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*****Example Report*****

Patient Age/Gender: Unknown Female
Printed: 19-Sep-19 09:39:43

Procedure	Result	Units	Ref Interval	Accession	Collected	Received	Reported/ Verified
Specimen HBG FGS	Whole Blood			19-262-900055	19-Sep-19 08:40:00	19-Sep-19 09:05:00	19-Sep-19 09:32:15
HBG FGS Interpretation	**Positive *f**			19-262-900055	19-Sep-19 08:40:00	19-Sep-19 09:05:00	19-Sep-19 09:32:15

19-Sep-19 08:40:00 HBG FGS Interpretation:
TEST PERFORMED - 3001957
TEST DESCRIPTION - Gamma Globin (HBG1 and HBG2) Sequencing
INDICATION FOR TEST - Not Provided

RESULT
One pathogenic variant was detected in the HBG2 gene. No pathogenic variants were detected in the HBG1 gene.

DNA VARIANT
Classification: Pathogenic
Gene: HBG2
Nucleic Acid Change: c.85C>A; Heterozygous
Amino Acid Alteration: p.Leu29Met
Commonly Known As: Hb F-M Viseu, Leu28Met
Variant Phenotype: Neonatal cyanosis

INTERPRETATION
One pathogenic variant, c.85C>A; p.Leu29Met, was detected in the HBG2 gene by sequencing. Heterozygous carriers of Hb F-M Viseu 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. Offspring of this individual have a 50 percent chance to inherit the pathogenic Hb F-M Viseu variant.

Evidence for variant classification: The HBG2 c.85C>A; p.Leu29Met variant, also known as Leu28Met in traditional nomenclature, is reported in the medical literature in several individuals with neonatal cyanosis (Bento 2013, Carreira 2015, Marks 2013). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. The leucine at codon 29 is highly conserved and computational algorithms (PolyPhen-2, SIFT) predict this variant is deleterious. Considering available information, this variant is classified as pathogenic.

RECOMMENDATIONS
Medical management should rely on clinical findings. Correlation with hematologic parameters and hemoglobin electrophoresis results is recommended. Hematologic and genetic consultations are recommended. At-risk family members should be offered testing for the identified pathogenic variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

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 Hb F-M Viseu in HbVar database: http://globin.bx.psu.edu/cgi-bin/hbvar/query_vars3?mode=output&display_format=page&i=3108&.cgifields=histD

Bento C et al. Transient neonatal cyanosis associated with a new Hb F variant: Hb F viseu. J Pediatr Hematol Oncol. 2013 Mar;35(2):e77-80.

Carreira R et al. An unusual cause of neonatal cyanosis…. BMJ Case Rep. 2015 Mar 9;2015. pii: bcr2014208371.

Marks A et al. Hemoglobin Shady Grove: a novel fetal methemoglobin variant. Pediatr Blood Cancer. 2013 Aug;60(8):E55-6.

This result has been reviewed and approved by Rong Mao, M.D.

19-Sep-19 08:40:00 HBG FGS Interpretation:
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, proximal promoters, and 5' and 3' untranslated regions 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.

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