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

Physician: Doctor, Example

Patient: Patient, Example

DOB	7/9/1994
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Alpha Thalassemia (HBA1 and HBA2) Deletion/Duplication with reflex to Hb Constant Spring, Fetal

ARUP test code 3003656

Maternal Contamination Study Fetal Spec	Fetal Cells Single fetal genotype present; no maternal cells present. Fetal and maternal samples were tested using STR markers to rule out maternal cell contamination.
Maternal Contam Study, Maternal Spec	Whole Blood
Specimen HBA DDCSFE	Cultured Amnio
HBA DDCSFE Interpretation	See Note

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

Indication for testing: Prenatal testing for alpha thalassemia.

RESULT
Negative for the requested alpha globin deletion.

INTERPRETATION
According to information provided to ARUP, both parents of this fetus are carriers for alpha thalassemia, each harboring a pathogenic --SEA deletion. No large deletions or duplications, including the familial --SEA deletions, were detected in this fetal sample by deletion/duplication analysis of the alpha globin gene cluster and its HS-40 regulatory region. In addition, hemoglobin Constant Spring was not detected. Based on the reported family history, this fetus is predicted to be neither affected with, nor a carrier of, alpha thalassemia.

Evidence for variant classification: The pathogenic --SEA deletion (HbVar ID: 1086) is a common large deletion observed in East Asian 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. However, this testing was negative for this deletion.

RECOMMENDATIONS
Genetic consultation is recommended.

COMMENTS
Reference Sequences: GenBank # NM_000517.4 (HBA2), NG_000006.1 (alpha globin gene cluster)
Nucleotide numbering begins at the "A" of the ATG initiation codon.

References:
Link to HbVar database: https://globin.bx.psu.edu/hbvar/menu.html

This result has been reviewed and approved by [redacted]

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INTERPRETIVE INFORMATION: AlphaThal (HBA1/2) DelDup w/rflx HbCS FE

Characteristics of Alpha Thalassemia: Decreased or absent synthesis of the hemoglobin (Hb) alpha-chain resulting in clinical presentations ranging from asymptomatic silent carriers to severe anemia and fetal lethality. Alpha thalassemia silent carrier commonly results from deletion of a single alpha globin gene (-a/aa) and is clinically asymptomatic. Alpha thalassemia trait may be caused by deletion of a single alpha globin gene from both chromosomes (-a/-a), or deletion of the HBA1 and HBA2 globin genes from the same chromosome (--/aa). Heterozygosity for Hb Constant Spring (HbCS) is usually asymptomatic but may be associated with mild microcytic anemia. Homozygous HbCS is characterized by overt hemolytic anemia, jaundice and splenomegaly. Hemoglobin H disease occurs due to inactivation of three alpha globin genes and results in hemolysis with Heinz bodies, moderate anemia, and splenomegaly. Hb Bart hydrops fetalis syndrome results from deletion of all four alpha globin genes (--/--) and is lethal in the fetal or early neonatal period. Alpha globin gene duplication results in three or more active alpha globin genes on a single chromosome.
Epidemiology: Carrier frequency of alpha thalassemia in African, African-American (1:3), Mediterranean (1:30-50), Middle Eastern, Southeast Asian (1:20).
Inheritance: Autosomal recessive.
Cause: Pathogenic variants in the alpha globin gene cluster (HBZ, HBM, HBA2, HBA1, HBQ1) or regulatory region.
Clinical Sensitivity: Varies by ethnicity, at least 90 percent.
Methodology: Multiplex ligation-dependent probe amplification (MLPA) for the HBZ, HBM, HBA2, HBA1, and HBQ1 genes, the HS-40 regulatory region, and Hb Constant Spring (HbCS) HBA2 c.427T>C; p.Ter143Gln. To determine copy number of HbCS in absence of a concurrent deletion of HBA2, PCR and bidirectional sequencing for HbCS is performed.
Analytical Sensitivity and Specificity: 99 percent.
Limitations: Diagnostic errors can occur due to rare sequence variations. Specific breakpoints of large deletions/duplications will not be determined; therefore, it may not be possible to distinguish variants of similar size. Non-deletional variants within the coding or regulatory regions of the alpha globin cluster genes, other than HbCS, will not be targeted. Fetuses 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 gene variants 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.

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Maternal Contamination Study Fetal Spec	24-096-401983	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Maternal Contam Study, Maternal Spec	24-096-401983	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Specimen HBA DDCSFE	24-096-401983	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
HBA DDCSFE Interpretation	24-096-401983	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

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