ROSWELL PARK COMPREHENSIVE CANCER CENTER | PATIENT EDUCATION

Von Hippel-Lindau (VHL) Syndrome

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What is VHL?

Von Hippel-Lindau, also called VHL syndrome or VHL disease, is a rare genetic disorder that causes tumors and cysts (fluid-filled sacs) to grow in your body.

It is caused by an abnormal change (*mutation*) in the VHL gene. Normally, this gene prevents tumors from growing. If you have the mutation, it stops the gene from working the way it should, and tumors and cysts form.

The tumors may be malignant (cancer) or benign (not cancer)and all of the tumors involve the abnormal growth of blood vessels. Most are not cancerous but tumors in kidneys, adrenal glands, and pancreas can become malignant and spread to other parts of the body (*metastasize)*. Even if benign, tumors in locations such as the eye, brain, spinal cord or adrenal gland can cause dangerous and sometimes life-threatening symptoms. Tumors usually appear in early adulthood but VHL symptoms can occur at any time.

What is the VHL gene?

The *VHL* gene gives cells instructions for making a protein that works as part of a protein *complex* called VCB-CUL2. The VCB-CUL2 complex helps cells break down proteins when they are no longer needed. Breaking down proteins is a normal process that removes damaged or unnecessary proteins and helps the cells continue their normal functions.

One of the targets of the VCB-CUL2 complex is a protein (HIF-2α), which is part of the HIF (Hypoxia-inducible factor) family of proteins. HIFs help your body maintain its biochemical balance when your oxygen levels go below normal.

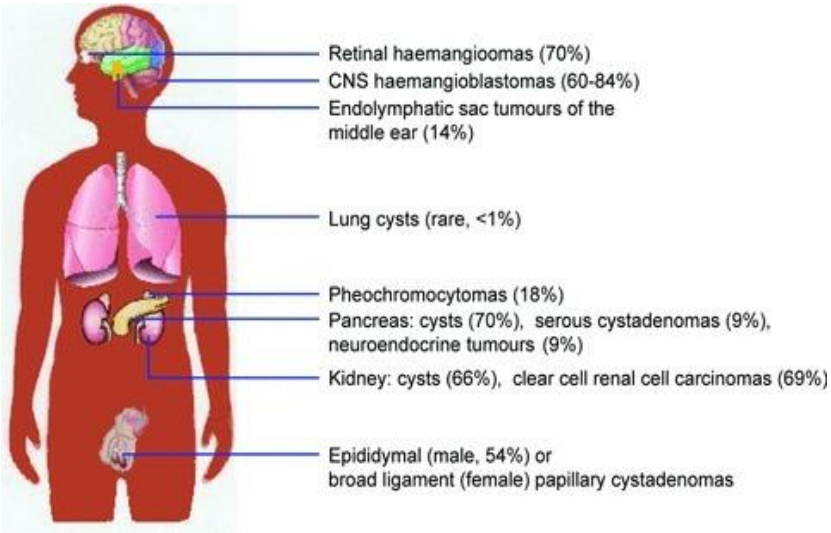
In response to low oxygen, HIF activates several genes that are involved in cell division (*proliferation*) and growth, the formation of new blood vessels to support cell growth, and the production of red blood cells to deliver more oxygen to cells. (HIF activates the gene for the hormone *erythropoietin*, which controls red blood cell production.)

When there IS enough oxygen, VCB-CUL2 prevents too much HIF from building up in the cells. If the VHL gene is mutated, the VCB-CUL2 complex no longer works to properly degrade HIFs when oxygen levels are normal. This means the HIFs accumulate to high levels and trigger repeated cell division, which contributes to the birth of a tumor.

Because the VHL protein seems to play a role in preventing cell division (reproduction), it is classified as a tumor suppressor. This means it prevents cells from growing and dividing too rapidly or in an uncontrolled way. It is unclear why mutation of VHL leads to tumors in some organs but not others.

Where VHL Strikes

- Brain and spinal cord
- Pancreas
- Kidneys
- Eyes
- Adrenal glands
- Reproductive system (men & women)
- Ears
- Liver
- Lungs



Tumor Types

Clear cell renal cell carcinoma is the most common type of kidney cancer. One of its hallmark features is an abundance of blood vessels. This cancer is most common reason for lethality in patients with the VHL syndrome.

Hemangioblastomas are tumors made up of newly formed blood vessels, and they are common in VHL. Though they are usually benign, they can cause serious problems. Symptoms depend on location. In the brain and spinal cord, they can cause headaches, vomiting, weakness, and a loss of muscle coordination (*ataxia*). In the eye, these tumors are called *retinal angiomas* and they can cause vision loss.

Pheochromocytomas are usually benign tumors and form in the adrenal glands (which sit on top of each kidney). They may not cause any symptoms or they can cause headaches, panic attacks, excess sweating, or dangerously high blood pressure that may not respond to medication. Pheochromocytomas are particularly dangerous in times of stress or trauma, such as surgery, injury, or pregnancy.

Pancreatic neuroendocrine tumors (PNETs) may be malignant or benign. If malignant, you may hear it called islet cell carcinoma. Islet cell cancer starts in the cells that make the hormones that control blood sugar levels. Islet cell cancers are less common than (exocrine) pancreatic cancer, grow more slowly, and offer a better chance of recovery. PNETs may be functional (make hormones) or nonfunctional (do not make hormones).

Functional tumors can cause early symptoms such as diarrhea, indigestion, changes in blood sugar levels, weight loss, stomach pain, and jaundice (yellowed skin or eyes).

Since nonfunctional tumors don't make hormones, there may not be any early symptoms, which makes these tumors harder to diagnose.

Endolymphatic sac tumors are benign tumors in the inner ear that can cause problems with hearing and balance and cause ringing in the ears (*tinnitus)*. They cause total deafness if not treated. These tumors affect about 10 % of people with VHL.

Epididymal tumors may form in the small gland attached to the back of the testicles. These tumors are benign.

Noncancerous cysts may develop in the liver and lungs but do not appear to cause any signs or symptoms. Cysts are abnormal sacs filled with liquid substance. They can also develop in the kidneys, pancreas, and reproductive organs.

Challenges of VHL

Although there is no **cure** for **VHL**, early detection and treatment of tumors significantly improves a patient's life. Early diagnosis, close monitoring, and treatment can lower the chances of severe consequences of VHL such as blindness, brain damage, and death.

Monitoring is very important. Tumors and cysts need to be found and watched – even if there are no symptoms - so that treatment can be given at the appropriate times. However, VHL can be difficult to diagnose for a number of reasons.

- There is no one specific symptom for VHL. Tumors can affect up to ten parts of the body and symptoms vary widely from person-to-person.
- There is no way to predict how or when VHL will affect any one specific person
- Severity of symptoms is wide-ranging. Some people have only mild issues and some people have severe problems
- Most people show symptoms by young adulthood but some people don't have symptoms until they are over age 60.

Genetics 101

Most of the cells in our bodies have copies of two genes – one from mother and one from father. VHL is caused by an *autosomal dominant mutation*, which means a child only needs to inherit the abnormal gene from one parent. (In contrast, for an autosomal recessive disease to be present, a child would need to get the abnormal gene from both parents.)

Each child of a person with VHL has a 50% change of having VHL. To confirm someone has the VHL genetic mutation, DNA (genetic) testing must be done, which is done with a blood test. Approximately 80% of people with VHL inherited the abnormal gene from a parent. The other 20% seem to have VHL from a random genetic mutation that took place during fetal development. Either way, the mutated VHL gene is already present at birth.

Surveillance

There is clear evidence that following the recommended surveillance guidelines will keep people with VHL healthier, and for a longer time. After diagnosis, surveillance involves screening for early evidence of the disease throughout the body. Depending on what is found, your doctor will work with you to create a monitoring/surveillance program that will monitor your symptoms and watch for new symptoms. Surveillance includes physical exams and imaging studies such as an MRI or CT scan.

You can review the current surveillance guidelines at https://www.vhl.org/patients/clinical-care/screening

Your doctor may modify these guidelines based on your individual condition and your family history.

Treatment Options

Treatments are even more individualized than surveillance programs. If you have tumors that could become cancerous, your doctor may recommend surgery to remove them before they become malignant and spread to other tissues and organs.

Sometimes the best initial management may be to survey (monitor) a tumor, and delay treatment.

For example: VHL patients with multiple kidney cancers have a high life-time risk for kidney failure and dialysis due to repeated kidney treatments. **By delaying treatments via careful monitoring with a specialist, patients can safely reduce the number of kidney treatments needed and reduce the likelihood of needing dialysis.**

See the VHL Handbook for more details on surgical treatment for specific types of tumors. You can purchase it on Amazon or you download it for free here: vhl.org/patients/vhl-handbook

Preventing Complications After Surgery

You can start preparing for your recovery before surgery by doing whatever you can to improve your general health, such as healthy eating, exercise/activity, and not using tobacco products. One common post op complication is blood clots. When they occur in the leg/groin, they are called DVTS (deep vein thrombosis).

DVTs occurs when a blood clot, also known as a *thrombus*, forms inside a vein. The clot can partially or completely block the flow of blood through that vessel. If a blood clot breaks off and travels to the lung, it is called a pulmonary embolus (PE), which can be life-threatening and must be treated immediately.

Questions to Ask Your Doctor

- Do I need to make any changes in my daily life?
- What about my family – do they need to get tested?
- How often will I need checkups?
- What I can I do to help prevent VHL manifestations?
- Who is the main person responsible for coordinating my care and communications among my team of specialists?
- How will this impact my ability to get/keep health, life, or long term care insurance?
- Do you offer any financial aid services?
- What symptoms should I watch for and what should I do if they appear?
- What is the significance of the size of a tumor or cyst?
- At what size should I worry about them?
- At what point will surgery be considered?
- Are there any clinical trials available for me?

Treatment Questions

- What are the risks and benefits of this treatment?
- Are there options/alternative treatments available?
- What surgical procedure are you recommending and why?
- Can the surgery be done laparoscopically?
- Can the surgery be done using robotic surgery?
- What kind of anesthesia will be used?
- How long will I be in the hospital?
- Are my treatments covered by my insurance? What will my out of pocket cost be?
- What would happen if I delay treatment?
- What would happy if I didn't have any treatment?
- If there anything I should avoid during treatment?
- How will I know if the medication is working?
- Will treatment affect my job or lifestyle?

Resources and Support

The VHL Alliance is a nonprofit dedicated to research, education, and support to improve awareness, diagnosis, treatment, and quality of life for those affected by VHL.

VHLA Services

- VHLA Wellness Coaching Program: Practical, science-based training program that provides patients, caregivers, and providers with practical tools and techniques to improve medical outcomes and overall wellbeing .
  vhl.or/wellness-coaching
- VHLA Free Hotline **800-767-4845 X1**
- VHL Handbook: vhl.org/patients/vhl-handbook
- Better Together Peer Mentoring: email info@vhl.org if interested or to learn more.
- Facilitated Discussion Calls
  - Patient/Caregiver Call vhl.org/ptcgcall
  - VHL Low/No Vision Call vhl.org/lownovisioncall
  - Parents of VHLers Call: vhl.org/parentscall

Glossary

adrenal glands: two small glands, each sits on top of a kidney. Between the outer (cortex) and inner (medulla) parts, the glands product hormones such as cortisol and aldosterone (necessary to maintain life), and adrenaline

adrenaline: hormone made by adrenal glands and released in response to stress (the 'fight or flight' response)

angiogenesis: creation (building) of new blood vessels

angiogram/angiography: a diagnostic test that uses a special dye (contrast material) and x-rays to see how blood is flowing

benign: not malignant, not cancer

biomarker: biological molecule found in body fluids or tissues that is a sign of a normal or abnormal process, or of a condition or disease. May be used to see how well the body responds to a treatment for a disease or condition

biopsy: removal of cells or tissues for examination by a pathologist

catecholamine: a neurohormone (a chemical that is made by nerve cells and used to send signals to other cells)

chromosome: Part of a cell that contains genetic information

cortisol: one of the hormones made by the adrenal glands

cyst: closed, sac-like pocket of fluid/tissue that can form anywhere in the body

deoxyribonucleic acid (DNA): The closed, sac-like pocket of tissue that can form anywhere in the body

familial: relating to family. In genetics, m=refers to a trait or gene that runs in the family

genotype: the genetic make-up of an individual organism

glomuler filtration rate (GFR): blood test that checks how well your kidneys are working

hemangioma: abnormal buildup of blood vessels in the skin or internal organs. (aka angioma)

hemorrhage: profuse bleeding

hypoxia: decreased oxygen supply to the tissues

insulin: hormone made by islet cells of the pancreas that allows glucose to move from the blood into cells islet cells

lipase: a protein made by the pancreas that helps you digest fats

mass effect: the effect of a growing mass has from the pressure it causes on tissues and organs

metanephrines: products of the breakdown of catecholamine hormones made by the adrenal glands

mineralocorticoids: a class of corticosteroid hormones made in the adrenal cortex that influences the body's electrolyte and fluid balances

mutation: a change in the DNA of a gene

neoplasia: uncontrolled, abnormal new growth of cells (tumor); may be benign or malignant

octreotide: hormone drug used to treat some cancers

pancreatitis: inflammation of the pancreas

polycystic kidney disease (PKD): genetic disorder that causes multiple cysts to form in the kidneys, which can eventually damage the kidneys and reduce their ability to function

proliferation: rapid reproduction of a cell or organism

radiofrequency ablation: procedure that uses radio waves to create heat that is used to kill tissue.

ribonucleic acid (RNA): a nucleic acid present in all cells that acts as a messenger, carrying instructions from DNA to control the cells' production of proteins

selective serotonin re-uptake inhibitor (SSRI): a type of antidepressant that increases the level of serotonin in the brain

serotonin: a neurotransmitter (relays signals between nerve cells) that is believed to play a role in mood and well being

serous microcystic adenomas: benign pancreatic neoplasm made of many small cysts

surveillance watching: in VHL, testing before symptoms appear

tumor: abnormal growth of tissue; may be benign(not cancer) or malignant (cancer)

tumor suppressor gene: normal *genes* that slow down cell division, repair DNA mistakes, or tell cells when to die. If they are not working as they should, abnormal cells can multiply without control and form tumors

ultrasound: diagnostic test that bounces sound waves off organs and tissues to create images

VHL protein: a tumor suppressor that helps control cell growth, cell division, and other important cell functions