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Genetic predisposition to kidney cancer

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Abstract

Kidney cancer is not a single disease but is made up of a number of different types of cancer classified by histology that are disparate in presentation, clinical course, and genetic basis. Studies of families with inherited renal cell carcinoma (RCC) have provided the basis for our understanding of the causative genes and altered metabolic pathways in renal cancer with different histologies. Von Hippel-Lindau disease was the first renal cancer disorder with a defined genetic basis. Over the next two decades, the genes responsible for a number of other inherited renal cancer syndromes including hereditary papillary renal carcinoma, Birt-Hogg-Dubé syndrome, hereditary leiomyomatosis and renal cell carcinoma, and succinate dehydrogenase–associated renal cancer were identified. Recently, renal cell carcinoma has been confirmed as part of the clinical phenotype in individuals from families with BAP1-associated tumor predisposition syndrome and MiTF-associated cancer syndrome. Here we summarize the clinical characteristics of and causative genes for these and other inherited RCC syndromes, the pathways that are dysregulated when the inherited genes are mutated, and recommended clinical management of patients with these inherited renal cancer syndromes.

Keywords

Von Hippel-Lindau; Hereditary papillary renal carcinoma; Birt-Hogg-Dubé syndrome; Hereditary leiomyomatosis and renal cell carcinoma; Kidney neoplasms; Inherited renal cancer syndromes

1. Overview: Hereditary forms of kidney cancer

An estimated 62,700 new cases of kidney cancer will be diagnosed in the United States in 2016, resulting in 14,200 deaths and a steadily increasing incidence over the last decade [1]. It is important for the clinician to recognize whether a patient has an inherited form of kidney cancer or sporadic renal tumors because this will impact patient management. Early onset (<40 years of age), family history of renal cancer, and bilateral or multifocal renal tumor presentation are suggestive of an inherited predisposition. Presence of a particular

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Conflicts of interest

None.

group of manifestations in a patient or family may suggest a specific inherited renal cancer syndrome, and it is helpful for the clinician to be aware of the major inherited renal cancer syndromes, their manifestations, the causative genes and implicated pathways, patient management practices and available therapeutic options (Table 1, Fig. 1).

2. Von Hippel-Lindau: Clear cell renal carcinoma

2.1. Clinical manifestations

Von Hippel-Lindau (VHL) is an autosomal dominant inherited multisystem disorder in which affected individuals are at risk for the development of clear cell kidney tumors and cysts, adrenal gland tumors (pheochromocytomas), pancreatic cysts and islet cell tumors, hemangioblastomas of the central nervous system (CNS) and retina, endolymphatic sac tumors of the inner ear, and epididymal cystadenomas (Fig. 2). Kidney cancer develops in 25%–45% of VHL patients and is uniformly clear cell, bilateral, and multifocal. VHL-related kidney cancer tends to occur in the 2nd to 4th decades of life with a penetrance of 70% by the age of 60 [2]. It has been estimated that up to 600 tumors and as many as 1100 cysts may develop in a single kidney of a VHL patient [3].

2.2. Patient management

A multidisciplinary approach is recommended to manage VHL patients to monitor the development of the benign and malignant lesions associated with this disorder. At-risk individuals undergo lifelong surveillance for kidney tumors, most often with either computed tomography (CT) or magnetic resonance imaging (MRI). Since these individuals are at risk to develop multiple tumors that may require repeat surgeries during their lifetime, nephron-sparing surgery is recommended when possible to preserve kidney function. It is recommended that VHL patients be managed by active surveillance and undergo surgical intervention when the largest tumor reaches 3 cm in diameter to potentially reduce risk for metastatic disease while minimizing the number of repeat surgeries and preserving renal function [4].

2.3. Genetics of VHL disease: VHL gene

Genetic linkage analysis was performed in families with VHL in order to identify the *VHL* locus at chromosome 3p25 [5]. Germline *VHL* mutations are detected in nearly 100% of families with more than 420 unique mutations of all types reported worldwide [6] and genotype–phenotype correlations have emerged. The majority of families that develop RCC and CNS hemangioblastomas without pheochromocytomas, classified as type 1, have truncating mutations or intragenic deletions. Type 2 VHL families have predominantly missense mutations and present with pheochromocytomas either without (type 2A) or with (type 2B) RCC and hemangio-blastomas (types 2A and 2B) [2]. *VHL* is a classic tumor-suppressor gene in which both copies of the gene must be inactivated for tumor development.

2.4. VHL gene mutations in sporadic clear cell renal carcinoma

VHL mutations with subsequent inactivation of the wild-type *VHL* allele are also found in a high percentage of tumors from patients with sporadic clear cell RCC [7]. Nickerson and

colleagues detected *VHL* mutation or hypermethylation in 92% of sporadic clear cell RCCs [8].

2.5. Consequence of VHL gene mutation: upregulation of hypoxia-inducible factor and its target genes

The VHL protein (pVHL) is part of an E3 ubiquitin ligase multi-protein complex, including elongins B and C [9,10], cullin-2 [11], and Rbx1 [12] that targets proteins for ubiquitin-mediated degradation by the proteasome. pVHL functions as the substrate recognition site for the hypoxia-inducible factor alpha (HIFα) family of transcription factors [13]. During normoxia, HIFα becomes hydroxylated on critical prolines by HIF prolyl hydroxylase (PHD), enabling HIFα binding to pVHL and degradation by the E3 ligase complex [14,15]. PHD requires cofactors α-ketoglutarate, ascorbate, iron and molecular oxygen to function. Under hypoxia, HIFα is not hydroxylated by PHD and, therefore, not targeted by pVHL. Either reduced cellular oxygen levels or *VHL* mutations that abrogate elongin C or HIFα binding lead to HIFα accumulation, driving expression of HIFα transcriptional targets that support neo-angiogenesis [erythropoietin (EPO), vascular endothelial growth factor (VEGF)], cell proliferation [platelet-derived growth factor (PDGFβ), transforming growth factor (TGF-α)], and glucose metabolism [glucose transporter 1 (GLUT 1)] [16].

2.6. Targeted therapy for VHL disease and clear cell RCC

Targeting the HIF pathway has been an approach to treating advanced VHL-associated and sporadic clear cell RCC. There are a number of drugs approved by the US Food and Drug Administration (FDA) for metastatic renal carcinoma: five drugs that target the HIF-VEGF pathway, including sunitinib and sorafenib (VEGFR2/3, PDGFRβ), bevacizumab (VEGF), pazopanib (VEGFR1/2/3, PDGFRβ, c-kit), and axitinib (VEGFR 1/2/3); and two drugs that target the mechanistic target of rapamycin (mTOR) pathway, everolimus and temsirolimus. Most patients, however, do not achieve complete response and will eventually progress on treatment [17].

3. Hereditary papillary renal carcinoma: Type 1 papillary renal carcinoma

3.1. Clinical manifestations

Hereditary papillary renal carcinoma (HPRC), another autosomal dominant inherited renal cancer syndrome, is characterized by the development of bilateral, multifocal papillary type 1 renal tumors [18]. It was estimated that more than 3,000 microscopic papillary tumors (“incipient” lesions) [19] may develop in apparently normal renal parenchyma within a single HPRC kidney representing multiple independent early events [20]. HPRC is rare, with fewer than 35 families reported worldwide [21]. Renal tumors develop most often in the 6th and 7th decades of life [18,22], although early-onset families have been reported [21]. HPRC displays nearly complete penetrance by age 80 [22].

3.2. Patient management

Hereditary papillary renal tumors may be difficult to image due to their hypovascularity [23] and can often be confused with cysts necessitating taking tumor measurements with and without contrast enhancement. Active surveillance with MRI or CT rather than ultrasound is

recommended for at-risk HPRC family members [24]. Tumors tend to be slow-growing and patients are often managed by surgical intervention when the largest tumor dimension reaches 3 cm, using nephron-sparing surgery where possible to maintain maximum renal function [4].

3.3. Genetics of HPRC: MET gene

Linkage analysis in HPRC families localized the disease locus to chromosome 7q31, and mutations in the *MET* proto-oncogene were identified in the germline of affected family members [25]. HPRC-associated *MET* mutations are missense (amino acid substitution), located in the intracellular tyrosine kinase domain, and predicted to constitutively activate the Met kinase [22,25,26].

3.4. Consequence of MET gene mutation: constitutive activation of Met

The *MET* proto-oncogene encodes the receptor for hepatocyte growth factor/scatter factor (HGF/SF). HGF binding to Met causes autophosphorylation of critical tyrosines in the Met kinase domain resulting in recruitment of intracellular effectors triggering a signal cascade that drives programs supporting cell growth, motility, migration, differentiation, and branching morphogenesis [27]. The germline *MET* mutations in HPRC are predicted to destabilize the inactive (or stabilize the active) Met kinase conformation supporting ligand-independent constitutive kinase activation [28], and have shown oncogenic potential in both in vitro and in vivo models [29]. Papillary type 1 renal tumors are characterized by trisomy of chromosome 7 [30], and nonrandom duplication of the chromosome 7 bearing the mutant *MET* allele has been demonstrated in HPRC tumors [31], which may give kidney tumor cells a growth advantage.

Although *MET* mutations have been identified in fewer than 15% of sporadic papillary renal carcinoma [26,32], Met amplification may provide one mechanism by which sporadic papillary RCC develops [32].

3.5. Met-targeted therapy for HPRC

The discovery that activating *MET* mutations are responsible for HPRC led to assessment of therapeutic agents that target the Met kinase. A multicenter phase 2 study of foretinib, an oral agent that targets Met, VEGFR2, RON and AXL, in patients with HPRC and sporadic papillary RCC was recently completed. The overall response rate was 13.5% with median progression-free survival of 9.3 months. The presence of a germline *MET* mutation was found to be highly predictive of response. Among patients with *MET* germline mutations, 5 of 10 (50%) responded with a reduction in largest tumor dimension ranging from 30%–60% compared to a 9% response rate (5 of 57) among patients with wild-type *MET* [33]. A phase 2 study to evaluate the efficacy of INC280, a selective Met kinase inhibitor, in hereditary and sporadic papillary RCC patients, is currently in the recruitment phase (clinicaltrials.gov; NCT02019693).

4. Birt-Hogg-Dubé syndrome: Hybrid oncocytic and chromophobe renal carcinoma

4.1. Clinical manifestations

Individuals with the autosomal dominant inherited disorder Birt-Hogg-Dubé (BHD) syndrome are at risk for developing benign cutaneous hair follicle tumors (fibrofolliculomas), multiple lung cysts, and spontaneous pneumothorax (Fig. 3) [34,35]. More than 80% of BHD-affected individuals develop fibrofolliculomas or lung cysts, and 27%–30% will experience at least one pneumothorax episode [35,36]. Approximately one third of BHD-affected individuals develop renal tumors that are usually bilateral and multifocal [35–38] with variable histologies including hybrid oncocytic tumors containing features of both chromophobe RCC and oncocytoma (50%), chromophobe RCC (34%), clear cell RCC (9%), and benign oncocytomas (5%) [39]. Renal “oncocytosis”, defined as microscopic oncocytic tumors scattered in the grossly normal renal parenchyma, are characteristic of BHD-associated tumors [39].

4.2. Patient management

BHD is phenotypically variable within families and among different families with the same germline genetic alteration. Patients at risk for BHD are evaluated by a dermatologist for fibrofolliculomas and may undergo both thoracic and abdominal imaging to screen for lung cysts, evidence of pneumothorax, and for presence of renal tumors. Surveillance by annual or biannual CT or MRI is recommended starting at the age of 20 [40,41]. As with VHL and HPRC, current recommendations for managing BHD renal tumors include active surveillance until the largest diameter reaches 3 cm, at which time surgical intervention is recommended. Nephron-sparing surgery to preserve normal renal function is recommended, since BHD patients are at risk to develop multiple tumors and may undergo repeated surgeries during their lifetime [40].

4.3. Genetics of BHD syndrome: FLCN gene

The disease locus for BHD was mapped to chromosome 17p by genetic linkage analysis in BHD families, and germline mutations in a novel gene *folliculin (FLCN*) were identified in BHD-affected individuals [42]. The majority of the 149 unique *FLCN* mutations reported in BHD families are protein truncating and predicted to be inactivating, although *FLCN* missense mutations have been reported [43]. The overall mutation detection rate approaches 85% [36,38]. Loss or mutation of the wild-type *FLCN* allele in 70% of BHD-associated renal tumors [44] and tumor development in mice injected with *FLCN*-deficient human kidney cells [45] support a role for FLCN as a tumor-suppressor.

4.4. Consequence of FLCN gene mutation: modulation of mTOR activity

In experiments to elucidate FLCN function, a novel interacting protein, folliculin interacting protein 1 (FNIP1), was identified [46] and, subsequently, a second folliculin interacting partner, FNIP2, was discovered by bioinformatics searches, which had 49% identity to FNIP1 [47]. Both FNIP1 and FNIP2 interact with the carboxy-terminus of FLCN, and also with 5′-AMP–activated protein kinase (AMPK) [46,47], an important cellular energy-sensor

and negative regulator of mTOR, which controls protein synthesis and cell growth [48]. In some *Flcn*-deficient mouse kidneys and human *FLCN*-null renal tumors, mTORC1 [49,50] and mTORC2 [51] were activated, suggesting a possible target for therapeutic intervention. Other in vivo data suggest that *FLCN* deficiency results in mTOR inactivation [52,53]. Multiple lines of evidence support potential roles for FLCN in a number of cellular processes and metabolic pathways including TFE3 transcriptional activation, regulation of PGC-1α expression and mitochondrial biogenesis, membrane trafficking, TGF-β signaling, autophagy, cell–cell adhesion and cell polarity [54]. Research efforts in multiple laboratories are focused on determining which of these critical pathways/processes, when dysregulated by loss of FLCN, results in BHD-associated kidney cancer.

4.5. Targeting the FLCN pathway

Currently there are no therapeutic agents with proven efficacy for treating BHD-associated renal tumors. In a single report, the mTOR inhibitor everolimus provided a longer time to progression when used as a second-line treatment against metastatic papillary RCC in a BHD-affected patient who failed to respond to other anti-VEGF systemic therapies [55]. The finding that mTOR was activated in some *FLCN*-deficient in vivo and in vitro models provided the basis for a phase 2 study to evaluate the efficacy of everolimus in BHD patients and patients with advanced sporadic chromophobe RCC (clinicaltrials.gov; NCT02504892).

5. Hereditary leiomyomatosis and renal cell carcinoma: Type 2 papillary renal carcinoma

5.1. Clinical manifestations

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is an autosomal dominant inherited cancer disorder that predisposes to cutaneous leiomyomas, multiple uterine leiomyomas (fibroids), and an increased risk for type 2 papillary renal tumors (Fig. 4). Cutaneous leiomyomas, small flesh-colored nodules usually on the trunk or extremities that often exhibit pain and paresthesias, are the most common manifestations occurring in 76%–100% of HLRCC patients [56,57]. Uterine leiomyomas develop at an early age in most female HLRCC patients, cause pain and menorrhagia, and often necessitate hysterectomy before the age of 40 [58]. Renal tumors, which can be early onset, may develop in up to 18% of HLRCC patients [56,57,59]. Tumors are often unilateral and solitary but can be bilateral and multifocal, are highly aggressive, and can metastasize even when small [60]. Histologically, HLRCC tumors are characterized by large nuclei with prominent orangiophilic nucleoli and perinucleolar clearing, and a unique type 2 papillary architecture, but can also be tubular, solid, or mixed [61].

5.2. Patient management

HLRCC patients are managed with a multidiscipline approach for early detection of cutaneous and uterine leiomyomas and kidney tumors. In contrast to recommended management of patients with VHL, HPRC, and BHD, renal masses in HLRCC patients are not managed by active surveillance. HLRCC-associated renal tumors may be aggressive with rapid growth rates; advanced disease at presentation with nodal involvement or distant

metastases can occur even when tumors are small [60]. Consequently, at-risk individuals are screened by annual abdominal MRI. Screening begins early in at-risk children, since tumors have been detected as early as 11 years of age [62]. Nephron-sparing surgical excision is often recommended with open procedures and wide surgical margins. Enucleative resection and ablative procedures are not recommended for patients with HLRCC, and avoidance of intraoperative tumor spillage is a high priority.

5.3. Genetics of HLRCC: FH gene

Launonen et al [63] described the association of cutaneous and uterine leiomyomas with renal tumors in two kindreds, and mapped the HLRCC locus to chromosome 1q42-44. Subsequently, germline mutations in the *fumarate hydratase* (*FH*) gene were identified in HLRCC kindreds [64]. More than 130 unique *FH* mutations of all types have been reported [65] with a mutation detection rate approaching 90% [56,58]. *FH* encodes the Krebs cycle enzyme fumarate hydratase that converts fumarate to malate and is located in the mitochondrial matrix. Fumarate hydratase enzyme activity is reduced in lymphoblastoid and fibroblast cell lines established from HLRCC patients [66,67], and was lower in cell lines with *FH* missense mutations than in cells carrying *FH* protein truncating mutations [58,64,66]. Since FH is a homotetrameric protein, it has been proposed that the FH missense mutant proteins would abrogate formation of almost all homotetramers, thereby having a more severe effect on fumarate hydratase activity than protein truncating mutations [59]. The *FH* gene acts as a tumor suppressor based on the identification of LOH or “second hit” somatic mutations in the wild-type *FH* allele in syndromic uterine and cutaneous leiomyomas [63,64,66] and HLRCC-associated renal tumors [66,68].

5.4. Consequence of FH gene mutation: activation of HIF and antioxidant response pathways

Loss of fumarate hydratase activity as a result of germline *FH* mutation and LOH at chromosome 1q42 leads to accumulation of fumarate in the cytoplasm of renal cells and tissues of HLRCC patients resulting in aberrant activation of two pathways: (a) HIFα pathway and (b) Nrf2 antioxidant response pathway. Excess fumarate competitively inhibits prolyl hydroxylase (PDH), resulting in HIFα stabilization as seen during hypoxia or when *VHL* is mutated. The subsequent upregulation of HIFα transcriptional targets supports neo-vascularization and elevated glucose uptake resulting in a metabolic switch to aerobic glycolysis (“Warburg effect”) for energy production, which contributes to the aggressive phenotype of HLRCC-associated renal tumors [68–70]. In addition, since *FH*-deficient tumors have an altered Krebs cycle that does not generate acetyl CoA for lipogenesis, cells have adapted to utilizing glutamine as a carbon source for fatty acid production by isocitrate dehydrogenase (IDH)-dependent reductive carboxylation of α–ketoglutarate, and generation of acetyl-CoA by ATP-citrate lyase cleavage of citrate [71].

Fumarate is an electrophile and can spontaneously react with sulfhydryl groups in cysteines in a number of proteins, a process known as succination [72]. One of the proteins succinated by fumarate is Kelch-like ECH-associated protein 1 (KEAP1), the substrate recognition component of a cullin 3 (CUL3)-based E3 ubiquitin ligase complex that targets nuclear factor erythroid 2-related factor 2 (Nrf2) for proteasomal degradation [73,74]. Nrf2

facilitates a cellular adaptive response to electrophilic and oxidative stress by transcriptionally upregulating its target genes through anti-oxidant response elements located in their promoters. KEAP1, in complex with CUL3, binds to Nrf2, targeting it for ubiquitin-mediated degradation [75]. Fumarate can act as an oncometabolite using its electrophilic properties to succinate specific cysteines in KEAP1, which results in a conformational change that inhibits KEAP1 binding to Nrf2, thereby permitting Nrf2 accumulation and activation of the antioxidant response pathway [73,74]. Targeting HIF and its targets, components of the glutamine reductive carboxylation pathway, or the components of the antioxidant response pathway may be potential therapeutic options for HLRCC.

5.5. Targeted therapy for HLRCC involving HIF and antioxidant response pathways

Therapeutic targeting of *FH*-deficient renal tumors in HLRCC patients may be approached in several ways. First, elevated fumarate inhibits PHD, thereby stabilizing HIFα and driving expression of target genes *VEGF* and *GLUT1* that can be targeted by anti-angiogenic therapies. A phase 2 study of bevacizumab and erlotinib in patients with advanced HLRCC-associated type 2 papillary RCC and sporadic papillary RCC is currently in progress (clinicaltrials.gov; NCT01130519).

Second, drug screening identified the tyrosine kinase inhibitor vandetanib as a potent inhibitor of cell growth in an HLRCC-derived kidney cancer cell line, and stable reintroduction of wild-type *FH* abrogated its cytotoxicity [76]. Evaluation of FH-deficient in vitro and in vivo models revealed that the nonreceptor tyrosine kinase ABL1 was activated in *FH*-deficient kidney tumors. ABL1 upregulated aerobic glycolysis through the mTOR/HIFα pathway and promoted nuclear localization and activation of Nrf2, the master regulator of the antioxidant response pathway that allows tumor cells to tolerate the oxidative stress caused by fumarate accumulation [76]. Vandetanib was shown to be an effective inhibitor of ABL1 phosphorylation, glucose transporter GLUT1 upregulation, and lactate secretion (measure of aerobic glycolysis) in *FH*-deficient kidney cancer cells. Treatment with vandetanib resulted in regression of a murine xenograft derived from an *FH*-deficient kidney tumor cell line [76]. On the basis of these findings, a phase 1/2 study of the effect of vandetanib in combination with metformin is currently in progress in patients with HLRCC or advanced sporadic papillary RCC (clinicaltrials.gov, NCT02495103).

6. Succinate dehydrogenase-deficient kidney cancer

6.1. Mutations in another Krebs cycle enzyme predispose to RCC

Succinate dehydrogenase–deficient kidney cancer (SDH-RCC) is characterized by bilateral, multifocal early onset (<40 years of age) renal tumors that are inherited in an autosomal dominant manner and can be found in the setting of inherited head and neck paragangliomas (PGLs) and adrenal or extra-adrenal pheochromocytomas (PCCs). Vanharanta et al reported PGL/PCC and RCC in two families with early age of renal tumor onset (<30 years) and variable histologies who harbored germline mutations in the *SDHB* gene encoding subunit B of the Krebs cycle enzyme succinate dehydrogenase [77]. Three families with germline *SDHB* mutations and RCC as the only manifestation were subsequently reported [78]. Ricketts et al have described 11 families with germline *SDHB* mutations of various types

and clinical manifestations that included only renal tumors (45.5%), or renal tumors and PGL/PCC (54.5%) [79]. The renal tumors were solid or mixed solid/cystic lesions, but most shared common “oncocytic neoplastic” features and were characterized by early age of onset (average 33 years) and the presence of metastases in 1/3 of cases. Two families with RCC and germline *SDH subunit C* (*SDHC*) mutations have been reported [79,80], as well as one family with RCC and a germline *SDH subunit D (SDHD)* mutation [79].

6.2. Patient management

Annual abdominal imaging of at-risk *SDHB/C/D* mutation carriers by MRI or CT is recommended for early detection of renal tumors. Given the paucity of SDH-RCC, the clinical experience managing these patients is limited. However, considering the early age of onset and tendency of these tumors to potentially metastasize even when small, it is recommended that surgical excision of tumors be performed with nephron-sparing procedures promptly when tumors are detected following the management approach for HLRCC [79].

6.3. Consequence of SDHB/C/D gene mutation: activation of the HIF pathway

SDH is a multi-subunit enzyme that functions as Complex II in the inner mitochondrial membrane and converts succinate to fumarate generating reducing equivalents to drive the electron transport chain for energy production. Mutations in any of the subunits will interfere with proper complex assembly and result in succinate accumulation that will in turn block PHD by product inhibition, thereby stabilizing HIFα and its transcriptional targets [81]. Studies with an *SDH*-deficient renal tumor cell line derived from a patient with a germline *SDHB* mutation have shown that, as in HLRCC, oxidative phosphorylation was severely compromised, and SDH activity was abrogated, causing increased levels of intra-cellular succinate that resulted in elevated HIF1α protein levels presumably through succinate-mediated competitive inhibition of PHD [82]. Metabolic profiling demonstrated that, in the absence of mitochondrial respiration, these tumor cells underwent a metabolic shift to aerobic glycolysis to generate ATP, and displayed a dependence on reductive carboxylation of α–ketoglutarate derived from glutamine [82].

7. Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder that presents with a variety of manifestations in multiple tissues including severe neurologic disorders due to the presence of cerebral cortical tubers, facial angiofibromas, lymphangioleio-myomatosis (LAM) of the lung, and renal angiomyolipomas (AML). TSC patients develop renal carcinoma at a frequency similar to that of the general population (2%–3%) but with an earlier age of onset [83]. Germline mutations in the *TSC1* gene on chromosome 9q34 that encodes hamartin or the *TSC2* gene on chromosome 16p13 encoding tuberin are responsible for this multisystem disorder [84,85]. TSC1/TSC2 form a protein complex that negatively regulates the mTOR axis and mutations in either gene can abrogate the function of the complex leading to mTOR activation [83]. mTOR inhibitors including rapamycin analogs have been used to treat angiomyolipomas and lymphangioleiomyomatosis in TSC patients. In a phase 3 clinical trial of TSC patients with AMLs treated with everolimus, the response

rate (50% reduction in AML volume from base line and no progression) was 42% compared to placebo (0%) with 80% of patients demonstrating at least 30% reduction in AML volume relative to the placebo group [86]. Inhibition of mTOR with everolimus may provide an alternative treatment for TSC patients for whom surgical intervention may otherwise not be an option.

8. BAP1-associated tumor predisposition syndrome

BRCA1-associated protein-1 (*BAP1*), a tumor-suppressor gene that encodes a nuclear deubiquitinase, part of the polycomb group repressive deubiquitinase complex that is involved in cell cycle progression and chromatin modification, has been found to be both somatically and germline inactivated in uveal melanoma and malignant mesothelioma [87]. Recently, *BAP1* was reported to be mutated in up to 14% of sporadic clear cell RCCs and is associated with more aggressive tumors and poor patient prognosis [88,89]. Two reports have described *BAP1* mutations in the germline of individuals with early-onset, bilateral and multifocal clear cell RCCs that cosegregate with RCC in those families. *BAP1*-associated tumors displayed LOH at chromosome 3p where *BAP1* is located and loss of BAP1 protein staining by immunohistochemistry [90,91]. Additional reports of uveal melanoma, cutaneous melanoma, and malignant mesothelioma families with germline *BAP1* mutations and a family history of RCC have been summarized by Rai et al [92]. Testing for *BAP1* mutations should be considered in patients with early-onset, clear cell RCC, family history of RCC, and/or one of the BAP1-associated malignancies who test negative for mutations in genes known to be associated with inherited RCC syndromes. Annual or biannual abdominal screening of at-risk individuals will enable early detection and monitoring of these potentially aggressive kidney tumors.

9. MiTF-associated cancer syndrome

Microphthalmia-associated transcription factor (MiTF), one member of the MiTF family of transcription factors, plays a critical role in melanocyte homeostasis, and deregulation of MiTF is associated with melanoma disease characterizing it as a melanoma oncogene [93]. A germline missense variant of *MITF* (c.952G→A; p.E318K) has been identified at higher frequency in patients with family history of cutaneous malignant melanoma or primary multiple melanomas relative to healthy controls [94,95]. Interestingly, epidemiological studies have noted a phenotypic association of melanoma with renal cancer, and sequencing of *MITF* revealed a higher frequency of the germline *MITF* p.E318K variant in patients with either RCC or RCC and melanoma [94–96]. Individuals that inherited the missense variant had a greater than fivefold increased risk of developing melanoma, RCC, or both compared to non-carriers [94]. MiTF transcriptionally upregulates HIF-1α, which is known to drive renal tumorigenesis, and MiTF transcriptional activity is suppressed by SUMOylation, a post-translational modification, at a SUMO consensus site involving the E318 codon. However, negative regulation of MiTF by SUMOylation was severely impaired in the MiTF p.E318K variant, thereby deregulating MiTF and promoting transcriptional activation of HIF-1α [94]. Although further research is necessary, the evidence strongly supports a role for the MiTF p.E318K variant as a medium-penetrance, germline mutation that predisposes to melanoma and RCC and potentially other cancers as well.

10. Conclusion

Eleven renal cancer predisposing genes—*VHL, MET, FLCN, FH, SDHB/C/D, TSC1, TSC2, BAP1,* and *MiTF*—have now been identified through studies of families with the inherited renal cancer syndromes VHL disease, HPRC, BHD syndrome, HLRCC, SDH-RCC, TSC, BAP1 tumor predisposition syndrome, and MiTF-associated cancer syndrome. Valuable insight into the genetic basis of kidney cancer has been gained from familial kidney cancer studies. The identification of pathways dysregulated as a result of germline mutations in these genes has laid the foundation for developing more effective targeted therapies for patients with inherited renal cancer syndromes that may also be promising for treatment of sporadic forms of kidney cancer.

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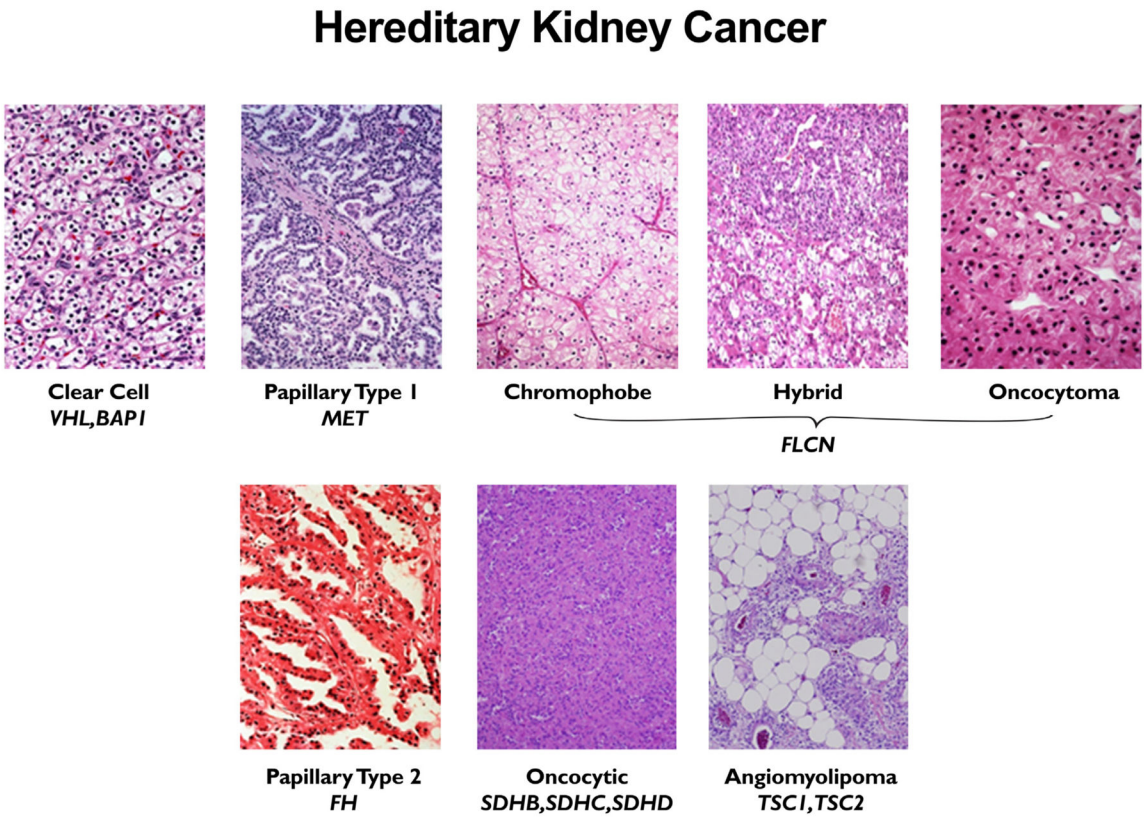

Fig. 1.

Hereditary kidney cancer. Kidney cancer is not a single entity but made up of a number of different types of cancer, each with a distinct histology, caused by a different gene, with a different clinical course, and responding differently to therapy. Germline *von Hippel-Lindau* (*VHL)* gene mutations cause von Hippel-Lindau disease and clear cell kidney tumors. Germline *MET* oncogene mutations predispose to hereditary papillary renal carcinoma with type 1 papillary tumors. Germline mutations in the *folliculin* (*FLCN)* gene are inherited in patients with Birt-Hogg-Dubé syndrome who present with hybrid oncocytic tumors, chromophobe renal tumors and benign oncocytomas. Germline *fumarate hydratase* (*FH)* gene mutations in patients with hereditary leiomyomatosis and renal cell carcinoma predispose affected individuals to develop renal tumors with papillary type 2 histology. Germline mutations in the genes encoding subunits of succinate dehydrogenase, *SDHB/SDHC/SDHD*, predispose to renal tumors with an oncocytic phenotype in SDH-deficient RCC patients. Patients with tuberous sclerosis complex inherit germline mutations in *tuberous sclerosis complex 1* or *2* (*TSC1, TSC2)* genes and are at risk to develop angiomyolipomas in the kidney and, occasionally, renal tumors. Adapted and reprinted with permission [97].

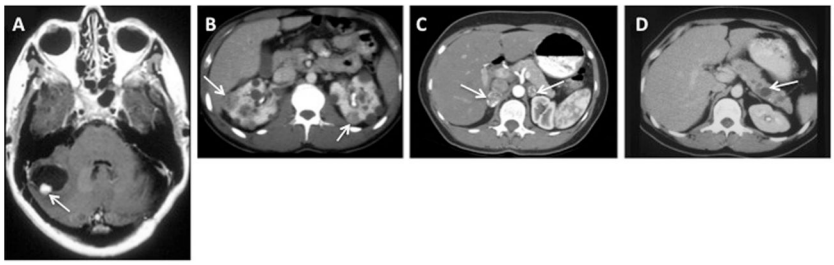

Fig. 2.

Clinical manifestations of von Hippel-Lindau disease. (A) Contrast-enhanced MRI of a cerebellar hemangioblastoma (arrow) with an associated cyst (adjacent dark area) in a 40-year-old VHL patient. (B) Bilateral multifocal renal tumors (arrows) and multiple cysts in a 22-year-old VHL patient. (C) Bilateral pheochromocytomas (arrows) in the adrenal glands of a 29-year-old VHL patient. (D) Pancreatic neuroendocrine tumor (arrow) in the pancreas of a VHL patient. Adapted and reprinted with permission [98].

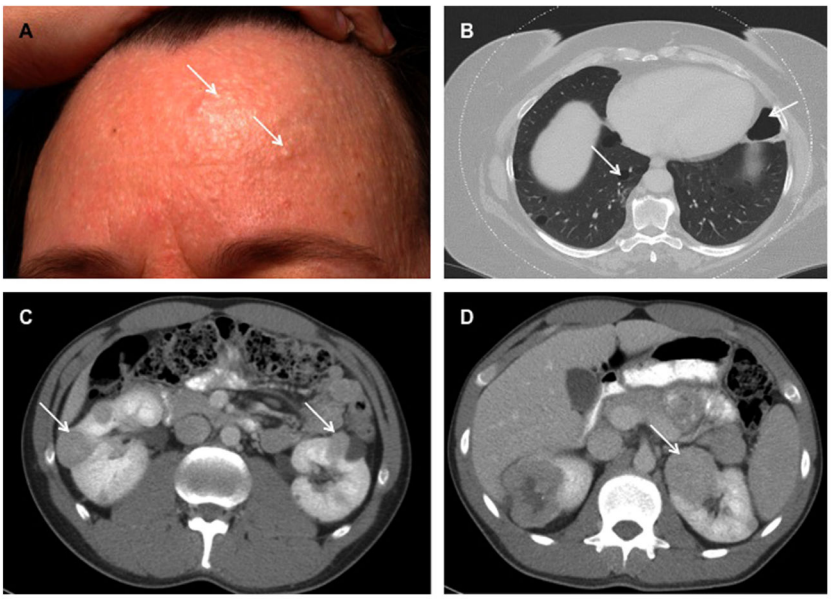

Fig. 3.

Clinical manifestations of Birt-Hogg-Dubé syndrome. (A) Multiple fibrofolliculomas on the forehead of a BHD patient (arrows). (B) Chest CT scan of a BHD patient showing bilateral multiple pulmonary cysts (arrows) that can lead to spontaneous pneumothorax. (C,D) Abdominal CT scans demonstrating bilateral multifocal renal tumors in BHD patients (arrows). Adapted and reprinted with permission [54].

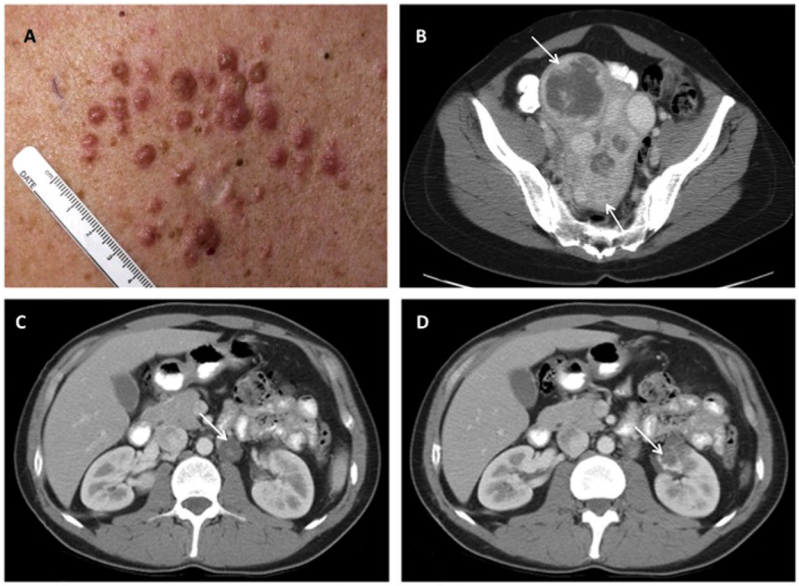

Fig. 4.

Clinical manifestations of hereditary leiomyomatosis and renal cell carcinoma. (A) Multiple cutaneous leiomyomas in an HLRCC patient. (B) CT image showing multiple large uterine leiomyomas (arrows) that occur in HLRCC. (C) Para-aortic nodal disease (arrow) and (D) renal tumor (arrow) in patients with HLRCC. Adapted and reprinted with permission [60].

Table 1

Inherited renal cancer syndromes.

Syndrome	Chromosome location	Predisposing gene	Renal tumor histology	Recommended surgical management	Potential therapeutic targets
Von Hippel-Lindau disease (VHL)	3p25	*VHL*	Clear cell	Active surveillance <3 cm; surgical excision ≥3 cm	HIF-VEGF pathway
Hereditary papillary renal carcinoma (HPRC)	7q31	*MET*	Type 1 papillary	Active surveillance <3 cm; surgical excision ≥3 cm	Met kinase
Birt-Hogg-Dubé syndrome (BHD)	17p11.2	*FLCN*	Chromophobe, hybrid oncocytic, clear cell, oncocytoma	Active surveillance <3 cm; surgical excision ≥3 cm	mTOR pathway
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)	1q42–43	*FH*	Type 2 papillary	Wide margin surgical excision	HIF-VEGF pathway; antioxidant response pathway; reductive carboxylation pathway
Succinate dehydrogenase-deficient renal cancer (SDH-RCC)	1p36.13 1q23.3 11q23.1	*SDHB* *SDHC* *SDHD*	Clear cell, chromophobe, oncocytic neoplasm	Surgical excision	HIF-VEGF pathway; reductive carboxylation pathway
Tuberous sclerosis complex (TSC)	9q34 16p13.3	*TSC1* *TSC2*	Angiomyolipoma, RCC, variable	AML, embolization; RCC, surgical excision	mTOR pathway
BAP1 tumor predisposition syndrome	3p21.2	*BAP1*	Clear cell, can be high grade	Surgical excision	TBD
MiTF-associated cancer syndrome	3p14.1-p12.3	*MiTF*	ND	TBD	TBD

ND, not determined; TBD, to be determined; RCC, renal cell carcinoma.