

Walker-Warburg Syndrome: *POMT1* Gene Deletion/Duplication

Test Code: DPOM1

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.

Walker-Warburg syndrome (WWS) is the most severe of the dystroglycanopathies. Features are similar to muscle-eye-brain disease, but there is phenotypic heterogeneity. Affected individuals lack spontaneous movement at birth, have a weak cry and suck, and have generalized hypotonia and weakness. Feeding difficulties can require gavage feeding. They may have microcephaly, hydrocephalus, contractures, cleft lip and palate, seizures, genital anomalies in males, and encephalocele. Eye abnormalities can include congenital cataracts, microphthalmia, glaucoma, and iris malformations. Brain malformations can include complete lissencephaly type II with pontocerebellar hypoplasia with Dandy-Walker malformation, fusion of the hemispheres, and absence of corpus callosum. Life expectancy is often a few years.

Serum creatine kinase (CK) levels are elevated at 2-15 times normal. Histology reveals a general myopathic pattern, and immunohistochemistry shows deficiency of glycosylated alpha dystroglycan while laminin alpha 2 (merosin) levels can be normal or reduced.

WWS is an autosomal recessive disorder with genetic heterogeneity. Approximately 20% of individuals with a clinical diagnosis of WWS have mutations in the *POMT1* gene (9q34.1). Mutations have also been found in the *POMT2*, *FKTN*, *FKRP*, *POMGNT1*, and *LARGE* genes. Other as yet unidentified genes are thought to be a major cause of WWS.

Mutations in the *POMT1* gene have also been identified in individuals with a milder form of disease, limb-girdle muscular dystrophy type 2K (LGMD2K). Characteristics include mild, slowly progressive proximal weakness with difficulty climbing stairs and running, along with mild mental retardation with limited language development. Other features include hypertrophy of the calves and thighs, contractures, and microcephaly. Age of onset was approximately 1-3 years with the age at being wheelchair bound was approximately 17 years. CK levels were elevated 20-40 times normal, neuroimaging was normal, and immunohistochemistry showed decreased glycosylated alpha dystroglycan.

For patients with suspected WWS, 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

[POMT1](#)

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of Walker-Warburg syndrome in an individual in whom sequence analysis was negative
- Carrier testing in adults with a family history of Walker-Warburg syndrome 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: 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 24 hours of collection. Do not refrigerate or freeze.

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.

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 *POMT1* gene is required before deletion/duplication analysis
- Analysis of the *POMT2*, *FKTN*, *FKRP*, *POMGNT1*, and *LARGE* genes is also available.
- 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.