### 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 \textit{POMGNT1} gene (1p34-p33), although not all clinically affected individuals have been shown to have mutations. \textit{POMGNT1} mutations correlate with a reduction in \textit{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


### Genes

\textit{POMGNT1}

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of MEB disease in an individual in whom sequence analysis was negative
- Carrier testing in adults with a family history of MEB disease 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.

Please note that a "backbone" of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

### 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
* 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**

- Sequence analysis of the POMGNT1 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.