THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Neuromuscular Disorders

Clinical Features:

Neuromuscular disorders (NMD) are a clinically and genetically diverse group of conditions affecting the peripheral nervous system and muscle, including muscular dystrophies, congenital myopathies and congenital myasthenic syndrome [1]. Most NMDs have an underlying genetic basis, although there are also acquired forms NMD such as botulism and pharmaceutical induced myopathies [1]. Onset of symptoms is variable between different NMD, and can range from prenatal onset to childhood or adult onset conditions. It is becoming increasingly recognized that many genes associated with NMD can lead to multiple disease phenotypes in different families, and some can be associated with both autosomal dominant and recessive inheritance [1].

Our Neuromuscular Disorders Panel includes mutation analysis of all 113 genes listed below.

Neuromuscular Disorders Panel					
ACTA1	CHST14	DYSF	LAMA2	PLEC	SPEG
AGRN	CNTN1	EMD	LAMB2	POMGNT1	STAC3
ALG14	COL12A1	FHL1	LAMP2	POMGNT2	STIM1
ALG2	COL13A1	FKBP14	LARGE	POMK	SYNE1
ANO5	COL6A1	FKRP	LDB3	POMT1	SYNE2
B3GALNT2	COL6A2	FKTN	LIMS2	POMT2	SYT2
B3GNT1	COL6A3	FLNC	LMNA	PREPL	TCAP
BAG3	COLQ	GAA	LMOD3	PTPLA	TMEM43
BIN1	CRYAB	GBE1	LRP4	PYGM	TMEM5
CAPN3	DAG1	GFPT1	MEGF10	RAPSN	TNNT1
CAV3	DES	GMPPB	MTM1	RYR1	TNPO3
CCDC78	DMD	GNE	MUSK	SCN4A	TNXB
CFL2	DNAJB6	HNRNPDL	MYF6	SEPN1	TPM2
CHAT	DNM2	HRAS	MYH2	SGCA	TPM3
CHKB	DOK7	ISPD	MYH7	SGCB	TRAPPC11
CHRNA1	DPAGT1	ITGA7	MYL2	SGCD	TRIM32
CHRNB1	DPM1	KBTBD13	MYOT	SGCG	TTN
CHRND	DPM2	KLHL40	NEB	SIL1	VCP
CHRNE	DPM3	KLHL41	ORAI1	SNAP25	

Myopathies

Disorder	Description	Typically Associated Genes
Bethlem myopathy	Bethlem myopathy (BM) is a variable autosomal dominant condition, associated with proximal muscle weakness and variable contractures. Onset ranges from the prenatal period to adulthood [2].	COL6A1 [2], COL6A2 [2], COL6A3 [2], COL12A1 [3]
Central core disease	Central core disease is characterized by mild to severe muscle weakness and the finding of characteristic cores on muscle biopsy [4]. Most individuals have a milder form of the condition with mild proximal muscle weakness, however more severe forms of the disease with severe infantile hypotonia and respiratory dysfunction have also been reported [4]. Inheritance is typically autosomal dominant, although cases with autosomal recessive inheritance have also been observed.	RYR1 [5]

Centronuclear myopathy	Centronuclear myopathy (CNM), also known as myotubular myopathy, is a rare muscle disease associated with non-progressive or slowly progressive muscle weakness that can develop from infancy to adulthood [6, 7]. On muscle histopathology, patients with CNM have increased frequency of central nuclei, as well as predominance of type 1 fibers and hypotrophy, in the absence of other significant abnormalities. Approximately 80% of males with a diagnosis of myotubular myopathy by muscle biopsy will have a mutation in *MTM1* identifiable by sequence analysis, which is an X-linked gene. Dominant and recessive forms of CNM also exist.	BIN1 [8], CCDC78 [9] DNM2 [6], MTM1 [10], MYF6 [11], RYR1 [5], SPEG [12]
Congenital Fiber-Type Disproportion	Congenital fiber-type disproportion (CFTD) is a type of congenital myopathy characterized by hypotonia and muscle weakness that varies from mild to severe[13]. The majority of individuals have static weakness. Other features can include feeding difficulties, respiratory failure, ophthalmoplegia, ptosis, contractures and spinal deformities [13]. Histopathologic findings of the condition include type 1 fibers that are at least 12% smaller than type 2 fibers on muscle biopsy. CFTD can be inherited in an autosomal dominant or recessive manner. X-linked inheritance has also been described in some affected families, however the associated gene has not been identified to date.	ACTA1 [14], LMNA [15], MYH7 [16], RYR1 [17], SEPN1 [18], TPM2 [19], TPM3 [20],
Congenital Myopathy - Other	Congenital myopathies are typically characterized by the presence of specific structural and histochemical features on muscle biopsy and clinical presentation can include congenital hypotonia, muscle weakness, delayed motor milestones, feeding difficulties, and facial muscle involvement [21]. Serum creatine kinase may be normal or elevated. Heterogeneity in presenting symptoms can occur even amongst affected members of the same family.	CNTN1 [22], PTPLA [23], RYR1 [5], TTN [24], HRAS [25], MEGF10 [26], STAC3 [27], MYL2 [28]
Inclusion body myopathy	Inclusion body myopathies are a rare group of disorders with variable clinical presentations, typically including slowly progressive muscle weakness. Findings on muscle biopsy include rimmed vacuoles and collection of cytoplasmic or nuclear 15-21 nm diameter tubulofilaments [29]. Other associated symptoms vary depending on the causative gene, and may also include ophthalmoplegia, Paget's disease of bone, and frontotemporal dementia [29]. Inheritance may be autosomal dominant or recessive.	GNE [29], VCP [29], MYH2 [29]
Danon disease	Danon disease is an X-linked dominant condition affecting primarily cardiac muscle. Intellectual disability and skeletal muscle involvement is variable, with men more severely affected than women. Danon disease is thought to be a form of autophagic vacuolar myopathy, characterized by intracytoplasmic autophagic vacuoles with sarcolemmal features [30]	LAMP2 [31]
Laing distal myopathy	Heterozygous mutations in *MYH7* have been associated with Laing distal myopathy, which is characterized by weakness in childhood, that initially involves the dorsiflexors of the ankles and great toes, followed by the finger extensors [32].	MYH7 [32]

Marinesco-Sjogren syndrome	Homozygous or compound heterozygous mutations in *SIL1* are associated with Marinesco-Sjogren syndrome. This condition is characterized by congenital cataracts, myopathy, and delayed psychomotor development. Other features include short stature, hypergonadotropic hypogonadism and skeletal deformities secondary to muscle weakness.	SIL1 [33]
Multiminicore disease	The classic form of multiminicore disease (MmD) is associated with hypotonia, delayed motor development, axial muscle weakness and respiratory dysfunction [34]. Onset is typically in infancy or early childhood. Other subtypes of MmD include a moderate form with hand involvement, a severe prenatal form with arthrogryposis, and an ophthalmoplegic form [34]. MmD is typically inherited in an autosomal recessive manner.	RYR1 [5], SEPN1 [34]
Myofibrillar myopathy	Myofibrillar myopathy is characterized by slowly progressive muscle weakness that can affect both proximal and distal muscles. Other features may include muscle stiffness and aching, peripheral neuropathy, and cardiomyopathy. EMD can be inherited in an autosomal dominant, autosomal recessive or X-linked manner.	BAG3 [35], CRYAB [35], DES [35], DNAJB6 [36], FHL1 [35, 37], FLNC [35], LDB3 [35], MYOT [35]
Myopathy with tubular aggregates	Dominant mutations in *STIM1* and *ORAI1* are related to myopathy with tubular aggregates present in fibers on muscle biopsy. These aggregates represent a non-specific finding occurring in a number of different conditions including late-onset forms of familial myopathy.	ORAI1 [38], STIM1 [39]
Nemaline myopathy	Nemaline myopathy is characterized by weakness, hypotonia and depressed or absent deep tendon reflexes. Weakness is typically proximal, diffuse or selective, with or without facial weakness and the diagnostic hallmark is the presence of distinct rod-like inclusions in the sarcoplasm of skeletal muscle fibers [40]. Inheritance may be either autosomal dominant or recessive, and some genes have been observed in association with both inheritance patterns.	ACTA1 [41], CFL2 [42], KBTBD13 [43], NEB [44], LMOD3 [45], TNTT1 [46], TPM2 [19], TPM3 [20], KLHL40 [47], KLHL41 [48]

Muscular Dystrophies

Disorder	Description	Typically Associated Genes
Congenital muscular-dystrophy-dystroglycanopathies	Congenital muscular-dystrophy-dystroglycanopathes are a genetically heterogenous group of autosomal recessive conditions. Dystroglycanopathies are characterized by a broad congenital muscular dystrophy phenotypic spectrum with and without intellectual disability, eye involvement and brain findings [49].	DAG1 [50], FKTN [51], FKRP [51], ISPD [51], GMPPB [52], LARGE [51], POMK, POMT1 [51], POMT2 [51], POMGNT1 [51], POMGNT2, TMEM5 [53], B3GALNT2 [54], B3GNT1 [55],
Congenital muscular dystrophy - Other	Congenital muscular dystrophies are a genetically and clinically heterogeneous group of disorders typically characterized by weakness and dystrophic pattern on muscle biopsy that is present at birth or during the first months of life. Affected infants typically appear 'floppy' and have low muscle tone and poor spontaneous movements [56]. The clinical course is broadly variable [2]. CMDs can be further classified by the mutated gene, the respective protein's localization and the protein's predicted function [57].	CHKB [58], DPM2 [59], DPM3 [60], ITGA7 [61], LAMA2 [62], LMNA [51], SEPN1 [51], DPM1 [63]

Dystrophinopathies	Dystrophinopathies include a spectrum of muscle diseases associated with the *DMD* gene, such as Duchenne and Becker muscular dystrophy [64]. The DMD is an X-linked gene, and carrier females can be asymptomatic, or may develop cardiomyopathy.	DMD [64]
Emery Dreifuss muscular dystrophy	Emery Dreifuss muscular dystrophy (EMD) is a skeletal muscle disorder characterized by progressive muscle weakness, contractures and cardiac disease [65]. Onset is typically in early childhood. EMD can be inherited in an autosomal dominant, autosomal recessive or X-linked manner.	EMD [65], LMNA [65], SYNE1 [66], SYNE2 [66], TMEM43 [67]
Limb girdle muscular dystrophy	Limb girdle muscular dystrophy (LGMD) is a term generally used to describe progessive weakness and wasting restricted to the limb musculature (proximal greater than distal), due to a genetic defect that is distinct from X-linked dystrophinopathy [68]. Muscle biopsy can show diffuse variation in fiber size, necrosis, regeneration and fibrosis [68]. Onset of symptoms can range from early childhood to late adulthood, and progression and distribution of the weakness and wasting can vary considerably amongst individuals and subtypes [69]. Inheritance of LGMD can be either autosomal recessive or autosomal dominant.	ANO5 [70], CAPN3 [71], CAV3 [72], DAG1 [73], DES [74], DNAJB6 [75], DYSF [76], FLNC [74], HNRNPDL [77], LIMS2 [74], LMNA [78], MYOT [79], PLEC [80], SGCA [81], SGCB [81], SGCD [81], SGCG [81], TCAP [82], TNPO3 [83], TRAPPC11 [84], TRIM32 [85], TTN [86]
Oculopharyngeal muscular dystrophy	Oculopharyngeal muscular dystrophy (OPMD) is caused by heterozygous mutations in the *PABPN1* gene. OPMD is characterized by late-onset progressive dysphagia, ptosis of the eyelids, and proximal limb weakness.	PABPN1
Ullrich Congenital Muscular Dystrophy	Ullrich congenital muscular dystrophy (UCMD) is an autosomal recessive condition associated with congenital weakness, hypotonia, joint contractures, and hyperlaxity of distal joints [2].	COL6A1 [2], COL6A2 [2], COL6A3 [2]

Other Neuromuscular Disorders

Disorder	**Description**	**Typically Associated Genes**
Congenital myasthenic syndrome	Congenital myasthenic syndromes (CMS) are heterogeneous inherited disorders of neuromuscular transmission characterized by fatigable weakness of the skeletal muscle with onset at or shortly after birth or in early childhood [87]. Severity and progression can vary. Major findings in the neonatal onset subtype include feeding difficulties, poor suck and cry, choking spells, ptosis, facial, bulbar and generalized weakness [87]. Later childhood onset subtypes show abnormal muscle fatigability, delayed motor development, ptosis, and fixed or fluctuating extraocular muscle weakness [87]. Inheritance of CMS can be either autosomal recessive or autosomal dominant.	ALG14 [88], ALG2 [88], AGRN [89], CHAT [87], CHRNA1 [87], CHRNB1 [87], CHRND [87], CHRNE [87], COLQ [90], DOK7 [91], GFPT1 [92], LRP4 [93], MUSK [87], PREPL [94], RAPSN [95], SCN4A [96], DPGAT1 [97], SYT2 [98], COL13A1 [99], LAMB2 [100], SNAP25[101]
Pompe disease	Biallelic mutations in GAA are associated with glycogen storage disease type II (Pompe disease). Classic infantile Pompe disease is characterized by infantile onset hypotonia, muscle weakness, cardiomegaly and hypertrophic cardiomyopathy [102]. Non-classic infantile onset and late-onset forms of the disease also exist, which are also associated with slowly progressive muscle weakness [103].	GAA [104]

McArdle disease	Biallelic mutations in *PYGM* are associated with McArdle disease, or glycogen storage disease type V. This condition is characterized by muscle cramping and exercise intolerance with onset in childhood or adolescence, with progressive muscle weakness and atrophy into adulthood. Rhabdomyolysis leading to myoglobinuria can cause renal failure in some patients with McArdle disease. [OMIM#232600]	*PYGM*
Glycogen storage disease IV	Type 4 glycogen storage disease (GSD4) is caused by biallic mutations in *GBE1*. GSD4 is characterized by liver disease in childhood which progresses to lethal cirrhosis. The neuromuscular presentation of GSD4 is distinguished by age of onset. These forms include a perinatal lethal type, congenital, childhood with or without cardiomyopathy, and adult with isolated myopathy or adult polyglucosan body disease.	GBE1 [105]
Ehlers-Danlos syndrome	Biallelic mutations in *CHST14* are associated with a musculocontractural form of EDS which is characterized by craniofacial dysmorphism, congenital contractures of the thumbs and fingers, clubfeet, kyphoscoliosis, hypotonia, hyperextensibility and hypermobility, and ocular involvement. Homozygous or compound heterozygous mutations in *FKBP14* are associated with Ehlers-Danlos syndrome with progressive kyphoscoliosis, myopathy and hearing loss.	CHST14 [106]; FKBP14 [107], TNXB [108]

Test methods:
Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All novel and/or potentially pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. **This assay also includes analysis for the recurrent c.930+189C>T deep intronic variant in the *COL6A1* gene.**

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Neuromuscular Disorders Panel (mutation analysis of 113 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2,000
CPT codes:	81406
	81407
Turn-around time:	8 weeks

Note: We cannot bill insurance for the this panel

Congenital Muscular Dystrophy-Dystroglycanopathy Panel (mutation analysis of 14 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2,000
CPT codes:	81406
	81407
Turn-around time:	8 weeks

Note: We cannot bill insurance for the this panel

Nemaline Myopathy Panel (mutation analysis of 10 genes)

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $2,000
CPT codes: 81406
81407
Turn-around time: 8 weeks
Note: We cannot bill insurance for the this panel

Bethlem Myopathy and Ullrich Muscular Dystrophy Panel (mutation analysis of 4 genes)
Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $2,000
CPT codes: 81406
81407
Turn-around time: 8 weeks
Note: We cannot bill insurance for the this panel

Centronuclear Myopathy Panel (mutation analysis of 7 genes)
Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $2,000
CPT codes: 81406
81407
Turn-around time: 8 weeks
Note: We cannot bill insurance for the this panel

Congenital Myopathy with Fiber-Type Disproportion Panel (mutation analysis of 7 genes)
Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $2,000
CPT codes: 81406
81407
Turn-around time: 8 weeks
Note: We cannot bill insurance for the this panel

Multiminicore Disease Panel (mutation analysis of *RYR1* and *SEPN1*)
Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $2,000
CPT codes: 81406
81407
Turn-around time: 8 weeks
Note: We cannot bill insurance for the this panel

Myopathy with Tubular Aggregates Panel (mutation analysis of *ORAI1* and *STIM1*)
Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $2,000
CPT codes: 81406
81407
Turn-around time: 8 weeks
Note: We cannot bill insurance for the this panel

Emery-Dreifuss Muscular Dystrophy Panel (mutation analysis of 6 genes)
Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $2,000
CPT codes: 81406
81407
Turn-around time: 8 weeks
Note: We cannot bill insurance for the this panel

Results:
Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire Neuromuscular Disorders Sequencing Panel. All abnormal results are reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

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