

Congenital Disorders of Glycosylation, Type Id (CDG Id) via *ALG3* Gene Sequencing (Test # 539)

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. The first reported case of CDG Id (OMIM #601110) exhibited microcephaly, severe epilepsy, minimal psychomotor development, and partial deficiency of sialic acids in serum glycoproteins (Körner et al. *EMBOJ* 18:6816-6822, 1999). A second case presented with arthrogryposis multiplex present at birth, clubfeet and contractures of the hands, dysmorphic facies including epicanthus, strabismus, and broad, flat nasal bridge, and severe visual impairment (Denecke et al. *Pediat Res* 58:248-253, 2005). A third case was remarkable for hyperinsulinemic hypoglycemia secondary to islet cell hyperplasia, Dandy-Walker malformation, dysmorphic facies, and profound hypotonia (Sun et al. *J Clin Endocrin* 90:4371-4375, 2005).

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 *ALG3* gene (OMIM #608750) encodes a mannosyltransferase that catalyzes the transfer of mannose from dolichyl-phosphate mannose to a lipid linked oligosaccharide intermediate. Missense mutations and a silent exonic mutation that activates a cryptic splice site are thus far the only reported mutation types. Segmental uniparental isodisomy, in combination with a *de novo* missense mutation, was found to be the etiology of CDG Id in one patient (Schollen et al. *Eur J Med Genet* 48:153-158, 2005).

Description of This Particular Test: Dolichyl-P-Man:Man₅GlcNAc₂-PP-dolichyl mannosyltransferase is encoded by exons 1 – 9 of the *ALG3* gene on chr 3q27. 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_000003.10 mRNA: NM_005787.4 Protein: NP_005778.1

Indication for Testing: Individuals with clinical symptoms consistent with CDG Id. Individuals with disialylated transferrin isoform apparently smaller than control serum transferrin (Körner et al. 1999).

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 page 4 of Requisition Form.

Price: **Sequencing of the *ALG3* 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 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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