PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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Protein O-Mannosyltransferase 2 (*POMT2*) Gene Sequencing (Test #349)

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

Brief Description of Clinical Features: Mutations in the *POMT2* 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 (van Reeuwijk et al. *J Med Genet.* 42:907-912, 2005). Other patients with *POMT2* mutations present with muscle-eye-brain disease (MEB; OMIM 253280; Mercuri et al. *Neuromuscul Disord* 16:446-448, 2006) while still others present with congenital muscular dystrophy (CMD) (Yanagisawa et al. *Neurol* 69:1254-1260,2007) or limb girdle muscular dystrophy (LGMD) (Godfrey et al. *Brain* 130:2725-2735, 2007). Brain involvement appears to be a consistent finding in cases due to *POMT2* mutations.

Genetics: The dystroglycanopathies are inherited in an autosomal recessive manner. Protein O-mannosyltransferase 2 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 dystroglycanopthy 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). The *POMT2* p.Tyr666Cys mutation has been found repeatedly in CMD cases (Yanagisawa et al. *Neurol* 69:1254-1260 2007). Other missense, splice site and nonsense mutations are distributed throughout the gene (POMT2 @ www.dmd.nl). It should be noted that five other genes (*POMT1, POMGNT1, FCMD, FKRP, LARGE*) encode proteins required for processing of ADG.

Description of This Particular Test: Testing is accomplished by amplifying all coding exons (1-21) 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_000014.7 mRNA: NM_013382.3 Protein: NP_037514.2

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

Sensitivity of test: Mutations in *POMT2* gene have been found in ~10% of a patient cohort having clinical indications of CMD or LGMD and demonstrated hypoglycosylation of ADG in muscle (Godfrey et al. *Brain* 130:2725-2735, 2007). Because dystroglycanopathies exhibit extensive locus and allelic heterogeneity, a negative *POMT2* 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 *POMT2* Gene** **$ 990**

CPT Codes:

Sample Ascertainment	83890	$ 30	DNA Isolation	83891	$ 40
Amplification x19	83898	$300	Sequencing x19	83904	$470
Separation	83894	$ 60	Interpretation/Report	83912	$ 90

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

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