Review – Kidney Cancer

Hereditary Renal Cancer Syndromes: An Update of a Systematic Review

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Article info

Abstract

Context: Hereditary renal cancers (HRCs) comprise approximately 3–5% of renal cell carcinomas (RCCs).
Objective: Our aim was to provide an overview of the currently known HRC syndromes in adults.
Evidence acquisition: Data on HRC syndromes were analysed using PubMed and Online Mendelian Inheritance in Man with an emphasis on kidney cancer, clinical criteria, management, treatment, and genetic counselling and screening.
Evidence synthesis: Ten HRC syndromes have been described that are inherited with an autosomal dominant trait. Eight genes have already been identified (*VHL, MET, FH, FLCN, TSC1, TSC2, CDC73,* and *SDHB*). These HRC syndromes involve one or more RCC histologic subtypes and are generally bilateral and multiple. Computed tomography and magnetic resonance imaging are the best imaging techniques for surveillance and assessment of renal lesions, but there are no established guidelines for follow-up after imaging. Except for hereditary leiomyomatosis RCC tumours, conservative treatments favour both an oncologically effective therapeutic procedure and a better preservation of renal function.
Conclusions: HRC involves multiple clinical manifestations, histologic subtypes, genetic alterations, and molecular pathways. Urologists should know about HRC syndromes in the interest of their patients and families.

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1. Introduction

Renal cell carcinoma (RCC) in Europe represents 2% of all malignant diseases in adults (approximately 88 400 patients) and accounts for 2.3% of all cancer-related deaths (approximately 39 300 patients) [1]. Most cases of RCC are believed to be sporadic. Smoking, obesity, hypertension, chemical exposure, and end-stage renal disease are the leading known environmental risk factors for RCC [2,3]. Hereditary renal cell carcinomas (HRCs) comprise an estimated 3–5% of RCCs [4–6] and are of practical and biologic importance [5].

To date, 10 HRC syndromes have been described. All are inherited with an autosomal dominant trait (Table 1) [4,7,8]. Because several mutations are required for cancer to develop, it is a susceptibility to cancer, not cancer per se, that is inherited. The occurrence of RCC varies in these syndromes. It can be the main feature (eg, hereditary papillary renal carcinoma [HPRC]) or an uncommon manifestation of disease (eg, tuberous sclerosis complex [TSC]). Finally, in each of these HRC syndromes, phenotypic features vary among and within families (variable expressivity and penetrance). This review describes in detail the currently known HRC syndromes to help identify patients in clinical practice and to provide suggestions for their management.

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 disease, Birt-Hogg-Dubé syndrome, hereditary leiomyomatosis RCC, hereditary papillary RCC, tuberous sclerosis complex, hereditary hyperparathyroidism-jaw tumour syndrome, papillary thyroid carcinoma with associated papillary renal neoplasia,* SDHB-*associated hereditary paraganglioma, constitutional chromosome 3 translocations, familial clear cell RCC, genetic counselling, genetic screening, treatment,* and *management.* References from the identified articles were

Table 1 – Hereditary renal cancer syndromes

Syndrome	Causative gene, location	Gene product	Renal tumours	Other tumours
VHL disease	*VHL*, 3p25-26	pVHL	Clear cell RCC: solid and/or cystic, multiple, and bilateral Clear cell renal cysts	Retinal and CNS haemangioblastomas, phaeochromocytoma, pancreatic cyst and endocrine tumour, endolymphatic sac tumour, epididymal and broad ligament cystadenomas
Hereditary papillary RCC	*MET*, 7q31	MET	Type 1 papillary RCC: multiple and bilateral	None
Hereditary leiomyomatosis and RCC	*FH*, 1q42-43	Fumarate hydratase	Papillary RCC (non–type 1): solitary and aggressive	Uterine leiomyoma and leiomyosarcoma, Cutaneous leiomyoma and leiomyosarcoma
BHD syndrome	*FLCN (BHD)*, 17p11.2	Folliculin	Hybrid oncocytic RCC, chromophobe RCC, oncocytoma, clear cell RCC: multiple and bilateral	Cutaneous lesions (fibrofolliculoma +++, trichodiscoma, acrochordon), lung cysts, spontaneous pneumothorax, colonic polyps or cancer
Tuberous sclerosis complex	*TSC1*, 9q34	Hamartin	Angiomyolipoma, clear cell RCC, cyst, oncocytoma: bilateral and multiple	Facial angiofibroma, subungual fibroma, hypopigmentation and café au lait spots, cardiac rhabdomyoma, seizure, mental retardation, CNS tubers, lymphangioleiomyomatosis
	TCS2, 16p13.3	Tuberin		
Hereditary hyperparathyroidism-jaw tumour syndrome	*CDC73 (HRPT2)*, 1q24-32	Parafibromin	Papillary RCC, hamartoma, nephroblastoma, cyst	Parathyroid tumour, fibro-osseous mandibular and maxillary tumour, uterine tumour
Papillary thyroid carcinoma with associated papillary renal neoplasia	Unknown gene, 1q21	Unknown	Papillary RCC and adenoma, oncocytoma	Papillary thyroid cancer, nodular thyroid disease
SDHB-associated hereditary paraganglioma/phaeochromocytoma	*SDHB*, 1p36	SDHB	Clear cell RCC	Paraganglioma, phaeochromocytoma
Constitutional chromosome 3 translocations	Unknown gene	Unknown	Clear cell RCC: multiple and bilateral	None
Familial clear cell RCC	Unknown gene	Unknown	Clear cell RCC: solitary	None

BHD = Birt-Hogg-Dubé; CNS = central nervous system; RCC = renal cell carcinoma; SDHB = succinate dehydrogenase complex subunit B; VHL = von Hippel-Lindau.

Table 2 – Clinical criteria for the diagnosis of von Hippel-Lindau disease

Patients with a family history of VHL disease
One major manifestation
CNS or retinal haemangioblastoma
Phaeochromocytoma
Clear cell renal cell carcinoma
Patients with no relevant family history of VHL disease
Two major manifestations
Two or more haemangioblastomas
One haemangioblastoma and a visceral tumour (with exception of epididymal and renal cysts)
CNS = central nervous system; VHL = von Hippel-Lindau.

also investigated. Only papers published in English with no date restrictions were included. In a final step, an expert panel of coauthors conducted an interactive peer review.

3. Evidence synthesis

3.1. Von Hippel-Lindau disease

Von Hippel-Lindau (VHL) disease (OMIM 193300) is the most common type of HRC syndrome [6]. An autosomal dominant inherited multisystem tumour syndrome, with an incidence estimated at 1 in 35 000 live births, it has >90% penetrance at 65 yr of age [9]. VHL disease includes the several benign and malignant tumours listed in Table 1. In this review we only discuss the characteristics of VHL-associated renal tumours (for reviews, see Lonser et al, Kaelin, and Clifford and Maher [9–11]). Useful information can also be obtained on the Web site of the VHL Family Alliance (http://www.vhl.org/).

3.1.1. Clinical, imaging, and histologic findings of renal tumours

RCCs are seen in 24–45% of VHL patients (60% when renal cysts are added [9]). They appear at a mean age of 39 yr and are often multiple and bilateral [9]. VHL patients are at risk of developing up to 600 tumours and 1100 cysts per kidney [12].

Cystic lesions vary from simple to complex cysts with solid enhancing septa or masses. The Bosniak classification system can be used to describe and follow the evaluation of VHL-related cystic lesions, but its management implications cannot be directly applied to VHL disease. All VHL renal masses are potentially if not already malignant and typically low grade and slow growing. Management of these lesions is based on the size of the largest solid component rather than the guidelines proposed for sporadic lesions [13].

Clear cell renal cell carcinoma (ccRCC) is the unique VHL-related RCC subtype [9]. Either singly or together, computed tomography (CT) and magnetic resonance imaging (MRI) are key ways to detect and evaluate renal lesions, allowing serial monitoring of individual lesions [13]. Metastatic ccRCC has become the most common cause of mortality in VHL patients [10].

3.1.2. Clinical diagnosis

Table 2 describes the diagnosis of VHL disease, often based on clinical criteria.

3.1.3. The VHL gene and function

VHL disease is caused by germ-line mutations in the VHL tumour-suppressor gene (TSG) located on 3p25–26. Gene mutation analysis is able to identify VHL mutation in nearly 100% of affected families [14]. This germ-line mutation is accompanied by inactivation of the wild-type copy of the VHL gene in target organs, through loss of heterozygosity, promoter hypermethylation, or, more rarely, somatic mutation [4]. In fact, these molecular events are documented very early in microscopic preneoplastic renal lesions and cysts [15]. Additional mutations affecting other loci are probably required to convert these lesions into ccRCCs [10]. Alteration of the VHL gene is found in up to 70% of sporadic ccRCCs [7].

The VHL protein (pVHL) forms a multiprotein complex with Cullin 2, Rbx1 (or Roc1), NEDD8, and elongin B and C, which acts as an E3 ubiquitin ligase. This complex then targets α subunits of hypoxia inducible factor (HIF), that is, HIF-1α and HIF-2α, for ubiquitin-mediated degradation, which is an oxygen-mediated process. Under a hypoxic condition, pVHL is unable to bind to HIF-α and mediate its degradation. Inactivating mutations of both copies of VHL produce a similar effect to hypoxia. Thus HIF accumulation ensues and activates expression of many hypoxia-inducible factors, such as vascular endothelial growth factor, glucose transporter-1, platelet-derived growth factor-β, transforming growth factor-α, and erythropoietin. Each of these genes plays a significant role in tumour formation and growth [10].

3.1.4. Genotype-phenotype correlations

Closely related genotype-phenotype correlations have emerged from the analysis of VHL mutations identified in various VHL kindreds (Table 3).

3.2. Hereditary papillary renal carcinoma

HPRC (OMIM 164860) is a rare autosomal dominant HRC syndrome with high penetrance (90% likelihood of developing RCC at 80 yr of age) [16]. Its incidence is still unknown. Although typically late onset (between 50 and 70 yr of age), an early form was described in 2004 [17].

3.2.1. Clinical, imaging, and histopathologic findings

Papillary renal tumours are the only phenotype associated with this syndrome [5,6,18]. HPRC patients develop myriad papillary tumours, ranging from microscopic lesions (papillary adenomas) to clinically symptomatic carcinomas. Thus HPRC patients are at risk of developing 1100–3400 microscopic tumours in a single kidney [19]. HPRC tumours always belong to type 1 papillary renal cell carcinoma (pRCC) with low nuclear grade (Fuhrman grade 1–2). Imaging assessment is often difficult due to the small size of these lesions and their hypovascularity. In this context, CT is the imaging modality of choice for HPRC patient screening [20]. Although HPRC tumours are usually well differentiated and a local prognosis, some do metastasize [17].

3.2.2. The MET gene and function

The HPRC gene is located on 7q31.3 and corresponds to the MET gene [21]. MET is a proto-oncogene that encodes cell

Table 3 – Genotype-phenotype correlations[*]

VHL type	Phenotype	Genotype	HIF activity
Type 1	Low risk of phaeochromocytoma Haemangioblastoma, high risk of ccRCC Pancreatic endocrine tumour and cyst	Deletion, truncation	↑↑↑
Type 2	High risk of phaeochromocytoma		
Type 2A	Haemangioblastoma, low risk of ccRCC	Missense	↑
Type 2B	Haemangioblastoma, high risk of ccRCC, Pancreatic endocrine tumour and cyst	Missense	↑↑
Type 2C	Phaeochromocytoma only	Missense	Approximately normal

ccRCC = clear cell renal cell carcinoma; HIF = hypoxia inducible factor; VHL = von Hippel-Lindau; pVHL = VHL protein.
Comments
VHL type 1, representing about 75% of VHL families, is characterised by a predisposition to develop retinal and central nervous system (CNS) haemangioblastomas and bilateral ccRCCs. VHL type 1 is caused by mutations in the *VHL* gene that have a drastic effect on the structure of pVHL. Typically, these mutations are partial or complete deletions of *VHL*, nonsense mutations, frameshift mutations, and missense mutations. These mutations abrogate the ability of pVHL to bind elongin C and to regulate HIF [11].
VHL type 2 is characterised by a predisposition to develop phaeochromocytomas. VHL type 2 is subdivided into subtypes 2A, 2B, and 2C depending on the spectrum of tumours in family members. VHL type 2A is characterised by a predisposition to develop retinal and CNS haemangioblastomas as well as phaeochromocytomas. Note: ccRCCs are rare in this VHL subtype. Mutations characteristic of VHL type 2A do not interfere with the ability of pVHL to bind elongin C; some degree of HIF regulation is thus retained. VHL type 2B is characterised by a predisposition to develop phaeochromocytomas, ccRCCs, and retinal and CNS haemangioblastomas. Mutations in this group also abrogate the ability of pVHL to bind elongin C and to regulate HIF. Phaeochromocytoma is the only disease manifestation in families with VHL type 2C. Mutations characteristic of VHL type 2C do not interfere with the ability of pVHL to bind elongin C; complete HIF regulation is retained [11].
[*] According to Kaelin [10].

surface receptor for hepatocyte growth factor (HGF). HPRC-associated mutations constitutively activate the tyrosine kinase domain of *MET*. Upon activation of HGF, these activating gain-of-function mutations involve unregulated proliferation, transformation, and invasion at the origin of the oncogenic pathway of HPRC tumours [5]. Contrary to sporadic type 1 pRCC, only trisomy 7 is found in HPRC with consistent duplication of the mutant *MET* allele, implicating this event in tumourigenesis [5,19,22]. A low frequency of *MET* mutations was noted in a sporadic form, suggesting that the latter may develop by a different mechanism [21].

3.2.3. Genotype-phenotype correlations

No genotype-phenotype correlations were identified in HPRC.

3.3. Hereditary leiomyomatosis and renal cell cancer

Hereditary leiomyomatosis and renal cell cancer (HLRCC) (OMIM 605839) is a recently identified HRC syndrome [23]. In fact, it is a variant of another syndrome called multiple cutaneous and uterine leiomyomatosis (MCUL; OMIM 150800) in which individuals rarely develop RCC [24]. Affected patients are susceptible to developing multiple cutaneous and uterine leiomyomas. In a subset of families, predisposition to early-onset RCC and leiomyosarcomas can be detected [23,25]. HLRCC and MCUL are inherited as an autosomal dominant condition with an incomplete phenotype penetrance. Their incidences are unknown. One limited study estimated the presence of a heterozygous *FH* gene mutation in 1 in 676 individuals in the United Kingdom [24].

3.3.1. Clinical, imaging, and histopathologic findings

3.3.1.1. Renal cancer. RCC is found in approximately 20% of HLRCC families with an early onset (mean age: 36–39 yr) [23,26,27]. In contrast to other forms of HRC, HLRCC-associated RCCs are typically solitary and unilateral, and their nuclear grade is predominantly high (Fuhrman grade 3–4) [23,28]. The first description suggested that type 2 pRCC was the predominant histologic subtype [25]. However, Merino and al showed that HLRCC tumours displayed a predominant papillary pattern in only 62.5% of cases. The hallmark of these tumours was the presence of a large eosinophilic nucleolus with a clear perinucleolar halo, noted in most of the tumour cells [28]. At imaging, HLRCC tumours tend to be hypovascular [20]. HLRCC-related RCCs are the most aggressive renal tumours occurring in HRC syndromes. Most patients have died of metastatic disease within 5 yr after diagnosis. This aggressiveness also characterises the small tumours (pT1) [29].

The presence of renal cysts was previously associated with fumarate hydratase (FH) deficiency (up to 42% of patients) and could be an indicator of a particular predisposition to RCC development [30].

3.3.1.2. Cutaneous leiomyomas and leiomyosarcomas. Cutaneous leiomyomas (CLs) typically present in the second to fourth decade of life as skin-coloured or brownish red grouped papules or nodules, ranging in size from 0.5 to 2 cm, localised on the trunk and limbs. These benign tumours are characteristically painful in response to pressure or low temperature. The extent of CLs is extremely variable, even within one family [31]. Interestingly, the lack of multifocal kidney disease and the presence of a segmental distribution of CLs could indicate the existence of mosaicism in some affected individuals [27]. The malignant transformation of CL is rare [27,32].

3.3.1.3. Uterine leiomyomas and leiomyosarcomas. Uterine leiomyomas occur in >90% of women with MCUL. These patients may have a medical history of menorrhagia and pelvic pressure or pain, frequently requiring a hysterectomy at <30 yr of age [31]. A minority of MCUL/HLRCC patients,

observed only in the Finnish population, are predisposed to developing highly aggressive uterine leiomyosarcoma [23,31].

3.3.2. The FH gene and function

The HLRCC gene was mapped on 1q42.3-q43 and corresponds to the *FH* gene. Biallelic inactivation was detected in almost all HLRCC tumours, suggesting that the *FH* gene is a TSG [19]. *FH* gene encodes a protein called fumarate hydratase (or fumarase) (FH), which is an enzyme of the Krebs cycle that catalyzes the conversion of fumarate to malate. Several studies suggest a pseudohypoxic drive in HLRCC pathogenesis. That is, fumarate intracellular accumulation induces HIF-α stabilization as VHL disease [33,34]. Recently, a critical role of FH in DNA damage response was also suggested [35]. In sporadic RCCs, somatic *FH* mutations seem to be relatively rare [5].

3.3.3. Genotype-phenotype correlations

There are no clear genotype-phenotype correlations in HLRCC [32,36].

3.4. Birt-Hogg-Dubé syndrome

Birt-Hogg-Dubé (BHD) syndrome (OMIM 135150) is a rare autosomal dominant genodermatosis essentially characterised by the development of skin, lung, and kidney lesions [37,38]. It occurs in about 1 in 200 000 people with great clinical variability, which is probably responsible for its underdiagnosis [37]. By comparison to the general population, the risk of developing kidney tumours and spontaneous pneumothorax are 7- and 50-fold higher, respectively [4].

3.4.1. Clinical, imaging, and histopathologic findings

3.4.1.1. Renal tumours. Renal tumours occur in 25–35% of BHD patients with a wide range of onset (mean age: 50 yr) [5,38–40]. Contrary to other HRC syndromes, BHD-related renal tumours have different histologic subtypes. Chromophobe RCCs (chRCCs) and hybrid oncocytic tumours (mixed pattern of chRCCs and oncocytomas) are the main subtypes (23% and 67%, respectively); oncocytomas (3%), ccRCCs (7%), and pRCCs are rarely noted [41]. Various subtypes can be observed in the same family, in the same patient, and sometimes in the same kidney [8]. Multifocal oncocytosis is evident in surrounding normal parenchyma in approximately 60% of tumour-bearing kidneys [40].

RCC is the most threatening complication of BHD syndrome because some cases of metastatic RCC have been reported [39,41]. However, prospective studies with a large number of patients are needed to determine the risk evaluation of BHD-related RCCs.

3.4.1.2. Skins lesions. Skin lesions, classically the primary clinical manifestation of BHD syndrome, are highly penetrant (about 75–90% of patients) [37,38,42]. Skin lesions usually appear after 20 yr as multiple, dome-shaped, whitish, 1- to 3-mm papules mainly present at the sites of hair follicles on the nose, cheeks, neck, and sometimes on the trunk or behind the ears. These benign hair follicle tumours are designated as fibrofolliculomas. They are part of the cutaneous triad of BHD, which also includes trichodiscomas and acrochordons. Fibrofolliculomas and trichodiscomas are currently considered part of a morphologic spectrum. Acrochordons, or skin tags, common in the general population, may represent a phenotypic variant of fibrofolliculomas [37]. Although these skin lesions can be a cosmetic concern, they are not malignant.

3.4.1.3. Pulmonary lesions. Most affected patients (>90%) ≥60 yr of age have developing symptomatic or asymptomatic lung cysts and blebs, and nearly 30% experience a pneumothorax once or several times [39,43]. Contrary to a sporadic pneumothorax, pulmonary cysts are frequently located in basal lung regions. They are consistent with emphysematous changes [37]. Despite multiple lung cysts, lung function is generally unaffected [39,43].

3.4.1.4. Other manifestations. The co-occurrence of BHD and a range of tumours have been reported. A susceptibility to colonic polyps and colon cancer should be taken into account in the clinical follow-up [42,44].

3.4.2. Criteria for diagnosis

BHD syndrome was formerly defined by the presence of at least 5–10 fibrofolliculomas, of which at least one papule was diagnosed histologically. However, new data in penetrance and clinical variability have appeared with the identification of new BHD families. Indeed, skin lesions are not mandatory [39]. Thus new diagnostic criteria based on clinical manifestations and the outcome of DNA testing were recently proposed (Table 4) and need to be validated in prospective studies [37].

Table 4 – Diagnostic criteria for Birt-Hogg-Dubé syndrome*

Major criteria
- At least five fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset**
- Pathogenic *FLCN* germ-line mutation

Minor criteria
- Multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax
- Renal cancer: early onset (<50 yr of age) or multifocal or bilateral renal cancer or renal cancer of mixed chromophobe and oncocytic histology
- A first-degree relative with BHD syndrome

Patients should fulfil one major or two minor criteria for diagnosis
**Fibrofolliculoma and trichodiscoma are two possible presentations of the same lesion. For the differential diagnosis, angiofibroma in TSC should be considered. Childhood-onset familial fibrofolliculoma or trichodiscoma without other syndromic features might be a distinct entity.

* According to Menko et al [37]..

3.4.3.   The FLCN gene and function

BHD syndrome results from a germ-line mutation of the FLCN gene (previously known as BHD) located on 17p11.2. More than 50 mutations in the FLCN gene have been reported, located in all translated exons (4–14) and intronic borders [38,42]. Germ-line insertion or deletion of a cytosine in the hypermutable polycytosine (C8) tract in exon 11 is considered a mutation "hot spot" [38]. Most FLCN germ-line mutations are frameshift or nonsense mutations that are predicted to truncate the BHD protein, called folliculin, which acts as a tumour-suppressor protein involved in the regulation of adenosine monophosphate (AMP)-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) signalling pathways [38, 42,45].

The FLCN gene is infrequently mutated in sporadic renal tumours (<10%), suggesting that the gene probably plays a minor role in sporadic RCC development [4].

3.4.4.   Genotype-phenotype correlations

There are no established genotype-phenotype correlations in BHD syndrome [43].

3.5.   Additional hereditary kidney cancer syndromes

3.5.1.   Tuberous sclerosis complex

TSC (OMIM 191100) is a genetic neurocutaneous disorder characterised by the formation of hamartomas in multiple organ systems (Table 1) [46,47]. The incidence at birth of TSC is estimated to be approximately 1 in 6000 to 1 in 10 000 [46]. TSC occurs by a spontaneous germ-line mutation in approximately 70% of affected individuals. In the remaining 30%, disease is inherited as an autosomal dominant trait, with almost complete penetrance but variable expressivity [46,48].

TSC results from inactivating mutations in either TSC1, located on 9q34 and encoding for hamartin, or TSC2, located on 16p13.3 and encoding for tuberin [46,48]. Hamartin and tuberin bind to each other and form a functional hetero-dimer that inhibits downstream pathways of mTOR. Consequently, mTOR inhibitors have a potential therapeutic interest in TSC as BHD tumours [8].

We only discuss TSC-related renal tumours in this review (for reviews, see Rosser et al, Crino et al, and Leung and Robson [46–48]). Useful information can also be obtained on the Tuberous Sclerosis Alliance Web site (http://www.tsalliance.org/).

Renal lesions occur in 50–80% of TSC patients and include angiomyolipomas (AMLs), cysts, oncocytomas, and RCCs [46,48]. AMLs are the most common renal lesions, occurring in approximately 75–80% of affected children >10 yr of age [47,48]. RCC has been reported in 1–4% of TSC patients [6,8]. Although the overall incidence of RCC approximates that of the general population, it occurs at a younger age (average age: 28 yr) [47]. TSC-associated RCCs are principally ccRCCs, but chRCCs, pRCCs, and oncocytomas have been reported [47]. Renal manifestations present with neurologic complications, the main causes of morbidity and mortality in TSC patients [46].

3.5.2.   Hereditary hyperparathyroidism- jaw tumour syndrome

Hereditary hyperparathyroidism-jaw tumour syndrome (HPT-JT; OMIM 145001) is a rare inherited autosomal dominant disorder characterised by a predisposition to develop primary hyperparathyroidism, caused by solitary or multiple parathyroid adenomas, or more rarely by parathyroid carcinoma (15% of patients), combined with multiple ossifying jaw fibroma [49,50]. Several renal manifestations associated with HPT-JT have been described (approximately 15% of patients), including polycystic kidneys, renal hamartomas, late-onset Wilms' tumour, renal cortical adenomas, and RCCs [4,49,50]. Benign (adenofibromas, leiomyomas, or adenomyosis) or malignant (adenosarcomas) uterine tumours have been reported in up to 75% of women with HPT-JT [50].

The HPT-JT gene was recently identified on 1q24-32 and corresponds to the cell division cycle protein 73 homolog (CDC73) gene, also called the hyperparathyroidism type 2 (HRPT2) gene, which acts as a TSG [4,50]. CDC73 gene encodes a protein called parafibromin that interacts directly with β-catenin and forms part of the RNA polymerase-associated factor-1 complex, an inhibitor of the c-myc proto-oncogene [51].

3.5.3.   Papillary thyroid carcinoma with associated papillary renal neoplasia

Genetic predisposition to papillary thyroid carcinoma occurs in about 5% of cases [4]. An unusually large three-generation family with familial papillary thyroid carcinoma (FPTC; OMIM 188550) was described in which two affected members had papillary renal neoplasms (PRNs), that is, pRCC and multifocal papillary adenomas, whereas another member had a renal oncocytoma [52]. This FPTC-PRN phenotype (OMIM 605642) is linked to 1q21 [52], indicating a new RCC-associated gene could be responsible for this familial syndrome.

3.5.4.   SDHB-associated hereditary paraganglioma/ phaeochromocytoma

Hereditary paraganglioma/phaeochromocytoma is an autosomal dominant hereditary condition in which affected individuals are at risk for the development of phaeochromocytoma and paraganglioma (extra-adrenal phaeochromocytoma). It is characterised by the germ-line mutation of three of the four subunits of succinate dehydrogenase (SDH) implicated in the Krebs cycle (ie, SDHB, SDHC, and SDHD [53]). Renal tumours, including ccRCCs, chRCCs and oncocytomas, were identified as novel extraparaganglial lesions of SDHB-associated hereditary paraganglioma (OMIM 115310) [53,54]. Like the BHD syndrome, SDHB-associated hereditary paraganglioma could be associated with various histologic subtypes of renal tumour [55]. No corresponding somatic mutation has been found in sporadic RCCs [54,56].

3.5.5.   Constitutional chromosome 3 translocations

Constitutional balanced chromosome 3 translocations (OMIM 603046 and 144700) are a rare cause of hereditary ccRCC. Thirteen different constitutional translocations

with ccRCC susceptibility have been described. In seven cases, translocations were associated with familial disease: t(3;8)(p14;q24), t(2;3)(q35;q21), t(3;6)(q12;q15), t(2;3)(q33;q21), t(1;3)(q32;q13.3), t(3;8)(p13;q24), and t(3;8)(p14;q24.1). The remaining six cases involved translocation-positive individuals who developed ccRCC: t(3;12)(q13.2;q24.1), t(3;6)(p13;q25.1), t(3;4)(p13;p16), t(3;15)(p11;q21), t(3;6)(q22;q16.2), and t(3;4)(q21;q31) [57,58]. Positional cloning has led to identification of a number of additional ccRCC candidate genes: FHIT, TRC8, DIRC1, DIRC2, DIRC3, HSPBAP1, LSAMP, RASSF5 (alias NORE1), KCNIP4, and FBXW7 (alias CDC4) [57,58]. However, several genes that were not implicated in ccRCC pathogenesis have also been identified at break points. In such cases, susceptibility to ccRCC may result from chromosome 3 instability or because translocations have long-range effects on gene expression [57,58]. Thus a "three-hit" model of tumourigenesis has been proposed to explain ccRCC development in some translocation-positive families: (1) occurrence of a germ-line chromosome 3 translocation, (2) nondisjunctional loss of derivative chromosome carrying 3p segment, and (3) somatic mutation in remaining 3p allele of one or more ccRCC-related TSG(s), such as VHL gene [57,58]. Annual renal surveillance should not be routinely offered to chromosome 3 translocation carriers unless there is a personal or family history of ccRCC and/or the translocation break point involves a TSG [57].

3.5.6. Familial clear cell renal cell carcinoma

Familial ccRCC is defined by the development of ccRCC in two or more family members and no evidence of the ccRCC susceptibility syndrome as VHL disease and constitutional chromosome 3 translocations [59,60]. More than 70 families have been reported [4,60]. Usually one family member developed ccRCC between 50 and 70 yr of age as a single tumour. These families may represent evidence of a multigenic inheritance mechanism [4]. For this reason, an extensive recruitment effort is now underway internationally to map cancer-susceptibility genes in familial ccRCC [4,5].

3.6. General comments

3.6.1. When to suspect a hereditary renal cancer syndrome

HRC should be systematically suspected in patients with (1) familial or individual history of renal tumours, (2) bilateral and/or multiple renal tumours, or (3) early-onset renal tumours (<50 yr of age) [4,7,61]. HRC should also be suspected when a patient and/or his or her relatives harbour nonrenal clinical symptoms belonging to any syndromic forms such as fibrofolliculomas or pneumothorax. Patients must then be referred for genetic counselling.

3.6.2. Genetic counselling

Clinical diagnosis can be confirmed by genetic testing in most cases because analysis of the predisposing genes (VHL, MET, FLCN, FH, TSC, SDHB, and CDC73) is now available [4,7,61]. Following complete explanations concerning suspected disease and informed consent, genetic testing is always proposed. Updated information on available genetic testing for inherited disorders can be found on the GeneTest Web site (http://www.ncbi.nlm.nih.gov/sites/GeneTests/). In all cases, a detailed pedigree with family history should be obtained by a genetic practitioner who specialises in genetic predisposition to cancer, with specific attention to relatives with a known history of cancer. A thorough clinical examination should be carried out, focusing on skin, eye, brain, lung, parathyroid, and thyroid abnormalities. Genetic investigation depends on the RCC subtype, and a careful slide review by an experienced uropathologist is fundamental. In patients with ccRCC, VHL analysis is the first step. If negative, it should be followed by karyotyping to look for a potential chromosome 3 translocation. Genetic analysis of SDHB and FLCN genes can also be discussed. Patients with type 1 pRCC should be considered for MET analysis, and those with non–type 1 pRCC or collecting duct carcinoma should have an FH analysis. In patients with a hybrid oncocytic tumour, chRCC, and/or oncocytoma, a genetic analysis of the FLCN gene is indicated. The presence of clinical symptoms related to any of the syndromic forms is also fundamental in choosing the first gene to screen.

Once a specific genetic anomaly has been demonstrated in a proband, genetic testing may be offered to at-risk relatives (presymptomatic diagnosis), and clinical follow-up has to be initiated for carriers of the familial germ-line mutation [4,7]. Because not all syndromes have been characterised genetically, close surveillance is recommended in the proband and relatives when there is clinical suspicion of an HRC syndrome or when a mutation could not be characterised in families [4].

3.6.3. Imaging characterisation and follow-up

Contrast-enhanced CT and MRI are the best imaging techniques for surveillance and assessment of renal lesions, allowing serial monitoring of an individual lesion [61,62]. MRI surveillance may be preferred to avoid the radiation burden of repeat CT examinations in this young patient population [13]. However, there are no established guidelines regarding imaging follow-up. Annual abdominal surveillance examinations would be appropriate in VHL disease [63]. In the remaining HRC syndromes, imaging surveillance can be very distinct, ranging from every 3–6 mo to every 2–3 yr, depending on the size of lesions and the type of syndrome [20,61]. Surveillance could be started at 30–35 yr of age and/or 10 yr before the earlier age of onset of an RCC in a given family.

3.6.4. Principle of treatment

Treatment aims at preserving renal function and controlling the risk for metastasis. RCCs usually acquire metastatic potential when their size reaches >3–7 cm [4]. The standard recommendation is the removal of all lesions in the same kidney once a single solid lesion or the largest solid component of VHL-associated cystic lesions is >3 cm [4,13,64].

Nephron-sparing surgery (NSS) is now the standard method of HRC treatment [64]. It could also be proposed for patients with multifocal tumours >4 cm [64].

Percutaneous image-guided tumour ablations (ie, radio-frequency ablation and cryotherapy) may profoundly modify the therapeutic approach of HRC because they can be repeated as necessary and they better preserve renal function and quality of life than NSS. However, long-term data are lacking [65].

HLRCC is the exception in management because HLRCC-related RCCs are often already metastatic at presentation. Radical surgery is therefore recommended when HLRCC-related RCCs are detected at any size before metastases occur [4,29,61]. Due to limited experience, no formal recommendations regarding surgical approach (NSS or nephrectomy) can be made [29].

4.   Conclusions

HRC involves multiple clinical manifestations, histologic subtypes, genetic alterations, and molecular pathways. Although HRC syndromes are uncommon, their studies have led to a better understanding of sporadic RCC, and insights into their molecular pathways provide rationales for new molecular therapeutic approaches. Consulting urologists should know about HRC syndromes in the interest of patients and their families.

Appendix A. List of abbreviations used in the paper

AML	Angiomyolipoma
BHD	Birt-Hogg-Dubé syndrome
ccRCC	Clear cell renal-cell carcinoma
CDC73	Cell division cycle protein 73 homolog
chRCC	Chromophobe renal-cell carcinoma
CL	Cutaneous leiomyoma
CT	Computed tomography
FH	Fumarate hydratase
FLCN	Folliculin
FPTC	Familial papillary thyroid carcinoma
HIF	Hypoxia inducible factor
HLRCC	Hereditary leiomyomatosis renal-cell carcinoma
HPRC	Hereditary papillary renal-cell carcinoma
HPT-JT	Hereditary hyperparathyroidism-jaw tumour syndrome
HRC	Hereditary renal carcinoma
HRPT2	Hyperparathyroidism type 2
MCUL	Multiple cutaneous and uterine leiomyomatosis
MRI	Magnetic resonance imaging
mTOR	Mammalian Target Of Rapamycin
NSS	Nephron-sparing surgery
OMIM	Online Mendelian Inheritance in Man
pRCC	Papillary renal-cell carcinoma
PRN	Papillary renal neoplasm
RCC	Renal-cell carcinoma
SDH	Succinate dehydrogenase
SDHB	β subunit of succinate dehydrogenase
TSC	Tuberous sclerosis complex
TSG	Tumour suppressor gene
VHL	Von Hippel-Lindau

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