# Mutations in *VHL* and Renal Cell Carcinoma – an Overview

## Introduction

Von Hippel-Lindau disease is the primary cause of hereditary renal cell carcinoma, accounting for about 1.6% of all cases (1,2). Diagnosis of VHL is important, since this hereditary cancer syndrome is associated with often multifocal occurrence of other neoplasms such as retinal, cerebellar, and/or spinal hemangioblastomas and pheochromocytomas (2-4). Since VHL has been associated with autosomal dominant mutations in the gene *VHL* (5), genetic testing can confirm a diagnosis of VHL. Genetic testing can also be used to identify both family members at risk for developing the disease, who should undergo annual tumor screening, and family members who do not carry the familial pathogenic mutations in VHL and do not need annual tumor surveillance (6). In individuals confirmed to carry a VHL-associated germline mutation in the gene *VHL*, annual tumor screening can help to detect neoplasms before they become symptomatic, enabling early therapeutic intervention. Incidence of VHL has been estimated at 1 in 36,000 births (7), with RCC believed to occur in up to 75% of VHL patients (2).

## Molecular Pathophysiology

*VHL* codes for the VHL protein, which binds to the transcription factors elongin B and C and acts as a component of an E3-ubiquitin ligase complex involved in targeting hypoxia-inducible factor 1alpha (HIF-1alpha) for degradation (see 2,3 for review). Loss-of-function mutations in *VHL* allow HIF-1alpha to persist in absence of hypoxic conditions and lead to increased transcription of hypoxia-inducible genes, resulting in the overexpression of proteins such as vascular endothelial growth factor and transforming growth factor alpha. VHL protein may also play a role in extracellular matrix formation and cell cycle control. *VHL* is believed to act as a tumor suppressor gene, where defects in both copies of the *VHL* gene within the same cell dramatically increase the risk for certain neoplasms. While in the general population two independent somatic events are necessary to disable both copies of the *VHL* gene in a given cell, only one such somatic event is required in carriers of a germline loss-of-function mutation in *VHL*. Therefore, VHL carriers have a greatly increased risk of developing tumors compared to the general population. This risk is inherited in an autosomal dominant manner and is associated with multifocal neoplasms in several target organs at a young age. In contrast, somatic mutations in both VHL gene copies, which are associated with 60% of all sporadic renal cell carcinoma, generally lead to solitary and unilateral cancer occurring at a later age (1,8).

Of note, certain loss-of-function mutations in *VHL* are associated in a recessive mode of inheritance with congenital polycythemia and may account for up to 50% of congenital polycythemia with normal to elevated level of erythropoietin (9). Risk of VHL-associated tumors is low in patients with congenital polycythemia.

## Clinical Presentation

VHL-associated renal cell carcinoma typically occurs about 20 years earlier than sporadic renal cell carcinoma, and is often associated with renal cysts (1,4,10,11). Other VHL-associated tumors include cerebellar, retinal, or spinal hemangioblastomas, pheochromocytomas, paragangliomas, endolymphatic sac tumors, pancreatic neuroendocrine tumors, and pancreatic, epididymal, and broad ligament cysts. Penetrance of VHL has been reported to be almost complete by age 65 (12). Based on the risk of pheochromocytoma and renal cell carcinoma, several different subtypes of VHL are distinguished. Type 1 is characterized by a low risk of pheochromocytoma and a high risk of renal cell carcinoma. Type 2 shows a high risk of pheochromocytoma and is further separated into types 2A and 2B, which are characterized by low and high risks of renal cell carcinoma, respectively, and type 2C, in which pheochromocytoma remains the sole manifestation (2-4). Type 1 and type 2B, which share a high risk of renal cell carcinoma, are often associated with large deletions in or truncations of the VHL protein (13). In contrast, types 2A and 2C are usually caused by missense mutations in *VHL*.

## Diagnosis

Clinical diagnosis of VHL is based on the presence of two characteristic tumors or, in the presence of a family history of VHL, occurrence of one characteristic tumor. However, a family history is often difficult to recognize due to the variability in clinical presentation of VHL both between and within affected families. In addition, up to 20% of VHL occurs in patients without a family history (12). Genetic testing can confirm a diagnosis of VHL after the appearance of only one characteristic tumor and can identify family members at risk for VHL before they become symptomatic. Up to 60% of VHL-associated mutations can be detected by gene sequencing (14). Large deletions, which account for about 40% of mutations, require a different detection technology.

## Treatment

Symptomatic cerebellar and spinal hemangioblastomas, pheochromocytomas, and renal cell carcinomas typically require surgery. Treatment with laser photocoagulation or cryotherapy can prevent vision loss due to retinal hemangioblastomas. Once a diagnosis of VHL or the risk of VHL has been established, the patient should undergo annual tumor surveillance (2-4).

## References


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