

# Von Hippel-Lindau Disease: Insights and advances

## Background and History

Von Hippel-Lindau disease is an inherited cancer syndrome associated with retinal and central nervous system (especially cerebellar) haemangioblastomas. Although rare it is scientifically important as it has recently given fascinating insights into how cells adapt to changes in oxygen supply. The disease was first described in 1904 by von Hippel when he described multiple retinal angiomas, but it was not until 1924 that the Swedish pathologist Lindau linked retinal angioma with CNS haemangioblastomas and the visceral manifestations.<sup>1</sup>

The syndrome has an incidence of approximately 1 in 50000 and is inherited as an autosomal dominant condition<sup>2</sup> with a high penetrance rate such that 95% of cases present by the age of 60.<sup>3</sup> It typically presents around the third decade of life although it can be much earlier.<sup>2</sup> The underlying gene was mapped to chromosome 3 in 1988 and was isolated in 1993<sup>4</sup>, and is small with only 3 exons, and is highly conserved in evolution as the same gene is found in *C.elegans*. The clinical syndrome is only caused by mutations in the VHL gene, and the detection of the mutation or deletion has been found in all families studied to date.<sup>5</sup>

The VHL gene encodes for a protein (pVHL) which consists of 213 amino acids,<sup>4</sup> and is a tumour suppressor protein. It requires both copies to be inactive before any problems arise and in the inherited syndrome one defective copy is present in the germline. A second acquired mutation occurs at the somatic level and it is only when the second gene inactivation takes place that susceptible target organ tumours develop - an example of Knudson's 2 hit model for tumourgenesis.

## Clinical management

The clinical syndrome of VHL disease was classified in 1964.<sup>1</sup> The diagnostic criteria for classical VHL disease (Type 1, 2A or 2B) are 2 or more haemangioblastoma or a single haemangioblastoma and a visceral manifestation. If there is a positive family history for VHL, just one clinical manifestation permits the diagnosis. More recently, phaeochromocytomas alone (type 2C) and autosomal recessive polycythaemia (type 3) have been recognised.<sup>6,7</sup> (See Table 1).

Table 1

Classification of von Hippel-Lindau disease, the clinical characteristics, genetic abnormality and the effect on HIF regulation

Type	Mutation	Clinical Manifestations	Effect on HIF regulation	Transmission
1	Typical deletion or truncation	Haemangioblastoma Renal cell carcinoma Low risk phaeochromocytoma	Abolished	Autosomal dominant
2A	e.g. Tyr 112 His	Haemangioblastoma Phaeochromocytoma Low risk renal cell carcinoma	Abolished	Autosomal dominant
2B	e.g. Arg 167 Gln	Haemangioblastoma Phaeochromocytoma Renal cell carcinoma	Abolished	Autosomal dominant
2C	e.g. Leu 188 Val	Phaeochromocytoma	Unaffected	Autosomal dominant
3	Arg 200 Typ	Chuvash Polycythaemia	Slightly impaired	Autosomal recessive

## Haemangioblastomas

The most common and early feature of VHL are CNS haemangioblastomas and retinal haemangioblastomas. They occur in up to 80% of VHL patients<sup>3</sup>, with the CNS tumours most frequently located in the cerebellum followed by the spinal cord, although they can occur rarely in the cerebral hemispheres. Haemangioblastomas are benign and do not metastasise and symptoms are due either to their mass effect or haemorrhage. The tumours are frequently cystic, with the cysts growing more rapidly than the underlying tumours<sup>8</sup> (see Figure 1) and are best managed symptomatically with surgery or radiosurgery.

Retinal haemangioblastomas are histologically indistinguishable from CNS lesions and around 60% of VHL patients have them during their lifetime.<sup>9</sup> They are often multiple and occur in the peripheral region of the retina and are entirely treatable (for example by laser photocoagulation) which is important in preventing blindness<sup>10</sup>.

## Renal cysts and neoplasms

The risk of developing clear cell renal cell carcinoma with VHL is greater than 70% during a lifetime and is the most common cause of death<sup>11</sup>. The tumours are frequently multiple and unlike haemangioblastomas have malignant potential. Surgical intervention is usually nephron sparing to delay the need for dialysis and if the lesions are less than 3cm in size then they are usually monitored, since growth is very variable and metastasis appears not to occur below this threshold<sup>12</sup>.

Phaeochromocytomas: About 10% of VHL patients develop a phaeochromocytoma during their lifetime<sup>11</sup>. Of recent interest is the finding that some mutations are associated with the development of phaeochromocytomas but not haemangioblastomas or clear cell renal cell carcinoma (Table 1).

Pancreatic Lesions: These are usually limited to cysts and any symptoms are secondary to local compression. In some cases non-secreting pancreatic islet cell tumours occur<sup>13</sup>.

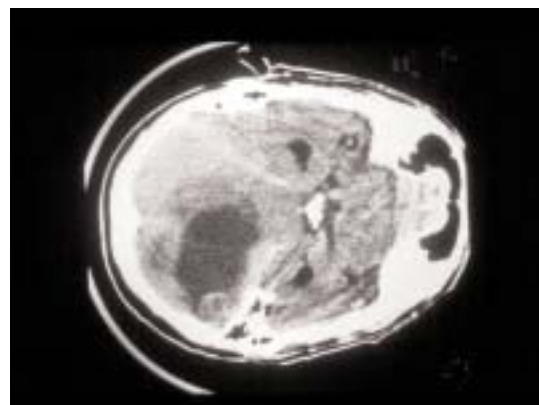


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Figure 1. CT scan on head showing a haemangioblastomas in the cerebellum.



**Epididymal Cysts:** These are found in around 30-40% of male VHL patients and are benign<sup>14</sup>.

**Endolymphatic Sac Tumours:** These have only been recently recognised as a manifestation of VHL. Up to 10% of VHL patients have these slow growing tumours arising from the petrous-temporal region. They can be frequently bilateral and invasion locally results in deafness or disturbed balance<sup>14</sup>.

**Clinical management:** This is based on regular monitoring of affected or at risk individuals (ie unknown genetic status). It needs to include annual indirect ophthalmoscopy, screening for pheochromocytoma, abdominal imaging for clear cell renal cell carcinoma and neurological evaluation.

## Science

Observations that this rare disease is associated with very vascular tumours has provided major insights into the way cells respond to oxygen. When pVHL was first discovered it had no known function, but is now recognised that it regulates Hypoxia Inducible Factor-1.

Hypoxia Inducible Factor (HIF) is a transcription factor that responds to changes in oxygen tensions and influences expression of a large number of target genes. The short-term changes include altering glucose uptake and metabolism and more chronic adaptive changes, include increasing angiogenesis and erythropoiesis. (Figure 2)

The alpha unit of the HIF complex is regulated by oxygen. In low oxygen tensions (hypoxia) the HIF complex is activated and results in increased gene transcription. Under normal oxygen tensions HIF- $\alpha$  is rapidly degraded. Following hydroxylation of HIF- $\alpha$ , pVHL binds to it acting as a ubiquitin E3 ligase which leads to the destruction of HIF by the proteasome after ubiquitination<sup>15</sup>. (Figure 2)

The initial step of hydroxylation is carried out by Prolyl Hydroxylase (PHD) enzymes<sup>16</sup>. The PHD enzymes use oxygen, and the reaction rate responds to the concentration of molecular oxygen. Additional regulation of HIF- $\alpha$  involves hydroxylation of a different part of HIF by another enzyme, FIH-1, (Factor Inhibiting HIF) which prevents the HIF complex binding other transcription factors. So enzymatic hydroxylation is acting as an 'oxygen sensor'. In the presence of oxygen it turns HIF off both by enabling capture of VHL and preventing it interacting with transcriptional co-activators.

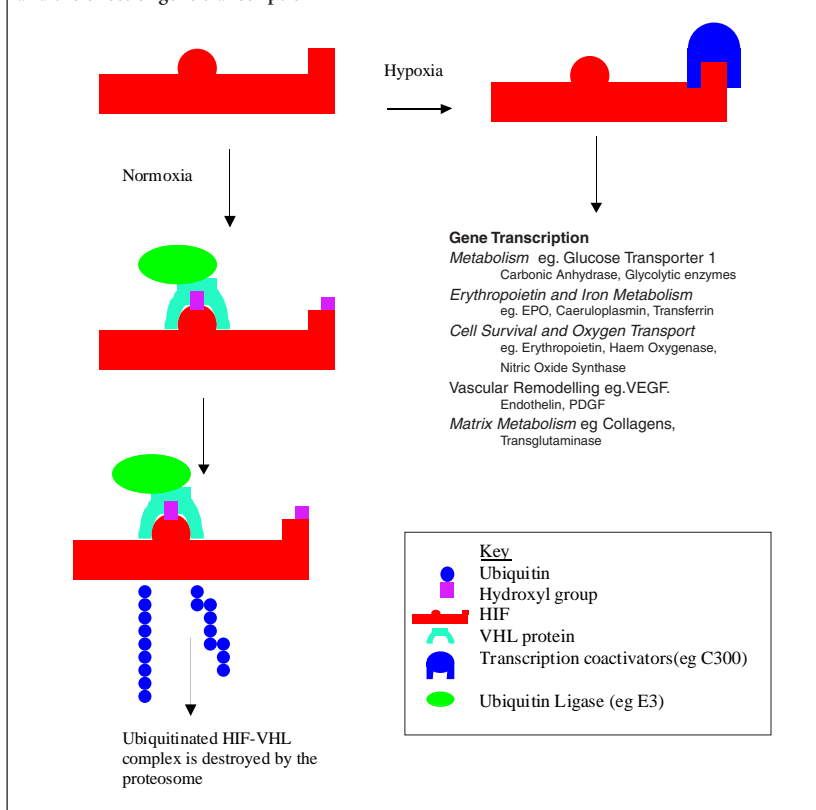
When cells lose VHL function, HIF is constitutively stable and activates target genes such as angiogenic growth factors, explaining the angiogenic phenotype.

## Summary

The rare hereditary cancer syndrome VHL is associated with multiple vascular and cystic tumours. These are caused by a germline mutation in VHL followed by somatic inactivation or loss of the second copy of the gene. The protein product of VHL inhibits the accumulation of hypoxia inducible factor and its target genes under normoxic conditions. Manipulation of the HIF-VHL system may lead to new therapies. In the treatment of cancer if the HIF system can be switched off, the production of VEGF and other growth factors involved in tumour growth can be reduced and may aid conventional therapies.

In ischaemia augmenting the activation of HIF may provide benefit.

**Figure 2. The pathway of HIF activation and destruction according to oxygen concentration and the effect of gene transcription**



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