

REVIEW ARTICLE

Familial adult renal neoplasia

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Our understanding of the molecular mechanisms underlying the tumorigenesis of renal cell carcinoma (RCC) has partially come from studies of RCC related familial cancer syndromes such as von Hippel-Lindau (VHL) disease and hereditary papillary RCC (HPRC). These studies have led to the identification of RCC related genes, which, besides allowing accurate diagnosis of these diseases, have been found mutated or abnormally expressed in the sporadic counterparts of these familial renal tumours. To date, a number of renal tumour related syndromes have been described. We review recent advances in this field and discuss a genetic approach to managing familial cases of renal tumours occasionally encountered by cancer geneticists and urologists.

Adult renal tumours are known to have different histological types, with distinct genetic profiles.¹ The most well known, perhaps, is the inactivation of the *VHL* (von Hippel-Lindau disease) gene, which is specific for clear cell renal cell carcinoma (CCRCC) in both VHL disease and sporadic cases. However, not all sporadic CCRCC have alterations in the *VHL* gene and there are known families with CCRCC that are not associated with the *VHL* gene, thus pointing to the existence of other CCRCC related genes.^{2,3} Similarly, the *MET* gene in chromosome 7q has been found to be involved in hereditary papillary RCC (HPRC) and only a small subset of sporadic papillary RCC (PRCC). In addition, PRCC has also been described in other distinct familial cancer syndromes, which are not mapped to 7q, suggesting the existence of multiple PRCC related genes. Here, we review recent advances in the field of familial adult renal neoplasia (table 1) and formulate a management plan (fig 1) in dealing with these cases.

VON HIPPEL-LINDAU DISEASE (VHL)

VHL (OMIM 193300) is an autosomal dominant disease characterised by retinal haemangioma, CCRCC, cerebellar and spinal haemangioblastoma, phaeochromocytoma, endocrine pancreatic tumours, and epididymal cystadenoma.⁴ The *VHL* gene was isolated from chromosome 3p25⁵ and has characteristics of a tumour suppressor gene, that is, loss of function in both copies of the gene in CCRCC. The inactivation of the *VHL* gene, in the form of either mutation, loss of heterozygosity (LOH), or hypermethylation, has been frequently found in sporadic CCRCC but not in PRCC.^{6–8}

The VHL protein associates with the elongin B and C and Cul2 proteins to form a ubiquitin-ligase complex which is involved in the ubiquitination of hypoxia induced factor (HIF)-1 α .^{9–11} In the presence of mutated VHL protein, HIF-1 α accumulates and increases its transcriptional activity resulting in overexpression of angiogenic peptides like vascular endothelial growth factor,¹² resulting in the hypervascularised state of the majority of VHL related tumours.

Genotype-phenotype correlation in VHL disease has resulted in subdivisions of the disease. Type 1 VHL is characterised by predisposition to classical VHL related lesions apart from phaeochromocytomas. Type 2A involves all VHL features except for RCC and type 2B has all VHL features. Type 2C is characterised by isolated phaeochromocytoma. Genetically, type 1 is more commonly caused by deletions or nonsense mutations, whereas type 2 is more commonly caused by missense point mutations.¹³ In addition, evidence for the existence of VHL modifier genes has been reported¹⁴ and the identification of these genes may further explain the underlying molecular mechanisms of these clinical subtypes.

FAMILIAL NON-VHL CCRCC WITH CHROMOSOME 3 TRANSLOCATION

A well known familial CCRCC was described over 20 years ago.¹⁵ The interesting feature about this family was its association with a balanced translocation, t(3;8)(p14;q24), suggesting that a RCC related gene must be located in chromosome 3p14. Today, both breakpoint genes have been isolated.^{16,17} The 3p14 breakpoint gene, which is named *FHIT* (for fragile histidine triad), has been found altered in a number of cancers but surprisingly not in sporadic RCC. While its role in RCC remains controversial, a different concept has emerged based on the findings of *VHL* mutations and loss of heterozygosity in the tumours of this particular family. This so called three step process involves the initial constitutional translocation followed by somatic loss of chromosome 3 and *VHL* mutations.¹⁸ The mechanism underlying the sequence of these events is not known. To date,

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Abbreviations: RCC, renal cell carcinoma; VHL, von Hippel-Lindau disease; HPRC, hereditary papillary renal cell carcinoma; PRCC, sporadic papillary renal cell carcinoma; CCRCC, clear cell renal cell carcinoma; LOH, loss of heterozygosity; HPT-JT, hyperparathyroidism-jaw tumour; TSC, tuberous sclerosis complex; BHD, Birt-Hogg-Dubé syndrome; HLRCC, hereditary leiomyomatosis and renal cell cancer; FPTC-PRN, familial papillary thyroid carcinoma-papillary renal neoplasia; FO, familial oncocytoma; HNPCC, hereditary non-polyposis colorectal cancer

Table 1 Familial adult renal neoplasia

Disease	Molecular genetics		Clinical features	
	Gene location/translocation	Gene	Main lesions	Other associated lesions
Von Hippel-Lindau disease (VHL)	3p25	<i>VHL</i>	Retinal haemangioma, CCRCC, cerebellar haemangioblastoma, pheochromocytoma	Endocrine pancreatic tumours, epididymal cystadenoma
Familial non-VHL CCRCC with chromosome 3 translocation	3p14 3q13.3 3q21	<i>FHIT</i> Unknown Unknown	CCRCC	Thyroid cancer, bladder cancer, pancreatic cancer, gastric cancer
Familial non-VHL CCRCC without chromosome 3 translocation	Unknown	Unknown	CCRCC	
Hereditary papillary RCC (HPRC)	7q34	<i>c-MET</i>	PRCC (type 1)	Breast cancer, pancreatic cancer, biliary tract cancer, lung cancer, malignant melanoma
Hyperparathyroidism-jaw tumour (HPT-JT)	1q21-q32	Unknown	Parathyroid adenoma/carcinoma, ossifying jaw tumours	Renal cysts, renal hamartoma, adult Wilms tumours, PRCC (type 1)
Tuberous sclerosis complex (TSC)	9q34 16p13.3	<i>TSC1</i> <i>TSC2</i>	Renal angiomyolipoma, rhabdomyoma	CCRCC
Birt-Hogg-Dube syndrome (BHD)	17p12-q11.2	Unknown	Multiple fibrofolliculoma trichodiscoma, renal oncocytoma, chromophobe RCC	PRCC (type 1), CCRCC, multiple lipoma, pulmonary cysts
Hereditary leiomyomatosis and renal cell cancer (HLRCC)	1q42-q44	Unknown	Uterine leiomyoma, PRCC (type 2)	Uterine leiomyosarcoma, skin leiomyoma, breast cancer, bladder cancer
Familial papillary thyroid carcinoma-papillary renal neoplasia (FPTC-PRN)	1q21	Unknown	Papillary thyroid carcinoma	PRCC (type 1), papillary renal adenoma, renal oncocytoma
Familial oncocytoma (FO)	Unknown	Unknown	Renal oncocytoma, renal cyst	
Hereditary non-polyposis colorectal cancer (HNPCC)	2p22-p21 3p22-p21 2q31-q33 7p22 2p16	<i>hMSH2</i> <i>hMLH1</i> <i>hPMS1</i> <i>hPMS2</i> <i>hMSH6</i>	Colorectal cancer, endometrial cancer	Gastric cancer, ovarian cancer, hepatobiliary cancer, renal pelvic and ureteral cancer (transitional cell), small intestine cancer

two other CCRCC families have been reported but both were associated with distinct constitutional chromosome 3q (instead of 3p) translocations.^{19, 20} Again, both the loss of chromosome 3 and *VHL* mutations were identified in the tumours of these two families. Although at a much lower frequency, other malignancies have also been found in all these families, including thyroid cancer, bladder cancer, pancreatic cancer, and gastric cancer. To date, germline translocations involving distinct chromosome 3 breakpoints have been reported in four multiple RCC families and in three RCC patients without a family history,²⁰ making chromosome 3 translocations a risk factor for RCC.²¹ It will be interesting to isolate all these breakpoint genes to see if they share any homology to the *FHIT* gene and have any direct functional roles in CCRCC.

FAMILIAL, NON-VHL CCRCC WITHOUT CHROMOSOME 3 TRANSLOCATION

In 1997, two families with hereditary CCRCC not genetically associated with VHL were reported.² In both families, a total of nine affected cases were found and the pattern of transmission appeared to be autosomal dominant. No cytogenetic abnormality was detected. Mutation analysis including direct sequencing of the *VHL* gene and Southern blotting did not show any mutation and *VHL* was excluded by linkage analysis. There are two unique features regarding these two families as compared with VHL. The first is its relatively late onset of disease with eight of the nine affected being over the age of 50. Furthermore, no tumour was found on radiological screening

in >20 at risk members who are below the age of 40. The second is that the tumours are usually unilateral and solitary in contrast with other familial renal carcinomas, which are usually bilateral and multifocal. To date, more families with non-VHL CCRCC without chromosome 3 translocations have been identified.^{3, 22} It remains unclear if these isolated CCRCC families represent a single entity or a group of heterogeneous disease. Work is currently continuing to dissect the genetic basis of these families.

HEREDITARY PAPILLARY RCC (HPRC)

Papillary RCC is further divided into two types.^{23, 24} Type 1 is a basophilic tumour characterised by papillae and tubular structures covered by cells with scanty cytoplasm, small oval nuclei, foamy macrophages in papillary cores, and frequent psammoma bodies. Type 2 is an eosinophilic tumour consisting of papillae covered by large cells with abundant eosinophilic cytoplasm and large nuclei with prominent nucleoli. Type 1 PRCC has been found to behave less aggressively than type 2 PRCC.²⁵

HPRC (OMIM 605074) is a familial cancer syndrome characterised predominantly by type 1 PRCC, although tumours in the breast, pancreas, lung, skin, and stomach have been described.²⁶⁻²⁸ The syndrome is associated with activating mutations of *c-MET* proto-oncogene on 7q34.²⁷ The *c-MET* gene encodes the receptor for hepatocyte growth factor/scatter factor (HGF/SF) and is a 190 kDa heterodimeric membrane spanning tyrosine kinase that is involved in a wide range of

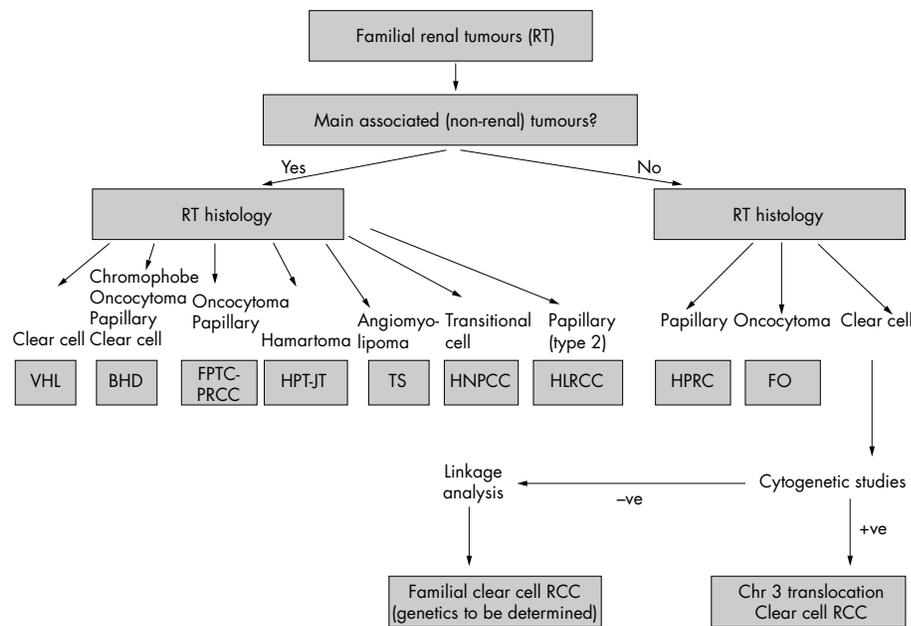


Figure 1 Genetic approach to familial adult renal neoplasia.

cancer related activities, such as angiogenesis, cellular motility, growth, invasion, and morphogenic differentiation. Upregulation of *c-MET* as a consequence of its activating mutations can promote these events.²⁹ The renal tumours of HPRC commonly show trisomy 7 and two of these chromosome copies harbour the *c-MET* mutants, suggesting that the duplication is a non-random event and may represent a two hit activation that is important in their tumorigenesis.³⁰

FAMILIAL RENAL HAMARTOMAS ASSOCIATED WITH HYPERPARATHYROIDISM-JAW TUMOUR (HPT-JT) SYNDROME

HPT-JT (OMIM 145001) is an autosomal dominant disease characterised by primary hyperparathyroidism (parathyroid adenoma or carcinoma) and ossifying fibroma of the jaw.^{31 32} The *HPT-JT* gene is mapped to chromosome 1q21-q32. Recently, we described a HPT-JT family with four cases of renal hamartomas, which were characterised by three components, the mesenchymal, blastemic, and epithelial.³² No haemorrhage or necrosis was found and the number of mitoses was small with a low index of proliferation. The family is also mapped to 1q21-q32 and, in addition, the renal hamartomas showed loss of wild type alleles of 1q suggesting that the *HPT-JT* gene is likely to be a tumour suppressor gene. In addition, renal cysts are a common finding in HPT-JT and in some cases they have been clinically diagnosed as polycystic kidney disease. More recently, in a large HPT-JT family, a case of bilateral type 1 PRCC was found in a gene carrier.³³ Cloning efforts are currently continuing to isolate the gene, which may play a role in a whole spectrum of renal tumorigenesis.

TUBEROUS SCLEROSIS COMPLEX (TSC)

TSC (OMIM 191100) is an autosomal dominant disease involving multiple tissues and organs.³⁴ The patients present with dermatological lesions such as facial angiofibromas (adenoma sebaceum), periungual fibromas, shagreen patches, and hypopigmented macules. Seizures and learning difficulties are also common features. The patients also present with multiple renal angiomyolipomas, which are macroscopically yellow and grey in colour, and microscopically characterised by clusters of adipocytes, sheets of smooth muscle, and blood vessels. To date, several cases of multifocal CCRCC have also been described.^{35 36}

Two TSC genes, *TSC1* and *TSC2*, have been mapped to chromosomes 9q34³⁷ and 16p13.3 respectively.³⁸ *TSC1* encodes a protein of 130 kDa called hamartin, which is involved in cell adhesion through the ezrin-radixin-moesin (ERNM) family of actin binding proteins and the GTPase Rho.³⁹ The *TSC2* gene encodes a protein product called tuberlin, which functions as a GTPase activating protein for Rap1, a member of the superfamily of Ras-related proteins.⁴⁰ Its inhibition induces quiescent cells to enter S phase in the cell cycle.⁴¹ Several studies have shown that both proteins are physically interactive and therefore possibly involved in the same physiological pathways.

BIRT-HOGG-DUBÉ SYNDROME (BHD)

BHD (OMIM 135150) is an autosomal dominant syndrome involving multiple organ systems, although classically characterised by a triad of cutaneous lesions including multiple fibrofolliculomas, trichodiscomas, and acrochordons.⁴² The trichodiscomas and fibrofolliculomas typically appear as multiple, small, dome shaped, yellowish or skin coloured papules, scattered over the face, neck, scalp, and upper trunk. The third component, acrochordons, is less specific and there are BHD patients who have fibrofolliculomas and trichodiscomas but not acrochordons.⁴³⁻⁴⁶ The second most commonly associated tumour type is renal tumour, which varies in histological features. To date, oncocytomas and chromophobe RCC are the most frequently described, but papillary and CCRCC have also been reported.⁴⁷⁻⁴⁹ Renal cysts are also a common finding.⁴⁹ In addition, the syndrome has been associated with colonic neoplasms,^{50 51} multiple lipoma, and lung diseases such as spontaneous pneumothorax,⁵² bronchiectasis, and bronchospasm.⁴⁶ The *BHD* gene has been mapped to chromosome 17p12-q11.2 but has yet to be cloned.⁴⁹ Whether it acts as an oncogene or a tumour suppressor gene is not known, but judging by the spectrum of renal tumours that are associated with BHD, it may play an important role in the differentiation process of renal cells.

HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER (HLRCC)

Very recently, a new syndrome with predisposition to uterine leiomyomas and PRCC was described (OMIM 605839).⁵³ In a large Finnish family, 11 members were found to have uterine leiomyoma and two had uterine leiomyosarcoma. In addition, four cases of unilateral solitary type 2 PRCC were found. The

patients were female (aged between 33 and 48) and had distant metastasis at the time of diagnosis. Other tumours found in this family included skin leiomyomas, breast cancers, and bladder cancers. The gene was mapped to chromosome 1q42-q44 which is distal and separate from the HPT-JT locus. Although a case of bilateral PRCC has also been described in the HPT-JT syndrome,³³ the tumours are type 1 PRCC in contrast to the type 2 PRCC found in this new syndrome. The cloning of the *HLRCC* gene will certainly contribute to the repertoire of molecular signatures for RCC.

FAMILIAL PAPILLARY THYROID CARCINOMA-PAPILLARY RENAL NEOPLASIA (FPTC-PRN)

Malchoff *et al*⁵⁴ recently described a multigenerational family with five cases of papillary thyroid carcinoma (PTC) and two cases of papillary neoplasia (OMIM 605642). One patient had both PTC and papillary RCC while the other had a multifocal papillary renal adenoma. One patient who is a gene carrier had an 8 cm renal oncocytoma. Linkage analysis in this family mapped the gene to 1q21. Interestingly, a case of bilateral papillary RCC has also been described in HPT-JT syndrome (see above), which was also mapped to this region. Again, it will be interesting to examine the role of the gene, once it is identified, in renal tumorigenesis.

FAMILIAL ONCOCYTOMA (FO)

Renal oncocytoma is usually a benign entity composed of acinar arranged, large eosinophilic cells and is considered to have a different genetic background from CCRCC.⁵⁵ It accounts for about 5% of all renal tumours⁵⁶ and a number of families with hereditary renal oncocytoma have been described,⁵⁷ but a number of them have been subsequently found to have Birt-Hogg-Dubé syndrome (see above). A patient with bilateral multiple renal oncocytomas and cysts associated with a constitutional reciprocal translocation (8;9)(q24.1;q34.3) has been reported.⁵⁸ Whether the breakpoints are causally linked to renal oncocytoma has yet to be established.

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC)

HNPCC (OMIM 114500) is an autosomal dominant disease mainly characterised by cancers of the colon and endometrium. It is also associated with an increased incidence of cancers in other organ systems including stomach, ovary, small intestine, and hepatobiliary and urinary tracts. Typically, the renal neoplasia involved are transitional cell carcinomas of the renal pelvis and ureter. The syndrome is associated with germline mutation in one of the DNA mismatch repair genes (for example, *hMSH2*, *hMLH1*, *hPMS1*, *hPMS2*, *hMSH6*) and the tumours show a hypermutable feature called microsatellite instability.⁵⁹ The latter results from the defective functions of DNA mismatch repair genes that subject the affected cells to mutations in other cancer related genes, therefore speeding up the multistep process of tumorigenesis.⁶⁰

GENETIC APPROACH TO FAMILIAL ADULT RENAL NEOPLASIA

A flow chart of our proposed approach is shown in fig 1. Besides establishing the heredity of the tumours by family history, it is equally important to establish the associated clinical features including other type of tumours in the family and the exact histology of the renal tumours. Some of the syndromes have very distinct associated features, such as the angiomas and phaeochromocytomas in VHL. If these tumours are found together with CCRCC, genetic testing for VHL should be initiated. On the other hand, the histology of PRCC should straightaway divert the clinician from VHL. If type 1 PRCC is found, it should be considered for *MET* mutation

analysis. For type 2 PRCC, the new syndrome of hereditary leiomyomatosis and RCC should be considered and therefore further radiological investigations for uterine leiomyoma and skin examination are indicated. Genetic testing using linkage analysis of chromosome 1q markers can also be performed if the family has a number of affected cases. In the case of familial CCRCC without the classical VHL related features, the first genetic test should be cytogenetic studies to look for chromosome 3 translocations. Those families without chromosome 3 translocation most likely represent new genetic entities and should be further investigated by linkage analysis. Undoubtedly, with time, more familial renal tumours will be characterised better both clinically and genetically.

Besides the hereditary cases, the patients with bilateral tumours should also be taken into consideration because they are more likely to have underlying genetic defects. Even in the absence of family history, these patients may carry "de novo" mutations representing the "first mutants" of a syndrome. Therefore they should be assessed and followed up.

CONCLUSION

The integration of clinical and pathological information, coupled with relevant genetic tests, will lead clinicians to the right diagnosis and better management in familial adult renal neoplasia. The identification of genes responsible for familial renal tumours will result in better understanding of renal tumorigenesis, not only in familial settings but also in the commoner non-familial setting. These insights may improve our management of the disease and lead to novel therapeutic agents.

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