Limb-Girdle Muscular Dystrophy (LGMD) Type 2A: CAPN3 Gene Sequencing

**Test Code:** SCAP3
**Turnaround time:** 4 weeks
**CPT Codes:** 81406 x1

**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).

LGMD 2A, also referred to as calpainopathy, is likely the most frequent form of LGMD, although there are geographic differences in frequency. Average age of onset is 8-15 years of age. Onset usually occurs in the lower extremities with proximal weakness, followed by weakness in the upper extremities some years later. Other features include scapular winging, difficulties running and walking, toe walking, waddling gait, slight hyperlordosis, and muscle atrophy with only rare hypertrophy. There is no cardiac involvement. LGMD 2A is slowly and steadily progressive, with loss of ambulation occurring approximately 20 years after onset. Intra- and interfamilial variability has been observed. Serum CK levels can be normal but are often 5-80 times normal and calpain-3 is usually, but not always, absent by IHC. Secondary deficiency of calpain-3 can also be seen in several other muscular dystrophies. LGMD 2A is inherited in an autosomal recessive manner.

Mutations in the **CAPN3** gene (15q15.1-q21.1) cause LGMD 2A.

For patients with suspected LGMD 2A, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.


**References:**


**Genes**

**CAPN3**

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of LGMD 2A.
- Carrier testing in adults with a family history of LGMD 2A.

**Methodology**

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient’s genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Detection**

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%.

**Specimen Requirements**

Submit only 1 of the following specimen types

* 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**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

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**

- Deletion/duplication analysis of the CAPN3 gene by CGH array is available for those individuals in whom sequence analysis is negative.
- An LGMD sequencing panel that includes 11 LGMD genes is also available.
- 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 to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.