

Muscle-Eye-Brain (MEB) Disease: *POMGNT1* Gene Sequencing

Test Code: SPOMG

Turnaround time: 4 weeks

CPT Codes: 81406 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.

Muscle-eye-brain disease (MEB) is an autosomal recessive condition that presents with generalized neonatal hypotonia and weakness, mental retardation, and ocular abnormalities. The ocular abnormalities can include glaucoma, progressive myopia, optic nerve hypoplasia, retinal hypoplasia, and juvenile cataracts. Findings can range from severe with no motor control (similar to Walker-Warburg syndrome) to mild (similar to pure CMD). Severe symptoms include decreased neonatal movements in utero, the inability to sit independently, no head control, and very poor visual control, while the milder end of the spectrum includes the ability to walk independently for several years and little visual impairment. Other symptoms can include elbow contractures, seizures, and hydrocephalus. Clinical variability can be seen within the same family.

MRI shows white matter changes early in infancy and the changes are consistent with disease severity: more severely affected individuals may show lissencephaly type II and cobblestone complex while those with milder symptoms may show flattening of the brain stem and cerebellar cysts. The disease progress for MEB is pathologically and clinically slower than that of other forms of syndromic CMD. Serum creatine kinase (CK) levels are elevated (2-15X normal) and muscle biopsy shows general dystrophic changes. Immunohistochemistry reveals a partial reduction in laminin alpha 2 (merosin) and glycosylated alpha dystroglycan.

MEB disease is caused by mutations in the *POMGNT1* gene (1p34-p33), although not all clinically affected individuals have been shown to have mutations. *POMGNT1* mutations correlate with a reduction in *POMGNT1* activity in skeletal muscle, although the type of mutation is not related to clinical severity. Mutations have been found in individuals from around the world, although the largest number of cases seems to be in Finland, where there is likely a founder mutation.

For patients with suspected MEB disease, 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=genetests&book=cmd-overview>
- Mendell, JR et al. The congenital muscular dystrophies: Recent advances and molecular insights. *Ped and Dev Pathology.* 2006; 9:427-443.

Genes

[POMGNT1](#)

Indications

This test is indicated for:

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

Methodology

PCR amplification of 21 exons contained in the *POMGNT1* 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: 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: 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: 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 *POMGNT1* 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.