Congenital Disorder of Glycosylation Ia: **PMM2 Gene Deletion/Duplication**

**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.

The typical clinical course of CDG Ia has been divided into an infantile multisystem stage, late-infantile and childhood ataxia-mental retardation stage, and adult stable disability stage. Recent reports have widened the phenotypic spectrum to include hydrops fetalis at the severe end and a mild neurologic phenotype in adults with multisystemic involvement at the mild end. Clinical presentation and course are highly variable, ranging from infants who die in the first year of life to mildly involved adults. Clinical presentations do, however, tend to be similar in siblings.

Because the presentation of this disorder is highly variable, the diagnosis should be considered in a child with developmental delay and hypotonia in combination with any of the following findings:

- Failure to thrive
- Hepatic dysfunction (elevated transaminases)
- Coagulopathy with low serum concentration of factors IX and XI, antithrombin, protein C, and/or protein S
- Hypothyroidism, hypogonadism
- Esotropia
- Pericardial effusion
- Abnormal subcutaneous fat pattern including increased suprapubic fat pad, skin dimpling, and inverted nipples or subcutaneous fat pads having a toughened, puffy, or uneven consistency
- Seizures
- Stroke-like episodes
- Osteopenia, scoliosis
- Cerebellar hypoplasia/atrophy and small brain stem

The diagnosis of CDG Ia should be considered in adolescents or adults with suggestive histories and any of the following findings:

- Cerebellar dysfunction (ataxia, dysarthria, dysmetria)
- Non-progressive cognitive impairment
- Stroke-like episodes
- Peripheral neuropathy with or without muscle wasting
- Absent puberty in females, small testes in males
- Retinitis pigmentosa
- Progressive scoliosis with truncal shortening
- Joint contractures

Confirmation of the diagnosis in a proband requires molecular genetic testing following the finding of a type I transferrin isoform pattern. Individuals with the clinical diagnosis of CDG Ia and biochemical diagnosis of PMM enzyme deficiency with normal transferrin glycosylation, however, have been reported. Mutations in the **PMM2** gene (16p13.3-p13.2) cause CDG Ia, and in individuals with enzymatically proven CDG Ia, the mutation detection rate in **PMM2** approaches 100%. The prevalence of CDG Ia could be as high as 1:20,000.

For patients with suspected CDG Ia, 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

PMM2

Indications

This test is indicated for:

- Individuals with a clinical/biochemical diagnosis consistent with CDG Ia in whom sequence analysis was negative.
- Carrier testing in individuals with a family history of CDG Ia in whom sequence analysis was negative.

Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

Detection

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) or ACD (yellow 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:

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

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

Special Instructions

Please submit copies of diagnostic biochemical test results along with the sample. 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

- Sequence analysis of the PMM2 gene is available and is required before deletion/duplication analysis.
- 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.