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Von Hippel-Lindau Disease

E.R. Maher

INTRODUCTION

GERMLINE MUTATIONS in the von Hippel-Lindau (*VHL*) tumour suppressor gene predispose to a variety of benign and malignant tumours which may develop during childhood or in adults. Recent advances in the molecular genetics of VHL disease culminated in the identification of the *VHL* gene which has enabled presymptomatic diagnosis by DNA analysis to be offered to VHL disease families and has provided opportunities to investigate the role of the *VHL* gene product in normal cellular growth and differentiation and the involvement of *VHL* gene mutations in human cancer.

EPIDEMIOLOGY

Although VHL disease has been considered to be rare, it is likely that diagnosis is underreported. The minimum birth incidence of VHL disease in eastern England is 1 per 36 000 [1], and the prevalence of VHL disease in southwestern Germany was estimated at 1 per 39 000 [2]. VHL disease is the commonest cause of familial renal cell carcinoma [3], and approximately 30–40% of patients with cerebellar haemangioblastoma have VHL disease (more in early onset cases) [4]. Recently, Neumann and associates [5] reported that 19% of unselected patients with phaeochromocytoma had VHL disease.

INHERITANCE AND CLINICAL FEATURES

VHL disease is inherited as a dominant trait with variable expression, and age- and tumour-dependent penetrance. The penetrance of VHL disease is almost complete by age 65 years [1], but VHL disease may present in infancy or only be diagnosed in the seventh decade [6–11]. Retinal and cerebellar haemangioblastomas are the most common presenting features of VHL disease, but renal cell carcinoma and phaeochromocytoma are the initial complications in 10 and 5% of patients, respectively (Table 1). The mean age at onset of renal cell carcinoma is later than for retinal or cerebellar haemangioblastomas, but the cumulative risks of a VHL disease patient developing a retinal angioma, cerebellar haemangioblastoma and renal cell carcinoma by age 60 years are in excess of 70% for each tumour [6]. Hence, the majority of patients with VHL disease will develop a renal cell carcinoma if they live long enough and renal cell carcinoma is the most common cause of death in VHL disease. Patients with VHL disease develop cerebellar haemangioblastomas and renal cancers at an earlier age than those who develop sporadic forms of these tumours (29 versus 48 years and 45 versus 62 years, respectively) [4], and VHL disease tumours are frequently multiple or bilateral. The earliest age at onset of renal cell carcinoma is 16 years [12].

Although phaeochromocytoma occurs in approximately 10% of patients overall [6, 11], in some families this is the most frequent complication and in others it is rare [6–8, 13]. In most VHL families with phaeochromocytoma, the predisposition to renal cell carcinoma is similar to that in families without phaeochromocytoma, but in rare families with phaeochromocytoma, renal cell carcinoma may be infrequent [13]. Recently interfamilial differences in phaeochromocytoma incidence have been correlated with the type of *VHL* gene mutation (see below). Phaeochromocytoma in VHL disease cases occurs at an earlier age than in nonfamilial cases, and is frequently multifocal (55% of cases) [5].

Pancreatic tumours in VHL disease are usually islet cell adenomas or carcinomas, which are frequently asymptomatic and detected on routine radiographic screening [14]. Although endocrine disturbances can occur, most are non-functional.

Correspondence to E.R. Maher at the University of Cambridge, Box 134, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, U.K.

Table 1. *Clinical features of von Hippel-Lindau disease. The incidence of complications is percentage of patients affected, and the data are derived from a single centre study* [6] *and a literature review of* 554 *patients* [8]. *Age at diagnosis is taken from Maher and colleagues* [6]

	Lamiell *et al.* [8] $n = 554$	Maher *et al.* [6] $n = 152$	Mean age at diagnosis (years)
Retinal haemangioblastoma	57%	50%	25
Cerebellar haemangioblastoma	55%	59%	29
Spinal cord haemangioblastoma	14%	13%	34
Renal cell carcinoma	24%	28%	44
Phaeochromocytoma	19%	7%	20

Renal, pancreatic and epididymal cysts are frequent in VHL disease. Renal cysts occur in up to 76% of patients with a mean age at diagnosis of 36 years [11, 15]. Histopathological examination reveals a continuum from simple renal cysts, through to atypical cysts and cysts with frank carcinoma-*in-situ* in the lining epithelium [11, 16]. This led to suggestions that renal carcinomas arose from renal cysts. However, follow-up by CT scan of renal lesions in VHL disease has revealed that most simple renal cysts grow slowly and do not transform to renal cancer. In contrast, complex cysts and solid lesions contained renal carcinoma and enlarge with a mean doubling time of 10 months [17]. Pancreatic cysts occur frequently but are usually asymptomatic. Rarely, severe cystic disease may produce pancreatic endocrine insufficiency or biliary obstruction [18, 19].

A variety of other tumours have been reported infrequently including visceral angiomas, paraganglioma, testicular tumours, meningioma and others [20, 21]. In some cases the association may be fortuitous, but a recently recognised complication of VHL, which may produce hearing loss, is a low-grade papillary adenocarcinoma of the endolymphatic sac [22]. Similar tumours have been classified as choroid plexus papillomas [23] and occur in approximately 8% of VHL patients [22].

DIAGNOSIS

Conventional criteria for the diagnosis of VHL disease in isolated cases are: two or more haemangioblastomas (retinal or central nervous system) or a single haemangioblastoma in association with a visceral manifestation [24]. Where there is a family history of retinal or central nervous system haemangioblastoma, a diagnosis of VHL disease can be made from the presence of a single haemangioblastoma or visceral complication. However, in familial cases, these criteria may not always be reliable if a diagnosis is made because of the presence of epididymal cysts, pancreatic cysts or renal cysts alone [25]. Recently, Ravine and colleagues [26] have described data for the age-related incidence of simple renal cysts in the normal population, which is useful for interpreting the significance of renal cysts in individuals at risk of VHL disease.

SCREENING AND MANAGEMENT

Early diagnosis of VHL disease complications, particularly retinal haemangioblastomas and renal cell carcinoma, reduces morbidity and mortality. When an individual is diagnosed with VHL disease, all at risk relatives should be screened with a standard protocol [6]. Such screening frequently identifies asymptomatic relatives with subclinical VHL disease [27]. Affected individuals require lifelong follow-up and annual screening for subclinical complications [6]. At risk individuals should be followed up until 65 years of age before being reassured that they are at low risk. Presymptomatic diagnosis of gene carriers by molecular genetic testing improves the efficiency of screening programmes by enabling screening to be performed less frequently, or discontinued in relatives shown to be at low risk [28, 29].

A diagnosis of VHL disease must be considered in all patients with a retinal or central nervous system haemangioblastomas, particularly in young patients. Screening for VHL disease should be performed in patients with familial renal cancer or phaeochromocytoma. Young patients with renal cancer or phaeochromocytoma, or patients with multiple tumours may also have VHL disease.

MOLECULAR GENETICS OF VHL DISEASE

The *VHL* disease gene was identified in 1993, 5 years after the initial mapping of the gene to chromosome 3p [30, 31]. The isolation of the *VHL* disease gene was achieved using a positional cloning strategy, and was expedited by the identification of families with critical recombination events and VHL patients with submicroscopic deletions, detected by pulsed field gel electrophoresis [32–35]. The cloned coding sequence of the *VHL* gene is represented in three exons which encode 284 amino acids. An unknown amount of 5′ coding sequence remains to be cloned. Sequence analysis of the predicted *VHL* gene product does not reveal homology to other tumour suppressor gene products. Within the first exon there are eight repeats of an acidic pentamer repeat that is similar to a pentameric repeat in the procyclic membrane protein of *Trypanasoma brucei*. Although this may indicate that the *VHL* gene product is membrane-bound and involved in signal transduction, detailed information on the normal function of the *VHL* gene is not yet available.

The detailed mapping of the *VHL* gene by genetic linkage studies [25, 36, 37], enabled presymptomatic diagnosis with linked DNA markers to be offered to families with a suitable structure [28, 29]. Since these studies were published, even more closely linked microsatellite markers and intragenic polymorphisms have been identified [33, 38–42], enabling accurate

presymptomatic diagnosis with linked DNA markers in most families with a suitable family structure.

Recent data suggest that presymptomatic diagnosis by direct mutation analysis will be possible in approximately 70% of VHL disease families [43, 44]. Approximately 22% of patients will have large germline deletions detectable by pulsed field gel electrophoresis or Southern analysis, and 47% will have small intragenic mutations. The latter group is heterogenous, and consists of deletions, insertions and base substitutions. Germline deletions detected by Southern analysis are also heterogenous. Almost half of *VHL* intragenic mutations are missense mutations, and missense mutations at codon 238 account for 9% of patients with VHL disease [44]. The frequency of codon 238 mutations in unrelated kindreds appears to reflect the deamination of 5-methylcytosine at a CpG dinucleotide. The identification of further 5′ coding sequence may increase the mutation detection rate in VHL disease patients.

The characterisation of *VHL* gene mutations allowed the relationship between the molecular pathology and the phenotypic expression of VHL disease to be investigated. Germline *VHL* gene deletions are heterogenous, but there are no phenotypic differences between patients with non overlapping 5′ and 3′ gene deletions [43]. However, whereas phaeochromocytoma is uncommon in patients with germline deletions, insertions or nonsense mutations, most patients with phaeochromocytoma have missense mutations [44]. In particular, the substitution of an arginine residue at codon 238 is associated with a high risk of phaeochromocytoma. It is not clear why patients who do not have a full length VHL protein have a low risk for phaeochromocytoma, but some missense mutations could act in a dominant-negative manner, or the genotype–phenotype correlations may reflect tissue-specific protein interactions.

SOMATIC *VHL* GENE MUTATIONS AND HUMAN CANCER

The loss of function germline mutations detected in VHL patients suggests that the *VHL* disease gene functions as a tumour suppressor gene. The finding of chromosome 3p25-p26 allele loss in four tumour types from VHL disease patients (haemangioblastoma, renal cell carcinoma, phaeochromocytoma and pancreatic tumours) is compatible with a common mechanism of tumorigenesis in VHL disease tumours which is similar to that found in the retinoblastoma paradigm [45, 46]. Furthermore, the allele loss involves the wild type allele of the *VHL* disease gene. Statistical analysis of the age at onset of cerebellar haemangioblastoma and renal cell carcinoma in VHL disease and in sporadic cases is compatible with one-hit and two-hit mutation models, respectively [4]. The retinoblastoma paradigm would predict that somatic *VHL* gene mutations would be involved in the pathogenesis of sporadic renal cell carcinoma. However, although chromosome 3p allele loss is a frequent and early finding in sporadic renal cell cancers, detailed analysis of chromosome 3p allele loss suggested that further tumour suppressor genes mapping to chromosome 3p13-14 and 3p21 may also be involved in sporadic renal cell carcinoma [47–49]. Recently, Gnarra and associates [50] detected somatic *VHL* gene mutations in 57% of clear cell renal carcinomas. In 98% of cases with a *VHL* gene mutation, there was loss of the remaining *VHL* allele so that the tumours were homozygous for inactivation of the *VHL* gene. Furthermore, *VHL* gene mutations occurred early in tumorigenesis, and were present in renal carcinoma cell lines, and in the primary tumour from which the cell line was derived. These results suggest that the *VHL* gene is the major tumour suppressor gene inactivated in clear cell renal cancer. However, further work is needed to determine if there is a role for mutations in other tumour suppressor gene(s) in chromosome 3p13-p21 in the pathogenesis of nonfamilial renal cancer. The association of familial renal cancer with a reciprocal 3;8 translocation involving 3p14.2 is frequently taken as an indication that there is a tumour suppressor gene at the translocation breakpoint [51]; Gnarra and colleagues [50] demonstrated a somatic *VHL* mutation in a tumour from a patient with familial renal cell carcinoma and a t(3;8)(3p14;q24). The *VHL* mutation had occurred on the normal chromosome 3, the derivative chromosome 8 carrying chromosome 3p telomeric to the breakpoint was lost in the tumour, so tumour cells were homozygous for *VHL* inactivation. This may imply that the t(3;8) predisposes to renal cancer, not by disrupting a tumour suppressor gene at 3p14, but by predisposing to loss of the *VHL* gene. Nevertheless the presence of interstitial deletions of chromosome 3p proximal to the *VHL* gene [47–49], and the finding by Sanchez and associates [52] that the introduction of a chromosomal fragment of proximal 3p suppressed the tumorigenicity of a renal carcinoma cell line suggests that a tumour suppressor gene(s) in chromosome 3p12-p21 may also be involved in the pathogenesis of renal cancers.

A feature of many familial cancer genes is a high incidence of somatic mutations in sporadic tumours, for which there is no excess risk in patients with germline mutations [53]. Chromosome 3p allele loss is a frequent finding in many nonfamilial human cancers including breast, ovary, lung and testicular cancers [54], perhaps implicating somatic mutations of the *VHL* tumour suppressor gene in the pathogenesis of these tumours. However, preliminary data suggest that *VHL* gene mutations are infrequent in non-renal sporadic cancers [50], although further research is necessary to confirm that this is one aspect in which the *VHL* and *RB1* tumour suppressor genes differ.

Increased recognition of the importance of screening in VHL disease has improved the prognosis for affected patients. Advances in molecular genetic diagnosis further improves the management of families by enabling accurate presymptomatic diagnosis. The next challenge will be to build on these advances to elucidate the precise function of the *VHL* gene product, and to develop novel therapies for VHL disease and related sporadic tumours.

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