Limb-Girdle Muscular Dystrophy (LGMD) Type 2L: ANO5 Gene Deletion/Duplication

**Condition Description**

Limb-girdle muscular dystrophy (LGMD) is a descriptive term applied to a clinically and genetically heterogeneous group of childhood- or adult-onset muscular dystrophies. LGMD is characterized by weakness and wasting restricted to the limb musculature, proximal greater than distal. Most individuals with LGMD show relative sparing of the heart and bulbar muscles, although exceptions occur, depending on the genetic subtype. Onset, progression, and distribution of the weakness and wasting vary considerably among individuals and genetic subtypes. Serum creatine kinase (CK) levels in individuals with LGMD are usually elevated, and muscle biopsy reveals dystrophic changes. Immunohistochemistry (IHC) testing of a muscle biopsy sample can be used to determine the presence or absence of specific proteins, and confirmatory genetic testing is available in some cases. LGMDs are distinct from the much more common X-linked dystrophinopathies, which include Duchenne and Becker muscular dystrophy (DMD/BMD).

Mutations in the ANO5 gene (11p14.3)(OMIM #608662) have been shown to cause the autosomal recessive disorders limb-girdle muscular dystrophy type 2L (LGMD 2L) and Miyoshi myopathy type 3 (MMD3), and the autosomal dominant disorder gnathodiaphyseal dysplasia (GDD), a rare skeletal syndrome. LGMD 2L is characterized by late-onset (mean age 35) proximal weakness with prominent asymmetrical quadriiceps femoris and biceps brachii atrophy. A milder degree of distal lower limb weakness may be observed and affected individuals usually remain ambulatory for several decades, although they may have difficulty climbing stairs. There is significant interfamilial variability.

MMD3 is a distal muscular dystrophy, particularly of calf muscles. Affected individuals may have calf weakness with or without atrophy, and have difficulty walking on their toes. Later manifestations include asymmetric involvement of the proximal muscles of the lower and upper limb-girdle, with quadriiceps atrophy.

Serum creatine kinase levels are elevated in affected individuals (mean 4000-5000 IU). Cardiac and respiratory function is normal. Females appear to be less frequently affected. Muscle biopsy reveal myopathic or dystrophic changes with variation in fiber size, central nuclei, fiber splitting, degeneration of muscle fibers, and an increase in connective tissue. EMG shows myopathic changes.

In the Bolduc study (2010), two mutations in the ANO5 genes were found in three of ten LGMD 2L families (30%) and in two of two MMD3 families with linkage to the ANO5 gene region. In the Hicks study (2011), two mutations in the ANO5 gene were found in 15 of 59 LGMD/MMD affected families without DYSF mutations (25.4%). The Hicks study suggested a minimum prevalence of ANO5 mutations of 0.27/100,000 in the North of England population.


**References:**


**Genes**

ANO5

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of limb-girdle muscular dystrophy type 2L in an individual in whom sequence analysis was negative.
- Carrier testing in adults with a family history of limb-girdle muscular dystrophy type 2L in whom sequence analysis was negative.

**Methodology**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types

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Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Sequence analysis of the ANOS5 gene is available and is required before deletion/duplication analysis.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.