

VHL gene

von Hippel-Lindau tumor suppressor

Normal Function

The *VHL* gene provides instructions for making a protein that functions as part of a complex (a group of proteins that work together) called the VCB-CUL2 complex. This complex targets other proteins to be broken down (degraded) by the cell when they are no longer needed. Protein degradation is a normal process that removes damaged or unnecessary proteins and helps maintain the normal functions of cells.

One of the targets of the VCB-CUL2 complex is a protein called hypoxia-inducible factor 2-alpha (HIF-2 α). HIF-2 α is one part (subunit) of a larger protein complex called HIF, which plays a critical role in the body's ability to adapt to changing oxygen levels. HIF controls several genes involved in cell division, the formation of new blood vessels, and the production of red blood cells. It is the major regulator of a hormone called erythropoietin, which controls red blood cell production. HIF's function is particularly important when oxygen levels are lower than normal (hypoxia). However, when adequate oxygen is available, the VCB-CUL2 complex keeps HIF from building up inappropriately in cells.

The VHL protein likely plays a role in other cellular functions, including the regulation of other genes and control of cell division. Based on this function, the VHL protein is classified as a tumor suppressor, which means it prevents cells from growing and dividing too rapidly or in an uncontrolled way. The VHL protein is also involved in the formation of the extracellular matrix, which is an intricate lattice that forms in the spaces between cells and provides structural support to tissues.

Health Conditions Related to Genetic Changes

Nonsyndromic paraganglioma

Mutations in the *VHL* gene increase the risk of developing tumors of the nervous system called paragangliomas or pheochromocytomas (a type of paraganglioma). Pheochromocytomas are a feature of von Hippel-Lindau syndrome, but they and other paragangliomas can also occur nonsyndromically (without the other signs and symptoms of the syndrome).

VHL gene mutations associated with nonsyndromic paraganglioma or

pheochromocytoma can be inherited or can occur spontaneously. Some spontaneous mutations associated with this condition occur during the formation of reproductive cells (eggs or sperm) or just after fertilization and are called de novo mutations. This type of mutation is found in every cell of the body. Other spontaneous mutations found in this condition, called somatic mutations, are acquired during a person's lifetime and are present only in the tumor cells.

The *VHL* gene mutations found in nonsyndromic paraganglioma or pheochromocytoma change single amino acids in the VHL protein or create an abnormally short protein. These changes disrupt the function of the protein. As in von Hippel-Lindau syndrome, when the VHL protein is altered, the HIF-2 α protein is not broken down, and instead builds up in cells. Excess HIF stimulates cells to divide abnormally and triggers the production of blood vessels when they are not needed, which can lead to the development of paraganglioma or pheochromocytoma.

Familial erythrocytosis

At least 10 inherited mutations in the *VHL* gene have been found to cause familial erythrocytosis, a condition characterized by an increased number of red blood cells and an elevated risk of abnormal blood clots. When familial erythrocytosis results from *VHL* gene mutations, it is often designated ECYT2.

The first *VHL* gene mutation related to familial erythrocytosis was identified in the Chuvash population of Russia. (It has since been found in other geographic regions as well.) The mutation changes a single protein building block (amino acid) in the VHL protein, replacing the amino acid arginine with the amino acid tryptophan at position 200 (written as Arg200Trp or R200W). This mutation disrupts the function of the VHL protein, particularly its ability to target HIF-2 α to be broken down. As a result, HIF accumulates in cells even when adequate oxygen is available. The presence of extra HIF leads to the production of red blood cells when no more are needed, which leads to an excess of these cells in the bloodstream.

The other *VHL* gene mutations that can cause familial erythrocytosis also change single amino acids in the VHL protein. These genetic changes are thought to have similar effects on protein function to those of the Arg200Trp mutation. These mutations have been identified in the Chuvash population and in other regions worldwide.

Von Hippel-Lindau syndrome

More than 370 inherited mutations in the *VHL* gene have been identified in people with von Hippel-Lindau syndrome, a disorder characterized by the formation of tumors and fluid-filled sacs (cysts) in many different parts of the body. *VHL* gene mutations associated with this condition either prevent the production of any VHL protein or lead to the production of an abnormal version of the protein.

When the VHL protein is altered or missing, the VCB-CUL2 complex cannot target HIF-2 α and other proteins to be broken down. As a result, HIF can build up in cells. Excess HIF stimulates cells to divide abnormally and triggers the production of blood vessels

when they are not needed. Rapid and uncontrolled cell division, along with the abnormal formation of new blood vessels, can lead to the development of cysts and tumors in people with von Hippel-Lindau syndrome.

Other disorders

Mutations in the *VHL* gene have been identified in a type of tumor called a hemangioblastoma. These tumors are made of newly formed blood vessels and tend to develop in the brain and spinal cord. Hemangioblastomas are a characteristic feature of von Hippel-Lindau syndrome, but they can also occur sporadically (without the other signs and symptoms of that condition). When these tumors develop in people without von Hippel-Lindau syndrome, they are associated with somatic mutations in the *VHL* gene. The somatic mutations associated with hemangioblastomas are acquired during a person's lifetime and are present only in the cells that give rise to blood and blood vessels.

It is unclear how inherited and somatic mutations in the *VHL* gene are associated with such a wide variety of different conditions.

Cancers

Somatic (noninherited) mutations in the *VHL* gene are associated with a form of kidney cancer called clear cell renal cell carcinoma. This type of cancer is described as sporadic when it develops in people without inherited *VHL* mutations.

Instead of occurring in every cell in the body, somatic *VHL* mutations occur only in certain kidney cells. These genetic changes prevent the cells from producing functional VHL protein. A lack of this protein allows the cells to grow and divide abnormally, which may contribute to the development of sporadic kidney tumors. In addition, somatic mutations in the *VHL* gene in kidney cells may promote the growth of existing kidney tumors.

Other Names for This Gene

- pVHL
- VHL1
- VHL_HUMAN

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of VHL ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=7428\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=7428[geneid]))

Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28%28VHL%5BTI%5D%29+OR+%28von+Hippel-Lindau%5BTI%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D>)

Catalog of Genes and Diseases from OMIM

- RENAL CELL CARCINOMA, NONPAPILLARY; RCC (<https://omim.org/entry/144700>)
- VON HIPPEL-LINDAU TUMOR SUPPRESSOR; VHL (<https://omim.org/entry/608537>)

Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/7428>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=VHL\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=VHL[gene]))

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Genomic Location

The *VHL* gene is found on chromosome 3 (<https://medlineplus.gov/genetics/chromosome/3/>).

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