

Dystroglycan-Related Muscular Dystrophy Sequential Testing (Test #340)

Brief Description of Clinical Features: Mutations in the six known or putative glycosyltransferase genes 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 presentations include muscle-eye-brain disease (MEB; OMIM 253280), Fukuyama congenital muscular dystrophy (FCMD; OMIM 253800), and congenital or limb girdle muscular dystrophy with associated mental retardation (MR), but without structural brain abnormalities (*eg.*, LGMD2K, OMIM #609308 and CMD-MR, respectively (Godfrey et al. *Brain* 130:2725-2735, 2007). At the mild side of the spectrum is LGMD2I (OMIM #607155), which may first present in adulthood. Dystroglycanopathy may manifest as a primarily cardiomyopathy with minimal skeletal muscle involvement (Margeta et al. *Muscle Nerve* 40:883-889, 2009).

Genetics: The dystroglycanopathies are inherited in an autosomal recessive manner. Glycosyltransferase activity is necessary for proper post translational processing of alpha dystroglycan (ADG), a protein encoded by *DAG1* (OMIM #128239). In the absence of these proteins, ADG remains hypoglycosylated and diverse pathologies follow (Barresi and Campbell, *J Cell Sci* 119:199-207, 2005). Molecular diagnosis (and classification) of the dystroglycanopathy subtypes is complex because extensive genetic heterogeneity exists for each disorder (Godfrey et al. *Brain* 130:2725-2735, 2007), and because the reported phenotypes caused by the six 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, aid in a diagnostic evaluation. See also the individual gene Test Descriptions for more information.

Description of This Particular Test: Testing is accomplished by sequentially amplifying the coding exons and ~50 bp of adjacent noncoding sequence of each gene, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. The genes will be sequenced in the order specified by the client on the test Requisition Form.

Reference Sequences:

Gene:	Genomic: NC_	mRNA: NM_	Protein: NP_	mRNA and Protein: CCDS
<i>FKRP</i>	000019.8	001039885.1	001034974.1	12691.1
<i>FKTN</i>	000009.10	006731.2	006722.1	6766.1
<i>LARGE</i>	000022.9	004737.3	004728.1	13912.1
<i>POMGNT1</i>	000001.9	017739.1	060209.1	531.1
<i>POMT1</i>	000009.10	007171.2	009102.2	6943.1
<i>POMT2</i>	000014.7	013382.3	037514.2	9857.1
<i>DAG1</i>	0000003.10	004393.2	004384.2	2799.1

Indications for Testing: Individuals with symptoms consistent with any of the congenital or limb girdle muscular dystrophies. Individuals with immunofluorescence results demonstrating hypoglycosylation of ADG in muscle.

Sensitivity of test: Extensive genetic and clinical heterogeneity of the dystroglycanopathies precludes an accurate estimate of overall test sensitivity. Godfrey et al. (*Brain* 130:2725-2735, 2007) evaluated ninety-two dystroglycanopathy patients and found mutations in 34%. However, this cohort excluded *FKRP*-positive cases. In patients of Northern European ancestry with an LGMD2I phenotype, *FKRP* accounts for ~75% of all cases (Brockington et al., *Hum Mol Genetics* 10:2851-2859, 2001). A negative sequence result does not rule out a diagnosis of dystroglycanopathy when classic clinical findings are present. If a muscle biopsy is available, immunostaining may also be an appropriate diagnostic approach. This test will not detect the *FKTN* Japanese founder mutation underlying Fukuyama CMD. If FCMD is suspected in a person of Japanese heritage, a separate test procedure (Test #352) should be performed to rule-out presence of the ancestral mutation.

Turn Around Time: Maximum of 70 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequential Sequencing of: *FKRP, FKTN, LARGE, POMGnT1, POMT1, POMT2, DAG1*

CPT Codes	<i>FKRP</i>	<i>FKTN</i>	<i>LARGE</i>	<i>POMGnT1</i>	<i>POMT1</i>	<i>POMT2</i>	<i>DAG1</i>	Panel
83890	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 x1	\$ 30 x1
83891	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 x1	\$ 40 x1
83898	\$ 90 (x3)	\$160(x8)	\$230(x14)	\$170(x10)	\$310(x17)	\$300(x19)	\$190 x10	\$1,505 x81
83904	\$ 140 (x3)	\$230(x8)	\$500(x14)	\$270(x10)	\$380(x17)	\$470(x19)	\$290 x10	\$2,260 x81
83894	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 x1	\$ 250 x1
83912	\$ 60 (x1)	\$100(x1)	\$ 60 (x1)	\$ 60 (x1)	\$ 60 (x1)	\$ 60 (x1)	\$ 60 x1	\$ 190 x1
Totals:	\$ 390	\$ 590	\$ 890	\$ 640	\$ 890	\$ 990	\$ 640	\$ 4,275*

*When four or more of the genes on this panel are sequentially tested, a 15% discount will apply to the total cost.

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

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