

Congenital Disorders of Glycosylation, Type Ii (CDG Ii) via *ALG2* Gene Sequencing (Test #536)

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 only reported case of CDG Ii (OMIM #607906) presented at 2 months of age after an uneventful pregnancy (Thiel et al *J. Biol. Chem.* 278:22498-22505, 2003). The first noted symptoms were bilateral colobomas of the iris and unilateral cataract. Vision was determined to be affected and irregular nystagmus was often present. At 4 months of age a seizure disorder presented with infantile spasms. Imaging at 5 months of age revealed severe hypomyelination, and three months later follow up studies showed a markedly reduced volume of white matter. Consequently, mental and motor development were both severely delayed. Non CNS findings included borderline hepatomegaly and coagulopathy. Western blot of serum transferrin showed a typical CDG I pattern and further studies revealed accumulation of Man₁GlcNAc₂ and Man₂GlcNAc₂ lipid-linked oligosaccharide in the patient’s fibroblasts. The patient was found to have compound heterozygous mutations in the *ALG2* gene that could be compensated in a cell-based assay with wild type *ALG2* gene product.

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 *ALG2* gene (OMIM #607905) encodes a mannosyltransferase that functions at the cytosolic side of the endoplasmic reticulum to transfer mannosyl residues from GDP-Man to Man₁GlcNAc₂-PP-dolichol (Theil et al. 2003). The one reported CDG Ii patient was found to be compound heterozygous for *ALG2* missense and frame shift mutations.

Description of This Particular Test: GDP-Man:Man₁GlcNAc₂-PP-dolichol mannosyltransferase is encoded by exons 1 – 2 of the *ALG2* gene on chr 9q22. 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_000009.1 **mRNA and Protein:** CCDS 6739.1

Indication for Testing: Individuals with symptoms consistent CDG Ii along with accumulation of excess Man₁GlcNAc₂ and Man₂GlcNAc₂ lipid-linked oligosaccharide in cultured fibroblasts.

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 *ALG2* Gene** **\$ 470**

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x5	83898 \$ 120	Sequencing x5	83904 \$ 170
Separation x1	83894 \$ 40	Interpretation/Report x1	83912 \$ 70

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

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