Hereditary Renal Cancer Predisposition Syndromes

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Renal cell carcinoma (RCC) comprises a heterogenous group of cancers with distinct histopathological appearance and molecular drivers. In addition to smoking, obesity and hypertension, genetic factors are implicated in the pathogenesis of the disease. Pathogenic germline variants in at least 12 genes (Table 1) are associated with an increased lifetime risk of RCC, accounting for 4–6% of all RCC diagnoses [1]. It is likely that other undescribed genes and background germline genetic factors contribute to the development of familial RCC.

Hereditary RCC syndromes are usually inherited in an autosomal dominant manner, although a lack of family history of RCC may occur if there is incomplete penetrance or if the mutation has arisen *de novo*.

Most guidance agree that individuals with bilateral and/or multicentric disease; early age of onset (<= 46 years of age [1]); or a first or second degree relative with any renal tumour should be referred for genetic counselling [2]. In addition, the presence of additional non-RCC clinical features in a patient or histopathological features might suggest the diagnosis of a specific hereditary RCC syndrome and guide molecular genetic investigations (Table 1).

Herein, we discuss the well described clinical syndromes, their molecular pathogenesis and clinical management strategies. The clinical features, suggested renal screening and management recommendations are summarised in Table 2.

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Table 1 Summary of known hereditary RCC syndromes, the associated variant germline gene and RCC histological subtype

Syndrome	*Gene*	Locus	Protein	Type	Renal Cancer Histology	Lifetime risk of RCC
von Hippel-Lindau (vHL) disease	*VHL*	3p25	pVHL	Tumour suppressor	ccRCC Clear cell papillary Cysts	60–70%
Hereditary papillary RCC	*MET*	7q31	Hepatocyte growth factor	Proto-oncogene	Type 1 papillary	100%
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)	*FH*	1q43	Fumerate hydratase	Tumour suppressor	HLRCC-associated RCC (formally papillary type 2)	15–35%
Hereditary paraganglioma-phaeochromocytoma syndrome	*SDHA* *SDHB* *SDHC* *SDHD*	5p15 1p36 1q23 11q23	Succinate dehydrogenase complex, subunit A Succinate dehydrogenase complex, subunit B Succinate dehydrogenase complex, subunit C Succinate dehydrogenase complex, subunit D	Tumour suppressor	SDH-deficient RCC	–
Birt-Hogg-Dubé	*FLCN*	17p11	Folliculin	Tumour suppressor	Chromophobe oncocytic hybrid Oncocytoma Papillary ccRCC	15–29%
BAP1 tumour predisposition syndrome	*BAP1*	3p21	BRCA1-associated protein 1	Tumour suppressor	Clear cell	–
Tuberous sclerosis	*TSC1* *TSC2*	9q34 16p13	Hamartin Tuberin	Tumour suppressor Tumour suppressor	Angiomyolipoma Oncocytoma Chromophobe ccRCC	2–3%
Cowden syndrome	*PTEN*	10q23	Phosphatase and tensin homolog	Tumour suppressor	Papillary Chromophobe ccRCC	34% [1]

Table 2 Clinical features and summarised renal screening and management reccomendations

Syndrome	*Gene*	Extrarenal manifestations	Suggested RCC surveillance imaging	Management of renal manifestations
von Hippel-Lindau (vHL) syndrome	*VHL*	– Phaeochromocytoma/paraganglioma – Pancreatic neuroendocrine tumours – Retinal/CNS hemangioblastomas – Cystic disease: Pancreatic, broad ligament, epididymal – Endolymphatic sac tumours	– From age 16 years [1] – Annual MRI abdomen alternating with USS [1]	– Active surveillance with delayed intervention when >3 cm – Nephron sparing surgical approach or thermal/cryoablation may be considered [1]
Hereditary papillary RCC syndrome	*MET*	– None	– Abdominal imaging at least every 36 months (MRI preferred) [2]	– Active surveillance with delayed intervention when >3 cm [2] – Nephron sparing approach/ enucleation favoured over ablation [2]
Hereditary leiomyatosis and renal cell carcinoma (HLRCC) syndrome	*FH*	– Uterine leiomyomas – Cutaneous leiomyomas – Uterine leiomyosarcoma	– From age 10 [3] – Annual MRI (preferred) or contrast enhanced CT	– Low threshold for surgical intervention [2] – Wide surgical margins
Hereditary paraganglioma-phaeochromocytoma syndrome	*SDHA* *SDHB* *SDHC* *SDHD*	– Phaeochromocytoma – Paraganglioma – GIST	– Abdominal MRI every 2 years [4]	– Immediate extirpative surgery
Birt-Hogg-Dubé (BHD) syndrome	*FLCN*	– Cutaenous fibrofolliculomas – Cystic disease: Lung and kidney	– Abdominal imaging at least every 36 months (MRI preferred) [2]	– Active surveillance with delayed intervention when >3 cm – Nephron sparing surgical approach or thermal/cryoablation may be considered [1]

(continued)

Table 2 (continued)

Syndrome	*Gene*	Extrarenal manifestations	Suggested RCC surveillance imaging	Management of renal manifestations
BAP1 tumour predisposition syndrome	*BAP1*	– Uveal melanoma – Cutaneous melanoma – Mesothelioma	– Abdominal MRI every 2 years [5]	– No specific published guidance – Immediate extirpative surgery advised [6]
Tuberous sclerosis complex (TSC)	*TSC1* *TSC2*	– Cutaneous lesions: Hypopigmented macules, angiofibromas and others – CNS lesions: Cortical dysplasia, hamartomas, giant cell astrocytoma – Retinal haemartomas – Cardiac rhabdomyomas	– Abdominal MRI every 1–3 years [7]	– Consider biopsy to differentiate RCC vs AML – mTOR inhibitor (e.g. sirolimus) is preferred therapy for AML – Nephron sparing surgery for RCC
Cowden syndrome	*PTEN*	– Cutaneous lesions: Hamartomas, trichilemmomas, oral fibromas, and punctate palmoplantar keratoses – Breast cancer – Thyroid cancer – Endometrial cancer – Colorectal polyps/carcinoma	– Abdominal MRI every 2 years [8]	– No specific published guidance

Von Hippel Lindau (VHL) Disease

Clinicopathological Hallmarks

VHL disease is an autosomal dominant multi-organ tumour predisposition syndrome caused by inactivating germline variants in the von Hippel-Lindau tumour suppressor gene (*VHL*). Incidence is approximately 1:34,000 live births and penetrance approaches 100% by age 60 [3, 4]. Affected individuals can develop a variety of VHL deficient lesions across differing tissue contexts, including many hundreds of renal cysts and clear cell renal cacners (ccRCCs) in addition to benign pancreatic cysts, central nervous system (CNS) and retinal haemangioblastomas (HB), and neuroendocrine tumors (NET) such as pheochromocytoma. Classifications have been proposed based on predilection for phaeochromocytoma (Table 3) although clinical phenotypes vary considerably between and within families [5].

The lifetime risk of developing a renal cancer is 60–70% at a mean age onset of 44 years (two decades earlier than sporadic ccRCC) although cases affecting teenagers have been described [6]. In-situ RCC growth is typically indolent [7] and primary tumour size appears to be an important determinant of outcome with the risk of metastasis virtually nil below 3 cm in size [8].

Genetics and Molecular Pathogenesis

The *VHL* gene is located on the short arm of chromosome 3 (3p25) [9] and encodes a 213 amino acid product, pVHL. pVHL forms the substrate recognition component of a E3 ubiquitin ligase complex with Elongin B and C (collectively, VCB complex) and plays a central role in cellular oxygen sensing and orchestrating the transcriptional response to hypoxia (Fig. 1). The VCB complex targets the hypoxia-inducible

Table 3 VHL disease subgroup categorisation and genotype/phenotype correlations (see further [1, 2]). HB, haemangioblastoma; PCC/PGL, phaeochromocytoma/paraganglioma; ccRCC clear cel renal cell carcinoma; VHL, von Hippel-Lindau

VHL Subtype	*VHL* Variant Type	Clinical phenotype	
		High Risk	Low Risk
Type 1	Deletions, insertions, truncations, missense	CNS/retinal HB, ccRCC	PCC/PGL
Type 1B	Contiguous gene deletions encompassing VHL	CNS/retinal HB	PCC/PGL, ccRCC
Type 2A	Missense	CNS/retinal HB, PCC/PGL	ccRCC
Type 2B	Missense	CNS/retinal HB, PCC/PGL, ccRCC	
Type 2C	Missense	PCC/PGL	CNS/retinal HB, ccRCC absent

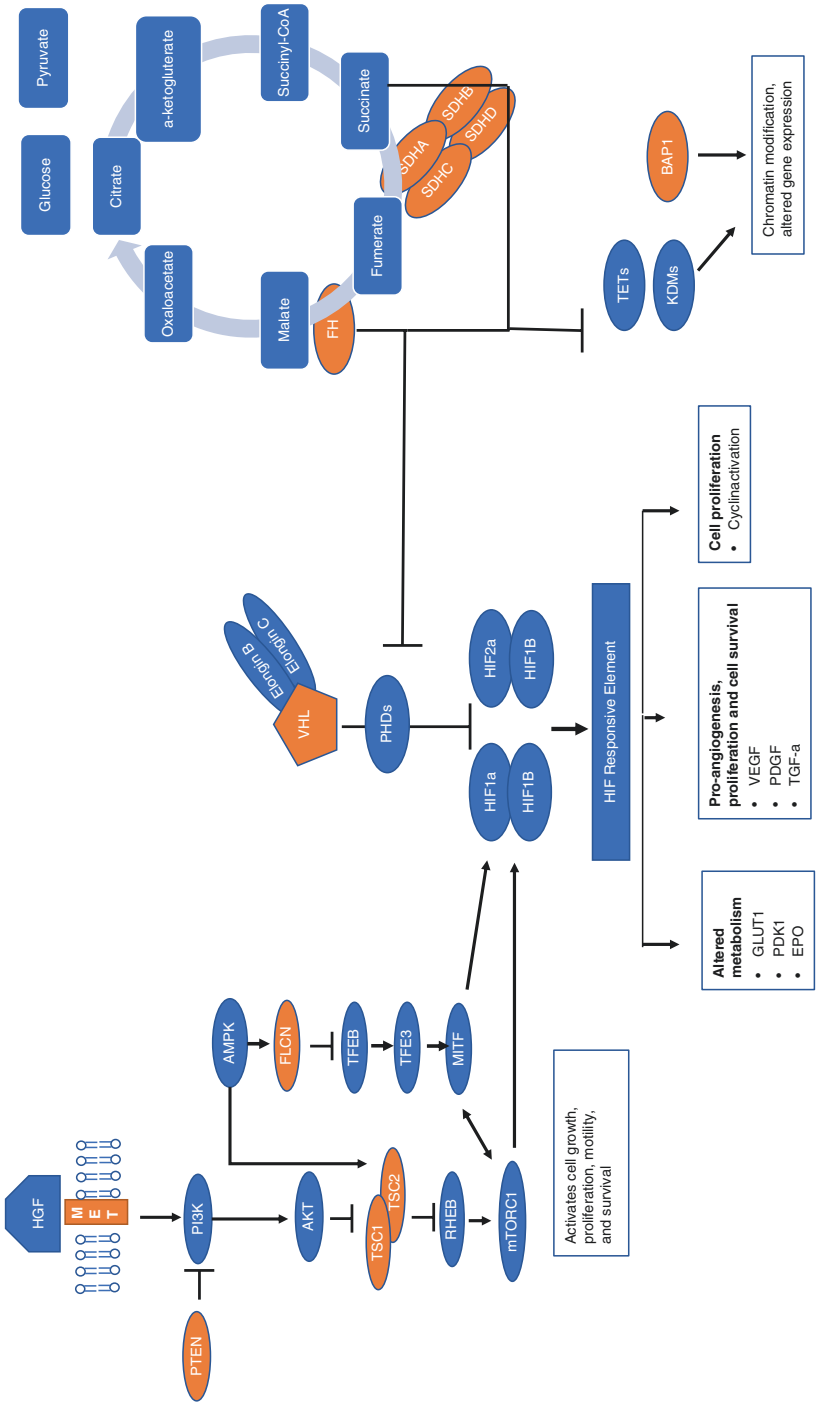
Pyruvate
Glucose
Citrate
a-ketogluterate
Succinyl-CoA
Succinate
Oxaloacetate
Malate
Fumerate
FH
SDHA
SDHB
SDHC
SDHD
TETs
KDMs
BAP1
Chromatin modification, altered gene expression
HGF
MET
PI3K
PTEN
AKT
TSC1
TSC2
RHEB
mTORC1
AMPK
FLCN
TFEB
TFE3
MITF
Activates cell growth, proliferation, motility, and survival
VHL
Elongin B
Elongin C
PHDs
HIF2a
HIF1B
HIF1a
HIF1B
HIF Responsive Element
Cell proliferation
• Cyclinactivation
Pro-angiogenesis, proliferation and cell survival
• VEGF
• PDGF
• TGF-a
Altered metabolism
• GLUT1
• PDK1
• EPO

Fig. 1 Pathogenic germline variants in a number of genes (coloured red figure) are associated with increased lifetime risk of RCC. pVHL loss in tumors results in the inability of the VHL E3 ubiquitin ligase complex to target the HIF transcription factors for proteosomal degradation, leading to stabilisation of HIF and activation of the hypoxia response. Pseudohypoxia is pro-tumourigenic through expression of growth factors that induce proliferation, survival, and angiogenesis, including VEGF, PDGF, and TGFα, and increases expression of proteins that regulate glucose metabolism and cell proliferation, including GLUT1, LDHA, PDK1, and CCND1. Activating mutations of *MET*, inactivating mutations of *PTEN*, *TSC1, TSC2*, and *FLCN* in tumors result in increased activation of the PI3K/AKT/mTOR pathway which regulates cell growth, proliferation, and survival. Dysregulation of the PI3K/AKT/mTOR pathway results in increased production of the HIF transcription factors via MTORC1 and MITF signalling, indirectly influencing the VHL/HIF oxygen-sensing pathway. Loss of fumarate hydratase (FH) or components of succinate dehydrogenase (SDHB, SDHC, SDHD) changes the activity ofthe TCA cycle, leading to altered metabolism, and the accumulation of the oncometabolites fumarate and succinate, respectively. Fumarate or succinate can both inhibit α-ketoglutarate–dependent prolylhydroxylase enzymes that regulate the HIF transcription factors, resulting in inhibition of the VHL/HIF oxygen-sensing pathway. Other α-ketoglutarate–dependent enzymes include the Ten-eleven translocation (TET) and Lysine-specific demethylase (KDM) enzymes that regulate DNA/histone methylation, acetylation and effect chromatin remodeling. Loss of chromatin remodelling protein, BAP1 also alters gene-expression profiles in RCC

factors (HIF1a and HIF2a) for proteasomal degradation in an oxygen dependant fashion. Under hypoxic conditions, there is an accumulation of HIF leading to transcriptional activation of the so-called hypoxia response element (HRE) genes, resulting in metabolic re-programming, increased proliferation, angiogenesis and cellular survival. Inactivation of *VHL* leads to HRE activation in the absence of hypoxia, 'pseudohypoxia', and is characteristic of both sporadic and hereditary ccRCCs.

More than 500 unique germline pathogenic variants have been described in over 900 families with VHL disease [10, 11] from specific missence mutations to exon or whole gene deletions (Table 3). Genotype/phenotype correlations have been described based on predilection for phaeochromocytoma but these are imperfect and manifestations of VHL vary considerably between and within kindred with an identical inactivating mutation [5].

Clinical Management and Therapeutic Approaches

Regular radiological surveillance is the mainstay of management in individuals found to have or be at risk of carrying a pathogenic variant in *VHL*. Surveillance imaging protocols to monitor renal and non-renal manifestations of the disease have been published and recommend imaging modalities that limit exposure to ionising radiation [12].

In the kidney, management involves serial radiological monitoring and surgical intervention when the dominant lesion reaches 3 cm in maximal diameter [8].

The risk of metastasis is minimal in lesions <3 cm in size, with the risk of systemic spread increasing stepwise beyond this cut off [8]. Nephron sparing approaches (partial nephrectomy or enucleation) are undertaken wherever feasible to preserve renal clearance (surgical approach reviewed in [13]). Kidney transplantation in patients with end-stage renal disease appears to be safe and does not appear to be associated with worse graft or overall survival outcomes than non-VHL patients [14].

Receptor tyrosine kinase inhibitors targeting the VEGF-pathway have shown clinical activity in patients with clinically localised disease [15, 16]. Objective response to pazopanib was seen in 42% of VHL patients in one non-randomised phase 2 tral; partial responses were observed in 52% of RCCs, 53% of pancreatic lesions but only 4% of CNS haemangioblastomas. Median shrinkage varied between organ site and was 40·5% (IQR 21–53) in the renal lesions, 30·5% (IQR 18–36) in pancreatic lesions, and 13% (IQR 7–23) in the haemangioblastomas suggestive of tissue specific sensitivity to VEGF-tareted therapy. Treatment related toxicity was signficiant with 23% discontinuing therapy due to adverse events. Responses to VEGF inhibition have been also been described in the context of metastatic disease outwith clinical trial setting [17, 18]. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-belzutifan-cancers-associated-von-hippel-lindau-disease.

Germline MET Variants: Hereditary Papillary Renal Cell Carcinoma (HPRC) Syndrome

Clinicopathological Hallmarks

HPRC is a rare autosomal dominant hereditary renal cancer syndrome characterised by the development of multifocal, bilateral type 1 papillary RCC. HPRC is highly penetrant (approaching 100%) although the age at onset varys widely (median 41 years (range, 19–66) [1, 19]. A single kidney may harbour over 3000 microscopic papillary tumours [20, 21]. There are no known extra renal manifestations [19, 22].

Genetics and Molecular Pathogenesis

Germline missence mutations [23, 24] in the tyrosine kinase domain of *MET* (7q31) result in ligand independent MET activation [23–25] and downstream signalling associated with cell proliferation, survival and motility [26]. Specific missence *MET* mutation might influence the age of onset [19]. Altered *MET* gene status or increased chromosome 7 copy number is seen in 81% of sporadic type 1 pRCC in the TCGA dataset [27].

Clinical Management and Therapeutic Approaches

HPRC related tumours have been reported to metastasise [21] however growth is typically indolent and patients are managed with active surveillance until the dominant lesion reaches 3 cm in size. When considering surgery, a nephron sparing approach is employed where possible [28].

The presence of activating *MET* mutations in patients with hereditary and sporadic papillary renal cancer has led to the evaluation of a targeted therapy approach. Foretinib, an oral multikinase inhibitor targeting *MET* and VEGFR, demonstrated a 100% disease control rate in patients with advanced disease and a germline *MET* mutation [29], leading to FDA approval for this indication. Clinical responses in patients with *MET* mutations have also been observed with *MET* kinase inhibitors crizotinib [30] and savolitinib [31] and a randomised study involving a number of *MET* targeting agents in papillary renal cancer is ongoing (NCT02761057).

Herediatry Leiomyomatosis and Renal Cell Carcinoma (HLRCC) Syndrome

Clinicopathological Hallmarks

HLRCC is an autosomal dominant familial cancer syndrome and affected individuals are at risk to develop benign cutaneous and uterine leiomyomas and an aggressive form of RCC: HLRCC-associated RCC (formally type 2 papillary renal cancer) [32]. The prevalence is unknown, although several hundred families have been described in the literature. Given its rarity, it is likely that HLRCC is an underdiagnosed clinical entity although establishment of HLRCC-associated RCC in the most recent WHO pathological classification and improved access to molecular diagnostics may increase diagnoses.

The most common manifestations of HLRCC are cutaneous leiomyomata, which occur in 76%–100% of patients [33–35] and present as multiple firm, flesh-colored nodules (10 to >100, <2.5 mm in size) that develop on the trunk and extremities [36]. Uterine leiomyomas are reported in over 80% of affected women and many experience frequent, severe irregular bleeding requiring hysterectomy [33]. Uterine leiomyomas have rarely been reported to transform to uterine leiomyosarcoma [37].

Lifetime risk of developing RCC is estimated 15–35% [33, 38, 39] with median age at presentation 41 years (range 10–90 years) and 5% of cases diagnosed under the age of 20 [38]. RCC lesions are typically solitary and have the potential for rapid primary tumour growth and early metastatic seeding, even when the primary tumour is small [40].

Germline Genetics and Molecular Pathogenesis

Pathogenic germline variants in the fumerate hydratase (*FH)* gene (1q43) [41, 42] are detected in affected individuals. No genotype-phenotype correlations have been described [42].

The FH enzyme plays an essential role in the Kreb's Cycle which enables hydration of fumerate to malate (Fig. 1). FH-deficient cells undergo a Warburg metabolic shift [43], characterised by a dependence on aerobic glycolysis, impaired oxidative phosphorylation and an intracellular accumulation of fumerate (see below *oncometabolites in RCC*). These changes give rise to a tumourigenic phenotype via stabilisation of HIFs, increased production of reactive oxygen species and histone hypermethylation (reviewed, [44, 45]).

Clinical Management and Therapeutic Considerations

Radiological surveillance screening for HLRCC-associated RCC is recommended from age 8 years [46]. Given the aggressive phenotype, prompt extiripation with wide resection margins is undertaken in individuals with a detectable renal mass. Lymphadenectomy may improve accuracy of staging given the frequency of lymph node metastasis [38].

Synthetic lethality occurs when the simultaneous perturbation of two genes results in cell death and this approach is being used to specifically target FH deficient cells. For example, the combination of bevacizumab and erlotinib (anti-VEGF-A and anti-EGFR, respectively) may constrain glucose delivery to tumour cells, exploiting reliance on aerobic glycolysis. This combination has demonstrated 100% disease control rate and median progression free survival of >24 months in HLRCC-associated RCC in one study [47]. Another strategy under clinical evaluation is the sensitisation of FH/SDH deficient RCCs to poly(ADP)-ribose polymerase (PARP) inhibition (see below *oncometabolites in RCC*).

Succinate Dehydrogenase Deficient RCC

Clinicopathological Hallmarks

Germline pathogenic *SDH* variants are associated with hereditary phaeochromocytoma (PCT) and paraganglioma (PGL) syndrome and at lower penetrance gastrointestinal stromal tuomurs (GIST) and RCCs [48]. The incidence is unknown.

The lifetime tumour risk exceeds 70% and clinical manifestations vary dependant on the mutated SDH subunit (reviewed [49]). The lifetime risk of developing a renal tumour has been estimated at approximately 5% for *SDHB* carriers but may be

less in other affected subunits [48]. RCCs are typically solitary and unilateral. Median age of diagnosis was 37 years [50], although presentation with RCC as young as 14 has been reported [51]. Distant metastasis occurred in 9 of the 27 patients in one series and may be associated with sarcomatoid differentiation in the priamry [28].

Genetics and Molecular Pathogenesis

SDH is a tetrameric enzymatic complex consisting of four subunits (*SDHA, SDHB, SDHC, SDHD*) that localise to the inner mitochondrial membrane and are involved in both the Kreb's cycle and electron transport chain, catalysing the oxidation of succinate to fumerate (Fig. 1) [52].

SDH-deficient RCC was added to the WHO classification of renal tumours as a unique subtype in 2016 [32]. In patients with RCC, the most commonly mutated gene is *SDHB*, followed by *SDHC, SDHD*, and *SDHA* [50, 53]. Biallelic inactivation of SDH leads to a Warburg shift to aerobic glycolysis and impaired oxidative phosphorylation and intracellular accumulation of succinate (*see oncometabolites in RCC below*).

Clinical Management and Therapeutic Considerations

There are no specific clinical guidelines for the management of *SDH* deficient RCC. Proposed surveillance strategies [51, 54] reccomend lifelong radiological surveillance for metachronous RCCs and/or PCT/PGL. Upon detection of a renal mass, prompt extirapative surgery is performed given the risk of early metastatic seeding. SDH and HLRCC related RCCs are profoundly FDG PET avid which may be useful in identifying occult metastatic disease.

Disruption of the TCA Cycle: Oncometabolites in RCC

Loss of function of the SDH and FH enzymes leads to an accumulation of succinate and fumerate (so-called oncometabolites) that have pro-oncogenic functions [45]. Oncometabolites inhibit a family of enzymes known as α-ketoglutarate (αKG)-dependent dioxygenases, leading to epigenetic dysregulation and induction of a pseudohypoxic phenotype. Inhibition of specific αKG-dependent dioxegenases, KDM4A and KDM4B, leads to suppression of the homologous recombination DNA-repair pathway and a loss of genome integrity. Homologous recombination deficiency was shown to confer sensitivity to PARP inhibition in pre-clinical models and might offer a novel targeted therapy approach [55].

Birt-Hogg-Dube (BHD) Syndrome

Clinicopathological Hallmarks

BHD syndrome is an autosomal dominant cancer predisposition syndrome characterised by benign cutaenous fibrofolliculomas and cystic lung disease (occurring in >85% of kindred) that present in in young adulthood [56–58]. Lung cysts can predispose to spontaneous pneumothorax [59]. The exact prevalence is unknown but BHD has been reported in more than 200 families globally [12].

Bilateral and multifocal renal neoplasms occur in 15–29% of BHD patients; the median age at tumour diagnosis is 46–50 years although may occur as young as 20 years [58, 60]. The histological subtype can vary between and within patients (Table 1) with hybrid oncocytic tumours (50%) the most commonly seen followed by chromophobe RCC (chRCC) (34%) and oncocytoma (9%) [56, 57]. Macroscopically normal kidney contain scattered microscopic foci of oncocytic cells which may be precursor lesions [56].

Genetics and Molecular Pathogenesis

Pathogenic germline variants in the *FLCN gene* (17p11) are detected in affected kindred with [61, 62] no clear genotype/phenotype correlation [58, 60]. Inactivation of the *FLCN* gene promotes RCC tumourigenesis through dysregulation of the PI3K/AKT-mTOR pathway and activation of mitochondrial biogenesis leading to ROS production and activation of HIF transcriptional activity [52].

Clinical Management and Therapeutic Approaches

Life-long radiological surveillanve for renal tumours is reccomended [12, 46] and a nephron sparing surgical approach should be considered once the largest lesion reaches 3 cm in maximal diameter [63]. Metastasis can occur when patients are not receiving regular radiological surveillance [59] and are typically of clear cell histology and associated with a poor prognosis [56, 59]. There are no specific targeted therapy approaches for patients with BHD related RCC.

BRCA1-Associated Protein (BAP1) Tumour Predisposition Syndrome

Clinicopathological Hallmarks

This autosomal dominant tumour predisposition syndrome is characterised by an increased life-time risk of mesothelioma, uveal and cutaneous melanoma and RCC [64] with the full spectrum of associated tumours still to be defined. Penetrance is

high with 85% of mutation carriers affected with a cancer [65]. The lifetime risk of RCC is approximately 10%, at a mean age of diagnosis for RCC 42 years (range 36–70). RCCs are typically solitary and of the clear cell subtype although other histologies have been described [66] and larger cohorts are needed to more clearly define the phenotype. Germline *BAP-1* mutation was detected in 0.8% of the TCGA ccRCC cohort, suggesting that *BAP1* tumour predisposition may be an underrecognised clinical entity [67].

Genomics and Molecular Pathogenesis

BAP1 (3p21) encodes a multifunctional deubiquitinating hydrolase enzyme that is involved in a number of biological processes including a key role in regulating chromatin dynamics, the DNA damage response and cell growth [68–70]. BAP1 alterations are seen in about 10–15% of patients with sporadic RCC, and are associated with a poor prognosis [67].

Pathogenic germline variants in *BAP1* (3p21) are detected in affected kindred with at least 46 unique mutations reported [65] and no clear genotype/phenotype correlations noted. Most families have at least two different tumour types diagnosed amongst kindred.

Clinical Management and Therapeutic Approaches

Evidence based guidelines have not been established but management involves regular examination/screening of affected organs to facilitate early diagnosis of tumours. Patients with a renal mass have have immediate surgery with wide surgical margins [65]. There are no approved targeted therapies for BAP1 driven malignancies.

Tuberous Sclerosis Complex (TSC) Syndrome

Clinicopathological Hallmarks

TSC is an autosomal dominant multiorgan tumour predisposition syndrome characterised by cutaneous lesions (hypopigmented macules, angiofibromas), CNS lesions (hamartomas, cortical dysplasia, subependymal giant cell astrocytoma), cardiac rhabdomyomas, retinal hamartomas and neurocognitive deficits and renal tumours [71]. The incidence of TSC is 1 in 6000–10,000 live births [72].

In the kidney, benign manifestations include angiomyolipomas (AMLs, present in up to 70%), oncocytomas and renal cysts. TSC associated RCCs occur in less than 5% of carriers and various histolopathological subtypes including ccRCC, pRCC and chRCC are seen (Table 1).

Genetics, Molecular Pathogenesis and Morphology

Pathogenic germline variants in either *TSC1* (chromosome 9p34; encoding hamartin) or *TSC2* (chromosome 16p13; encoding tuberin) are associated with TSC syndrome. Approximately 2/3 of carriers are new presentations with no family history. Hamartin and tuberin form part of a heterotrimeric complex with GTPase-activity involved in the negative regulation of the mTOR complex 1 (mTOR1), the key effector of the PI3K/AKT/mTOR pathway.

Clinical Management and Therapeutic Approaches

MRI surveillance to screen/monitor AMLs and/or RCCs is conducted and renal tumour biopsy may be necessary to differentiate between benign AMLs and RCC [73]. AMLs >3 cm in diameter are at risk of acute haemorrhage and should be treated with an mTOR inhibitor as the most effective first-line therapy [73–75]. This approach appears to be effective and well tolerated with surgery/ablation reserved as second line therapy [74]. Suspected malignant epithelial tumours are biopsied to confirm the diagnosis (if safe and practical to do so) and referred for nephron sparing surgery.

Cowden Syndrome

Clinicopathological Hallmarks

Cowden syndrome is an autosomal dominant tumour predisposition syndrome characterised by hamartomas, cutaneous manifestations (trichilemmomas, oral fibromas, and punctate palmoplantar keratoses), and an increased risk of breast, endometrial, thyroid, kidney and colorectal cancers [76]. There is an estimated incidence of 1 in 200,000 live births and nearly 100% of patients present in their 20s with mucocutaneous lesions.

Germline Genetics and Molecularpathogenesis

Pathogenic missense germline variants in *PTEN* (10q23) [77] are typically seen. *PTEN* is a negative regulator of the PI3K-AKT-mTOR signalling pathway. Heterogeneity of the genetic locus is observed in 20–34% of patients with clinical diagnosis of Cowden Syndrome, where germline variants are observed in related

proteins such as *KLLN, PIK3CA* and *AKT1* [78, 79]. There are no clear genotype phenotype correlations. Estimated lifetime risk of renal cancer may be as high as 34% with increased risk from 40 years [80]. Histopathological subtype can vary, with case reports describing pRCC, chRCC, and ccRCC.

Conclusions

Hereditary RCC syndromes are caused by a number of pathogenic germline variants and each syndrome is associated with varying incidence of renal neoplasms and specific extrarenal manifestations. Management of such syndromes should be in the context of a bespoke specialist multidisciplinary team with underlined by principles of careful surveillance and patient centred management.

Identification of the culprit genes has given insight into the molecular drivers of the various RCC subtypes and highlights that an interconnected signalling network involving cellular sensing to oxygen, nutrients and/or energy production drive renal cancer growth. An improved understanding of these cellular processes can lead to rationally designed targeted therapeutic approaches to improve outcomes in both hereditary and sporadic manifestations of the disease.

Hereditary RCC syndromes are likely an under diagnosed clinical entitiy and this has implications for screening and surveillance of metachronous cancers and for identification of at risk family members. As manifestations of herediatary syndromes become clinically tractable, prompt diagnosis will optimise outcomes through use of novel targeted therapeutic strategies.

Key Points

1. Hereditary RCC syndromes account for 4–6% of all RCC diagnoses but some syndromes may be underecognised in the clinic.
2. Diagnosis may be suspected on the basis of family history, clinical features (multifocal or bilateral lesions; <46 years of age) or histopathological findings (e.g. HLRCC-associated RCC).
3. Management should be in the context of a multidisciplinary team, expert in the management of the renal and non-renal manifestations of the disease.
4. Active surveillance is the mainstay of management in asymptomatic patients with or suspected to have a pathogenic germline variant.
5. Wherever possible and clinically appropriate, imaging modalities such as MRI should be employed to minimise exposure to ionising radiation.
6. In syndromes where growth is likely to be indolent and the risk of metastasis is small, deferral of surgery until the solid component of the dominant lesion >3 cm is recommended.

7. In syndromes where risk of metastasis is high even when the primary tumour is small, immediate exiripative intervention with wide surgical margin is recommended.
8. A nephron sparing surgical approach (partial nephrectomy/enucleation) to preserve renal clearance is important in patients with a predisposition to bilateral and multifocal tumours that might require repeated surgical intervention.
9. An understanding of the consequences of the germline genetic event is leading to the development of targetetd therapeutic strategies in some syndromes and patients should be entered into clinical studies where possible.

References

1. Shuch B, et al. Defining early-onset kidney cancer: implications for germline and somatic mutation testing and clinical management. J Clin Oncol. 2014;32(5):431–7.
2. Hampel H, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of genetic counselors: referral indications for cancer predisposition assessment. Genet Med. 2015;17(1):70–87.
3. Maher ER, et al. Von Hippel-Lindau disease: a genetic study. J Med Genet. 1991;28(7):443–7.
4. Maddock IR, et al. A genetic register for von Hippel-Lindau disease. J Med Genet. 1996;33(2):120–7.
5. Chen F, et al. Germline mutations in the von Hippel-Lindau disease tumor suppressor gene: correlations with phenotype. Hum Mutat. 1995;5(1):66–75.
6. Maher ER, Webster AR, Moore AT. Clinical features and molecular genetics of Von Hippel-Lindau disease. Ophthalmic Genet. 1995;16(3):79–84.
7. Jilg CA, et al. Growth kinetics in von Hippel-Lindau-associated renal cell carcinoma. Urol Int. 2012;88(1):71–8.
8. Duffey BG, et al. The relationship between renal tumor size and metastases in patients with von Hippel-Lindau disease. J Urol. 2004;172(1):63–5.
9. Latif F, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. Science (New York, NY). 1993;260(5112):1317–20.
10. Nordstrom-O'Brien M, et al. Genetic analysis of von Hippel-Lindau disease. Hum Mutat. 2010;31(5):521–37.
11. Beroud C, et al. Software and database for the analysis of mutations in the VHL gene. Nucleic Acids Res. 1998;26(1):256–8.
12. Genetics of Kidney Cancer (Renal Cell Cancer) (PDQ(R)): Health Professional Version, in PDQ Cancer Information Summaries. 2002: Bethesda (MD).
13. Metwalli AR, Linehan WM. Nephron-sparing surgery for multifocal and hereditary renal tumors. Curr Opin Urol. 2014;24(5):466–73.
14. Goldfarb DA, et al. Results of renal transplantation in patients with renal cell carcinoma and von Hippel-Lindau disease. Transplantation. 1997;64(12):1726–9.
15. Jonasch E, et al. Pazopanib in patients with von Hippel-Lindau disease: a single-arm, single-Centre, phase 2 trial. Lancet Oncol. 2018;19(10):1351–9.
16. Jonasch E, et al. Pilot trial of sunitinib therapy in patients with von Hippel-Lindau disease. Ann Oncol. 2011;22(12):2661–6.
17. Kim HC, et al. Sunitinib treatment for metastatic renal cell carcinoma in patients with von hippel-Lindau disease. Cancer Res Treat. 2013;45(4):349–53.

18. Eric JF, et al. Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease. N Engl J Med. 2021;385(22):2036–46. https://doi.org/10.1056/NEJMoa2103425.
19. Schmidt LS, et al. Early onset hereditary papillary renal carcinoma: germline missense mutations in the tyrosine kinase domain of the met proto-oncogene. J Urol. 2004;172(4 Pt 1):1256–61.
20. Ornstein DK, et al. Prevalence of microscopic tumors in normal appearing renal parenchyma of patients with hereditary papillary renal cancer. J Urol. 2000;163(2):431–3.
21. Lubensky IA, et al. Hereditary and sporadic papillary renal carcinomas with c-met mutations share a distinct morphological phenotype. Am J Pathol. 1999;155(2):517–26.
22. Zbar B, et al. Hereditary papillary renal cell carcinoma. J Urol. 1994;151(3):561–6.
23. Schmidt L, et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet. 1997;16(1):68–73.
24. Schmidt L, et al. Novel mutations of the MET proto-oncogene in papillary renal carcinomas. Oncogene. 1999;18(14):2343–50.
25. Dharmawardana PG, Giubellino A, Bottaro DP. Hereditary papillary renal carcinoma type I. Curr Mol Med. 2004;4(8):855–68.
26. Organ SL, Tsao MS. An overview of the c-MET signaling pathway. Ther Adv Med Oncol. 2011;3(1 Suppl):S7–S19.
27. Cancer Genome Atlas Research Network, et al. Comprehensive molecular characterization of papillary renal-cell carcinoma. N Engl J Med. 2016;374(2):135–45.
28. Walther MM, et al. Renal cancer in families with hereditary renal cancer: prospective analysis of a tumor size threshold for renal parenchymal sparing surgery. J Urol. 1999;161(5):1475–9.
29. Choueiri TK, et al. Phase II and biomarker study of the dual MET/VEGFR2 inhibitor foretinib in patients with papillary renal cell carcinoma. J Clin Oncol. 2013;31(2):181–6.
30. Schoffski P, et al. Crizotinib in patients with advanced, inoperable inflammatory myofibroblastic tumours with and without anaplastic lymphoma kinase gene alterations (European Organisation for Research and Treatment of Cancer 90101 CREATE): a multicentre, single-drug, prospective, non-randomised phase 2 trial. Lancet Respir Med. 2018;6(6):431–41.
31. Choueiri TK, et al. Biomarker-based phase II trial of Savolitinib in patients with advanced papillary renal cell Cancer. J Clin Oncol. 2017;35(26):2993–3001.
32. Moch H, et al. The 2016 WHO classification of Tumours of the urinary system and male genital organs-part a: renal, penile, and testicular Tumours. Eur Urol. 2016;70(1):93–105.
33. Toro JR, et al. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. Am J Hum Genet. 2003;73(1):95–106.
34. Wei MH, et al. Novel mutations in FH and expansion of the spectrum of phenotypes expressed in families with hereditary leiomyomatosis and renal cell cancer. J Med Genet. 2006;43(1):18–27.
35. Smit DL, et al. Hereditary leiomyomatosis and renal cell cancer in families referred for fumarate hydratase germline mutation analysis. Clin Genet. 2011;79(1):49–59.
36. Schmidt LS, Linehan WM. Hereditary leiomyomatosis and renal cell carcinoma. Int J Nephrol Renovasc Dis. 2014;7:253–60.
37. Ylisaukko-oja SK, et al. Analysis of fumarate hydratase mutations in a population-based series of early onset uterine leiomyosarcoma patients. Int J Cancer. 2006;119(2):283–7.
38. Menko FH, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. Familial Cancer. 2014;13(4):637–44.
39. Muller M, et al. Reassessing the clinical spectrum associated with hereditary leiomyomatosis and renal cell carcinoma syndrome in French FH mutation carriers. Clin Genet. 2017;92(6):606–15.
40. Grubb RL 3rd, et al. Hereditary leiomyomatosis and renal cell cancer: a syndrome associated with an aggressive form of inherited renal cancer. J Urol. 2007;177(6):2074–9. Discussion 2079–80
41. Alam NA, et al. Localization of a gene (MCUL1) for multiple cutaneous leiomyomata and uterine fibroids to chromosome 1q42.3-q43. Am J Hum Genet. 2001;68(5):1264–9.

42. Tomlinson IP, et al. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet. 2002;30(4):406–10.
43. Sudarshan S, et al. Fumarate hydratase deficiency in renal cancer induces glycolytic addiction and hypoxia-inducible transcription factor 1alpha stabilization by glucose-dependent generation of reactive oxygen species. Mol Cell Biol. 2009;29(15):4080–90.
44. Linehan WM, Rouault TA. Molecular pathways: fumarate hydratase-deficient kidney cancer--targeting the Warburg effect in cancer. Clin Cancer Res. 2013;19(13):3345–52.
45. Linehan WM, Ricketts CJ. The metabolic basis of kidney cancer. Semin Cancer Biol. 2013;23(1):46–55.
46. Board., P.C.G.E., Genetics of Kidney Cancer (Renal Cell Cancer) (PDQ®): Health Professional Version. 2019.
47. Srinivasan R, Su D, Stamatakis L, Siddiqui MM, Singer E, Shuch B, Nix J, Friend J, Hawks G, Shih J, Choyke P, Linehan WM. Mechanism based targeted therapy for hereditary leiomyomatosis and renal cell cancer (HLRCC) and sporadic papillary renal cell carcinoma: interim results from a phase 2 study of bevacizumab and erlotinib. Eur J Cancer. 2014;50(Supp 6):8.
48. Andrews KA, et al. Tumour risks and genotype-phenotype correlations associated with germline variants in succinate dehydrogenase subunit genes SDHB, SDHC and SDHD. J Med Genet. 2018;55(6):384–94.
49. Pasini B, Stratakis CA. SDH mutations in tumorigenesis and inherited endocrine tumours: lesson from the phaeochromocytoma-paraganglioma syndromes. J Intern Med. 2009;266(1):19–42.
50. Gill AJ, et al. Succinate dehydrogenase (SDH)-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients. Am J Surg Pathol. 2014;38(12):1588–602.
51. Ricketts CJ, et al. Succinate dehydrogenase kidney cancer: an aggressive example of the Warburg effect in cancer. J Urol. 2012;188(6):2063–71.
52. Linehan WM, et al. The metabolic basis of kidney Cancer. Cancer Discov. 2019;9(8):1006–21.
53. Yakirevich E, et al. A novel SDHA-deficient renal cell carcinoma revealed by comprehensive genomic profiling. Am J Surg Pathol. 2015;39(6):858–63.
54. Tufton N, Sahdev A, Akker SA. Radiological surveillance screening in asymptomatic succinate dehydrogenase mutation carriers. J Endocr Soc. 2017;1(7):897–907.
55. Sulkowski PL, et al. Krebs-cycle-deficient hereditary cancer syndromes are defined by defects in homologous-recombination DNA repair. Nat Genet. 2018;50(8):1086–92.
56. Pavlovich CP, et al. Renal tumors in the Birt-Hogg-Dube syndrome. Am J Surg Pathol. 2002;26(12):1542–52.
57. Schmidt LS, Linehan WM. Molecular genetics and clinical features of Birt-Hogg-Dube syndrome. Nat Rev Urol. 2015;12(10):558–69.
58. Toro JR, et al. BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dube syndrome: a new series of 50 families and a review of published reports. J Med Genet. 2008;45(6):321–31.
59. Houweling AC, et al. Renal cancer and pneumothorax risk in Birt-Hogg-Dube syndrome; an analysis of 115 FLCN mutation carriers from 35 BHD families. Br J Cancer. 2011;105(12):1912–9.
60. Schmidt LS, et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dube syndrome. Am J Hum Genet. 2005;76(6):1023–33.
61. Nickerson ML, et al. Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dube syndrome. Cancer Cell. 2002;2(2):157–64.
62. Lim DH, et al. A new locus-specific database (LSDB) for mutations in the folliculin (FLCN) gene. Hum Mutat. 2010;31(1):E1043–51.
63. Pavlovich CP, et al. Evaluation and management of renal tumors in the Birt-Hogg-Dube syndrome. J Urol. 2005;173(5):1482–6.
64. Popova T, et al. Germline BAP1 mutations predispose to renal cell carcinomas. Am J Hum Genet. 2013;92(6):974–80.

65. Rai K, et al. Comprehensive review of BAP1 tumor predisposition syndrome with report of two new cases. Clin Genet. 2016;89(3):285–94.
66. Carlo MI, et al. Prevalence of germline mutations in Cancer susceptibility genes in patients with advanced renal cell carcinoma. JAMA Oncol. 2018;4(9):1228–35.
67. Ricketts CJ, et al. The Cancer genome atlas comprehensive molecular characterization of renal cell carcinoma. Cell Rep. 2018;23(1):313–326 e5.
68. Jensen DE, et al. BAP1: a novel ubiquitin hydrolase which binds to the BRCA1 RING finger and enhances BRCA1-mediated cell growth suppression. Oncogene. 1998;16(9):1097–112.
69. White AE, Harper JW, Cancer. Emerging anatomy of the BAP1 tumor suppressor system. Science. 2012;337(6101):1463–4.
70. Scheuermann JC, et al. Histone H2A deubiquitinase activity of the Polycomb repressive complex PR-DUB. Nature. 2010;465(7295):243–7.
71. Randle SC. Tuberous sclerosis complex: a review. Pediatr Ann. 2017;46(4):e166–71.
72. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci. 1991;615:125–7.
73. Krueger DA, Northrup H, G. International tuberous sclerosis complex consensus, tuberous sclerosis complex surveillance and management: recommendations of the 2012 international tuberous sclerosis complex consensus conference. Pediatr Neurol. 2013;49(4):255–65.
74. Bissler JJ, et al. Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis: extension of a randomized controlled trial. Nephrol Dial Transplant. 2016;31(1):111–9.
75. McCormack FX, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med. 2011;364(17):1595–606.
76. Pilarski R. Cowden syndrome: a critical review of the clinical literature. J Genet Couns. 2009;18(1):13–27.
77. Nelen MR, et al. Localization of the gene for Cowden disease to chromosome 10q22-23. Nat Genet. 1996;13(1):114–6.
78. Orloff MS, et al. Germline PIK3CA and AKT1 mutations in Cowden and Cowden-like syndromes. Am J Hum Genet. 2013;92(1):76–80.
79. Pilarski R, et al. Predicting PTEN mutations: an evaluation of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome clinical features. J Med Genet. 2011;48(8):505–12.
80. Mester JL, et al. Papillary renal cell carcinoma is associated with PTEN hamartoma tumor syndrome. Urology. 2012;79(5):1187. e1-7