Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	11/3/2024
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Beta Globin (HBB) Sequencing

ARUP test code 3004547

BG Specimen: Whole Blood

BG Interp: Positive

RESULT
Two pathogenic variants were detected in the HBB gene.

PATHOGENIC VARIANT
Gene: HBB (NM_000518.5)
Nucleic Acid Change: c.20A>T; Heterozygous
Amino Acid Alteration: p.Glu7Val
Commonly Known As: Hb S
Inheritance: Autosomal recessive

PATHOGENIC VARIANT
Gene: HBB (NM_000518.5)
Nucleic Acid Change: c.19G>A; Heterozygous
Amino Acid Alteration: p.Glu7Lys
Commonly Known As: Hb C
Inheritance: Autosomal recessive

INTERPRETATION
One copy of the Hb S pathogenic variant and one copy of the Hb C pathogenic variant were detected in the beta globin (HBB) gene by massively parallel sequencing; thus, this individual is predicted to have hemoglobin SC disease. Based on the sequencing reads, we were able to determine that these two pathogenic variants are on opposite chromosomes. Hemoglobin SC disease is characterized by moderate hemolytic anemia and frequent splenomegaly (Zimmerman 2000), yet clinical manifestations may be milder than sickle cell anemia. The clinical presentation may vary due to other genetic modifiers or co-existing conditions.

Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classifications:
The Hb S variant (HBB: c.20A>T; p.Glu7Val, also known as Glu6Val when numbered from the mature protein, HbVar ID: 226, rs334) is a common pathogenic beta globin variant. Heterozygosity for Hb S is consistent with sickle cell trait. Homozygosity for Hb S results in sickle cell anemia. Hb S in combination with a different pathogenic HBB variant on the opposite chromosome results in various forms of sickle cell disease (see HbVar link and references therein).

The Hb C variant (HBB: c.19G>A; p.Glu7Lys, also known as Glu6Lys when numbered from the mature protein, rs33930165, HbVar ID: 227) is a common pathogenic beta globin variant. Heterozygosity

H=High, L=Low, *=Abnormal, C=Critical

is consistent with Hb C trait. Homozygosity is consistent with a clinical presentation of mild to moderate hemolytic anemia with mild microcytosis and frequent target cells. Hb C in combination with a beta thalassemia variant on the opposite chromosome is often associated with mild microcytic anemia (Cook 2013, HbVar database).

RECOMMENDATIONS
Hematologic and genetic consultations are recommended. Family members should be offered carrier testing for the identified pathogenic variants (Familial Targeted Sequencing, ARUP test code 3005867). This individual's future reproductive partner should be offered carrier testing for hemoglobinopathies.

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations: None

REFERENCES
Cook C et al. The clinical and laboratory spectrum of Hb C (beta6(A3)Glu>Lys, GAG>AAG) disease. Hemoglobin. 2013; 37(1):16-25. PMID: 23297836.
Link to HbVar database: https://globin.bx.psu.edu/hbvar/menu.html
Zimmerman SA et al. Palpable splenomegaly in children with haemoglobin SC disease: haematological and clinical manifestations. Clin Lab Haematol. 2000; 22(3):145-50. PMID: 10931162.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Beta Globin (HBB) Sequencing

CHARACTERISTICS: Beta thalassemia is caused by decreased or absent synthesis of the hemoglobin beta-chain resulting in variable clinical presentations ranging from mild anemia to transfusion dependence. Structural hemoglobinopathies may result in sickling disorders, microcytic or hemolytic anemia, cyanosis, or erythrocytosis.

EPIDEMIOLOGY: Incidence varies by ethnicity.

CAUSE: Pathogenic germline variants within the HBB gene.

INHERITANCE: Usually autosomal recessive, infrequently autosomal dominant.

CLINICAL SENSITIVITY: Up to 99 percent, depending upon ethnicity, for beta thalassemia and hemoglobinopathies associated with the HBB gene.

GENE TESTED: HBB (NM_000518)
Deletion/duplication analysis is not available for this gene.

METHODOLOGY: Probe hybridization-based capture of all coding exons, exon-intron junctions, 5' proximal promoter and untranslated region, 3' polyadenylation signal, and intronic variants c.93-21G>A (IVS-I-110), c.316-197C>T (IVS-II-654), c.316-146T>G (IVS-II-705), and c.316-106C>G (IVS-II-745) of the HBB gene, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a diagnosis of beta thalassemia. This test detects variants within the coding regions and intron-exon boundaries of the HBB gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants upstream of c.-250, deep intronic variants (other than those described in methodology section above), and large deletions/duplications will not be identified. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) variants, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

H=High, L=Low, *=Abnormal, C=Critical

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
BG Specimen	24-355-401111	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
BG Interp	24-355-401111	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical