The growing family of hereditary renal cell carcinoma

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Keywords: Birt–Hogg–Dubé (BHD); chromosome 3 translocations; fumarate hydratase; hereditary renal cell carcinoma; MET proto-oncogene; von Hippel–Lindau (VHL)

Introduction

Renal cell carcinoma (RCC) accounts for ~3% of human malignancies and its incidence appears to be rising [1]. RCC is diagnosed in ~150 000 people each year worldwide and 78 000 die from the disease [1]. The main histological subtypes of renal epithelial tumours include clear cell RCC (75%), papillary RCC (10–15%), chromophobe RCC (5%) and oncocytomas (5%) [2]. Complete surgical resection is considered to be curative for localized RCC, but there is no effective treatment for metastatic disease that is already present in 30% of cases at diagnosis [1]. Most cases of RCC are thought to be sporadic; smoking, obesity and occupational exposures are the main known risk factors [1]. Hereditary RCC syndromes are estimated at <3% but have major clinical and scientific implications [3,4]. First, the identification of predisposing genes offers the possibility of genetic testing; surveillance of mutation carriers results in earlier diagnosis and treatment. Secondly, the involvement of the same genes is demonstrated in a number of sporadic RCCs, providing insight into the various mechanisms of renal tumorigenesis [5]. Major progress has been made in


doi:10.1093/ndt/gfh535

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the last decade in recognition of new syndromes and identification of the main predisposing genes. To date, 10 familial syndromes associated with one or more of the various histological types of RCC have been described that are all inherited with an autosomal dominant trait (Table 1) [3,4].

**Familial clear cell RCC**

*Von Hippel–Lindau (VHL) disease (OMIM 193300)*

VHL is the main cause of inherited RCC and represents the model of tumoral angiogenesis [6]. Clinical manifestations include central nervous system (CNS) and retinal haemangioblastomas, clear cell RCC and renal cysts, phaeochromocytomas, neuroendocrine tumours and pancreatic tumours, and pancreatic cysts, and endolymphatic sac tumors [7]. Birth incidence of VHL is ~1/36,000 per year, and RCC affects up to 75% of patients by the age of 60 years. RCC is predominantly multiple and bilateral and occurs at a mean age of 39 years [7,8]. VHL is caused by germline mutations in the *VHL* tumour suppressor gene located on 3p25–26 that is pivotal in the oxygen-sensing pathway [9]. The *VHL* gene product targets for ubiquitylation and proteasomal degradation of the α-subunit of the hypoxia-inducible factor (HIF) that regulates expression of hypoxia-inducible genes such as those for vascular endothelial growth factor (VEGF), platelet-derived growth factor β, erythropoietin and transforming growth factor-α [10,11]. VHL also plays a role in the regulation of cell cycle exit, epithelial cell differentiation, and assembly of the extracellular fibronectin matrix [10]. More than 150 different *VHL* germline mutations have been identified, and genotype–phenotype correlations have led to the recognition of distinct VHL types [3,7,10]. Type 1 is characterized by predisposition to all manifestations except for phaeochromocytoma and is commonly caused by deletions or mutations resulting in truncated protein. Type 2 is associated with a predominant risk of phaeochromocytoma and is mainly associated with missense substitutions: type 2B includes all tumours from the VHL spectrum whereas type 2A is associated with a low risk of RCC and pancreatic tumours. Finally, type 2C predisposes almost exclusively to phaeochromocytoma. Specific germline VHL mutations affecting both alleles were demonstrated recently as the cause of a recessive form of polycythaemia occurring in the Chuvash region of Russia [12].

*Somatic inactivation of the VHL gene by mutation or hypermethylation is found in up to 70% of sporadic clear cell RCCs [3,13].*

**Constitutional chromosome 3 translocations**

Seven balanced translocations involving chromosome 3 have been reported in families with clear cell RCC since the first description of a balanced translocation t(3;8)(p14;q24) in a large family with 10 RCCs...
over four generations. RCCs are mainly multifocal and bilateral [3,14,15]. Both loss of heterozygosity and VHL mutations were identified in tumours from such patients, and a three-step model for the development of RCC was proposed. Inheritance of a germline chromosome 3 balanced translocation would be followed by a non-disjunctional loss of the derivative chromosome that carries the 3p segment, then a somatic inactivation by mutation or hypermethylation of the remaining VHL gene. Other tumour suppressor genes disrupted by translocations breakpoints could also be involved in renal tumorigenesis (FHIT, TRC8, DIRC2, DIRC3, LSAMP and NORE1A) [15–17].

**Familial clear cell renal cell cancer (FCRC)**

FCRC is characterized by the inherited occurrence of clear cell RCC without any other clinical manifestation [3]. A few families have been reported worldwide with 2–5 affected members. Usually the diagnosis of RCC is made relatively late in life (>50 years) and tumours are generally solitary. Patients harbour no VHL germline mutations and linkage to chromosome 3p has been excluded [18,19]. Efforts to recruit families are currently being made in order to map the causal gene(s).

**SDHB-associated heritable paraganglioma** (OMIM 185470 and 605373)

Hereditary multiple paragangliomas are associated with germline mutations in the genes encoding the different subunits of the mitochondrial enzyme succinate dehydrogenase (SDHB, SDHC and SDHD). Three cases of clear cell RCC occurring at a young age have been reported recently in patients with germline mutations in the SDHB gene (located in 1p36) [20]. No corresponding somatic mutation has been found in sporadic RCC.

**Tuberous sclerosis (OMIM 191100)**

Tuberous sclerosis is well known by nephrologists because of multiple renal angiomyolipomas and cysts, but clear cell RCCs are also observed in ~1–2% of cases [21]. Two genes have been mapped to chromosome 9q34 (TSC1) and 16p13.3 (TSC2), respectively, that act as tumour suppressors. TSC1 encodes hamartin and TSC2 encodes tuberin that are critical regulators of cell growth and proliferation and are physically interactive. No corresponding mutation has been found in sporadic RCC.

**Familial papillary RCC**

**Hereditary papillary RCC (HPRC) (OMIM 605074)**

HPRC is characterized by the development of multifocal, bilateral papillary type-1 RCCs (low-grade tumours with basophilic cells and a favourable prognosis) occurring at a late age in ~20% of gene carriers [3]. HPRC is caused by activating missense mutations in the MET proto-oncogene located in 7q31, encoding a receptor tyrosine kinase that is normally activated by hepatocyte growth factor (HGF) [22]. The MET–HGF signalling pathway is important for cell proliferation, epithelial–mesenchymal transitions, branching morphogenesis, differentiation and regulation of cell migration in many tissues. Most of the germline mutations occur within the MET activation loop or in the ATP-binding pocket and cause ligand-independent MET activation. Duplication of chromosome 7 that carries the mutated MET allele provides the second activating event in the renal cells [23]. Somatic mutations of MET are encountered in 13% of sporadic papillary type-1 RCC [22].

**Hereditary leiomyomatosis renal cell cancer (HLRCC) (OMIM 605839)**

HLRCC predisposes to multiple cutaneous and uterine leiomyomas and solitary papillary type 2 RCCs (high-grade tumours with large eosinophilic cells, an aggressive course and a bad prognosis) [3,24]. The disease is caused by germline mutations in the tumour suppressor gene FH located in 1q42–43 that encodes the mitochondrial Krebs cycle enzyme fumarate hydratase [24]. About 40 different FH mutations have been identified and are distributed throughout the entire gene without genotype–phenotype correlation [25]. Somatic mutations of FH are very rarely encountered in sporadic tumours. Biallelic mutations in the FH gene are responsible for fumarase deficiency, a metabolic disease occurring in newborns with gross development delay and death in the first decade [25].

**Hyperparathyroidism–jaw tumour (HPT-JT) (OMIM 145001)**

HPT-JT predisposes to multiple parathyroid adenomas, fibro-osseous tumours of the jaw and a variety of renal lesions including cystic kidney disease, hematomas, mesoblastic nephromas and late-onset Wilms’ tumour. A papillary RCC was described in only one patient. The HRPT2 gene was identified recently on 1q24–32 [26]. It acts as a tumour suppressor gene and encodes a new protein with unknown function, termed parafibromin.

**Papillary thyroid carcinoma with associated renal neoplasia (FPTC-PRN) (OMIM 605642)**

In ~5% of cases, papillary thyroid carcinomas occur in a familial context in association with benign nodular thyroid disease. A large three-generation family has been reported, with two affected members having associated multifocal papillary RCC or adenomas and another member with renal oncocytomas [27]. No mutation in the MET gene was found and linkage analysis mapped the gene to 1q21.
Familial chromophobe RCC and oncocytomas

Birt–Hogg–Dubé syndrome (BHD) (OMIM 135150)

BHD is a genodermatosis that predisposes individuals to benign cutaneous lesions of the face and neck (fibrofolliculomas, trichodiscomas and acrochordons), spontaneous recurrent pneumothorax and/or lung cysts, and renal tumours [3,4]. RCC occurs in 15–30% of gene carriers, with a variable age at diagnosis. Renal tumours display various histological features, including mostly chromophobe and chromophobe–oncocytic hybrid RCCs, but clear cell RCC, oncocytomas and rarely papillary RCCs have also been observed [3,4,28]. Colorectal polyps and tumours are also found in some families [29]. The disease is caused by germline mutations in the BHD gene recently identified on chromosome 17p11.2 [26]. BHD encodes folliculin, a new protein with unknown function. Nearly half of the mutations occur in a mononucleotide tract of cytosines thought to be hypermutable because of slippage in the DNA polymerase during replication [28,29]. BHD somatic mutations are very rare in sporadic RCC but hypermethylation are encountered in ~30% of all RCC histological types [30].

Diagnostic and therapeutic recommendations

It is of great importance that nephrologists be aware of familial RCC syndromes in order to avoid delayed recognition or misdiagnosis, that could result in dramatic complications for patients and their relatives [4,6]. Effective clinical management of patients with an inherited predisposition to RCC requires an early diagnosis of the syndrome, close kidney surveillance and specific treatment of renal tumours, in addition to other potential manifestations specific to each condition.

Most syndromes are associated with distinct clinical and radiological features. Their diagnosis should be systematically suspected in patients with a demonstrable familial or individual disease history [3,4,31]. The clinical diagnosis can be confirmed by genetic testing in most cases as analysis of the main predisposing genes (VHL, MET, BHD and FH) is now available [3]. It is critical also to suspect an inherited syndrome in patients presenting with an apparent sporadic RCC, when the tumour is bilateral and/or multiple, or appears at a young age. In all cases, a detailed pedigree with family history should be obtained and a thorough clinical examination carried out. Genetic investigations depend on the histological type of renal tumour [3]. In patients with clear cell RCC, VHL analysis is the first step and, if negative, should be followed by karyotyping to look for potential chromosome 3 translocation. Patients with papillary type 1 RCC should be considered for MET analysis, and those with papillary type 2 RCC for FH analysis. In patients with chromophobe RCC or oncocytomas, genetic analysis of the BHD gene is indicated. Once a specific genetic anomaly has been demonstrated in the proband, genetic testing may be offered to at-risk relatives and clinical follow-up has to be initiated for carriers of the familial germline mutation [3]. As not all syndromes have been genetically characterized as yet, a close surveillance of the kidneys is recommended in the proband and relatives when there is clinical suspicion of an inherited syndrome.

Nephron-sparing surgery is now the standard method of treatment for patients with inherited RCC who tend to have multiple tumours, often requiring recurrent operations, but nephrectomy may be necessary in the course of the disease or because of the diagnosis of locally advanced RCC [32]. Novel methods aimed to minimize damage to the kidneys with a minimally invasive technique would be an advance over current therapy and a definitive advantage for preservation of renal function. Recently, radiofrequency ablation and cryotherapy that could be of great interest to obviate or delay surgery have been introduced for treating small renal tumours in VHL and HPRC patients. Promising results have been obtained, but close follow-up with imaging studies of treated lesions is imperative and long-term experience is still lacking [33,34].

Future directions

The identification of genes responsible for inherited RCC has resulted in a better understanding of renal tumorigenesis including sporadic RCC and is paving the way for new therapeutic approaches [3,4]. For VHL, recent and ongoing insights into the functions of the VHL gene, especially the HIF-ubiquitylation pathway, provide an attractive molecular basis for the development of specific inhibitors of HIF and/or its downstream targets [10]. Drugs are in development that could represent major advances in the treatment of VHL disease, as well as of clear cell sporadic RCC in which the hypoxia pathway is activated. A successful trial using anti-VEGF antibody (bevacizumab) in metastatic sporadic RCC has been reported recently [36]. In VHL itself, preliminary studies with the VEGF receptor inhibitor SU5416 led to interesting results, and new protein kinase receptor inhibitors are emerging [35]. In HPRC, MET inhibitors gave encouraging results in in vitro studies, but no clinical trial has been presented to date [37].

Therapeutic gene replacement is a future challenge for syndromes that involve an inactivated tumour suppressor gene such as VHL, BHD or FH, but this approach does not appear to be clinically applicable in the foreseeable future [3]. The development of animal models should be of great interest in this perspective, but to date the available Vhl-knockout mouse models develop no renal cancer and a mouse model in which the gene is specifically inactivated in the proximal tubule of the kidney remains to be developed [3,38]. In contrast, two spontaneous animal models of BHD that look promising were reported recently with specific germline mutations in the BHD
autologous genes, resulting in hereditary renal tumours (the Nihon rat RCC model and a strain of German shepherd dog) [39,40].

Acknowledgements. We thank Professor Jean-François Foncin and Dr Guy Allègre for help in preparing this manuscript. This was supported by grants from the Comité du cher de la ligue Nationale contre le Cancer.

Conflict of interest statement. None declared.

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