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 gastronomy feeding. They may have microcephaly, hydrocephalus, contractures, cleft lip and palate, seizures, genital anomalies in males, and encephalocoele. 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:

Genes

**POMT1**

Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of Walker-Warburg syndrome.
- Carrier testing in adults with a family history of Walker-Warburg syndrome.

Methodology

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient’s genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient’s gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

Detection

Clinical Sensitivity: Approximately 20% of individuals with a clinical diagnosis of WWS have mutations in the POMT1 gene. 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™ 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.

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.

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 POMT1 gene by CGH array is available for those individuals in whom sequence analysis is negative.
- Analysis of the POMT2, FKTN, FKRP, POMGNT1, and LARGE genes is also available.
- 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.