EGL Genetics | Eurofins Clinical Diagnostics
2460 Mountain Industrial Boulevard | Tucker, Georgia 30084
Phone: 470-378-2200 or 855-831-7447 | Fax: 470-378-2250
eglgenetics.com

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

- Bonnemann, Carsten. Personal communication. July 8, 2009.
- Conti Reed, U. Congenital muscular dystrophy part I: A review of phenotypical and diagnostic aspects. Arq Neuropsiquiatr. 2009; 67:144-168.
- GeneTests: Congenital Muscular Dystrophy Overview. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene?=cmd-overview
- Mendell, JR et al. The congenital muscular dystrophies: Recent advances and molecular insights. Ped and Dev Pathology. 2006; 9:427-443.

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 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

Type: Whole Blood (EDTA)

Specimen Requirements:
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old: 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

2460 Mountain Industrial Boulevard | Tucker, Georgia 30084
Phone: 470-378-2200 or 855-831-7447 | Fax: 470-378-2250
eglgenetics.com

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Type: DNA, Isolated

Specimen Requirements:
Microtainer
8µg
Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:
Oragene™ Saliva Collection Kit
Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

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.