

# von Hippel-Lindau (VHL) Sequencing and Deletion/ Duplication

## TO CONFIRM A DIAGNOSIS OF VON HIPPEL-LINDAU SYNDROME

### Disease Overview

- The von Hippel-Lindau protein (pVHL) has a significant role in regulating the cellular response to oxygen levels.
- During normoxia, a protein complex containing pVHL binds to the alpha subunit of the hypoxia-induced factor 1 (HIF-1 $\alpha$ ) transcription factor and targets it for degradation. During hypoxia, HIF-1 $\alpha$  dimerizes with HIF-1 $\beta$  resulting in the activation of genes involved with vasculogenesis, energy and iron metabolism, and erythropoiesis. This reaction may also occur due to a mutated *VHL* gene.
- pVHL has additional roles that may also contribute to the phenotype of von Hippel-Lindau syndrome.
- Disease expression varies among families but characteristic findings may include: retinal (73 percent), cerebellar (57 percent), spinal (25 percent) hemangioblastoma, renal-cell carcinoma (35 percent), pheochromocytoma (10–20 percent), endolymphatic sac tumors (11 percent), pancreatic endocrine tumors (5–10 percent), and hemangiomas of adrenals, lungs, and liver.
- Polycythemia is not a common manifestation of VHL syndrome.
- Mean age of disease onset is 26 years.
- Life expectancy for individuals with VHL syndrome is <50 years. The most common causes of mortality are cerebellar hemangioblastoma and metastatic RCC.
- Surveillance for associated tumors using suggested protocols (e.g., National Institutes of Health) and early intervention may result in improved prognosis for individuals with VHL syndrome.

### Prevalence

The incidence of VHL syndrome is one in 36,000 births for Caucasians.

### Genetics

- Autosomal dominant; de novo mutations occur in 20 percent of cases.
- Penetrance is nearly complete by age 65.
- The tumor suppressor gene, *VHL*, is the only gene associated with VHL syndrome.
- Approximately 72 percent of causative mutations are *VHL* sequence mutations, and 28 percent are large deletions.
- Mosaicism for germline *VHL* mutations has been reported.
- Genotype-phenotype correlations have allowed for differentiation based on risk for pheochromocytoma and RCC.
- Type 1 VHL: low risk for pheochromocytoma, associated with loss-of-function mutations.
- Type 2 VHL: high risk for pheochromocytoma, associated with missense mutations.
- Type 2A: low risk for RCC.
- Type 2B: high risk for RCC.
- Type 2C: associated only with familial pheochromocytoma.

### Indications for Ordering

- To confirm a clinical diagnosis of VHL syndrome in affected individuals.
- To determine if at-risk family members have a *VHL* mutation when the familial mutation is unknown and affected relatives are not available for testing.

### Contraindications

- Testing for individuals with a previously identified familial *VHL* mutation. 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 must be provided for targeted sequencing.
- Prenatal testing.

### Interpretation

- Identification of a known deleterious *VHL* mutation in a symptomatic individual confirms a diagnosis of VHL syndrome.
- Lack of an identifiable *VHL* mutation in a clinically affected individual greatly reduces the chance for VHL syndrome; management should rely on clinical findings.
- *VHL* mutations of unknown clinical significance may be detected by this assay.

### Methodology

- Bidirectional sequencing and multiplex ligation-dependent probe amplification (MLPA) of the entire *VHL* coding region and intron-exon borders.
- Analytical sensitivity and specificity of sequencing are 99 percent. Analytic sensitivity and specificity of MLPA are 90 and 98 percent, respectively.
- The combined clinical sensitivity of *VHL* sequencing and deletion/duplication testing is 99 percent for VHL syndrome.

### Limitations

- Deep intronic mutations and regulatory region mutations are not detected.
- Rare diagnostic errors may occur due to primer- or probe-site mutations.
- Breakpoints of large deletions/duplications detected in *VHL* will not be determined.

### Related Tests

- [Von Hippel-Lindau \(VHL\) Sequencing \(2002970\)](#)
- [Von Hippel-Lindau \(VHL\) Deletion/Duplication \(2002988\)](#)
- [Familial Mutation, Targeted Sequencing \(2001961\)](#)

### References

1. Choyke PL, et al. Von Hippel Lindau disease: genetic, clinical and imaging features. *Radiology* 1995;146:629–42.

2. Ong KR, et al. Genotype-phenotype correlations in von Hippel-Lindau Disease. *Hum Mutat* 2007;28(2):143–9.
3. Sgambati MT, et al. Mosaicism in von Hippel-Lindau disease: lessons from kindreds with germline mutations identified in offspring with mosaic parents. *Am J Hum Genet* 2000;66:84–91.
4. Online GeneTests: von Hippel-Lindau Syndrome. [www.genetests.org](http://www.genetests.org) (accessed on April 1, 2009).

## Test Information

### 2002965 von Hippel-Lindau (VHL) Sequencing and Deletion/Duplication

For specific collection, transport, and testing information, refer to the ARUP website at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).