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Patient Report

Patient Age/Gender: Unknown

Specimen Collected: 11-Mar-21 12:41

AlphaThal (HBA1/2) DelDup w/rflx HbCS FE | **Received: 11-Mar-21 12:41** | **Report/Verified: 22-Mar-21 17:02**

Procedure	Result	Units	Reference Interval
Maternal Contamination Study Fetal Spec	Fetal Cells [f1]		
Maternal Contam Study, Maternal Spec	Whole Blood [i1]		
Specimen HBA DDCSFE	Cultured Amnio		
HBA DDCSFE Interpretation	See Note [f2 i2]		

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 DDCSFE Interpretation

Indication for testing: Prenatal testing for alpha thalassemia.

RESULT
Two copies of the familial alpha globin deletion were detected.

DNA VARIANT
Pathogenic Deletion: --SEA; Homozygous
Predicted Fetal Genotype: --/--

INTERPRETATION
According to information provided to ARUP, both parents of this fetus are carriers of alpha thalassemia and each harbors a heterozygous Southeast Asian (--SEA) deletion. Two copies of the pathogenic --SEA deletion were detected in this fetal sample by deletion/duplication analysis of the alpha globin gene cluster. This result is consistent with the deletion of the HBM, HBA2, HBA1, and HBQ1 globin genes from both chromosomes; thus, this fetus is predicted to be affected with Hb Bart hydrops fetalis syndrome.

Evidence for variant classification: The pathogenic --SEA deletion 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.

RECOMMENDATIONS
Genetic consultation is recommended. For quality assurance purposes, ARUP Laboratories will confirm the above result at no charge following delivery. Order Confirmation of Fetal Testing and include a copy of the original fetal report (or the mother's name and date of birth) with the test submission. Please contact an ARUP genetic counselor (800-242-2787 ext 2141) prior to specimen submission.

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
HbVar --(SEA) link:
http://globin.bx.psu.edu/cgi-bin/hbvar/query_vars3?mode=output&display_format=page&i=1086

Result Footnote

f2: HBA DDCSFE Interpretation

This result has been reviewed and approved by Pinar Bayrak-Toydemir, M.D., Ph.D.

Test Information

i1: Maternal Contam Study, Maternal Spec

For quality assurance purposes, ARUP Laboratories will confirm the above result at no charge following delivery. Order Confirmation of Fetal Testing and include a copy of the original fetal report (or the mother's name and date of birth) with the test submission. Please contact an ARUP genetic counselor at (800) 242-2787 extension 2141 prior to specimen submission.

i2: HBA DDCSFE Interpretation

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

Test Information

i2: HBA DDCSFE Interpretation

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.