Chapter 14: Hereditary Renal Cancer Syndromes

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INTRODUCTION

Inherited forms of renal cancer are estimated to account for 2%–5% of all kidney cancer (1). Currently, 10 inherited cancer susceptibility syndromes are definitively associated with an increased risk of renal cancer (Table 1) and are described in more detail below. Patients with these inherited syndromes develop kidney cancer at an earlier age; furthermore, the lesions can be multifocal, bilateral, and heterogeneous. Several, including Birt-Hogg-Dubé syndrome (BHD), familial clear cell renal cancer due to chromosome 3 translocation, hereditary papillary renal cancer, hereditary leiomyomatosis and renal cell cancer (HLRCC), and von Hippel-Lindau disease (vHL) have renal cancer as a primary feature, whereas in another inherited cancer susceptibility syndrome, such as *BAP1* mutation–associated disease, Lynch syndrome, phosphatase and tensin homologue (PTEN) hamartoma syndrome, hereditary pheochromocytoma and paraganglioma (due to SDHx mutations), and tuberous sclerosis complex, it is a secondary feature. Recently, mutations in *CDKN2B* and *PBRM1* also have been reported to predispose to clear cell renal cancer in single case series (2,3) and, as such, need further validation. Many of the genes identified through the studies of familial renal cancer have proven to play a critical role in renal cancer development through somatic mutation, with vHL disease being the exemplar of this paradigm. The description of families with inherited cancer susceptibility syndromes associated with an increased risk of renal cancer has and will lead to the discovery of mutated genes important in the pathogenesis of renal cancer. Below, the features of the inherited cancer susceptibility syndromes associated with an increased risk of renal cancer, with a focus on the renal manifestations and pathologic features, are reviewed.

VON-HIPPEL LINDAU DISEASE

Patients with this highly penetrant autosomal dominant cancer susceptibility syndrome can present with a wide spectrum of hemangioblastomas of the brain, spine, and retina, pancreatic cysts and neuroendocrine tumors, renal cysts and clear cell renal tumors, endolympatic sac tumors, and pheochromocytomas. vHL disease is found across all ethnic groups, with approximately one-quarter of the incidence due to *de novo* mutations; genetic testing for mutations in *VHL* detects nearly 100% of individuals with vHL disease (6). Disease usually presents in the late teens to early 20s, although an occasional individual may be diagnosed in their mid-40s. The presentation of renal disease is quite variable even within family members, with some patients never developing renal cancer, others having a few renal cysts, and others with who have bilateral renal cancers and hundreds of lesions within each kidney. In part, this variability is due to a strong genotype–phenotype correlation that is seen with a mutational type predictive of disease (7). Patients with type 1 (truncating) mutations have a decreased incidence of pheochromocytoma compared with those with type 2 (missense) mutations (8). Frameshift and nonsense mutations in *VHL* are associated with a high penetrance of clear cell renal cancer, with a risk at age 50 of 70% (8). Full and partial gene deletions of *VHL* confer a lower risk at age 50 of 40%. Families with type 2 mutations have either a low (type 2A) or high risk of clear cell renal cell carcinoma (ccRCC) (type 2B); type 2C families develop pheochromocytoma only. Type 2A disease is associated with the "Black Forest' founder mutation (Tyr98His) originating from southwestern Germany, commonly found in the "Pennsylvania Dutch" population (9). Despite the variability in phenotype, screening recommendations for vHL patients are standardized, and in adult include annual CNS (brain, spine) and abdominal/pelvic magnetic resonance

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Table 1. Inherited cancer susceptibility syndromes associated with an increased risk of renal cancer

Syndrome	Gene	Protein	Predominant renal Cancer Type	Other Cancers	Non-Neoplastic Findings
BAP1 mutation associated cancer susceptibility	*BAP1*	BRCA associated protein	Clear cell	Melanoma Uveal melanoma Mesothelioma	Epithelioid atypical Spitz tumors
Birt-Hogg-Dubé syndrome	*FLCN*	folliculin	Oncocytic, chromophobe, hybrid	—	Fibrofolliculomas Lung cysts, pneumothorax
Familial clear cell renal cancer due to chromosome 3 translocation	Translocation chr 3		Clear cell	—	—
Hereditary Leiomyomatosis and Renal Cell Cancer	*FH*	fumarate hydratase	Papillary type 2	—	Cutaneous leiomyomas Uterine leiomyomas
Hereditary Papillary Renal Cancer	*MET*	c-MET	Papillary type 1	—	—
Hereditary Pheochromocytoma and Paraganglioma	*SDHB* *SDHC* *SDHD*	succinate dehydrogenase subunits B, C, D	Clear cell (distinct phenotype)	Paraganglioma Pheochromocytoma Gastrointestinal Stromal Tumor	—
Lynch Syndrome	*MLH1* *MSH2* *MSH6* *PMS2*	Mismatch repair proteins	Urothelial cancer (upper tract)	Colorectal cancer Endometrial (uterine) cancer Ovarian cancer	
PTEN Hamartoma Syndrome (Cowden syndrome)	*PTEN*	PTEN	Clear cell	Breast cancer Thyroid cancer	Mucocutaneous papules, hamartomas, lipomas, macrocephaly
Tuberous Sclerosis Complex	*TSC1* *TSC2*	hamartin Tuberin	Angiomyolipoma Epitheliod angiomyolipoma	Angiomyolipomas Subependymal giant cell astrocytomas	Facial angiofibroma Hypomelanotic macule Connective tissue nevus Forehead plaque Ungal and peri-ungal fibromas
Von Hippel Lindau disease	*VHL*	pVHL	Clear cell Clear cell papillary	CNS - hemangioblastoma (brain, spine, retina) Adrenal - pheochromocytoma Inner ear - endolymphatic sac tumors Pancreas - neuroendocrine tumors	Pancreatic, renal cysts

(MR) imaging, ophthalmologic evaluation, plasma metanephrines, and consultation with vHL expert. The implementation of screening guidelines has led to vast improvements in survival (10).

Classically, vHL disease and mutations in *VHL* have been associated with clear cell renal cancers. However, clear cell papillary renal cell carcinoma (CCPRCC), a relatively recently described entity with prominent papillary architecture, exclusive clear cell morphology, and a partially cystic appearance, has been reported in patients with vHL disease (11). The exact characteristics of CCPRCC in this context, and relationship to sporadic disease are somewhat controversial, due to loss of chromosome 3p in these tumors and differing findings in regards to cytokeratin 7 staining (12). Based on multiple natural history studies done at the National Cancer Institute, the standard of care for timing of resection of renal cancer in patients with vHL disease is when there is a solid component of 3 cm. In the initial series, with a follow-up of >5 years, Walther *et al.* reported no evidence of metastatic disease progression and no need for renal transplantation or dialysis among 52 patients with tumors <3 cm at diagnosis. In contrast, distant metastases developed in 11 of 44 patients (25%) with lesions >3 cm in size, including 3 of 27 patients (11%) with lesions between 3 and 6 cm (13). Similar results were obtained in a follow-up study 5 years later (14).

HEREDITARY PAPILLARY RENAL CELL CARCINOMA (TYPE 1 PAPILLARY)

Hereditary papillary renal cell carcinoma (HPRCC) is an autosomal dominant syndrome characterized by multifocal, bilateral type 1 papillary renal cell carcinomas, with hundreds of tumors observed due to mutations in *MET* (15). The tumors are indistinguishable pathologically from sporadic type 1 papillary renal cancer. Mutations of the *MET* gene on 7q31 have been causally associated with HPRCC. Families with inherited mutations in *MET* leading to multifocal papillary renal cancer (type 1) are quite rare, more so than other described inherited renal cancer syndromes.

HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER (TYPE 2 PAPILLARY)

Hereditary leiomyomatosis and renal cell cancer (HLRCC), otherwise known as Reed's syndrome, is an autosomal cancer susceptibility syndrome characterized by the development of cutaneous and uterine leiomyomas and renal cancer, due to mutations in fumarate hydratase (*FH*) (16). The lifetime risk of renal cancer is currently estimated to be 15% (17). The pattern of renal cancer in HLRCC differs from other inherited renal cancer susceptibility syndromes in that the tumors tend to be solitary and unilateral and have a more aggressive course of disease. Independent of underlying architecture, which is most commonly described as a subtype of type 2 papillary renal cancer, cells in the renal cancers associated with HLRCC have a characteristic pathologic appearance with large nuclei, with inclusion-like orangiophilic or eosinophilic nucleoi surrounded by a clear halo, which can be recognized by knowledgeable pathologists (18).

Recently, several studies have focused on using immunohistochemistry with S-(2-succinyl) cysteine (2SC) as a surrogate for FH deficiency, as an adjunct to pathologic features to accurately diagnose HLRCC associated renal cancer. An initial study from Bardella *et al.* suggested that positive staining with 2SC was sensitive and specific to detect renal cancers associated with *FH* mutations (19). An independent follow-up study confirmed that 2SC demonstrated diffuse and strong cytoplasmic staining in the confirmed HLRCC tumors compared with other tumor types (20). Thus, in addition to family and personal history, histology and immunohistochemistry can be used to assist in the diagnosis of HLRCC when the initial presenting manifestation is renal cancer. The mean age of renal cancer diagnosis is 40 years, but metastatic renal cancer can present in the teens. Given the potential early age of renal cancer diagnosis, genetic testing is recommended at age 8–10 for familial *FH* mutations with annual MRI; however, the risk of renal cancers is relatively low before age 20, so the drawbacks of screening should be considered (17).

BIRT-HOGG-DUBÉ DISEASE

BHD disease is an autosomal dominant cancer susceptibility syndrome characterized by the development of fibrofolliculomas (dysplastic hair follicles), lung cysts and spontaneous pneumothorax, and renal cancer, and is due to mutations in folliculin (*FLCN*) (21). The dermatologic features and lung disease are the most common presenting features; BHD is underdiagnosed due to its variable, often mild, presentation. A wide spectrum of renal cancers (papillary RCC, ccRCC, mixed, and oncocytomas) has been observed in patients with BHD, even within the same kidney (22). The renal parenchyma surrounding the renal tumor can often contain multifocal oncocytosis. The most common type of tumor is an unusual hybrid oncocytic tumor (mixed oncocytoma and chromophobe). As a hybrid oncocytic tumor is characteristic of BHD, any patient presenting with one should be evaluated for BHD. Renal cancer is observed in approximately 30% of patients with a highly variable age of diagnosis ranging from 20 to 83 years, with an average age of 46 years (23). Given the low malignant potential of these tumors, it is generally recommended that screening with abdominal MRI take place every 2 years and that the tumors can be observed until they are 3 cm in diameter prior to resection (24).

OTHER INHERITED SYNDROMES WITH AN INCREASED RISK OF RENAL CANCER

BAP1 mutations and familial renal cancer

Mutations in *BAP1* (BRCA-associated protein 1) were initially identified through somatic sequencing of renal tumors. One of the tumors in the initial study was found to carry a germ-line BAP1 mutation, and subsequent studies suggested that *BAP1* mutations predispose to familial clear cell renal cancer, along with uveal and cutaneous melanoma and mesothelioma (25,26).

Chromosome 3 translocations associated with clear cell renal cancer

The first genetic changes identified as associated with inherited risk of clear cell renal cancer were balanced translocations involving chromosome 3; since then, multiple families have been reported with multifocal bilateral disease (27). The mechanism behind the increased risk of multifocal clear cell renal cancer is thought to be loss of the rearranged chromosome during mitosis, which requires a quadrivalent (four chromosomes coming together), leading to greater errors during chromosomal segregation. As multiple genes involved in the pathogenesis of clear cell renal cancer are located on chromosome 3p, including *VHL*, *PBRM1*, *BAP1*, and *SETD2* (28), it is not surprising that a mechanism of increased loss of one allele leads to an increased risk of clear cell renal cancer. Histologically, the clear cell renal cancers are indistinguishable from those associated with *VHL* mutations, although the age of onset tends to be later than in vHL disease.

Lynch syndrome

Although Lynch syndrome (also known hereditary nonpolyposis colorectal cancer), due to mutations in the mismatch repair genes (MMR) *MLH1*, *MSH2*, *MSH6*, and *PMS2*, is most commonly associated with an increased risk of colorectal, endometrial, and ovarian cancers, upper tract urothelial cancers are a well-recognized feature (29). The estimated risk ranges from 2.6% to 11% (30,31). The risk appears to be highest in patients with *MSH2* and *MLH1* mutations and presents at earlier ages than sporadic disease (32). A recent review for urologists suggests that evaluation for Lynch syndrome should be done when a patient with upper tract urothelial cancer presents before age 60 or the family meets Amsterdam I or II criteria, which includes colorectal, small bowel, ureter, endometrial, and ovarian cancers (29). Screening for Lynch syndrome can be done using immunohistochemistry for the MMR proteins, in which loss of staining suggests the diagnosis.

PTEN hamartoma tumor syndrome

Mutations in *PTEN* are associated with a pleomorphic syndrome (PHTS, also known as Cowden disease and Bannayan-Riley-Ruvalcaba), which has a variety of disease manifestations ranging from cancer susceptibility to intellectual disability. Patients are at increased risk of benign and malignant tumors of the thyroid, breast, and endometrium; it has been suggested that renal cancer is an underappreciated component of the cancer spectrum (33). Recent estimates suggesting that 3%–5% of of patients with PHTS have renal cancer, with a standardized incidence ratio of 31.7 (95% CI, 15.4–58.4); however, these estimates are based on small numbers and may be due to ascertainment basis (34). When centrally reviewed, the pathology of the renal cancers was either papillary or chromophobe (34). Screening for renal cancers is part of the standard surveillance recommendations for patients with PHTS and is recommended biennially starting at age 40.

SDHx-associated paraganglioma/pheochromocytoma

Mutations in the five proteins (*SDHA*, *SDHB*, *SDHC*, *SDHD,* and associated cofactor *SDHAF2*) that comprise the succinate dehydrogenase complex, which participates in both the Krebs cycle, converting fumarate to succinate, and as mitochondrial respiratory chain complex II, have been associated with an increased risk of pheochromocytomas, paragangliomas, gastrointestinal stromal tumors, and renal cancer (35). Renal cancer has been most commonly observed in association with patients carrying *SDHB* mutations, which has the highest risk of malignant disease, and these renal tumors have been reported to be particularly aggressive (36). SDHB-associated renal cancer displays a characteristic histopathology with solid or focally cystic growth, uniform cytology with eosinophilic flocculent cytoplasm, intracytoplasmic vacuolations and inclusions, and round to oval low-grade nuclei (37). Renal cancer can be the sentinel diagnosis in the family, so pathologists should be aware of and alert to this potential diagnosis. SDHB immunohistochemistry (absence of staining) also can be used to assist in making the diagnosis.

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder characterized by the formation of hamartomas in multiple organs, including brain, kidney, skin, and lung. The formation of hamartomas leads to neurologic disorders, including epilepsy, mental retardation, and autism, as well as dermatologic manifestations such as facial angiofibromas, renal angiomyolipomas, and pulmonary lymphangiomyomatosis (38). Inactivating mutations in *TSC1* encoding hamartin, or *TSC2* encoding tuberin are responsible for the phenotype. Patients with *TSC2* mutations are more severely affected with greater renal involvement among other features. Fifty percent to 80% of patients with TSC develop renal lesions including angiomyolipomas (AMLs), cysts, and oncocytomas; renal cell cancer is estimated to occur in $<$5% (with precise estimates varying across studies) (39). A recent review of TSC-associated renal cancer demonstrated young age at diagnosis, multifocal disease, an indolent clinical course, and three morphologies: renal angiomyoadenomatous tumor, chromophobe renal cancer, and a granular eosinophilic-macrocystic morphology (40). In patients with *TSC2* mutations and multiple renal tumors, it has been shown that they are due to a "shower" of second hits with different secondary *TSC2* mutations in each tumor (41). Everolimus is US Food and Drug Administration (FDA) approved for treating AMLs in the setting of TSC and also should be considered for TSC-associated renal cancer.

CONTROVERSIES IN GENETIC TESTING FOR INHERITED SUSCEPTIBILITY TO RENAL CANCER

Two questions recently have arisen in relationship to genetic testing for inherited susceptibility to renal cancer. Marston Linehan and colleagues from the National Cancer Institute have suggested that all patients with renal cancer diagnosed under the age of 45 should have consideration of genetic counseling/germline mutation testing, even in the absence of a personal or family medical history suggestive of an inherited syndrome (4). The rates of renal cancer in patients under age 50 is steadily increasing and has doubled since 1995, going from 3 per 100,000 to 6 per 100,000 (5), presumably due to the increasing number of incidental renal cancers detected on imaging studies. Although a cutoff age of 45 for detecting cases of inherited renal cancer may be quite sensitive, with the background rate increasing so dramatically, it would require testing of many individuals to identify only a few with inherited disease. Population-based studies of mutation testing in early-onset renal cancer are required to answer the question of utility of general genetic counseling and testing in this setting. An earlier age cutoff, such as at 30, may emerge as a more feasible alternative. As with many other genetic diseases, multiplex gene panels using massively parallel

sequencing have emerged as an alternative for genetic testing for renal cancer susceptibility syndromes (*e.g.*, RenalNext from Ambry Genetics). Given the usefulness of renal pathology and extra-kidney manifestations to guide genetic testing, which is relatively unusual for other cancer types, the usefulness of panels that include genes in which mutations predispose to vastly different diseases (*e.g.*, vHL and HLRCC) is not immediately apparent. However, many institutions do not always differentiate renal cancer pathologies to the degree needed for prioritization of genetic testing studies, and even at experienced centers, discrimination of renal cancer pathologies can be complex on occasion. Thus, there has been uptake of massively parallel sequencing panels for renal cancer–associated syndromes, but not to the same extent as for other cancer types (*e.g.*, breast and ovarian cancers, pheochromocytoma).

TAKE HOME POINTS

- Many different types of hereditary renal cancer exist, and in general, each is associated with a histologic subtype.
- Renal cancer can either be a major or a minor feature of a cancer susceptibility syndrome, but early age of onset, unusual or pathognomic pathology, and multiplicity of tumors all should be red flags, which prompt questions about family history and consideration of inherited disease.
- Standard of care surveillance recommendations are available for essentially all renal cancer susceptibility syndromes and should be followed.

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REVIEW QUESTIONS

1. What is the exception to the "3-cm rule" of tumor removal in hereditary renal cancer syndromes?

   a. von Hippel Lindau disease
   b. Birt-Hogg-Dubé syndrome
   c. Hereditary leiomyomatosis and renal cell cancer

Answer: c is correct. Hereditary leiomyomatosis and renal cell cancer (HLRCC or Reed's syndrome) is associated with a very aggressive form of renal cancer, and tumors should be removed as soon as they are detected.

2. A patient with renal cancer tells you that a sister had a pheochromocytoma. What further evaluation might that prompt?

   a. Review of pathology of the renal cancer and potentially additional immunohistochemistry
   b. Further family history collection and potentially genetics evaluation
   c. Nothing, probably unrelated
   d. a and b

Answer: d is correct. Renal cancer is associated with hereditary pheochromocytoma and paraganglioma syndromes caused by SDHx mutations. These renal cancers have a characteristic pathology, which is well described. The renal cancers associated with *SDHB* mutations also have loss of staining on SDHB immunohistochemistry. Collection of additional history also could be useful, in that further history of pheochromocytomas and paragangliomas in the family supports the diagnosis of an SDHx-related tumor. However, it is important to note that genetic testing is recommended for all patients with pheochromocytoma, so the family should be referred to a cancer geneticist independent of family history.

3. One of your patients has a hybrid chromophobe/oncocytic renal tumor, but is aged 65 and has no family history of renal cancer or other cancers. You vaguely remember reading this chapter, and remember that tumor type is a red flag,and deserves further evaluation, but can't remember for what?

   a. BAP-1–associated renal cancer
   b. Birt-Hogg-Dubé syndrome
   c. Lynch syndrome

Answer: b is correct. The three major manifestations of Birt-Hogg-Dubé (BHD) are fibrofolliculomas (facial), lung cysts and pneumothorax, and renal cancer. A hybrid chromophobe/oncocytic renal tumor is considered characteristic of BHD, and the finding on pathology should prompt further evaluation. All three manifestations of BHD are incompletely penetrant, particularly renal cancer. Thus, the lack of family history of renal cancer and older age of diagnosis should not preclude evaluation for BHD.