

Protein O-mannose β 1,2-N-acetylglucosaminyltransferase (*POMGNT1*) Gene Sequencing (Test #351)

**Muscle-Eye-Brain Disease (OMIM 253280)
 Walker-Warburg Syndrome (OMIM 236670)**

Brief Description of Clinical Features: Mutations in the *POMGNT1* gene cause muscular dystrophies in the dystroglycanopathy spectrum. Walker-Warburg syndrome (WWS; OMIM 236670), a severe congenital muscular dystrophy with defective neuronal migration and associated structural brain and eye abnormalities, is the most severe manifestation. Other patients with *POMGNT1* mutations present with muscle-eye-brain disease (MEB; OMIM 253280), while still others present with a severe form of Fukuyama congenital muscular dystrophy (FCMD; OMIM 253800, Godfrey et al. *Brain* 130:2725-2735, 2007).

Genetics: The dystroglycanopathies are inherited in an autosomal recessive manner. Protein O-mannose beta-1,2-N-acetylglucosaminyltransferase activity is necessary for proper post translational processing of the protein, alpha dystroglycan (ADG). In the absence of this enzyme, ADG remains hypoglycosylated and diverse pathologies follow (Barresi and Campbell *J Cell Sci* 119:199-207, 2006). Molecular diagnosis (and classification) of the dystroglycanopathy subtypes is complex because extensive locus heterogeneity exists for each disorder (Godfrey et al. *Brain* 130:2725-2735, 2007), and because the phenotypes caused by the six demonstrated and putative glycosyltransferase genes continue to expand (see for example van Reeuwijk et al. *Hum Mut* 27:453-459, 2006). Evaluation of a patient’s muscle biopsy by immunofluorescence can detect abnormal glycosylation of ADG and can, therefore, help direct a diagnostic evaluation. It should be noted that five other genes (*POMT1*, *POMT2*, *FCMD*, *FKRP*, *LARGE*) also encode proteins required for processing of ADG.

Description of This Particular Test: Testing is accomplished by amplifying all coding exons (2-22) and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

Reference Sequences: Genomic: NC_000001.9 mRNA: NM_017739.1 Protein: NP_060209.1

Indication for Testing: Individuals with symptoms consistent with WWS, MEB, or severe FCMD. Individuals with immunofluorescence results demonstrating hypoglycosylation of ADG in muscle.

Sensitivity of test: *POMGNT1* mutations were found in approximately 7% of a patient cohort with ADG hypoglycosylation in muscle (Godfrey et al. *Brain* 130:2725-2735, 2007). Clinical phenotypes included WWS, MEB-FCMD, and LGMD without mental retardation. Missense, small deletions and duplications, and nonsense mutations are distributed throughout the gene (*POMGNT1* @ www.dmd.nl). Because dystroglycanopathies exhibit extensive locus and allelic heterogeneity a negative *POMGNT1* sequence result does not rule out a diagnosis of a one of these disorders when classic clinical findings are present. If a muscle biopsy is available, immunostaining may also be an appropriate diagnostic approach.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *POMGNT1* Gene \$ 640

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x10	83898	\$170	Sequencing x10	83904	\$270
Separation	83894	\$ 50	Interpretation/Report	83912	\$ 80

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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