Limb-Girdle Muscular Dystrophy (LGMD) Type 1C: CAV3 Gene Sequencing

Test Code: SCAV3
Turnaround time: 4 weeks
CPT Codes: 81404 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 1C, also referred to as caveolinopathy, has an average age of onset of five years, although it can range from early childhood to late adulthood. Individuals with childhood onset typically show a Gower sign, calf hypertrophy, mild to moderate proximal weakness, and muscle cramps after exercise. LGMD 1C may also present with muscle cramping and pain, hyperCKemia, or both instead of weakness. Serum CK levels are 4-25 times normal levels and caveolin-3 is reduced on IHC and Western blot. LGMD 1C is inherited in an autosomal dominant manner.

Mutations in the CAV3 gene (3p25) cause LGMD 1C. Mutations in the CAV3 gene also cause rippling muscle disease, familial hypertrophic cardiomyopathy, and distal myopathy, in addition to LGMD 1C and hyperCKemia. These phenotypes all demonstrate intrafamilial variability.

For patients with suspected LGMD 1C, 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**

**CAV3**

**Indications**

This test is indicated for:
- Confirmation of a clinical diagnosis of LGMD 1C

**Methodology**

PCR amplification of 2 exons contained in the CAV3 gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

**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 CAV3 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 individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.