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 2012032
  - 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
  - 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

- Manifestations and severity are highly variable within and between families; may be influenced by age and sex
- Characteristic manifestations of VHL syndrome with estimated penetrance in affected individuals (van Leeuwaarde, 2018)
  - CNS hemangioblastoma – prototypic lesion; 80% occur in brain, 20% in spinal cord
  - Retinal hemangioblastoma – 70%
  - Renal cell carcinoma – 70%
  - Endolymphatic sac tumor – 10-16%
  - Pancreatic endocrine tumor – 5-17%
  - Pheochromocytoma or paraganglioma
  - Other manifestations
    - 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