

Congenital Disorders of Glycosylation, Type Ig (CDG Ig) via *ALG12* Gene Sequencing (Test #534)

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 result in disturbed 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. The first reported case of CDG Ig (OMIM #607143) presented with poor suck and was found to have progressive microcephaly, severe psychomotor involvement, severe hypotonia, and dysmorphic facies (Chantret et al. *J Biol Chem* 277:25815-25822, 2002). The patient developed frequent ear, nose, throat, and respiratory infections and was found to have low IgG levels. A small number of additional patients with like presentations have been described (Grubenmann et al. *Hum Mol Genet* 11:2331-2339, 2002; Eklund et al. *Mol Genet Metab* 84:25-31, 2005; Thiel et al. *Biochem J* 367:195-201, 2002). Additional clinical findings in CDG Ig patients include genital hypoplasia (Eklund et al. 2005), and convulsions (Thiel et al. 2002). Fibroblasts from CDG Ig patients accumulate the intermediate oligosaccharide Man₇ GlcNAc₂-PP-Dol (Thiel et al. 2002; Chantret et al. 2002; Grubenmann et al. 2002).

Genetics: 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 small number of 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 reported. The *ALG12* gene (OMIM #607144) encodes a mannosyltransferase that catalyzes the transfer of the eighth mannose to a lipid linked oligosaccharide precursor. Missense and nonsense mutations are thus far the only reported mutation types.

Description of This Particular Test: Dolichyl-P-Man:Man₇GlcNAc₂-dolichyl mannosyltransferase is encoded by exons 2 – 10 of the *ALG12* gene on chr 22q13. Testing is accomplished by amplifying all coding exons and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and capillary electrophoresis.

Reference Sequences: **Genomic:** NC_000022.9 **mRNA and Protein:** CCDS 14081.1

Indication for Testing: Individuals with clinical symptoms consistent with CDG Ig. Individuals with demonstrated dolichyl-P-Man:Man₇GlcNAc₂-dolichyl mannosyltransferase deficiency and accumulation of Man₇ GlcNAc₂-PP-Dol.

Sensitivity of Test: Due to the low incidence of this disorder clinical sensitivity cannot be estimated.

Turn Around Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See bottom of page 2 of Requisition Form.

Price: **Sequencing of the *ALG12* Gene** **\$ 590**

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x9	83898	\$ 160	Sequencing x9	83904	\$ 230
Separation x1	83894	\$ 50	Interpretation/Report x1	83912	\$ 80

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/11) (CAP#: 7185561, AU ID: 1407125 expires 12/20/10)

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