

## Congenital Disorders of Glycosylation Panel: Sequencing and CNV Analysis

**Test Code:** MCDG1

**Turnaround time:** 6 weeks

**CPT Codes:** 81406 x1, 81404 x1, 81405 x1

### Condition Description

Congenital disorders of glycosylation (CDG) are a group of autosomal recessive genetic disorders caused by the alteration in synthesis and structure of protein and lipid glycosylation. In the past decade, over 30 genetic diseases have been identified that alter glycan synthesis, structure and ultimately the function of nearly all organ systems.

CDG type I (CDGI) disorders result from impaired synthesis of the incomplete lipid linked oligosaccharide (LLO) and/or its attachment to the growing polypeptide chain. CDG-Ia is the most common form reported, due to phosphomannomutase deficiency, an enzyme that converts mannose-6-phosphate to mannose-1-phosphate. CDG-Ib (phosphomannose isomerase, MPI deficiency) is the only known treatable form, by giving mannose orally. CDG type II (CDGII) includes defects in processing of N-glycans.

Phenotypes of this disorder are extremely variable. Manifestations range from severe developmental delay and hypotonia with multiple organ system involvement beginning in infancy, to hypoglycemia and protein-losing enteropathy with normal development. Most subtypes have been described in only a few individuals, however, thus understanding of the phenotypes is limited.

The current diagnostic test for CDG is analysis of serum transferrin glycoforms, also called "transferrin isoforms analysis", or "carbohydrate-deficient transferrin analysis." If positive, this testing can be followed by DNA testing to identify mutations in the gene involved. If a sample is not available for biochemical testing or if biochemical test results are inconclusive, this panel offers next generation sequence of CDG-associated genes.

Note: This test does not detect the retrotransposon insertion in the 3' UTR of the *FKTN* gene common in some Asian populations. For patients with suspected Fukuyama congenital muscular dystrophy, testing for the *FKTN* insertion is recommended. Analysis for the *FKTN* insertion is available as a separate assay.

#### References:

- Freeze HH. Congenital disorders of glycosylation: CDG-I, CDG-II, and beyond. *Curr Mol Med* 2007; 7:389-396.
- [GeneTests: Congenital Disorders of Glycosylation Overview](#)
- Jaeken J, Matthijs G. Congenital disorders of glycosylation: A rapidly expanding disease family. *Annu Rev Genomics Hum Genet* 2007; 8:261-278.

### Genes

[ALG1](#), [ALG11](#), [ALG12](#), [ALG13](#), [ALG14](#), [ALG2](#), [ALG3](#), [ALG6](#), [ALG8](#), [ALG9](#), [ATP6V0A2](#), [B3GAT3](#), [B3GLCT](#), [B4GALT1](#), [B4GALT7](#), [CHST14](#), [CHST3](#), [CHST6](#), [CHSY1](#), [COG1](#), [COG4](#), [COG5](#), [COG6](#), [COG7](#), [COG8](#), [DDOST](#), [DHDDS](#), [DOLK](#), [DPAGT1](#), [DPM1](#), [DPM3](#), [EXT1](#), [EXT2](#), [FKRP](#), [FKTN](#), [GALNT3](#), [GFPT1](#), [GNE](#), [LARGE1](#), [LFNG](#), [MAN1B1](#), [MGAT2](#), [MOGS](#), [MPDU1](#), [MPI](#), [NGLY1](#), [PGM1](#), [PIGA](#), [PIGL](#), [PIGM](#), [PIGO](#), [PIGV](#), [PMM2](#), [POMGNT1](#), [POMT1](#), [POMT2](#), [RFT1](#), [SEC23B](#), [SLC35A1](#), [SLC35C1](#), [SLC35D1](#), [SRD5A3](#), [ST3GAL3](#), [ST3GAL5](#), [TMEM165](#), [TUSC3](#)

### Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of a CDG, or when CDG is suspected and biochemical results are unavailable or inconclusive.
- Carrier testing in adults with a family history of a CDG.

### Methodology

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Copy Number Analysis:** Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

### Detection

**Next Generation Sequencing:** Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical sensitivity for sequence variant detection is ~99%.

**Copy Number Analysis:** The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (< 500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

## Specimen Requirements

*Submit only 1 of the following specimen types*

### Type: DNA, Isolated

**Specimen Requirements:**

Microtainer

15µg

Isolation using the Perkin Elmer™ Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

### Type: Saliva

**Specimen Requirements:**

Oragene™ Saliva Collection Kit

Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

**Specimen Collection and Shipping:**

Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

### Type: Whole Blood (EDTA)

**Specimen Requirements:**

EDTA (Purple Top)

Infants and Young Children ( 2 years of age to 10 years old: 3-5 ml

Older Children & Adults: 5-10 ml

Autopsy: 2-3 ml unclotted cord or cardiac blood

**Specimen Collection and Shipping:**

Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

## Special Instructions

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

## Related Tests

- Individual sequence analysis and deletion/duplication analysis is available for each of the genes in the panel.
- Congenital Disorders of Glycosylation: Deletion/Duplication Panel.
- Biochemical testing for CDGs is available. See the test menu for details.
- [Custom diagnostic mutation analysis \(KM\)](#) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to adult couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.