### 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.

Mutations in the \( \text{SRD5A3} \) gene (4q12) have been identified in individuals with intellectual disability and ophthalmologic and cerebellar defects, with transferrin N-glycosylation profiles indicative of a type I congenital disorder of glycosylation (CDG). Characteristics of affected individuals included congenital eye malformations with variable degree of visual loss, nystagmus, muscle hypotonia, motor delay, intellectual disability, and facial dysmorphism. Other features present included microcytic anemia, elevated liver enzymes, coagulation abnormalities, and decreased antithrombin III levels. Common presenting features were ocular coloboma or hypoplasia of the optic disk with cerebellar atrophy or vermis malformation. Sporadic features included ichthyosiform erythroderma, dry skin, and congenital heart malformations.

\( \text{SRD5A3} \) mutations were identified in 7 of 40 individuals with CDG type Ix (CDG type I negative for known gene mutations). \( \text{SRD5A3} \)-related CDG is inherited in an autosomal recessive manner. The protein product of the \( \text{SRD5A3} \) gene is necessary for the synthesis of the oligosaccharide precursor used for N-glycosylation.

### References:
- Cantagrel et al. (2010). \( \text{SRD5A3} \) is required for converting polyisoprenol to dolichol and is mutated in a congenital glycosylation disorder. Cell 142: 203.

### Genes

\( \text{SRD5A3} \)

### Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of \( \text{SRD5A3} \)-Related Congenital Disorder of Glycosylation.
- Carrier testing in adults with a family history of \( \text{SRD5A3} \)-Related Congenital Disorder of Glycosylation.

### Methodology

PCR amplification of 5 exons contained in the \( \text{SRD5A3} \) 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 dideoxy 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. 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

Disclaimer: This information is confidential and subject to change without notice. It may not be reproduced in whole or part unless authorized in writing by an authorized EGL representative.
* Preferred specimen type: Whole Blood

**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:

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**

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

**Related Tests**

- 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 only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.