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EDITORIAL REVIEW

Renal cysts, renal cancer and von Hippel-Lindau disease

Renal cysts and renal cancer (Fig. 1 and Table 1), usually occur sporadically but are typical findings in von Hippel-Lindau disease (VHL) and are considered cornerstones among the clinical criteria for the diagnosis of this condition [1–3]. Although epidemiological studies have revealed a prevalence of 1:30,000 to 1:50,000 [4–6], this disease is seen rarely by the nephrologist or urologist. The goals of this review are to describe the clinical characteristics of VHL and to present current knowledge of the genetic basis of VHL.

History

In 1904 and 1911, Eugen von Hippel, a German ophthalmologist (1867–1938), published his classical clinical and histological descriptions of retinal angiomatosis [7, 8]. One of his patients was later shown to have renal cancer [9]. In 1926, Arvid Lindau, a Swedish pathologist (1892–1952), published his studies on a large series of cystic cerebellar tumors [10]. He provided with convincing arguments that both retinal and cerebellar lesions are of the same origin, and also noted renal cysts and renal cancer in four of his cases. Lindau considered a familiar predisposition for the disease.

Clinical criteria for diagnosis of VHL

VHL is an inherited illness, transmitted as an autosomal dominant trait. Individuals who inherit a mutant *VHL* gene are predisposed to develop hemangioblastomas of the cerebellum, brain stem and spinal cord, retinal angiomas, renal cysts and renal cancers, pancreatic cysts and pancreatic tumors, pheochromocytomas, and epididymal cystadenomas (Table 1) [1]. However, (i) isolated cases of VHL, and (ii) small families with affected individuals showing only one feature, or frequently, only visceral lesions, require more specific diagnostic criteria [2]. The diagnosis of VHL in a member of a family with VHL can be made if that individal develops any one of the cardinal manifestations of the disease (except renal cysts which occur frequently in the normal population). The diagnosis of VHL in an individual without a family history of the disease requires at least two of the cardinal disease manifestations which must include either retinal or central nervous system involvement. Some families that do not meet these clinical criteria have been shown to have germline mutations in the VHL gene [11]. Such families should be considered to have VHL and be managed like typical VHL families.

Kidney involvement in VHL

Renal involvement in VHL is characterized by multiple, bilateral renal cell carcinomas (RCC) and renal cysts. The mean age at presentation is 35 to 40 years [2, 3, 12, 13]. The youngest reported patient was 16 years old [14]. In VHL, men and women are equally affected with RCC in contrast to the male predominance in sporadic RCC [15]. The clinical course of RCC in VHL is characterized by metastases to the liver, lungs and bones. RCC appears to account for about 50% of deaths in VHL [3].

RCC may present with hematuria or with back pain (Fig. 1). Usually, renal cancer in VHL is detected as an incidental finding during CT or ultrasound examination requested for other reasons, or when VHL families are screened for occult kidney disease (Figs. 2 and 3).

The histopathology of renal tumors is clear cell carcinoma (Fig. 4) [12, 16]. Careful macroscopic examination of cystic renal lesions show a typical epithelium, or even small foci of carcinoma. Because of these findings, renal cysts have been proposed to be the cancer-predisposing lesion in VHL-associated RCC [17, 18]. The clear cell renal carcinomas found in VHL are distinct from the tumors found in hereditary papillary renal carcinoma. Although RCC can metastasize to the central nervous system, a tumor in the central nervous system in a patient with VHL is likely to be a hemangioblastoma, not a metastasis from a clear cell renal carcinoma [19]. Immunohistochemistry using epithelial markers may be useful in distinguishing RCC metastases from central nervous system hemangioblastomas [20–22].

VHL can be considered among the conditions associated with cystic kidney disease (Table 3). The typical lesion in the kidney of a VHL patient is several renal cysts, although, rarely, the kidney may have large numbers of renal cysts simulation the appearance of polycystic kidney disease; deterioration of renal function due to cystic kidney disease has been reported in VHL, but is exceptional [23].

Differential diagnosis

The differential diagnosis of VHL-associated renal lesions includes a number of hereditary and non-hereditary conditions summarized in Table 3. Autosomal dominant polycystic kidney disease (ADPKD), like VHL affects both sexes with a similar mean age (38.5 years, unpublished Freiburg ADPKD study) at presentation. Kidney involvement in VHL is characterized by a few bilateral cysts, RCC, normal kidney shape, normotension and normal renal function. ADPKD is associated with secondary hypertension, chronic renal failure and innumerable cysts scattered throughout the parenchyma, with enlargement and alteration of the shape of the kidneys. Cyst infection, a frequent finding in ADPKD, does not occur in VHL. RCC is not generally considered a component feature of ADPKD, but has been coincidentally reported rarely [24]. Extrarenal manifestations of both syndromes occur in several organs. Type and pattern, however, differ considerably. Cysts in the liver are frequent in ADPKD, but rare in VHL (Table 1). Pancreatic cysts are rare in ADPKD, but can be numerous and scattered through the pancreas in VHL (Fig. 5) [25]. The central nervous system in ADPKD

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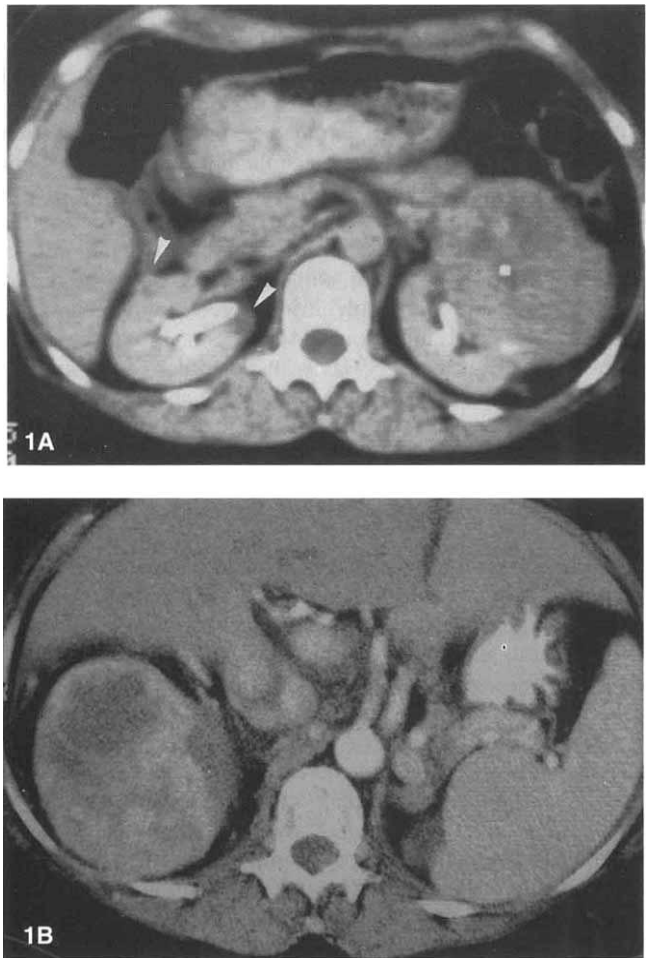


Fig. 1. *Symptomatic carcinoma of the left kidney (7 × 5 × 5 cm) in a 40-year-old female VHL patient (abdominal CT scan).* Nephrectomy specimen disclosed only one tumor and no cysts; note two cystic, in part solid lesions of the contralateral kidney (arrows). **A.** The patient refused regular follow-up and was admitted 10 years later, because of hematuria, and showed a large contralateral renal carcinoma (**B**).

Table 1. Frequent and rare lesions in von Hippel-Lindau syndrome

Eye	Retinal angiomas[a]	49%
	Hemangioblastoma of the optic nerve [86]	
CNS	Hemangioblastoma[a]	54%
	Astrocytoma	0.5%
	Choroid plexus papilloma [87]	
	Ependymoma [2, 88]	
	Neuroblastoma [2, 89]	
Kidney	Renal cell carcinoma[a]	26%
	Renal cysts[a]	30%
Pancreas	Multiple cysts[a]	26%
	Serous cystadenoma	1%
	Islet cell tumor	1%
	Hemangioblastoma [39]	
	Adenocarcinoma [39]	
Adrenal gland, Paraganglia	Pheochromocytoma[a] (adrenal and extra-adrenal)	29%
	Hemangioblastoma [90]	
Pituitary gland	Adenoma	0.5%
Apud cells	Carcinoid	1%
Epididymis	Cystadenoma[a] and cysts	13%
Testis	Germ cell tumor [91]	
Mesosalpinx	Cystadenoma [92, 93]	
Liver	Cysts	1%
	angioma, adenoma, carcinoma [39, 88, 94]	
Spleen	Cysts	0.5%
	Angioma [88]	
Lung	Cysts, angioma [88]	
Bone	Cysts [9]	
Skin	Angioma	0.5%
	Angioblastoma [88]	
Ear	Endolymphatic sac tumor	0.5%

Presented are the incidences in the Freiburg VHL Register as of December 1995, including 228 patients. Rare lesions not observed in the register are cited from literature.
[a] Denotes principal lesions in VHL

Table 2. Characteristics of VHL-associated kidney lesions

Young age (30–40 years old)
Bilateral lesions
Multiple lesions
Solid renal masses and renal cysts
Clear cell carcinoma
Foci of incipient cancer in cysts
Multiple pancreatic cysts
Other principal VHL-associated lesions (Table 1)
Family history for lesions associated with VHL

is affected by arterial aneurysms, but in VHL the central nervous system is affected by tumors.

The tuberous sclerosis complex (TSC) should be considered in the differential diagnosis of multiple renal tumors. In both, TSC and VHL, multiple renal cysts occur. However, the TSC-associated renal tumor is usually an angiomyolipoma. Angiomyolipomas are clinically characterized by an echodense appearance on sonography and the presence of fat detectable by CT scan and MR imaging. In TSC, extrarenal lesions, such as facial or periungual fibroma, cranial periventricular calcifications and cortical tubera are diagnostic for TSC [26]. Mental retardation, epilepsy, and neuropsychiatric manifestations occur in TSC.

Clinical management

Surgery is the only accepted treatment of RCC in VHL. The critical questions are the time of the operation and the surgical technique. For surgery to be effective, it must be performed before renal vein invasion and distant metastases occur. But should small renal tumors 1 to 3 cm in diameter be removed? The answer to this question is not available yet. Previously, VHL patients with bilateral renal tumors were treated with bilateral nephrectomy [27–29]. Currently, nephron sparing surgery is accepted as the method of choice [13, 30–33]. Most urologists prefer tumor resection after clamping the artery and vein and superficial cooling using crushed ice which enables an operation time of up to two hours. Repeated surgical procedures may be required to treat the renal tumors that continue to develop in VHL patients [13]. Laparoscopy is just being introduced for the treatment of renal cancers and may have a role in the management of patients with VHL-associated RCC [34].

Bilateral nephrectomy and renal transplantation might be an acceptable alternative to repeated nephron sparing surgeries in

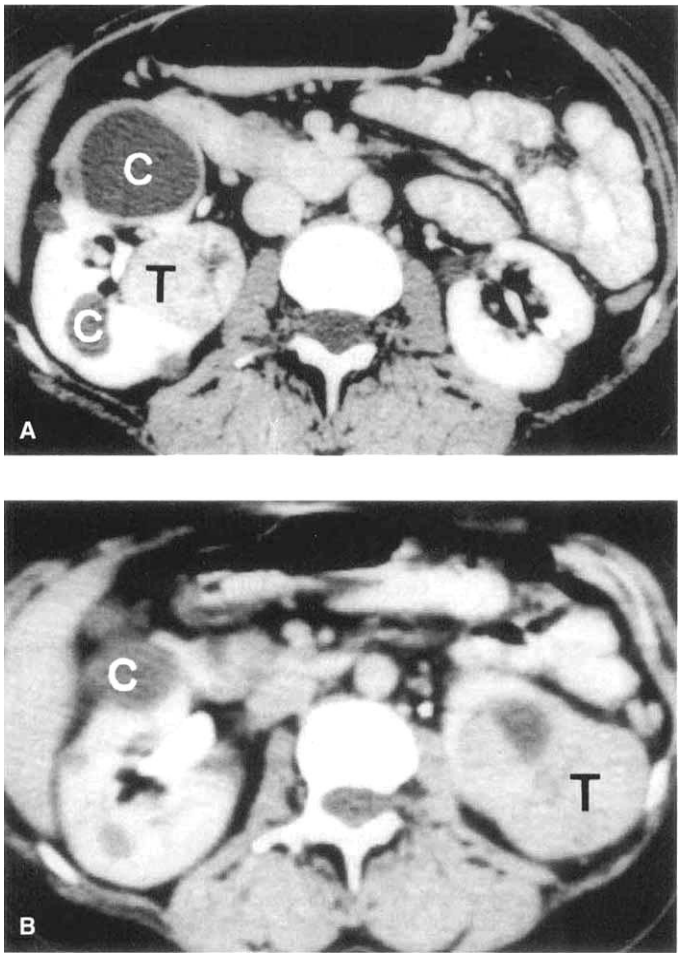


Fig. 2. *Asymptomatic bilateral renal cysts (C) and renal carcinoma (T) in von Hippel-Lindau disease, abdominal CT scan at two levels (***A** *and* **B***) with intravenous contrast from a 45-year-old female.*

patients with VHL-associated RCC. Since the first report in 1977 [35], about 20 VHL patients have received a kidney transplant (VHL Family Alliance, Boston, and the Freiburg VHL Register). It is time for a careful evaluation of the prognosis of these patients. It is not known whether the immunosuppressive drugs required for kidney transplantation promote the growth of the retinal and central nervous system hemangioblastomas and other lesions found in patients with VHL.

Extrarenal VHL-associated lesions

The identification of extrarenal VHL-associated lesions (Table 1) may confirm the diagnosis of VHL in a patient with renal lesions, suggestive of VHL. Available abdominal CT scans should be carefully examined for the presence of pancreatic lesions (Fig. 5) and pheochromocytomas [36–40]. Up to 30% of VHL-associated pheochromocytomas have been found in the paraganglia [41]. Unilateral blindness and symptoms of cerebellar dysfunction may point to ocular and central nervous system manifestations of VHL [42, 43].

Currently, the following screening program is recommended for a patient suspected of having VHL: Gadolinium-enhanced MRI of the brain and spinal cord, detailed examination of the retina, a 24-hour urine collection for catecholamines, and an abdominal CT scan. Central nervous system hemangioblastoma are best detected with Gadolinium-enhanced MRI. Pheochromocytomas are best detected with MRI and metaiodobenzylguanidine scintigraphy (MIBG) [41]. So far, clinical studies cannot be replaced by laboratory tests, since only 70% of VHL families have been shown to have VHL mutations [44].

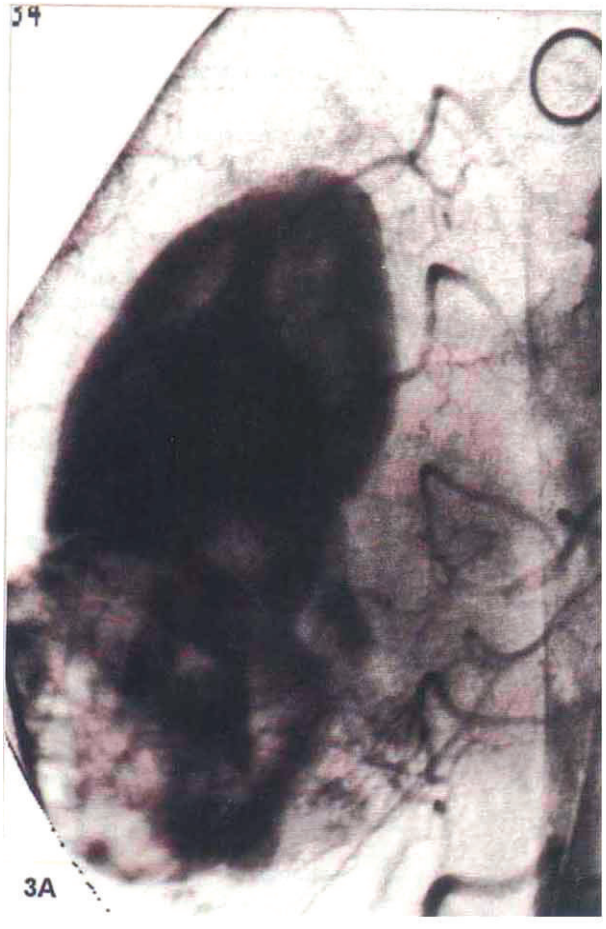
Once the diagnosis of VHL is made, other family members must be contacted to discuss the presence of an inherited disorder in their family and to institute effective medical management.

Knudson's two-mutation theory of cancer

Knudson's two mutation theory helps us understand the pathogenesis of von Hippel-Lindau disease (see below). Knudson's theory of cancer has come to occupy a dominant position in studies of the genetics of human cancer [45]. Knudson studied retinoblastoma, a tumor of the eye that occurs in children in sporadic and inherited forms. He determined the age of onset of disease and the number of tumors per eye in sporadic and inherited forms of the disease. Hereditary retinoblastomas occurred at a younger age than sporadic retinoblastomas, and tumors in patients with hereditary retinoblastoma were often multiple. The epidemiologic data could be explained best by a two mutation model (Fig. 6). In hereditary retinoblastoma, the first mutation was inherited, and therefore was present in all cells of the patient. This initial mutation was necessary but not sufficient to produce eye tumors. A second mutation was required (after fertilization) to trigger a cell along the path of malignant transformation. The explanation for the earlier onset and multiplicity of tumors in hereditary compared to sporadic retinoblastoma is that after fertilization, only one mutation is necessary to trigger tumor formation in hereditary retinoblastoma, while two mutations after fertilization are required to produce sporadic retinoblastomas. According to Knudson's theory, in order for a cell to become transformed, the function(s) of a critical growth control gene must be inactivated by mutations, or by epigenetic events that affect both copies of the gene (Fig. 7). One assumption of this model is that sporadic and inherited forms of cancer are caused by mutation of the same genes. The model suggests that it should be possible to use the methods of classical genetics to determine the chromosomal location of cancer genes in families with inherited forms of cancer, to clone these cancer genes, and then to test these genes to determine whether they are mutated in sporadic versions of the tumors. By studies of inherited forms of colon, breast and kidney cancer, many of the genes responsible for these disorders have been identified. Because normal function of these genes is required for regulation of cell growth, these genes have been named "tumor suppressor" genes.

Fig. 3. *Asymptomatic carcinoma of the right kidney in a 36-year-old male VHL patient.* Note that angiography (a) shows only one tumor, but surgery disclosed additional small carcinomas at the upper pole (b, c - arrows).

Fig. 4. *Histology of renal tumors in VHL showing clear cell carcinoma, in part solid (***a***) or cystic (***b***).* Hematoxylin and eosin staining. Reproduction of Figures 3 and 4 in color is made possible by a grant from Fresenius Medical Care, Germany.



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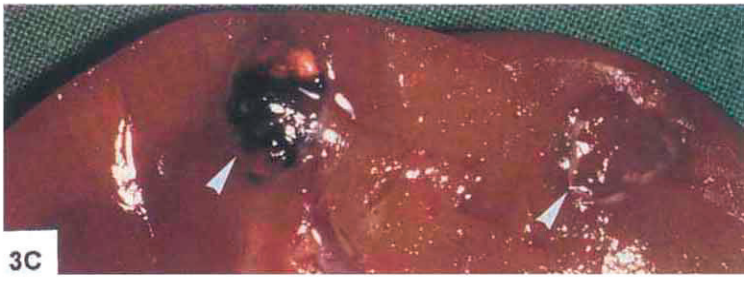

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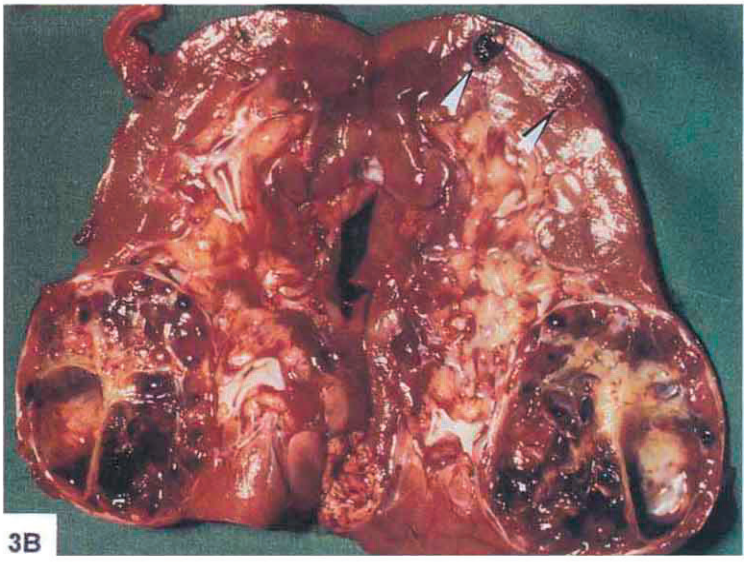

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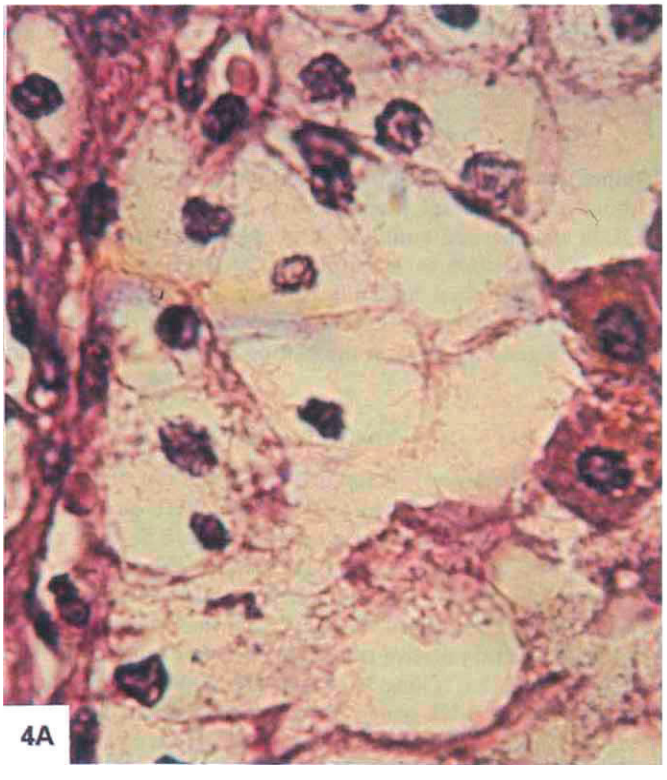

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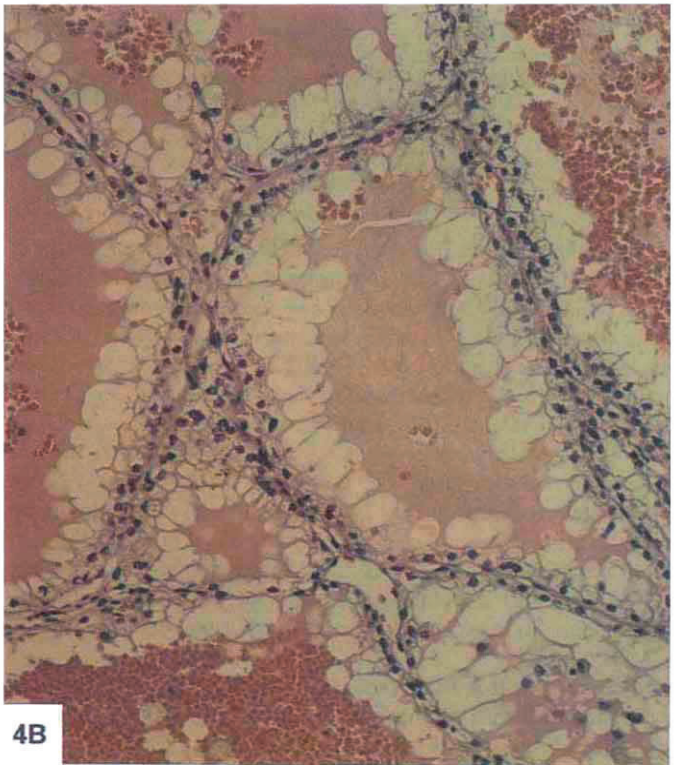

4B

Table 3. Differential diagnosis of renal cysts in adulthood

Entity	Renal characteristics	Extrarenal lesions	Affected relatives	Transmission mode[a]	Renal function	Gene
Polycystic kidney disease (PKD)						
Autosomal dominant PKD1	Innumerable cysts scattered all over the parenchyma	Liver cysts, pancreas and spleen cysts, cranial aneurysms	Parents, siblings, children	AD	Chronic renal failure starting in adulthood	# 16p13 cloned[b]
Autosomal dominant PKD2						# 4q13–23 cloned[b]
Autosomal dominant PKD non1-non2						
Autosomal recessive PKD		Periportal fibrosis	Siblings	AR	Chronic renal failure in childhood or adolescence	# 6p21 mapped[c]
Acquired polycystic kidney disease	Shrunken kidneys with cysts	None	None		End-stage renal failure	
Nephronophthisis	Cysts at the cortico-medullary boundary	Mostly none	Siblings	AR	Chronic renal failure in adolescence	type 1 # 2q13 mapped[c] type 2 not mapped
Senior-Loken syndrome	Cysts at the cortico-medullary boundary	Retinitis pigmentosa	Siblings	AR	Chronic renal failure in adolescence	not mapped
Medullary cystic disease	Cysts in the cortico-medullary boundary	None	Parents, siblings, children	AD	Chronic renal failure in young adulthood	not mapped
von Hippel-Lindau disease	Cysts and tumors	(see this article)	Parents, siblings, children	AD	Normal	# 3p25-26 cloned[b]
Tuberous sclerosis complex types 1 and 2	Angiomyolipoma, cysts	(see paragraph 5)	Parents, siblings, children	AD	Normal or late onset of chronic renal failure	type 1 # 9q34 mapped[c] type 2 # 16p13 cloned[b]
Echinococcosis	Structures within cyst calcification of cyst wall	Sometimes also liver hydatides	None		Normal	
Simple cysts		None	None		Normal	

[a] AD, autosomal dominant; AR, autosomal recessive
[b] Direct genetic diagnosis in an increasing number of cases/families available
[c] Genetic diagnosis in large families by linkage analysis with high likelihood possible

Knudson's model of carcinogenesis applied to renal cancer and von Hippel-Lindau disease

Cytogenetic studies demonstrated that the short arm of chromosome 3 (3p) was consistently deleted in sporadic renal carcinomas [46]. A family was identified with a constitutional (germline) balanced translocation between the short arm of chromosome 3 and long arm of chromosome 8 [47]. This inherited translocation segregated with a predisposition to develop renal cancer. Family members who inherited the translocation had a 90% chance of developing renal cancer by age 60. Family members who did not inherit the translocation did not have an increased risk of developing renal cancer. Both studies pointed to chromosome 3p as the location of a gene that might be involved in the pathogenesis of renal carcinoma. This conclusion was supported by molecular studies that demonstrated a loss of DNA sequences on chromosome 3p in most sporadic clear cell renal carcinomas [48, 49].

To search for this RCC (renal cell carcinoma) gene required finding families with an inherited form of renal cancer to determine the chromosomal location of the VHL gene. We were unable to find families with "pure" inherited renal cancer, that is, families with an inherited predisposition to develop renal cancer without a concomitant predisposition to develop other tumors. VHL is an inherited multisystem neoplastic disorder associated with a predisposition to develop renal cancer as well as tumors of the eyes, brain, spinal cord, adrenal glands and pancreas [1]. We decided to isolate the VHL gene, suspecting that this VHL gene might be a gene involved in the pathogenesis of sporadic kidney cancer.

The VHL gene

The VHL gene was isolated in 1993 by the use of genetic and physical mapping techniques [50–55]. The VHL gene is located near the tip of chromosome 3p at 3p25 to 26. The gene encodes a 213 amino acid protein in three exons. The gene is widely expressed in all the tissues that have been tested by Northern analysis. The promoter of the VHL gene has been identified; it contained several putative transcription factor binding sites [56]. The VHL gene has a long 3′ untranslated region whose function is unknown. The VHL gene was found to be mutated in sporadic clear cell renal carcinomas, and in the germline of patients with VHL (see below), indicating that the gene plays an important role

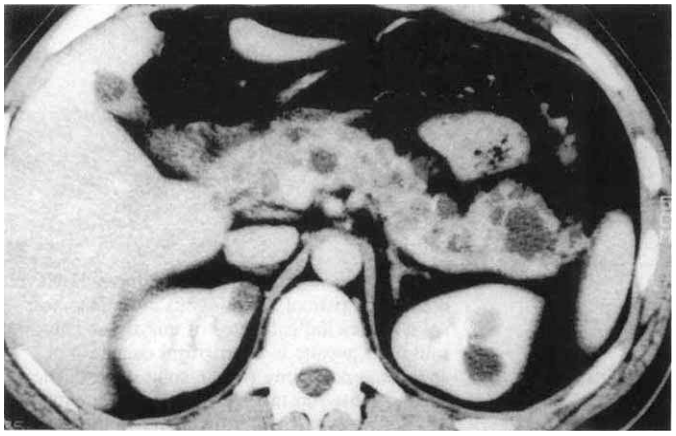

Fig. 5. *Multiple pancreatic cysts, bilateral renal cysts and (not shown) right kidney cancer in a 37-year-old male VHL patient.*

in the pathogenesis of clear cell renal carcinoma. The VHL gene is involved as a first event in the pathway of the renal cell to malignancy.

The VHL protein (pVHL)

One of the major recent discoveries in VHL research is the function and cellular location of the VHL protein. The function of the VHL protein was found by identifying cellular proteins that bound to pVHL [57–60]. Two molecular weight proteins that bound to pVHL were shown to be subunits B and C of Elongin. Elongin is a protein that regulates the rate of transcription elongation mediated by RNA polymerase II [61–65; see below].

The binding of Elongin B and Elongin C by pVHL was detected by several different methods. Duan et al and Kibel et al overexpressed VHL in monkey kidney cells, precipitated pVHL with antibodies and identified proteins that bound to pVHL by SDS-PAGE [66–69]. Kishida et al and Kibel et al prepared VHL fusion proteins bound to a solid support, and used these VHL fusion proteins to identify cellular proteins that bound to pVHL (Fig. 7). These different experimental approaches led to the identification of the same proteins, Elongins B and C.

Studies by Kishida and Kibel have localized the Elongin B and C binding domain of the VHL protein to a COOH terminal peptide [68, 69]. These workers used a panel of GST fusion proteins that contained either the wild type, or mutant VHL proteins. Mutant VHL proteins included recombinant VHL proteins prepared with various deletions of the VHL gene, and proteins prepared with changes in single amino acids. The amino acid changes were selected from known naturally occurring VHL germline missense mutations. Of particular interest, the region of the VHL protein identified as the Elongin binding domain, has been shown to contain a cluster of germline missense mutations in the VHL gene. This observation suggests that the structural integrity of this region is critical to the normal functioning of the VHL protein.

Cellular location of pVHL

Kibel et al [69, 70] located pVHL in the cytoplasm; Duan et al [66] demonstrated that the location of the VHL protein in cells was dependent on cell density. When cells were in contact, the VHL protein was located in the cytoplasm; when cells were not in contact with each other, the VHL protein was located in the nucleus.

Elongin

Elongin was isolated as an enzymatic activity that facilitated the rate of transcription elongation as defined by *in vitro* transcription assays. The Elongin protein is a heterotrimer, composed of a 110,000 kDa (Elongin A), a 15 kDa (Elongin B), and a 10 kDa (Elongin C) subunits. These three subunits have been cloned [71–77].

Transcription, the process of converting a gene's DNA sequence into a corresponding RNA, is a remarkably complex biological process. Transcription can be divided into transcription initiation, elongation and termination. Transcription initiation requires at least six general transcription initiation factors, RNA polymerase II and in some genes, tissue specific regulatory proteins. After transcription has been initiated there are points within the nucleotide sequence encoding the protein that cause the RNA polymerase II complex to pause during the process of addition of RNA nucleotides to the nascent RNA chain. Elongin facilitates the elongation of the nascent RNA chain by reducing the pausing of the polymerase.

Elongin A is the transcriptionally active component of Elongin; Elongin B and C are regulatory subunits. Elongin B serves a chaperone-like function facilitating assembly and enhancing stability of the Elongin complex. Elongin C appears to function as a direct activator of Elongin A. Elongin A and VHL compete for binding to Elongins B and C. The presence of highly purified VHL during assembly of the Elongin ABC complex resulted in substantial inhibition of Elongin activity in both the runoff transcription assay and the tailed-template assay. pVHL inhibits the stimulatory effects of Elongin on transcription by binding to the Elongin B and C subunits of the protein.

Is binding of Elongins B and C by the VHL protein the main function of the VHL protein?

Missense mutations located outside the Elongin binding domain cause VHL. This observation indicates that changes in amino acids outside the Elongin-binding domain can produce disease, and suggest that there may be other regions of the protein with other, as yet unknown, functions. It will be important to evaluate a panel of mutant pVHL proteins in assays of RNA transcription to determine whether the Elongin-binding domain coincides with the transcription domain.

Regulation of vascular endothelial growth factor by the von Hippel-Lindau tumor suppressor protein

The hemangioblastomas of the eye and central nervous system found in patients with von Hippel-Lindau disease are composed of endothelial cells and immature primitive blood vessels. These hemangioblastomas, as well as clear cell renal carcinomas are characterized by infiltration of the tumor with new blood vessels. Recent studies [70, 78, 79] suggest that the basis of this angiogenic response is the secretion of large amounts of vascular endothelial growth factor (VEGF) by VHL tumors. Transfection of wild-type VHL gene into renal carcinoma cells led to reduction of vascular endothelial growth factor secretion and corrected regulation of VEGF.

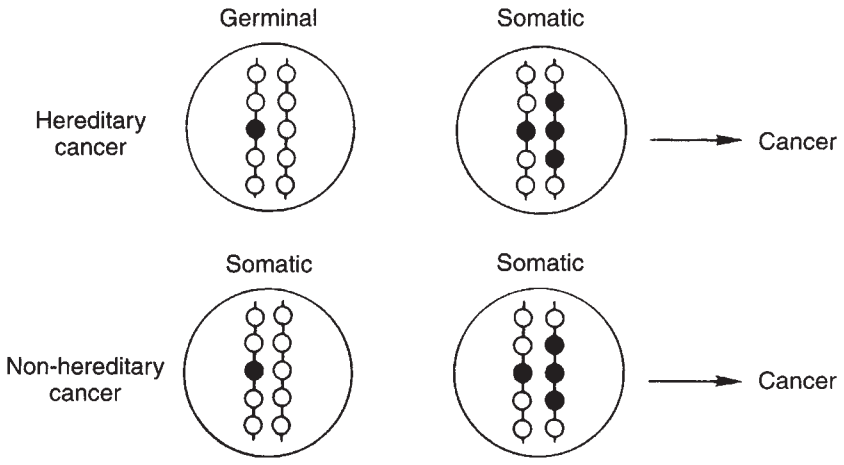

Fig. 6. *Two-mutation theory of cancer.* Each cell contains a pair of homologous chromosomes: solid circles indicate sites of mutation. The first mutation usually is a structural change in a specific cancer gene (single solid circle). The second mutation involves a much larger region of chromosome by mitotic errors (multiple solid circles).

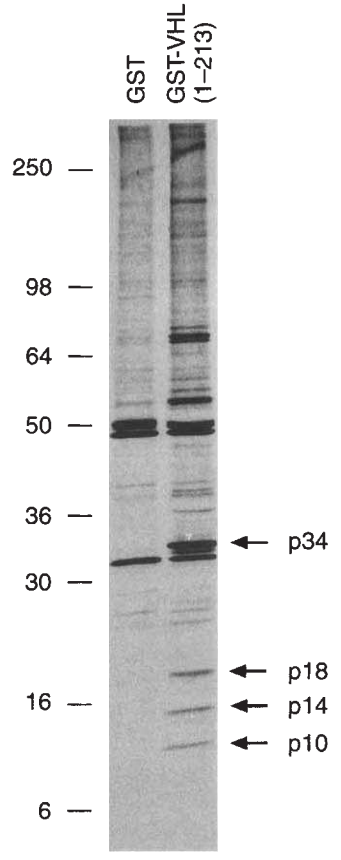

Fig. 7. *Cellular proteins that bind pVHL.* ^{35}S labeled proteins from a renal carcinoma line (A498) were incubated with sepharose GST or sepharose GST-VHL. Bound proteins were eluted and resolved by SDS-PAGE. The p14 and p10 proteins are, respectively, Elongin B and Elongin C. Left scale is in kDa.

Germline mutations in the VHL gene

In contrast to some inherited disorders in which the disease is produced by a limited number of mutations, VHL is caused by many different mutations. More than 140 distinct intragenic mutations in the VHL gene have been found. Most of these mutations were found in one to two families, suggesting that most VHL mutations are of recent origin [44]. Founder effects are rare in VHL. A single example of a founder effect was identified with VHL families in the Black Forest region of Germany [80].

Germline mutations of the VHL gene can be divided into those predicted to produce a truncated VHL proteins (deletion or insertion of 1 to 2 nucleotides, mutations that encode a stop codon, splice site mutations, or mutations that delete large parts of the gene) and those predicted to produce intact VHL proteins with a change in a single amino acid (missense mutations). Mutations that produce truncated VHL proteins produce a disease characterized by retinal angiomas, spinal and cerebellar hemangioblastomas, pancreatic cysts and kidney cancer (VHL type 1). Mutations that produce intact VHL proteins with changes in a single amino acids produce a disease characterized by pheochromocytomas in addition to the tumors described for VHL type 1. In a few rare instances, pheochromocytoma is the predominant neoplasm, while renal carcinomas are rare or non existent (Figs. 8 and 9).

Classification of VHL would be improved, if it was based on the specific germline mutation present in the family. There are several types of VHL based on the differences in cancer phenotype produced by different germline missense mutations.

Somatic VHL mutations

As predicted by the Knudson model [81], the VHL gene is inactivated in sporadic clear cell carcinomas of the kidney. The VHL mutation is specific for clear cell renal carcinoma, a particular histologic type of kidney cancer. Somatic inactivation of the VHL gene takes place by intrageneic mutations, and in some cases by hypermethylation of the VHL gene [82–84]. About 70 to 75% of clear cell carcinomas of the kidney show inactivation of both copies of the VHL gene either by intragenic mutation, or by hypermethylation of the VHL gene combined with physical loss of the normal counterpart of the VHL gene.

The types of mutations found in the germline differ from those found in sporadic renal tumors. Large deletions in the VHL gene are found in 14% of VHL families; such mutations are not found in the VHL gene in sporadic clear cell renal carcinomas. Meiotic events may produce large deletions in the VHL gene. Somatic mutations in VHL gene are clustered in exon 2 [85].

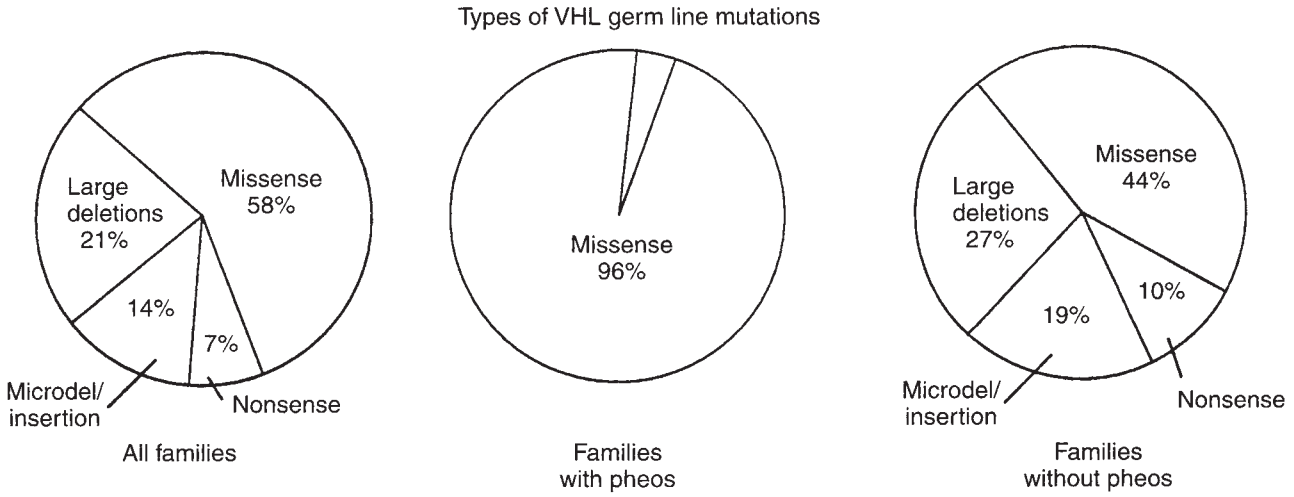

Fig. 8. *Correlation between the types of germline VHL mutation and pheochromocytoma.*

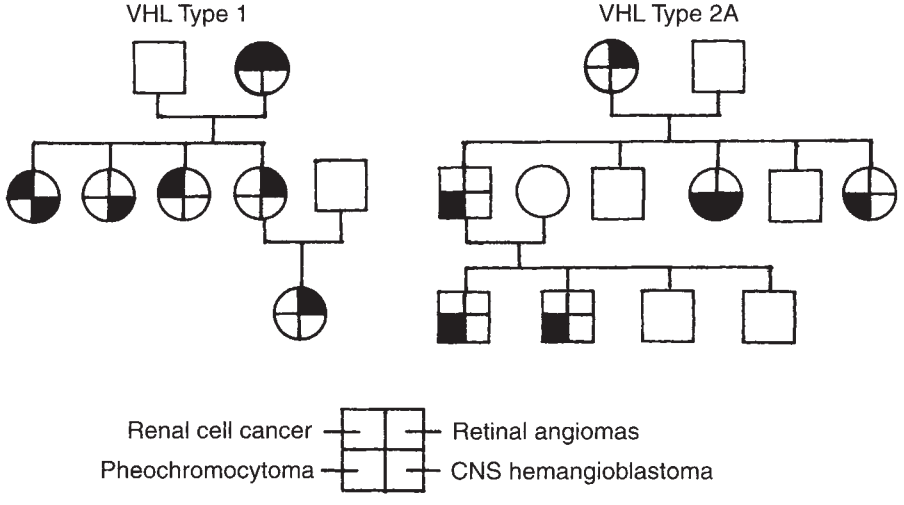

Fig. 9. *Pedigrees of families with different types of VHL.* **Left.** Family with Von Hippel-Lindau disease from Louisiana. Note: No family member had pheochromocytoma. This family had a germline deletion in the VHL gene detected with the gp7 cDNA and is an example of VHL type 1. **Right:** Family with Von Hippel-Lindau disease from the Black Forest Area/ Germany. Note: All but one of the affected members had pheochromocytoma. This family had a nucleotide 505 T/C (Tyr98His) mutation and is an example of VHL type 2A.

Impact of molecular medicine on the diagnosis and treatment of patients/families with von Hippel-Lindau disease

Before the advent of molecular medicine, when a diagnosis of von Hippel-Lindau disease was made, it led to recommendations to screen the at-risk members, such as first degree relatives, of the family throughout their lifetimes to determine whether they had manifestations of the disease. Asymptomatic parents, siblings and children of affected individuals were advised to have abdominal CT scans, spinal and brain MRI, and ophthalmologic exams once a year for life. This recommendation imposed a considerable burden on asymptomatic members of VHL families. The advent of molecular medicine changes the practice of medicine for patients with inherited forms of cancer (like VHL). Once the germline mutation has been identified for a given family with VHL, at-risk members of the family can be tested for the presence of the germline mutation characteristic of their family [85]. If no germline mutation is identified in an at-risk member of a VHL family, it is not necessary to subject that individual to periodic medical testing for occult manifestations of VHL. If a germline VHL mutation is detected, that individual should be periodically examined for manifestations of the disease taking the specific mutation into account, as well as the age specific incidence of VHL tumors.

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