Limb girdle muscular dystrophies is a term generally used to describe progressive weakness and wasting restricted to the limb musculature (proximal greater than distal), due to a genetic defect that is distinct from X-linked dystrophinopathy (1). Muscle biopsy can show diffuse variation in fiber size, necrosis, regeneration and fibrosis (1). 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 (2).

Our Limb Girdle Muscular Dystrophy Sequencing Panel includes all 31 genes listed below.

Our Limb Girdle Muscular Dystrophy Del/Dup Panel includes all 25 genes listed in bold below.

<table>
<thead>
<tr>
<th>Autosomal Dominant Genes</th>
<th>Autosomal Recessive Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAV3</td>
<td>ANO5</td>
</tr>
<tr>
<td>DES</td>
<td>CAPN3</td>
</tr>
<tr>
<td>DNAJB6</td>
<td>DAG1</td>
</tr>
<tr>
<td>FLNC</td>
<td>DYSF</td>
</tr>
<tr>
<td>HNRNPDLD</td>
<td>FKRP</td>
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<tr>
<td>LMNA</td>
<td>FKTN</td>
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<tr>
<td>MYOT</td>
<td>GAA</td>
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<tr>
<td>TNPO3</td>
<td>GMPPB</td>
</tr>
<tr>
<td>DES</td>
<td>POMGnT1</td>
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<tr>
<td>FLNC</td>
<td>PLEC</td>
</tr>
<tr>
<td>HNRNPDLD</td>
<td>POMK</td>
</tr>
<tr>
<td>ISPD</td>
<td>LIMS2</td>
</tr>
<tr>
<td>SGCB</td>
<td>SGCd</td>
</tr>
<tr>
<td>SGCD</td>
<td>SGCG</td>
</tr>
<tr>
<td>TRIM32</td>
<td>TCAP</td>
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<tr>
<td>TRAPPC11</td>
<td></td>
</tr>
<tr>
<td>SGCA</td>
<td></td>
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</tbody>
</table>

Genes and Associated Disorder | Inheritance | Clinical Features/Molecular Pathology |
---|---|---|
ANO5 [OMIM#608662] | AR | Penttila et al, 2012 identified 11 different recessive mutations in the ANO5 gene in 25/101 patients with undiagnosed distal calf myopathy or LGMD (3). The function of anoctamin-5 is still being elucidated. |
CAPN3 [OMIM#114240] | AR | Mutations in CAPN3 account for approximately 10% of individuals (4) of European descent and up to 80% of individuals in the Basque country (5). CAPN3 codes for calpain-3, a calcium-activated neutral protease, that is involved in muscle remodeling. |
CAV3 [OMIM#601253] | AD and AR | Caveolinopathies account for 1-2% of unclassified LGMD and other phenotypes including isolated HCK, RMD and proximal and distal myopathy (6). Caveolin-3 plays a role in muscle development and physiology. |
DES [OMIM#125660] | AD | McDonald et al, 2012 identified a splicing mutation in DES by exome sequencing in a family with LGMD (8). Most desmin mutations result in other phenotypes, such as Dilated Cardiomyopathy and Myofibrillar Myopathy. |
DNAJB6 [OMIM#611332] | AD | Heterozygous mutations in DNAJB6 have been identified in families with autosomal dominant LGMD (9, 10). DNAJB6 is part of a family of molecular co-chaperones involved in protecting proteins from irreversible aggregation during protein synthesis or cellular stress. |
DYSF [OMIM#603009] | AR | Mutations in DYSF account for approximately 5% of individuals (2). Dysferlin plays an important role in muscle fiber repair. |
<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>OMIM Number</th>
<th>Inheritance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLNC</td>
<td>OMIM#102565</td>
<td>AD</td>
<td>McDonald et al, 2012 identified a nonsense mutation in FLNC by exome sequencing in a family with LGMD (8). Most FLNC mutations result in other phenotypes, such as Distal and Myofibrillar Myopathy.</td>
</tr>
<tr>
<td>FKRPA, GMPBP, ISPD, POMT1, FKN, POMK, POMGNT1, POMT2</td>
<td>OMIM numbers vary</td>
<td>AR</td>
<td>Mutations in these genes are associated with a wide spectrum of muscular dystrophies ranging from congenital muscular dystrophies with various eye and brain involvement, to milder forms with later onset limb girdle muscular dystrophies. Relatively few individuals with an LGMD phenotype and mutations in these genes have been reported (2).</td>
</tr>
<tr>
<td>GAA</td>
<td>OMIM#606800</td>
<td>AR</td>
<td>Late-onset Pompe disease may present from the second to as late as the seventh decade of life with progressive proximal muscle weakness primarily affecting the lower limbs, as in a limb-girdle muscular dystrophy or polymyositis (11).</td>
</tr>
<tr>
<td>HNRNPDL</td>
<td>OMIM# 607137</td>
<td>AD</td>
<td>Heterozygous mutations in HNRNPDL have been reported in two families with LGMD type 1G (12).</td>
</tr>
<tr>
<td>LIMS2</td>
<td>OMIM# 607908</td>
<td>AR</td>
<td>Exome sequencing of two siblings with severe LGMD revealed compound heterozygous mutations in LIMS2 (13). In addition to features of LGMD these siblings also had distinctive triangular shaped tongues.</td>
</tr>
<tr>
<td>MYOT</td>
<td>OMIM#604103</td>
<td>AD</td>
<td>Hauser et al, 2000 identified a mutation in the myotilin gene in a large North American Family of German ancestry (15). Mutations in MYOT have also been identified in patients with myofibrillar myopathy and spheroid body myopathy. Myotilin is a sarcomeric protein that binds to alpha-actinin and is associated with the Z-line.</td>
</tr>
<tr>
<td>PLEC1</td>
<td>OMIM#601282</td>
<td>AR</td>
<td>Gundesli et al, 2010 identified a homozygous 9bp deletion in the PLEC1 gene in a Turkish family with AR LGMD (16). PLEC1 is believed to provide mechanical strength to cells and tissues by acting as a crosslinking element of the cytoskeleton.</td>
</tr>
<tr>
<td>SGCAG, SGCAG, SGCAG, SgcD</td>
<td>OMIM numbers vary</td>
<td>AR</td>
<td>Mutations in SGCA, SGCB, SGCG and SGCD account for up to 66% of individuals with childhood onset and 10% of individuals with adult onset (17). The sarcoglycanopathy genes encode proteins that form a tetrameric complex at the muscle cell plasma membrane.</td>
</tr>
<tr>
<td>TCAP</td>
<td>OMIM#604488</td>
<td>AD</td>
<td>Moreira et al, 2000 identified homozygous TCAP mutations in four Brazilian families (18). The TCAP protein is found exclusively in striated and cardiac muscle and serves as both a structural anchor and a signaling center.</td>
</tr>
<tr>
<td>TNPO3</td>
<td>OMIM# 610032</td>
<td>AD</td>
<td>A heterozygous mutation in TNPO3 has been described in a large Spanish family with LGMD type 1F (19).</td>
</tr>
<tr>
<td>TRAPPCC11</td>
<td>OMIM# 614138</td>
<td>AR</td>
<td>Homozygous mutations in TRAPPCC11 have been reported in a Syrian family with LGMD type 2S, and also in 2 Hutterite families with overlapping phenotypes including neuromuscular dysfunction (20).</td>
</tr>
<tr>
<td>TTN</td>
<td>OMIM#188840</td>
<td>AR</td>
<td>Hackman et al, 2002 identified a homozygous 11bp indel of the TTN gene in a large Finnish family with LGMD (23). This mutation is a common founder mutation in the Finnish population. Mutations in TTN have also been described in patients with hereditary myopathy with early respiratory failure, tardive 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.</td>
</tr>
</tbody>
</table>
**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.

**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
- Congenital Myopathy with Prominent Contractures Sequencing Panel (11 genes)
- Limb Girdle Muscular Dystrophy Sequencing Panel (31 genes)

**UCGS panel**
- Congenital Myopathy Sequencing Panel (19 genes)
- Congenital Muscular Dystrophy Sequencing Panel (24 genes)
- Congenital Myopathy with Prominent Contractures Sequencing Panel (11 genes)
- Limb Girdle Muscular Dystrophy Sequencing Panel (31 genes)

**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.

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.

**Limb Girdle Muscular Dystrophy Sequencing Panel (31 genes)**
- Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
- Cost: $3,900
- CPT codes: 81407
- Turn-around time: 8 weeks

*Note: We cannot bill insurance for the above test.*

**Limb Girdle Muscular Dystrophy Deletion/Duplication Panel (25 genes)**
- Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
- Cost: $2,500
- CPT codes: 81407
- Turn-around time: 4 - 6 weeks
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.

References: