Limb-Girdle Muscular Dystrophy (LGMD) Type 2D: SGCA Gene Deletion/Duplication

Test Code: DSGCA
Turnaround time: 2 weeks
CPT Codes: 81228 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).

Mutations in any of the four genes for sarcoglycan that make up the sarcoglycan complex in skeletal muscle can cause LGMD. LGMD 2C is caused by mutation in the SGCG gene (13q12), LGMD 2D is caused by mutations in the SGCA gene (17q12-q21.3), LGMD 2E is caused by mutations in the SGCB gene (4q12), and LGMD 2F is caused by mutations in the SGCD gene (5q33). LGMD 2C-F are sometimes referred to as the sarcoglycanopathies.

Age of onset in the sarcoglycanopathies is variable and ranges from early childhood to adulthood, with the majority of affected individuals presenting in the first decade of life and loss of ambulation by the third decade. Phenotype is somewhat similar to that of Duchenne and Becker muscular dystrophy. Proximal weakness in the pelvic girdle occurs before the shoulder girdle becomes affected, which can lead to difficulty running, climbing stairs, and a positive Gowers' maneuver. There may be calf hypertrophy and about 30% of affected individuals develop dilated cardiomyopathy. Language or cognitive delays have not been reported. Significant discordance in phenotypes between siblings has been observed.

Serum CK levels are significantly elevated and IHC shows absence of the sarcoglycan complex. Mutation in any one of the sarcoglycan genes will lead to secondary deficiency of all four sarcoglycans on IHC; gene analysis is necessary to determine which gene has a mutation. LGMD 2C-F are inherited in an autosomal recessive manner, although there have been reports of individuals heterozygous for a mutation in SGCA with mild clinical symptoms including scapular winging and calf hypertrophy.

For patients with suspected LGMD 2D, 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

SGCA

Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of LGMD 2D in individuals who have tested negative for sequence analysis
- Carrier testing in adults with a family history of LGMD 2D who have tested negative for sequence analysis

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
* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple 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 EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Full gene sequence analysis of the \textit{SGCA} gene by CGH array is available and is required before deletion/duplication analysis.
- A sarcoglycanopathies sequencing panel that includes the \textit{SGCG}, \textit{SGCA}, and \textit{SGCB}, and \textit{SGCD} genes is also available.
- An LGMD sequencing panel that includes 11 LGMD genes is also available.
- 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.