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Patient Report

Patient Age/Sex: Male

**Specimen Collected: 08-Mar-22 07:42**

**Beta Globin by NGS Fetal** | **Received: 08-Mar-22 07:42** **Report/Verified: 08-Mar-22 08:41**

| Procedure | Result | Units | Reference Interval |
|---|---|---|---|
| Maternal Contamination Study Fetal Spec | Fetal Cells [f1] | | |
| Maternal Contam Study, Maternal Spec | Whole Blood [i1] | | |
| BG FE Specimen | Cultured Amnio | | |
| BG FE Interp | Positive [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: BG FE Interp
RESULT
Two 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
According to information provided to ARUP Laboratories, both parents of this fetus are reported to be heterozygous for the HBB c.20A>T; p.Glu7Val (Hb S) pathogenic variant via previous molecular testing at an outside laboratory. Two apparent copies of the pathogenic HBB Hb S variant were detected in this fetal sample by massively parallel sequencing, consistent with a diagnosis of sickle cell anemia in this fetus. Although sequence analysis is not able to detect large HBB deletions, based on the parental beta globin results and given HBB full gene deletions are not common (Origa, 2018), this fetus is predicted to have two copies of Hb S. 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
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 x2141) prior to specimen submission.

COMMENTS
Likely benign and benign variants are not reported.

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

## Result Footnote

f2: BG FE Interp
REFERENCES
Link to HbVar database for HBB:
http://globin.bx.psu.edu/cgi-bin/hbvar/query_vars3?mode=output&display_format=page&i=226

Origa R. Beta-thalassemia. 2000 (Updated Jan 2018). In: Adam MP, et al., eds. GeneReviews: University of Washington; 1993-2021. Available from https://www.ncbi.nlm.nih.gov/books/NBK1426/

This result has been reviewed and approved by [redacted]

## 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: BG FE Interp
BACKGROUND INFORMATION: Beta Globin (HBB) Sequencing, Fetal

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 detection 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

## Test Information

i2: BG FE Interp

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. 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.

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