

PRACTICAL GENETICS

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von Hippel–Lindau disease: A clinical and scientific review

The autosomal dominantly inherited disorder von Hippel–Lindau disease (VHL) is caused by germline mutations in the *VHL* tumour suppressor gene (TSG). *VHL* mutations predispose to the development of a variety of tumours (most commonly retinal and central nervous system haemangioblastomas, clear cell renal carcinoma and pheochromocytomas). Here, we review the clinical and genetic features of VHL disease, briefly review the molecular pathogenesis and outline clinical management and tumour surveillance strategies.

In brief

- Autosomal dominant.
- Results from mutations in the *VHL* tumour suppressor gene.
- Tumours are initiated by biallelic *VHL* inactivation (two hit model of tumourigenesis) and are associated with abnormal activation of hypoxic gene response pathways
- Intrafamilial variation may be marked and interfamilial variation can reflect well established genotype-phenotype correlations for pheochromocytoma and renal cancer risks.
- Most common manifestations are retinal and central nervous haemangioblastomas but in many families there is also a high risk of renal cancers.
- Visceral cysts (renal, pancreatic and epididymal) are common but rarely compromise organ function.
- Less frequent tumours include adrenal and extra-adrenal pheochromocytomas, non-functioning pancreatic endocrine cancers, endolymphatic sac tumours and, occasionally, head and neck paragangliomas.

INTRODUCTION

von Hippel–Lindau (VHL) disease (MIM Number 193300) is an autosomal dominantly inherited neoplastic disorder that demonstrates marked phenotypic variability and age-dependent penetrance. The most frequent tumours are retinal and central nervous system haemangioblastomas, clear cell renal cell carcinoma (RCC), pheochromocytoma, pancreatic islet tumours and endolymphatic sac tumours (ELSTs)^{1–3} (see Figure 1). In addition renal and pancreatic cysts and epididymal or broad ligament cystadenomas occur. Following descriptions of familial retinal angiomas by Collins and von Hippel, Lindau recognised the association between retinal angiomas

and cerebellar haemangioblastoma.⁴ Although Lindau also described the presence of renal tumours and cysts, they were at that time thought to be benign. The term von Hippel–Lindau disease was first used in 1936 and has been in common use since the 1970s. Melmon and Rosen reviewed the literature on what had come to be known as VHL disease and suggested clinical diagnostic criteria. Thus if there is a confirmed family history of VHL disease, a diagnosis of VHL disease can be made by finding a single VHL tumour (eg, retinal or central nervous system haemangioblastoma, clear cell RCC, pheochromocytoma, pancreatic endocrine tumour or endolymphatic sac tumour) in an at risk relative. All of the tumours typically found in VHL disease can occur as a sporadic (non-familial) event and so a clinical diagnosis of VHL disease in a patient without a positive family history requires the presence of two tumours (eg, two haemangioblastomas or a haemangioblastoma and a visceral tumour). Approximately 20% of VHL disease patients result from a *de novo* mutation and do not have a family history.⁵ The characterisation of the *VHL* TSG as the cause of VHL disease⁶ has facilitated the early diagnosis of VHL disease and means that a diagnosis of VHL disease can be made in individuals who do not yet satisfy the clinical diagnostic criteria. In addition germline *VHL* gene mutations may be detected in patients with autosomal dominant familial non-syndromic pheochromocytoma^{7,8} and specific *VHL* missense mutations can cause an autosomal recessive form of polycythaemia without any evidence of VHL disease.^{9,10} Prior to the advent of molecular genetic testing VHL disease was estimated to have an incidence of 1/36 000 live births in Eastern England and prevalences of 1/39 000 in South-West Germany and 1/53 000 in Eastern England.^{11,12} VHL disease is suggested to account for approximately a third of patients with a CNS haemangioblastoma, > 50% of patients with a retinal angioma, 1% of patients with RCC, 50% of patients with apparently isolated familial pheochromocytoma and 11% of patients with an apparently sporadic pheochromocytoma^{5,8,13} (and unpub-

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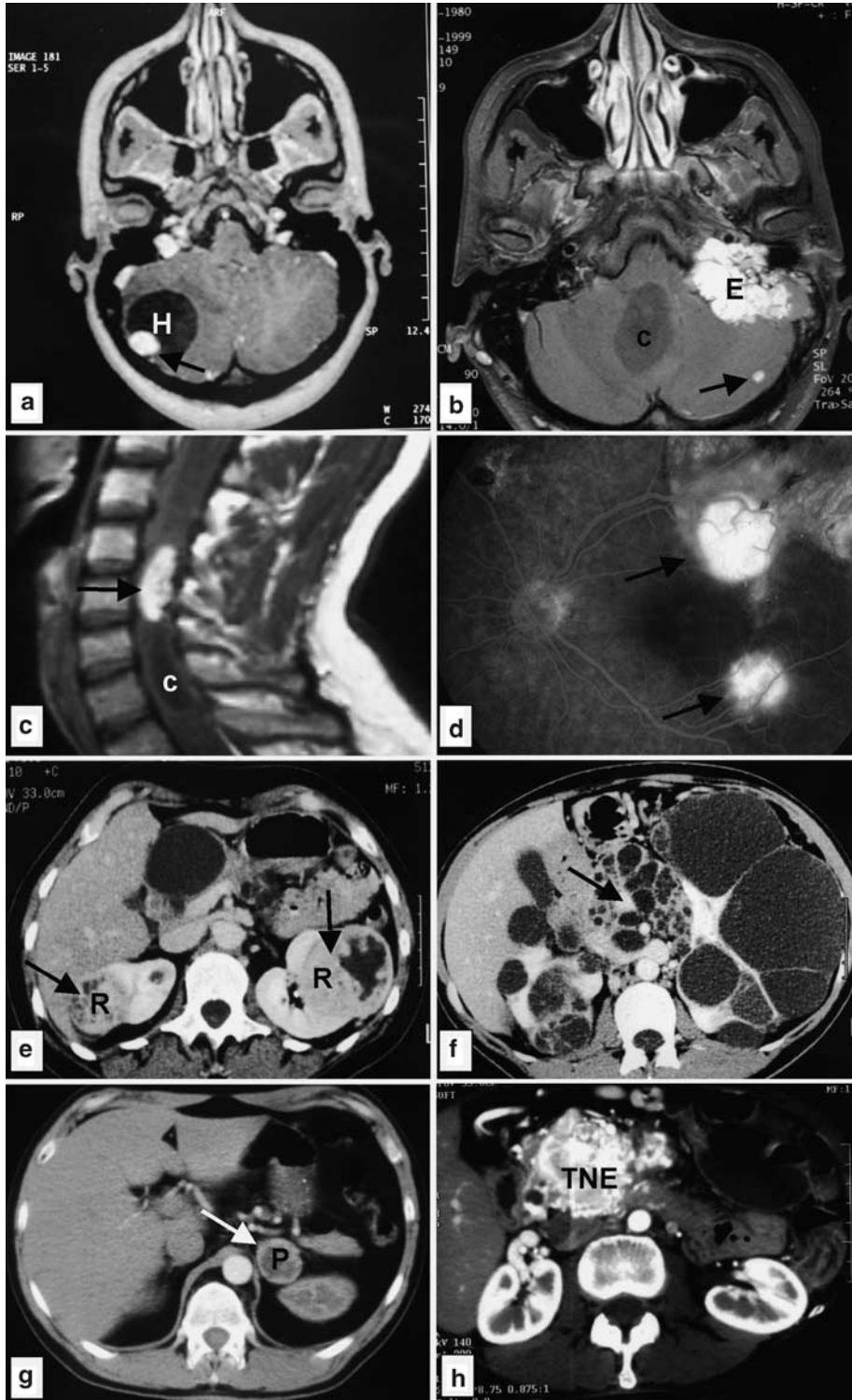


Figure 1 Main clinical manifestations of von Hippel-Lindau disease. (reprinted with permission from Richard S. von Hippel-Lindau disease: recent advances and therapeutic perspectives. *Exp Rev Anticancer Ther* 2003, 3: 215–233). (a) Right cerebellar haemangioblastoma with a large cyst in a 17 years old woman (T1-weighted contrast-enhanced MRI). (b) Endolymphatic sac tumor (E) in a 18 years old woman. Note also the presence of one haemangioblastoma cyst (C) and one quiescent cerebellar haemangioblastoma (arrow). (T1-weighted contrast-enhanced MRI). (c) Cervical spinal haemangioblastoma in a 35 yrs patient with a centromedullary cavitation below (c). (T1-weighted contrast-enhanced MRI). (d) Fluorescein angiography revealing two new large retinal haemangioblastomas (arrows) in an already previously laser-treated 44 years-old patient (courtesy of Professor Alain Gaudric). (e) Bilateral solid renal cell carcinoma (R) in a 38yrs patient. CT scan. (f) Multiple bilateral cysts and cystic renal cell carcinomas in the kidneys of a 40yrs patient. Note also the numerous pancreatic cysts (arrow). CT scan. (g) Left adrenal phaeochromocytoma (P) detected in an asymptomatic 24yrs patient. CT scan. (h) Large pancreatic neuroendocrine tumor (TNE) in a 45yrs patient. CT-scan (courtesy of Prof. Pascal Hammel).

lished observations). The mean age at diagnosis of patients with tumours in patients with VHL disease is considerably younger than in sporadic cases (eg, ~29 and 48 years respectively for cerebellar haemangioblastoma and 44.8 and 61.8 years for RCC).¹⁴

CLINICAL ASPECTS

CNS haemangioblastomas

Are a cardinal feature of VHL disease and are the presenting feature in ~40% of cases.¹ Overall CNS haemangioblastomas occur in 60–80% of VHL patients^{1,15,16} and most commonly occur in the cerebellum, spinal cord and brain stem with supratentorial lesions being rare. Patients with cerebellar haemangioblastomas typically present with symptoms of increased intracranial pressure and limb or truncal ataxia (depending on the precise location of the tumour) and the clinical presentation of CNS haemangioblastomas reflects their mass effect. Haemangioblastomas with an associated cyst tend to become symptomatic sooner.¹⁶

Microscopically, haemangioblastomas consist of large polygonal stromal cells enmeshed in a capillary network and stromal cells arise from mesoderm-derived embryologically arrested haemangioblasts.¹⁷

Although CNS haemangioblastomas tend to enlarge over time, they are benign tumours and the growth rate is variable so that some tumours may be static for a number of years and hence removal of asymptomatic lesions is not usually indicated. Generally the results of surgery for a single peripherally located cerebellar lesion are excellent, but surgical management of multicentric tumours and brain stem and spinal tumours can be challenging and patients can benefit from being treated in units with specialised experience and expertise in VHL disease. Stereotactic radiotherapy may be an alternative to conventional neurosurgery for non-cystic small haemangioblastomas though adverse reactions may occur.^{18,19}

Retinal angiomas (haemangioblastomas)

Have an identical histopathological appearance to CNS haemangioblastomas and the differing terminology reflects ophthalmological tradition and not histopathological diagnosis. Retinal angiomas are the most common presenting feature of VHL disease and are multiple and bilateral in about one half of cases.²⁰ The cumulative risk of visual loss from retinal angiomas was estimated as 35% in all gene carriers and 55% in patients with retinal angiomas at age 50 years.²¹ On average, potentially sight-threatening complications such as exudation, retinal traction or haemorrhage tend to be associated with larger angiomas. Hence management is directed towards identifying asymptomatic angiomas to prevent further complications. Most retinal angiomas respond well to laser photocoagulation or cryotherapy but optic disc angiomas are usually kept under surveillance (unless there is evidence of progression because of the risk of optic nerve damage if they are treated). Antiangiogenic agents may offer a possible option for lesions for which conventional therapy is contra-indicated.^{22,23}

Renal Cell Carcinoma (RCC)

Has a conventional (clear cell) appearance and is an important cause of death in VHL disease. Although the risk of RCC varies in different subtypes of VHL disease (see below) in the most common forms (Types 1 and 2B) the lifetime risk is ~70%.^{1,24} Although the mean age at clinical diagnosis is ~40 years, asymptomatic tumours are frequently detected earlier (though rarely below 16 years).^{24–26} Histopathological examination of kidneys removed from VHL patients shows large numbers of microscopic tumour foci in apparently normal parenchyma that explain the high risk of multiple and bilateral

RCC in VHL disease.²⁷ Multiple renal cysts are common in VHL disease and although they rarely compromise renal function, the lining epithelium may be dysplastic or show carcinoma-in-situ and give rise to RCC. It is generally agreed that a nephron-sparing approach is the optimum strategy for managing RCC in VHL disease. As most patients and gene carriers should be under regular surveillance (see below) many RCC are detected presymptomatically during routine annual renal imaging and usually do not require immediate intervention. Most small renal tumours enlarge slowly (mean <2 cm/year).²⁸ After establishing the growth rate, an individual renal lesion can be kept under regular surveillance until it reaches 3 cm diameter when partial nephrectomy (or an alternative technique such as radiofrequency ablation) is performed.^{29,25} At the time of surgery any additional smaller lesions that are accessible are removed in order to delay the need for reoperation. Follow-up of VHL patients treated by nephron-sparing surgery reveals a high incidence of local recurrence from new primary tumours, but a low risk of distant metastasis³⁰ whereas about 25% of VHL patients with more advanced RCC (>3 cm) develop metastatic disease.²⁹ Repeated renal surgery may compromise renal function so that renal replacement therapy is required. Renal transplantation has been undertaken successfully; and it appears that immunosuppression does not affect adversely the underlying course of VHL disease.³¹ Hence it has been suggested that the usual tumour free interval until an individual is accepted onto the transplantation waiting list can be shortened for VHL patients (unless RCC was >3 cm).

Phaeochromocytoma

Risk in VHL disease varies according to the clinical subtype and underlying *VHL* mutation (see below). Mean age at diagnosis of phaeochromocytoma in VHL disease is ~30 years. Although both adrenal and extra-adrenal phaeochromocytomas can occur in VHL disease, the presence of extra-adrenal phaeochromocytomas in familial phaeochromocytoma cases increases the probability of finding a germline succinate dehydrogenase (*SDH*) subunit gene mutation.⁸ Although the overall risk of malignancy in phaeochromocytomas is generally considered to be ~10%, the rate in VHL disease appears to be less than this (~5%).

Pancreas

Cysts and tumours are relatively common features of VHL disease.³² Multiple cysts are the most frequent pancreatic manifestation and are present in most older patients. However pancreatic cysts rarely impair pancreatic function.³² Pancreatic tumours occur in 5–10% of cases and are usually solid non-secretory islet cell tumours best detected by contrast enhanced MRI with early arterial phase imaging. A high frequency of that malignancy has been reported in VHL associated islet cell tumours and surgery is indicated in tumours >3 cm.^{33,34} Pancreatic tumours with cystic components are microcystic cystadenomas.³⁵

Other features

Endolymphatic sac tumours (ELST) can be detected by MRI or CT imaging in up to 11% of patients.³⁶ Bilateral ELSTs are considered pathognomonic for VHL disease. Although often asymptomatic, the most frequent clinical presentation is hearing loss (mean age 22 years), but tinnitus and vertigo also occur in many cases. *Parasympathetic paragangliomas* are characteristically associated with germline mutations in succinate dehydrogenase subunit genes (*SDHB*, *SDHC*, *SDHD*). However head and neck paragangliomas have been observed in 0.5% of VHL patients, mostly as carotid body tumours.³⁷ *Epididymal cystadenomas* occur in up to 60% of males with VHL disease and

are often bilateral.³⁸ They are usually asymptomatic and do not require treatment. *Broad ligament cystadenomas* may rarely occur.³⁹

MOLECULAR GENETICS

Following the mapping of a gene for VHL disease to the short arm of chromosome 3, large scale gene mapping studies and the identification of large germline deletions (100 kb) led to the identification of *VHL* gene.⁶ The *VHL* coding sequence is represented in three exons and encodes two VHL proteins: a full length 213 amino acid protein (pVHL₃₀) and a smaller protein (pVHL₁₉) that lacks the first 53 amino acids. Although evolutionary conservation of VHL sequence is very strong over most of the pVHL₁₉ sequence, the first 53 amino acids included in pVHL₃₀ are less well conserved and functional studies suggest that the two pVHL isoforms have equivalent effects.^{4,40} The *VHL* mRNA and protein is widely expressed in both fetal and adult tissues.^{41,42}

VHL gene mutations have been reported in >900 VHL disease kindreds,^{6,43,44} (http://www.umd.be/VHL/W_VHL), but although a wide variety of mutations have been described, no unequivocal mutations have been reported in the first 53 amino acids of pVHL₃₀. Germline *VHL* mutations are heterogeneous but the largest group, accounting for about 30–40% of cases, consists of deletions (ranging from 0.5 to 250 kb) that remove one or more VHL exons and usually arise from Alu-mediated recombination.⁴⁵ The remaining mutations fall into two groups, missense substitutions and mutations predicted to cause truncated protein (nonsense, indels, splice site). In non-mosaic patients with classical VHL disease mutation detection is >95%. Complex genotype-phenotype correlations have been described in VHL disease. In families with truncating mutations or exon deletions, pheochromocytoma is infrequent. Hence most of these patients have ‘Type 1 VHL disease’ which is characterised by kindreds with retinal and CNS haemangioblastomas and RCC but not pheochromocytoma. However a subgroup of patients with a contiguous deletion of all or part of VHL and the HSPC300 gene develop retinal and CNS haemangioblastomas but have a low risk of RCC (sometimes called Type 1B phenotype).^{45–47} Kindreds with pheochromocytoma are designated as Type 2 VHL disease and usually have a germline missense mutation. Most such families are further characterised as Type 2B and manifest haemangioblastomas, RCC and pheochromocytoma but Type 2A families manifest haemangioblastomas and pheochromocytoma with a lower risk of RCC.^{48–50} Finally families with specific *VHL* missense mutations in which pheochromocytoma is the only feature are designated as Type 2C VHL disease.⁷ This classification has been most helpful for research studies correlating the effects of a specific mutation with pVHL function and phenotype but is less useful for clinical management as a family may move from one subtype to another (eg, an individual may present with a retinal angioma and a RCC (Type 1 phenotype) but with the diagnosis of a pheochromocytoma in a relative it then becomes a Type 2B kindred).

Many intragenic mutations are non-recurrent but recurrent mutations (eg, c.481C>T, 499C>T, c.500G>A) may result from *de novo* mutations at mutation ‘hot-spots’⁵ or, less commonly, founder mutations. The c.292T>C (p.Tyr98His) missense mutation originated in South-West Germany, is prevalent locally and has been also found in North American kindreds of German origin.⁵¹ Interestingly, although initially classified as a Type 2A VHL mutation, RCC has occurred in a small number of p.Tyr98His mutation carriers (unpublished observations).

The finding of inactivation of the wild type allele in tumours from VHL patients is consistent with a classic ‘two hit’ model of tumorigenesis and, as for the retinoblastoma TSG (*RBI*) and bilateral and sporadic retinoblastoma, biallelic *VHL* inactivation is found in most

sporadic clear cell RCC.^{52–54} Reintroduction of wild-type *VHL* into a pVHL-null RCC cell line suppresses tumour growth.⁴⁰

FUNCTION OF THE *VHL* TUMOUR SUPPRESSOR GENE

Since the identification of the *VHL* TSG knowledge of the function of the *VHL* gene product has increased progressively. It is now clear that pVHL has multiple functions and influences many cellular pathways.⁵⁵ A full discussion of pVHL (the VHL TSG protein) function is beyond the scope of this review and we will focus on the two functions that have been most clearly correlated with clinical and genetics aspects of VHL disease.

Firstly pVHL has a critical role in regulating the proteolytic degradation of the α subunits of the HIF-1 and HIF-2 transcription factors.⁵⁶ Thus pVHL is the critical part of an ubiquitin ligase protein complex that binds (via two hydroxylated prolines) to the α subunits of the HIF-1 and HIF-2 transcription factors and targets them for ubiquitylation and proteosomal degradation.^{56,57} Under normoxic conditions the HIF- α subunits are rapidly degraded but oxygen is an essential co-factor for the proline hydroxylase (PhD) enzymes that must modify the HIF- α subunits for pVHL binding.^{58,59} In (a) hypoxia (when the prolines are unmodified and pVHL is unable to bind) or (b) if pVHL is absent or inactive, HIF-1 and HIF-2 are stabilised and activate the hypoxic gene response that consists of a large repertoire of target genes implicated in diverse processes such as angiogenesis, proliferation, apoptosis and metabolism (eg, VEGF, PDGF β , TGF α , Cyclin D1 etc)⁵⁵ (see Figure 2). HIF target genes are thought to have a key role not only in promoting the angiogenic phenotype characteristic of VHL disease tumours but also HIF-2 targets directly promote.^{60,61}

Missense mutations associated with Type 2 VHL disease occur at surface residues (presumably allowing some retention of function) whereas missense mutations associated with a type 1 phenotype often occur at codons within the hydrophobic core mutations and are predicted to disrupt pVHL tertiary structure.^{62,24} *In vitro* modelling of naturally occurring mutations associated with different subtypes of VHL disease suggest (a) a close correlation between the ability of a pVHL mutation to impair HIF regulation and the risk of haemangioblastoma and (b) that HIF dysregulation is necessary but not sufficient

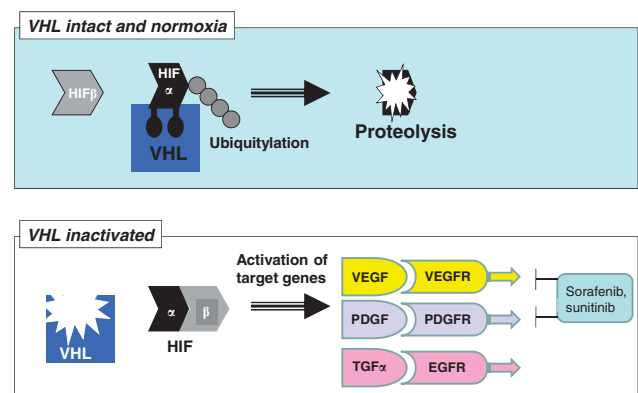


Figure 2 Top panel: in normoxic cells without VHL inactivation a pVHL containing complex ubiquitylates the α -subunits of the HIF transcription factors targeting them for proteasomal degradation. Lower panel: in VHL disease tumour cells the absence of wild type pVHL causes stabilization of the HIF α -subunits and the HIF transcription factors then activate downstream targets including VEGF (vascular endothelial growth factor), PDGF (platelet derived growth factor) and TGF α (transforming growth factor α). Tyrosine kinase inhibitors such as sorafenib and sunitinib inhibit the VEGF and PDGF receptors and so block some of the effects of VHL inactivation (modified from Woodward and Maher⁵⁰).

for the development of RCC.^{63,64} However although mutations associated with VHL disease Types 2A and 2B are associated with HIF dysregulation, Type 2C mutations did not show impaired ability to regulate HIF implicating HIF-independent mechanisms in the pathogenesis of pheochromocytoma in VHL disease.^{63,64} Several HIF-independent pVHL functions have been described⁵⁵ but Lee⁶⁵ implicated a HIF-independent pVHL pathway that links pathogenetic mechanisms for pheochromocytoma in VHL disease to other familial pheochromocytoma predisposition syndromes. Thus inherited pheochromocytomas are postulated to originate from sympathetic neuronal precursor cells that usually undergo apoptosis during late foetal development when availability of nerve growth factor (NGF) diminishes. Lee *et al*⁶⁵ reported that Type 2 VHL disease associated pVHL mutants tested (including 2C mutants that retain the ability to degrade HIF) impaired the apoptotic pathway leading to the hypothesis that specific *VHL* mutations promote pheochromocytoma development by allowing sympathetic neuronal progenitors to escape from developmental apoptosis. This hypothesis is consistent with the observation that somatic *VHL* mutations are infrequent in sporadic pheochromocytoma (in contrast to frequent somatic *VHL* inactivation in sporadic clear cell RCC).

Further evidence of the complexity of genotype-phenotype correlations in VHL disease was provided by reports that homozygous missense *VHL* mutations may cause congenital polycythaemia syndromes without evidence of VHL disease.^{9,10} The best characterized of these mutations is the c.598C>T (Arg200Trp) mutation which is found in a patients with Chuvash polycythaemia and is thought to have arisen as a founder effect 14 000–62 000 years ago.⁶⁶ Patients with Chuvash polycythaemia homozygous for a *VHL* 598C>T mutation are reported to have polycythaemia, vertebral haemangiomas, pulmonary hypertension, varicose veins and elevated serum VEGF concentrations, but, apparently not an increased risk of spinocerebellar haemangioblastomas, RCC or pheochromocytoma.¹⁰

In addition to the phenotypic variability associated with allelic heterogeneity, genetic modifiers may influence the phenotypic expression of VHL disease. Thus Webster *et al.*⁶⁷ reported that patients with retinal angiomas had a higher risk of cerebellar haemangioblastoma and RCC than those without retinal involvement. Furthermore allelic variants in the *CCND1*, *MMP1* and *MMP3* genes have been reported to influence haemangioblastoma development.^{68,69}

MANAGEMENT

VHL disease is a complex multisystem disorder that requires input from many different medical specialties. Co-ordinating the medical care of VHL families can be challenging but is essential to prevent

avoidable morbidity and mortality. Thus early diagnosis of most VHL complications improves prognosis and all VHL patients and at risk relatives should be entered into a comprehensive screening programme in childhood (unless VHL is excluded by molecular genetic testing) (for example see Table 1).

Screening for Retinal Angioma

Affected or at risk individuals should undergo careful ophthalmic examinations every 12 months beginning in infancy or early childhood.

Screening for CNS Haemangioblastoma:

It is suggested that individuals with or at risk for VHL-associated tumours should have MRI scans of the head (\pm spine) every 12–36 months beginning in adolescence.

Screening for Renal Cell Carcinoma

Individuals at risk for VHL-associated tumours should have MRI scans of the abdomen every 12 months from age 16 years. As a consequence of widespread renal surveillance the surgical management of RCC in VHL disease has shifted from the treatment of large symptomatic RCC, to how to manage small asymptomatic tumours. Computer tomography is the most sensitive method for detecting renal tumours (particularly in the presence of renal cysts),⁴⁰ but MRI or ultrasound scans are preferred for regular follow-up to avoid a large cumulative radiation load.

Screening for Pheochromocytoma

At risk individuals should undergo yearly screening for pheochromocytoma beginning in early childhood, for example 24-h urine studies to measure catecholamine metabolites. Measurement of plasma normetanephrine levels is reported to be the most sensitive test for detecting pheochromocytoma in VHL disease.⁷⁰ The MRI screening for RCC can also be used for screening for paraganglial tumours, although screening for pheochromocytoma should be started earlier than age 16 years in families at high risk of this tumour. Pheochromocytomas should be removed endoscopically.⁷¹ After operation on both adrenals in one operation or one adrenal after previous contralateral adrenalectomy, the sufficient supply by mineral- and glucosteroids must be clarified by an ACTH test.⁷²

CONCLUSIONS

Advances in understanding the genetic basis of VHL disease have facilitated diagnosis and provided insights into the biology of VHL disease. Surveillance of affected and asymptomatic gene carriers can reduce morbidity and mortality. However, the management of some aspects of VHL disease, in particular multiple central nervous lesions, is highly complex and challenging. Hence the care of VHL families should be concentrated on specialist referral centres. In addition, attention should be paid to the psychosocial aspects of VHL disease.⁷³ In the future, targeted drugs could offer new therapeutic opportunities for patients affected with VHL disease as it is already the case for tyrosine-kinase inhibitors (specially acting in VEGF pathway) in sporadic renal cell carcinoma.⁷⁴ To date, such drugs are under evaluation in a few number of clinical trials in VHL with good preliminary results in some tumours.⁷⁵

PATIENT SUPPORT GROUPS

Country and language-specific information for HHT patients and families is available through a number of websites (<http://www.vhl.org>). European support groups include:

Table 1 Example of a routine surveillance protocol for von Hippel-Lindau disease (modified from Maher⁷⁶)

Screen for retinal angioma: Annual ophthalmic examinations (direct and indirect ophthalmoscopy), beginning in infancy or early childhood.

Screen for CNS haemangioblastoma: MRI scans of the head for every 12–36 months, beginning in adolescence.

Screen for renal cell carcinoma and pancreatic tumours: MRI (or ultrasound) examinations of the abdomen every 12 months, beginning from the age of 16 years.

Screen for pheochromocytoma: Annual blood pressure monitoring and 24-h urine studies for catecholamine metabolites. More intense surveillance (eg, annual measurement of plasma normetanephrine levels, adrenal imaging, beginning from the age of 8 years should be considered in families at high-risk for pheochromocytoma).

Additional investigations may instigate in response to symptoms or signs of specific complications (eg, ELSTs).

Belgium: <http://www.vhl.org/belgie>
 Croatia: <http://www.vhl-europa.org/hr/>
 Denmark, Sweden, Norway, Finland, Iceland: <http://www.vhl-danmark.dk>
 France: <http://www.vhl.org/fr>
 Germany: <http://www.hippel-lindau.de/>
 Holland: <http://www.vhl.nfk.nl/>
 Hungary: E-mail: suline@para.chem.elte.hu
 Ireland: E-mail: riverfieldfarmhouse@eircom.net
 Italy: Website: <http://www.vhl.it/>
 Poland: E-mail: poland@vhl.org
 Portugal: <http://www.vhl-europa.org/pl/>
 Spain: <http://www.alianzavhl.org>
 Switzerland: <http://www.vhl-europa.org/switzerland/>
 Turkey: <http://www.vhl-europa.org/tr/>
 United Kingdom: <http://www.vhlcg.co.uk>

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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