founder mutation in the Northern European populations [2, 3] |
| *ASAH1* | AR | Spinal Muscular Atrophy | Rare[124] |
| *ATP2A1* | AR | Brody myopathy | Common in Brody myopathy [4] |
| *B4GAT1** *(B3GNT1)* | AR | Walker-Warburg syndrome | Rare [97] |
| *B3GALNT2* | AR | Walker–Warburg syndrome; Muscle-eye-brain disease (MEB) | Rare[5] |
| *BAG3* | AD | Myofibrillar myopathy 6 | ~5% of MFM is attributed to mutations in *BAG3* [6, 7] |
| *BICD2* | AD | Autosomal dominant congenital spinal muscular atrophy (DCSMA) | Rare [98, 99] |
| *BIN1* | AR | Centronuclear myopathy | Rare [8] |
| *BVES* | AR | Limb-Girdle Muscular Dystrophy 2X | Unknown[102] |
| *CACNA1S* | AD/AR | Hypokalemic periodic paralysis type 1 | ~60% of patients with hypokalemic periodic paralysis type 1 [9] |

| Gene | Inheritance | Disease Associations | Diagnostic Yield in Selected Population(s) |
|---|---|---|---|
| *CAPN3* | AR | LGMD type 2A | ~30% of LGMD in the United States. Founder mutations in the Amish, La Reunion Island, Basque (Spain) & Turkish populations [10, 11] |
| *CAV3* | AD | LGMD type 1C | ~3% of LGMD in the United States [11] |
| *CCDC78* | AD | Centronuclear Myopathy | Rare[103] |
| *CFL2* | AR | Nemaline myopathy | Rare [1, 12] |
| *CHKB* | AR | Mitochondrial CMD (congenital megaconial type muscular dystrophy) | Rare [13] |
| *CLCN1* | AD/AR | Myotonia congenita | ~95% of patients with myotonia congentia[9] |
| *CNTN1* | AR | Compton-North congenital myopathy | Rare [14] |
| *COL6A1* | AD/AR | Ullrich CMD/Bethlem myopathy | ~62% of patients with Ullrich or Bethlem myopathy have a mutation in one of the three collagen VI genes (*COL6A1, COL6A2, COL6A3*)[15] |
| *COL6A2* | AD/AR | Ullrich CMD/Bethlem myopathy | ~62% of patients with Ullrich or Bethlem myopathy have a mutation in one of the three collagen VI genes (*COL6A1, COL6A2, COL6A3*) [15] |
| *COL6A3* | AD/AR | Ullrich CMD/Bethlem myopathy | ~62% of patients with Ullrich or Bethlem myopathy have a mutation in one of the three collagen VI genes (*COL6A1, COL6A2, COL6A3*) [15] |
| *COL12A1* | AD/AR | Ullrich CMD/Bethlem myopathy | Rare[104] |
| *CRYAB* | AD/AR | Myofibrillar myopathy 2 | ~3% of MFM [7] |
| *DAG1* | AR | Primary dystroglycanopathy, LGMD with early onset and intellectual disability | Rare [37] |
| *DES* | AD/AR | LGMD type 1D/Myofibrillar myopathy 1 | ~7% of MFM<br>Rare in LGMD [7, 17] |
| *DMD* | X-linked | Duchenne / Becker muscular dystrophy (DMD/BMD) | 25-30% of mutations are caused by single point mutations or small rearrangements, the majority of which are detectable by this test. 65-70% of disease causing mutations in *DMD* are deletions/duplications. [18-20] |
| *DNAJB2* | AR | Spinal muscular atrophy | Rare[125] |
| *DNAJB6* | AD | LGMD type 1E, DNAJB6-related myofibrillar myopathy | Rare [21] |
| *DNM2* | AD | Centronuclear myopathy | Rare [8, 22] |
| *DOK7* | AR | Congenital myasthenia syndrome, with LGMD presentation | 10-21% of Congenital Myasthenia syndrome, Founder mutation in European, Canadian, and Brazilian populations [105.106.107.108.109] |
| *DPM1* | AR | Congenital disorder of glycosylation type Ie | Rare [23] |
| *DPM2* | AR | CMD with intellectual disability and severe epilepsy | Rare [24] |
| *DPM3* | AR | CMD with intellectual disability and severe epilepsy | Rare [23] |
| *DYNC1H1* | AD | Spinal muscular atrophy lower extremity | Rare [25-27] |
| *DYSF* | AR | LGMD type 2B | ~19% of LGMD in the United States [10, 28, 29] |
| *EGR2* | AD/AR | Charcot-Marie-Tooth | <2% of patients with CMT1[110] |
| *EMD*** | X-linked | Emery-Dreifuss muscular dystrophy (EDMD)- X-linked | ~61% of patients with XL-EDMD [10, 30] |
| *FHL1* | X-linked | X-linked myopathy with reducing bodies; Emery-Dreifuss muscular dystrophy; scapuloperoneal myopathy | ~10% of patients with XL-EDMD [31, 32]<br>Rare in scapuloperoneal myopathy |
| *FKRP** | AR | Walker–Warburg syndrome; CMD with/without intellectual disability and microcephaly; LGMD type 2 | ~6% of LGMD [11]<br>~9% of the alpha-dystroglycanopathies [10, 33] |

| Gene | Inheritance | Disease Associations | Diagnostic Yield in Selected Population(s) |
|---|---|---|---|
| *FKTN* | AR | Fukuyama congenital muscular dystrophy; LGMD type 2M | ~7% of the alpha-dystroglycanopathies<br>Includes the Japanese founder mutation in the 3' UTR and an intronic point mutation found in the Korean population [34-37]<br>Rare cause of LGMD |
| *FLNC* | AD | Myofibrillar myopathy 5 | ~3% of MFM is attributed to mutations in *FLNC* [7] |
| *GAA* | AR | Pompe disease (Glycogen storage disease type II) | c.-32-13 T>G has been reported in up to 42% of alleles in the adult onset form (detectable by this test); a large deletion of exon 18 is common in some European populations[38, 39] |
| *GBE1* | AR | Glycogen Storage Disease IV | 3% of glycogen storage disease[111] |
| *GMPPB* | AR | Muscular dystrophy-dystroglycanopathy (LGMD), type C; Walker–Warburg syndrome | Rare[40] |
| *GNE* | AR | GNE myopathy, hereditary inclusion body myopathy | 70-80% of individuals diagnosed with hereditary inclusion body myopathy or another *GNE* related myopathy [41, 42]<br>Common mutation in Middle Eastern Jewish population |
| *IGHMBP2* | AR | Spinal muscular atrophy with respiratory distress 1 (SMARD) | ~33% of patients with SMARD [43] |
| *ISPD* | AR | Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies type A7 | ~30% of Walker-Warburg syndrome and ~11% of alpha-dystroglycanopathies [35, 44, 45]<br>Rare in LGMD |
| *ITGA7* | AR | Integrin alpha 7-related CMD | Rare [46, 47] |
| *KBTBD13* | AD | Nemaline myopathy | Unknown [48, 49] |
| *KLHL40* | AR | Nemaline myopathy | ~20% of severe NM [50] |
| *KLHL41* | AR | Nemaline myopathy | Rare[112] |
| *LAMA2* | AR | Congenital merosin deficient muscular dystrophy (MDC1A) | ~30-50% of patients with congenital muscular dystrophy in the European population have MDC1A [51-53] |
| *LAMP2* | XL | Danon disease | Rare [54] |
| *LARGE* | AR | Walker–Warburg syndrome; MEB disease | ~3% of the alpha-dystroglycanopathies [37, 55] |
| *LDB3* | AD | Myofibrillar myopathy 4 | ~11% of MFM [7] |
| *LMNA* | AD/AR | Emery-Dreifuss muscular dystrophy , type 2 (AD); LGMD type 1B; congenital laminopathy (AR) | ~45% of patients with AD-EDMD<br>~12% of LGMD in United States<br>Rare in congenital muscular dystrophies [10, 30, 56-58] |
| *LMOD3* | AR | Nemaline Myopathy | Rare[113] |
| *MEGF10* | AR | Early onset myopathy areflexia, respiratory distress, dysphagia | Rare [59-61] |
| *MICU1* | AR | Myopathy with extrapyramidal signs | Rare[114] |
| *MTM1* | XL | Centronuclear/Myotubular myopathy | Rare [62, 63] |
| *MYH2* | AD/AR | Inclusion body myopathy | Rare[115] |
| *MYH7* | AD/AR | Laing early-onset distal myopathy; Scapuloperoneal myopathy | ~95% of individuals with Laing distal myopathy [64] |
| *MYOT* | AD | LGMD type 1A; Myofibrillar myopathy 3 | ~26% of patients with LGMD<br>~9% of MFM [7, 65] |
| *NEB* | AR | Nemaline myopathy | ~50% of patients with NM have mutations in this gene; Ashkenazi Jewish founder mutation (deletion containing exon 55) [66] |
| *PHKA1* | XL | Glycogen storage disease type IX (GSD IX) | Rare [100] |
| *PLEC* | AR | LGMD type 2Q; epidermolysis bullosa simplex with muscular dystrophy | Rare overall; founder mutation in the Turkish population [3, 35] |
| *PLEKHG5* | AR | Distal spinal muscular atrophy (aka: distal hereditary motor neuropathies-dHMN) | Rare [67] |
| *POMGNT1*** | AR | Walker–Warburg syndrome; MEB disease | 11-18% of the alpha-dystroglycanopathies [37, 68, 69] |

| Gene | Inheritance | Disease Associations | Diagnostic Yield in Selected Population(s) |
|---|---|---|---|
| *POMK* | AR | Walker-Warburg syndrome; Muscular dystrophy-dystroglycanopathy A12; LGMD C12 | Rare[116] |
| *POMT1* | AR | Walker–Warburg syndrome; CMD with intellectual disability and microcephaly; LGMD type 2K | 9-21% of the alpha-dystroglycanopathies [37, 68] |
| *POMT2* | AR | Walker–Warburg syndrome; CMD with intellectual disability and microcephaly; LGMD type 2N | 9-11% of the alpha-dystroglycanopathies [37, 70] |
| *PYGM* | AR | McArdle disease / glycogen storage disease type V | Rare [101,] |
| *RYR1* | AD/AR | Central core disease; Minicore myopathy with external ophthalmoplegia | ~89% of central core disease [71-73] |
| *SCN4A* | AD | Paramyotonia congenital; hyperkalemic periodic paralysis; hypokalemic periodic paralysis type 2 | ~20% of patients with hypokalemic periodic paralysis [9, 74] |
| *SEPN1* | AR | CMD with spinal rigidity (RSMD1); Minicore/multicore disease | 30-50% of patients with minicore/multicore disease [75, 76] |
| *SGCA* | AR | LGMD type 2D | ~9% of LGMD in the United States [10, 77] |
| *SGCB* | AR | LGMD type 2E | ~5% of LGMD in the United States [10] |
| *SGCD* | AR | LGMD type 2F | ~1% of LGMD in the United States [10] |
| *SGCG* | AR | LGMD type 2C | ~3% of LGMD in the United States; founder mutation in the North African and gypsy populations [10, 35] |
| *SIL1* | AR | Marinesco-Sjogren syndrome | Rare [78] |
| *SLC52A2* | AR | Riboflavin transporter deficiency neuronopathy | Rare, 30% of Riboflavin transporter deficiency neuronopathy cases [117, 118] |
| *SLC52A3* | AR | Riboflavin transporter deficiency neuronopathy | Rare, 70% of Riboflavin transporter deficiency neuronopathy cases[118] |
| *SYNE1* | AD/AR | Emery-Dreifuss muscular dystrophy, type 4 | Rare [79] |
| *TCAP* | AR | LGMD type 2G | Rare overall; founder mutation in the Italian population [35, 58] |
| *TMEM5* | AR | Walker–Warburg syndrome; MEB disease | Rare[80] |
| *TTN* | AR | LGMD type 2J; Early onset myopathy with fatal cardiomyopathy | Rare overall; founder mutation in the Finnish population [35] |
| *TNNI2*** | AD | Myopathy and distal arthrogryposis (DA) type 2B | ~6% of patients with DA1<br>~11% of patients with DA2B [81, 82] |
| *TNNT1*** | AR | Nemaline myopathy | Rare overall; founder mutation in the Old Order Amish population [83, 84] |
| *TNPO3* | AD | LGMD 1F | Rare [85, 86] |
| *TOR1AIP1* | AR | LGMD 2Y | Rare[119, 120] |
| *TPM2* | AD | Nemaline myopathy | <1% of NM [87] |
| *TPM3* | AD/AR | Nemaline myopathy | 2-3% of NM [87, 88] |
| *TRAPPC11* | AR | LGMD 2S | Rare[121] |
| *TRIM32* | AR | LGMD type 2H | Rare overall; founder mutation in Manitoba Hutterites [11, 89] |
| *TRIP4* | AR | Spinal Muscular Atrophy | Unknown[122] |
| *TRPV4* | AD | Scapuloperoneal spinal muscular atrophy | Rare [90-94] |
| *UBA1* | X-linked | X-linked SMA with arthrogryposis and congenital contractures; Spinal muscular atrophy- X-linked 2 | Rare [95] |
| *VCP* | AD | Inclusion body myopathy | Unknown [123] |
| *VRK1* | AR | Spinal muscular atrophy with pontocerebellar hypoplasia; pontocerebellar hypoplasia type 1 (Norman disease) | Rare overall; founder mutation in the Ashkenazi Jewish [96] |

***Sequence analysis only (no deletion/duplication testing) for the B4GAT1 and FKRP genes.**
**** Only whole gene deletions or duplications may be detected for EMD, POMGNT1, TNNI2, and TNNT1 genes.**

**References:** 1. North KN, Ryan MM. Nemaline Myopathy. 2002 Jun 19 [Updated 2015 Jun 11]. 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/NBK1288/. 2. Van der Kooi, A.J., et al. (2013). Neuromuscular Disord. 23, 456-460. 3. Mitsuhashi, S., Kang, P.B. (2012). Semin. Pediatr. Neurol. 19, 211-218. 4. Voermans, N.C., et al. (2012). Neuromuscular Disord. 22, 944-954. 5. Stevens, E., et al. (2013) Am. J. Hum. Genet. 92: 354-365, 2013. (PubMed: 23453667) 6 . Hayashi, Y.K. (2011). Brain Nerve 63, 1179-1188. 7 . Olivé, M., et al. (2013). Curr. Opin. Neurol. 26, 527-535. 8 . Böhm et al. (2010) Case report of intrafamilial variability in autosomal

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