Condition Description

Congenital disorders of glycosylation (CDG) are a group of mostly 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 isofoms analysis", or "carbohydrate-deficient transferrin analysis." If positive, this testing can be followed by DNA testing to identify mutations in the gene involved.

Timal et al. (2012) identified a hemizygous de novo pathogenic variant in the ALG13 gene (Xq23) in an individual with CDG-Ia. His features included epilepsy, hepatomegaly, recurrent infections, swelling, microcephaly, and bilateral optic nerve atrophy. The same pathogenic variant, also de novo, was identified by the Epi4K Consortium in an unrelated female with seizures and severe intellectual disability.

References:
- OMIM #300776: ALG13 gene
- OMIM #300884: CDG-Ia

Genes

ALG13

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of CDG-Ia.
- Carrier testing in adults with a family history of CDG-Ia.

Methodology

PCR amplification of 4 exons contained in the ALG13 gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dyeoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

Detection

Clinical Sensitivity: Unknown. Pathogenic variants in the promoter region, some pathogenic variants in the introns and other regulatory element pathogenic variants cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%

Specimen Requirements

Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

OrageneTM Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

### 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 EGL Genetics, please submit a copy of the sequencing report with the test requisition.

### Related Tests

- Deletion/duplication analysis of the **ALG13** gene by CGH array is available for those individuals in whom sequence analysis is negative.
- Analysis of other CDG genes is also available.
- Biochemical carbohydrate deficient transferrin analysis for CDGs is also available.
- 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.