MAYO CLINIC LABORATORIES

Test Definition: WBGDD

Beta-Globin Gene Cluster, Deletion/Duplication, Varies

Overview

Useful For

Determining the etiology of hereditary persistence of fetal hemoglobin (HPFH), delta-beta thalassemia, or other large deletions involving the beta-globin gene cluster

Diagnosing less common causes of beta thalassemia; these large deletional beta-thalassemia variants result in elevated hemoglobin (Hb) A2 and can have elevated HbF levels

Distinguishing homozygous HbS disease from a compound heterozygous HbS/large beta-globin cluster deletion disorder (ie, HbS/beta zero thalassemia, HbS/delta-beta zero thalassemia, HbS/HPFH, HbS/gamma-delta-beta thalassemia)

Diagnosing complex thalassemias where the beta-globin gene and one or more of the other genes in the beta-globin cluster have been deleted

Evaluating and classifying unexplained increased HbF percentages

Evaluating microcytic neonatal anemia

Evaluating unexplained long standing microcytosis in the setting of normal iron studies and negative alpha-thalassemia testing/normal Hb A2 percentages

Confirming gene fusion hemoglobin variants such as Hb Lepore and HbP-Nilotic

Confirming homozygosity vs hemizygosity of variants in the beta-like genes (*HBB*, *HBD*, *HBG1*, *HBG2*)

Investigating newborns with HbA levels greater than HbF on newborn screen in the absence of transfusion

This test is **not useful for** diagnosis or confirmation of alpha thalassemia, the most common beta thalassemias, or hemoglobin variants. It also does not detect non-deletional HPFH.

Genetics Test Information

This test can be used to identify a variety of conditions (see Highlights) that involve large deletions of the beta-globin gene cluster. These alterations will not be detected by DNA sequencing of the beta-globin gene.

Special Instructions

- Informed Consent for Genetic Testing
- Metabolic Hematology Patient Information
- Informed Consent for Genetic Testing (Spanish)

Highlights

This test is recommended to identify a variety of conditions involving large deletions or duplications within the

beta-globin gene cluster locus region including:
-Identifying large deletions causing increased hemoglobin (Hb) F levels, such as hereditary persistence of fetal hemoglobin, delta-beta thalassemias, and gamma-delta-beta thalassemia
-Identifying large deletions associated with elevated HbA2, such as beta-thalassemia (or rarely epsilon-gamma thalassemia) in cases where beta gene sequencing did not find a beta thalassemia variant
-Confirming gene fusion hemoglobin variants, such as Hb Lepore and HbP-Nilotic
-Investigating newborns and adults with unexplained microcytic anemia that is suspected to be caused by epsilon-gamma-delta-beta thalassemia
-Confirming homozygosity vs hemizygosity of variants in the beta-like genes (*HBB, HBD, HBG1, HBG2*)
-Investigating individuals older than 12 months with unexplained microcytosis and normal hemoglobin electrophoresis for whom more common causes of microcytosis, such as iron deficiency and alpha thalassemia have been excluded
-Investigating newborns with HbA levels greater than HbF on newborn screen in the absence of transfusion

Method Name
Polymerase Chain Reaction (PCR) Analysis/Multiplex Ligation-Dependent Probe Amplification (MLPA)

NY State Available
Yes

Specimen

Specimen Type
Varies

Additional Testing Requirements
Hemoglobin electrophoresis studies performed at Mayo Clinic Laboratories are highly recommended prior to this test to allow for more complete interpretation of results. See HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood or THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum.

Shipping Instructions
Specimens must arrive within 4 days (96 hours) of collection.

Necessary Information
Metabolic Hematology Patient Information (T810) **is required**. Send a completed form with the specimen. Document the reason for suspecting a large beta cluster locus deletion along with the hemoglobin F percentage and red blood cell indices for the patient.

Specimen Required
Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA)
Acceptable: Yellow top (ACD)
Specimen Volume: 4 mL

Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in the original tube. **Do not aliquot.**
Specimen Stability Information: Refrigerated (preferred)/Ambient

Forms
1. Metabolic Hematology Patient Information (T810) is required.
2. 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:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)
3. If not ordering electronically, complete, print, and send a Benign Hematology Test Request Form (T755) with the specimen.

Specimen Minimum Volume
2 mL

Reject Due To
All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information
Large deletions involving the beta-globin cluster locus on chromosome 11 manifest with widely variable clinical phenotypes. Up to 10% of beta-thalassemia cases (dependent on ethnicity) are caused by large deletions in the beta-globin cluster. Other thalassemias including delta-beta thalassemia, gamma-delta-beta-thalassemia, epsilon gamma thalassemia, and epsilon-gamma-delta-beta-thalassemia, also result from functional loss of genes or the locus control region that controls globin gene expression. In addition, hereditary persistence of fetal hemoglobin (HPFH) is caused by deletions of variable size along the beta-globin cluster locus. Most, but not all, of the large deletion beta-globin cluster disorders are associated with variably elevated hemoglobin F percentages that persist after 2 years of age. In addition, many manifest in microcytosis. A notable exception is HPFH, which can have normal to minimal decreased mean corpuscular volume values. The correct classification of these deletions is important as they confer variable predicted protective phenotypes, and some are more protective than others when found in combination with a second beta-globin variant, such as HbS or beta thalassemia. In addition, identification of these deletions can explain lifelong microcytosis in the setting of normal iron studies and negative alpha thalassemia molecular results.

Reference Values
An interpretive report will be provided

Interpretation

The alterations will be provided with the classification that fits the probe pattern, if known. Further interpretation requires correlation with protein studies and red blood cell indices.

Cautions

Non-deletional subtypes of beta thalassemia or hereditary persistence of fetal hemoglobin are not detected by this assay. In addition to disease-related probes, the multiplex ligation-dependent probe amplification technique utilizes probes localized to other chromosomal regions as the internal controls. In certain circumstances, these control probes may detect other diseases or conditions for which this test was not specifically intended. Results of the control probes are not normally reported. However, in cases where clinically relevant information is identified, the ordering physician will be informed of the result and provided with recommendations for any appropriate follow-up testing.

Clinical Reference

1. Hein MS, Oliveira JL, Swanson KC, et al. Large deletions involving the beta globin gene complex: genotype-phenotype correlation of 119 cases. Blood. 2015;126(23):3374
2. Kipp BR, Roellinger SE, Lundquist PA, Highsmith WE, Dawson DB. Development and clinical implementation of a combination deletion PCR and multiplex ligation-dependent probe amplification assay for detecting deletions involving the human alpha-globin gene cluster. J Mol Diagn. 2011;13(5):549-557. doi:10.1016/j.jmoldx.2011.04.001
3. Rund D, Rachmilewitz E. Beta-thalassemia. N Engl J Med. 2005;353(11):1135-1146
4. Nussbaum R, McInnes R, Willard H. Principles of molecular disease: Lessons from the hemoglobinopathies. In: Thompson and Thompson Genetics in Medicine. 7th ed. Saunders Elsevier; 2007:323-342
5. Wood WG. Hereditary persistence of fetal hemoglobin and delta beta thalassemia. In: Steinberg MH, Forget BG, Higgs DR, Nagel RL, eds. Disorders of Hemoglobin: Genetics, Pathophysiology, and Clinical Management. Cambridge University Press, 2001;356-388
6. Oliveira JL, Thompson CH, Saravanaperumal SA, et al. eg-Thalassemia, a new hemoglobinopathy category. Clin Chem. 2023;69(7):711-717. doi:10.1093/clinchem/hvad038

Performance

Method Description

Multiplex ligation-dependent probe amplification is utilized to test for the presence of large deletions or duplications in the beta-globin gene.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Wednesday, Friday

Report Available

25 to 30 days

Specimen Retention Time

Whole blood: 2 weeks; DNA: 3 months

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

81363-HBB (hemoglobin, beta, beta-globin) (e.g. beta thalassemia), duplication/deletion analysis

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
WBGDD	Beta Globin Gene Cluster, Del/Dup,V	101634-4

Result ID	Test Result Name	Result LOINC® Value
620981	Beta Globin Gene Cluster Del/Dup	101634-4
620982	Specimen	31208-2
620983	Reviewed by	18771-6
620980	Interpretation	69047-9