

Polycythemia, Congenital (*VHL*) Sequencing

TO DETERMINE THE ETIOLOGY OF CONGENITAL POLYCYTHEMIA

Disease Overview

- The von Hippel-Lindau protein (pVHL) is involved with hypoxia sensing, which is important in regulating energy metabolism, angiogenesis, erythropoiesis, and other bodily functions.
- During normoxia, pVHL binds to the alpha subunit of the hypoxia-induced factor 1 (HIF-1 α) transcription factor, and the complex is degraded. During hypoxia or secondary to a mutated *VHL* gene, HIF-1 α dimerizes with HIF-1 β , resulting in the activation of genes involved with vasculogenesis, energy and iron metabolism, and erythropoiesis.
- Chuvash polycythemia, also referred to as autosomal recessive benign congenital polycythemia, results in increased serum erythropoietin levels and hemoglobin concentrations in normoxia.
- Individuals with congenital polycythemia due to homozygous/compound heterozygous *VHL* mutations are not at risk for the tumors associated with VHL syndrome, but may have vascular abnormalities (i.e., benign vertebral hemangiomas, varicose veins, hypertension) or thrombosis.
- Thrombotic or hemorrhagic vascular complications often contribute to mortality. Life expectancy is typically <40 years.
- Individuals heterozygous for *VHL* mutations associated with congenital polycythemia typically do not exhibit disease.
- Patients may be managed with phlebotomy to maintain hematocrit below 45 percent. They may also be treated with anticoagulation therapy.

Prevalence

- Congenital polycythemia is rare worldwide but endemic in the Chuvash region of central Russia.

Genetics

- Autosomal recessive.
- The *VHL* mutation c.598C>T (p.R200W), although commonly detected in Russian Chuvashes, has also been detected in European, African-American, and Pakistani/Bangladeshi populations.
- Compound heterozygosity involving *VHL* mutations c.598C>T, c.235C>T (p.R79C), c.388G>C (p.V130L), c.562C>G (p.L188V), c.574C>T (p.P192A), as well as homozygosity for either the c.571C>G (p.H191D) or the c.598C>T (p.R200W) mutation, is associated with congenital polycythemia.
- To date, *VHL* deletions have not been reported in congenital polycythemia.

Indication for Ordering

- To determine the cause of congenital polycythemia in symptomatic individuals.

Contraindications

- Testing for individuals with previously identified familial *VHL* mutation(s). To test individuals for a specific sequence mutation, it is more cost-effective to order [Familial Mutation, Targeted Sequencing \(ARUP test #2001961\)](#). A copy of the lab report detailing the familial mutation(s) must be provided for targeted sequencing.
- Prenatal testing.

Interpretation

- The detection of two known deleterious *VHL* gene mutations predicts congenital polycythemia.
- When one or no mutations are detected in a clinically affected individual, medical management should rely on clinical findings.
- When one deleterious mutation is detected in a clinically unaffected individual, the individual is predicted to be at least a carrier.
- *VHL* mutations of unknown clinical significance may be detected by this assay.

Methodology

- Bidirectional sequencing of the entire *VHL* coding region and intron-exon borders.
- Analytical sensitivity and specificity are 99 percent.
- Clinical sensitivity of *VHL* sequencing is approximately 20 percent for congenital erythrocytosis.

Limitations

- Large deletions and duplications, deep intronic mutations, and regulatory region mutations are not detected.
- Rare diagnostic errors may occur due to primer-site mutations.
- Polycythemia due to causes other than *VHL* gene mutations will not be detected.

Related Tests

- [Von Hippel-Lindau \(*VHL*\) Sequencing and Deletion/Duplication \(2002965\)](#)
- [Von Hippel-Lindau \(*VHL*\) Deletion/Duplication \(2002988\)](#)
- [Familial Mutation, Targeted Sequencing \(2001961\)](#)
- [Erythropoietin \(0050227\)](#)

References

1. Gordeuk VR, et al. Congenital disorders of oxygen sensing: association of the homozygous Chuvash polycythemia VHL mutation with thrombosis and vascular abnormalities but not tumors. *Blood* 2005;103(10):3924–32.
2. Pastore Y, et al. Mutations of von Hippel-Lindau tumor-suppressor gene and congenital polycythemia. *Am J Hum Genet* 2003;73:412–9.
3. Online GeneTests: von Hippel-Lindau Syndrome. www.genetests.org (accessed on April 1, 2009).
4. Sergeyeva A, et al. Congenital polycythemia in Chuvashia. *Blood* 1997;89:2148–54.

Test Information

2002970 von Hippel-Lindau (VHL) Sequencing

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.