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Patient Report

Patient Age/Gender: Unknown

Specimen Collected: 22-Mar-21 16:12

Alpha Globin (HBA1 and 2) Seq, Del/Dup **|Received: 22-Mar-21 16:13** **Report/Verified: 22-Mar-21 16:19**

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

Section 79-1 of New York State Civil Rights Law requires informed consent be obtained from patients (or their legal guardians) prior to pursuing genetic testing. These forms must be kept on file by the ordering physician. Consent forms for genetic testing are available at www.aruplab.com. Incidental findings are not reported unless clinically significant but are available upon request.

TEST PERFORMED - 2011708TEST DESCRIPTION - Alpha Globin (HBA1 and HBA2) Sequencing and Deletion/DuplicationINDICATION FOR TEST - Carrier StatusRESULTTwo pathogenic deletions, resulting in the deletion of two alpha globin gene copies, were detected in the alpha globin gene cluster.DNA VARIANTSClassification: PathogenicDeletion: -alpha3.7; HeterozygousClassification: PathogenicDeletion: -alpha4.2; HeterozygousPredicted Genotype: -a/-aINTERPRETATIONOne copy each of the 3.7 Kb alpha globin gene deletion and the 4.2 Kb alpha globin gene deletion were detected by deletion/duplication analysis of the alpha globin gene cluster and its HS-40 regulatory region. No pathogenic variants were detected by sequencing of the single alpha globin gene present on each chromosome. This individual is predicted to have a single functional alpha globin gene on each chromosome. This result is consistent with alpha thalassemia trait often associated with mild anemia and microcytosis. The clinical presentation may vary due to other genetic modifiers or co-existing conditions.Evidence for variant classifications: The pathogenic -alpha3.7 deletion is a common large deletion observed in numerous populations, including African, Indian, Far East and Mediterranean (HbVar database and references therein). This deletion removes approximately 3.7kb of the alpha globin cluster, resulting in a single functional alpha globin gene on the affected chromosome. Heterozygosity for this deletion does not result in clinical symptoms, but may be mistaken for iron deficiency. Homozygosity for this deletion is often associated with mild anemia and microcytosis.The pathogenic -alpha4.2 deletion is a common large deletion observed in the East and South Asian populations (HbVar database and references therein). This deletion removes approximately 4.2kb of the alpha globin cluster, resulting in the loss of the HBA2 gene on the affected chromosome. Heterozygosity for this deletion does not result in clinical symptoms, but may be mistaken for iron deficiency. Homozygosity for this deletion is often associated with mild anemia and microcytosis.RECOMMENDATIONSMedical management should rely on clinical findings and family history. Carrier screening for alpha thalassemia should be offered to this individual's relatives and reproductive partner. Genetic consultation is recommended.COMMENTSReference Sequences: GenBank #NM_000558.5 (HBA1), NM_000517.6 (HBA2), NG_000006.1 (Alpha globin gene cluster)
Likely benign and benign variants are not included in this report.REFERENCES
Link to HbVar database for the 3.7kb deletion:
http://globin.bx.psu.edu/cgi-bin/hbvar/query_vars3?mode=output&display_format=page&i=1076Link to HbVar database for the 4.2kb deletion:
http://globin.bx.psu.edu/cgi-bin/hbvar/query_vars3?mode=output&display_format=page&i=1079
This result has been reviewed and approved by Pinar Bayrak-Toydemir, M.D., Ph.D.

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 (+)

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H-High, i-Test Information, L-Low, t-Interpretive Text, @=Performing lab

Test Information

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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. 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.

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.

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

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