Merosin-Deficient CMD Type 1D (MDC1D): LARGE1 Gene Sequencing

Test Code: SLARG  
Turnaround time: 4 weeks  
CPT Codes: 81479 x1

**Condition Description**

The congenital muscular dystrophies are a group of genetically and clinically heterogeneous hereditary myopathies characterized by congenital hypotonia and muscle weakness, contractures, and delayed motor development. Muscle biopsy usually reveals a nonspecific dystrophic pattern. The clinical course is broadly variable and can involve the brain and eyes. Initial testing often includes clinical evaluation, muscle imaging, electromyography, and muscle biopsy, followed by targeted genetic testing.

A single individual has been recognized with congenital muscular dystrophy type 1D (MDC1D). This individual was 17 years of age at the time of diagnosis and did not have any problems at birth, but was recognized to be developmentally delayed at 5 months of age. She was able to sit unsupported at two and a half years of age, and walked independently at four and a half years of age. Maximal motor function was obtained by nine years of age, after which she gradually worsened. She had contractures at the ankles and elbows, muscle hypertrophy of the quadriceps, calves, and arm muscles, and mild facial weakness.

The affected individual was profoundly mentally retarded with abnormal brain MRI that showed extensive and symmetrical cerebral white matter changes and neuronal migration defects, although brain MRI at age 4 years only showed minimal changes. Serum creatine kinase (CK) levels were elevated 2-20 times normal levels. Muscle biopsy showed uneven reduced staining of alpha dystroglycan, and normal laminin alpha 2 and beta-dystroglycan staining. Two mutations were identified in the **LARGE1** gene (22q12.3-q13.1).

For patients with suspected MDC1D, 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**

**LARGE1**

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of MDC1D
- Carrier testing in adults with a family history of MDC1D

**Methodology**

PCR amplification of 14 exons contained in the **LARGE1** 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 deoxy 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) 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**

- Deletion/duplication analysis of the **LARGE1** gene by CGH array is available for those individuals in whom sequence analysis is negative.
- **Familial mutation testing** 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.