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Patient Report

Patient Age/Sex: Female

Specimen Collected: 08-Mar-22 07:40

Beta Globin by NGS | **Received: 08-Mar-22 07:40** **Report/Verified: 08-Mar-22 08:47**

Procedure	Result	Units	Reference Interval
BG Specimen	Whole Blood		
BG Interp	Positive f1 i1		

Result Footnote

f1: BG Interp

RESULT
Two apparent copies of a pathogenic variant were detected in the HBB gene.

PATHOGENIC VARIANT
Gene: HBB (NM_000518.5)
Nucleic Acid Change: c.20A>T; Homozygous
Amino Acid Alteration: p.Glu7Val
Commonly known as: Hb S
Inheritance: Autosomal recessive

INTERPRETATION
Two apparent copies of the pathogenic Hb S variant were detected in the HBB gene by massively parallel sequencing, consistent with a diagnosis of sickle cell anemia. Although copy number cannot be determined by this assay, the Hb S variant is a common pathogenic variant in the HBB gene and large HBB deletions/duplications are rare (Origa 2018); therefore, this result most likely represents homozygosity for the identified variant. The clinical presentation may vary due to other genetic modifiers or coexisting conditions.

Please refer to the background information included in this report for the clinical sensitivity and limitations of this test.

Evidence for variant classification: The Hb S variant (HBB: c.20A>T; p.Glu7Val, also known as Glu6Val when numbered from the mature protein, rs334) is a common pathogenic beta globin variant. Heterozygosity for Hb S is consistent with sickle cell trait. Homozygosity for Hb S results in sickle cell anemia. Hb S in combination with a different pathogenic HBB variant on the opposite chromosome results in various forms of sickle cell disease (see HbVar link and references therein).

RECOMMENDATIONS
Hematologic and genetic consultations are recommended. Parental testing should be considered to confirm the specific variant in each family lineage. If the patient's clinical presentation is not consistent with the phenotype expected to result from homozygosity for the identified variant, HBB deletion/duplication analysis should be considered (Deletion/Duplication Analysis by MLPA, ARUP test code 3003144). Family members should be offered carrier testing for the identified variant. This individual's reproductive partner should be offered carrier testing for hemoglobinopathies. Genetic consultation is recommended.

COMMENTS
Likely benign and benign variants are not reported.

REFERENCES
GeneReviews (Internet). Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1426/
Link to HbVar database for Hb S:
http://globin.bx.psu.edu/cgi-bin/hbvar/query_vars3?mode=output&display_format=page&i=226
Origa R. Beta-Thalassemia. 2000 Sep 28 (Updated 2018 Jan 25). In: Adam MP et al., editors.

This result has been reviewed and approved by [redacted]

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

Test Information

i1: BG Interp

BACKGROUND INFORMATION: Beta Globin (HBB) Sequencing

CHARACTERISTICS: Beta thalassemia is caused by decreased or absent synthesis of the hemoglobin beta-chain resulting in variable clinical presentations ranging from mild anemia to transfusion dependence. Structural hemoglobinopathies may result in sickling disorders, microcytic or hemolytic anemia, cyanosis, or erythrocytosis.
EPIDEMIOLOGY: Incidence varies by ethnicity.
CAUSE: Pathogenic germline variants within the HBB gene.
INHERITANCE: Usually autosomal recessive, infrequently autosomal dominant.
CLINICAL SENSITIVITY: Up to 99 percent, depending upon ethnicity, for beta thalassemia and hemoglobinopathies associated with the HBB gene.
GENE TESTED: HBB (NM_000518)
Deletion/duplication analysis is not available for this gene.
METHODOLOGY: Probe hybridization-based capture of all coding exons, exon-intron junctions, 5' proximal promoter and untranslated region, 3' polyadenylation signal, and intronic variants c.93-21G>A (IVS-I-110), c.316-197C>T (IVS-II-654), c.316-146T>G (IVS-II-705), and c.316-106C>G (IVS-II-745) of the HBB gene, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics.
ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.
LIMITATIONS: A negative result does not exclude a diagnosis of beta thalassemia. This test detects variants within the coding regions and intron-exon boundaries of the HBB gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants upstream of c.-250, deep intronic variants (other than those described in methodology section above), and large deletions/duplications will not be identified. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) variants, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

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.

Test Information

i1: BG Interp

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

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