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PATIENT REPORT

Patient Age/Sex: Female

Specimen Collected: 4/17/2025 13:18 MDT

HBA1 and HBA2 Seq, Del/Dup, Fetal | Received: 4/17/2025 13:18 MDT | Report/Verified: 4/18/2025 11:01 MDT

Procedure	Result	Units	Reference Interval
Maternal Contamination Study Fetal Spec	Fetal Cells [f1]		
Maternal Contam Study,Maternal Spec	Whole Blood		
HBA FGA FE Int	Positive [f2] [i1]		

Result Footnote

f1: Maternal Contamination Study Fetal Spec

Single fetal genotype present; no maternal cells present. Fetal and maternal samples were tested using STR markers to rule out maternal cell contamination.

f2: HBA FGA FE Int

RESULT
One pathogenic deletion, resulting in the deletion of two alpha globin gene copies, and one copy of hemoglobin Constant Spring (HbCS) were detected in the alpha gene cluster.

DNA VARIANTS
Classification: Pathogenic
Gene: HBA2
Nucleic Acid Change: c.427T>C; One copy
Amino Acid Alteration: p.Ter143GlnextTer31
Commonly Known As: Hb Constant Spring

Classification: Pathogenic
Deletion: --SEA; Heterozygous

Predicted Overall Genotype: --/aCSa

INTERPRETATION
According to information provided to ARUP, the mother of this fetus harbors the Southeast Asian (--SEA) alpha globin deletion and the alpha globin carrier status of the father of this fetus is unknown. One copy of the pathogenic Hb Constant Spring variant was detected in the HBA2 gene by sequencing and one copy of the --SEA deletion was identified by deletion/duplication analysis in this prenatal sample. The --SEA deletion removes the HBM, HBA2, HBA1 and HBQ1 globin genes from the same chromosome; therefore, the identified sequence variant occurs on the opposite chromosome. This combination of pathogenic variants may be associated with Hemoglobin H-Constant Spring disease, a severe form of Hb H disease in the fetus. The clinical presentation may vary due to other genetic modifiers or co-existing conditions.

Evidence for variant classification: The Hb Constant Spring variant (HbCS, HBA2: c.427T>C; p.Ter143Gln, also known as Ter142Gln when numbered from the mature protein, rs41464951, HbVar ID: 703) is usually asymptomatic in the heterozygous state, but may be associated with microcytosis and mild hypochromia. Homozygosity for HbCS is characterized by overt hemolytic anemia, jaundice and splenomegaly, while HbCS paired with an alpha zero-thalassemia deletion commonly results in HbH disease (Lie-Injo 1974, Nguyen 2014, HbVar database). This variant is reported in ClinVar (Variation ID: 15624), and is found in the general population with an overall allele frequency of 0.006% (16/279,508 alleles) in the Genome Aggregation Database. This variant abolishes the canonical termination codon, resulting in an unstable, elongated protein (HbVar database). Based on available information, the HbCS variant is considered to be pathogenic.

The pathogenic --SEA deletion (HbVar ID: 1086) is a common large deletion observed in East Asian

Result Footnote

f2: HBA FGA FE Int
populations (HbVar database and references therein). This deletion removes approximately 20kb including both HBA1 and HBA2 on the same chromosome, and therefore no functional mRNA is produced. Heterozygosity for this deletion is often associated with mild anemia and microcytosis, whereas homozygosity for this deletion results in Hb Bart hydrops fetalis syndrome.

RECOMMENDATIONS
Genetic consultation is recommended.

COMMENTS
Reference Sequences: GenBank # NM_000558.5 (HBA1), NM_000517.6 (HBA2), NG_000006.1 (Alpha globin gene cluster)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not reported.

REFERENCES
Link to HbVar database: https://globin.bx.psu.edu/hbvar/hbvar.html
Lie-Injo L et al. Homozygous state for Hb Constant Spring (slow-moving Hb X components). Blood. 1974 Feb;43(2):251-9. PMID: 4810076.
Nguyen V et al. Hemoglobin Constant Spring is markedly high in women of an ethnic minority group in Vietnam: a community-based survey and hematologic features. Blood Cells Mol Dis. 2014 Apr;52(4):161-5. PMID: 24368026.

This result has been reviewed and approved by

Test Information

i1: HBA FGA FE Int
BACKGROUND INFORMATION: Alpha Globin (HBA1 and HBA2) Sequencing and Deletion/Duplication, Fetal

CHARACTERISTICS: Alpha thalassemia is caused by decreased or absent synthesis of the hemoglobin alpha chain resulting in variable clinical presentations. Alpha (+) thalassemia results from variants of a single HBA2 globin gene (-a/aa) and is clinically asymptomatic (silent carrier). Alpha (0) thalassemia (trait) is caused by variants of both HBA2 globin genes (-a/-a) or variants in the HBA1 and HBA2 globin genes on the same chromosome (--/aa) and results in mild microcytic anemia. Hemoglobin H disease occurs due to variants of three alpha globin genes (--/-a) and results in hemolysis with Heinz bodies, moderate anemia, and splenomegaly. Hb Bart Hydrops Fetalis Syndrome results when variants occur in all four alpha globin genes (--/--) and is lethal in the fetal or early neonatal period. Alpha globin gene triplications result in three active alpha globin genes on a single chromosome. Nondeletional alpha globin variants may be pathogenic or benign; both may result in an abnormal protein detectable by hemoglobin evaluation. Pathogenic nondeletional variants often have a more severe effect than single gene deletions.

INCIDENCE: Carrier frequency in Mediterranean (1:30-50), Middle Eastern, Southeast Asian (1:20), African, African American (1:3).

INHERITANCE: Autosomal recessive.

Test Information

i1: HBA FGA FE Int

CAUSE: Pathogenic variants in the alpha globin gene cluster.

CLINICAL SENSITIVITY: 99 percent.

METHODOLOGY: Bidirectional sequencing of the HBA1 and HBA2 coding regions, intron-exon boundaries and 3' polyadenylation signal. Multiplex ligation-dependent probe amplification (MLPA) of the alpha globin gene cluster (HBZ, HBM, HBA1, HBA2, HBQ1) and the regulatory region multispecies conserved sequence 2 (MCS-R2, also known as HS-40 regulatory region).

ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.

LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Sequence analysis will not detect all regulatory region variants or variants in alpha globin cluster genes other than HBA1 and HBA2. Sequencing of both HBA1 and HBA2 may not be possible in individuals harboring large alpha globin deletions on both alleles. This assay is unable to sequence HBA2-HBA1 fusion genes; thus, HBA1 or HBA2 sequence variants occurring in cis with a 3.7 kb deletion or other HBA2-HBA1 hybrid gene will not be detected (e.g., HbG Philadelphia will not be detected when in cis with the 3.7 kb deletion). It may not be possible to determine phase of identified sequence variants. Specific breakpoints of large deletions/duplications will not be determined; therefore, it may not be possible to distinguish variants of similar size. Individuals carrying both a deletion and duplication within the alpha globin gene cluster may appear to have a normal number of alpha globin gene copies. Rare syndromic or acquired forms of alpha thalassemia associated with ATRX variants will not be detected. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.

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 purposes.

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