Test Definition: CDG
Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum

Overview

Useful For
Screening for congenital disorders of glycosylation

This test is not useful for screening patients for chronic alcohol abuse.

Genetics Test Information
This testing is used to screen patients for suspected congenital disorders of glycosylation (N- and O-glycosylation defects as well as glycan structure analysis).

Congenital disorders of glycosylation (CDG) encompass over 150 genetic conditions spanning a broad clinical spectrum.

The main CDG profiles that can be identified by this analysis are type I, some type II, and mixed type CDG.

Testing Algorithm
Suggested Testing Strategy:

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Target</th>
<th>Mayo Test ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-glycan, core 1 mucin type O-glycosylation, and conserved oligomeric Golgi (COG) complex defects</td>
<td>Transferrin, apolipoprotein CIII</td>
<td>CDG / Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum</td>
</tr>
<tr>
<td>N-glycan, core 1 mucin type O-glycosylation, and COG complex defects</td>
<td>Serum total N-linked glycans, transferrin, and apolipoprotein CIII</td>
<td>CDGN / Congenital Disorders of N-Glycosylation, Serum (includes test ID CDG) Stepwise analysis of transferrin, apolipoprotein CIII, and serum total N-glycans</td>
</tr>
<tr>
<td>alpha-Dystroglycanopathies</td>
<td>Genes: DAG1, FKRP, FKTN, ISPD, LARGE1, POMGNT1, POMGNT2, POMT1, POMT2</td>
<td>CDGGP / Congenital Disorders of Glycosylation Gene Panel, Varies</td>
</tr>
</tbody>
</table>

For more information, see Epilepsy: Unexplained Refractory and/or Familial Testing Algorithm.

Special Instructions
- Biochemical Genetics Patient Information
- Epilepsy: Unexplained Refractory and/or Familial Testing Algorithm
- Transferrin and Apolipoprotein-CIII Isoform Analysis
Test Definition: CDG
Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum

Method Name
Affinity Chromatography-Mass Spectrometry (MS)

NY State Available
Yes

Specimen

Specimen Type
Serum

Ordering Guidance
This test is for congenital disorders of glycosylation. If the ordering provider is looking for evaluation of alcohol abuse, order CDTA / Carbohydrate Deficient Transferrin, Adult, Serum.

If either PMM2-CDG (CDG-Ia) or MPI-CDG (CDG-Ib) is suspected, order PMMIL / Phosphomannomutase and Phosphomannose Isomerase, Leukocytes.

Necessary Information
1. Patient's age is required.
2. Reason for testing is required.

Specimen Required
Collection Container/Tube:
Preferred: Red top
Acceptable: Serum gel
Submission Container/Tube: Plastic vial
Specimen Volume: 0.1 mL

Forms
1. Biochemical Genetics Patient Information (T602)
2. If not ordering electronically, complete, print, and send a Biochemical Genetics Test Request (T798) with the specimen.

Specimen Minimum Volume
0.05 mL

Reject Due To

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Gross hemolysis</td>
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</tr>
<tr>
<td>Gross lipemia</td>
<td></td>
</tr>
<tr>
<td>Gross icterus</td>
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</table>
Test Definition: CDG
Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum

**Specimen Stability Information**

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
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<tbody>
<tr>
<td>Serum</td>
<td>Frozen (preferred)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Refrigerated</td>
<td>28 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ambient</td>
<td>7 days</td>
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**Clinical & Interpretive**

**Clinical Information**

Glycosylation is the post-translational modification of proteins and lipids by the addition of glycans (sugars and sugar chains) in a complex stepwise fashion in the endoplasmic reticulum, Golgi apparatus, cytosol and sarcosomall membrane. Congenital disorders of glycosylation (CDG) are a group of over 150 inherited metabolic disorders characterized by abnormal protein and lipid glycosylation. There are 2 main groups of CDG: type I, characterized by defects in the assembly or transfer of the dolichol-linked glycan in either the cytosol or endoplasmic reticulum (ER) and type II, involving processing defects of the glycan in the ER and Golgi apparatus. In addition, there are 2 categories of glycosylation: N-glycosylation where N-linked glycans are attached to a protein backbone via an asparagine residue on the protein, and O-glycosylation where O-glycans are attached to the hydroxyl group of threonine or serine. Apolipoprotein CIII (Apo-CIII) isoforms, with a single core 1 mucin type O-glycosylate protein, is a complementary evaluation for the CDG type II profile. This analysis will evaluate mucin type O-glycosylation, a defect involving the Golgi apparatus, which is detected biochemically by the change in ratios of the 3 isoforms.

CDG typically present as multi-systemic disorders with a broad clinical spectrum including, but not limited to, developmental delay, hypotonia, with or without neurological abnormalities, abnormal magnetic resonance imaging findings, skin manifestations, and coagulopathy. There is considerable variation in the severity of this group of diseases ranging from a mild presentation in adults and children to severe multi-organ dysfunctions causing infantile lethality. In some subtypes, phosphomannose isomerase-CDG (MPI-CDG or CDG-Ib) in particular, intelligence is not compromised. CDG should be suspected in all patients with neurological abnormalities including developmental delay and seizures, brain abnormalities such as cerebellar atrophy or hypoplasia as well as unexplained liver dysfunction. Abnormal subcutaneous fat distribution and chronic diarrhea each may or may not be present. The differential diagnosis of abnormal transferrin patterns also includes liver disease not related to CDG including galactosemia, hereditary fructose intolerance in acute crisis, and liver disease of unexplained etiology.

Transferrin and apolipoprotein CIII isoform analysis are the initial screening tests for CDG. The results of the transferrin and apolipoprotein CIII isoform analysis should be correlated with the clinical presentation to determine the most appropriate follow-up testing strategy including enzyme, molecular, and research-based testing. Enzymatic analysis for phosphomannomutase and phosphomannose isomerase in leukocytes (PMMIL / Phosphomannomutase and Phosphomannose Isomerase, Leukocytes) should be performed if either PMM2-CDG (CDG-Ia) or MPI-CDG (CDG-Ib) is suspected.

Other glycosylation pathways, in addition to N- and O-glycosylation, have been elucidated, in particular, glycoprophosphatidylinositol (GPI)-anchored protein glycosylation disorders in which there is absent or decreased expression of all the GPI-linked antigens, and alpha-dystroglycanopathies caused by impaired synthesis of O-mannose
glycans. Neither class of disorders are routinely picked up by CDG analysis in serum but are typically diagnosed using molecular methods (CDGGP / Congenital Disorders of Glycosylation Gene Panel, Varies).

**Reference Values**

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<th>Ratio</th>
<th>Normal</th>
<th>Indeterminate</th>
<th>Abnormal</th>
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<tbody>
<tr>
<td>Transferrin mono-oligo/di-oligo ratio</td>
<td>$\leq 0.06$</td>
<td>0.07-0.09</td>
<td>$&gt; = 0.10$</td>
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<tr>
<td>Transferrin A-oligo/di-oligo ratio</td>
<td>$\leq 0.011$</td>
<td>0.012-0.021</td>
<td>$&gt; = 0.022$</td>
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<tr>
<td>Transferrin tri-sialo/di-oligo ratio</td>
<td>$\leq 0.05$</td>
<td>0.06-0.12</td>
<td>$&gt; = 0.13$</td>
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<tr>
<td>Apo CIII-1/Apo CIII-2 ratio</td>
<td>$\leq 2.91$</td>
<td>2.92-3.68</td>
<td>$&gt; = 3.69$</td>
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<td>Apo CIII-0/Apo CIII-2 ratio</td>
<td>$\leq 0.48$</td>
<td>0.49-0.68</td>
<td>$&gt; = 0.69$</td>
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**Interpretation**

Positive test results could be due to a genetic or nongenetic condition; additional confirmatory testing is required.

In serum, the bi-antennary transferrin (di-oligo) fraction is the most abundant transferrin isoform. Congenital disorders of glycosylation (CDG)-I generally show increases in mono-oligo- and/or a-oligo transferrin isoforms whereas CDG-II shows elevated increased transferrin with truncated glycans of varying degree depending on the type of defect.(1)

Results are reported as the mono-oligosaccharide/di-oligosaccharide transferrin ratio, the a-oligosaccharide/di-oligosaccharide transferrin ratio, the tri-sialo/di-oligosaccharide transferrin ratio, and the apolipoprotein CIII-1/apolipoprotein CIII-2 ratio, and the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio. The report will include the quantitative results and an interpretation.

The congenital disorders of glycosylation (CDG) profiles are categorized into 5 types:

1. CDG type I profile. Mono-oligosaccharide/di-oligosaccharide transferrin ratio and/or the a-oligosaccharide/di-oligosaccharide transferrin ratio are abnormal. This group should have the apolipoprotein C-III profile within the normal ranges, because the Golgi system is not affected in CDG type I.

2. CDG type II profile. The tri-sialo/di-oligosaccharide transferrin ratio is abnormal. In this category, the apolipoprotein C-III profile will have 2 scenarios:
   A. The apolipoprotein CIII-1/apolipoprotein CIII-2 ratio and/or the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio will be abnormal. In this case, the defect is most likely glycan processing in the Golgi apparatus; therefore, a CDG (conserved oligomeric Golgi [COG]) defect or defect that alters the Golgi apparatus is likely.
   B. The apolipoprotein CIII-1/apolipoprotein CIII-2 ratio and/or the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio are normal. In this case, the defects most likely do not involve the Golgi system, thus the molecular defect is different.

3. CDG mixed type profile (type I and II together). In this type of profile one can have abnormal tri-sialo/di-oligosaccharide transferrin ratio with the mono-oligosaccharide/di-oligosaccharide transferrin ratio and/or the a-oligosaccharide/di-oligosaccharide transferrin ratio abnormal and may have the apolipoprotein CIII-1/apolipoprotein CIII-2 ratio and the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio normal or abnormal, depending on if the defects involve Golgi apparatus.

4. CDG with normal transferrin and apolipoprotein profile. Some CDG (eg, PGM3, some ALG13, MOGS, NGLY1, SLC35C1, Fut8) pose a problem for their detection. Thus, a careful medical history, physical exam, and analysis of other protein
status may be informative for general protein glycosylation defects. If suspicious for either NGLY1- or MOGS-CDG, specific oligosaccharides in urine can be detected (OLIGU / Oligosaccharide Screen, Random, Urine).

5. When the profile cannot be categorized following the above classification, the abnormalities will be reported descriptively according to the molecular mass of the glycan isoform structures.

Reports of abnormal results will include recommendations for additional biochemical and molecular genetic studies to identify the correct form of CDG more precisely. If applicable, treatment options, the name and telephone number of contacts who may provide studies, and a telephone number for one of the laboratory directors (if the referring physician has additional questions) will be provided.

For more information, see Transferrin and Lipoprotein-CIII Isoform Analysis.

Cautions
Other conditions such as acute crisis of hereditary fructose intolerance, galactosemia, substance abuse, and acute liver disease may have a congenital disorders of glycosylation (CDG) profile that is indistinguishable from any other true CDG type I cases. Relevant clinical information and the indication for the analysis should be provided with the specimen.

Transferrin glycosylation patterns may normalize so repeat testing is warranted in patients with significant clinical suspicion.

Clinical Reference

Performance

Method Description
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Serum is diluted with water and then subjected to online immunoaffinity chromatography coupled to a quadrupole time-of-flight mass spectrometer. Relative quantitation of carbohydrate deficient transferrin and apolipoprotein CIII is achieved by comparing glycoform ratios in each protein. (Unpublished Mayo method).

PDF Report
No

Day(s) Performed
Monday, Thursday

Report Available
3 to 6 days

Specimen Retention Time
1 month

Performing Laboratory Location
Rochester

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification
This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
82373

LOINC® Information

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<td>A-oligo/Di-oligo Ratio</td>
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<td>50820</td>
<td>Interpretation</td>
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**Test Definition: CDG**

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<th>Description</th>
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<td>34474</td>
<td>Tri-sialo/Di-oligo Ratio</td>
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<td>34476</td>
<td>Apo CIII-1/Apo CIII-2 Ratio</td>
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<td>34475</td>
<td>Apo CIII-0/Apo CIII-2 Ratio</td>
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