Fukuyama Congenital Muscular Dystrophy: FKTN Gene Sequencing

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.

Fukuyama congenital muscular dystrophy (FCMD) was first described in 1960 and represents one of the most common autosomal recessive disorders in the Japanese population. FCMD is a severe CMD that is associated with mental retardation. Characteristics include hypotonia, symmetrical generalized muscle weakness, and CNS migration disturbances that result in changes consistent with cobblestone (previously type II) lissencephaly with cerebral and cerebellar cortical dysplasia. Mild, typical, and severe phenotypes are recognized.

Poor fetal movements and birth asphyxia may be the first signs. Onset typically occurs in early infancy, with a poor suck, weak cry, and floppiness. Affected individuals have contractures of the hips, knees, ankles, and elbows with onset before age one year. Later features include myopathic facial appearance; pseudohypertrophy of the calves, forearms, and tongue muscles; severe motor, mental, and speech retardation; convulsions; ophthalmologic abnormalities including myopia, cataracts, optic atrophy, and retinal detachment; and dilated cardiomyopathy and respiratory failure that become symptomatic in the second decade of life. Affected individuals may attain independent sitting but usually do not achieve independent ambulation. Death often occurs by age 20 years.

The clinical manifestations can show a variable degree of severity even among siblings. A few patients can walk without support, have a lesser degree of cognitive deficiency, and may obtain seizure control. The phenotypic spectrum ranges from a Walker-Warburg syndrome (WWS)-like phenotype at the severe end to a limb-girdle muscular dystrophy (LGMD)-like phenotype at the mild end.

Serum creatine kinase (CK) levels in individuals with FCMD are approximately 10-60 times higher than normal in affected children under six years of age. 5-20 times higher than normal after seven years of age, and normal in individuals who are bed-ridden. Muscle biopsy findings are characteristic of muscular dystrophy. Immunohistochemical staining using an alpha-dystroglycan antibody shows selective deficiency of alpha-dystroglycan in skeletal muscle, cardiac muscle, and brain.

Mutation of the FKTN gene (9q31) causes FCMD which is mostly found in the Japanese population. Approximately 80% of affected individuals of Japanese ancestry are homozygous for the founder mutation (a 3kb retrotransposal insertion into the 3' UTR), while an additional 15-20% are compound heterozygotes for the founder mutation and another point mutation. The average occurrence of heterozygous carriers identified in various regions of Japan is one in 188.

NOTE: For patients with suspected FCMD, sequence analysis for the Japanese founder mutation is recommended as the first step in mutation identification. This insertion is not part of this sequencing test but is available as a separate assay.

References

Genes

FKTN

Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of Fukuyama CMD
- Carrier testing in adults with a family history of Fukuyama CMD

Methodology

PCR amplification of 9 exons contained in the FKTN 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. Large deletions are not detected by this analysis. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

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Evaluation of the 3kb insertion is not done as part of this test.

**Detection**

Clinical Sensitivity: Approximately 80% of affected individuals of Japanese ancestry are homozygous for the founder mutation, while an additional 15-20% are compound heterozygotes for the founder mutation and another point mutation. 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) or ACD (yellow 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 Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Deletion/duplication analysis of the FKTN 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.