

Congenital Disorders of Glycosylation, Type If (CDG If) via *MPDU1* Gene Sequencing (Test # 538)

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 If (OMIM #609180) demonstrated major symptoms of severe psychomotor retardation, seizures, failure to thrive, dry and scaling skin, and impaired vision (Kranz et al. *J Clin Invest* 108:1613-1619, 2001). At birth the patient was hypotonic and had contractures. At 3 months of age nystagmus and lack of visual fixation were noted. At 5 months of age seizures began and continued frequently, and MRI scans revealed cerebral atrophy. The patient's skin was dry, hyperkeratotic and scaling. At 3-4 years of age GI symptoms included decreased food intake, abdominal pain, and frequent vomiting. At 5 years of age ataxia and profound psychomotor retardation were noted. At ten years of age the child could sit independently but walk only with support. Cultured fibroblasts from this patient accumulated excess Man₉GlcNAc₂ and Man₃GlcNAc₂ compared with control cells. Three additional unrelated CDG If patients have been reported (Schenk et al. *J Clin Invest* 108:1687-1695, 2001). Two of the patients had intractable seizures, profound psychomotor retardation, skin findings, and feeding problems. The third patient was affected with psychomotor retardation but had no skin or growth involvement. Seizures were present but controlled with medication. Cultured fibroblasts from these patients were found to have excess Man₉GlcNAc₂ and minor peaks of Man₈GlcNAc₂, Man₇GlcNAc₂, and Glc₁Man₉GlcNAc₂. Each patient in both studies was found to have homozygous or compound heterozygous mutations in the *MPDU1* gene.

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 *MPDU1* gene (OMIM #604041) encodes a protein required for efficient use of dolichol-P-mannose, termed 'mannose phosphate dolichol utilization defect 1'. CDG If is unique among the CDGs because its cause is inefficient use, not defective biosynthesis of donor substrates for lipid linked oligosaccharides. *MPDU1* missense mutations and a single base deletion are thus far reported.

Description of This Particular Test: The *MPDU1* protein is encoded by exons 1 – 7 of the *MPDU1* gene on chr 17p13. 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_000017.9 **mRNA and Protein:** CCDS 11115.1

Indication for Testing: Individuals with clinical symptoms consistent with CDG If and accumulation of excess Man₉GlcNAc₂ 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 the Requisition Form.

Price: **Sequencing of the *MPDU1* Gene** **\$ 540**

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x7	83898 \$ 140	Sequencing x7	83904 \$ 210
Separation x1	83894 \$ 40	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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