

Congenital Disorders of Glycosylation Sequential Testing - Panel 1 (Test #540)

Brief Description of Clinical Features: Congenital disorders of glycosylation (CDG) are a genetically heterogeneous group of disorders caused by defective synthesis of asparagine (N)-linked glycans. Abnormalities in these glycoconjugates cause disturbances in metabolism, cell recognition, cell adhesion, protease resistance, host defense, cell migration, and antigenicity (Marquardt and Denecke *Eur J Pediatr* 162:359-379, 2003). Consequently, clinical presentations are characterized by multisystem involvement. Individuals with CDG Ia (OMIM #212065) have cerebellar hypoplasia, dysmorphic facies, coagulopathy, strabismus, psychomotor retardation and sometimes unusual fat distribution and inverted nipples (de Lonlay et al. *J Med Genet* 38:14-19, 2001; Sparks and Krasnewich *GeneReviews* 2005). Presentation and clinical course can be highly variable, and three stages (*infantile multisystem stage, late infantile and childhood ataxia-mental retardation stage, adult stable disability stage*) have been delineated. Individuals with CDG Ib (OMIM #602579) exhibit diarrhea, protein-losing enteropathy, profound hypoglycemia, coagulopathy, and fibrotic liver disease (Jaeken et al. *Am J Hum Genet* 62:1535-1539, 1998). Patients are not dysmorphic and do not have cerebellar hypoplasia or unusual fat distribution. CDG Ib is treatable with oral mannose (Niehues et al. *J Clin Invest* 101:1414-1420, 1998). Individuals with CDG Ic (OMIM #603147) exhibit neurological symptoms including hypotonia, developmental delay, strabismus and seizures. Clinical features of CDG Ic overlap both types Ia and Ib, however, symptoms are generally not as severe as in type Ia, and multi-organ involvement is not observed. Minimal protein-losing enteropathy and minimal liver disease of CDG Ic can often differentiate this type from CDG Ib. Cerebellar hypoplasia, a consistent finding in type Ia, is not seen in type Ic patients (Grunewald et al. *Pediat Res* 52:618-624, 2002).

Genetics: All CDGs exhibit autosomal recessive inheritance. Thirteen forms of CDG have been characterized at the molecular level but only three, CDG Ia, CDG Ib, and CDG Ic, have been reported in more than a few individual patients. CDG Ia is the most common form with ~400 cases reported worldwide, followed by CDG Ib and CDG Ic, each with approximately 20 cases. Mutations in these three genes are most commonly missense mutations, and they are distributed throughout the coding regions.

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 tested in the order specified by the client on the Requisition Form.

Reference Sequences:

Gene:	CDG:	Genomic: NC_	mRNA: NM_	Protein: NP_	mRNA & Protein: CCDS_
<i>PMM2</i>	Ia	000016.8	000303.1	000294.1	10536.1
<i>MPI</i>	Ib	000015.8	002435.1	002426.1	10272.1
<i>ALG6</i>	Ic	000001.9	013339.2	037471.2	30735.1

Indication for Testing: Individuals with clinical and biochemical findings consistent with CDG.

Sensitivity of Test: In cases with demonstrated reduced phosphomannomutase or mannosephosphate isomerase activity plus diagnostic serum transferrin glycoforms, *PMM2* and *MPI* sequencing, respectively, is nearly 100% sensitive (Sparks and Krasnewich, *GeneReviews* 2005). Due to the low incidence of CDG Ic and lack of enzyme assay, test sensitivity for *ALG6* sequencing is difficult to estimate.

Turn Around Time: Maximum of 40 days for the first gene and 10 days for each subsequent gene.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequential Sequencing of: *PMM2*, *MPI*, *ALG6*

CPT Codes	Description	<i>PMM2</i>	<i>MPI</i>	<i>ALG6</i>	Panel
83890	Ascertainment	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)
83891	DNA Isolation	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)
83898	Amplification	\$ 120 (x8)	\$ 120 (x8)	\$ 200 (x13)	\$ 440 (x29)
83904	Mutation Ident. by Sequencing	\$ 180 (x8)	\$ 180 (x8)	\$ 290 (x13)	\$ 660 (x29)
83894	Separation	\$ 40 (x1)	\$ 40 (x1)	\$ 70 (x1)	\$ 130 (x1)
83912	Interpretation and Report	\$ 80 (x1)	\$ 80 (x1)	\$ 110 (x1)	\$ 170 (x1)
Totals:		\$ 490*	\$ 490*	\$ 740*	\$1,470

*When two or more of the genes in 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)

Contact for info: Thomas L. Winder, PhD, FACMG, tom.winder@preventiongenetics.com, www.preventiongenetics.com