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 isosforms analysis", or "carbohydrate-deficient transferrin analysis." If positive, this testing can be followed by DNA testing to identify mutations in the gene involved.

Two children have been reported with CDG IL. Both had microcephaly, hypotonia, developmental delay, seizures, and hepatomegaly. One individual also had failure to thrive, strabismus, inverted nipples, pericardial effusion, and renal cysts.

Both individuals were found to have mutations in the ALG9 gene (11q23).

For patients with suspected CDG IL, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

References:


Genes

ALG9

Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of CDG IL
- Carrier testing in adults with a family history of CDG IL

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.

Detection

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations 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 biochemical phenotype.

Analytical Sensitivity: ~99%
Specimen Requirements

Submit only 1 of the following specimen types

Type: DNA, Isolated

Specimen Requirements:
- Microtainer
- 8µg
- Isolation using the Perkin Elmer™ 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: 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 24 hours of collection. Do not refrigerate or freeze.

Type: Saliva

Specimen Requirements:
- Oralene™ Saliva Collection Kit
  - Oralene™ 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.

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 ALG9 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.