ARUP LABORATORIES
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Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	10/14/2006
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Hereditary Hemolytic Anemia Cascade

ARUP test code 3000894

Hereditary Hemolytic Anemia Interp

See Note

HEREDITARY HEMOLYTIC ANEMIA SUMMARY:
Slightly decreased osmotic fragility and normal blood cell surface band 3 fluorescence.
One pathogenic deletion, resulting in the deletion of one alpha globin gene copy, was detected in the alpha globin gene cluster.
Normal G6PD level and pyruvate kinase activity.
Negative unstable hemoglobin.
See comments.

COMMENTS:
These findings are not suggestive of hereditary spherocytosis, unstable hemoglobin, G6PD and pyruvate kinase deficiencies. One copy of the 3.7 kb alpha globin gene deletion is consistent with the deletion of a single alpha gene and predicts alpha (+) thalassemia (silent carrier). Heterozygosity for the 3.7 kb deletion does not result in clinical symptoms but may lead to erroneous diagnosis of and treatment for iron deficiency.
Please correlate with clinical and other laboratory findings

Summary of the tests performed:

Osmotic Fragility, Erythrocyte (2002257): Patient's red blood cells show decreased osmotic fragility.
Hemoglobin, Unstable (0049020): Negative
RBC Band 3 Protein Reduction (2008460): Normal
Glucose-6-Phosphate Dehydrogenase (0080135): 14.5 U/g Hb (Ref Interval: 9.9-16.6)
Pyruvate Kinase (0080290): 9.9 U/g Hb (Ref Interval: 4.6-11.2)
Peripheral Smear, Interpretation (3001947):
PERIPHERAL BLOOD SMEAR DIAGNOSIS:
- MORPHOLOGICALLY UNREMARKABLE PERIPHERAL BLOOD SMEAR
- EVALUATION LIMITED BY LACK OF CONCURRENT CBC DATA
- SEE COMMENTS

CLINICAL HISTORY:
The patient is a 16-year-old male undergoing hereditary hemolytic anemia testing.
Indication for review: HHA cascade

CBC ACCESSION: N/A (there is no concurrent CBC provided)
CBC DATE: N/A

MANUAL WBC DIFFERENTIAL (100 cells)
Neutrophils: 69%
Lymphocytes: 23%
Monocytes: 4%

H=High, L=Low, *=Abnormal, C=Critical

Eosinophils: 4%

MORPHOLOGY
ERYTHROCYTES: appear normal in number, appear normocytic and normochromic, minimal anisopoikilocytosis, no significant polychromasia
WHITE BLOOD CELLS: appear normal in number, normal morphology
PLATELETS: appear adequate in number, normal morphology

Hemoglobin Evaluation with Reflex (0050610):
Hemoglobin A:97.0(Ref Interval: 95.0 97.9)
Hemoglobin A2: 2.7(Ref Interval: 2.0 3.5)
Hemoglobin F:0.3(Ref Interval: 0.0 2.1)
Hemoglobin S: 0.0(Ref Interval: 0.0 0.0)
Hemoglobin C: 0.0(Ref Interval: 0.0 0.0)
Hemoglobin E: 0.0 (Ref Interval: 0.0 0.0)
Hemoglobin Other:0.0(Ref Interval: 0.0 0.0)
Sickle Cell Solubility: Not Performed
Hemoglobin, Capillary Electrophoresis: Performed
Impression: Normal HPLC evaluation.

This normal HPLC result does not rule out the possibility of alpha globin gene deletions associated with silent carrier status or alpha thalassemia trait. Individuals who carry a rare, Greek beta thalassemia variant often have a normal Hb A2 and may not be identified by this assay. Please correlate with clinical and laboratory findings.

Alpha Globin Deletion/Duplication (HBA DD, 2011622): Performed
RESULT
One pathogenic deletion, resulting in the deletion of one alpha globin gene copy, was detected in the alpha globin gene cluster.

DNA VARIANT(S)
Pathogenic Deletion: -alpha3.7; Heterozygous
Predicted Genotype: -a/aa

INTERPRETATION
One copy of the 3.7 kb alpha globin gene deletion was detected by deletion/duplication analysis of the alpha globin gene cluster and its HS-40 regulatory region. This result is consistent with the deletion of a single alpha gene and predicts alpha (+) thalassemia (silent carrier). Heterozygosity for the 3.7 kb deletion does not result in clinical symptoms but may lead to erroneous diagnosis of and treatment for iron deficiency. The variant is common among Black/African American individuals.

RECOMMENDATIONS
Medical management should rely on clinical findings and family history. This test detects only large deletions/duplications and not all pathogenic alpha globin variants. If clinical findings suggestive of alpha-thalassemia disease or trait are present, consider alpha globin gene sequencing. Carrier screening for alpha thalassemia should be offered to this individual's relatives and reproductive partner. Genetic consultation is recommended.

COMMENTS
Reference sequence for alpha globin gene cluster: NG_000006.1

REFERENCES
HbVar 3.7kb deletion link: http://globin.bx.psu.edu/cgi-bin/hbvar/query_vars3?mode=output&display_format=page&i=1076

Beta Globin (HBB) Deletion/Duplication: Not Performed

Hereditary Hemolytic Anemia Seq (HHA SEQ, 2012052): Not Performed

G6PD Deficiency (G6PD) Sequencing (G6PD FGS, 2007163): Not Performed

H=High, L=Low, *=Abnormal, C=Critical

Beta Globin Sequencing (BG NGS, 3004547): Not Performed

Alpha Globin (HBA1 and HBA2) Sequencing: Not Performed

Gamma Globin (HBG1 and HBG2) Sequencing: Not Performed

Controls were run and performed as expected.
This result has been reviewed and approved by [redacted]

INTERPRETIVE INFORMATION: Osmotic Fragility

For patients with acute hemolysis, a normal red cell osmotic fragility test result cannot exclude an osmotic fragility abnormality since the osmotically labile cells may be hemolyzed and not present. Recommend testing during a state of prolonged homeostasis with stable hematocrit.

INTERPRETIVE INFORMATION: RBC Band 3 Protein Reduction in HS

This test can be used to confirm a suspected diagnosis of Hereditary Spherocytosis (HS). HS is a common inherited hemolytic anemia characterized by the presence of spherical erythrocytes (spherocytes). HS is diagnosed based on family history and clinical features, along with clinical laboratory tests, including peripheral smear examination, osmotic fragility (OF), flow cytometry, or by genetic testing (Hereditary Hemolytic Anemia Panel Sequencing. ARUP test code 2012052).

Band 3 (or solute carrier family 4 member 1, SLC4A1) is the most abundant transmembrane protein found in human red blood cells (RBC). Eosin-5-maleimide (EMA) dye binds to band 3 on intact RBC's. A reduction of fluorescence intensity will be seen in hereditary spherocytosis. This test by flow cytometry has been reported to have a sensitivity of 93 percent for a diagnosis of HS. Congenital Dyserythropoietic Anemia Type II, Southeast Asian Ovalocytosis and Hereditary Pyropoikilocytosis are rare disorders that may also show a positive result.

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.

REFERENCE INTERVAL: Hemoglobin F

Access complete set of age- and/or gender-specific reference intervals for this test in the ARUP Laboratory Test Directory (aruplab.com).

BACKGROUND INFORMATION: Alpha Globin (HBA1 and HBA2) 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 mutation of a single alpha2 globin gene (-a/aa) and is clinically asymptomatic (silent carrier). Alpha (0) thalassemia (trait) is caused by mutation of both alpha2 globin genes (-a/-a), or mutations in the alpha1 and alpha2 globin genes on the same chromosome, (--/aa) and results in mild microcytic anemia. Hemoglobin H disease occurs due to mutation of three alpha globin genes (--/-a) and results in hemolysis with Heinz bodies, moderate anemia, and splenomegaly. Hb Bart Hydrops Fetalis Syndrome results when mutations 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.

INCIDENCE: Carrier frequency in Mediterranean (1:30-50), Middle Eastern, Southeast Asian (1:20), African, African-American (1:3).
INHERITANCE: Autosomal recessive.
CAUSE: Pathogenic mutations in the alpha globin gene cluster.
CLINICAL SENSITIVITY: Varies by ethnicity, up to 95 percent.
METHODOLOGY: Multiplex ligation-dependent probe amplification (MLPA) of the alpha globin gene cluster (HBZ, HBM, HBA2, HBA1, HBQ1) and its HS-40 regulatory region.
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 mutations of similar size. This assay does not assess for non-deletional mutations within the coding or regulatory regions of the alpha globin cluster genes. 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 mutations will not be detected.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Hereditary Hemolytic Anemia Interp	23-229-400445	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical