Hereditary Erythrocytosis Panel, Sequencing

Erythrocytosis (ECYT) is characterized by an overproduction of red blood cells (RBCs), which leads to elevated hemoglobin and hematocrit levels. Symptoms may include headaches, dizziness, dyspnea, and epistaxis. The overabundance of RBCs may lead to hemorrhagic or thrombotic events, including myocardial infarction and deep vein thrombosis, although many individuals with ECYT experience mild symptoms and may be asymptomatic.

Hereditary ECYT, also known as familial ECYT or congenital polycythemia, is a group of disorders in which ECYT is caused by inherited/germline pathogenic variants.

Featured ARUP Testing

Hereditary Erythrocytosis Panel, Sequencing 3005721

Method: Massively Parallel Sequencing

- Use to assess for **inherited/germline** DNA variants associated with familial erythrocytosis. **The preferred sample type is cultured skin fibroblasts; testing whole blood in affected patients may not definitively determine germline status.**
- Not intended to detect somatic variants; refer to the Laboratory Test Directory for test options to assess for acquired erythrocytosis or somatic variants of prognostic and/or therapeutic significance.

Genetics

ECYT can be categorized as primary ECYT, caused by pathogenic variants leading to intrinsic defects in hematopoietic stem cells that increase RBC production, or secondary ECYT caused by pathogenic variants that drive RBC production by increasing erythropoietin (EPO) levels. Hereditary ECYT is suspected when acquired ECYT (either primary or secondary) has been excluded in an individual, and hereditary ECYT is suspected in those with early age of onset or a family history of ECYT.

Genes Tested

Gene	MIM #	Disorders	Inheritance
BPGM	613896	Secondary ECYT Familial ECYT 8 (ECYT8)	AR
EGLN1 (*PHD2*)	606425	Secondary ECYT Familial ECYT 3 (ECYT3)	AD
EPAS1 (*HIF2A*)	603349	Secondary ECYT Familial ECYT 4 (ECYT4)	AD
EPOR	133171	Primary ECYT Familial ECYT 1 (ECYT1)	AD
HBB	141900	Secondary ECYT	AD

AD, autosomal dominant; AR, autosomal recessive

Gene	MIM #	Disorders	Inheritance
		High oxygen affinity hemoglobin variants Familial ECYT 6 (ECYT6)	
		Beta thalassemia Sickle cell anemia	AR
HIF1A	603348	Secondary ECYT	Unknown
JAK2	147796	Hereditary thrombocytosis	AD
		Polycythemia vera Myelofibrosis ECYT	Somatic
SH2B3	605093	Primary ECYT	Unknown
		ECYT Myelofibrosis Thrombocythemia	Somatic
VHL	608537	Secondary ECYT Familial ECYT 2 (ECYT2), Chuvash polycythemia	AR
		von Hippel-Lindau syndrome (VHL)	AD

AD, autosomal dominant; AR, autosomal recessive

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.

Sensitivity and/or Specificity

Clinical Sensitivity

Approximately 30% (up to 70% of cases of hereditary ECYT have no identifiable cause and are considered idiopathic ECYT)

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) Estimate (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9

[a]PPA values are derived from larger methods-based MPS and/or Sanger validations.

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a diagnosis of ECYT.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation, unless the sample analyzed is definitively from the recipient, such as cultured skin fibroblasts.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted genes
  - Regulatory region and deep intronic variants
  - The following exons are not sequenced due to technical limitations of the assay:
    - *VHL* (NM_001354723) exon 2
  - Large deletions/duplications in any of the tested genes
- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Some variants due to technical limitations in the presence of pseudogenes and/or repetitive or homologous regions
  - Low-level somatic variants
- The germline or somatic status of a detected variant cannot be definitively determined in patients with acquired ECYT or hematologic malignancy if the assay is performed on blood or other tissue that may be contaminated by clonal or malignant cells; testing a definitively germline specimen such as cultured fibroblasts may be recommended in such cases.

Related Information

Myeloproliferative Neoplasms - MPNs

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
Content Review August 2022 | Last Update September 2023