

State of the Art

Hereditary Renal Cancers¹

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Abbreviations:

AML = angiomyolipoma
 TS = tuberous sclerosis
 VHL = von Hippel–Lindau

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Hereditary renal cancer syndromes can lead to multiple bilateral kidney tumors that occur at a younger age than do nonhereditary renal cancers. Imaging plays an important role in the diagnosis and management of these syndromes. During the past decade, several new hereditary renal syndromes have been discovered but are not yet widely known. Whereas previously, the list of hereditary renal cancers in adults included von Hippel–Lindau disease and a rare form of chromosomal translocation, the list now includes the following syndromes: tuberous sclerosis, hereditary papillary renal cancer, Birt-Hogg-Dubé syndrome, hereditary leiomyoma renal cell carcinoma, familial renal oncocytoma, hereditary nonpolyposis colon cancer, and medullary carcinoma of the kidney. In addition, a number of newly described but poorly understood syndromes are under investigation. Even at this early stage, it is clear that elucidation of the underlying genetic mutations that cause hereditary renal cancer syndromes will have profound implications for understanding the origins of nonhereditary renal tumors. These studies will likely culminate in a better understanding of the causes of renal cancer, its prevention, and, ultimately, its cure.

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Each year, renal cancer is diagnosed in over 30,000 Americans and results in about 12,000 deaths, which represents approximately 3% of all cancer deaths in adults in the United States (1). The leading known environmental risk factors for renal cancer are smoking, chemical exposure, asbestosis, obesity, hypertension, and end-stage renal disease (1–3). There is a growing recognition, however, that heredity plays a larger role than was previously thought. It is estimated that approximately 4% of renal cancers are familial, but, as the past 10 years of discovery have shown, the proportion of renal cancers attributed to inherited causes is likely to increase (4).

In the past 10 years, there have been dramatic advances in the understanding of renal and non-renal cancer-predisposing syndromes. The number of specific genes associated with specific diseases has increased exponentially over the past decade; over 1,000 genes have been associated with heritable diseases (5). Advances in genomics and the widespread use of modern imaging techniques have contributed to the awareness of hereditary cancer syndromes. For instance, in the 1980s von Hippel–Lindau (VHL) disease and, in a few rare families, translocations of the third chromosome were the only known causes of hereditary renal cancer (6). Now, this list also includes tuberous sclerosis (TS), hereditary papillary renal cancer, Birt-Hogg-Dubé syndrome, hereditary leiomyoma renal cell carcinoma, familial renal oncocytoma, and hereditary nonpolyposis colon cancer, as well as several other diseases that are highly likely to have a hereditary link to renal cancer (Table). The recognition of “new” hereditary renal cancer syndromes not only is of scientific interest but is also directly relevant to radiologists, who are often the first to suggest a hereditary basis for a renal cancer.

Hereditary cancer syndromes are of practical and biologic importance (7). To patients, the discovery of a genetic predisposition to cancer often leads to early screening of themselves and their families and thus to early detection of tumors, when treatment is most successful. Knowledge of a genetic cancer syndrome allows for counseling. From a clinical standpoint, the identification of patients at high risk presents an opportunity to study the value of screening tests, develop new treatment approaches (eg, organ-sparing surgery), and investigate new prevention and control measures such as inhibitory drug treatments and gene therapy. From a scientific standpoint, the identification of a syndrome presents an opportunity to isolate a specific gene and, thus, a specific genetic mechanism of cancer development. The gene products that are altered, missing, or produced in excess owing to mutations in a gene can help elucidate basic mechanisms responsible for tumors, as well as for normal development and homeostasis. Ultimately,

Hereditary Renal Cancers in Adults

Syndrome	Chromosome Locus*	Frequency of Cancer (%)	Predominant Renal Tumor Type	Other Renal Tumor Types	Associated Abnormalities†
VHL	3p26 (pVHL)	28–45	Clear cell	Cysts	CNS hemangioblastomas, retinal angiomas, pancreatic cysts, neuroendocrine tumors of pancreas, pheochromocytoma
TS	9q34 (hamartin), 16p13 (tuberin)	1–2	Clear cell	Cysts, papillary chromophobe oncocytoma	CNS tubers, angiofibromas of skin, cardiac rhabdomyomas
Hereditary papillary renal cancer	7q34 (hepatocyte growth factor receptor)	19	Papillary type 1	None	None
Hereditary leiomyoma renal cell carcinoma	1q42–43 (fumarate hydratase)	Unknown	Papillary type 2	None	Cutaneous and uterine leiomyomas
Birt-Hogg-Dubé	17p11.2 (folliculin)	8–15	Chromophobe	Clear cell, papillary oncocytic neoplasm, oncocytoma	Fibrofolliculomas, lung cysts, pneumothorax
Hereditary renal oncocytoma	Unknown	Unknown	Oncocytoma	None	Renal dysfunction
Translocation from chromosome 3	To chromosome 2, 6, 8, or 11	Unknown	Clear cell	None	None
Lynch type 2	2p16 (MSH), 3p31 (MLH1)	2–9	Transitional cell carcinoma of renal pelvis	None	Cancer of colon, endometrium, ovaries, and stomach
Medullary carcinoma of kidney	11p	Unknown	Medullary carcinoma	None	Sickle cell trait

* Information in parentheses is the gene product.
 † CNS = central nervous system.

this knowledge is translated into treatments that benefit not only the few with hereditary forms of cancer but also the many with the more common sporadic forms of cancer.

Herein, we will review the features of hereditary renal cancers, the basic principles of genetics relevant to these syndromes, and the various histopathologic features of renal cancer. In addition, we will describe the known and suspected syndromes associated with hereditary renal cancers and the management strategies for these diseases.

WHAT IS HEREDITARY RENAL CANCER?

Hereditary renal cancer differs from sporadic renal cancers in several important respects (7,8) (Fig 1). A hallmark of hereditary renal cancer is that it is often multiple and bilateral. Unlike sporadic renal cancer, which develops in the 6th and 7th decades of life, hereditary cancers may develop much earlier in life, as early as the teenage years in some cases. Whereas sporadic tumors are more common in men, hereditary renal cancers are often found with equal frequency in both sexes and, in some cases, may be

present more often in females. Finally and importantly, there is often, but not always, a familial history of renal cancer. Disease “expressivity” or severity can be highly variable, even within a single family, and the absence of a family history never completely excludes the possibility of a hereditary cause for a renal cancer.

A PRIMER ON GENETICS

There are 23 pairs of human chromosomes, each pair consisting of one chromosome from each biologic parent. The

human genome is now estimated to contain approximately 30,000 genes. On the chromosomes, homologous loci contain two copies, called *alleles*, of each gene. Each of these genes encodes one or more proteins that, in turn, perform one or more functions. Syndromes are caused by mutations in genes that normally code for proteins thought to have important biologic properties, such as maintenance of normal homeostasis. These genes normally play important roles in the development and health of individuals.

One group of genes relevant to this

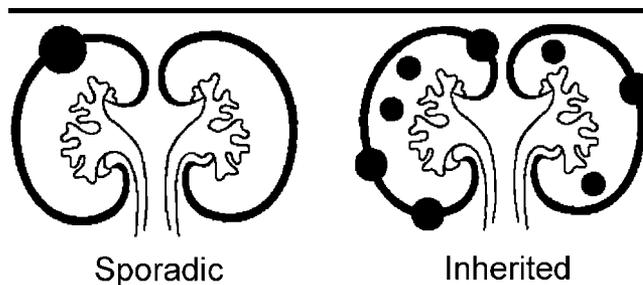


Figure 1. Schematic shows comparison between sporadic and inherited tumors. Inherited tumors of the kidney are more likely to be multiple and bilateral, to occur at a younger age, and are often detected at a smaller size during screening tests.

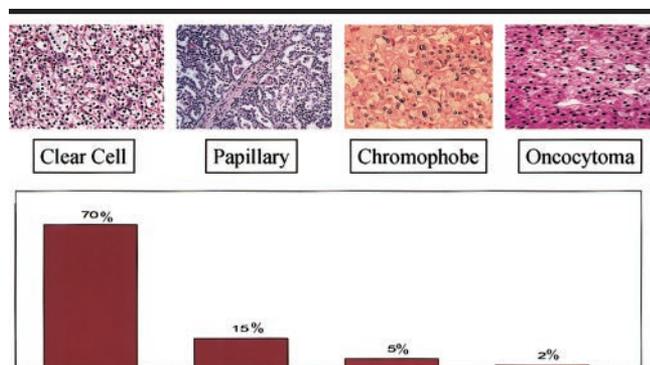


Figure 2. Photomicrographs show the most frequent histologic types of renal cancers, and bar graph shows their prevalence in the general population. Clear cell carcinoma contains lipid-laden cells that have a lucent cytoplasm. Fibrovascular stalks with frondlike projections are characteristic of papillary tumors. Chromophobe carcinomas stain poorly. Oncocytomas demonstrate large dense cells owing to cytoplasm rich in mitochondria. (Hematoxylin-eosin stain; original magnification, $\times 40$.)

discussion is the group of tumor-suppressor genes. They are called tumor suppressors because their normal function is to control cell growth. In their absence or when they are rendered nonfunctional due to mutation, tumors can develop, particularly when both copies of the gene are rendered nonfunctional. Typically, the absence or mutation of one copy of a tumor-suppressor gene is not sufficient to cause a tumor; both copies must be lost or mutated for the tumor to develop. This is known as the “two-hit,” or Knudson, hypothesis (9).

Another group of genes that regulate cell growth are the proto-oncogenes. These are genes that may promote cell growth normally but are highly regulated. When excess copies of the gene are generated or when the control mechanism is damaged, these genes become oncogenes, genes that promote the development of cancer.

Translocation is a genetic mechanism in which part of one chromosome is translocated to another chromosome. The “breakpoint”—that is, the point on the donor chromosome where the fragment detaches—can be the site of a tumor-suppressor gene. Damaged by the break in the chromosome, the cells become susceptible to tumor development (6). Another mechanism is a defective mismatch-repair gene. The function of this gene is to monitor the genome for errors in replication during mitosis. Defective mismatch-repair genes fail to recognize such errors, thus permitting mutations to persist that ordinarily would be quickly identified and fixed. Examples of all these mechanisms are present in the

group of syndromes causing hereditary renal cancers.

In a hereditary cancer syndrome, one inherits a predisposition to cancer rather than cancer itself. In a dominantly inherited syndrome, one copy of the mutated gene is inherited from one parent. Cancer does not necessarily develop until a second “hit” on the complementary (homologous) gene locus occurs. Thus, patients with a hereditary cancer syndrome are not necessarily predestined to develop tumors but are at a much higher risk than is the general population, because the former already lack one normal gene copy. In contrast to an inherited cancer syndrome, in which one is born with a defective copy of a gene and acquires a single additional mutation in the functioning, or “wild type,” allele, in spontaneously developing tumors both copies of the gene within the same cell must be mutated at some point in an individual’s lifetime. Since the likelihood of this is much lower, the Knudsen hypothesis states that the frequency of tumor development in the general population is commensurately lower but increases with age as “hits” accumulate.

There are two additional phenomena of relevance. The first is the concept of spontaneous mutation. Even though we describe a genetic disease as hereditary, the family history may not be positive. For instance, the disease may be so mild in the previous generation that it is not recognized. Alternatively, a true spontaneous mutation (first-time alteration) in a gene may develop in a patient and lead not only to a cancer syndrome but also to the ability to transmit the disease to the next generation. Depending on when in

the process of embryogenesis the mutation occurs, all or just some of the cells of the affected person may be mutated. When all cells, including the germ cells (oocytes and spermatocytes) undergo mutation, the event is termed a *spontaneous mutation* (a new mutation that may be associated with a heritable disease if the mutation is in the germline). When only a portion of the cells of the body are affected, the event is termed a *mosaic form* of the disease, because some cells have the mutated gene and others do not. Mosaic forms of a disease are of two types: one type that includes at least some of the germ cells among the affected cells and puts the individual’s offspring at risk for the full hereditary form of the disease and a second type in which the germ cells are not included in the affected cells and the disease is therefore not heritable (10). All of these events can be seen in hereditary renal cancers.

In this review, the standard terminology to describe genes will be used. As an example, the gene for VHL disease is at chromosomal location 3p25. The first number (“3”) refers to the number of the chromosome, the letter refers either to the short (“p” for petit) or long (“q”) arm of the chromosome from the centromere (the point where both alleles join). The last number (“25”) refers to a specific section of the chromosome. This “address” is not as specific as it initially appears, because the last number may encompass several genes, so that it is possible for two genes to share the same standard nomenclature.

HISTOPATHOLOGY OF RENAL CANCER

There are several histologic types of renal cancer, and each is linked with a specific hereditary condition (Fig 2). Each syndrome produces its own characteristic histologic type(s) of cancer. The most common histologic subtype of renal cancer is clear cell carcinoma. Clear cell carcinomas arise from the proximal tubular epithelium. The cells are typically rich in glycogen and, when stained, appear “clear” or lucent. Grossly, the tumors are yellow-tan owing to their lipid content, and the stroma is vascular owing to high levels of vascular growth factors. In addition to clear cells, granular cells and spindle cells can be found. Clear cell and/or granular cell carcinoma account for 70%–75% of renal cancers (11,12). VHL disease produces clear cell carcinomas of the kidney.

The second most common type of renal cancer is the papillary or chromophil

cell carcinoma. These lesions are villous, with vascularized stalks lined with characteristic densely stained cells and foamy histiocytes (13). Despite the presence of vascularized stalks, the tumors are hypovascular on contrast material-enhanced computed tomographic (CT) or magnetic resonance (MR) images (14). Papillary renal cancers account for approximately 15% of renal cancers. There are at least two types of papillary renal cancer. Type 1 is found in hereditary papillary renal cancer and is associated with a good long-term prognosis. Type 2 is found in hereditary leiomyoma renal cell carcinoma syndrome and is a more aggressive form of cancer than is type 1.

Chromophobe carcinomas are the third most common cell type. These tumors contain poorly staining cells with a reticular cytoplasm characterized by a perinuclear halo and peripheral cytoplasm rich in mitochondria. The lesions tend to be vascular on imaging studies and can be highly aggressive (15). The cell of origin is most likely the intercalated cell of the collecting duct (16). Chromophobe carcinomas account for approximately 5% of renal cancers. They are found in Birt-Hogg-Dubé syndrome.

Oncocytomas account for 2%–3% of renal tumors and are thought to be benign renal neoplasms. Oncocytomas are tan-brown in color owing to their mitochondria-rich cytoplasm. Microscopically, oncocytomas are composed of cells with abundant highly granular eosinophilic cytoplasm arranged in solid, tubular, or trabecular rests (11,17,18). The cells are large (*onco* means “large”) in comparison with the other cell types. They commonly grow centrifugally from a central avascular scar that can become calcified. Although oncocytomas are considered to be benign, reports of recurrence and even metastases following resection of oncocytomas suggest that these neoplasms have the capacity to become malignant since they can contain chromophobe cells (19). This observation raises the possibility that oncocytomas and chromophobe carcinomas represent two ends of the same spectrum. Oncocytomas can be found in Birt-Hogg-Dubé syndrome and familial renal oncocytoma.

Rare malignant tumors of the kidney include collecting duct (duct of Bellini tumors) and medullary carcinomas of kidney, which represent fewer than 1% of renal tumors. The latter is associated with the sickle cell trait. Transitional and squamous cell carcinomas of the renal pelvis with intraparenchymal extension are other causes of malignancy in the

kidney. The former is associated with hereditary nonpolyposis colon cancer syndrome.

A common benign tumor of the renal parenchyma is angiomyolipoma (AML). This is a hamartoma of the kidney that contains vascular, lipomatous, and myeloid elements (20). The majority of these tumors are small, slow growing, and non-invasive. AMLs rarely can become locally aggressive, with invasion into adjacent nodes or within the inferior vena cava (21,22). Reports of metastatic disease to the lungs have appeared (21); however, death due to a metastatic AML is rare. The primary risk associated with AML is hemorrhage, which becomes more likely as the tumor enlarges. AMLs are found in association with TS complex.

HEREDITARY RENAL CANCER SYNDROMES

VHL Disease

History.—VHL disease is a disorder that leads to the development of hemangioblastomas of the central nervous system and eyes, endolymphatic sac tumors, pancreatic cysts and neoplasms, pheochromocytomas, and renal cysts and renal cancers. In the early 1860s in European medical journals, reports first appeared from ophthalmologists who described angiomatous lesions of the retina that caused blindness. In 1894, Collins (23) demonstrated the hereditary nature of this disease by reporting on two siblings with retinal angioma. However, it was Eugen von Hippel (1867–1938), a German ophthalmologist in Göttingen, who published a report in 1904 describing retinal angioma in several generations in a small number of families (24). Arvid Lindau (1892–1958), a Swedish pathologist in Lund, recognized that retinal angioma and cerebellar hemangioblastoma, as well as cysts in the kidney, pancreas, and epididymis, were part of a familial syndrome and published this finding in 1926 as his doctoral thesis (25). Although subsequent reports appeared in which the clinical understanding of VHL disease was refined, Melmon and Rosen’s landmark summary of the disease (26) greatly increased awareness of VHL disease and established the first diagnostic criteria that included renal cancer. In 1988, Seizinger et al (27) demonstrated that the *VHL* gene is linked to the short arm of chromosome 3. In 1993, Latif et al (28) identified the gene responsible for VHL disease. Since then, 137 mutations have been identified. Recently, important insights into the molecular pathways have been gained.

Genetics.—VHL disease is an example of an autosomal dominant tumor-suppressor gene. The *VHL* gene is highly conserved (ie, is found in organisms ranging from insects to mammals), indicating that it has a basic life function. The *VHL* gene produces the VHL protein, pVHL, which normally acts as a gatekeeper, modulating transcription and the production of growth factors (29). Mutations of the gene result in clinical manifestations of VHL disease. The normal protein produced by *VHL* is thought to bind to elongins, proteins involved with reading the RNA message. The VHL protein forms a heterotrimeric complex with elongins c and b and Cul-2 and binds hypoxia inducible factor- α (HIF α), facilitating ubiquitin-mediated degradation. (30). When the *VHL* gene is mutated, however, this binding or targeting of HIF α may be inhibited, and HIF α overaccumulates, promoting the transcription of vascular growth factors such as vascular endothelial growth factor, Glut1, platelet-derived growth factor, and erythropoietin. (31,32). Vascular endothelial growth factor is a known promoter of tumor angiogenesis and vascular permeability, which likely accounts for the vascular appearance of VHL tumors on imaging studies. Mutation of the *VHL* gene also deregulates the cell cycle, leading to uncontrolled cell division (33).

A gene test is available for *VHL*, and investigators have used it to identify the genetic mutation in 93 of 93 families with known VHL disease (34). The finding of a germline *VHL* gene mutation is an indication for a lifetime of periodic screening for VHL tumors and cysts. Approximately 28%–45% of patients with a mutated *VHL* gene develop renal cancer during their lives, and all of these tumors are of the clear cell type (35). Interestingly, over 60% of sporadic clear cell renal cancers also demonstrate inactivation of the *VHL* gene locus (36,37). This provides strong evidence that the *VHL* gene is an important, if not the critical, gene in the development of clear cell carcinoma of the kidney.

Clinical features.—VHL disease is a complex neoplastic disorder that affects multiple specific organs. The prevalence of the disease in Europe and the North America is one in 36,000–40,000 (6,38). A full description of the syndrome can be found in several references (35,39). Briefly, retinal angiomas are an early manifestation and can lead to blindness if not rapidly treated with laser photocoagulation. Cerebellar and spinal hemangioblastomas can cause neurologic deficits and

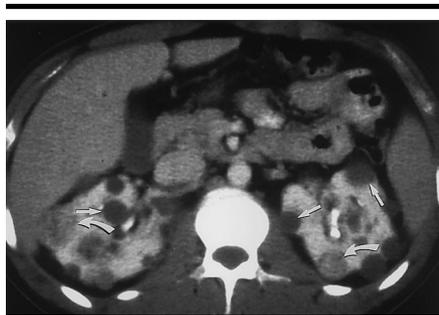


Figure 3. VHL disease in a 22-year-old man in whom multiple cysts (straight arrows) and solid renal cancers (curved arrows) were incidentally discovered on transverse CT image obtained because of abdominal pain. The appearance of cysts and solid masses is typical of lesions found in VHL disease.



Figure 4. VHL disease in a 31-year-old woman. Screening transverse CT image shows left cystic lesion. Solid nodules (arrows) composed of clear cell carcinoma are growing in the wall of the cyst. Complex cystic and solid lesions are a hallmark of VHL disease.

symptoms such as ataxia, paraplegia, sensory loss, and dysequilibrium. Spinal lesions can lead to secondary syringomyelia. Endolymphatic sac tumors are tumors that develop in the labyrinth of the inner ear and can lead to hearing loss and dysequilibrium. Although these tumors do not metastasize, they can be locally aggressive and may lead to complete deafness. The pancreas is most commonly affected by cysts that are classified histologically as serous cystadenomas. These can range in severity from single isolated cystic lesions or clusters of cysts to complete replacement of the pancreatic parenchyma with cysts. Occasionally, severe pancreatic cystic disease will cause exocrine insufficiency requiring pancreatic enzyme replacement. Large cysts can lead to partial bowel obstruction, pain, and early satiety. The cysts can be drained and sclerosed (35). Pancreatic neuroendocrine tumors are solid enhancing lesions occur-



Figure 5. VHL disease in a 44-year-old man who presented with hematuria. Transverse CT scan shows large solid renal cell carcinoma (solid arrow) which had metastasized to the lung. A smaller contralateral tumor (open arrow) is also present. While most VHL disease-associated renal cancers are low grade, lesions can become aggressive and lead to advanced-stage disease. This patient died of metastatic renal cancer approximately 8 months after this image was obtained.

ring in fewer than 8% of patients with VHL disease (40). Such tumors are usually asymptomatic and do not show endocrine hyperfunction. They can metastasize to the liver but are generally slow growing and indolent. Pancreatic neuroendocrine tumors are often found with pheochromocytomas and, thus, may be genetically linked; however, both can be found without the other. (7,40). Pheochromocytomas can be asymptomatic or “silent” when small but gradually produce levels of catecholamines sufficient to produce symptoms such as tachycardia, hypertension, and profuse sweating (41,42) and can be life threatening if not identified and treated prior to stressful events such as surgery or childbirth.

Imaging.—The hallmark of VHL disease manifestations in the kidney is bilateral cystic and solid renal neoplasms (Fig 3). The lesions run the gamut from simple cysts to complex cysts with solid enhancing septa or masses to almost entirely solid renal neoplasms (Fig 4). The key features are that the process is bilateral, occurs at a young age, and is associated with other manifestations of VHL disease (26,43). The cells lining the cysts, as well as the cells within tumors, have a clear cell appearance. Many of these lesions are below the resolution of imaging. Microscopic inspection of grossly normal tissue reveals that approximately 600 microscopic tumorlets may be found in each kidney at pathologic examination (44,45). Fortunately, only a few of these grow to become clinically important. At CT, the solid parts of the tumors enhance briskly (50–200 HU) after intravenous

administration of contrast material. This is likely related to the increased levels of vascular endothelial growth factor and other angiogenic factors produced by these tumors. Renal cancers associated with VHL disease will eventually metastasize if left untreated (Fig 5).

We have observed that the risk of metastatic disease is low with renal tumors smaller than 3 cm in diameter (46). There is a single case report (47) of a patient with VHL disease with a metastasizing renal cancer that was just under 3 cm in diameter. Given the high risk of recurrent disease and the risks associated with renal replacement therapy (dialysis or transplantation), therapies that are nephron sparing (eg, partial nephrectomy, enucleation, radio-frequency ablation, cryoablation) are preferred in patients with VHL disease (48).

TS Disease

History.—TS is a genetic disease characterized by hamartomas in the skin, brain, and viscera. Cardiac myomas and “cerebral sclerosis” were first described by von Recklinghausen in 1862, although TS was not initially recognized as a syndrome (49). The name *tuberous sclerosis* was first used by Bourneville and Brissaud in 1880, when they noted the hard nodules or tubers within the “cerebral circumvolutions” (49). In 1908, Vogt first described the well-known triad of adenoma sebaceum (now called *angiofibromas*), cerebral sclerosis (now called *intracranial tubers*), and cardiac and renal tumors (rhabdomyomas, renal cysts, and renal AMLs). The association of TS with renal cancer was recognized only in the past 2 decades (50).

TS has a prevalence of one in 10,000, although with more sensitive screening the prevalence may be as high as one in 6,000. Thus, approximately 50,000 Americans and over 1 million people worldwide are affected with this disorder. Approximately 1%–2% of patients with TS will develop renal cancers (51,52).

Genetics.—There are two genes associated with TS complex (53,54). Together, these genes account for the majority, but not all, cases of TS. *TSC1*, the gene that was first linked to TS is found on 9q34 and codes for the protein hamartin (55). This gene accounts for about 20% of sporadic cases of TS and about 50% of familial cases (53). It is thought to be a milder variant of the disease. *TSC2*, the second gene linked with TS, is found on 16p13 and codes for tuberin. Tuberin and hamartin are thought to cooperatively bind with each other. The *TSC2* locus is

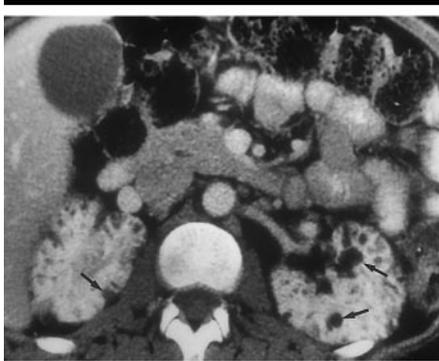
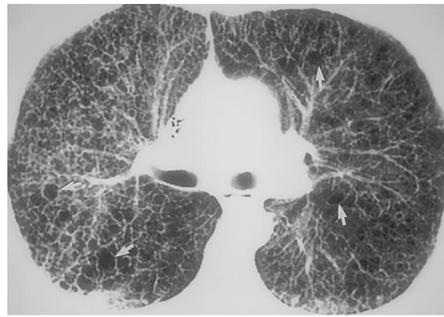


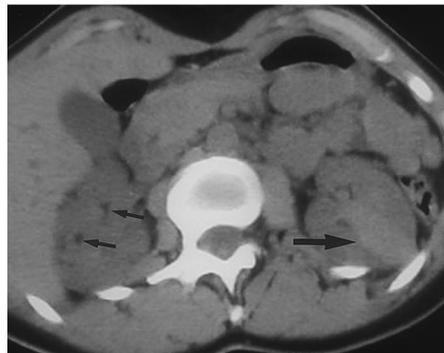
Figure 6. TS with AMLs in a 27-year-old woman. Transverse CT image demonstrates numerous bilateral AMLs (arrows). Facial angiofibromas were also present. Renal function was normal despite the number of lesions. Renal manifestations of TS include AMLs, cysts, and occasional renal cancers.

immediately adjacent to one of the genes (*PKD1*) for autosomal dominant polycystic kidney disease, or ADPKD. Occasionally, a genetic defect will encompass both *TSC2* and *PKD1* loci, resulting in a contiguous gene syndrome in which the disease manifests as both severe renal cystic disease manifesting at a young age (<15 years) and features typical of TS (53). Parenthetically, there is no increased risk of renal cancer in ADPKD alone. The few renal tumors found in ADPKD are likely chance occurrences or are related to long-standing dialysis (54). Both *TSC1* and *TSC2* are autosomal dominant genes. Despite this, most cases of TS are not inherited but are due to spontaneous mutations of the gene occurring during embryogenesis. A variant of TS is known as lymphangiomyomatosis, which occurs almost exclusively in women and results in progressive pulmonary cystic disease and renal cysts, AMLs, and retroperitoneal and pelvic lymphangiomas. Although the lesions in this disorder have the same genetic abnormalities as TS, the manifestations are confined to the lung and abdomen and are not hereditary, indicating that lymphangiomyomatosis is a mosaic form of TS that does not affect the germline tissues (56).

Clinical features.—The diagnosis of TS is based on well-defined signs (54) that include cortical tubers, giant cell astrocytomas, and retinal hamartomas. Facial angiofibromas, fibrous forehead plaques, subungual fibromas, and Shagreen patches (normal colored plaques on trunk with firmer texture than normal skin) are dermatologic signs of TS. Presumptive signs of TS include renal AMLs and cysts, cardiac rhabdomyomas, and pulmonary lymphangiomyomatosis. Additional



a.



b.



c.

Figure 7. Lymphangiomyomatosis in a 34-year-old woman who presented with severe shortness of breath. (a) Transverse CT image reveals numerous pulmonary cysts (arrows) characteristic of lymphangiomyomatosis. Transverse CT images obtained (b) before and (c) after contrast medium administration reveal tiny AMLs in the right kidney (small arrows) and a nonfatty AML (large arrow) in the left kidney that is hyperattenuating relative to kidney parenchyma before contrast material administration and enhances homogeneously after contrast administration. AML was confirmed at biopsy. Over one-third of patients with lymphangiomyomatosis demonstrate nonfatty AMLs in their kidneys. Such lesions may be confused with renal cancers, and biopsy may be needed.

findings include rectal polyps, bone islands and cysts, thyroid adenomas, and renal cancers.

AMLs in TS are typically multiple and bilateral and affect both sexes (Fig 6). This differs from the sporadic form of AML, in which women predominate and typically only one or two lesions are present (52,57). By the 3rd decade, 60% of patients with TS have AMLs, which can lead to hematuria, mass effect, hypertension, and renal insufficiency. AMLs in women with TS tend to be larger and more numerous, but both sexes can be severely affected. The major risk associated with AML is acute hemorrhage, which can be sudden and life threatening. Some authors advocate that intervention be considered for AMLs that are larger than 4 cm on the basis of their propensity to bleed, but this is a controversial practice. (58,59). Intervention can take the form of partial or complete nephrectomy, angioembolization, or radiofrequency ablation. Occasionally, AMLs can extend into the inferior vena cava or



Figure 8. TS and renal cancer in a 28-year-old woman. Transverse CT image demonstrates a solid mass (arrow) in the right kidney. Differential diagnostic considerations included nonfatty AML and renal cancer. Percutaneous biopsy demonstrated clear cell carcinoma, which was removed with partial nephrectomy.

adjacent nodes, mimicking a malignancy; however, death due to metastatic AMLs is exceedingly unusual (21,22).

Renal cysts can be a source of pain, infection, or renal insufficiency. This is especially true of the *TSC2-PKD1* contiguous gene syndrome, where cysts are ac-

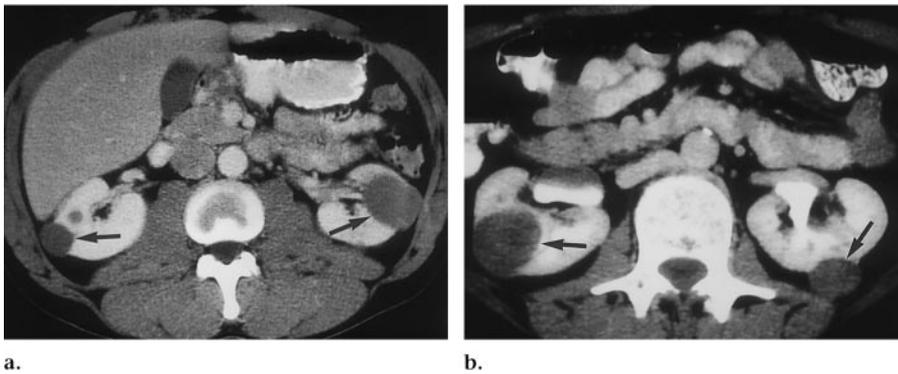


Figure 9. Hereditary papillary renal cancer. Transverse CT images demonstrate bilateral papillary renal cancers (arrows) in (a) a mother and (b) her son. The tumors are characteristically poorly enhancing and might be confused with cysts. Careful enhancement measurements may be necessary to be certain that the lesions are enhancing. Papillary renal cancers are considered less vascular than other tumor types.

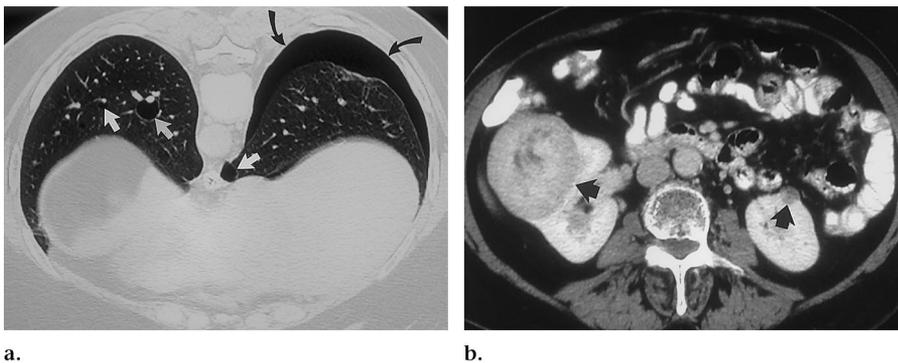


Figure 10. Birt-Hogg-Dubé syndrome in a 43-year-old man with a history of recurrent pneumothorax. Multiple fibrofolliculomas were present on the face. (a) Transverse chest CT image obtained with the patient prone demonstrates pneumothorax (black arrows) and several pulmonary cysts (white arrows). (b) Transverse abdominal CT image demonstrates bilateral solid renal cancers (arrows). Right-sided nephrectomy revealed chromophobe carcinomas.

accompanied by early onset of renal insufficiency. The cyst walls are characterized by a hyperplastic epithelium, which is considered a unique characteristic of TS (60). Unlike in VHL disease, the cysts of TS are not associated with malignancy.

There is a complex relationship between renal cancer and TS. Renal cancers are found with increased frequency in patients with TS, as compared with the frequency in the general population, and have been identified with mutations in both *TSC1* and *TSC2* (51,61) (Figs 7, 8). Occasionally, renal cancer is even the presenting sign of TS (62). Multifocal renal cancer has been found in siblings from a single family with *TSC1* (63). Features indicating an association with renal cancer include a striking female predominance (81% female vs 70% male predominance for sporadic renal cancers), median age of 28 years (vs 6th and 7th

decades for sporadic renal cancers), multifocality, and bilaterality (43%) (54,64). Supportive evidence comes from the animal model of TS, the Eker rat, which has an insertional mutation in the rat *TSC2* gene. The Eker rat develops tumors (adenomas and carcinomas) and cysts in the kidney (65).

A variety of cell types of renal cancers have been reported (66,67) in humans with TS, including clear cell (most common), papillary, and chromophobe carcinomas. Oncocytomas have also been reported with increased frequency in TS (68,69). Some doubt has been raised concerning the actual origin of renal tumors in TS, because some lesions may actually be malignant epithelioid AMLs, which can mimic renal cancers (70).

Imaging.—In most cases, renal lesions can be correctly characterized as cysts or AMLs on the basis of absence of enhance-

ment (cysts) or the presence of low-attenuating fat (AMLs). Nonfatty AMLs, however, are difficult to differentiate from renal cancers and occur in over one-third of cases of TS (Fig 7). Typically, such lesions have higher attenuation than surrounding renal parenchyma on unenhanced CT scans and are uniform in attenuation despite their large size (71). However, definitive characterization requires biopsy. An alternative to biopsy is close follow-up, because AMLs characteristically grow very slowly whereas malignancies tend to exhibit accelerated growth (72). The presence of calcification should also suggest a malignancy, because calcifications are unusual in AMLs. Most AMLs and renal cancers show dramatic enhancement after contrast material administration, so this is not a point of differentiation. On the basis of historical data, there is a very low risk of metastases when a cancer is smaller than 3 cm in diameter, which allows follow-up of small solid lesions in TS; however, a number of deaths from metastatic renal cancer have been reported, and a high index of suspicion is warranted for larger tumors (51,54,73). Renal-sparing surgery should be considered in patients with cancers exceeding 3 cm in diameter (52)

Hereditary Papillary Renal Cancer Type 1

History.—Hereditary papillary renal cancer syndrome is a condition that predisposes the affected individual to papillary renal cancer. The recognition of hereditary papillary renal cancer was established in a report by Zbar et al (74) in 1994. A patient with metastatic papillary renal cancer reported that his father, brother, nephew, and two uncles also had papillary renal cancer. Ultimately, three generations of family members were identified. Zbar and colleagues subsequently reported on 10 other families, mainly of European descent, with hereditary papillary renal cancer (75). It should be noted that the tumors of hereditary papillary renal cancer are of a specific cell type known as type 1 papillary renal cancer. The prevalence of this syndrome is still unknown.

Genetics.—Hereditary papillary renal cancer (type 1) is associated with a mutation of the *aMET* proto-oncogene at 7q31.3. The gene was originally described in 1984 but was linked with papillary renal cancer only in 1997 (76). This gene codes for a transmembrane receptor tyrosine kinase. Mutations lead to activation of the MET protein, which is also the

receptor for hepatocyte growth factor. The tumors produced in hereditary papillary renal cancer are well differentiated type 1 papillary renal cancers. (54,77–81)

Clinical features.—The diagnosis of hereditary papillary renal cancer is based on the detection of germline mutation of the *c-MET* gene. No additional pathologic manifestations have been observed to date. Because papillary renal cancers tend to be slower growing, patients present later in life or die of other causes.

Imaging.—Hereditary papillary renal tumors are generally hypovascular and enhance only 10–30 HU after intravenous administration of contrast material (Fig 9). This mirrors the experience with sporadic papillary renal cancers, which are also typically hypovascular (14,82–84). Papillary renal cancers can be mistaken for cysts, and one must be careful to obtain accurate attenuation measurements before and after contrast enhancement (14,75). Similarly, changes in signal intensity on MR images can be subtle (as low as 15% increase in signal intensity after contrast enhancement), reflecting the hypovascular nature of these tumors. Cysts are unusual in hereditary papillary renal cancer, but they do occur. Ultrasonography (US) can be particularly misleading with this disorder, because small tumors are often isoechoic. In one family in our experience, renal cancers were initially missed on repeated screening US studies. Nevertheless, US can be complementary to CT when enhancement is equivocal.

Hereditary Leiomyoma Renal Cell Carcinoma

History.—In 1995, Vikhlyeva et al (85) described familial predisposition to uterine leiomyomas. In 2001, Kiuru et al (86) reported on a family from Finland with multiple cutaneous leiomyomatosis, uterine leiomyomas, and a family member with a papillary renal cancer that occurred at the age of 35 years. The authors of subsequent reports on 25 families from the Multiple Leiomyoma Consortium, based in Finland, confirmed the early findings and identified the gene responsible (87). Families have now been found in Europe and the United States.

Genetics.—Hereditary leiomyoma renal cell carcinoma is an autosomal dominant condition caused by mutations in the fumarate hydratase (*FH*) gene located at 1q42.3-q43 (87). Fumarate hydratase is an enzyme of the tricarboxylic acid (Krebs) cycle; *FH* is characterized as a

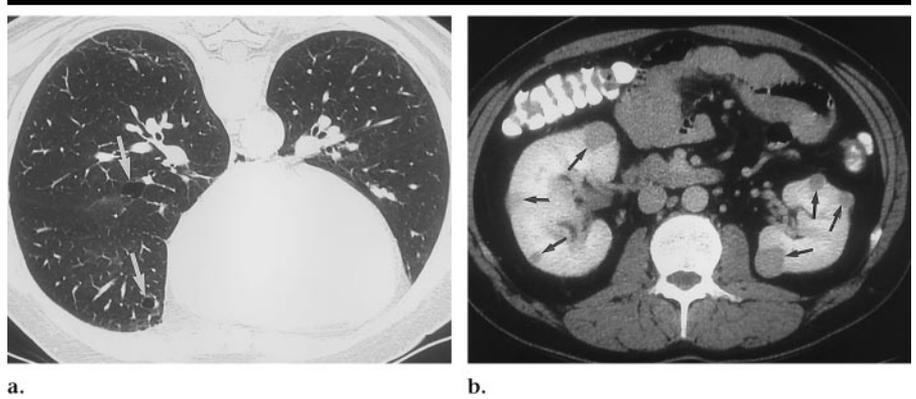


Figure 11. Birt-Hogg-Dubé syndrome in a 38-year-old woman who was asymptomatic but underwent screening because of family history of Birt-Hogg-Dubé syndrome (facial folliculomas). (a) Transverse chest CT image obtained with patient prone demonstrates several small pulmonary nodules (arrows). (b) Transverse abdominal CT image demonstrates multiple solid renal cancers (arrows) that were histologically classified as chromophobe carcinomas at surgery.

“housekeeping” gene, but its role in the development of cancers is unclear.

Clinical features.—Affected individuals develop skin leiomyomata and uterine fibroids, usually manifesting at age 20–35 years (88). Type 2 papillary renal cancers were reported in approximately 20% of the families (87). The papillary tumors found in hereditary leiomyoma renal cell carcinoma can be aggressive and metastasize early. They also tend to be single at the time presentation, in contrast to most hereditary tumor syndromes where the tumors are multiple.

Imaging.—The renal tumors associated with hereditary leiomyoma renal cell carcinoma tend to be hypovascular, are solitary, and may metastasize early. As these tumors enlarge, they become more vascular and may become less distinguishable from other types of hereditary renal cancers.

Birt-Hogg-Dubé Syndrome

History.—Birt-Hogg-Dubé syndrome is a dermatologic disorder characterized by cutaneous hair follicle tumors (fibrofolliculomas), pulmonary cysts, and renal tumors. In 1977, Birt, Hogg, and Dubé studied a large kindred with a familial occurrence of small papular lesions originating in hair follicles on the scalp, forehead, face and neck (89). The skin lesions were fibrofolliculomas, trichodiscomas (early fibrofolliculomas), and acrochordons. This hereditary cancer syndrome became known as Birt-Hogg-Dubé syndrome. In subsequent years, reports appeared describing visceral tumors, including renal cancer, in Birt-Hogg-Dubé syndrome (90). The association of Birt-

Hogg-Dubé syndrome and renal cancers, particularly chromophobe (34%), oncocytoma (5%), hybrid chromophobe-oncocytomas (50%), clear cell carcinoma (9%), and papillary renal cancer (2%), was confirmed in later reports. (91). A reported link with colonic polyps remains controversial; however, a strong association with lung cysts and spontaneous pneumothorax has been established (92). The prevalence of this disorder is still unknown.

Genetics.—The Birt-Hogg-Dubé syndrome gene has been found at 17p11.2, and the gene product is known as folliculin (91). Birt-Hogg-Dubé syndrome is inherited in an autosomal dominant manner. The Hornstein-Knickenberg syndrome overlaps Birt-Hogg-Dubé syndrome and is now considered to be the same entity (93).

Clinical features.—Diagnosis is based on the characteristic appearance and histologic features of fibrofolliculomas, which are multiple 2–4-mm-diameter, white to flesh-colored, smooth, dome-shaped papules on the scalp, face, neck, and upper trunk. These typically develop in the 3rd–4th decade of life (92). Accompanying the fibrofolliculomas may be acrochordons (skin tags), which are small furrowed papules that may occur on the eyelids, neck, and axilla. Acrochordons alone are not diagnostic because they occur commonly in the general population. Pulmonary cysts are often present on CT images (~70%) and are accompanied by a history of spontaneous pneumothorax in 25% (Figs 10, 11). Between 15%–30% of patients with cutaneous Birt-Hogg-Dubé syndrome develop renal cancer. The most common cell type is chromo-



Figure 12. Hereditary renal oncocyoma in a 58-year-old man. Transverse CT image demonstrates bilateral solid oncocyomas of the kidney. A stellate scar (arrow) is present within the lesion in the left kidney, suggesting the possibility of renal oncocyoma; however, the finding was nonspecific and surgery was performed. Renal oncocyomas were confirmed histologically. After removal of the left-sided lesion, the right-sided lesions (not shown) were followed. Although no other family members have been identified, the multiplicity of lesions in this cases suggests a genetic basis.

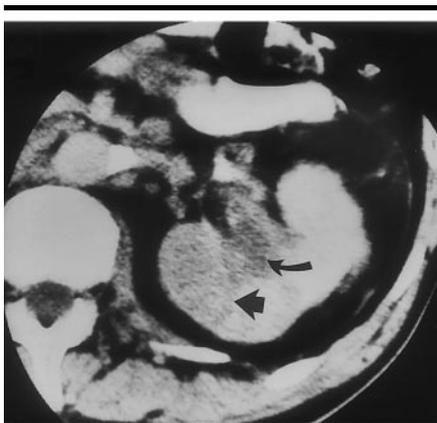


Figure 13. Hereditary nonpolyposis colon cancer (Lynch type 2) in a 56-year-old man who presented with hematuria. Family history was strongly positive for colon carcinoma in three relatives and for endometrial carcinoma in a first-degree female relative. Transverse CT image demonstrates invasive transitional cell carcinoma (curved arrow) of the renal pelvis with invasion into the renal parenchyma (arrow). Nephroureterectomy was performed. The family history suggests Lynch type 2 spectrum of hereditary tumors, which includes tumors of colon, endometrium, urothelium, stomach, small bowel, pancreas, biliary system, and ovaries.

phobe carcinoma, followed by clear cell and oncocyotic neoplasm. Oncocyomas have also been reported in this syndrome.

Imaging.—Patients with Birt-Hogg-Dubé syndrome demonstrate solid enhancing

renal masses. Cysts occur but are unrelated to the tumors. Typically, lesions enhance markedly after contrast material administration and are readily distinguished from cysts. Attention should be paid to the lung, since multiple cysts or pneumothoraces may be present, a feature not seen in VHL disease but which can be seen in lymphangiomyomatosis associated with TS (Figs 10, 11). The lung cysts are well circumscribed, round, air-filled structures and are more often found in the lower lobes. The presence of lung cysts and renal tumors leads to the differential diagnosis of Birt-Hogg-Dubé syndrome and TS. The ultimate diagnosis relies on other features, such as the presence of characteristic skin lesions (TS vs Birt-Hogg-Dubé syndrome) and of intracerebral lesions (diagnosis of TS) or AMLs (diagnosis of TS).

Familial Renal Oncocyoma

History.—Familial renal oncocyoma is an incompletely characterized condition in which affected individuals develop renal oncocyomas (94). Five families with a hereditary predisposition to renal oncocyoma were described by Weirich et al in 1998 (95). Some families had extensive bilateral oncocyomas and compromised renal function (96). Other families had mild manifestations of familial renal oncocyoma. There may be some overlap with Birt-Hogg-Dubé syndrome, as several families initially considered to have familial renal oncocyoma proved to have features of Birt-Hogg-Dubé syndrome. Renal dysfunction without extensive neoplastic disease was also noted. The prevalence of this entity is unknown, and no putative genetic locus has yet been identified.

Clinical and imaging features.—The diagnosis is based on the identification of multiple oncocyomas inherited in an autosomal dominant pattern. At imaging, the lesions are indistinguishable from malignant renal cancers and, thus, must be treated as if they were renal cancers (97) (Fig 12). When oncocyomas are extensive and confluent, the term *renal oncocyomatosis* can be applied (96). Because renal function is often compromised, these patients are often imaged with MR with gadolinium enhancement. Although metastases have not been seen in this small group of patients, the possibility of malignant transformation exists. Lifelong monitoring with imaging studies is recommended.

ADDITIONAL HEREDITARY RENAL CANCERS

Translocation of Chromosome 3

History.—Translocation is the transfer of a large segment of one chromosome to another chromosome. Although the genes that are transferred should function normally despite their abnormal location, the breakpoint—that is, the place where the translocated segment breaks from its original chromosome—may result in a functional mutation. In 1979, a report was published about a number of families with familial clear cell renal cancers who also had translocations (98). Clear cell renal cancer was the only cell type identified. All of the translocations involved the third chromosome, (3:2, 3:8, 3:11, and 3:6; ie, from chromosome 3 to chromosome 2, 8, 11, or 6), as the donor site and the tumors often have somatic mutations in the *VHL* gene (98). The kindreds had in common the translocation of a segment from the short arm of chromosome 3 to another chromosome (99). While it is attractive to consider the breakpoint to be located at the *VHL* locus 3p25, this is not where the breaks are usually found. Moreover, families with translocations do not have the other manifestations of VHL disease. Although it is clear that translocation plays a role in hereditary renal cancers, it is unclear how common this event is.

Imaging.—Translocations of chromosome 3 result in noncystic clear cell carcinomas that enhance intensely after contrast material administration. Typically, these carcinomas are unassociated with renal cysts or other manifestations of VHL disease in the abdomen.

Hereditary Nonpolyposis Colon Cancer

History.—Although it seems odd to be discussing a hereditary colon cancer syndrome among hereditary renal cancer syndromes, Hereditary nonpolyposis colon cancer is also associated with epithelial tumors of the renal pelvis. Hereditary nonpolyposis colon cancer was identified by Lynch and colleagues (100,101) in the early 1980s. It is distinguished from familial adenomatous polyposis syndrome, which is characterized by numerous colonic polyps that progress to colon cancer. Familial adenomatous polyposis syndrome is caused by the adenomatous polyposis coli, or *APC*, gene; in addition to colon cancer, mutations in *APC* are associated with cancers of the duodenum, stomach, and thyroid gland and

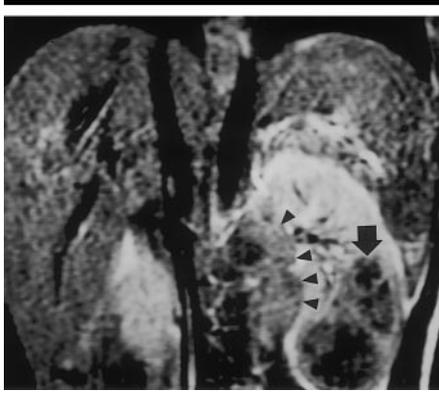
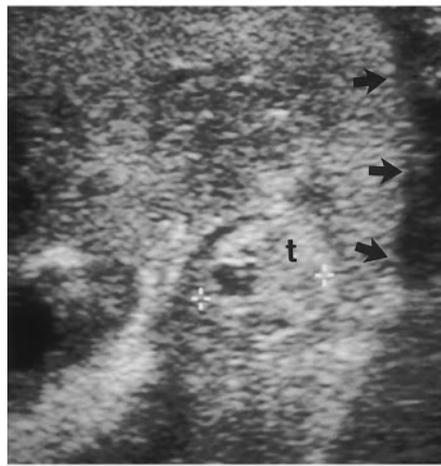


Figure 14. Medullary carcinoma of the kidney in a 14-year-old African American girl who had advanced renal cancer at the time of presentation. The patient had the sickle cell trait. Coronal T1-weighted gadolinium-enhanced MR image (repetition time, 500 msec; echo time, 12 msec) demonstrates a large left renal cancer (arrow) with extensive lymph node metastases (arrowheads). The pathologic diagnosis was medullary carcinoma of the kidney. The patient died within 5 months of this image acquisition.

with hepatoblastomas and medulloblastomas. The hereditary nonpolyposis colon cancer syndrome is divided into two types. Lynch type 1 is a hereditary predisposition to colon cancer with no or minimal antecedent polyposis. There are no other associated cancers in Lynch type 1. Lynch type 2, however, is a syndrome that carries a risk not only of colon cancer but also of carcinomas of the endometrium (second most common tumor), renal pelvis, urothelium, stomach, small bowel, pancreas, biliary system, and ovaries (102). Between 2% and 9% of patients with hereditary nonpolyposis colon cancer develop urinary tract tumors (102,103). Hereditary nonpolyposis colon cancer accounts for 2%–6% of colon cancers (104).

Genetics.—Lynch type 2 disease is caused by mutations of the *MSH2* (mutS homologue) gene at 2p16 (40% of cases) and the *MLH1* (mutL homologue) gene at 3p31.3 (30% of cases), as well as several other genes (*PMS1*, *PMS2*, *MSH6*) that account for a minority of cases (104,105). These are genes whose normal function is to repair DNA mismatches or replication errors that occur during mitosis. When tumors develop, they are characterized by microsatellite instability (in >90% of tumors); therefore, microsatellite instability is a molecular marker for this syndrome. The disease is inherited in an autosomal dominant pattern. Gene testing is now available.



a.



b.

Figure 15. Intraoperative US for guidance during nephron-sparing surgery in hereditary renal cancer (VHL disease). Intraoperative renal US is used to identify lesions deep to the renal surface that are not visible to the surgeon. (a) Transverse scan reveals a 1-cm solid renal mass (*t*) just below the renal surface (arrows) in a patient with VHL disease. Cursors were placed on the lesion margins in order to measure the diameter. (b) Longitudinal scan reveals a mixed solid and cystic lesion (arrows) deep in the parenchyma of kidney adjacent to the renal pelvis. Both lesions were successfully removed.

Clinical features.—The diagnosis is based on having at least three relatives with colon cancer, one of whom is a first degree relative (104). Two or more generations should be affected, and one of the colon cancers should have been diagnosed before the age of 50 years. Some families demonstrate a predisposition to transitional cell carcinoma of the bladder, ureter, and renal pelvis but not to renal parenchymal tumors (106). At-risk individuals should be screened with annual urinalysis or cytologic analysis beginning at age 25 years. Full colonoscopies are recommended every 1–3 years (107).

Imaging.—Little has been reported on the imaging of hereditary nonpolyposis colon cancer syndrome in the kidney and urinary tract. Filling defects within the collecting system or renal pelvis may be seen, and excretory urography may be performed to help better define the location of epithelial neoplasms. Advanced transitional cell carcinoma is often associated with infiltration of the renal parenchyma (Fig 13).

Medullary Carcinoma of the Kidney

History.—Medullary carcinoma of the kidney is a rare aggressive neoplasm that develops in young patients (age range, 11–39 years) with the sickle cell trait (108). Davis et al (108) provided an early description of this entity in 1995 in a review of the histologic findings in 34 cases of medullary

carcinoma in young patients. All were young patients and had the sickle cell trait. The sickle cell trait can be associated with microhematuria, which may be dismissed as simply part of the underlying disease. A high index of suspicion is needed if medullary carcinoma is to be diagnosed early (109). The tumors were highly aggressive and lethal in most cases, with a mean survival of only 15 weeks (110). In one reported case (111), the diagnosis of sickle cell trait was established after the postmortem discovery of medullary carcinoma of the kidney.

The genetic association is based on young age at the time of presentation and association with the sickle cell trait. The tumor is thought to arise from the collecting duct, which would account for its central location. The gene for sickle cell trait is located on the short arm of chromosome 11, and monosomy-11 has been noted in the medullary tumors (112). The frequency of medullary carcinoma of the kidney in patients with the sickle cell trait is very low, because few reports of the disease have appeared although one in 12 African Americans has the sickle cell trait (113).

Imaging.—In the appropriate demographic setting, it is possible to suggest the specific diagnosis of medullary carcinoma of the kidney. The tumors are usually large and centrally located and often have adjacent lymphadenopathy and distant metastases (114,115) (Fig 14).

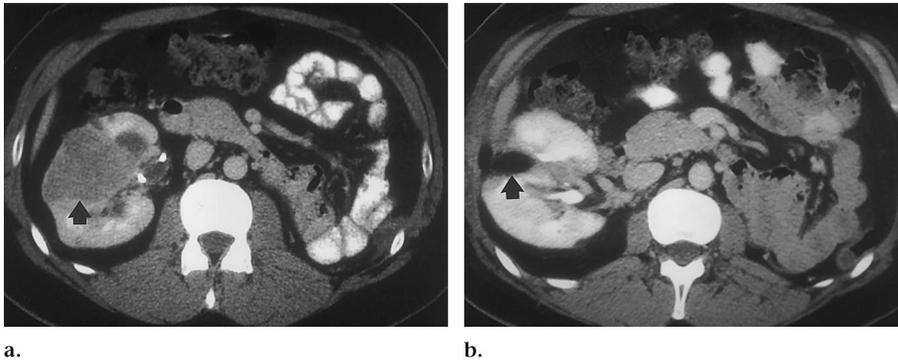


Figure 16. Nephron-sparing surgery in a 38-year-old man with hereditary renal cancer (VHL disease). The patient had undergone prior left nephrectomy. (a) Transverse CT image demonstrates a large mass (arrow) in the right kidney. To preserve renal function, nephron-sparing partial nephrectomy was performed and retroperitoneal fat was packed in the wound. (b) Post-operative transverse CT image demonstrates fat within the wound (arrow) at the site of disease. No recurrence has been observed during 4 years of observation.

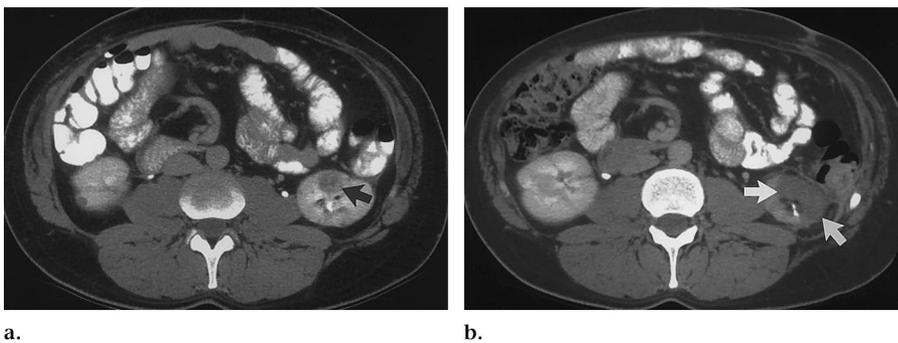


Figure 17. Radio-frequency ablation of renal tumor due to hereditary renal cancer in a 35-year-old man. (a) Transverse CT image demonstrates a growing solid mass (arrow) in the lower pole of the left kidney. Radio-frequency ablation was performed. (b) Follow-up transverse CT image obtained 9 months after ablation demonstrates damaged renal parenchyma (arrows) at the tumor site. Enhancement of this area was less than 10 HU. Regional defects can be seen for more than 2 years after radio-frequency ablation; however, this treatment method is much less invasive than surgery. (Images courtesy of Bradford J. Wood, MD, National Institutes of Health, Bethesda, Md.)

SCREENING GUIDELINES FOR HEREDITARY RENAL CANCER

There are no established guidelines regarding screening for hereditary renal cancers; however, a number of generalizations can be made. Based on its availability, accuracy, and consistency, CT is best single choice for screening (116). The benefits of improved diagnostic accuracy outweigh the theoretical risks of radiation. When patients cannot undergo contrast-enhanced CT, gadolinium-enhanced MR imaging is a suitable substitute. MR imaging, while theoretically ideal (no radiation, multiplanar capability, etc), cannot yet be widely recommended for screening because of wide variations in quality and because of the expense. US is insensitive for small renal masses and can lead to a false-negative diagnosis (116).

Patients with a hereditary renal cancer syndrome who exhibit an aggressive phenotype should undergo imaging relatively frequently (every 3–6 months), whereas patients with a mild phenotype may safely undergo imaging at 2–3-year intervals. Moreover, the interval may vary for each patient; when the patient has few small lesions, the interval may be longer than when the same patient has developed larger lesions.

MANAGEMENT OF HEREDITARY RENAL CANCERS

The management of hereditary renal cancers varies with the nature of the disease, but some generalizations can be made. Large tumors are often treated with traditional radical nephrectomy, even if the tumors have a genetic basis. Nephron-

sparing surgery in this setting is difficult. However, as awareness of genetic cancer syndromes increases, more patients are undergoing screening with imaging. Tumors are therefore discovered at smaller diameters, while they are still amenable to nephron-sparing approaches.

There are several reasons to consider nephron-sparing treatments for patients with hereditary renal cancers. The most important reason is to preserve renal function, because the likelihood of contralateral recurrence is high. The high mortality rate and low quality of life associated with renal replacement therapies (dialysis, transplantation) present a strong argument for renal preservation (46). Nephron-sparing approaches are aided by the low grade of most small tumors that arise in hereditary conditions. For instance, in the case of VHL disease, almost all tumors smaller than 3 cm in diameter are grade 1 or 2 and, therefore, have a very low risk of metastasis (48). This leads to a strategy wherein small tumors are observed until they reach approximately 3 cm, whereupon the patient undergoes a nephron-sparing intervention (46). Although this approach has been validated in VHL disease, it has not been fully explored in the other hereditary conditions. It is, however, logical that the same strategy may be effective for other conditions.

Nephron-sparing surgery is the method of treatment for which the largest clinical experience exists (48). Survival has been excellent; and recurrence rates, acceptable. Importantly, renal function can be preserved for long periods of time. Nephron-sparing surgery is assisted by intraoperative US, which can aid the surgeon in identification of lesions deep to the renal surface (Fig 15). Intraoperative US is also a useful aid for identification of the extent of the lesion and its relationship to the central renal sinus. In one study (117), intraoperative US enabled detection of additional important lesions in over 20% of cases. Even lesions larger than 3 cm are amenable to nephron-sparing surgery (Fig 16). Naturally, not all phenotypes can be treated with nephron-sparing surgery, and completion nephrectomy is eventually necessary.

Several new technologies offer less-invasive methods of treating hereditary renal cancers. Cryotherapy and radio-frequency ablation can be applied percutaneously, thus markedly reducing recovery times. Although studies to date are small in number, the early results are encouraging (118–120). One difficulty has been monitoring of posttherapy defects

in the kidney that may persist for long periods after treatment (121) (Fig 17). Laparoscopic cryotherapy or radio-frequency ablation have also been attempted in lesions that cannot be safely approached percutaneously (122). Laparoscopy can also be used to perform partial surgical nephrectomy, although, to date, candidate lesions must be peripheral and exophytic (123).

SUMMARY

During the past 10 years, there have been major developments in the recognition of the hereditary basis of renal cancer. Hereditary cancers are typically multifocal and bilateral, and it is often the radiologist who first raises the possibility of a hereditary cause for a particular renal cancer. It is, therefore, important to be familiar with the expanding list of diseases known to predispose to renal cancers. This list includes VHL disease, TS, hereditary papillary renal cancer, hereditary leiomyoma renal cell carcinoma, Birt-Hogg-Dubé syndrome, hereditary renal oncocytomas, hereditary nonpolypoid colon cancer, and medullary renal cancer. Improved awareness should lead to earlier diagnosis in individuals and their at-risk family members. The basic genetic and proteomic (identification of protein markers for disease) mechanisms underlying these conditions will likely form the basis for innovative prevention and treatment strategies in the future. It is predictable that additional types of hereditary renal cancers will be discovered, and refinements of the current classification will likely occur. Although these diseases currently account for only a minority of renal cancers, the lessons learned from them will have profound implications for the treatment of all forms of renal cancer in the future.

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