

## Overview

### Useful For

Determining the etiology of hereditary persistence of fetal hemoglobin (HPFH) or delta-beta thalassemia

Diagnosing less common causes of beta-thalassemia; these large deletional beta thalassemia alterations result in elevated hemoglobin (Hb) A2 and usually have slightly 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 1 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 Hb P-Null

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

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 nondeletional hereditary persistence of fetal hemoglobin.

### 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 (HPFH), delta-beta thalassemias, and gamma-delta-beta thalassemia
- Identifying beta thalassemia conditions in cases where beta gene sequencing did not find a beta thalassemia genetic variant
- Confirming gene fusion hemoglobin variants such as Hb Lepore and Hb P-Null
- Investigating newborns with unexplained microcytic anemia that is suspected to be caused by epsilon-gamma-delta-beta thalassemia
- Confirming homozygosity vs hemizyosity of genetic variants in the beta-like genes (*HBB*, *HBD*, *HBG1*, *HBG2*)
- Investigating individuals older than 12 months of age with unexplained microcytosis and normal hemoglobin electrophoresis for whom more common causes of microcytosis such as iron deficiency and alpha thalassemia have been excluded

**Method Name**

Only orderable as a reflex. For more information see:

- HAEV1 / Hemolytic Anemia Evaluation, Blood
- HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood
- MEV1 / Methemoglobinemia Evaluation, Blood
- REVE1 / Erythrocytosis Evaluation, Whole Blood
- THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum

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

**NY State Available**

Yes

**Specimen****Specimen Type**

Whole Blood EDTA

**Specimen Required**

Only orderable as a reflex. For more information see:

- HAEV1 / Hemolytic Anemia Evaluation, Blood
- HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood
- MEV1 / Methemoglobinemia Evaluation, Blood
- REVE1 / Erythrocytosis Evaluation, Whole Blood
- THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum

**Specimen Type:** Peripheral blood

**Collection 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.

**Specimen Minimum Volume**

2 mL

**Reject Due To**

No specimen should be rejected.

**Specimen Stability Information**

| Specimen Type    | Temperature  | Time | Special Container |
|------------------|--------------|------|-------------------|
| Whole Blood EDTA | Refrigerated |      |                   |

## 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, and epsilon-gamma-delta-beta thalassemia, also result from functional loss of genes or the locus control region (LCR) 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 (Hb) F percentages that persist after 2 years of age. In addition, most manifest in microcytosis. A notable exception is HPFH, which can have normal to minimal decreased mean corpuscular volume (MCV) values. The correct classification of these deletions is important as they confer variable predicted 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

Only orderable as a reflex. For more information see:

- HAEV1 / Hemolytic Anemia Evaluation, Blood
- HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood
- MEV1 / Methemoglobinemia Evaluation, Blood
- REVE1 / Erythrocytosis Evaluation, Whole Blood
- THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum

An interpretive report will be provided.

### Interpretation

[The alterations will be provided with the classification, if known. Further interpretation requires correlation with protein studies and red blood cell indices.](#)

### Cautions

Nondeletional subtypes of beta thalassemia or hereditary persistence of fetal hemoglobin (HPFH) are not detected by this assay.

Hemoglobin electrophoresis and sequencing analysis of the beta-globin gene will be performed prior to this test to exclude other diagnoses or to indicate the diagnostic utility of this testing platform.

In addition to disease-related probes, the multiplex ligation-dependent probe amplification technique utilizes probes localized to other chromosomal regions as 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;126:3374
2. Kipp BR, Roellinger SE, Lundquist PA, et al: 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 Sep;13(5):549-557. doi: 10.1016/j.jmoldx.2011.04.001
3. Rund D, Rachmilewitz E: Beta-thalassemia. *N Engl J Med*. 2005;353:1135-1146
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: Disorders of Hemoglobin, 1st ed. Cambridge University Press, 2001;356-388

**Performance****Method Description**

Multiplex ligation-dependent probe amplification (MLPA) is utilized to test for the presence of large deletions 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**

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 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. This test has not been cleared or approved by the US Food and Drug Administration.

**CPT Code Information**

81363-HBB (hemoglobin, beta, beta-globin) (eg, beta thalassemia), duplication/deletion analysis

**LOINC® Information**

| Test ID | Test Order Name                     | Order LOINC® Value |
|---------|-------------------------------------|--------------------|
| WBDDR   | Beta Globin Cluster Locus Del/Dup,B | In Process         |

| Result ID | Test Result Name                  | Result LOINC® Value |
|-----------|-----------------------------------|---------------------|
| 48356     | Beta Globin Cluster Locus Del/Dup | 50397-9             |
| 48355     | Reviewed by                       | 18771-6             |
| 48357     | Interpretation                    | 59466-3             |