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PATIENT REPORT

Patient Age/Sex: Female

Specimen Collected: 13-Sep-22 10:30

Alpha Globin (HBA1 and 2) Seq, Del/Dup | **Received: 13-Sep-22 10:33** **Report/Verified: 13-Sep-22 10:37**

Procedure	Result	Units	Reference Interval
HBA Seq,Del/Dup Interp	See Note [f1 i1]		
HBA Seq,Del/Dup Specimen	Whole Blood		

Result Footnote

f1: HBA Seq, Del/Dup Interp

RESULT
One pathogenic deletion, resulting in the deletion of two alpha globin gene copies, was detected in the alpha globin gene cluster.

DNA VARIANT
Classification: Pathogenic
Deletion: --FIL/THAI/RT; Heterozygous

Predicted Genotype: --/aa

INTERPRETATION
One copy of a pathogenic alpha globin gene deletion was detected by deletion/duplication analysis of the alpha globin gene cluster and its HS-40 regulatory region. This result indicates the deletion of the HBZ, HBM, HBA2, HBA1 and HBQ1 globin genes on a single chromosome and is consistent with alpha thalassemia trait. Heterozygosity for this deletion is predicted to result in mild anemia and microcytosis. The clinical presentation may vary due to other genetic modifiers or co-existing conditions. Because this assay cannot determine the exact breakpoints of the identified deletion, this deletion may represent the --FIL, --THAI or --RT deletion, or a rare alpha globin deletion of similar size.

No pathogenic variants were detected in the HBA1 or HBA2 genes by sequencing.

Evidence for variant classification:
The --FIL, --THAI, and --RT deletions are pathogenic globin variants found in the Filipino, Thai, and northern European population respectively. All three deletions remove the alpha2, alpha1 and zeta globin, resulting in the absence of alpha and zeta globin chain production. Individuals heterozygous for these deletions exhibit microcytosis and hypochromia, while fetuses homozygous for these deletions do not survive to term due to the absence of the zeta chain during embryonic development.

RECOMMENDATIONS
Medical management should rely on clinical findings and family history. Carrier screening should be offered to this individual's reproductive partner as the couple's offspring could be at risk for Hemoglobin H disease or Hb Bart hydrops fetalis syndrome, depending on the partner's alpha globin genotype. Family members should be offered carrier testing for the identified deletion. 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 included in this report, but are available upon request.

REFERENCES
Link to HbVar database for the --THAI deletion:
http://globin.bx.psu.edu/cgi-bin/hbvar/query_vars3?mode=output&display_format=page&i=1095
Link to HbVar database for the --FIL deletion:
http://globin.bx.psu.edu/cgi-bin/hbvar/query_vars3?mode=output&display_format=page&i=1094

Unless otherwise indicated, testing performed at:
ARUP Laboratories
500 Chipeta Way, Salt Lake City, UT 84108
Laboratory Director: Jonathan R. Genzen, MD, PhD

ARUP Accession: 22-256-900044
Report Request ID: 16418141
Printed: 13-Sep-22 10:42

Result Footnote

f1: HBA Seq, Del/Dup Interp
Link to HbVar database for the --RT deletion:
http://globin.bx.psu.edu/cgi-bin/hbvar/query_vars3?mode=output&display_format=page&i=1074

This result has been reviewed and approved by [redacted]

Test Information

i1: HBA Seq, Del/Dup Interp
BACKGROUND INFORMATION: Alpha Globin (HBA1 and HBA2)
Sequencing and Deletion/Duplication
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.
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 its 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

Test Information

i1: HBA Seq, Del/Dup Interp

syndromic or acquired forms of alpha thalassemia associated with ATRX 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 U.S. 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.