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

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Gamma Globin (HBG1 and HBG2) Sequencing

ARUP test code 3001957

Specimen HBG FGS	Whole Blood
HBG FGS Interpretation	Positive

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

RESULT
One pathogenic variant was detected in the HBG2 gene.

DNA VARIANT
Classification: Pathogenic
Gene: HBG2
Nucleic Acid Change: c.277C>T; Heterozygous
Amino Acid Alteration: p.His93Tyr
Commonly Known As: Hb FM-Fort Ripley
Variant Phenotype: Autosomal dominant neonatal cyanosis

INTERPRETATION
One copy of a pathogenic variant, c.277C>T; p.His93Tyr, was detected in the HBG2 gene by sequencing. Heterozygous carriers of Hb FM-Fort Ripley are reported to have neonatal cyanosis (see evidence for variant classification below). The clinical presentation may vary due to other genetic modifiers or coexisting conditions. This individual's future offspring have a 50 percent chance of inheriting the pathogenic Hb FM-Fort Ripley variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification: The Hb FM-Fort Ripley variant (HBA1: c.277C>T; p.His93Tyr, also known as His92Tyr when numbered from the mature protein, rs35103459, HbVar ID: 609) is reported in the literature in multiple individuals and segregates with disease in large families affected with transient neonatal cyanosis (see link to HbVar, Hain 1994, Hooven 2016, Priest 1989). This variant is also reported in ClinVar (Variation ID: 14989), and is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. The histidine at codon 93 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.893). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Hematologic and genetic consultations are recommended, including a discussion of medical screening and management. Correlation with hematologic parameters and hemoglobin electrophoresis results is recommended. At-risk family members should be offered testing for the identified pathogenic variant.

COMMENTS
Reference Sequences: GenBank # NM_000559.2 (HBG1), NM_000184.2 (HBG2)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not included in this report.

REFERENCES
Link to HbVar database: https://globin.bx.psu.edu/hbvar/menu.html
Hain RD et al. Hb FM-Fort Ripley: confirmation of autosomal dominant inheritance and diagnosis by PCR and direct nucleotide sequencing. Hum Mutat. 1994;3(3):239-42. PMID: 7517266.
Hooven TA et al. Diagnosis of a rare fetal haemoglobinopathy in the age of next-generation sequencing. BMJ Case Rep. 2016 Apr 19;2016:10.1136/bcr-2016-215193. PMID: 27095814.
Priest JR et al. Mutant fetal hemoglobin causing cyanosis in a newborn. Pediatrics. 1989 May;83(5):734-6. PMID: 2470017.

This result has been reviewed and approved by [redacted]

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

BACKGROUND INFORMATION: Gamma Globin (HBG1 and HBG2) Sequencing
CHARACTERISTICS: Variants in the gamma globin genes, HBG1 and HBG2, may occasionally result in either a quantitative defect (gamma thalassemia or nondeletional hereditary persistence of fetal hemoglobin) or a qualitative abnormality (gamma variant). Gamma variants resulting in unstable, high- and low-oxygen affinity or M hemoglobin variants may result in hemolytic anemia/hyperbilirubinemia, erythrocytosis/cyanosis, or methemoglobinemia in neonates, respectively. Clinical symptoms related to gamma globin variants commonly resolve after the first six months of life given the switch from fetal hemoglobin expression to adult hemoglobin expression.
INCIDENCE: Unknown.
INHERITANCE: Autosomal dominant.
CAUSE: Pathogenic germline variants in HBG1 or HBG2.
CLINICAL SENSITIVITY: Unknown. Gamma globin variants are a rare cause of neonatal hemolytic anemia, cyanosis, erythrocytosis, or methemoglobinemia.
METHODOLOGY: Long range PCR followed by nested PCR and bidirectional sequencing of all coding regions, intron-exon boundaries, and 5' proximal promoters of the HBG1 and HBG2 genes.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations or repeat element insertions. Large deletions/duplications, distal regulatory region variants, deep intronic variants, and hybrid gene events will not be detected.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US 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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Specimen HBG FGS	22-294-117642	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
HBG FGS Interpretation	22-294-117642	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