

## Merosin-Deficient CMD Type 1C (MDC1C): *FKRP* Gene Deletion/Duplication

**Test Code:** DFKRP

**Turnaround time:** 2 weeks

**CPT Codes:** 81228 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.

Mutations in the *FKRP* gene (fukutin-related protein; 19q13.3) can cause a milder form of congenital muscular dystrophy (CMD) called limb-girdle muscular dystrophy type 2I (LGMD2I) or a more severe form of CMD called merosin-deficient CMD type 1C (MDC1C). Both conditions are autosomal recessive in inheritance.

#### *Limb-Girdle Muscular Dystrophy Type 2I (LGMD2I)*

LGMD2I tends to be milder in presentation than MDC1C but has a variable phenotype depending on age of onset. The phenotype ranges from severe (similar to Duchenne muscular dystrophy) to mild with no clinically apparent skeletal involvement. Onset within the first few years of life predicts a Duchenne-like progression with muscle hypertrophy in the thigh and tongue, and lost independent walking during second decade of life. The milder end of the spectrum resembles Becker muscular dystrophy with later onset; some patients remain ambulatory into the fifth decade of life, have less hypertrophy of the calf, thigh, and tongue, and have muscle cramps following exercise. Cardiac involvement occurs in 10-55% of affected individuals and respiratory involvement in about 50%. Cardiomyopathy without skeletal muscle involvement has been reported.

#### *Merosin-Deficient CMD Type 1C (MDC1C)*

Individuals with MDC1C have severe hypotonia and contractures of the elbows, knees, and fingers; onset is usually between birth to six months and affected individuals do not usually achieve independent ambulation. Other clinical features include a normal MRI; a normal IQ (in most cases); hypertrophy of the calves and quadriceps; a myopathic EMG; and macroglossia. Some individuals have dilated cardiomyopathy or impaired left ventricular function. Respiratory failure often occurs in the second decade of life.

MDC1C can be distinguished from other nonsyndromic forms of CMD by the presence of calf pseudohypertrophy, dilated cardiomyopathy involving the left ventricle, and absence of white matter changes on MRI. A few affected individuals have had mental retardation, suggesting a syndromic form of the condition.

Serum creatine kinase (CK) concentration in individuals with LGMD2I and MDC1C is usually markedly increased. Immunostaining of muscle tissue reveals significantly reduced amounts of glycosylated alpha dystroglycan and deficiency of fukutin-related protein. Partial deficiency of merosin (laminin alpha 2) and alpha sarcoglycan can also be seen. *FKRP* mutations differ in LGMD2I and MDC1C. Individuals who are homozygous or compound heterozygous for missense mutations in *FKRP* have the LGMD2I phenotype. Individuals who are homozygous or compound heterozygous for nonsense mutations have the MDC1C phenotype. Two common mutations have been identified in LGMD2I. Asymptomatic individuals homozygous for either common mutation or compound heterozygous for both mutations have been reported.

For patients with suspected MDC1C or LGMD2I, 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>
- GeneTests: Limb-Girdle Muscular Dystrophy Overview. <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene?=&lgmd=overview>
- Mendell, JR et al. The congenital muscular dystrophies: Recent advances and molecular insights. *Ped and Dev Pathology.* 2006; 9:427-443.

### Genes

#### [FKRP](#)

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of MDC1C or LGMD2I in an individual in whom sequence analysis was negative
- Carrier testing in adults with a family history of MDC1C or LGMD2I in whom sequence analysis was negative

### 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.

## 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**

### Type: DNA, Isolated

#### Specimen Requirements:

Microtainer

3µg

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: 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

#### Specimen Collection and Shipping:

Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

## 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

- Sequence analysis of the *FKRP* is required before deletion/duplication 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.