

# VON HIPPEL-LINDAU SYNDROME (VHL)

Target Mutation Detection -Test 2

updated 08-10-09

## DESCRIPTION

Mendelian Inheritance in Man number: [193300](#)

Click here for [Gene Reviews](#) Clinical Summary.

VHL syndrome is an autosomal dominant disorder with a high penetrance (almost complete by 60 years of age) characterized by hemangioblastomas in central nervous system (CNS), retina and other visceral organs. This disorder is also associated with an increased risk of other tumors including clear cell carcinomas of the kidney, pheochromocytoma, renal cysts, pancreatic cystadenoma and pancreatic neuroendocrine tumors. VHL affects ~ 1:35,000 individuals. World-wide prevalence of VHL is approximately 1: 36,000 live births. All ethnic groups and both sexes are affected equally.

### Genetics of VHL

The official name for the *VHL* gene is von Hippel-Lindau tumor suppressor, which resides on chromosome 3p25.3. *VHL* gene contains 3 exons and encodes a ~ 4.5 kb mRNA. Loss of function mutations in *VHL* are the only known cause of VHL, and germline *VHL* mutations can be detected in up to 100% of *VHL* families. Germline mutations are scattered throughout the coding region of the gene. Missense mutations (leading to an amino acid substitution in the VHL protein product) are found in 40 % of the families with an identified *VHL* germline mutation. Microdeletions (1-18 bp.), insertions (1-8 bp.), splice site and nonsense mutations, predicted to lead to a truncated protein, are found in approximately 30 % of the families. Large deletions account for one-third of the *VHL* germline mutations, of which approximately 30 % (or some 10 % of all *VHL* germline mutations) are deletions encompassing the entire gene. The *de novo* mutation rate is estimated at 20% and mosaicism may occur in a small percentage of VHL patients.

## INDICATIONS FOR DIRECT TESTING

- Identification of pre-symptomatic carriers of a *VHL*-associated mutation among family members of patients.
- Exclusion of the diagnosis and thus eliminating unnecessary clinical testing among family member who are shown not to carry their family's *VHL* mutation.

## TESTING METHODOLOGY

We offer a **targeted detection** of a previously characterized *VHL* mutation within the family. Depending on the mutation identified previously in the family, targeted testing can involve direct sequencing of a specific region or copy number analysis by MLPA.

## SPECIMEN REQUIREMENTS

We require 1 milliliter of whole blood. Blood samples must be collected in EDTA (purple topped) tubes.

## TRANSPORT

If specimen is from clinics within UAB or Kirklin Clinic, please call 934-7107 for pick-up. If specimens are being sent from some other location, please ship via UPS or Federal Express.

1. Be sure that the shipping air bill is marked “**Priority**”, either Domestic or International.
2. Specimens must be packaged to prevent breakage and absorbent material must be included in the package to absorb liquids in the event that breakage occurs. Also, the package must be shipped in double watertight containers (e.g. a specimen pouch + the shipping companies Diagnostic Envelope). **You can use our collection kits, which we will send to physicians directly upon request.**

## TURN AROUND TIME

2 weeks

## CPT CODES AND PRICES

**Please note that prices listed correspond to institutional rates; please contact the lab for insurance rates.**

\$250, - USD ([currency converter](#))  
83891 (x1), 83894 (x4), 83898 (x4), 83904 (x3), 83912 (x1)

## REQUIRED FORMS

### [General Requisition](#)

**Note:** Requests for Molecular Genetic testing for VHL will **not** be accepted for the following reasons:

- No label (patients full name and date of collection) on the specimens
- No referring physician’s or genetic counselor’s names and addresses
- No billing information
- No informed consent

**For more information, test requisition forms, or sample collection and mailing kits, please call: 205-934-5562.**

## REFERENCES

Maher ER, Webster AR, Richards FM, Green JS, Crossey PA, Payne SJ, Moore AT (1996). Phenotypic expression in von Hippel-Lindau disease: correlations with germline VHL gene mutations. *J Med Genet* 33:328–32 ([pubmed](#))

Richards FM, Payne SJ, Zbar B, Affara NA, Ferguson-Smith MA, Maher ER (1995) Molecular analysis of de novo germline mutations in the von Hippel-Lindau disease gene. *Hum Mol Genet* 4:2139–43 ([pubmed](#))

Stolle C, Glenn G, Zbar B, Humphrey JS, Choyke P, Walther M, Pack S, Hurley K, Audrey C, Klausner R, Linehan WM (1998) Improved detection of germline mutations in the von Hippel-Lindau disease tumor suppressor gene. *Hum Mutat* 12:417–23. ([pubmed](#))

Yoshida M, Ashida S, Kondo K, Kobayashi K, Kanno H, Shinohara N, Shitara N, Kishida T, Kawakami S, Baba M, Yamamota I, Hosaka M, Shuin T, Yao M (2000) Germ-line mutation analysis in patients with von Hippel-Lindau disease in Japan: an extended study of 77 families. *Jpn J Cancer Res* 91:204–12 ([pubmed](#))