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

Physician: Doctor, Example

Patient: Patient, Example

DOB	11/1/2015
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Beta Globin (HBB) Gene Sequencing (Temporary Referral as of 12/07/20)

ARUP test code 0050578

BGSEQ Specimen — DNA

Beta Globin Full Gene Sequencing — **Positive** *

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TEST PERFORMED - 0050578
TEST DESCRIPTION - Beta Globin (HBB) Gene Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
Two pathogenic variants were detected in the HBB gene.

DNA VARIANTS
Classification: Pathogenic
Gene: HBB
Nucleic Acid Change: c.79G>A; Heterozygous
Amino Acid Alteration: p.Glu27Lys
Commonly Known As: Hb E

Classification: Pathogenic
Gene: HBB
Nucleic Acid Change: c.20delA; Heterozygous
Amino Acid Alteration: p.Glu7fs
Variant Phenotype: Beta (0) Thalassemia (absence of beta chain
synthesis)

INTERPRETATION
One copy of the Hb E pathogenic variant and one copy of a beta
(0) thalassemia pathogenic variant, c.20delA; p.Glu7fs, were
detected in the beta globin (HBB) gene by sequencing. Sequence
analysis indicates these variants occur on opposite chromosomes.
This molecular result is consistent with a diagnosis of Hb E /
beta (0) thalassemia, which is associated with variable
presentations ranging from severe thalassemia to clinically
asymptomatic. The clinical presentation may vary due to other
genetic modifiers or co-existing conditions.

Evidence for variant classifications: The Hb E variant (HBB:
c.79G>A; p.Glu27Lys, also known as Glu26Lys when numbered from
the mature protein, rs33950507) is a common pathogenic beta
globin variant. Functional characterization of the variant
indicates aberrant splicing of the beta globin mRNA, leading to
reduced mature protein (Orkin 1982). Heterozygous Hb E is a
clinically benign condition associated with mild microcytosis
and target cells without anemia. Homozygous Hb E is usually a
clinically benign condition but can be associated with mild
anemia and microcytosis. Hb E in combination with a different
pathogenic HBB variant on the opposite chromosome can produce a
range of clinical phenotypes (Vichinsky 2007, HbVar database and
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H=High, L=Low, *=Abnormal, C=Critical

references therein).

The HBB c.20delA; p.Glu7fs variant (also known as Glu6fs when numbered from the mature protein or as Codon 6 (-A), rs63749819) has been reported in multiple individuals with beta(0) thalassemia (Bouhass 1990, Gonzalez-Redondo 1988, Kazazian 1983, Rosatelli 1992, HbVar database and references therein). This variant is found in the general population with an overall allele frequency of 0.002% (4/251184 alleles) in the Genome Aggregation Database. This variant causes a frameshift by deleting a single nucleotide, so it is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
This molecular result should be correlated with this individual's hematological profile. Hematologic and genetic consultations are recommended. Family members, ideally beginning with the parents, should be offered carrier testing for the identified pathogenic variants (Familial Mutation, Targeted Sequencing; ARUP test code 2001961). This individual's future reproductive partner should be offered carrier testing for hemoglobinopathies.

COMMENTS
Reference Sequences: GenBank # NM_000518.5 (HBB)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not reported.

REFERENCES
Link to HbVar database for Codon 6 (-A):
http://globin.bx.psu.edu/cgi-bin/hbvar/query_vars3?mode=output&display_format=page&i=784

Link to HbVar database for Hb E:
http://globin.bx.psu.edu/cgi-bin/hbvar/query_vars3?mode=output&display_format=page&i=277

Bouhass R et al. A new mutation at IVS1 nt 2(T----A), in beta-thalassemia from Algeria. Blood. 1990; 76(5):1054-5.

Kazazian HH Jr et al. beta-Thalassemia due to a deletion of the nucleotide which is substituted in the beta S-globin gene. Am J Hum Genet. 1983; 35(5):1028-33.

Gonzalez-Redondo J et al. Clinical and genetic heterogeneity in black patients with homozygous beta-thalassemia from the southeastern United States. Blood. 1988; 72(3):1007-14.

Orkin S et al. Abnormal RNA processing due to the exon mutation of beta E-globin gene. Nature. 1982; 300(5894):768-9.

Rosatelli M et al. Molecular characterization of beta-thalassemia in the Sardinian population. Am J Hum Genet. 1992; 50(2):422-6.

Vichinsky E Hemoglobin e syndromes. Hematology Am Soc Hematol Educ Program. 2007:79-83.

This result has been reviewed and approved by [redacted]

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

BACKGROUND INFORMATION: Beta Globin (HBB) Sequencing

CHARACTERISTICS: Structural hemoglobinopathies or thalassemias (insufficient or absent beta-chain production).
INCIDENCE: Varies with ethnicity.
INHERITANCE: Usually autosomal recessive, infrequently autosomal dominant.
CAUSE: Pathogenic variants in the HBB gene.
CLINICAL SENSITIVITY: Up to 97 percent, depending upon ethnicity.
METHODOLOGY: Bidirectional sequencing of the HBB coding regions, intron-exon boundaries, 5' proximal promoter and untranslated region, 3'polyadenylation signal, and intronic variants c.93-21 (IVS-I-110), c.316-197 (IVS-II-654), c.316-146 (IVS-II-705), c.316-106 (IVS-II-745), and c.316-86_316-85 (IVS-II-765 L1).
ANALYTICAL SENSITIVITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Large deletions, and variants in distal regulatory elements are not detected.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
BGSEQ Specimen	20-219-111705	8/6/2020 10:45:00 AM	8/7/2020 2:55:00 PM	8/20/2020 6:19:00 PM
Beta Globin Full Gene Sequencing	20-219-111705	8/6/2020 10:45:00 AM	8/7/2020 2:55:00 PM	8/20/2020 6:19:00 PM

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