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 (1). 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 (1). 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 (2). 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 (3). Spinal rigidity can also be seen in patient with Emery Dreifuss Muscular Dystrophy. Clinical criteria 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 (4).

Our Congenital Myopathy with Prominent Contractures Sequencing Panel and Congenital Myopathy with Prominent Contractures Deletion/Duplication Panel include analysis of the 13 genes listed below.

<table>
<thead>
<tr>
<th>Gene (OMIM#)</th>
<th>Inheritance</th>
<th>Clinical Features/Molecular Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL6A1</td>
<td>AD and AR</td>
<td>The collagen type VI-related disorders represent a spectrum including Bethlem myopathy at the mild end, Ullrich congenital muscular dystrophy at the severe end, and autosomal dominant limb girdle muscular dystrophy and autosomal recessive myosclerotic myopathy in between. Mutations in COL6A1, COL6A2 and COL6A3 account for 38, 44 and 18% of affected individuals respectively (5).</td>
</tr>
<tr>
<td>COL6A2</td>
<td>X-linked</td>
<td>Mutations in EMD account for approximately 61% of XL-EDMD (2). Emerin is a ubiquituous protein that is found along the nuclear rim of many cell types and is a member of the nuclear lamina-associated protein family.</td>
</tr>
<tr>
<td>COL6A3</td>
<td>AR</td>
<td>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 (6).</td>
</tr>
<tr>
<td>EMD</td>
<td>AD and AR</td>
<td>Muscular dystrophy, congenital merosin-deficient</td>
</tr>
<tr>
<td>LAMA2</td>
<td>AR</td>
<td>Merosin-deficient congenital muscular dystrophy type 1A, caused by biallelic mutations in LAMA2, causes congenital muscle weakness, poor suck and cry and delayed ambulation. The majority of patients with LAMA2-related muscular dystrophy also have white matter abnormalities noted on MRI. Joint contractures have also been reported in patients with LAMA2-related congenital muscular dystrophy (6).</td>
</tr>
<tr>
<td>LMNA</td>
<td>AD/AR</td>
<td>Mutations in LMNA account for approximately 45% of AD-EDMD (2). AR-EDMD is rare, Raffaele Di Barletta et al, 2000 identified a homozygous mutation in LMNA leading to AR-EDMD (9). The LMNA gene encodes lamin A and lamin C, structural protein components of the nuclear lamina</td>
</tr>
<tr>
<td>MYH7</td>
<td>AD</td>
<td>Heterozygous mutations in MYH7 have been associated with isolated hypertrophic/dilated cardiomyopathy. Laing distal myopathy and myosin storage myopathy (10). Inheritance is generally dominant, but recessive</td>
</tr>
</tbody>
</table>
### [OMIM#606210]

**SEPN1**

Muscular dystrophy, rigid spine, 1

**AR**

Mutations in the **SEPN1** gene have been identified in patients with rigid spine muscular dystrophy (13). Homozygous or compound heterozygous mutations in **SEPN1** have also been seen in multiminicore disease, congenital myopathy with fiber-type disproportion and desmin-related myopathy with Mallory body-like inclusions.

### [OMIM#608441]

**SYNE1**

Emery-Dreifuss muscular dystrophy 4

**AD**

Zhang et al, 2007 identified a heterozygous mutation in **SYNE2** in a father and his 2 children with EDMD and identified 2 different heterozygous mutations in **SYNE1** in two unrelated patients (14).

### [OMIM#606210]

**SEPN1**

Muscular dystrophy, rigid spine, 1

**AR**

Mutations in the **SEPN1** gene have been identified in patients with rigid spine muscular dystrophy (13). Homozygous or compound heterozygous mutations in **SEPN1** have also been seen in multiminicore disease, congenital myopathy with fiber-type disproportion and desmin-related myopathy with Mallory body-like inclusions.

### [OMIM#608442]

**SYNE2**

Emery-Dreifuss muscular dystrophy 5, autosomal dominant

**AD**

Liang et al, 2011 identified heterozygous missense mutations in 2/41 individuals with Emery-Dreifuss muscular dystrophy (15).

### 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

**Serum creatine kinase**

- Normal or slightly elevated (2-5x)
- Slightly to Markedly 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)

**Possible diagnosis**

- Nemaline Myopathy, Core Myopathy, Centronuclear Myopathy, CFTD
- Congenital muscular dystrophy
- Emery Dreifuss Muscular Dystrophy
- Limb Girdle Muscular Dystrophy

**UCGS panel**

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

Cardamone et al., Semin Neurol. 28:250-9, 2008
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. In addition, targeted sequence analysis for the recurrent c.930+189C>T variant in the COL6A1 gene is performed by Sanger sequencing. This assay also includes analysis for the recurrent c.930+189C>T deep intronic variant in the COL6A1 gene.

Deletion/duplication analysis is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Congenital Myopathy with Prominent Contractures Sequencing Panel (13 genes)

<table>
<thead>
<tr>
<th>Sample specifications:</th>
<th>3 to 10 cc of blood in a purple top (EDTA) tube</th>
</tr>
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<tbody>
<tr>
<td>Cost:</td>
<td>$2,000</td>
</tr>
<tr>
<td>CPT codes:</td>
<td>81407</td>
</tr>
<tr>
<td>Turn-around time:</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

Note: We cannot bill insurance for the above test.

Congenital Myopathy with Prominent Contractures Del/Dup Panel (13 genes)

<table>
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<tr>
<th>Sample specifications:</th>
<th>3 to 10 cc of blood in a purple top (EDTA) tube</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost:</td>
<td>$1,545</td>
</tr>
<tr>
<td>CPT codes:</td>
<td>81407</td>
</tr>
<tr>
<td>Turn-around time:</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

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:


dnatesting.uchicago.edu • 773-834-0555