ARUP LABORATORIES
800-522-2787 | aruplab.com
500 Chipeta Way, Salt Lake City, UT 84108-1221
Tracy I. George, MD, Chief Medical Officer

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

Physician: Doctor, Example

Patient: Patient, Example

DOB	11/20/1979
Gender:	Male
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:
One pathogenic variant detected in the SLC4A1 gene.
Patients red blood cells show moderately increased osmotic fragility.
A reduction in RBC cell surface band 3 fluorescence.
Normal hemoglobin evaluation.
Normal result for G6PD, Pyruvate kinase and Unstable hemoglobin.
Peripheral smear evaluation only significant for rare spherocytes.
See comments.

COMMENTS:
The findings of a pathogenic SLC4A1 variant along with abnormal osmotic fragility and RBC Band 3 testing are consistent with a diagnosis of hereditary spherocytosis. Please correlate with clinical findings.

MOLECULAR RESULT SUMMARY:

PATHOGENIC VARIANT
Gene: SLC4A1 (NM_000342.3)
Nucleic Acid Change: c.2057+1G>C; Heterozygous
Inheritance: Autosomal Dominant

INTERPRETATION
One copy of a pathogenic variant, c.2057+1G>C, was detected in the SLC4A1 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic variants in SLC4A1 (which encodes erythrocyte membrane protein band 3) are inherited in an autosomal dominant manner and are associated with spherocytosis, type 4 (MIM: 612653). Therefore, this result is consistent with a diagnosis of spherocytosis. Offspring of this individual have a 50 percent chance of inheriting this pathogenic variant.

No other pathogenic variants or variants of uncertain significance were identified in the targeted genes by massively parallel sequencing. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant interpretation:
The SLC4A1 c.2057+1G>C variant, to our knowledge, is not reported in the medical literature or gene specific databases. However, an alternative change at this position (c.2057+1G>A) has been reported in on individuals affected with hereditary spherocytosis (Petkova-Kirova 2019). This variant is also absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This variant disrupts the canonical splice donor

Unless otherwise indicated, testing performed at:
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site of intron 16, which is likely to negatively impact gene function. Based on available information, this variant is considered pathogenic.

RECOMMENDATIONS
Hematologic and genetic consultations are recommended. Medical management should rely on clinical findings and family history. At-risk family members should be offered targeted testing for the identified pathogenic SLC4A1 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Benign and likely benign variants are not included in this report. Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics.

REFERENCES:
Petkova-Kirova P et al. Red Blood Cell Membrane Conductance in Hereditary Haemolytic Anaemias. Front Physiol. 2019 10:386.

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

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.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement B: aruplab.com/CS

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).

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Hereditary Hemolytic Anemia Interp	21-005-403063	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