Overview

Useful For

Diagnosing congenital disorders of glycosylation Ia (phosphomannomutase-2 deficiency: CDG-Ia or PMM2-CDG) and Ib (phosphomannose isomerase deficiency: CDG-Ib or MPI-CDG) as measured in leukocytes

Follow-up testing for patients with an abnormal transferrin isoform profile

This test is **not useful for** carrier testing.

Genetics Test Information

Congenital disorders of glycosylation (CDG) are a large and growing group of inborn errors of glycan metabolism that are clinically diverse, but most often present during infancy or childhood.

A diagnostic workup for a CDG should begin with transferrin analysis by liquid chromatography-mass spectrometry (CDG / Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum).

Follow-up testing of an abnormal transferrin isoform profile may include enzymatic analysis for the diagnosis of phosphomannomutase-2 deficiency (PMM2-CDG or CDG-Ia) and phosphomannose isomerase deficiency (MPI-CDG or CDG-Ib).

Special Instructions

- Informed Consent for Genetic Testing
- Biochemical Genetics Patient Information
- Informed Consent for Genetic Testing (Spanish)

Method Name

Colorimetric

NY State Available

Yes

Specimen

Specimen Type

Whole Blood ACD

Advisory Information

The initial screening test for congenital disorders of glycosylation is transferrin isoform analysis (CDG / Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum). The results of the transferrin isoform analysis should be correlated with the clinical presentation to determine the most appropriate testing strategy, which may include this test.

Shipping Instructions

For optimal isolation of leukocytes, it is recommended the specimen arrive refrigerated within 48 hours of collection to be stabilized. Collect specimen Monday through Thursday only and not the day before a holiday. Specimen should be collected and packaged as close to shipping time as possible.

Specimen Required

Container/Tube:

Preferred: Yellow top (ACD solution B)

Acceptable: Yellow top (ACD solution A)

Specimen Volume: 6 mL

Collection Instructions: Send in original tube. **Do not transfer** blood to other containers.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Biochemical Genetics Patient Information (T602) in Special Instructions

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

Specimen Minimum Volume

3 mL

Reject Due To

Gross hemolysis	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole Blood ACD	Refrigerated	72 hours	YELLOW TOP/ACD

Clinical and Interpretive

Clinical Information

Congenital disorders of glycosylation (CDG), formerly known as carbohydrate-deficient glycoprotein syndrome, are a group of inherited metabolic diseases that affect one of the steps of the pathway involved in glycosylation. CDG typically present as multisystemic disorders and may include developmental delay, hypotonia, abnormal magnetic resonance imaging (MRI) findings, hypoglycemia, and protein-losing enteropathy. There is considerable variation in the severity of this group of diseases, which can range from hydrops fetalis to a mild presentation in adults. In some subtypes (Ib, in particular) intelligence is not compromised.

Phosphomannomutase-2 deficiency (PMM2-CDG or CDG-Ia) is an autosomal recessive glycosylation disorder resulting from reduced or absent activity of the enzyme phosphomannomutase-2, encoded by the *PMM2* gene. It is the most common CDG worldwide. Patients with CDG-Ia have moderate to severe neurological disease, more or

less typical dysmorphology, and variable involvement of other organ systems. Severely affected individuals with CDG-Ia usually present in the neonatal period with failure to thrive, developmental delay, abnormal subcutaneous fat distribution, elevated liver transaminases, and abnormal MRI findings. Later presenting individuals can have clinical features that include ataxia, significantly delayed motor and language development, seizures, stroke-like episodes, retinitis pigmentosa, joint contractures and skeletal deformities. An adult form has also been described. Currently, there is no cure and treatment remains primarily supportive and symptomatic.

Phosphomannose isomerase deficiency (MPI-CDG or CDG-Ib) is an autosomal recessive glycosylation disorder resulting from reduced or absent activity of phosphomannose isomerase, an enzyme encoded by the *MPI* gene. This CDG subtype is unique in that there is little to no involvement of the central nervous system. It is mainly hepatic-intestinal without dysmorphology, and the primary clinical manifestations are a result of aberrant gastrointestinal function. In particular, individuals with CDG-Ib may present with failure to thrive, hypoglycemia, chronic diarrhea, and protein-losing enteropathy. CDG-Ib is also unique in that it can be effectively treated with mannose supplementation, though can be fatal if left untreated.

Reference Values

PHOSPHOMANNOMUTASE

Normal >350 nmol/h/mg protein

PHOSPHOMANNOSE ISOMERASE

Normal >1,300 nmol/h/mg protein

Interpretation

Normal results are not consistent with either phosphomannomutase-2 deficiency (PMM2-CDG or CDG-Ia) or phosphomannose isomerase deficiency (MPI-CDG or CDG-Ib).

Markedly reduced activity of phosphomannomutase is consistent with a diagnosis of CDG-Ia. Markedly reduced activity of phosphomannose isomerase is consistent with a diagnosis of CDG-Ib.

Mild to moderately reduced enzyme activities will be interpreted in the context of clinical and other laboratory test information submitted with the specimen.

Cautions

There are some known carriers of PMM2 who have reduced enzyme activity that falls in the range of affected patients with PMM2-CDG. However, white blood cell enzyme activity is still more reliable than fibroblast testing for PMM2-CDG.(1,2) The PMM2 enzyme result should be considered along with CDG transferrin,clinical phenotype, and genotype when determining a diagnosis.

Clinical Reference

1. Grunewald S, Schollen E, Van Schaftingen E, Jaeken J, Matthijs G: High residual activity of PMM2 in patients' fibroblasts: possible pitfall in the diagnosis of CDG-Ia (phosphomannomutase deficiency). Am J Hum Genet. 2001 Feb;68(2):347-354

2. Pirard M, Matthijs G, Heykants L, Schollen E, Grunewald S, Jaeken J, van Schaftingen E: Effect of mutations found in carbohydrate-deficient glycoprotein syndrome type IA on the activity of phosphomannomutase 2. FEBS Lett. 1999 Jun 11;452(3):319-322

3. Sparks SE, Krasnewich DM: Congenital disorders of N-linked glycosylation pathway overview. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2005. Updated January 30, 2014. Accessed July 30, 2020. Available at www.ncbi.nlm.nih.gov/books/NBK1332/

4. Sparks SE, Krasnewich DM: PMM2-CDG (CDG-Ia) In: Adam MP. Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2005. Updated October 29, 2015. Accessed July 30, 2020. Available at www.ncbi.nlm.nih.gov/books/NBK1110/

5. Scott K, Gadomski T, Kozicz T, Morava E: Congenital disorders of glycosylation: new defects and still counting. J Inherit Metab Dis. 2014 Jul;37(4):609-617.

6. Jaeken J, Matthijs G, Carchon H, Van Schaftingen E: Defects of N-glycan synthesis. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed July 30, 2020. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225081470

Performance

Method Description

Leukocytes are harvested from one 7-mL tube of ACD-treated blood and the resulting leukocyte cell pellet is subjected to 1 freeze-thaw cycle. The lysate is collected and the enzymatic activity for both phosphomannomutase and phosphomannose isomerase is measured by a colorimetric assay.(Personal communication: Dr. Otto van Diggelen, Erasmus University, Rotterdam, The Netherlands 2008; Cowan T, Pasquali M: Laboratory investigations of inborn errors of metabolism. In: Sarafoglou K, Hoffman GF, Roth KS, eds. Pediatric Endocrinology and Inborn Errors of Metabolism. 2nd ed. McGraw Hill Education; 2017:1139-1158)

PDF Report

No

Day(s) and Time(s) Test Performed

Varies

Analytic Time

30-45 days

Specimen Retention Time

WBC homogenate: 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

82657

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
PMMIL	PMM-PMI, Leukocytes	In Process

Result ID	Test Result Name	Result LOINC Value
50836	Specimen	31208-2
50837	Specimen ID	57723-9
50838	Source	31208-2
50839	Order Date	82785-7
50840	Reason For Referral	42349-1
50841	Method	49549-9
50842	Phosphomannomutase, Leuko	78970-1
50843	Phosphomannose Isomerase, Leuko	78963-6
50844	Interpretation	59462-2
50845	Amendment	48767-8
50846	Reviewed By	18771-6
50847	Release Date	82772-5