Von Hippel-Lindau Syndrome

Von Hippel-Lindau (VHL) syndrome is an inherited genetic disorder characterized by the formation of tumors and cysts throughout the body. Tumors may be benign or malignant and appear most often during youth or early adulthood, but can occur throughout life.

Hemangioblastomas are typically benign but can cause serious or life-threatening complications depending on location within the body. Hemangioblastomas that develop in the brain and spinal cord can cause headaches, vomiting, weakness, and a loss of muscle coordination (ataxia). Hemangiomas of the retina, called retinal angiomas, can cause vision loss.

Cysts and tumors may also occur in the kidneys, pancreas, and genital tract. Individuals with VHL syndrome are at increased risk of developing clear-cell renal cell carcinoma and pancreatic neuroendocrine tumors. Pheochromocytomas can occur and most commonly develop in the adrenal glands. Endolymphatic sac tumors as well as epididymal and broad ligament cysts have also been associated with VHL syndrome.[1]

Disease Overview

VHL Syndrome

Incidence

1/36,000 White births[2]

Symptoms

- Manifestations and severity are highly variable within and between families; may be influenced by age and sex[3]
- Characteristic tumor manifestations of VHL syndrome with estimated penetrance in affected individuals, if available[3]:
  - CNS hemangioblastoma: common
    - 80% occur in brain
    - 20% occur in spinal cord
  - Retinal hemangioblastoma: 70%
  - Renal cell carcinoma: 70% by 60 years of age
  - Endolymphatic sac tumor: 10-16%
  - Pancreatic endocrine tumor: 5-17%
  - Pheochromocytoma or paraganglioma
- Other manifestations[3]
  - Hemangiomas in glands, lungs, and liver
  - Cysts in kidneys, pancreas, and epididymis

VHL-Associated Polycythemia

Prevalence

Rare worldwide, endemic in the Chuvash region of Russia[3]

Tests to Consider

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

Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Preferred test to confirm a suspected diagnosis of VHL syndrome

von Hippel-Lindau (VHL) Sequencing 2002970

Method: Polymerase Chain Reaction/Sequencing

- 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

Method: Polymerase Chain Reaction/Sequencing

Useful when a familial pathogenic variant identifiable by sequencing is known

Deletion/Duplication Analysis by MLPA 3003144

Method: Multiplex Ligation-dependent Probe Amplification

Use to assess for large deletion/duplication previously identified in a family member

Hereditary Cancer Panel, Sequencing and Deletion/Duplication 2012032

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

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

Hereditary Renal Cancer Panel, Sequencing and Deletion/Duplication 2010214

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

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

Symptoms

- Increased serum erythropoietin levels and hemoglobin concentrations during normoxia[3]
  - Leads to increased circulating red blood cell mass
- Increased risk for mortality caused by thrombosis and/or hemorrhage[3]
- No increased risk for tumors that are associated with VHL syndrome[3]

Genetics

Gene

VHL

Inheritance

- VHL syndrome: autosomal dominant
- VHL-associated polycythemia: autosomal recessive

Penetrance

Nearly complete by age 65 for VHL syndrome[2]

De novo Variants

~20% of VHL syndrome cases[1]

Pathogenic Variants

>700 identified[4]

- Specific *VHL* sequence variants have been associated with VHL-associated polycythemia (eg, c.598C>T, p.R200W)[5]

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity:
  - VHL syndrome: >99%[4]
  - ~89% for sequence analysis
  - ~11% for deletion/duplication analysis
  - VHL-associated polycythemia (familial erythrocytosis, Chuvash polycythemia): ~20%[5]
- Analytical sensitivity/specificity of sequencing: 99%
- Analytical sensitivity of deletion/duplication analysis: 90%
- Analytical specificity of deletion/duplication analysis: 98%

Results

- Positive
  - One VHL pathogenic variant detected
    - Diagnosis of VHL syndrome
  - Two VHL pathogenic variants associated with polycythemia are identified
    - VHL-associated polycythemia is confirmed
- Negative
  - No VHL pathogenic 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

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2. Maher ER, Iselius L, Yates JR, et al. Von Hippel-Lindau disease: a genetic study. J Med Genet. 1991;28(7):443-447. PubMed
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4. Nordstrom-O'Brien M, van der Luijt RB, van Rooijen E, et al. Genetic analysis of von Hippel-Lindau disease. Hum Mutat. 2010;31(5):521-537. PubMed
5. Cario H, Schwarz K, Jorch N, 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. PubMed

Related Information

Pheochromocytoma - Paraganglioma
Pheochromocytoma Testing Algorithm

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