Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: arup, arup

Patient: Test, ECYT NGS Pos

DOB

Sex: Female

Patient Identifiers: 44263

Visit Number (FIN): 44590

Collection Date: 11/15/2022 10:59

Hereditary Erythrocytosis Panel, Sequencing

ARUP test code 3005721

ECYT Specimen	Whole Blood
ECYT Interp	Positive

RESULT
One pathogenic variant was detected in the EGLN1 gene.

PATHOGENIC VARIANT
Gene: EGLN1 (NM_022251.3)
Nucleic Acid Change: c.661C>T; heterozygous
Amino Acid Alteration: p.Gln221Ter
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.661C>T; p. Gln221Ter, was detected in the EGLN1 gene by massively parallel sequencing in this cultured fibroblasts specimen. Pathogenic EGLN1 variants are inherited in an autosomal dominant manner and are associated with familial erythrocytosis 3 (MIM: 609820). This result is consistent with a diagnosis of familial erythrocytosis. This individuals offspring have a 50 percent chance of inheriting the pathogenic variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The EGLN1 c. 661C>T; p. Gln221Ter variant, also known in the literature as PHD2, is reported in the literature in multiple individuals from a single family affected with erythrocytosis (Wilson, 2016). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. Close correlation with clinical findings, family history, and laboratory data including hematologic parameters is recommended. At-risk family members should be offered testing for the identified pathogenic variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected with sufficient confidence in this sample due to technical

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

limitations:
NONE

REFERENCES
Wilson R, et al. Erythrocytosis due to PHD2 mutations: a review of clinical presentation, diagnosis, and genetics. Case Rep Hematol. 2016 [Published online ahead of print Feb 2016] PMID: 27034858

BACKGROUND INFORMATION: Hereditary Erythrocytosis Panel, Sequencing

CHARACTERISTICS: Hereditary erythrocytosis, also known as familial erythrocytosis or congenital polycythemia, is a group of disorders in which inherited/germline pathogenic variants cause increased red blood cell (RBC) production, leading to elevated hemoglobin and hematocrit levels. Symptoms may include headaches, dizziness, dyspnea, and epistaxis. Overabundance of RBC may lead to hemorrhagic or thrombotic events, including myocardial infarction and deep vein thrombosis, although many individuals with erythrocytosis experience mild symptoms and may even be asymptomatic. Hereditary erythrocytosis can be categorized as primary, caused by pathogenic variants leading to intrinsic defects in hematopoietic stem cells that increase RBC production, or secondary caused by pathogenic variants that drive RBC production by increasing erythropoietin (EPO). Hereditary erythrocytosis is suspected in individuals for whom acquired erythrocytosis (either primary or secondary) has been excluded, and in those with early age of onset or a family history of erythrocytosis.

EPIDEMIOLOGY: Hereditary erythrocytosis is rare but the exact prevalence is unknown. Up to 70 percent of cases have no identified cause and are classified as idiopathic erythrocytosis.

CAUSE: Pathogenic germline variants in genes associated with erythrocytosis

INHERITANCE: Mostly autosomal dominant with some autosomal recessive disorders

GENES TESTED: BPGM, EGLN1 (PHD2), EPAS1 (HIF2), EPOR, HBB, HIF1A, JAK2, SH2B3, VHL*
*One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, 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. Human genome build 19 (Hg 19) was used for data analysis.

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. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a diagnosis of erythrocytosis. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants, deep intronic variants, 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 variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) mutations, or repeat expansions. This assay is also not intended to detect somatic variants associated with hematologic malignancy, though such variants may be detected incidentally. Though this test is designed to identify germline variants associated with erythrocytosis, it cannot definitively determine the germline or somatic origin of detected variants when the patient has acquired erythrocytosis or hematologic malignancy and the assay is performed on blood or other tissue that may be contaminated by clonal or malignant cells. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

SNVs and indels will not be called in the following regions due to technical limitations of the assay: VHL (NM_001354723) exon 2

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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
ECYT Specimen	22-319-105076	11/15/2022 10:59:00 AM	11/15/2022 10:59:16 AM	11/15/2022 11:02:00 AM
ECYT Interp	22-319-105076	11/15/2022 10:59:00 AM	11/15/2022 10:59:16 AM	11/15/2022 11:02:00 AM

END OF CHART

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