

von Hippel-Lindau Syndrome

Indications for Ordering

- Confirm diagnosis of von Hippel-Lindau (VHL) syndrome
 - Indicated for all individuals known to have or suspected of having VHL syndrome
 - Evaluate individuals with single *VHL*-associated tumor and negative family history for VHL syndrome
- Confirm diagnosis of *VHL*-associated polycythemia (Chuvash polycythemia)
- Determine whether at-risk family members have a *VHL* gene variant

Test Description

- Polymerase chain reaction followed by bidirectional sequencing of *VHL* coding regions and intron/exon boundaries
- Multiplex ligation-dependent probe amplification to detect large deletions/duplications

Tests to Consider

Primary tests

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

- Preferred test to confirm a suspected diagnosis of VHL syndrome

[von Hippel-Lindau \(VHL\) Sequencing 2002970](#)

- Acceptable initial test to confirm a suspected diagnosis of VHL syndrome
- Preferred test to confirm a suspected diagnosis of *VHL*-associated polycythemia

Related tests

[Familial Mutation, Targeted Sequencing 2001961](#)

- Useful when a familial pathogenic variant identifiable by sequencing is known

[Cancer Panel, Hereditary, Sequencing and Deletion/Duplication, 47 Genes 2012032](#)

- Confirm diagnosis of a hereditary cancer syndrome with personal or family history consistent with features of more than one cancer syndrome

[Renal Hereditary Cancer Panel, Sequencing and Deletion/Duplication, 15 Genes 2010214](#)

- Preferred test to confirm a diagnosis of hereditary renal cancer syndrome in individuals with personal or family history of renal cancer

Disease Overview

VHL syndrome

Incidence – 1/36,000 Caucasian births (Maher, 1991)

Age of onset

- Mean age – 26 years
- Life expectancy – <50 years

Symptoms

- Penetrance of symptoms in individuals with VHL syndrome (Frantzen, 2015)
 - CNS hemangioblastoma – 80% brain, 20% spinal cord
 - Retinal hemangioblastoma – 70%
 - Renal cell carcinoma – 70%
 - Pheochromocytoma – 10-20%
 - Endolymphatic sac tumor – 10%
 - Pancreatic endocrine tumor – 5-10%
- Other symptoms
 - Hemangiomas in adrenals, lungs, and liver
 - Cysts in kidneys, pancreas, and epididymis

VHL-associated polycythemia

Prevalence – rare worldwide, endemic in the Chuvash region of Russia

Age of onset

- Birth to early childhood
- Life expectancy – <40 years

Symptoms

- Increased serum erythropoietin levels and hemoglobin concentrations during normoxia
 - Leads to increased circulating red blood cell mass
- Increased risk for mortality caused by thrombosis and/or hemorrhage
- No increased risk for tumors that are associated with VHL syndrome

Genetics

Gene – *VHL*

Inheritance

- VHL syndrome – autosomal dominant
- *VHL*-associated polycythemia – autosomal recessive

Penetrance – nearly complete by age 65 for VHL syndrome

De novo variants – ~20% of VHL syndrome cases

Pathogenic variants – >300 identified

- Specific *VHL* sequence variants have been associated with *VHL*-associated polycythemia (eg, c.598C>T, p.R200W)

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity
 - *VHL* syndrome – >99% (Stolle, 1998)
 - ~72% for sequence analysis
 - ~28% for deletion/duplication analysis
 - *VHL*-associated polycythemia (familial erythrocytosis, Chuvash polycythemia) – ~20% (Cario, 2005)
- Analytical sensitivity/specificity of sequencing – 99%
- Analytical sensitivity of deletion/duplication analysis – 90%
- Analytical specificity of deletion/duplication analysis – 98%

Results

- Positive
 - *VHL* pathogenic variant detected
 - Diagnosis of *VHL* syndrome
 - Two pathogenic variants associated with polycythemia are identified
 - *VHL*-associated polycythemia is confirmed
- Negative
 - No *VHL* gene variant detected
 - *VHL*-related syndrome is unlikely, but not excluded
- Inconclusive
 - *VHL* gene variant detected, but whether variant is benign or pathogenic is unknown

Limitations

- Not detected
 - Deep intronic or regulatory region variants
- Large deletion/duplication breakpoints will not be determined
- Diagnostic errors can occur due to rare sequence variations

References

- Cario H, et al. Mutations in the von Hippel-Lindau (*VHL*) tumor suppressor gene and *VHL*-haplotype analysis in patients with presumable congenital erythrocytosis. *Haematologica*. 2005;90(1):19-24
- Frantzen C, Klasson TD, et al. Von Hippel-Lindau Syndrome. 2000 May 17 [Updated 2015 Aug 6]. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016 (www.ncbi.nlm.nih.gov/books/NBK1463/)
- Maher ER, Iselius L, et al. Von Hippel-Lindau disease: a genetic study. *J Med Genet*. 1991;28(7):443-447
- Stolle C, et al. Improved detection of germline mutation in the von Hippel-Lindau disease tumor suppressor gene. *Human Mutation*. 1998;12(6):417-23