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# Genetic Testing for Congenital Myopathies/Muscular Dystrophies

## 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 all seventeen genes listed below.*

| Nemaline Myopathy | | Centronuclear/Core Myopathy | | |
|---|---|---|---|---|
| *ACTA1* | *TNNT1* | *BIN1* | *MTM1* | *SEPN1* |
| *CFL2* | *TPM2* | *CCDC78* | *MYF6* | *TTN* |
| *KBTBD13* | *TPM3* | *CNTN1* | *MYH7* | |
| *NEB* | | *DNM2* | *RYR1* | |

Congenital Myopathy Sequencing Panel (17 genes)

| | |
|---|---|
| Sample specifications: | 3 to10 cc of blood in a purple top (EDTA) tube |
| Cost: | $3890 |
| CPT codes: | 81407 |
| Turn-around time: | 8 – 10 weeks |

## Congenital Muscular Dystrophy

Congenital muscular dystrophies are a genetically and clinically heterogeneous group of disorders typically characterized by weakness and dystrophic pattern on muscle biopsy present at birth or during the first months of life. Affected infants typically appear 'floppy' and have more low muscle tone and poor spontaneous movements (6). The clinical course is broadly variable and can comprise the involvement of the brain and eyes (7). CMDs can be classified by the mutated gene, the respective protein's localization and the protein's predicted function (8)

*Our Congenital Muscular Dystrophy Panel includes all twenty-one genes listed below.*

| Congenital Muscular Dystrophy Panel | | | | |
|---|---|---|---|---|
| *CHKB* | *DPM2* | *GTDC2* | *LARGE* | *POMT2* |
| *COL6A1* | *DPM3* | *ISPD* | *LMNA* | *RYR1* |
| *COL6A2* | *FKRP* | *ITGA7* | *POMGNT1* | *SEPN1* |
| *COL6A3* | *FKTN* | *LAMA2* | *POMT1* | *TMEM5* |
| *DAG1* | | | | |

Congenital Muscular Dystrophy Sequencing Panel (21 genes)

| | |
|---|---|
| Sample specifications: | 3 to10 cc of blood in a purple top (EDTA) tube |
| Cost: | $3,890 |
| CPT codes: | 81407 |
| Turn-around time: | 8 – 10 weeks |

## Congenital Myopathy with Prominent Contractures

### Emery Dreifuss Muscular Dystrophy

Emery Dreifuss Muscular Dystrophy is characterized by joint contractures (onset in early childhood), slowly progressive muscle wasting and weakness and cardiac conduction defects (9). Muscle wasting and weakness exhibit a distinctive humero-peroneal distribution early in the course of the disease, with weakness later extending to the proximal limb girdle musculature (9). Cardiac involvement, which usually occurs after the second decade and is the most serious aspect of the disease, may manifest as palpitations, presyncope and syncope, poor exercise tolerance and congestive heart failure (10). Heterogeneity in presenting symptoms can occur even amongst affected members of the same family.

### Rigid Spine Muscular Dystrophy

Rigid Spine syndrome is a condition found in a subset of patients affected by myopathy with early contractures. It is characterized by marked limitation in flexion of the whole dorsolumbar and cervical spine, owing to contracture of the spinal extensors and leading to loss of movement of the spine and thoracic cage (11). Spinal rigidity can also be seen in patient with Emery Dreifuss Muscular Dystrophy. Clinical critieria for patients with rigid spine syndrome are similar to those observed in congenital muscular dystrophies, as such, the rigid spine syndrome phenotype has been proposed as a subtype of CMD (12).

*Our Congenital Myopathy with Prominent Contractures Panel includes all twelve genes listed below.*

| Congenital Myopathies with Prominent Contractures | | | |
|---|---|---|---|
| *COL6A1* | *EMD* | *MYH7* | *SYNE1* |
| *COL6A2* | *FHL1* | *RYR1* | *SYNE2* |
| *COL6A3* | *LMNA* | *SEPN1* | *TMEM43* |

Congenital Myopathy with Prominent Contractures Sequencing Panel (12 genes)

| | |
|---|---|
| Sample specifications: | 3 to10 cc of blood in a purple top (EDTA) tube |
| Cost: | $3,500 |
| CPT codes: | 81407 |
| Turn-around time: | 8 – 10 weeks |

## Limb Girdle Muscular Dystrophy

Limb girdle muscular dystrophies 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 (13). Muscle biopsy can show diffuse variation in fiber size, necrosis, regeneration and fibrosis (13). 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 (14).

*Our Limb Girdle Muscular Dystrophy Panel includes all twenty four genes listed below.*

| Autosomal Dominant | | Autosomal Recessive | | | | | |
|---|---|---|---|---|---|---|---|
| Disorder | Gene | Disorder | Gene | Disorder | Gene | Disorder | Gene |
| LGMD1A | *MYOT* | LGMD2A | *CAPN3* | LGMD2G | *TCAP* | LGMD2M | *FKTN* |
| LGMD1B | *LMNA* | LGMD2B | *DYSF* | LGMD2H | *TRIM32* | LGMD2N | *POMT2* |
| LGMD1C | *CAV3* | LGMD2C | *SGCG* | LGMD2I | *FRKP* | LGMD2O | *POMGnT1* |
| LGMD1D | *DES* | LGMD2D | *SGCA* | LGMD2J | *TTN* | LGMD2P | *DAG1* |
| LGMD1F | *DNAJB6* | LGMD2E | *SGCB* | LGMD2K | *POMT1* | LGMD2Q | *PLEC1* |
| | *FLNC* | LGMD2F | *SGCD* | LGMD2L | *ANO5* | | *GAA* |
| | | | | | | | |

Limb Girdle Muscular Dystrophy Sequencing Panel (24 genes)

| | |
|---|---|
| Sample specifications: | 3 to10 cc of blood in a purple top (EDTA) tube |
| Cost: | $3,900 |
| CPT codes: | 81407 |
| Turn-around time: | 8 – 10 weeks |

## Congenital Myasthenic syndromes

Congenital myasthenic syndromes (CMS) are heterogeneous inherited disorders of neuromuscular transmission characterized by fatigable weakness of the skeletle muscle with onset at or shortly after birth or in early childhood (15). In CMS, the safety margin of neuromuscular transmission is compromised, and clinical evaluation should involve detalied electromyographic (EMG) studies to demonstrate a defect in neuromuscular transmission (16). 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 (15). Later childhood onset subtypes show abnormal muscle fatiability, motor milestones may be delayed, ptosis, and fixed or fluctuating extraocular muscle weakness (15).

*Our Congenital Myasthenic Syndromes Panel includes all thirteen genes listed below.*

| Congenital Myasthenic Syndrome Panel | | | | |
|---|---|---|---|---|
| *AGRN* | *CHRNB1* | *COLQ* | *GFPT1* | *SCN4A* |
| *CHAT* | *CHRND* | *DOK7* | *MUSK* | |
| *CHRNA1* | *CHRNE* | *DPAGT1* | *RAPSN* | |

Congenital Myasthenic Syndrome Sequencing Panel (13 genes)

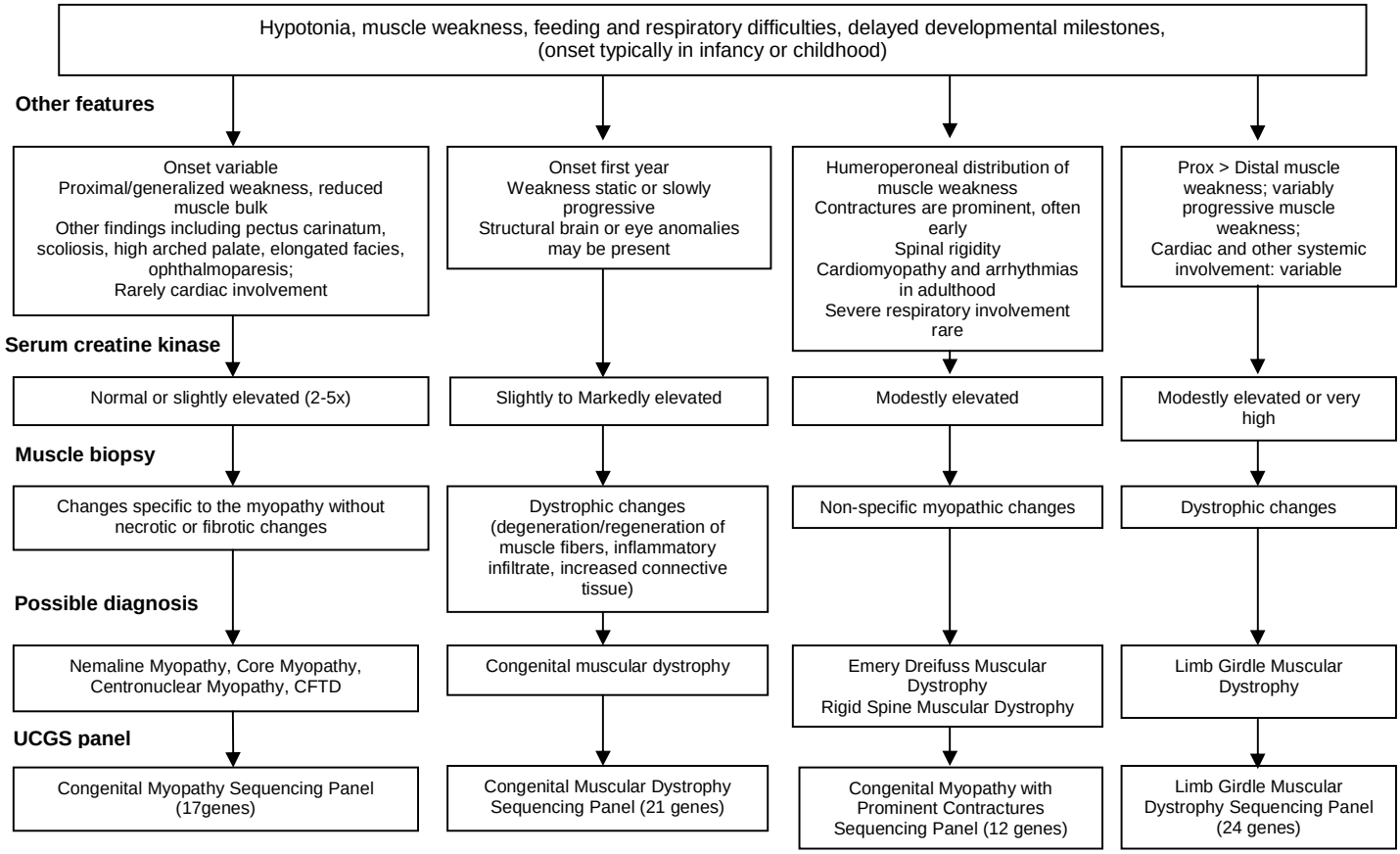
| | |
|---|---|
| Sample specifications: | 3 to10 cc of blood in a purple top (EDTA) tube |
| Cost: | $3,600 |
| CPT codes: | 81407 |
| Turn-around time: | 8 – 10 weeks |

## 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.

## 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.




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

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The above tests will be available August 2013.
We are excited to bring these and other new tests to your patients and families.
Let us know if there are other tests that you would like to see offered.
Please refer to our website dnatesting.uchicago.edu or contact us for more information

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