Chapter 14
Hereditary Cancer and Genetics in Renal Cell Carcinoma

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Introduction

Renal cell carcinoma (RCC) represents a spectrum of kidney cancer classified by distinct histologic subtypes, clinical course, and molecular drivers. Most cases of RCCs are sporadic with risk factors that include smoking, obesity, hypertension, chronic renal insufficiency on dialysis, and environmental exposure. About 5%–8% of RCC cases are associated with hereditary RCC syndromes. To date, nine hereditary RCC syndromes have been characterized that are related to inheritance of monogenic germline alteration (Table 14.1). The histologic subtypes and relative risks of RCC vary in these syndromes. Compared to sporadic RCC, hereditary RCC is more likely to occur at an earlier age [1] and is more likely to be multifocal or bilateral [2, 3]. Studies of patients with hereditary RCC syndromes have yielded clues regarding the natural history and molecular pathogenesis of sporadic RCC. Diagnosis of hereditary RCC syndromes allows for screening, early detection, and timely intervention for patients and cascade testing for at-risk family members. Therefore, it is critical for physicians to recognize clinical phenotypes of patients with hereditary RCC syndromes and refer appropriate patients for genetic counseling and germline testing. In this chapter, we review the genetic and clinical features of well-characterized hereditary RCC syndromes and provide a framework on screening and appropriate workup for patients at risk of hereditary RCC syndromes.

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Table 14.1 Hereditary renal cell carcinoma syndromes

Syndrome	Chromosome location	Gene(s)	RCC histology	Common extra-renal clinical manifestations
von Hippel-Lindau	3p25.3	*VHL*	Clear cell	Retinal and CNS hemangioblastomas Retinal angiomas Adrenal or paraganglioma Endolymphatic sac tumors Broad ligament and epididymal cystadenomas Pancreatic cysts and neuroendocrine tumors
Hereditary leiomyomatosis and RCC	1q43	*FH*	FH deficient Papillary type 2 HLRCC-associated RCC	Cutaneous and uterine leiomyomas Leiomyosarcomas Adrenal adenoma
Birt-Hogg-Dubé	17p11.2	*FLCN*	Chromophobe Oncocytoma Clear cell Oncocytic hybrid Mixed histology	Cutaneous fibrofolliculoma Pulmonary cysts Spontaneous pneumothorax
Hereditary papillary RCC	7q31.2	*MET*	Papillary type 1	None
Tuberous sclerosis	9q34.13 16p13.3	*TSC1* *TSC2*	Angiomyolipoma Clear cell Oncocytoma Chromophobe	Cardiac rhabdomyoma Angiofibromas, hypomelanotic macules, and other dermatological lesions Cortical dysplasia Subependymal giant cell astrocytoma Retinal nodular and other nonrenal hamartomas Ungual fibromas Oral mucosal lesions
BAP1 tumor predisposition syndrome	3p21.1	*BAP1*	Clear cell Chromophobe	Uveal and cutaneous melanoma Malignant pleural mesothelioma
Hereditary paraganglioma-pheochromocytoma	5p15.33 1p36.13 1q23.3 11q23.1	*SDHA* *SDHB* *SDHC* *SDHD*	SDH deficient Unclassified/ eosinophilic variant	Pheochromocytoma Paraganglioma Gastrointestinal stromal tumor
MITF cancer syndrome	3p13	*MITF*	Undefined	Cutaneous melanoma
Cowden syndrome	10q23.31	*PTEN*	Clear cell Papillary Chromophobe	Macrocephaly Breast cancer Thyroid cancer Endometrial cancer

Germline Genetic Testing in Kidney Cancer Patients

Knowledge of clinical features of patients with hereditary RCC syndromes is critical for determining which patients with kidney cancer should be referred for genetic counseling and germline testing. Assessment of genetic risk factors in patients with kidney cancer includes age of diagnosis of kidney cancer, tumor histology, multifocality, stage at presentation, personal history of extra-renal malignancies, and family history. While the median age of onset of patients with sporadic RCC in SEER-17 was 64 years, the median age at presentation of patients with known hereditary RCC syndromes was 37 years [1]. About 70% of hereditary RCC cases were diagnosed at 46 years or younger. Therefore, early age of presentation of kidney cancer may be a sign of an underlying genetic predisposition and has been adopted as a referral criterion for genetic counseling by both the National Comprehensive Cancer Network (NCCN) and the American Urological Association (AUA) kidney cancer guideline panels [4, 5]. Other indications for genetic counseling for RCC include synchronous or metachronous tumor multifocality, bilaterality, and those with histologic characteristics suggestive of a hereditary RCC syndrome such as FH-/SDH-deficient RCC and angiomyolipomas (AMLs) in patient with additional features of tuberous sclerosis complex (TSC). Traditionally, clinically directed single-gene testing has been done for patients with personal or family history suggestive of an underlying hereditary RCC syndrome or in those with first- or second-degree relatives with a known mutation in a cancer susceptibility gene. More recently, kidney cancer multigene panels, assessing 10–20 genes relevant to kidney cancer development, have been more commonly used to streamline testing for patients who meet referral criteria, such as those with early-onset RCC or multifocal/bilateral renal tumors, who lack distinguish clinical features of a classic hereditary cancer syndrome [6].

Surgical Management of Patients with Localized Hereditary Renal Tumors

The goals of surgical management of patients with bilateral, multifocal, or hereditary renal tumors are to prevent development of metastasis, preserve renal function, and minimize treatment-related morbidities. Longitudinal follow-up of patients with hereditary RCC syndromes has made it possible to tailor surgical management based on the underlying genetic alterations, which impact the natural history and clinical outcomes of renal tumors. Tumor growth rates varied significantly between different genetic subtypes. The growth rates of VHL-deficient (0.37 cm/year, interquartile range [IQR] 0.25–0.57 cm/year), FLCN-deficient (0.10 cm/year, IQR 0.04–0.24 cm/year), and MET-activation (0.15 cm/year, IQR 0.05–0.32 cm/year) tumors tend to be slower than BAP1-deficient tumors (0.6 cm/year, IQR 0.57–0.68 cm/year) [7]. For patients with less biologically aggressive tumors, namely, those associated with von Hippel-Lindau (VHL), Birt-Hogg-Dubé (BHD),

and hereditary papillary RCC (HPRC) syndromes, an initial period of active surveillance until the largest tumor reaches 3 cm has been adopted to reduce the numbers of renal surgeries and their associated morbidities [8, 9]. The treatment strategy of choice for these patients is tumor enucleation to balance oncologic control and maximal preservation of normal renal parenchyma. On the opposite end of the genetically driven spectrum, hereditary leiomyomatosis and RCC (HLRCC), hereditary paraganglioma-pheochromocytoma, and BAP1 tumor predisposition syndromes are associated with more aggressive tumors. In particular, FH-deficient RCC associated with HLRCC is highly aggressive, and small tumors have the potential to metastasize [10, 11]. The majority of FH-deficient renal tumors have infiltrative margins and invaded renal sinus fat [11]. Therefore, prompt upfront surgical intervention is recommended. A radical nephrectomy or partial nephrectomy with wide margin, when feasible, should be utilized [12].

Implications of Germline Genetics in Management of Metastatic RCC

There is no standard treatment for metastatic RCC in the context of a hereditary syndrome, and treatment is often based on the histology of the original tumor. That being said, several clinical trials have examined regimens in patients with certain genetic syndromes. For VHL, agents that have been used in the treatment of metastatic clear cell RCC seem to have similar efficacy in tumor response, which is expected given that sporadic clear cell RCC is also mostly driven by *VHL* biallelic loss of function. A phase 2 study of pazopanib for patients with VHL reported objective responses in 13 (42%) of 31 patients and 31 (52%) of 59 VHL-associated RCC tumors [13]. In August 2021, the US Food and Drug Administration (FDA) approved the first-in-class, HIF-2 alpha inhibitor belzutifan for patients with VHL-associated RCC, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumors [14]. In a phase 2 trial, HIF-2 alpha inhibitors achieve an overall response rate (ORR) of 49% of patients with VHL-associated RCC. The median duration of response was not reached with 56% of responders having duration of response over 12 months [15]. Belzutifan is currently being studied in sporadic clear cell RCC, with promising results seen in a phase 1 trial [16].

Other therapeutic studies have prospectively included patients with hereditary RCC. A phase 2 trial conducted by the National Cancer Institute (NCI) investigated the efficacy of erlotinib and bevacizumab in patients with advanced papillary RCC. The ORR was 31 (72%) of 43 patients with HLRCC and 14 (35%) of 40 patients with sporadic papillary RCC [17]. The treatment was well tolerated, with 41 (49%) of 83 patients experiencing grade 3 or higher adverse events. Currently, this regimen is included in the NCCN guidelines with special consideration for patients with HLRCC [4]. Additionally, recent retrospective analyses of other phase 2 trials have shown that other regimens also appear active in patients with FH-deficient RCC. In a report of patients with non-clear cell RCC treated with everolimus and bevacizumab, there were seven patients identified with germline *FH*

mutations, of whom 4 (57%) had a response [18]. In a phase 2 study of the combination of cabozantinib and nivolumab in patients with non-clear cell RCC, there were five patients identified with germline *FH* mutations, of whom four had a response [19].

MET is known to be a driver in papillary hereditary RCC (where patients mainly present with type 1 papillary RCC) and in sporadic papillary tumors. A study of the *MET* inhibitor foretinib included 10 patients with germline *MET* mutations; of these, 5 patients had an objective response, compared to 5 of 57 patients without germline *MET* mutations [20]. Finally, although metastatic RCC in TSC is rare, everolimus has been shown to have significant activity in the treatment of localized AMLs associated with germline *TSC1* and *TSC2* mutations. 118 patients with AMLs were treated with everolimus. An ORR of 42% was seen, although once agent was discontinued, the AMLs appeared to grow back [21]. Based on this study, everolimus is approved by the FDA for patients with TSC-associated renal AMLs.

Hereditary Renal Cell Carcinoma Syndromes

Von Hippel-Lindau Syndrome (OMIM 193300)

VHL syndrome, the most well-characterized hereditary RCC syndrome, is a highly penetrant autosomal dominant syndrome that predisposes to malignant and benign tumors in multiple organs. VHL is caused by mutations in the *VHL* tumor suppressor gene located on chromosome 3p25.3 that encodes for the VHL protein, an essential part of a multi-protein complex that includes elongin B/C, cullin-2, and Rbx1 [22–24]. VHL protein functions as the recognition site for hypoxia-inducible factor alpha (HIF-alpha) to target proteins for ubiquitin-mediated degradation. Mutations in *VHL* lead to accumulation of HIF-1 and HIF-2 and upregulation of downstream pathways including vascular endothelial growth factor (VEGF), platelet-derived growth factor, and glucose transporters, leading to angiogenesis and cell proliferation [25]. Over 200 distinct mutations have been identified in the *VHL* gene including missense (52%), frameshift (13%), nonsense (11%), deletions (11%), splice site (7%), and inframe deletion/insertion (6%) mutations [26].

The cardinal features of VHL syndrome include clear cell RCC, cerebellar and spinal hemangioblastomas, pheochromocytomas, and endolymphatic sac tumors [27]. Patients with VHL may also have pancreatic cysts and solid tumors. Specific genotypes are associated with certain syndromic manifestations and can guide surveillance and management of patients with VHL. While nonsense and frameshift mutations are associated with higher susceptibility to clear cell RCC, missense mutations are associated with high risk of pheochromocytomas [26]. The lifetime risk of RCC in patients with VHL syndrome approached 75% with median age of onset of 39 years (range 13–70) [26]. VHL-associated RCC tend to be bilateral, multifocal, and recurrent. Clear cell RCC associated with VHL tends to be less biologically aggressive with a robust pseudocapsule. Patients with VHL-associated kidney tumors are recommended to undergo active surveillance until the largest

tumors reach 3 cm in diameter. Tumor enucleation is the preferred surgical approach to preserve renal function without compromising oncologic control.

Hereditary Leiomyomatosis and RCC Syndrome (OMIM 150800)

HLRCC syndrome is an autosomal dominant cancer susceptibility syndrome caused by mutations in the *FH* gene, a tumor suppressor, located on chromosome 1q43, which encodes for the enzyme fumarate hydratase, a critical component of the Krebs cycle [28]. *FH* mutations impair oxidative phosphorylation and lead to the accumulation of oncometabolites. HLRCC is characterized by variable development of three tumors: cutaneous leiomyoma, uterine leiomyomata (fibroids), and rarely leiomyosarcomas, and HLRCC (or FH-deficient)-associated RCC. Cutaneous leiomyomas appear firm, flesh-colored to light red/brown papules and develop in nearly all patients by the age of 40 years, but can be subtle to detect. Cutaneous leiomyomas can cause symptoms of variable severity including pain and pruritus in response to touch or temperature changes [29]. Uterine fibroids occur in most women with HLRCC, often causing pelvic symptoms including menorrhagia and pain necessitating hysterectomy at an early age, in many cases before the age of 30 [29, 30]. In rare instances, cutaneous and uterine leiomyosarcomas have been reported in patients with *FH* germline mutations [31, 32]. The lifetime risk of RCC is estimated to be 10–20% with an early age of onset (median age of onset of 37 years, range 10–77 years) [1]. Although rare, RCCs have been reported in children [33]. Unlike other hereditary RCC syndromes, patients with HLRCC tend to have solitary and unilateral tumors with a more aggressive clinical course.

Since 2016, HLRCC-associated RCC has been added as a new RCC entity in the WHO classification of tumors. HLRCC-associated RCC has mixed architectural features including predominantly papillary pattern with tubular, tubulopapillary, tubulocystic, solid, cystic, and collecting duct carcinoma-like elements. Characteristic histologic findings of HLRCC-associated RCC are large nuclei with very prominent eosinophilic nucleolus surrounded by a clear perinucleolar halo. Immunohistochemical analysis of HLRCC-associated RCC reveals loss of FH expression (hence *FH*-deficient RCC is often used to refer to HLRCC-associated renal tumors) and 2-succino-cysteine (2SC) positive immunoreactivity. On CT and MR imaging, FH-deficient RCC tumors appear infiltrative, without circumscribed margins, and have heterogeneous MRI signal and enhancement. Most FH-deficient RCCs are locally advanced with radiographic evidence of invasion into the renal sinus fat or metastatic, particularly through lymph node chains, at the time of diagnosis [11]. However, there are no specific or unique features that would potentially distinguish FH-deficient RCC from other RCC subtypes [11]. Given the potential early age of renal cancer development, annual abdominal screening beginning at the age of 11 years has been recommended.

Of note, the *FH* c.1431_1433dupAAA (p.Lys477dup) germline variant, which is relatively common in certain populations, has conflicting reports on pathogenicity in the heterozygous state. Although in the homozygous state, it is associated with FH deficiency, in the heterozygous state, it does not appear to be associated with increased risk of RCC. In a study of 7571 patients with cancer who underwent germline genetic testing with a multigene panel, 24 patients had the variant, and none had RCC [34]. In another case report, in two patients with the variant and RCC, further pathologic and immunohistochemical studies showed that the RCCs did not have the morphologic features of FH-deficient RCC and had retained FH and no increase in 2SC [35].

Birt-Hogg-Dube Syndrome (OMIM 135150)

BHD is an autosomal dominant cancer predisposition syndrome caused by germline mutations in the *FLCN* gene, which encodes for folliculin. Folliculin is a GTPase-activating protein for RAGC and is involved in the regulation of mTORC1 and TFEB [36, 37]. Although the mechanism by which loss of function of *FLCN* leads to renal tumors is not completely understood, recent work shows the transcription factor TFEB may be a main driver of kidney abnormalities in BHD and that depletion of TFEB in a BHD mouse model leads to rescue of the disease phenotype [38]. BHD is likely underdiagnosed due to the variability in clinical expression, with some mutation carriers having subtle clinical features [39].

Patients with BHD are predisposed to renal tumors, which can vary in spectrum from oncocytomas, chromophobe tumors, or chromophobe oncocytic hybrid, with eosinophilic cytoplasm [40, 41]. As opposed to frequently seen somatic *VHL* mutations in sporadic clear cell RCC, *FLCN* as a somatic driver of sporadic RCC is rarely seen. Fibrofolliculomas are the hallmark cutaneous feature of BHD. These flesh-colored papules are most common in the face, and their incidence increases with age, but in some cases their appearance can be subtle [42]. Additionally, patients with BHD have a high prevalence of pulmonary cysts, and an estimated third of patients develop spontaneous pneumothorax [41]. There is controversy on whether patients with BHD are at increased risk of colon polyps or colorectal cancer. One recent study found an elevated risk of colorectal cancer in BHD patients vs controls (5.1 vs 1.5%, p-value .0068) [43]. However, another report from a Dutch registry with 399 patients with BHD and 382 relatives without BHD noted no increased prevalence of colorectal cancer [44]. In that study the rate of colorectal cancer was 3.6% in BHD patients vs 2.6% in relatives ($p = 0.54$). The rate of polyp removal was higher in BHD (12.2 vs 6.3%, $p = 0.005$), but there was no significant difference between the number of polyps and histology in the two groups.

Although there is no prospective data studying the benefits of screening in BHD, consensus guidelines recommend renal imaging, ideally with MRI, every 3 years [4, 45]. There may be limitations with ultrasound in the identification of tumors. In one retrospective study of BHD patients undergoing renal imaging, of 18 who had renal

ultrasounds at time of diagnosis of renal mass, half had the tumors identified by CT or MRI and not seen in ultrasound [46]. In terms of management, BHD-associated renal tumors are thought to be relatively slow growing with a lower malignant potential; in a study by Ball et al., the growth rate of these tumors was 0.10 cm/year (IQR 0.04–0.24 cm/yr) [7].

Hereditary Papillary RCC (OMIM 164860)

Hereditary papillary RCC (HPRC) is an extremely rare autosomal dominant condition caused by heterozygous germline mutation in *MET* protooncogene on chromosome 7q31, which encodes for a receptor tyrosine kinase. *MET* mutations lead to constitutive activation of the MET protein and result in uncontrolled cell growth [47, 48]. Patients with HPRC are predisposed to multifocal and bilateral papillary type 1 RCC. Unlike other hereditary RCC syndromes, patients with HPRC do not harbor extra-renal manifestation, making its diagnosis difficult unless the physicians have a high index of suspicion based on tumor multifocality, histology, and family history of papillary type 1 RCC. Due to its indolent nature, MET-activated renal tumors associated with HPRC syndrome are best observed until the tumors reach 3-cm diameter and are amenable to enucleation to preserve renal function without compromising oncologic control [12].

BAP1 Tumor Predisposition Syndrome (OMIM 614327)

BAP1 tumor predisposition syndrome is an autosomal dominant cancer predisposition syndrome caused by germline loss-of-function mutations in the *BAP1* gene. *BAP1* encodes for a deubiquitinating enzyme and is involved in chromatin regulation among other cellular processes [49, 50]. *BAP1* somatic mutations are common in clear cell RCC and associated with worse prognosis [51, 52]. Individuals with *BAP1* germline mutations are at increased risk of cutaneous and uveal melanoma, mesothelioma (both peritoneal and pleural), RCC, and likely other tumors. Compared to other RCC hereditary conditions, BAP1 tumor predisposition syndrome is relatively recently described, and the full phenotypic syndrome, including its penetrance, is not fully understood [53, 54].

In the largest reported series of *BAP1* carriers to date, the incidence of RCC was between 5% and 10% when including probands and relatives [55]. Although it appears that clear cell RCC is the predominant histology, there are also reports of patients with chromophobe tumors with loss of BAP1 on IHC [56]. As opposed to RCCs in patients with VHL and BHD, RCCs in patients with *BAP1* somatic or germline mutations are thought to be aggressive, and consensus recommendations are to perform renal imaging every 2 years [4].

Hereditary Paraganglioma-Pheochromocytoma Syndromes (OMIM 185470)

Hereditary paraganglioma-pheochromocytoma syndrome is an autosomal dominant cancer predisposition syndrome caused by mutations in genes within the SDH complex (*SDHA, SDHB, SDHC, SDHD, SDHAF2,* collectively SDHx), *MAX*, and *TMEM127*. Germline mutations in these genes have been associated with an increased risk of mainly pheochromocytoma and paraganglioma, but gastrointestinal stromal tumors and RCC have also been reported. The majority of cases of RCC within the context of this syndrome are due to germline *SDHB* mutations, and the presenting RCC subtype has typical characteristic histologic features, with the prominent being the presence of cytoplasmic vacuoles and SDHB deficiency on IHC [57, 58]. In 2016, SDHB-deficient RCC was added as a new histologic subtype to the World Health Organization classification of tumors [59]. If SDH deficiency is identified in a renal tumor, there is a high likelihood that it is due to a germline mutation. SDH-deficient RCCs range from slow growing to aggressive. Although there are reports of patients with RCC and germline mutations in *TMEM127* and *MAX*, the association of these genes and the pathogenesis of the RCC have not yet been well established [60, 61].

The incidence of RCC in patients with SDHx mutations is not well established. In a large retrospective study of individuals referred for genetic testing due to a personal or family history of pheochromocytoma or paraganglioma, 876 individuals with *SDHB/C/D* mutations were identified, of which 16 had RCC, all but one in individuals with *SDHB* mutations [62]. The risk of RCC by age 60 in *SDHB* carriers was estimated at 4–5%. Although there are reports of patients with RCC and *SDHA* mutations, the role of the mutation in the pathogenicity of the tumor has not yet been established [63, 64].

Screening for RCC in SDHx carriers is usually obtained within the context of screening for pheochromocytomas and paragangliomas, for which head and neck, thoracic, abdominal, and pelvic MRIs are recommended every 2–3 years[65, 66]. FDG PET may be very sensitive to detect SDH-related tumors, and patients with advanced SDH-deficient RCC can have very high FDG uptake. To date, there is no particular systemic regimen that has been studied in SDH-deficient metastatic RCC.

Other Hereditary Syndromes with Increased Risk of Renal Cancer

There are several other genetic conditions that can predispose to renal tumors. Patients with tuberous sclerosis complex (TSC, OMIM 191100) are at high risk of AML, a renal lesion composed of smooth-muscle-like cells, adipocyte-like cells, and epithelioid cells [67]. Although rare, RCC can also occur with TSC, and several

reports have shown a wide spectrum of morphologies and a propensity for bilateral or multifocal lesions [68, 69]. International consensus guidelines recommend imaging, preferably with MRI, every few years and more often if lesions are identified [4].

Patients with Cowden syndrome (OMIM 158350) caused by germline mutations in *PTEN* are also at risk for several malignancies, including breast, endometrial, and thyroid cancer. They are also at increased risk of RCC, although to a lesser extent. RCCs within the context of Cowden typically have non-clear cell histology, with chromophobe and papillary subtypes predominating, although clear cell RCC is also seen [70, 71]. Current NCCN guideline recommends consideration of renal ultrasound every 1–2 years for patients with Cowden syndrome [72].

A germline missense variant in *MITF* p.E318K has been identified to confer a genetic predisposition to melanoma and RCC. Patients with the *MITF* p.E318K variant had a higher than fivefold increased risk of developing melanoma, RCC, or both cancers compared to controls with *MITF* wild type [73]. Therefore, presence of personal or familial melanoma and RCC should prompt referral for genetic counseling.

Conclusions

Knowledge of inherited genetics of patients with RCC continues to evolve. Twelve RCC predisposition genes, *VHL, MET, FH, TSC1/2, FLCN, SDHA/B/C/D, BAP1*, and *MITF*, leading to nine hereditary RCC syndromes have been identified. Studies of hereditary RCC have led to breakthrough discoveries into the genetic basis of kidney cancer and revolutionized the surgical management and more effective targeted therapies for patients with both hereditary and sporadic forms of RCC. It is critical that physicians managing patients with RCC recognize and refer patients at risk of hereditary RCC syndromes for genetic counseling and germline testing because well-defined RCC management strategies exist for these patients, and early screening, detection, and intervention of at-risk organs minimize cancer-specific morbidity and mortality.

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