

Congenital Disorders of Glycosylation, Type 1h (CDG 1h) via *ALG8* Gene Sequencing (Test # 537)

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 1h (OMIM #608104) demonstrated gastrointestinal symptoms but no complications involving the central nervous system (Chantret et al. *J Biol Chem* 278:9962-9971, 2003). At 4 months of age the patient was found to have severe hypoalbuminemia resulting from protein losing enteropathy, severe diarrhea and moderate hepatomegaly. She had normal psychomotor development and no dysmorphic features. Western blot of serum transferrin showed a typical CDG I pattern and further studies revealed accumulation of Man₉GlcNAc₂ lipid-linked oligosaccharide in the patient's fibroblasts. Three additional CDG 1h patients from two families were reported with severe, life-threatening GI symptoms whose central nervous systems were also spared (Schollen et al. *J Med Genet* 41:550-556, 2004). One patient was affected with IUGR, oligohydramnios, and reduced fetal movement in utero. After birth the patient failed to thrive and developed diarrhea, vomiting and massive abdominal ascites. Based on clinical exam and imaging, there was no evidence of CNS involvement. This patient's sibling presented similarly. The third patient of this series presented after birth with cardio respiratory symptoms secondary to thorax and lung hypoplasia. This child was found to have dysmorphic features including asymmetric skull, wide fontanel, hypertelorism, low set and abnormally positioned ears, long philtrum, short neck, cryptorchism, camptodactyly and talipes equinovarus. Each patient in both studies was found to have compound heterozygous mutations in the *ALG8* gene that could be compensated in patient cell-based assays with wild type *ALG8* 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 1b and CDG Ic, each with approximately 20 cases reported. The *ALG8* gene (OMIM #608103) encodes a protein required for the addition of the second glucose residue onto lipid-linked oligosaccharides (Chantret et al. 2003). Missense, splicing, and a single base deletion and insertion are thus far the mutation types reported for *ALG8*.

Description of This Particular Test: Dolichyl-P-glucose:Glc-1-Man-9-GlcNAc-2-PP-dolichyl-alpha-3-glucosyltransferase is encoded by exons 1 – 13 of the *ALG8* gene on chr 11pter-p15.5. 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_000011.8 **mRNA and Protein:** CCDS 8258.1

Indication for Testing: Individuals with mild to severe GI symptoms but absent CNS symptoms along with accumulation of excess Man₉GlcNAc₂ and, to a lesser extent, Glc₁Man₉GlcNAc₂ 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 <i>ALG8</i> Gene	\$ 790
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x13	83898 \$ 220	Sequencing x13 83904 \$ 340
Separation x1	83894 \$ 70	Interpretation/Report x1 83912 \$ 90

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