MAYO CLINIC LABORATORIES

Test Definition: PMMIL

Phosphomannomutase and Phosphomannose Isomerase, Leukocytes

Overview

Useful For

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

Follow-up testing for patients with an abnormal type I CDG 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 type 1 CDG transferrin isoform profile may include enzymatic analysis for the diagnosis of phosphomannomutase-2 deficiency (PMM2-CDG) and phosphomannose isomerase deficiency (MPI-CDG).

Testing Algorithm

For more information see Congenital Disorders of Glycosylation: Screening Algorithm.

Special Instructions

- Informed Consent for Genetic Testing
- Biochemical Genetics Patient Information
- Informed Consent for Genetic Testing (Spanish)
- Congenital Disorders of Glycosylation: Screening Algorithm

Method Name

Colorimetric

NY State Available

Yes

Specimen

Specimen Type

Whole Blood ACD

Ordering Guidance

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 6 days 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 specimen in original tube. **Do not aliquot**.

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 a Biochemical Genetics 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 (preferred)	6 days	YELLOW TOP/ACD
	Ambient	6 days	YELLOW TOP/ACD

Clinical & Interpretive

Clinical Information

Congenital disorders of glycosylation (CDG) are a group of over 150 inherited metabolic disorders largely affecting N- and O-glycosylation of proteins. CDG typically present as multisystemic disorders and may include developmental delay, hypotonia, abnormal magnetic resonance imaging 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 such as phosphomannose isomerase intelligence is not compromised.

Phosphomannomutase-2 deficiency (PMM2-CDG)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 with phenotypic variability ranging from severely affected infants to mildly affected adults. In infancy, patients with PMM2-CDG will typically present with neurological involvement such as axial hypotonia, hyporeflexia, developmental delay, cerebellar hypoplasia, failure to thrive, hepatopathy, and abnormal subcutaneous fat distribution. There is variable involvement of other organ systems including features such as heart defects, epilepsy, strabismus, retinitis pigmentosa, liver dysfunction, endocrine abnormalities such as hypothyroidism and hypoglycemia, and skeletal deformities. Currently, there is no cure and treatment, while becoming more effective, remains primarily supportive and symptomatic.

Phosphomannose isomerase deficiency (MPI-CDG) 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. Individuals with MPI-CDG may present with failure to thrive, hypoglycemia, chronic diarrhea, and protein-losing enteropathy. MPI-CDG is also unique in that it’s 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 phosphomannose isomerase deficiency (MPI-CDG).

Markedly reduced activity of phosphomannomutase is consistent with a diagnosis of PMM2-CDG. Markedly reduced activity of phosphomannose isomerase is consistent with a diagnosis of MPI-CDG.

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 phosphomannomutase-2 deficiency (PMM2) who have reduced enzyme activity that falls in the range of affected patients with PMM2-congenital disorders of glycosylation (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;68(2):347-354
2. Pirard M, Matthijs G, Heykants L, et al. Effect of mutations found in carbohydrate-deficient glycoprotein syndrome type IA on the activity of phosphomannomutase 2. FEBS Lett. 1999;452(3):319-322
3. Lam C, Krasnewich DM. PMM2-CDG. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2005. Updated May 20, 2021. Accessed January 19, 2024. Available at: www.ncbi.nlm.nih.gov/books/NBK1110/
4. Schiff M, Roda C, Monin ML, et al. Clinical, laboratory and molecular findings and long-term follow-up data in 96 French patients with PMM2-CDG (phosphomannomutase 2-congenital disorder of glycosylation) and review of the literature. J Med Genet. 2017;54(12):843-851
5. Girard M, Douillard C, Debray D, et al. Long term outcome of MPI-CDG patients on D-mannose therapy. J Inherit Metab Dis. 2020;43(6):1360-1369
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 January 19, 2024. 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) Performed

Preanalytical processing: Monday through Saturday
Assay performed: Twice per month

Report Available

30 to 45 days

Specimen Retention Time

WBC homogenate: 1 month

Test Definition: PMMIL

Phosphomannomutase and Phosphomannose Isomerase, Leukocytes

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

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 account representative. 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. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

82657

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
PMMIL	PMM-PMI, Leukocytes	100735-0

Result ID	Test Result Name	Result LOINC® Value
50842	Phosphomannomutase, Leuko	78970-1
50843	Phosphomannose Isomerase, Leuko	78963-6
50840	Reason For Referral	42349-1
50836	Specimen	31208-2
50837	Specimen ID	57723-9
50838	Source	31208-2
50839	Order Date	82785-7
50841	Method	85069-3
50845	Amendment	48767-8
50847	Release Date	82772-5
50844	Interpretation	59462-2
50846	Reviewed By	18771-6