THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Congenital Myopathies

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 (1). Serum creatine kinase may be normal or elevated. Heterogeneity in presenting symptoms can occur even amongst affected members of the same family. Congenital myopathies can be divided into three main clinicopathological defined categories: nemaline myopathy, core myopathy and centronuclear myopathy (2).

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 (3).

Core Myopathy
Core Myopathy is characterized by areas lacking histochemical oxidative and glycolytic enzymatic activity on histopathological exam (2). Symptoms include proximal muscle weakness with onset either congenitally or in early childhood. Bulbar and facial weakness may also be present. Patients with core myopathy are typically subclassified as either having central core disease or multiminicore disease.

Centronuclear Myopathy
Centronuclear Myopathy (CNM) is a rare muscle disease associated with non-progressive or slowly progressive muscle weakness that can develop from infancy to adulthood (4, 5). On muscle histopathology, patients with CNM have increased frequency of central nuclei, as well as type 1 fiber predominance and hypotrophy, in the absence of other significant abnormalities. Other neuromuscular conditions can have similar findings on muscle biopsy, so these features are not always diagnostic for CNM.

Our Congenital Myopathy Panel includes analysis of the 28 genes listed below.

Congenital Myopathy Panel				
ACTA1	COL12A1	LMOD3	PTPLA	TNNT1
BIN1	DNM2	MEGF10	RYR1	TPM2
CFL2	HRAS	MTM1	SCN4A	TPM3
CCDC78	KBTBD13	MYF6	SEPN1	TTN
CNTN1	KLHL40	MYH7	SPEG	
CHKB	KLHL41	NEB	STAC3	

Genes and Associated Disorder	Inheritance	Clinical Features/Molecular Pathology
ACTA1 [OMIM#102610] Myopathy, Nemaline 3 [OMIM#161800]	AR/AD	Mutations in *ACTA1* account for approximately 15-25% of patients with Nemaline Myopathy (3). Mutations in *ACTA1* account for less than 6% of patients with Congenital Fiber-Type Disproportion (6). Nonsense, frameshift, missense, splicing and indels have all been reported in the *ACTA1* gene (7). The *ACTA1* gene encodes skeletal muscle alpha-actin, the principal actin isoform in adult skeletal muscle.
CFL2 [OMIM#601443] Myopathy, Nemaline 7 [OMIM#610687]	AR	Mutations in *CFL2* are a rare cause of nemaline myopathy. Agrawal *et al* 2007 screened a total of 171 patients with nemaline myopathy/congenital myopathy and identified a one homozygous missense change in 2 sibs from a consanguineous Middle Eastern family (8). The *CFL2* gene encodes a skeletal-muscle-specific isoform localized to the thin filaments where it interacts with tropomyosins.

CHKB [OMIM#612395] Muscular dystrophy, congenital, megaconial type	AR	Homozygous and compound heterozygous mutations in *CHKB* are associated with a recessive form of congenital muscular dystrophy characterized by early-onset muscle wasting and intellectual disability. Muscle biopsy in affected patients shows enlarged mitochondria at the periphery of the fibers which are sparse towards the center (9).
COL12A1 [OMIM#120320] Bethlem myopathy 2	AD	A heterozygous missense mutation in the *COL12A1* gene was identified in a patient with Bethlem myopathy and normal collagen VI. After this mutation was identified a cohort of 24 patients with a Bethlem myopathy-like phenotype were tested, with identification of mutations in the *COL12A1* gene in 5 members of 2 families, with the mutation segregating with the disease. (10) Individuals with Bethlem myopathy are typically affected with loose joints, infantile hypotonia, and contractures of the fingers, wrists, elbows, and ankles presenting in childhood. Progressive muscle weakness typically leads to the need for walking assistance by the age of 50, and older individuals may develop respiratory complications.
HRAS [OMIM#190020] Congenital myopathy with excess of muscle spindles	AD	*HRAS*-related congenital myopathy represents an autosomal dominant variant form of Costello syndrome. Patients with this condition present with Noonan syndrome-like features, hypertrophic cardiomyopathy, and an excess of muscle spindles noted on muscle biopsy (11).
KBTBD13 [OMIM#613727] Myopathy, Nemaline 6 [OMIM609273]	AD	Sambuughin *et al,* 2010, identified 3 different missense mutations in *KBTBD13* in patients with nemaline myopathy (12). KBTBD13 is expressed in the skeletal muscle and cardiac muscle, although to date no cardiac abnormalities have been identified in individuals with *KBTBD13* mutations.
KLHL40 [OMIM#615340] Myopathy, nemaline 8 [OMIM#615348]	AR	Ravenscroft et al, 2013, identified 19 mutations in *KLHL40* in 28 unrelated kindreds with severe autosomal recessive nemaline myopathy. Clinical features included fetal akenisia and contractures, fractures, respiratory failure and swallowing difficulties at birth (13).
KLHL41 [OMIM#607701] Myopathy, nemaline 9 [OMIM#615731]	AR	Gupta VA, *et al* 2013, identified biallic deletions and missence mutations in 4 individuals with nemaline myopathy. Genotype-phenotype correlation was seen in these families, with the framshift mutations resulting in a severe phenotype with early death, and the missense mutations resulting in impaired motor function with survival into late childhood and/or early adulthood (14)
MEGF10 [OMIM#612453] Myopathy, areflexia, respiratory distress, and dysphagia, early-onset	AR	Biallelic mutations in *MEGF10* are associated with early-onset proximal and generalized muscle weakness, respiratory issues, joint contractures and scoliosis. Variable severity between affected individuals has been reported. *MEGF10* is highly expressed in satellite cells and is involved in their proliferation, differentiation and fusion into multinucleated myofibers. Skeletal muscle biopsies in affected patients show small and incompletely fused muscle fibers and decreased sparsely nucleated syncytia (15).
NEB [OMIM#161650] Myopathy, Nemaline 2 [OMIM#256030]	AR	Pie *et al,* 1999 identified 6 mutations (frameshift, nonsense and splicing) in affected members of 5 unrelated families with congenital autosomal recessive nemaline myopathy (16). It is likely that over half of nemaline myopathy cases are caused by *NEB* mutations (3). Nebulin is large protein component of the cytoskeletal matrix and accounts for up to 4% of the total myofibrillar protein.
LMOD3 [OMIM# 616165] Myopathy, Nemaline 10	AR	Yuen et al, 2014, identified homozygous or compound heterozygous mutations in the LMOD3 gene in 14 families with nemaline myopathy (17). The first two families were identified through whole exome sequencing, the others were identified through screening of 540 additional individuals with unresolved nemaline myopathy. 13 out of the 14 families identified had a severe congenital nemaline myopathy, and most patients died in the neonatal period.

Gene	Inheritance	Description
SCN4A [OMIM#603967] Fetal hypokinesia or severe congenital myopathy (18)	AD	In a study by Zaharieva *et al*, homozygous or compound heterozygous mutations in *SCN4A* were identified in 11 individuals from six unrelated families with congenital myopathy. Affected individuals presented in utero or neonatal-onset muscle weakness varying in severity. In seven cases, muscle weakness resulted in death in the third trimester or shortly after birth. Muscle biopsy showed myopathic features including variable fiber size, fibrofatty tissue, and no specific structural abnormalities (18)
SPEG [OMIM#615590] Centronucelar myopathy-5 [OMIM#615959]	AR	Biallic mutations in *SPEG* are associated with centronuclear myopathy-5, which is characterized by severe hypotonia in the neonatal period, respiratory insufficiency, and feeding difficulty. Severity varies between affected individuals, and ranges from death in infancy to survival into childhood with dilated cardiomyopathy. Muscle biopsy demonstrates the presence of hypotrophic myofibers with central nuclei (19)
STAC3 [OMIM#615521] Native American myopathy [OMIM#255995]	AR	Native American myopathy is characterized by congenital weakness and arthrogryposis, cleft palate, ptosis, myopathic facies, short stature, kyphoscoliosis, club feet, and susceptibility to malignant hyperthermia provoked by anesthesia. In five Native American families with myopathy, all five affected individuals were identified to be homozygous for a missense mutation in the *STAC3* gene. Functional studies of this missense mutation in zebrafish showed decreased excitation-contraction coupling (20)
TNTT1 [OMIM191041] Nemaline Myopathy, Amish type [OMIM#605355]	AR	Mutations in *TNTT1* have been described in a group of Old Order Amish individuals with Nemaline myopathy (21). The *TNTT1* gene encodes the slow skeletal muscle troponin.
TPM2 [OMIM190990] Myopathy, Nemaline 4 [OMIM#609285]	AD	Donner *et al*, 2002 identified missense mutations in *TPM2* in 2/66 patients with nemaline myopathy (22). Mutations in *TPM2* are also a rare cause of Congenital Fiber-Type Disproportion. Mutations in *TPM2* can also cause distal arthrogryposis. The *TPM2* gene encodes beta-troposmyosin, an isoform of tropomyosin that is mainly expressed in slow type 1 muscle fibers.
TPM3 [OMIM#191030] Myopathy, Nemaline 1 [OMIM#609284]	AD/AR	Homozygous, heterozygous and compound heterozygous mutations in *TPM3* account for approximately 2-3% of patients with Nemaline Myopathy (23). Mutations in *TPM3* have been identified in 20-40% of patients with Congenital Fiber-Type Disproportion(6). *TPM3* related CFTD has been inherited in both an autosomal dominant and autosomal recessive manner. *TPM3* produces multiple transcripts, one of which is muscle specific. The TPM3 protein is a component of the thin filament and plays a role in muscle contraction.
BIN1 [OMIM#601248] Myopathy, Centronuclear, 2 [OMIM#255200]	AR	*BIN1* mutations appear to be relatively rare, accounting for approximately 25% of cases of CNM with apparent recessive inheritance but only a small percentage of all CNM cases combined (24). To date, only a small number of mutations have been described in the *BIN1* gene, including several missense changes and nonsense mutations. The *BIN1* gene codes for Bridging Integrator 1, also known as amphiphysin II, and has a muscle specific isoform. Amphiphysin II is regulated by phosphoinositides and is believed to be involved in membrane remodeling and T tubule organization.
CCDC78 [OMIM#614666] Myopathy, centronuclear, 4 [OMIM#614807]	AD	Majczenko *et al*, 2012, identified a heterozygous mutation in *CCDC78* in a family with AD CNM (25). The *CCDC78* gene encodes a protein that is important in skeletal muscle function.
CNTN1 [OMIM#600016] Myopathy, congenital, Compton-North [OMIM#612540]	AR	Compton *et al*, 2008 identified a homozygous frameshift mutation in the *CNTN1* gene in affected individuals of a large consanguineous Egyptian family (26). The *CNTN1* gene encodes for contactin-1, a neural adhesion molecular of the immunoglobulin superfamily.

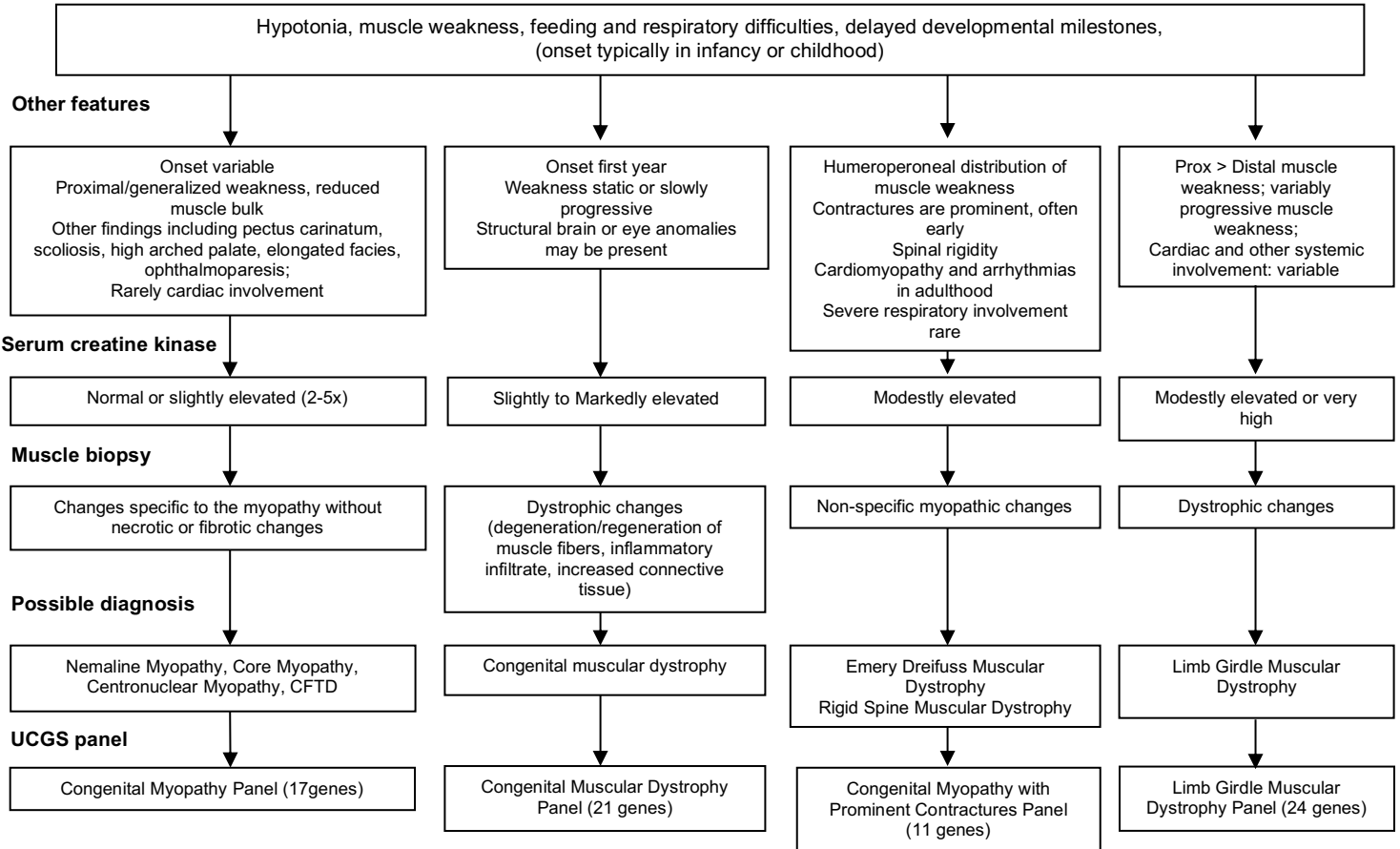|		
DNM2 [OMIM#602378] Myopathy, Centronuclear, 1 [OMIM#160150]	AD	The majority of patients with autosomal dominant or later onset CNM, including *DNM2*-associated CNM, are ambulatory into adulthood (4). Intelligence is usually normal but at least one family with a *DNM2* mutation has been reported to have mild cognitive impairment, as well as mild axonal peripheral nerve involvement (27). *DNM2* mutations account for most, but not all, cases of CNM with autosomal dominant inheritance or later onset (28). NADH staining of patients with *DNM2* mutations often reveals radial arrangement of sarcoplasmic strands, which is highly characteristic, but not diagnostic, of *DNM2*-associated CNM.
MTM1 [OMIM#300415] Myopathy, Centronuclear, X-linked [OMIM#310400]	X-linked	Patients with X-linked myotubular myopathy (XLMTM) generally present with hypotonia, feeding difficulties, respiratory distress, and delayed motor milestones. Death in infancy is common in males with the classic form of this condition. Milder forms of XLMTM have been identified and are characterized by fewer respiratory complications and longer life expectancy than observed in the severe cases (29). Truncating and splice site *MTM1* mutations are more likely to be associated with the severe neonatal form, whereas the milder phenotypes are often caused by missense mutations outside of the functional domains (29). Missense mutations may result in a mild or severe phenotype based on their position in the *MTM1* gene (30). Approximately 80% of males with a diagnosis of myotubular myopathy by muscle biopsy will have a mutation in *MTM1* identifiable by sequence analysis. About 7% of mutations in *MTM1* are deletions (31).
MYF6 [OMIM#159991] Myopathy, centronuclear, 3 [OMIM#614408]	AD	Kerst *et al,* 2000 identified a heterozygous missense mutation in the *MYF6* gene in a boy with myopathy and an increase of muscle fibers with central nuclei (32). The *MYF6* gene is a novel member of the human gene family of muscle determination factors
MYH7 [OMIM#160760] Myopathy, myosin storage [OMIM#608358]	AD	Heterozygous mutations in *MYH7* have been associated with isolated hypertrophic/dilated cardiomyopathy, Laing distal myopathy and myosin storage myopathy (33). Inheritance is generally dominant, but recessive inheritance has been reported in at least one family with a more severe presentation that included cardiomyopathy.
PTPLA [OMIM# 610467]	AR	Muhammad *et al,* 2013, identified a homozygous truncating mutation in *PTPLA* (also known as *HACD1*) in a consanguineous family with congenital myopathy (34). Functional studies showed this mutation completely abrogated the activity of the enzyme encoded for by PTPLA, leading to a reduction in very long chain fatty acid (VLCFA) synthesis (34). The authors hypothesized that this reduction of VLCFAs, which are essential components of membrane lipids, leads to the congenital myopathy phenotype (34).
RYR1 [OMIM#180901]	AR	*RYR1* is typically associated with autosomal recessive CNM, although a *de novo* autosomal dominant mutation in this gene has also been reported (35). CNM-associated mutations identified in *RYR1* have included missense, frameshift, and intronic (36). Mutations in *RYR1* have also been associated with malignant hyperthermia [OMIM#145600], central core disease [OMIM#117000] and multi-minicore disease [OMIM#255320]. The *RYR1* gene, located at 19q13.2, encodes the skeletal muscle ryanodine receptor, which is the principal sarcoplasmic reticulum calcium release channel with a crucial role in excitation-contraction coupling (36).
SEPN1 [OMIM#606210] Myopathy, congenital with fiber-type disproportion [OMIM#255310]	AR	Clarke *et al,* 2006 identified a homozygous mutation in the *SEPN1* gene in two sisters with congenital fiber type disproportion (37). Homozygous or compound heterozygous mutations in *SEPN1* have also been seen in multi-minicore disease, rigid spine muscular dystrophy and desmin-related myopathy with Mallory body-like inclusions.
TTN [OMIM#188840]	AR/AD	Mutations in *TTN* have been described in patients with hereditary myopathy with early respiratory failure, tibial muscular dystrophy, and dilated cardiomyopathy type 1G. Titin is a muscle protein expressed in the cardiac and skeletal muscles and plays a key role in muscle assembly.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interest 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.

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.

Testing algorithm:

There is wide variation in onset, presentation and severity of congenital myopathies/muscular dystrophies. The flowchart below is only intended to be a general guide in considering which UCGS test may be most appropriate for your patient. Physicians should utilize their discretion and medical expertise in determining which testing panel to order.

Hypotonia, muscle weakness, feeding and respiratory difficulties, delayed developmental milestones, (onset typically in infancy or childhood)

Other features

| Onset variable Proximal/generalized weakness, reduced muscle bulk Other findings including pectus carinatum, scoliosis, high arched palate, elongated facies, ophthalmoparesis; Rarely cardiac involvement | Onset first year Weakness static or slowly progressive Structural brain or eye anomalies may be present | Humeroperoneal distribution of muscle weakness Contractures are prominent, often early Spinal rigidity Cardiomyopathy and arrhythmias in adulthood Severe respiratory involvement rare | Prox > Distal muscle weakness; variably progressive muscle weakness; Cardiac and other systemic involvement: variable |

Serum creatine kinase

| Normal or slightly elevated (2-5x) | Slightly to Markedly elevated | Modestly elevated | Modestly elevated or very high |

Muscle biopsy

| Changes specific to the myopathy without necrotic or fibrotic changes | Dystrophic changes (degeneration/regeneration of muscle fibers, inflammatory infiltrate, increased connective tissue) | Non-specific myopathic changes | Dystrophic changes |

Possible diagnosis

| Nemaline Myopathy, Core Myopathy, Centronuclear Myopathy, CFTD | Congenital muscular dystrophy | Emery Dreifuss Muscular Dystrophy Rigid Spine Muscular Dystrophy | Limb Girdle Muscular Dystrophy |

UCGS panel

| Congenital Myopathy Panel (17genes) | Congenital Muscular Dystrophy Panel (21 genes) | Congenital Myopathy with Prominent Contractures Panel (11 genes) | Limb Girdle Muscular Dystrophy Panel (24 genes) |

Cardamone et al., Semin Neurol. 28:250-9, 2008

Congenital Myopathy Panel (28 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 – 10 weeks

Note: We cannot bill insurance for the above test.

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be 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.

References:
1. Taratuto AL. Congenital myopathies and related disorders. Curr Opin Neurol 2002: 15: 553-561.
2. Nance JR, Dowling JJ, Gibbs EM et al. Congenital myopathies: an update. Curr Neurol Neurosci Rep 2012: 12: 165-174.
3. North K, Ryan MM. Nemaline Myopathy. 1993.
4. Pierson CR, Tomczak K, Agrawal P et al. X-linked myotubular and centronuclear myopathies. J Neuropathol Exp Neurol 2005: 64: 555-564.
5. Fardeau M, Tome F. Congenital Myopathies. In: Engel A, Franzini-Armstrong C, eds. Myology. New York, NY: McGraw-Hill, 1994: 1500-1505.
6. DeChene ET, Kang PB, Beggs AH. Congenital Fiber-Type Disproportion. 1993.
7. Laing NG, Dye DE, Wallgren-Pettersson C et al. Mutations and polymorphisms of the skeletal muscle alpha-actin gene (ACTA1). Hum Mutat 2009: 30: 1267-1277.
8. Agrawal PB, Greenleaf RS, Tomczak KK et al. Nemaline myopathy with minicores caused by mutation of the CFL2 gene encoding the skeletal muscle actin-binding protein, cofilin-2. Am J Hum Genet 2007: 80: 162-167.
9. Mitsuhashi S, Ohkuma A, Talim B et al. A congenital muscular dystrophy with mitochondrial structural abnormalities caused by defective de novo phosphatidylcholine biosynthesis. Am J Hum Genet 2011: 88: 845-851.
10. Hicks D, Farsani GT, Laval S et al. Mutations in the collagen XII gene define a new form of extracellular matrix-related myopathy. Hum Mol Genet 2014: 23: 2353-2363.
11. van der Burgt I, Kupsky W, Stassou S et al. Myopathy caused by HRAS germline mutations: implications for disturbed myogenic differentiation in the presence of constitutive HRas activation. J Med Genet 2007: 44: 459-462.
12. Sambuughin N, Yau KS, Olive M et al. Dominant mutations in KBTBD13, a member of the BTB/Kelch family, cause nemaline myopathy with cores. Am J Hum Genet 2010: 87: 842-847.
13. Ravenscroft G, Miyatake S, Lehtokari VL et al. Mutations in KLHL40 are a frequent cause of severe autosomal-recessive nemaline myopathy. Am J Hum Genet 2013: 93: 6-18.
14. Gupta VA, Ravenscroft G, Shaheen R et al. Identification of KLHL41 Mutations Implicates BTB-Kelch-Mediated Ubiquitination as an Alternate Pathway to Myofibrillar Disruption in Nemaline Myopathy. Am J Hum Genet 2013: 93: 1108-1117.
15. Logan CV, Lucke B, Pottinger C et al. Mutations in MEGF10, a regulator of satellite cell myogenesis, cause early onset myopathy, areflexia, respiratory distress and dysphagia (EMARDD). Nat Genet 2011: 43: 1189-1192.
16. Pelin K, Hilpela P, Donner K et al. Mutations in the nebulin gene associated with autosomal recessive nemaline myopathy. Proc Natl Acad Sci U S A 1999: 96: 2305-2310.
17. Yuen M, Sandaradura SA, Dowling JJ et al. Leiomodin-3 dysfunction results in thin filament disorganization and nemaline myopathy. J Clin Invest 2014: 124: 4693-4708.
18. Zaharieva IT, Thor MG, Oates EC et al. Loss-of-function mutations in SCN4A cause severe foetal hypokinesia or 'classical' congenital myopathy. Brain 2016: 139: 674-691.
19. Agrawal PB, Pierson CR, Joshi M et al. SPEG interacts with myotubularin, and its deficiency causes centronuclear myopathy with dilated cardiomyopathy. Am J Hum Genet 2014: 95: 218-226.
20. Horstick EJ, Linsley JW, Dowling JJ et al. Stac3 is a component of the excitation-contraction coupling machinery and mutated in Native American myopathy. Nat Commun 2013: 4: 1952.
21. Johnston JJ, Kelley RI, Crawford TO et al. A novel nemaline myopathy in the Amish caused by a mutation in troponin T1. Am J Hum Genet 2000: 67: 814-821.
22. Donner K, Ollikainen M, Ridanpaa M et al. Mutations in the beta-tropomyosin (TPM2) gene--a rare cause of nemaline myopathy. Neuromuscul Disord 2002: 12: 151-158.
23. Ryan MM, Schnell C, Strickland CD et al. Nemaline myopathy: a clinical study of 143 cases. Ann Neurol 2001: 50: 312-320.
24. Nicot AS, Toussaint A, Tosch V et al. Mutations in amphiphysin 2 (BIN1) disrupt interaction with dynamin 2 and cause autosomal recessive centronuclear myopathy. Nat Genet 2007: 39: 1134-1139.
25. Majczenko K, Davidson AE, Camelo-Piragua S et al. Dominant mutation of CCDC78 in a unique congenital myopathy with prominent internal nuclei and atypical cores. Am J Hum Genet 2012: 91: 365-371.
26. Compton AG, Albrecht DE, Seto JT et al. Mutations in contactin-1, a neural adhesion and neuromuscular junction protein, cause a familial form of lethal congenital myopathy. Am J Hum Genet 2008: 83: 714-724.
27. Echaniz-Laguna A, Nicot AS, Carre S et al. Subtle central and peripheral nervous system abnormalities in a family with centronuclear myopathy and a novel dynamin 2 gene mutation. Neuromuscul Disord 2007: 17: 955-959.
28. Bitoun M, Bevilacqua JA, Prudhon B et al. Dynamin 2 mutations cause sporadic centronuclear myopathy with neonatal onset. Ann Neurol 2007: 62: 666-670.
29. Herman GE, Kopacz K, Zhao W et al. Characterization of mutations in fifty North American patients with X-linked myotubular myopathy. Hum Mutat 2002: 19: 114-121.
30. McEntagart M, Parsons G, Buj-Bello A et al. Genotype-phenotype correlations in X-linked myotubular myopathy. Neuromuscul Disord 2002: 12: 939-946.
31. Laporte J, Biancalana V, Tanner SM et al. MTM1 mutations in X-linked myotubular myopathy. Hum Mutat 2000: 15: 393-409.

32.	Kerst B, Mennerich D, Schuelke M et al. Heterozygous myogenic factor 6 mutation associated with myopathy and severe course of Becker muscular dystrophy. Neuromuscul Disord 2000: 10: 572-577.

33.	Tajsharghi H, Oldfors A. Myosinopathies: pathology and mechanisms. Acta Neuropathol 2013: 125: 3-18.

34.	Muhammad E, Reish O, Ohno Y et al. Congenital myopathy is caused by mutation of HACD1. Hum Mol Genet 2013: 22: 5229-5236.

35.	Jungbluth H, Zhou H, Sewry CA et al. Centronuclear myopathy due to a de novo dominant mutation in the skeletal muscle ryanodine receptor (RYR1) gene. Neuromuscul Disord 2007: 17: 338-345.

36.	Wilmshurst JM, Lillis S, Zhou H et al. RYR1 mutations are a common cause of congenital myopathies with central nuclei. Ann Neurol 2010: 68: 717-726.

37.	Clarke NF, Kidson W, Quijano-Roy S et al. SEPN1: associated with congenital fiber-type disproportion and insulin resistance. Ann Neurol 2006: 59: 546-552.

Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS' NEEDSa