VON HIPPEL-LINDAU SYNDROME

GENETIC TESTING

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What is the *VHL* gene?

Genes are present in every cell of your body. They carry instructions for making proteins that control how each cell functions. The *VHL* gene is known as a tumor suppressor gene. It contains the code for a protein that keeps cells from growing and dividing too rapidly.

Genes can undergo abnormal changes (mutations) that may lead to cells not working properly. This can result in health problems that can be passed from parent to child (inherited). When there is a mutation in the *VHL* gene, the VHL protein is either not made or it does not work the way it should, so cells grow and divide without control. This uncontrolled cell growth leads to the formation of tumors and cysts (fluid-filled sacs).

Some of the health problems related to VHL mutations are described in this flyer.

What is von Hippel-Lindau syndrome?

Von Hippel-Lindau (VHL) syndrome is a genetic disorder that causes tumors and fluid-filled sacs (cysts) to form in many parts of the body.

- Tumors can either be cancerous or noncancerous (benign).
- Tumors and cysts can grow inside blood vessels in the back of the eye (retina), the brain and spinal cord (central nervous system), the inner ear, kidneys, adrenal glands, pancreas, or the male genital tract.

The health problems caused by VHL syndrome and their severity can vary from person to person, even among affected people within the same family.[1,2]

What are retinal hemangioblastomas?

Hemangioblastomas are noncancerous tumors that arise from newly formed blood vessels. They are a common feature of VHL syndrome. Even though these tumors are not cancerous, they can cause serious health problems.

Retinal hemangioblastomas form in the back of the eye. Without treatment, they can cause vision loss. About 70% of people affected with VHL syndrome have retinal hemangioblastomas.[2] They may be the first complication to arise in people with this disease, and they may develop during childhood.[2] Treatment of these tumors may prevent vision loss; however people affected with VHL syndrome are likely to develop more of these tumors over time.[2]

What is renal cell carcinoma?

Renal cell carcinoma is a type of kidney cancer. About 70% of people affected with VHL syndrome will develop renal cell carcinoma by 60 years of age.[1,2] This cancer the main cause of death in people with VHL syndrome.[1,2] Early detection and treatment of renal cell carcinoma may prolong a person's life.[1]

How is VHL syndrome inherited?

Normally, each of your cells carries 2 copies of all your genes. You inherit 1 copy of a gene from each of your parents. Von Hippel-Lindau syndrome is inherited in an autosomal dominant manner.[1,2] That means a child only needs to inherit 1 copy of the *VHL* mutation to be at increased risk of developing tumors and cysts.

A person who is affected with VHL syndrome has a 50% chance of passing the *VHL* mutation on to each of his or her children.[2]

About 80% of people with VHL syndrome have a parent who is affected with this disorder. In the remaining 20% of cases, the gene mutation is *de novo*.[2] This means the mutation occurs for the first time in the affected child instead of being passed from parent to child.

How is VHL syndrome diagnosed?

A diagnosis of von Hippel-Lindau syndrome may be given to a person who[2]:

- Has no known family history of VHL syndrome **and** has 2 or more of the following:
  - 2 or more hemangioblastomas of the retina, brain, or spine or a single hemangioblastoma plus multiple cysts in an organ such as the kidney or pancreas
  - Renal cell carcinoma
  - Tumors in or around the adrenal glands (these glands sit on top of the kidneys)

  - Tumors in the inner ear, pancreas, or male genital tract
- Has a known family history of VHL syndrome **and** has:
  - Retinal hemangioblastoma(s)
  - Hemangioblastoma(s) in the brain or spinal cord
  - Renal cell carcinoma
  - Tumor(s) in or around the adrenal glands
  - Multiple cysts in the kidney or pancreas

What is *VHL* full gene sequencing?

VHL full gene sequencing is a procedure that reads the instructions (DNA) that make up the *VHL* gene. This is a way to identify the presence of one or more altered *VHL* genes in a person's cells, helping a doctor confirm the diagnosis of VHL syndrome. The test can be performed on a sample of blood or cells obtained by swabbing the inside of the mouth (buccal swab).

When might *VHL* full gene sequencing be recommended?

If you have a personal or family history of retinal hemangioblastomas or renal cell carcinoma, your doctor or a genetic counselor may recommend *VHL* full gene sequencing.

- It is important to identify VHL syndrome as the cause of retinal hemangioblastomas, since people who have VHL syndrome are likely to develop more of those tumors over time, as well as other tumors and cysts in other parts of the body.
- Early diagnosis of VHL syndrome has been shown to help patients who develop renal cell carcinoma as a result of the disease live longer.1

What possible results can be reported, and what might they mean?

- **Negative:** After scanning the *VHL* gene, no mutations were found. A negative result may reduce the chance that a person is affected with VHL syndrome but cannot completely rule it out. Additionally, other genetic changes or factors can cause VHL syndrome.
- **Positive:** After scanning the *VHL* gene, a mutation was found, confirming the diagnosis of VHL syndrome.
- **Variant of unknown significance:** After scanning the *VHL* gene, a mutation was found that has not been reported before. It is unclear if the mutation is the cause of the person's signs and symptoms. Genetic testing of family members may provide more information. If all affected family members have the same mutation, then it is likely to be linked to the inherited disorder. If some affected family members do not have the mutation, it is less likely to be linked to the disorder.

Full gene sequencing test results should be combined with clinical findings and reviewed by a heath professional who specializes in medical genetics.

Where can I find more information?

If you have questions or want more information about genetic testing for von Hippel-Lindau syndrome, ask your doctor or genetic counselor. You may search for a genetic counselor in your area using an online address book provided by the National Society of Genetic Counselors at **www.nsgc.org**.

Other information resources include:

von Hippel-Lindau Family Alliance
Telephone: 617-277-5667 or
800-767-4VHL (800-767-4845)
Home page: **www.vhl.org**

- Genetic Alliance
  Telephone: 202-966-5557
  Home page: **www.geneticalliance.org**

Note: This material is provided for general information purposes only. It is not intended as a substitute for medical advice and/or consultation with a physician or technical expert.

References

1. Richards FM, Webster AR, McMahon R, Woodward ER, Rose S, Maher ER. Molecular genetic analysis of von Hippel-Lindau disease. *Journal of Internal Medicine*. 1998;243:527-533.
2. Frantzen C, Links TP, Giles RH. Von Hippel-Lindau disease. In: Pagon RA, Bird TD, Dolan CR, et al, eds. *GeneReviews*™ [Internet]. Seattle, WA: University of Washington, Seattle; 1993-. http://www.ncbi.nlm.nih.gov/books/NBK1463/. Updated June 21, 2012. Accessed June 24, 2012.

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