Von Hippel-Lindau (VHL) syndrome is a genetic predisposition to develop growths in different parts of the body, and is caused by pathogenic (or harmful) variants in the *VHL* gene. These growths may be benign (non-cancerous) or malignant (cancerous), and most commonly occur in the brain/central nervous system, kidneys, adrenal glands, reproductive organs, and pancreas. Both men and women can be diagnosed with VHL. While signs of VHL can appear in childhood and the teenage years, some individuals do not know they have it until they are older adults.

Individuals with VHL can live normal lives, but they may develop serious health problems if they are not closely monitored by a healthcare provider who has experience with it. VHL can potentially affect multiple body systems, and can affect individuals very differently.

Genetics and Inheritance

We have over 20,000 different genes in the body. These genes are like instruction manuals for how to build a protein, and each protein has an important function that helps to keep our body working how it should. The *VHL* gene makes a protein called the VHL protein. The VHL works with other proteins to form a complex (think of it like a vacuum) that picks up other proteins that are damaged or not needed any longer and gets rid of them. Getting rid of these extra proteins helps to make sure the cells can function how they are supposed to.

Pathogenic variants in the *VHL* gene are inherited in an autosomal dominant pattern, meaning that children of someone who has a pathogenic variant in the *VHL* gene have a 50% risk to inherit the variant and associated cancer risks. In 4 out of 5 (80%) cases of VHL, someone has inherited a variant in the *VHL* gene from a parent. In the other 1 in 5 (20%) cases, the variant was not inherited from a parent and is something that is new to that person in the family (called de novo). Notably, women and men both have the *VHL* gene and have the same chances to inherit and pass down variants in these genes. Therefore, both sides of the family are important when assessing inherited risk.

Genetic Testing for VHL

Genetic testing for pathogenic variants in the *VHL* gene is currently available, but there are a few different ways to approach testing:

- *Single site analysis*: Testing specific to a known pathogenic variant in the family
- Full gene sequencing and rearrangement analysis: Comprehensive testing to search for all currently detectable variants in the gene
- Gene panels: Newer, more broadly based gene tests that would include not only the

VHL gene, but other genes known or suspected to be associated with increased risk for tumors and cancer

A diagnosis of VHL can be complex and therefore may be best conducted by a clinician familiar with VHL. A diagnosis can be made based on a review of medical records (clinical diagnosis), or by genetic testing for mutations in the *VHL* gene. Nearly all people who have a clinical diagnosis will be found to have a mutation in the *VHL* gene upon testing.

VHL can be divided into two subgroups defined by the chance for particular types of tumors or cancer. Genetic testing can also help to distinguish these subtypes:

VHL type 1	Very low	Increased
VHL type 2a	Increased	Low
VHL type 2b	Increased	High
VHL type 2c	Increased	None

Associated Health Risks

There can be many different findings throughout many parts of the body in someone who has VHL. Here are some things that a doctor may look for to diagnose someone with VHL:

CENTRAL NERVOUS SYSTEM

- Hemangioblastoma (a benign tumor that involves blood vessels) of the brain or spinal cord

AUDITORY SYSTEM

- Endolymphatic sac tumor (ELST; benign tumor of the inner ear)

EYES

- Hemangioblastoma of the retina (back of the eye)

KIDNEYS

- Renal cell carcinoma (30 – 70% chance)
- Kidney cysts

ADRENAL GLANDS

- Pheochromocytoma (a benign tumor that causes elevated hormone levels)
- Paraganglioma (tumor similar to a pheochromocytoma that occurs outside of the adrenal glands)

PANCREAS

- Neuroendocrine tumor (PNET)
- Pancreatic cysts

REPRODUCTIVE ORGANS

- Broad ligament cystadenomas (benign tumor of the tissue that connects the female reproductive organs to the pelvis)
- Epididymal cystadenomas in males (benign tumor of the duct that carries sperm from the testis)

Medical Management for VHL

Medical management for someone with VHL can be complex, and should be overseen by a medical provider who is familiar with VHL. Because VHL affects people in very different ways, medical management should be tailored to an individual's specific needs. The frequency of each screening tool is tailored to an individual's age. Some options for surveillance include:

- Eye exam and neurological exam
- Imaging of the abdomen using ultrasound and MRI
- Blood and urine testing for metanephrines
- Audiological (hearing) assessment
- MRI of the brain and spinal cord

This is not a comprehensive list of recommendations, as many of these are tailored to meet someone's specific needs and current health concerns.

Click here to learn more about scheduling a genetic counseling appointment for questions about hereditary cancer predisposition.

RESOURCES

VHL Alliance