Von Hippel-Lindau Syndrome: VHL Gene Deletion/Duplication

**Condition Description**

Von Hippel-Lindau syndrome (VHL syndrome) is characterized by hemangioblastomas of the brain, spinal cord, and retina; renal cysts and clear cell renal cell carcinoma; pheochromocytoma; and endolymphatic sac tumors. Cerebellar hemangioblastomas may be associated with headache, vomiting, and gait disturbances or ataxia. Retinal hemangioblastomas may be the initial manifestation of VHL syndrome and can cause vision loss. Renal cell carcinoma occurs in about 40% of individuals with VHL and is the leading cause of mortality. Pheochromocytomas can be asymptomatic but may cause sustained or episodic hypertension. Endolymphatic sac tumors can cause hearing loss of varying severity, which can be a presenting symptom.

The diagnosis of VHL syndrome is suspected in individuals with characteristic lesions including hemangioblastomas, renal cysts and renal cell carcinoma, pheochromocytoma, and endolymphatic sac tumors. The clinical diagnosis of VHL syndrome is established in a simplex case (an individual with no known family history of VHL syndrome) presenting with two or more characteristic lesions or in an individual with a positive family history of VHL syndrome in whom one or more of the following disease manifestations is present: retinal angioma, spinal or cerebellar hemangioblastoma, pheochromocytoma, multiple pancreatic cysts, epididymal or broad ligament cystadenomas, multiple renal cysts, or renal cell carcinoma before age 60 years.

VHL is the only gene known to be associated with VHL syndrome. Molecular genetic testing of the VHL gene detects mutations in nearly 100% of affected individuals. Approximately 72% of VHL mutations are point mutations detected by sequence analysis. Approximately 28% of VHL mutations are partial or complete gene deletions detectable by gene-targeted CGH array. VHL syndrome is inherited in an autosomal dominant manner. Approximately 80% of individuals with VHL syndrome have an affected parent and about 20% have VHL syndrome as the result of a de novo gene mutation. The manifestations and severity of the disease are highly variable both within and between families, even among those with the same mutation.

[Click here](#) for the GeneTests summary on this condition.

**Genes**

**VHL**

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of VHL in individuals who have tested negative for sequence analysis
- Individuals at-risk for VHL due to family history who have tested negative for sequence analysis

**Methodology**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient’s clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types
* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Sequencing analysis of the *VHL* gene by sequencing is available (UV) and is required before deletion/duplication analysis.
- Prenatal testing is available to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.