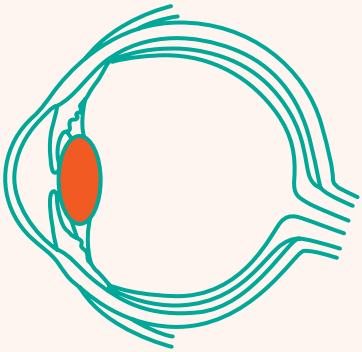
SingHealth DukeNUS
ACADEMIC MEDICAL CENTRE

Genomic
Medicine Centre

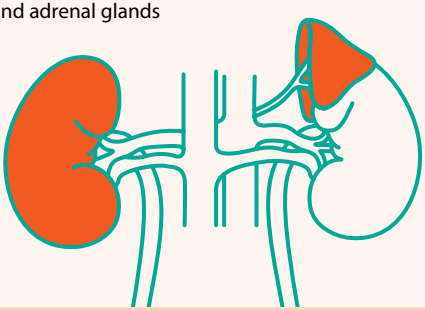
Von Hippel-Lindau Syndrome

Eye



Brain

Kidney and adrenal glands



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Von Hippel-Lindau syndrome is a hereditary cancer syndrome.

What is hereditary cancer?

Hereditary cancer makes up about 5-10% of all cases of cancer. Some genes function to protect us from cancer. When they are not working well, it causes hereditary cancer. We refer to genes that are not working well as faulty genes.

Individuals who carry a faulty cancer gene(s) have a higher chance of developing certain cancers over their lifetime compared to the general population. The types of cancers that they may be at increased risk of will depend on the gene(s) involved.

If you have a faulty cancer gene, you may be at increased risk of developing certain cancers. As genes are shared among family, other family members may have inherited the faulty gene and may be at increased risk of cancer too.

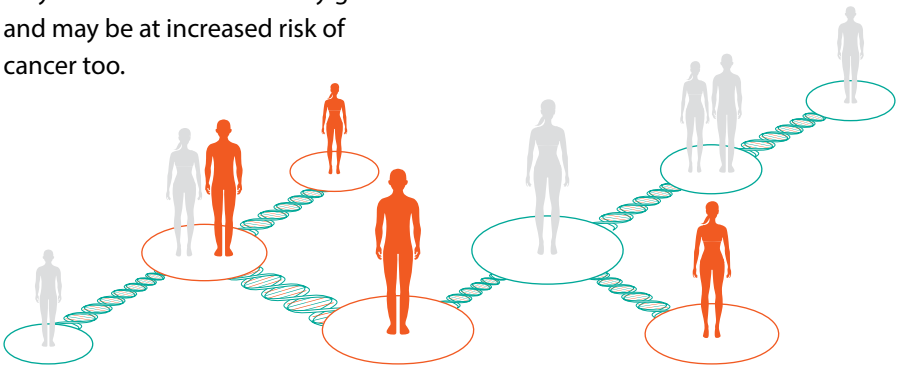
What is genetic testing?

Genetic testing is offered to individuals where a hereditary cause of their personal and/or family history of cancer is suspected.

Genes contain the instructions that our body reads to carry out different functions. Genetic testing involves analysing your genes to understand if there are faults (i.e., mutations) that may increase the risk of diseases like cancer.

How is genetic testing done?

- Genetic testing is typically a one-time blood test.
- If a blood sample cannot be taken, other sample sources (e.g., skin or saliva) may be used.



What are the possible results of genetic testing?

There are 3 types of results you may receive:

Positive

Faulty gene(s) identified

General Population Risk — Elevated Risk

Increased risk of developing certain tumours and cancers (depends on faulty gene(s) involved)

Your family (parents, siblings, children and extended relatives) may have inherited the faulty gene(s) and should consider genetic testing to clarify this

Uncertain

Variant of Uncertain Significance (VUS)

Uncertain gene change(s) identified, unclear if these change(s) increase risk for tumours and cancers

General Population Risk — Elevated Risk

May be clarified by testing other family members

May be reclassified over time as 'positive' or 'negative' when more information is known

Negative

No faulty gene(s) identified

General Population Risk — Elevated Risk

Tumour and cancer risk is similar to that of general population

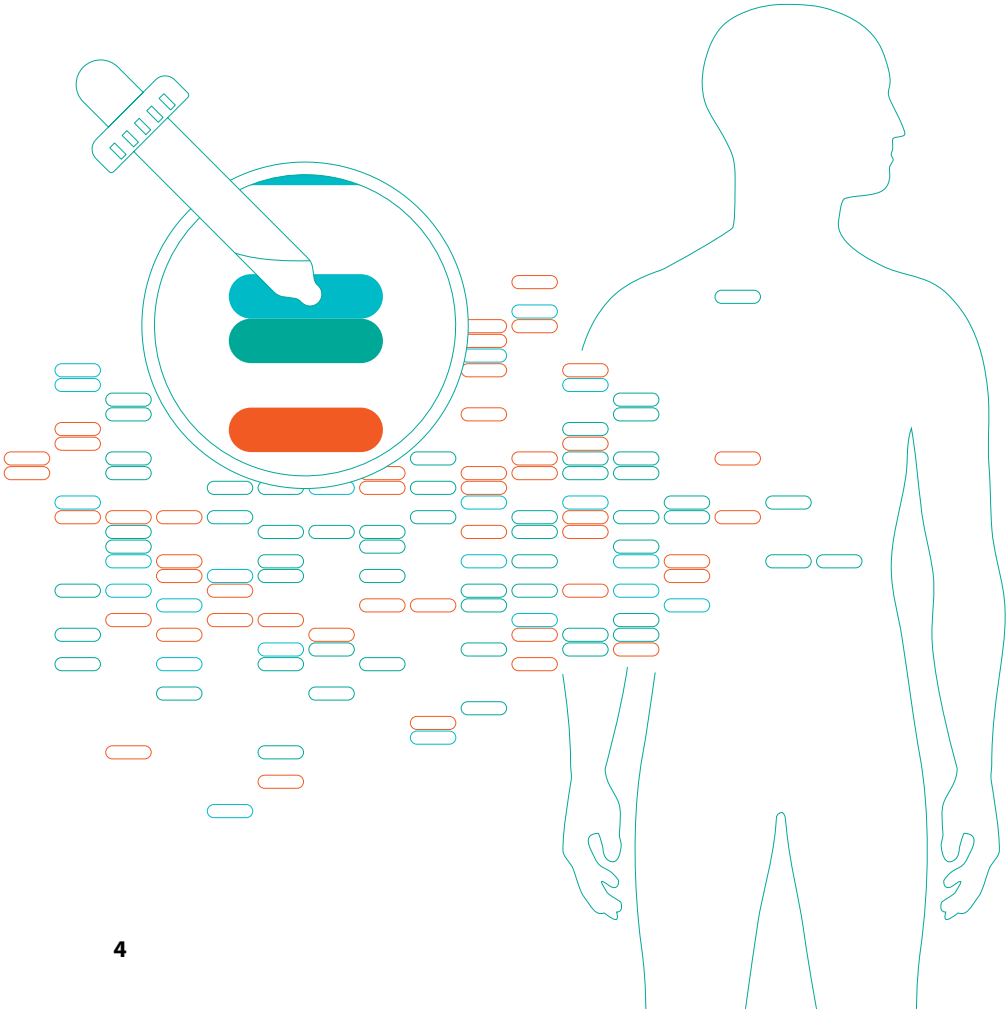
Test limitations will be explained in the context of your personal and family history of tumours and cancers

What is von Hippel-Lindau syndrome (VHL)?

Von Hippel-Lindau syndrome (VHL) is a hereditary condition where cancerous and non-cancerous tumours and cysts can grow in certain parts of the body.

VHL is associated with a faulty (disease-causing) copy of the *VHL* gene.

Individuals who carry a faulty *VHL* gene face an increased risk of certain tumours and cancers over their lifetime, but it does not mean that they will definitely develop cancer/tumours.



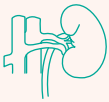
Body parts commonly affected in VHL

1 Brain and spine

Tumours called hemangioblastomas can occur in the brain and spinal cord.

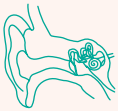
5 Retina (eyes)

Tumours can occur at the back of the eye (retina).



2 Kidneys

Increased risk of developing a type of kidney cancer.



6 Inner ears

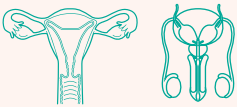
Non-cancerous tumours can occur in the inner ear.

3 Pancreas

A type of pancreatic cancer called pancreatic neuroendocrine tumour can occur. Pancreatic cysts can also occur.

7 Adrenal glands

Tumours called phaeochromocytomas can occur in the adrenal glands.



4 Reproductive tract

Benign tumours/cysts can occur in the genital tract.

What are the symptoms that patients with VHL may have?

1 Brain and spine

Tumours known as **hemangioblastomas** can form in the blood vessels of the brain and along the spinal cord. While these tumours are non-cancerous, they can cause symptoms depending on where they are located.

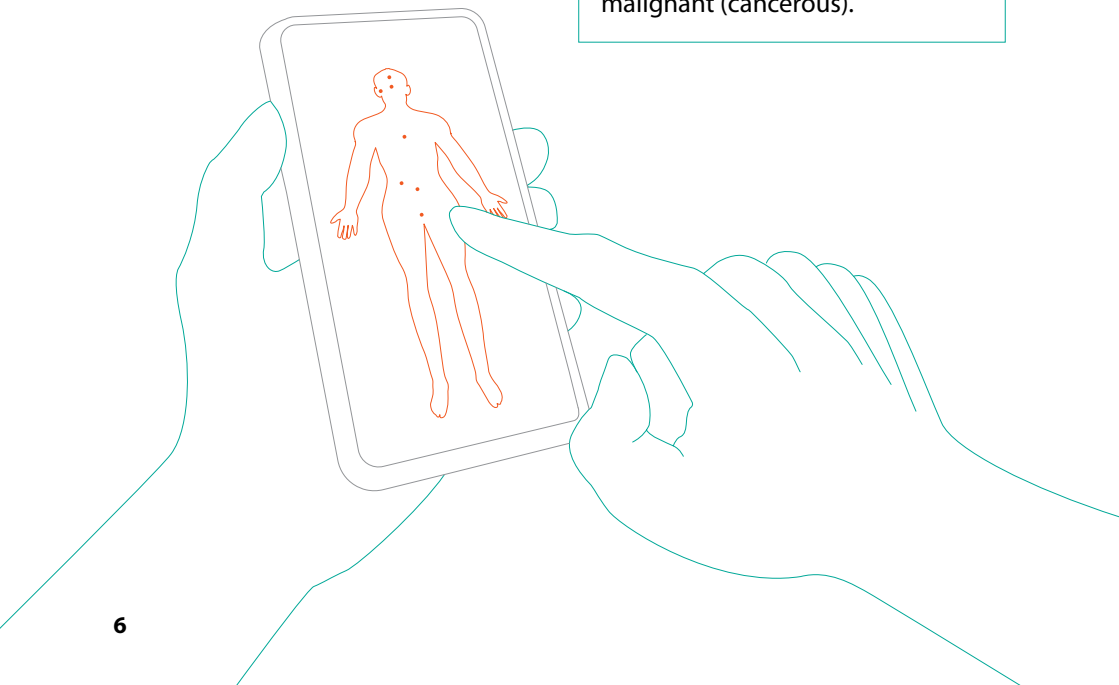
- **Brain.** Headaches, nausea, vomiting and loss of coordination and balance
- **Spinal cord.** Muscle weakness and numbness

2 Kidneys

Cysts in the kidneys are also common in individuals with VHL. Individuals are also at increased risk of developing a type of kidney cancer called **clear cell renal cell carcinoma.**

3 Pancreas

Individuals with VHL may develop cysts in their pancreas which are non-cancerous. A tumour called a **pancreatic neuroendocrine tumour** (pNET) can also develop in the pancreas. These tumours can be benign (non-cancerous) or malignant (cancerous).



4 Reproductive tract

Benign tumours/cysts called **cystadenomas** can develop in the reproductive tract of both females and males. These tumours or cysts can cause discomfort or pain and surgery can be considered to remove them.

5 Retina (eyes)

Tumours can occur at the back of the retina and are called **retinal angiomas**. These tumours can lead to problems with vision or even blindness if not treated. Symptoms affecting vision usually present early in life.

6 Inner ears

Non-cancerous tumours can form in the endolymphatic duct of the inner ear, which regulates the balance of an individual. These tumours are called **endolymphatic sac tumours**, which can cause problems such as hearing loss or deafness. Other symptoms include ringing in the ears, balance problems and dizziness.

7 Adrenal glands

Adrenal glands are found on top of the kidneys and are involved in hormone regulation. A type of tumour called a **phaeochromocytoma** can occur within the adrenal glands. While these tumours are usually non-cancerous, they can cause symptoms such as high blood pressure, headaches, excessive sweating and a fast heart rate, which can lead to other more serious medical complications (such as a heart attack) if undetected and untreated.

It is important to seek prompt medical action when you experience any of the above symptoms associated with VHL, as it will help to minimise irreversible complications and also to ensure you receive screening for the early detection of any tumours and cancers.

What are the tumour and cancer risks associated with VHL?

Individuals with VHL can develop tumours and cysts in various parts of their body, such as their eyes, ears, brain, spinal cord, kidneys, adrenal glands, pancreas and reproductive tract.

Lifetime tumour and cancer risks for individuals with a faulty *VHL* gene

Tumour/cancer type	VHL carrier risk	General population risk
Blood vessel tumours		
Eye *(retinal angiomas)*	Up to 92%	0.15% for all eye cancers
Brain *(cerebellar hemangioblastomas)*	Up to 85%	Less than 1% for malignant tumours
Spine (*spinal hemangioblastomas)*	Up to 50%	Less than 1% for malignant tumours
Cancers / tumours		
Kidney cancer *(renal cell carcinoma)*	Up to 80%	1-2%
Adrenal gland *(phaeochromocytomas)*	Up to 30%	Rare
Pancreas *(neuroendocrine tumours)*	10 - 17%	Around 0.03%
Ears *(endolymphatic sac tumours)*	Up to 4%	Less than 1%
Reproductive tract *(epididymal cystadenoma)* *For males only*	Up to 54%	Rare
Reproductive tract *(broad ligament cystadenomas)* *For females only*	10%	Rare

Note: The conditions associated with a faulty VHL gene and their risk estimates may change as more information is available.

What can I do to manage my increased risk of tumours and cancer?

Frequent and regular screening is recommended for early detection of tumours/cancers, so that interventions or treatment can happen in a timely manner.

Screening

General

- Regular MRI scans focusing on the brain stem, spine and abdomen to check for tumours
- Consider abdominal ultrasounds to detect for pancreatic tumours and kidney cancers
- Report unusual symptoms (especially in your vision/hearing/balance) to your doctor

Adrenal tumours (phaeochromocytomas)

- Blood pressure measurement
- Blood/urine test to test for hormone levels
- Further imaging such as CT/MRI scans may be ordered when there are abnormal blood test results

Eye tumours (retina angiomas)

- Regular eye examinations by an eye specialist
- Report unusual symptoms such as changes in vision

Ear tumours (endolymphatic sac tumours)

- Regular hearing tests
- Further imaging (CT/MRI) may be ordered when hearing problems are reported

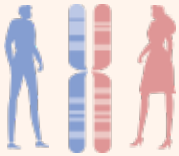
Your managing doctor(s) will discuss screening recommendations with you in greater detail. The age and onset of screening may depend on your personal and/or family history of cancer. Screening guidelines may change as more information is known.

How is VHL inherited?

VHL runs in families and can be passed down. It can affect both males and females.

VHL follows a **dominant inheritance pattern**. This means that having one faulty copy of the *VHL* gene can cause the condition.

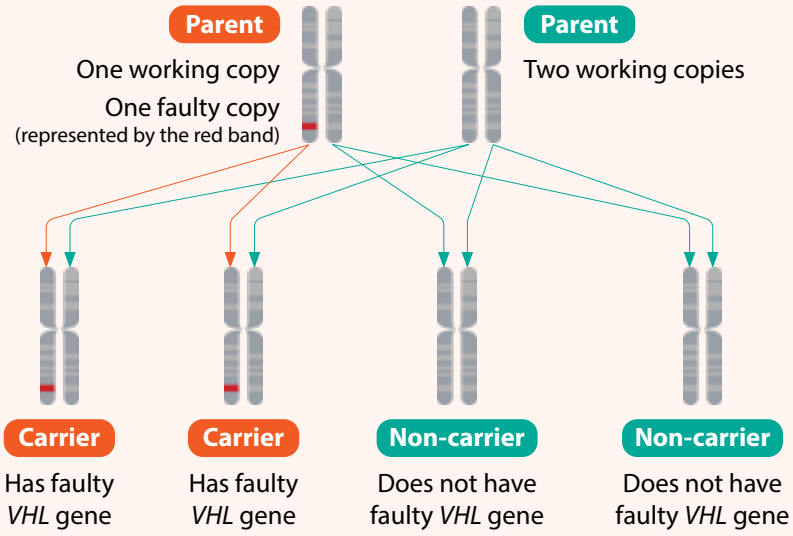
Everyone has 2 copies of each gene in their body's cells:



1 copy comes from our father

1 copy comes from our mother

Dominant inheritance pattern



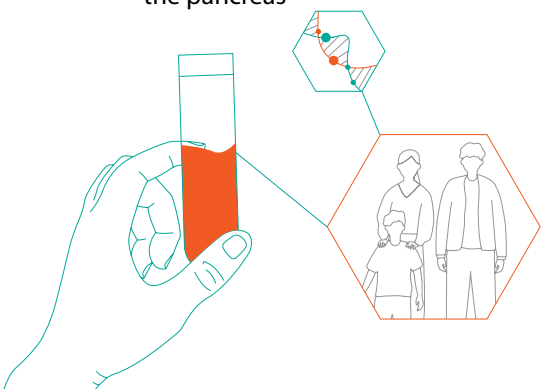
- A parent with a faulty gene(s) has a 50% chance of passing down their faulty gene(s) to their children.
- A child, sibling or parent of a family member with a faulty gene(s) has a 50% chance of also inheriting the same faulty gene(s).
- Extended relatives may also inherit the faulty gene(s).

While VHL may run in families, an estimated 20% of individuals with VHL may have acquired a faulty VHL gene at birth *(de novo)*. Therefore, genetic testing may be offered in the absence of relevant family history if an individual's personal history is suspicious for VHL.

How is VHL diagnosed by doctors?

You may be clinically diagnosed with VHL if you meet two or more of following criteria:

- Two or more hemangioblastomas of the retina, spine or brain, or a single hemangioblastoma in association with multiple kidney or pancreatic cysts
- Renal cell carcinoma
- Phaeochromocytoma
- Endolymphatic sac tumours (ELST), papillary cystadenomas of the epididymis or broad ligament, or neuroendocrine tumours of the pancreas



Who should undergo genetic testing for VHL?

You should consider genetic testing if you or your family members meet one or more of the following criteria:

- Clinically diagnosed with VHL
- Clear cell renal cell carcinoma before the age of 40
- Bilateral or multifocal clear cell renal cell carcinoma
- Retinal angioma before the age of 40
- Brain hemangioblastoma before the age of 30
- Phaeochromocytoma before the age of 50
- A family history of phaeochromocytoma/ paraganglioma
- Pancreatic neuroendocrine tumour
- ELST at any age
- Consideration of pregnancy with a known family history of VHL
- A previously identified faulty *VHL* gene in the family

The genetic testing criteria and guidelines for VHL testing may change as more information is available.

How can your genetic test result help you?

Personalised management

There are several hereditary conditions (associated with different genes) which can predispose to features/symptoms similar to what is seen in individuals with VHL.

Genetic testing is therefore beneficial to confirm a diagnosis of VHL, to determine whether personalised recommendations such as early and regular screenings are necessary to reduce risks associated with the condition.

As VHL is a hereditary condition, testing can also help inform of reproductive risks, and help determine if testing is necessary for your family members and facilitate testing if so.

Familial implications

Your genetic test result can also help you understand if other family members are at risk of VHL. They can subsequently consider their own testing (predictive testing) to clarify their carrier status to determine tumour and cancer risks.

Family members who ***have inherited*** the same faulty VHL gene may be at increased risk of tumours and cancer and can benefit from management options such as screening (to detect tumours and cancer at an early and manageable stage) or surgery (to reduce their risk of cancer).

Family members who ***did not inherit*** the faulty VHL gene can avoid unnecessary screening and worry. Their children will also not be at risk.

Frequently Asked Questions (FAQs)

Q: Who is the best person in the family to undergo genetic testing?

A: Genetic testing is initially recommended for **a family member whose cancer diagnosis/medical history is most suggestive of a hereditary cause** (e.g., young or unusual cancer/tumours). It is usually not advisable to test someone without a history of cancer, tumours or clinical features suggestive of VHL.

The genetic test results of an asymptomatic individual may have limitations:

- If they were to receive a negative result, it may not mean that there is no hereditary cause of cancer/tumours/clinical features in the family. The individual being tested may not have inherited it, but others in the family may have, or the faulty gene may not have been identified yet.
- The result is only useful to the asymptomatic person being tested and their children, but not to their parents, siblings and other extended family members.

Once the faulty gene in the family is identified, genetic testing can be offered to other family members (including those who do not have cancer) to understand if they have inherited the faulty gene and if so, tailor their management to manage or reduce their risks.

Common Myths & Misconceptions

If my genetic test result is positive, it means that I have or will have tumours/cancer, or my tumour/cancer will recur.

FALSE. The genetic test result cannot determine the likelihood of tumour/cancer recurrence or the presence of a tumour/cancer. A positive result only indicates an increased risk of developing a tumour/cancer or a new tumour/cancer developing.

If I test positive, it means that my children will also have VHL.

FALSE. If you have a positive genetic test result where a faulty gene(s) is identified confirming VHL, it means each of your children has a 50% (1 in 2) chance of inheriting the same faulty gene(s).

Your grandchildren would only be at risk if their parent (i.e., your child) has inherited the faulty *VHL* gene. The faulty *VHL* gene does not skip generations.

Even if an individual inherits the faulty gene, it does not guarantee that they will develop tumours/cancer associated with VHL. They only have an increased risk as compared to the general population.

My daughter looks a lot like me, so she must have inherited the faulty gene(s) since I have it.

FALSE. Genes that govern your appearance are different from the genes that determine the risk of VHL syndrome like *VHL*. All first-degree relatives (siblings, children, parents) have a 50% (1 in 2) chance of inheriting the faulty *VHL* gene.

I have two brothers, so one will inherit the faulty gene(s) and one will not, because there is a 50% chance.

FALSE. Each first-degree relative (parents, siblings, children) has a 50% (1 in 2) chance of inheriting the faulty gene(s). The genetic test result of one sibling does not determine the chances of the other sibling.

If you have any questions, please contact:

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Mondays to Fridays: 8.30am to 5.30pm
Weekends and Public Holidays: Closed

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Acknowledgements

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