

Merosin-Deficient CMD Type 1C (MDC1C): *FKRP* Gene Sequencing

Test Code: SFKRP

Turnaround time: 4 weeks

CPT Codes: 81404 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
- Carrier testing in adults with a family history of MDC1C or LGMD2I

Methodology

PCR amplification of 1 exon contained in the *FKRP* 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

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

Oragene™ 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 *FKRP* 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.