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Familial Kidney Cancer: Implications of New Syndromes and Molecular Insights

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Abstract

Context: Hereditary cases account for about 5% of all cases of renal cell carcinoma (RCC). With advances in next-generation sequencing, several new hereditary syndromes have been described in the last few years.

Objective: To review and summarise the recent preclinical and clinical literature in hereditary renal cancer.

Evidence acquisition: A systematic review of the literature was performed in November 2018 using PubMed and OMIM databases, with an emphasis on kidney cancer, genetics and genomics, clinical criteria, and management.

Evidence synthesis: Several autosomal dominant hereditary RCC syndromes have been described, including those related to germline pathogenic variants in *VHL, MET, FH, TSC1/TSC2, FLCN, SDHA/B/C/D, BAP1, CDC73*, and *MITF*. Clinical spectrum of *SDH, BAP1*, and *MITF* is still being defined, although these appear to be associated with a lower incidence of RCC than the former. *FH* and likely *BAP1* RCC are associated with more aggressive disease. Preclinical

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and clinical studies show that using systemic therapy that exploits specific genetic pathways is a promising strategy.

Conclusions: There are several well-described hereditary RCC syndromes, as well as recently identified ones, for which the full clinical spectrum is yet to be defined. In the new era of precision medicine, identification of these syndromes may play an important role in management and systemic treatment selection.

Patient summary: This review covers updates in the diagnosis and management of familial kidney cancer syndromes. We describe updates in testing and management of the most common syndromes such as von Hippel-Lindau, and hereditary leiomyomatosis and renal cell carcinoma. We also provide insights into recently described familial kidney cancer syndromes.

Keywords

Birt-Hogg-Dubé syndrome; Genetic counselling; Hereditary cancer; Hereditary leiomyomatosis renal; cell carcinoma; Hereditary papillary renal cell; carcinoma; Kidney cancer; Renal cell carcinoma; Tuberous sclerosis complex; von Hippel-Lindau disease

1. Introduction

Worldwide, there is an increasing incidence of renal cell carcinoma (RCC), with over 400 000 new cases estimated in 2018 [1]. RCC encompasses many histological subtypes with different molecular drivers [2]. Clear cell RCC (ccRCC) is the most prevalent subtype, accounting for about 75%. The remaining subtypes include papillary, chromophobe, MiT family translocation, and other rare types. Many of these histologies are associated with distinct RCC hereditary syndromes. In 2016, the World Health Organization (WHO) classification of tumours included subtypes specifically associated with genetic syndromes, including hereditary leiomyomatosis and RCC (HLRCC) syndrome, and succinate dehydrogenase (SDH)-deficient RCC [3]. With recent advances in pathological and molecular characterisation, hereditary aetiologies are becoming more evident. Urologists, medical oncologists, and other practitioners play a critical role in identifying familial RCC.

Since the last review in this journal in 2010, there have been advances in our understanding of the genetics of RCC, and several new hereditary syndromes have been described [4]. This review will update genetic and clinical features of the well-characterised and emerging hereditary RCC syndromes. We will discuss contemporary surgical and medical management of bilateral and metastatic familial RCC, and comment on screening and appropriate workup for suspicious cases seen in the clinic.

2. Evidence acquisition

Data for this review were acquired by searches of PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Online Mendelian Inheritance in Man (OMIM; http://www.ncbi.nlm.nih.gov/omim/) using combinations of these terms: hereditary, kidney cancer, clinical criteria, von Hippel-Lindau syndrome, Birt-Hogg-Dube syndrome, hereditary leiomyomatosis RCC, BAP1 RCC, PTEN RCC, hereditary papillary RCC, tuberous sclerosis complex, MITF predisposition to familial RCC, hereditary hyperparathyroidism jaw tumour syndrome,

hereditary paraganglioma-pheochromocytoma syndrome, chromosome 3 translocations, familial clear cell RCC, genetic counselling, genetic screening, treatment, and management. References from the identified articles were also investigated. Only papers published in English with no date restrictions were included. A flowchart of the selection process is shown in Fig. 1.

3. Evidence synthesis

3.1. Prevalence of hereditary RCC syndromes and recognition of patients with familial renal tumours

Until recently, there were no large-scale studies analysing the prevalence of germline, likely pathogenic or pathogenic, variants (henceforth, referred together as “pathogenic variants”) in RCC cases. With the Cancer Genome Atlas (TCGA) efforts, the germline was also analysed, which provides an estimate in such a population [5]. Of 387 cases of ccRCC, 6% had a germline pathogenic variant. In papillary and chromophobe cases, 9% and 6%, respectively, had a germline pathogenic variant. Although some of these cases are due to the well-known hereditary syndromes, the prevalence of emerging syndromes may be higher than previously thought. In the ccRCC TCGA cohort, *BAP1* germline mutations were the second most common, found in 0.8% of cases, and associated with an inherited tumour syndrome not described until 2011.

There are several well-described hereditary RCC syndromes, as well as recently identified syndromes, for which the full clinical spectrum is still being investigated (Table 1). Clinical features can vary widely from syndrome to syndrome. For some, such as hereditary papillary RCC (HPRC), the only manifestation is kidney tumours, whereas for von Hippel-Lindau (VHL), other tumours, such as retinal and cerebellar haemangioblastomas, are usually present. There can also be wide variability even within a family.

Although there are no standardised referral criteria for genetic testing of patients with RCC, the American College of Medical Genetics has outlined referral indications for genetic assessment [6]. Some studies also provide insight. One analysed the age distributions of kidney cancer in the SEER-17 program and the National Cancer Institute hereditary kidney cancer population [7]. Of hereditary cases, 70% have an age of onset at 46 yr or younger; this age cut-off maximises sensitivity and specificity for genetic testing. In two studies examining factors associated with positive genetic testing results, an early age of onset of RCC cancer seemed to be the only predictive factor [8,9]. Another study examined the prevalence of germline pathogenic variants in patients with advanced RCC unselected for a suspicion of hereditary syndromes [10]. Of patients with non-ccRCC, 12% had a germline pathogenic variant in an RCC-associated gene.

3.2. Importance of recognition of hereditary RCC syndromes for surgical management

Recognition of clinical syndromes is paramount for surgical management. Several others have provided guidelines for management and overviews of surgical considerations [11,12]. Briefly, for VHL, HPRC, and Birt-Hogg-Dubé (BHD), tumours are generally followed by active surveillance until they reach 3 cm, at which time surgery is recommended [13,14]. For

HLRCC, tumours can be aggressive and metastasise even when small, and the 3-cm rule does not apply. For other syndromes, such as SDH-associated RCC, BAP1-RCC, and MITF-related RCC, full phenotypic features are yet to be defined and no generalisable surgical recommendations are available. Further standard and clinical trial options for advanced RCC will be discussed in each section. Although historically, systemic treatment of metastatic RCC has not relied on specific genetics, recent developments make such a prospect promising.

3.3. VHL syndrome (OMIM 193300)

VHL is an autosomal dominant syndrome associated with multifocal ccRCC, renal cysts, central nervous system (CNS) haemangioblastomas, pheochromocytomas, and other tumours [15].

3.3.1. Genetics and gene function—*VHL* is located on 3p25.3 and encodes for the VHL protein, an essential component of the VHL complex. The VHL complex targets hypoxia-inducible factors (HIFs) for proteosomal degradation through ubiquitination. Virtually all tumours of VHL patients lose the remaining allele, most commonly through loss of heterozygosity (LOH). Inactivation of VHL leads to accumulation of HIF-1 and HIF-2 and their downstream targets, which include vascular endothelial growth factor (VEGF), glucose transporter-1, platelet-derived growth factor-b, and transforming growth factor-a, which likely leads to the development of RCC.

Genomic analyses of germline VHL-associated tumours have shed light on tumour evolution, and inter- and intrapatient heterogeneity [16,17]. Aside from the common loss of 3p, intrapatient tumours are clonally independent, showing different molecular trajectories following the VHL/3p founding event.

3.3.2. Clinical/radiographic features—VHL disease has traditionally been divided into types 1 and 2, based on the risk of pheochromocytoma, with type 1 families having a substantially lower risk [18]. Genotype-phenotype studies have shown that the risk of pheochromocytomas is associated with missense mutations, while there are earlier age of onset of RCC, and higher risks of RCC and retinal angiomas with nonsense or frameshift mutations rather than with deletions or missense mutations [19]. Additional manifestations of VHL syndrome are shown in Table 1 and reviewed elsewhere [15,20].

Among patients with VHL disease, the lifetime risk of RCC is about 70% with an average age of 40–45 yr, about 1 decades earlier than the average age presentation of RCC in the USA [15,19]. Kidneys typically have numerous cystic and solid lesions, ranging from simple to complex and the majority being of low grade. Cystic masses are measured by the solid component of individual cysts.

3.3.3. Morphological features—Renal manifestations in patients with VHL syndrome histologically range from simple cysts lined by bland, one to two layers of clear cells, atypical cysts with more complex epithelial proliferations, and scattered aggregates of clear cell proliferation in renal parenchyma to ccRCC arising either within cysts or de novo from noncystic renal parenchyma [21,22]. The ccRCCs in VHL patients typically exhibit low

nuclear grade and stage, as they are often closely monitored and removed early. Recent studies have described rare tumours either exhibiting clear cell papillary (ccPap) like features or consisting of ccPap based on morphological criteria and immunoprofile [23,24]. However, the presence of 3p loss in these tumours suggests that they are distinct from sporadic RCC and may reflect a wider spectrum of ccRCC disease seen in VHL patients.

3.3.4. Management—For localised renal tumours, surgical management remains the mainstay therapy. Regardless of the surgical approach, tumours are removed with enucleation to maximally debulk the kidney from any tumours that are visible or ultrasound detected in the OR and to maximally preserve renal parenchyma. The tumours are monitored until the largest solid tumour or solid component reaches 3 cm [25]. In cases of surgical recurrence, repeat surgical resection is often necessary [26].

Tyrosine kinase inhibitors that target VEGF have efficacy in localised germline VHL-associated ccRCC. In a phase 2 trial of pazopanib for patients with VHL, objective responses were seen in 13 (42%) of 31 patients, including in 31 (52%) of 59 RCCs [27]. In another trial of 15 patients with VHL disease treated with sunitinib to assess for toxicity, partial responses were observed in six patients with renal tumours [28].

Data on the efficacy of VEGF inhibitors in metastatic ccRCC in VHL syndrome are limited, although partial responses have been reported [29]. In a Zebrafish model, an HIF2a small molecule inhibitor reversed the clinical phenotypes of VHL syndrome and partially rescued VHL−/− embryos from early lethality [30]. An on-going phase 2 trial is testing the HIF-2 alpha inhibitor PT2977 in patients with VHL-associated RCC (NCT03401788).

3.4. Hereditary leiomyomatosis and RCC (OMIM 150800)

HLRCC is an autosomal dominant syndrome associated with increased risks of cutaneous and uterine leiomyomas, and RCCs, recently termed HLRCC syndrome-associated RCC.

3.4.1. Genetics and gene function—HLRCC is caused by mutations in *FH*, which encodes the Krebs cycle enzyme fumarate hydratase (FH), which catalyses the hydration of fumarate to malate. Germline mutations and concomitant loss of the second allele in the tumour are present in 90% of families, but biallelic somatic inactivation of FH is also seen in sporadic cases. FH inactivation leads to a pseudohypoxic state via stabilization of HIF-1 alpha through inhibition of prolyl hydroxylase [31,32]. Inability to metabolise glucose through the Krebs cycle shifts the cell towards glycolytic metabolism. Recent studies have also demonstrated that the accumulation of fumarate in FH-deficient tumours lead to upregulation of antioxidant response genes, a signature that is shared amongst both hereditary and sporadic type 2 papillary RCCs [33,34]. Excess fumarate can inhibit α-ketoglutarate-dependent dioxygenases, which are involved in histone and DNA demethylation [35]. Fumarate may serve as an epigenetic modifier by triggering epithelial-to-mesenchymal transition [36]. Work by Sulkowski et al. [37] also showed that elevated fumarate suppresses the homologous recombination DNA-repair pathway, potentially rendering cells vulnerable to synthetic lethal targeting with poly (ADP)-ribose polymerase (PARP) inhibitors.

3.4.2. Clinical/radiographic features—While there is high penetrance for cutaneous and uterine leiomyomas, the penetrance of RCC is still incompletely understood, ranging from 2% to 21% [38,39]. Affected women are often treated with hysterectomies at young ages due to symptoms. Cutaneous leiomyomas appear as firm, flesh coloured to light red/brown papules, and can be subtle. Renal tumours in these patients can develop at young age, and some have recommended beginning screening with abdominal imaging at the age of 11 yr in selected cases [39]. HLRCC-associated RCC is often aggressive and frequently presents with metastatic disease, particularly through lymph node chains [40]. FH-deficient tumours are exquisitely dependent on glycolysis for energy production, explaining their high fluorodeoxyglucose (FDG) uptake on positron emission tomography scan [41]. Germline FH mutations may also be detected rarely in patients with paraganglioma/pheochromocytoma [42].

3.4.3. Morphological features—HLRCC syndrome-associated RCC was added as a new tumour entity in the WHO classification of tumours. Tumours tend to show mixed architectural features. Aside from papillary, a spectrum of growth patterns can be seen, including tubulopapillary, tubular, tubulocystic, solid, cystic elements, sarcomatoid differentiation, and collecting duct carcinoma-like or tubulocystic carcinoma-like regions [43,44]. A hallmark cytological feature of HLRCC tumours is a very prominent eosinophilic nucleolus surrounded by a clear halo. However, this feature alone is not adequately specific and/or sensitive for establishing the diagnosis. Immunohistochemical detection of covalent modification of cysteine residues to S-(2-succinyl) cysteine or the loss of FH expression have been utilised as ancillary tests for detecting FH deficiency [45-47]. The development of these ancillary tools has improved and demonstrated a key role of pathological examination in the diagnosis of HLRCC patients. With increased utilisation of diagnostic biomarkers, rare cases of FH-deficient RCC with low-grade morphological features have also been reported [48,49].

3.4.4. Management—HLRCC is one exception to the so-called “3-cm rule” in that they are thought to metastasise early, and should therefore be resected promptly and widely. There is no standard treatment for metastatic disease; however, in addition to agents already approved for all RCCs, several other approaches are being studied. While FH deficiency in tumour cells sensitises them to glucose deprivation, and inhibiting glycolysis is a rational strategy, one case report failed to show activity of the glycolytic inhibitor 2-deoxy-d-glucose [50]. The National Cancer Institute is studying the combination of bevacizumab and erlotinib, with the idea that combined VEGF and epidermal growth factor receptor blockade will impair blood flow and glucose delivery to the tumour. Both retrospective data and interim findings of the trial show that this regimen can achieve objective responses, and this is now a regimen for non-ccRCC listed by the National Comprehensive Cancer Network (NCCN) guidelines.

3.5. BHD syndrome (OMIM 135150)

BHD is an autosomal dominant syndrome characterised by skin lesions, lung cysts, spontaneous pneumothorax, and multifocal renal tumours [51].

3.5.1. Genetics and gene function—BHD is caused by mutations in the *FLCN* tumour suppressor gene; concomitant LOH or somatic mutations in the wild-type allele are frequently observed [52,53]. *FLCN* mutations in sporadic chromophobe RCC have not been observed to our knowledge. The recent TCGA analysis, for example, did not find any FLCN mutations, although whole chromosome 17 loss was common.

3.5.2. Clinical/radiographic features—Most patients with BHD develop fibrofolliculomas (benign, smooth papules that predominantly occur in the face and upper torso) from the 3rd decade, but may also have acrochordons. Bilateral pulmonary cysts and concomitant risk for pneumothorax are also common [54]. About one-third of BHD patients develop renal tumours of multiple histologies as described below.

3.5.3. Morphological features—The associated RCCs have primarily hybrid or chromophobe histological type, although papillary RCCs, ccRCCs, and angiomyolipomas (AMLs) have also been described [55]. The most characteristic type of tumour observed in 50% of cases is a hybrid oncocytic tumour (mixed features of oncocytoma and chromophobe RCC), and these should prompt genetic evaluation of BHD. The renal parenchyma surrounding the renal tumour often displays features of oncocytosis, such as numerous microscopic oncocytic nodules, cysts lined by oncocytic cells, and oncocytic changes in non-neoplastic renal tubules [56].

3.5.4. Management—BHD oncocytic and chromophobe tumours tend to be indolent when small. Masses reaching 3 cm are generally managed with nephron-sparing approaches. Metastases are rare, especially with routine surveillance and management, but can occur usually from tumours that either are clear cell, or have clear cell or papillary features. In one series of 115 germline *FLCN* carriers, of the many individuals who had not been undergoing routine surveillance, 14 had renal cancer, of which five metastasised. [50]. Since a few cases of metastatic BHD RCC have been reported, the best systemic treatment approach is unknown.

3.6. Hereditary papillary RCC (OMIM 164860)

HPRC is an autosomal dominant inherited syndrome in which affected individuals are at a risk of multifocal type 1 papillary RCC [30].

3.6.1. Genetics and gene function—HPRC is caused by pathogenic activating variants in the *MET* protooncogene, located in chromosome 7, which encodes for a receptor tyrosine kinase. The binding of its ligand, a hepatocyte growth factor, activates MET and downstreams multiple signalling cascades associated with cell proliferation and survival [34]. TCGA showed that nearly all papillary type 1 RCCs have gains of chromosome 7 and 17, and 17% of 75 had *MET* mutations, including three germline pathogenic variants [36].

3.6.2. Clinical/radiographic features—The hallmark of HPRC is multifocal and bilateral papillary renal tumours. Unlike other RCC syndromes, there are no known extrarenal manifestations. Age of onset can vary, with individuals as young as 30 yr old being reported; but the penetrance appears to be close to 100% by age 80. Like sporadic

papillary RCCs, HPRC tumours are usually hypovascular and enhance only 10–30 Hounsfield units after IV contrast administration on computed tomography (CT) scan. On ultrasound images, the lesions are often isoechoic to background renal parenchyma, and can be missed, so either CT or magnetic resonance imaging is recommended for surveillance.

3.6.3. Morphological features—Lubensky et al. [57] described histological features of papillary RCC from patients with germline or somatic *MET* mutations. All germline cases had multiple bilateral tumours on gross examination, and most (16 of 21) had papillary renal adenomas or microscopic papillary renal lesions in grossly normal parenchyma. All *MET*-mutant tumours had predominant papillary/tubulopapillary features and had papillary type 1 histology; most tumours were of ISUP grade 1 or 2, although some grade 3 tumours were seen.

3.6.4. Management—Kidney tumours in HPRC individuals are generally followed until 3 cm [37]. For advanced disease, the identification of activating *MET* mutations in patients with HPRC and sporadic papillary type 1 RCC has led to trials of MET pathway inhibitors. Foretinib, a pan-kinase inhibitor of MET, VEGFR2, RON, and AXL, was evaluated in patients with papillary RCC [58]. Foretinib appeared to be most beneficial in patients with germline pathogenic variants in *MET*; five (50%) of 10 patients experienced a partial response compared with five (9%) of 57 sporadic patients.

3.7. Hereditary paraganglioma-pheochromocytoma syndromes (OMIM 185470)

Pathogenic variants in the SDH genes (*SDHA, SDHB, SDHC, SDHD*, and *SDHAF2*) are associated with the development of paragangliomas, pheochromocytomas, gastrointestinal stromal tumours, and RCCs [52]. SDH-deficient RCC was added as a new tumour entity in the WHO classification of tumours [3]. They are characterised by a loss of immunohistochemical expression of SDHB, which indicates disruption of the SDH complex, not just *SDHB* mutation. Patients with SDH-deficient RCC most often have a mutation in *SDHB*, but mutations have also been reported in the other SDH genes [59].

3.7.1. Genetics and gene function—SDH is a mitochondrial enzyme complex made up of four protein subunits (SDHA, SDHB, SDHC, and SDHD). The enzyme catalyses the oxidation of succinate to fumarate in the Krebs cycle. Mutations in Krebs cycle enzymes shift the cells towards increased glucose uptake, aerobic glycolysis, and fatty acid synthesis.

3.7.2. Clinical/radiographic features—The prevalence of SDH-deficient RCC is unknown, although it has been estimated at 0.1–0.2% of all RCCs [59]. A small case series have shown an earlier age of onset (median age 30–40 yr, range 15–72 yr), and rare bilateral tumours [60,61]. Tumours can exhibit aggressive behaviour, and 33% of patients in one series developed metastatic disease [59]. Andrews et al. [62] estimated the lifetime risk of developing RCC at about 5% in *SDHB* mutation carriers. Similar to HLRCC-associated RCCs, SDH-deficient RCCs appear to be highly FDG avid [63].

3.7.3. Morphological features—SDH-deficient RCCs are characterised by neoplastic cells with vacuolated cytoplasm and cytoplasmic inclusions that contain pale eosinophilic

fluid of flocculent material [64]. These inclusions correspond to giant mitochondria on ultrastructural examination. Suggested features prompting evaluation of SDH on immunohistochemistry (IHC) include monomorphic oncocytic renal tumours with a solid architecture, intratumoural mast cells, and cytoplasmic inclusion of flocculent material [64]. Loss of SDHB on IHC is a sensitive and specific marker for these neoplasms, and should prompt genetic assessment [59].

3.7.4. Management—Given the possibility of metastasis even with small tumours, RCCs in patients with SDH germline pathogenic variants should be treated similarly to HLRCC, with aggressive wide excision. Once metastasised, these are often treated in a way similar to other RCCs, although advances in the understanding of this disease is yielding novel therapeutic targets. For example, increased dependence of SDH-deficient RCCs and HLRCCs on glycolytic pathways suggests that inhibitors of glucose uptake, glycolysis, and fatty acid synthesis could exploit this vulnerability [65]. A clinical trial of vandetanib in combination with metformin is underway for SDH-deficient RCCs and HLRCCs (NCT02495103).

3.8. BAP1 tumour predisposition syndrome (OMIM 614327)

BAP1 tumour predisposition syndrome is an autosomal dominant syndrome associated with increased risks of mesothelioma, uveal melanoma, cutaneous melanoma, RCC, and possibly other malignancies.

3.8.1. Genetics and gene function—*BAP1*, located on 3p21.1, encodes for a multifunctional protein that was initially found to bind to the BRCA1 RING finger and enhance BRCA1-mediated cell growth suppression [66]. It subsequently was found to interact with ASXL1 to form the Polycomb group Repressive Deubiquitinase complex, which plays a key role in chromatin by mediating nuclear deubiquitination of histone H2A and HCFC1 [67]. BAP1 alterations are seen in about 10–15% of sporadic ccRCCs.

3.8.2. Clinical/radiographic features—Germline mutations in *BAP1* were first linked to cancer in 2011, when studies identified increased risks of melanoma and mesothelioma [65,68]. In 2013, several groups identified germline *BAP1* mutations that cosegregated in families with multiple cases of ccRCC, showing that RCC is one of the core tumours of the syndrome [69,70]. The full spectrum of tumours associated with BAP1 syndrome, however, is a subject of on-going analysis.

The risk of RCC in *BAP1* carriers is estimated at 10%, but this number may be inflated due to an ascertainment bias [71]. Owing to the small number of reported cases, the phenotype of BAP1-associated RCC is still not fully elucidated. Predominantly ccRCC cases have been described, but there are at least two published cases of non-ccRCCs [10]. Whether carriers present with earlier-onset RCC is still unknown. Somatic ccRCC with *BAP1* mutations is associated with a higher tumour grade and decreased survival, but whether this also applies to germline BAP1-associated RCC needs further study [72,73].

3.8.3. Management—At this time, BAP1-associated RCC is treated similarly to sporadic RCC, although some centres have seen aggressive outcomes, and recommend

consideration of early intervention and close screening [12]. Although there are no evidence-based guidelines for cancer screening in individuals with germline BAP1 pathogenic variants, consensus recommendations suggest annual abdominal imaging to screen for RCC.

3.9. Tuberous sclerosis complex (OMIM 191100)

Tuberous sclerosis complex (TSC) is an autosomal dominant condition characterised by abnormalities of the skin, neurocognitive deficits and brain lesions, renal tumours, and other conditions.

3.9.1. Genetics and gene function—TSC is caused by heterozygous germline pathogenic variants in *TSC1* or *TSC2*, which act as tumour suppressors. TSC1 and TSC2 are part of a heterotrimeric complex that functions as a GTPase-activating protein for Rheb, which in turn binds and activates mTOR complex 1 (mTORC1). The mTORC1 is a major regulator of growth and metabolism. About two-thirds of individuals with TSC have de novo mutations.

3.9.2. Clinical/radiographic features—TSC is a multiorgan syndrome [74]. Almost all TSC patients have associated skin findings, including hypopigmented macules, facial angiofibromas, and periungual fibromas. Most individuals have CNS lesions (including cortical dysplasia, subependymal nodules, and, at a lesser frequency, subependymal giant cell astrocytomas). Associated neurological conditions include seizures and autism spectrum disorder. Other manifestations include lymphangioleiomyomatosis (LAM) of the lung (which primarily affects women), cardiac rhabdomyomas, and retinal hamartomas. Diagnostic criteria from the International TSC Consensus Conference were updated in 2012.

Individuals with TSC are at an increased risk of benign AML (seen in about 50–70%), cysts, oncocytomas, and, more rarely, malignant AML and RCC. In one case series of sporadic and TSC AMLs, the mean age of onset of AML in TSC carriers was 26, with tumours seen in childhood. Acute haemorrhage is the most concerning risk for patients with AMLs. Patients with de novo disease or *TSC2* mutations may be at higher risks of AML and renal cysts.

Up to 5% of renal tumours are malignant, most commonly ccRCC, often at a younger age. AMLs typically contain areas of low attenuation on CT images corresponding to fat content. However, one-third of patients with TSC present with lipid-poor AMLs, which may be enhancing, making differentiation from other renal tumours challenging [22]. Often biopsy is necessary to distinguish between fat-poor AMLs and renal tumours.

3.9.3. Morphological features—TSC-associated RCCs exhibit a spectrum of histomorphologies. Recent series described subsets of tumours with distinctive features: some have clear cells and papillary/alveolar architectures and fibromuscular stroma, resembling ccRCCs or *TCEB1*-mutated RCCs; some mimic chromophobe or oncocytoma; other tumours are with granular eosinophilic cytoplasm and unclassified features [75-77]. Recently reported sporadic RCCs characterised by somatic TSC1/TSC2/MTOR mutations show a morphological overlap with tumours in TSC patients [78,79].

3.9.4. Management—In cases of a suspicious solid tumour, a biopsy is recommended as many solid tumours are benign lipid-poor AMLs. The management depends on the histological type and size of the renal mass. In cases of lipid-rich or biopsy-proven lipid-poor AML, surveillance is the preferred method until the largest tumour reaches about 4 cm, at which point selective angioembolisation is considered. It is important to acknowledge that the 4 cm threshold is based on historical data for AML management based on higher propensity for spontaneous haemorrhage. It is not unreasonable to monitor these patients past 4 cm. Malignant tumours are treated by surgical resection.

The randomised, placebo-controlled EXIST-II trial examined the efficacy of everolimus in 118 patients (113 with TSC and five with sporadic LAM) with AML [80]. Response rate (50% or more reduction in the total volume of all target AMLs) was 42% versus 0% for everolimus versus placebo ($p < 0.001$). Tumour regrowth can be observed if everolimus is discontinued. Based on these findings, everolimus was approved by the Food and Drug Administration for use in TSC-related AMLs.

3.10. Other familial syndromes

Other genetic syndromes have been linked to an increase risk of RCC. PTEN hamartoma syndrome/Cowden syndrome (OMIM 158350) is a multiorgan syndrome that predisposes individuals to multiple benign and malignant tumours, with a high prevalence of breast, thyroid, and endometrial cancer; macrocephaly; and other conditions. Lifetime risk of RCC has been estimated to be as high as 34%, with an increased risk beginning at age 40 in one study [81]. In a series of 219 prospectively accrued individuals with PTEN mutations, nine (4%) had RCC; patients with papillary RCC, chromophobe RCC, and ccRCC have been described [82,83]. Hereditary hyperparathyroidism jaw tumour syndrome (OMIM 145001) is an inherited autosomal dominant disorder caused by mutations in *CDC73* and characterised by susceptibility to parathyroid adenomas, ossifying jaw fibromas, and renal abnormalities, most commonly renal cysts, but also ccRCC and Wilms' tumour [84].

The *MITF* E318K variant has been linked to a fivefold increased risk of melanoma or RCC or both cancers. Although no guidelines are available, referral for genetic counselling should be considered in case of a familial or personal history of RCC and melanoma. Constitutional chromosome 3 translocations have also been identified to cosegregate in families with multiple cases of RCC, and testing for a translocation can be considered if inherited RCC is suspected. The risk of RCC is unknown in an individual with a chromosome 3 translocation without a personal or family history of RCC, and the risk may be related to the type of translocation [85].

Many families with multiple cases of RCC and no other syndromic features have no identified RCC-associated germline mutation. These families should be enrolled in clinical studies whenever possible.

4. Conclusions

Hereditary RCC syndromes are caused by several different genetic alterations, and involve a wide spectrum of clinical manifestations and varying incidences of RCC. With advances in

sequencing and more widespread applications, new genetic causes of RCC are being uncovered. The molecular pathways involved in the pathogenesis of VHL-associated ccRCC were successfully exploited in the development of anti-VEGF agents now standard for sporadic RCC. Similarly, the last few years have seen exciting preclinical and clinical data exploiting other oncogenic pathways, such as those driven by MET activation or those caused by abnormal metabolite accumulation.

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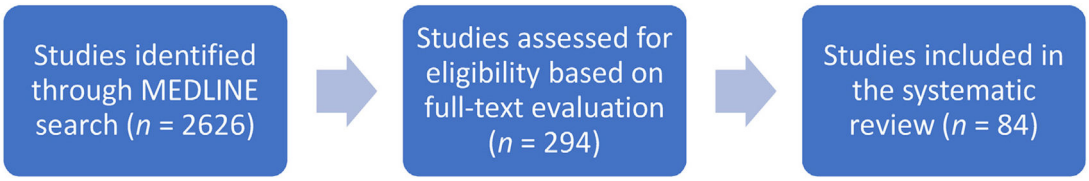

Fig. 1 –.
Flowchart outlining literature review process.

Table 1 –

Hereditary renal cell carcinoma syndromes

Gene	Syndrome	Histology	Selected associated extrarenal clinical features	Example initial screening recommendations	
VHL	von Hippel-Lindau	ccRCC Clear cell papillary	• Retinal and CNS haemangioblastomas • Pancreatic cysts and neuroendocrine tumours • Endolymphatic sac tumour • Pheochromocytoma • Others	Renal: • Annual abdominal ultrasound • MRI of abdomen every 2 yr 28620007	Other: • Ophthalmological exam • Blood pressure check and neurological assessment • Audiology assessment • Plasma-free metanephrines/urinary metanephrines • MRI of brain and cervical spine
FH	Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)	HLRCC-associated RCC Papillary type 2 Others	• Cutaneous leiomyomas • Uterine leiomyomas • Leiomyosarcomas	Renal: • Annual MRI with renal protocol 28620008	Other: • Dermatological exam Gynaecological exam for women
FLCN	Birt-Hogg-Dubé	Chromophobe Oncocytoma Hybrid Clear cell	• Fibrofolliculomas and other skin findings • Renal and lung cysts	Renal: • CT or MRI of abdomen every 3 yr 23703644	Other: • CT of the chest • Dermatological exam
MET	Hereditary papillary renal cell carcinoma	Papillary type 1	• None	Renal: • Renal ultrasound every 2 yr	Other: • None
TSC1/ TSC2	Tuberous sclerosis	Angiomyolipoma ccRCC cystic oncocytoma	• Angiomyofibromas and other dermatological lesions • Cortical dysplasia • Subependymal giant cell astrocytoma • Lymphangioleiomyomatosis • Others	Renal: • MRI of abdomen every 1–3 yr 24053983	Other: • Dermatological exam • Dental exam • Ophthalmological exam • Assessing renal function and blood pressure yearly • Screening neuropsychiatric disorders • Brain MRI • Routine EEG by clinical indication • ECG • CT of the chest every 5–10 yr for asymptomatic patients
BAP1	BAP1 tumour predisposition syndrome	Undefined	• Uveal and cutaneous melanomas • Mesothelioma	Renal: • CT or MRI of abdomen every 2 yr 29413689	Other: • Ophthalmological exam • Dermatological exam • Consider CT or MRI of chest/abdomen
SDHA/B/ C/D	Hereditary paraganglioma-pheochromocytoma syndromes	SDH-deficient RCC	• Paragangliomas • Pheochromocytoma • GIST	Renal: • Abdominal MRI every 2 yr 28620007	Other: • Blood pressure • Plasma methoxytyramine, PFM/urine metanephrines • Serum chromogranin A • Complete blood counts • Whole-body MRI (skull base of pelvis)

Gene	Syndrome	Histology	Selected associated extrarenal clinical features	Example initial screening recommendations	
MITF	MITF predisposition to familial RCC	Undefined	• Melanoma	Renal: • Renal ultrasound every 1–2 yr	Other: • Dermatological exam
PTEN	Cowden syndrome	Papillary Chromophobe ccRCC	•Dermatological lesions • Breast cancer • Thyroid cancer • Endometrial cancer • Others	Renal: • Renal ultrasound every 1–2 yr 28040716	Other: • Thyroid exam • Dermatological exam • Breast exam, mammogram and breast MRI (women) • Thyroid ultrasound • Colonoscopy • Consider endometrial cancer screening (women)
CDC73	Hyperparathyroidism jaw tumour syndrome	Renal cysts Renal hamartomas Wilms tumours Other	• Primary hyperparathyroidism • Ossifying fibromas of the mandible or maxilla • Parathyroid carcinoma • Uterine tumours	Renal: • Renal ultrasound at least every 5 yr 20301744	Other: • Serum calcium, intact parathyroid hormone, and 25-(OH) vitamin D levels • Dental panoramic X-ray with neck shielding • Screening for uterine tumours (women)

ccRCC = clear cell RCC; CNS = central nervous system; CT = computed tomography; ECG = electrocardiography; EEG = electroencephalography; GIST = gastrointestinal stromal tumour; MRI = magnetic resonance imaging; PFM = plasma-free metanephrine; RCC = renal cell carcinoma; SDH = succinate dehydrogenase.

Summary of the known syndromes, genetic alterations, associated histology, and selected associated extrarenal features is given. Example initial screening and surveillance recommendations are also provided.

* Renal screening recommendations are applicable for initial screening. If a renal tumour or an abnormality is found, then imaging interval and modality should be determined by the treating provider.