

## Congenital Disorders of Glycosylation, Type Ic (CDG Ic) via *ALG6* Gene Sequencing (Test # 533)

**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 Pediat* 162:359-379, 2003). Consequently, clinical presentations are characterized by multisystem involvement. 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 CDG type Ia, is not seen in CDG Ic patients and can help clarify a diagnosis on clinical grounds alone (see review by 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 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 *ALG6* gene (OMIM 604566) encodes a glucosyltransferase that catalyzes the addition of the first glucose residue to lipid-linked oligosaccharide precursors. Mutations in *MPI* are distributed throughout the coding region. Missense mutations are the most common type observed.

**Description of This Particular Test:** Man(9)GlcNAc(2)-PP-Dol alpha-1,3-glucosyltransferase is encoded by exons 2 – 15 of the *ALG6* gene on chr 1p22. 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\_000001.9      mRNA: NM\_013339.2      Protein: NP\_037471.2

**Indication for Testing:** Individuals with clinical symptoms consistent with CDG Ic. Individuals with diagnostic serum transferrin isoform results (decreased tetrasialotransferrin and increased asialotransferrin and disialotransferrin).

**Sensitivity of Test:** Due to the low incidence of this disorder and lack of enzyme assay, molecular test sensitivity is difficult to estimate. A common mutation (p.Ala333Val) was found in the homozygous state in eight of eleven CDG Ic patients and other mutations were identified in the remaining three patients (Imbach et al. *Proc Nat Acad Sci* 96:6982-6987, 1999; Imbach et al. *Hum Genet* 106:538-545, 2000). Another recurring mutation is the c.167+5 G>A splice site mutation (Westphal et al. *Mol Genet Metab* 70:219-223, 2000).

**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 *ALG6* Gene**    **\$ 740**

**CPT Codes:**

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x13	83898	\$ 200	Sequencing x13	83904	\$ 290
Separation	83894	\$ 70	Interpretation/Report	83912	\$ 110

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