Overview

Useful For

Screening for congenital disorders of glycosylation

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 100 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's.

Testing Algorithm

Suggested Testing Strategy:

Disorder	Target	Mayo Test
N-glycan, O-glycan, and conserved oligomeric Golgi (COG) complex defects	Transferrin, apolipoprotein CIII	CDG / Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum
N-glycan, O-glycan, and COG complex defects	Serum total N-linked glycans, transferrin, and apolipoprotein CIII	CDGN / Congenital Disorders of N-Glycosylation, Serum
glycophosphatidylinositol (GPI)-anchored protein glycosylation disorders	CD59, CD55, CD16b, ALP, and aerolysin (FLAER)	Testing may be available on a research basis for these disorders. Contact a BGL genetic counselor for more information.
alpha-dystroglycanopathies	Genes: *DAG1, FKRP, FKTN, ISPD, LARGE1, POMGNT1, POMGNT2, POMT1, POMT2*	CDGNP / CDG Normal Transferrin Panel

See Epilepsy: Unexplained Refractory and/or Familial Testing Algorithm in Special Instructions.

Special Instructions

- Biochemical Genetics Patient Information
- Epilepsy: Unexplained Refractory and/or Familial Testing Algorithm

Method Name

AffinityChromatography-MassSpectrometry(MS)

NY State Available

Yes

Specimen

Specimen Type

Serum

Advisory Information

This test is for congenital disorders of glycosylation. If the ordering physician 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 referral 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) in Special Instructions.

2. If not ordering electronically, complete, print, and send an Inborn Errors of Metabolism Test Request (T798) with the specimen.

Specimen Minimum Volume

0.05 mL

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Frozen (preferred)	45 days	
	Refrigerated	28 days	
	Ambient	7 days	

Clinical and Interpretive

Clinical Information

Congenital disorders of glycosylation (CDG), formerly known as carbohydrate-deficient glycoprotein syndrome, are a group of over 100 inherited metabolic disorders affecting several steps of the pathway involved in the glycosylation of proteins. CDG are currently classified into 2 main groups. Type I CDG is characterized by defects in the assembly or transfer of the dolichol-linked glycan, while type II involves processing defects of the glycan. Apolipoprotein CIII (Apo-CIII) isoforms, a protein 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, and will change the ratios, increasing the asialo or monoisalo forms and decreasing the fully sialylated (disialo) forms of the apolipoprotein-CIII.

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 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 [PMM] and Phosphomannose Isomerase [PMI], 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, glycophosphatidylinositol (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.

Reference Values

Ratio	Normal	Indeterminate	Abnormal
Transferrin Mono-oligo/Di-oligo Ratio	< or =0.06	0.07-0.09	> or =0.10
Transferrin A-oligo/Di-oligo Ratio	< or =0.011	0.012-0.021	> or =0.022
Transferrin Tri-sialo/Di-oligo Ratio	< or =0.05	0.06-0.12	> or =0.13
Apo CIII-1/Apo CIII-2 Ratio	< or =2.91	2.92-3.68	> or =3.69
Apo CIII-0/Apo CIII-2 Ratio	< or =0.48	0.49-0.68	> or =0.69

Interpretation

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

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 can be 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 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, most likely the defects 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 if the defects involve Golgi apparatus.

4. CDG with normal transferrin and apolipoprotein profile. Some CDG (eg, PGM3; ALG13; 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.)

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 more precisely identify the correct form of CDG. If applicable, treatment options, the name and telephone number of contacts who may provide studies at Mayo Clinic or elsewhere, and a telephone number for one of the laboratory directors (if the referring physician has additional questions) will be provided.

Cautions

Other conditions such as acute crisis of hereditary fructose intolerance, galactosemia, 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, in particular for nonpediatric patients.

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

Clinical Reference

1. Freeze HH: Congenital disorders of glycosylation: CDG-I, CDG II, and beyond. Curr Mol Med 2007;7:389-396

2. Freeze HH, Eklund EA, Ng BG, Patterson MC: Neurology of inherited glycosylation disorders. Lancet Neurol 2012;11:453-466

3. Hennet T, Cabalzar J: Congenital disorders of glycosylation: a concise chart of glycocalyx dysfunction. Trends Biochem Sci 2015 Jul;40(7):377-384

4. Freeze HH, Chong JX, Bamshad MJ, Ng BG: Solving glycosylation disorders: fundamental approaches reveal complicated pathways. Am J Hum Genet 2014 Feb 6;94(2):161-175

5. Sparks SE, Krasnewich DM: Congenital Disorders of N-Linked Glycosylation and Multiple Pathway Overview. In GeneReviews. Edited by RA Pagon, MP Adam, HH Ardinger, et al: University of Washington, Seattle. Accessed 01/16/2018. Available at www.ncbi.nlm.nih.gov/books/NBK1332/

6. Ng BG, Freeze HH: Human genetic disorders involving glycosylphosphatidylinositol (GPI) anchors and glycosphingolipids (GSL). J Inherit Metab Dis 2015;38(1):171-178 doi:10.1007/s10545-014-9752-1.

7. Sparks SE, Quijano-Roy S, Harper A, et al: Congenital Muscular Dystrophy Overview. In GeneReviews. Edited by MP Adam, HH Ardinger, RA Pagon, et al. University of Washington, Seattle. Accessed 01/16/2018. Available at www.ncbi.nlm.nih.gov/books/NBK1291/

Performance

Method Description

Samples are prepared by diluting serum in water. The sample is injected into an immunoaffinity column and washed. Following 2 wash steps, proteins are then eluted and introduced into an API 4000 tandem mass spectrometer equipped with a Turbo V source configured for electrospray ionization. The mass spectrometer is operated in positive Q1 scan mode with 2 scan ranges; m/z 1090-2000 for apolipoprotein CIII and m/z 2000-3000 for transferrin. Relative quantitation of carbohydrate deficient transferrin and apolipoprotein CIII is achieved by comparing glycoform ratios in each protein.(Lacey JM, Bergen R, Magera MJ, et al: Rapid determination of transferrin isoforms by immunoaffinity liquid chromatography and electrospray mass spectrometry. Clin Chem 2001;47:513-518)

PDF Report

No

Day(s) and Time(s) Test Performed

Monday, Thursday; 8 a.m.

Analytic Time

5 days (Not reported Saturday or Sunday)

Maximum Laboratory Time

10 days

Specimen Retention Time

1 month

Performing Laboratory Location

Rochester

Fees and 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 U.S. Food and Drug Administration.

CPT Code Information

82373

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
CDG	CDG, S	90417-7

Result ID	Test Result Name	Result LOINC Value
BG160	Reason for Referral	42349-1
31721	Mono-oligo/Di-oligo Ratio	35469-6
31720	A-oligo/Di-oligo Ratio	35475-3
34474	Tri-sialo/Di-oligo Ratio	90420-1
34476	Apo CIII-1/Apo CIII-2 Ratio	90421-9
34475	Apo CIII-0/Apo CIII-2 Ratio	90419-3
50820	Interpretation	53808-2
50822	Reviewed By	18771-6