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Hereditary Renal Cancer Syndromes

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Abstract

Inherited susceptibility to kidney cancer is a fascinating and complex topic. Our knowledge about types of genetic syndromes associated with an increased risk of disease is continually expanding. Currently, there are 10 syndromes associated with an increased risk of all types of renal cancer, which are reviewed herein. Clear cell renal cancer is associated with von Hippel Lindau disease, chromosome 3 translocations, PTEN hamartomatous syndrome and mutations in *BAP1*, as well as several of the genes encoding the proteins comprising the succinate dehydrogenase complex (*SDHB*/*C*/*D*). Type 1 papillary renal cancers arise in conjunction with germline mutations in *MET* and type 2 as part of Hereditary Leiomyomatosis and Renal Cell Cancer (*FH* mutations). Chromophone and oncocytic renal cancers are predominantly associated with Birt Hogg Dubé syndrome. Angiomyolipomas are commonly and their malignant counterpart epitheliod angiomyolipomas rarely are found in patients with Tuberous Sclerosis Complex. The targeted therapeutic options for the renal cancer associated with these diseases are just starting to expand, and are an area of active clinical research.

Keywords

von Hippel Lindau disease; Birt Hogg Dube; kidney cancer; genetic susceptibility; genetic disease

Introduction

Hereditary kidney cancer accounts for 3 to 5% of all kidney cancer; however this number is likely an underestimate. Currently, ten inherited cancer susceptibility syndromes are associated with inherited risk of kidney cancer and 12 genes have been identified (Table 1). The number of families with identified hereditary conditions leading to kidney cancer continues to increase. The description of families with inherited syndromes associated with an increased risk kidney cancer has and will lead to the discovery of mutated gene critical to the pathogenesis of kidney cancers. Patients with these inherited syndromes develop kidney cancer at an earlier age; furthermore the lesions can be multifocal, bilateral and

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heterogeneous. Herein, we describe the most prevalent of these syndromes. Many of the gene identified through the study of familial renal cancer have also proven to be important in sporadic rneal cancers with von Hippel Lindau disease (VHL) being the exemplar of this paradigm. The recent Cancer Genome Atlas and other massively parallel sequencing studies will no doubt raise our awareness of other processes important to causality and aggressive behavior, related to the inherited genetics of kidney cancer.

von Hippel Lindau (vHL) Disease

Patients with this autosomal dominant cancer susceptibility syndrome can present with a wide spectrum of hemangioblastomas of the brain, spine and retina, pancreatic and renal cysts and neuroendocrine tumors, endolympatic sac tumors and pheochromocytomas. Some but not all patients develop clear cell renal cancer presenting as bilateral and sometimes hundreds of lesions within the kidney.

The first patients with this syndrome were described in 1860 and it recognized as a familial by Von Hippel some thirty years later; Lindau recognized that the retinal lesions were part of a larger heritable syndrome that affected the central nervous system.[1,2] In 1993, the (loss of) gene responsible for these families and von Hippel-Lindau disease (vHL), *VHL*, was found through the study of multiple case families to be located at 3p25–26.[3–6]

In vHL disease, there is significant variation in phenotype, which had been observed prior to gene identification.[7] Subsequent to the identification of the vHL gene, a strong genotype-phenotype correlation was seen with mutational type predictive of disease.[8] Patients with type 1 mutations (in general, truncating mutations) have a decreased incidence of pheochromocytoma as compared to those with type 2 mutations (in general, missense mutations).[9–12] Families with type 2 mutations have either a high (type 2A) or low risk of ccRCC (type 2B); type 2C families only develop pheochromocytoma. Type 2A disease is associated with the “Black Forest’ founder mutation (Tyr98His) originating from southwestern Germany, which is commonly found in the ‘Pennsylvania Dutch’ population.[13]

vHL occurs in all ethnic groups at a rate of 1 in 35,000 people.[14] Ninety percent of people with vHL will manifest disease findings by age 65.[15] Genetic testing for mutations in *VHL*, which includes screening for point mutations as well as large deletions, detects nearly 100% of individuals with vHL disease.[16] Twenty to twenty-five percent of patients are the first person in their families to develop vHL disease. There have been several case reports of mosaicism for a *VHL* mutation identified in parents when children were diagnosed with vHL.[17,18] Gondal mosaicism, which more than one children have vHL, without either parent being affected also has been observed (Nathanson, unpublished).

The *VHL* gene is a classic tumor suppressor and loss of the wild type allele is found in hemangioblastomas, pancreatic neuroendocrine tumors, renal cysts and clear cell renal cancer from patients with vHL.[19–22] The wild type allele of *VHL* is lost consistently in renal cysts in vHL pateints, suggesting that loss of that allele is an important initiating event in tumorigenesis.[22] pVHL (VHL protein) contains two functional domains, the α- and β-domain, which are involved in binding to elongin C and pVHL substrates, respectively.[23–26] *VHL* encodes an E3 ligase the major substrate of which are the hypoxia-inducible factors (HIFs), transcription factors that regulate a broad program of hypoxia-responsive genes including vascular endothelial growth factor (VEGF).[27] Inactivation of *VHL* results in up-regulation of hypoxia inducible factor (HIF)-1α and -2α, which drive angiogenesis and proliferation, and in addition, have profound effects on energy metabolism.[28] *VHL* is mutated not only in inherited ccRCC, but also in most sporadic ccRCCs with both copies

lost in 86% and genetic or epigenetic changes found in 96%.[29] Studies by our group at Penn further identified two subgroups of VHL-inactivated clear cell cancers, one with a HIF-1α and -2α driven genotype, and another with a HIF-2α dominant genotype.[30,31] The HIF-2α genotype is associated with a c-myc-driven metabolic pathway and upregulation of DNA damage response, specifically double strand break repair. Discovery and characterization of the VHL pathway has been critical to the development of drug therapies for sporadic clear cell renal carcinoma.

Frameshift and nonsense mutations in *VHL* are associated with a high penetrance of clear cell renal cancer, with risk at age 50 of 70%.[9] Full and partial gene deletions of *VHL* confer a lower risk, at age 50 of 40%. As discussed above, type 2A missense mutations also confer a high risk of renal cancer, whereas other missense mutations, types 2B and 2C, do not appear to be associated with renal cancer.[32] Type 2B mutations have been characterized as 'deep missense' mutations, meaning they are buried within the core of the protein when it is normally folded.[33] Type 2B mutations impair binding of Elongin C to pVHL, while 2A do not impair binding but are within the HIF-binding site (β-domain).[34] Knauth et al. showed that *VHL* 2A mutations had higher stability and higher ubiquitin ligase activity in respect to HIF1α, as compared to 2B mutations.[35] Li et al. demonstrated that 2A mutations retain their ability to regulate HIF1α and HIF2α.[33] In contrast, 2A mutations have associated with the retention of HIF2α activity and increased growth in contrast to 2B mutations. These data implicate a biological difference accounting for the variability risk of renal cancer associated with different types of renal cancer.

Treatment of vHL

Increased awareness of this disease has led to earlier diagnosis and intervention. Familial genetic screening, routine imaging, and an aggressive surgical approach to kidney tumors in early stage disease can help prolong quality of life with low morbidity. As these patients present with multifocal disease at an early age and the tumors vary in aggressiveness, every effort should be made to preserve renal function through nephron sparing approaches (partial nephrectomy, thermal ablative therapies, or observation) in these patients with disease limited to the kidneys. However, in patients with locally advanced disease, the likelihood of recurrent disease and end-stage renal disease is much higher, and thus bilateral resection of the kidneys followed by renal transplantation is a more accepted approach.[36] In contemporary series, 85–90% of vHL patients now are diagnosed with renal masses less than 6 cm, and only 11% of patients have progressed to distant metastases.[37] Given the low reported rate of metastasis among patient with sporadic renal cortical neoplasms less than three cm in size, investigators have adopted a policy of initial observation for tumors less than 3 cm in size and immediate intervention for lesions greater than 3 cm in vHL patients. Over a follow-up of 5 years, Walther et al. reported no evidence of metastatic disease progression and no need for renal transplantation or dialysis among 52 patients with tumors less than 3 cm at diagnosis. In contrast, distant metastases developed in 11 of 44 patients (25%) with lesions greater than 3 cm in size, including 3 of 27 patients (11%) with lesions between 3 and 6 cm.[37] In an update of this series, Duffey et al. confirmed the safety of this approach.[38] Over a median follow-up of 41 months, all 108 patients with lesions less than 3 cm remained free of distant metastases, all avoided renal transplantation and dialysis, 37 (34%) remained on observation without intervention and 104 (96%) retained both kidneys. Of the 71 patients (66%) that required intervention for interval growth of lesions > 3 cm, an average of 1.7 procedures per patient was performed and 97% of these were nephron-sparing (partial nephrectomy or percutaneous ablative procedures). In contrast, of the 63 patients with lesions greater than 3 cm who underwent treatment for renal tumors, a nephron-sparing approach was successfully employed in only 68% of instances and only 34 patients (54%) retained both kidneys at their last follow-up.

Clinical trials in VHL mutant disease

The studies of *VHL* mutational status as a prognostic marker in advanced sporadic RCC have been inconsistent. Choueiri et al. examined *VHL* status as a predictive biomarker in 123 patients treated with a variety of VEGF-inhibitors suggested that loss of function mutations in *VHL* were associated with treatment response.[39] There are ongoing clinical trials using the current VEGF-tyrosine kinase inhibitors specifically in patients with vHL (http://www.clinicaltrials.gov). As these patients often have hemangioblastomas in extra-renal sites, the goals of these therapies are to control malignant disease but also to temper symptoms from hemangioblastomas. Thus the dose of agent and the duration of therapy as well as tolerability are important issues.

Other trials specific to *VHL* mutation in sporadic clear cell RCC are ongoing. Recently, a pilot study was conducted testing the feasibility of vaccinating advanced RCC patients with the corresponding mutant VHL peptides.[40] A mutant VHL peptide vaccine was administered to six patients with *VHL* mutant RCC. Four out of five evaluable patients (80%) generated specific immune responses against the corresponding mutant VHL peptides. The vaccine was well tolerated. No grade III or IV toxicities occurred. The median overall survival (OS) and median progression-free survival (PFS) were 30.5 and 6.5 months, respectively.

Additionally, since the *VHL* gene is functionally lost through hypermethylation in up to 19% of sporadic ccRCC cases, re-expressing VHL silenced by methylation in ccRCC cells, using a hypo-methylating agent, may be an approach to treatment in patients with this type of cancer. A pilot experiment was conducted in mouse xenografts using two hypo-methylating agents to re-express VHL in cell culture and in mice bearing human ccRCC and evaluate the effects of re-expressed VHL in these models.[41] Real-time reverse transcription-PCR was used to evaluate the ability of zebularine and 5-aza-2′-deoxycytidine (5-aza-dCyd) to re-express VHL in four ccRCC cell lines with documented VHL gene silencing through hypermethylation as well as in vHL methylated ccRCC xenografted tumors. 5-Aza-dCyd was able to re-express VHL in our cell lines both in culture and in xenografted murine tumors. Well described phenotypic changes of VHL expression including decreased invasiveness into Matrigel, and decreased vascular endothelial growth factor and glucose transporter-1 expression were observed in the treated lines. VHL methylated ccRCC xenografted tumors were significantly reduced in size in mice treated with 5-aza-dCyd. Mice bearing nonmethylated but *VHL*-mutated tumors showed no tumor shrinkage with 5-aza-dCyd treatment.

Hereditary papillary renal cancer

Hereditary papillary renal cell carcinoma (type 1 papillary)

Hereditary papillary renal cell carcinoma (HPRCC) is an autosomal dominant syndrome characterized by multifocal, bilateral type I papillary renal cell carcinomas.[42,43] Mutations of the *MET* gene on 7q31 have been causally associated with HPRCC,[44–48] but *MET* is mutated in less than 10% of sporadic type papillary renal cancers. Families with inherited mutations in *MET* leading to multi-focal papillary renal cancer (type 1) are quite rare, much more so than vHL, and most of the other described inherited renal cancer syndromes, including HLRCC and BHD.

Hereditary leiomyomatosis and renal cell cancer (type 2 papillary)

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is an autosomal cancer susceptibility syndrome characterized by the development of cutaneous and uterine leiomyomas and renal cancer.[49,50] Papillary type 2 renal cancer is the pathological type most commonly associated with HLRCC, and tends to have an early age of onset, be high grade

and have an aggressive course.[51] The mean age of renal cancer diagnosis is 40, but metastatic renal cancer can present in the teens. Other types of renal cancers also can occur, including collecting duct and clear cell cancers.[50,52,53] Independent of underlying architecture, cells in the renal cancers associated with HLRCC have a characteristic pathological appearance with large nuclei with inclusion-like orangiophilic or eosinophilic nucleoi surrounded by a clear halo, which can be recognized by knowledgeable pathologists.[51]

The gene fumarate hydratase (*FH*), which encodes the enzyme which converts fumarate to malate in the Kreb's cycle, is mutated in HLRCC.[53,54] All types of point mutations have been reported, with missense mutations by far the most predominant (57%; 191/337) in the *FH* mutation database (http://chromium.liacs.nl/lovd_sdh/home.php?select_db=FH).[55] The lower fumarate hydratase enzymatic activity found in affected patients has been proposed as a method for screening of family members, however genetic testing remains a more efficient method to detect affected individuals.[56]

Intrafamilial heterogeneity has been observed in multiple cases, despite similar decreases in FH activity.[57] The penetrance for the complete phenotypic manifestations of HLRCC has yet to be fully defined, although similarly to many cancer susceptibility syndromes, as more families are tested, individuals with mutations but no manifestations of disease have been identified. No modifiers of penetrance have yet been identified.[58]

The mutated FH gene behaves as a tumor suppressor gene, as loss of the wild type allele is observed in renal cancer from individuals with *FH* mutations. Patients with biallelic mutations (homozygous or compound heterozygotes) develop Fumarate Hydratase Deficiency (FHD) characterized by fumaric aciduria, progressive encephalopathy, hypotonia, failure to thrive and seizures.[59–62] These patients usually do not survive beyond the first few months of life, although some more mildly affected individuals have been described.[63,64] Relatives with only one mutation, can go on to develop papillary type 2 renal cancer. Mutations have not been observed in sporadic RCC, but in part the lack of observation may arise due to the limited number of papillary type 2 tumors included in the screening series.[57]

In renal cancers with fumarate hydratase mutations, HIF accumulation increases when high levels of fumarate inhibit the HIF proline hydoxylases and increased transcription of downstream targets.[65] The perturbation of metabolic intermediates has the potential to alter function of several other 2-oxoglutarate-dependent enzymes including a family of histone-regulating demethylases that have in common a jumonji-C domain, several of which have been linked to kidney cancer. This metabolic-epigenetic link is of high interest, given the newly recognized epigenetic findings in renal cell carcinoma. Two studies have demonstrated that FH loss results on activation of Nrf2-dependent activation of antioxidant pathways.[66,67] NRF2, a transcription factor, is a key regulator of the antioxidant response, with multiple target genes that contain NRF2 response elements.[68] Cellular levels of NRF2 are regulated by KEAP1 (Kelch-like ECH-associated protein 1), which is the substrate recognition subunit of a Cul3-based E3 ubiquitin ligase. Through tandem mass spectrometry, Ooi et al. and Adam et al. showed that fumarate modifies critical cysteine residues (Cys155 and Cys288) within KEAP1, so that it is unable to bind to NRF2 and target it for degradation.[66,67] Upregulation of NRF2 may be an alternative pathway, other than through 'pseudohypoxia', which may lead to FH-deficient associated tumorigenesis, although the exact mechanism remains to be elucidated. Additionally, diminished AMPK is found in FH deficient renal cancer, which facilitates increased fatty acid and protein biosynthesis, as decreased iron and increased HIF-1α levels.[69]

Immunohistochemistry for FH is not a reliable marker to detect renal papillary type II tumors associated with HLRCC which contain missense mutations in *FH*, as these leave stable but inactive protein. Fumarate reacts spontaneously with cysteine sulphydryl groups to chemically modify proteins in process termed succination. Therefore, immunohistochemistry for S-(2-succinyl) cysteine (2SC) has been proposed as a marker of FH loss, and thus mutations in *FH* [70] and has been validated in over 1000 specimens.[70,71] Use of immunochemistry to identify patients who need evaluation for HLRCC and subsequent genetic testing for mutations in *FH* may become part of clinical practice. Array based comparative genomic hybridization (aCGH) has been done to characterize FH-deficient renal cancers. Loss of chromosome 1q was found as expected consistent with the tumor suppressor role of *FH*, as was gains of chromosomes 2, 7, 17 and losses of 13q12-q21.1, 14, 18 and X, suggesting a distinct genetic profile for these renal tumors.[72] However, specific genetic associations have not yet been identified.

Uterine leiomyomas (fibroids) are benign tumors that arise from the smooth muscle cells of the uterus. They are the most frequent non-renal manifestation of HLRCC and develop in 75–98% of women.[53,73,74] The leiomyomas tend to be early onset and severe, diagnosed on average 10 years earlier than in sporadic disease, with 68% diagnosed before the age of 30 in one series.[53,75] The histopathology of the uterine leiomyomas associated with HLRCC appear to be quite similar to the renal tumors, in particular the nuclear features with prominent eosinophilic nucleoli surrounded by a clear halo.[76] Cutaneous leiomyomas (piloleiomyomas) are painful pink-purplish nodules that affect individuals in a disseminated or segmental distribution. Cutaneous leiomyomas are benign tumors that arise from the piloerector apparatus.[49] Cutaneous leiomyomas occur in 80–100% of individuals with a mean age of presentation of 25 years (range 10–47 years), but can develop later into the 40s.[77]

Other tumor manifestations

Wilm's tumor has been reported in two pediatric patients with FH mutations, suggesting a possible associated predisposition.[54,78] Leydig cell tumors also have been reported in patient with HLRCC. Screening of sporadic leydig cell tumors also identified a second male with a germline mutation, suggesting that patients with leydig cell tumors should be asked about pertinent family history.[79] Gastrointestinal stromal tumors (GIST), adrenocortical disease and ovarian cystadenomas also have been described in patients with HLRCC.[80,81]

Trials for papillary RCC

Clinical trials of MET inhibitors for type 1and 2 papillary renal cancers, including foretinib, cabozantinib and arq 197 have been completed or are underway (www.clinicaltrials.govv).[82] A phase II trial of two dosing schedules of foretinib, an oral multikinase inhibitor targeting MET, VEGF, RON, AXL, and TIE-2 receptors, was conducted in 74 patients with metastatic papillary RCC based on MET pathway activation (germline or somatic MET mutation, MET [7q31] amplification, or gain of chromosome 7.[83] The primary end point was overall response rate (ORR). The presence of a germline MET mutation was highly predictive of a response (five of 10 vs. five of 57 patients with and without germline MET mutations, respectively). The most frequent adverse events of any grade associated with foretinib were fatigue, hypertension, gastrointestinal toxicities, and nonfatal pulmonary emboli. In another trial of 150 mg once daily erlotinib, an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, was evaluated in histologically confirmed, advanced, or metastatic pRCC where the overall RR was 11% (five of 45 patients; 95% CI, 3% to 24%), and the disease control rate was 64% (ie five partial response and 24 stable disease).[84] The median overall survival time was 27 months (95% CI, 13 to 36 months). Probability of freedom from treatment failure at 6 months was 29% (95% CI, 17% to 42%).

There was one grade 5 adverse event (AE) of pneumonitis, one grade 4 thrombosis, and nine other grade 3 AEs.

Birt-Hogg-Dubé disease

Patients with Birt-Hogg-Dubé disease (BHD) have an autosomal dominant syndrome characterized by the development of fibrofolliculomas (dysplastic hair follicles), lung cysts and spontaneous pneumothorax, and renal cancer.[85,86] This syndrome occurs in approximately 1 of 200,000 people and is underdiagnosed due to its variable, and often mild, presentation. The gene for BHD maps to 17p12q11.2, was identified through linkage in affected families, and thus named folliculin (*FLCN*).[87] Both point mutations and large genomic rearrangements have been found in *FLCN*, and are causative of BHD.[88] The FLCN protein has no homology to previously identified proteins, and its function has been controversial. Most recently, it has been suggested that it is a ciliopathy, is involved in cell polarity, regulates cell-cell adhesion and negative regulates rRNA synthesis.[89–91] A wide spectrum of renal cancers (papillary RCC, ccRCC, mixed and oncocytomas) has been observed in patients with BHD, even within the same kidney.[92] The renal parenchyma surrounding the renal tumor can often contain multifocal oncocytosis. The most common type of tumor is an unusual hybrid oncocytic tumor (mixed oncocytoma and chromophobe). Because a hybrid oncocytic tumor is characteristic of BHD, any patient presenting with one should be evaluated for BHD. *FCLN* functions as a tumor suppressor gene in BHD; mutations in *FLCN* have been identified in sporadic chromophobe renal cancers, although not commonly.[93,94]

Criteria for the diagnosis of BHD have been proposed and include major criteria of 1) at least five fibrofolliculomas, at least one histologically confirmed, of adult onset or 2) pathogenic FLCN mutation and minor criteria of 1) multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous pneumothorax; 2) renal cancer: early onset (<50 years) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology; and 3) a first degree relative with BHD.[95] Patients should have one major or two minor criteria for diagnosis. BHD is vastly under diagnosed.

Treatment of BHD-associated kidney cancer

Chromophobe tumors when diagnosed early are often curable with surgery. Metastatic disease, especially if the histology is chromophobe, is challenging to treat due to the rarity of the presentation and the lack of defined therapeutic targets. Sporadic chromophobe tumors can contain mutations in *KIT*,[96] but it is unknown if treatment with imatinib or sunitinib which have kit as a target, are active.

Other inherited syndromes with an increased risk of renal cancer

BAP1 mutations and familial renal cancer

Somatic mutations in *BAP1* (BRCA associated protein 1) were identified through whole exome sequencing studies.[97] *BAP1* mutations have been associated with a higher tumor grade and decreased overall survival, as compared to those with PBRM1 mutations, which are negatively correlated.[98] In the massively parallel sequencing of clear cell renal cancer, germline mutations also were identified. Two recent studies have suggested that *BAP1* mutations predispose to familial clear cell renal cancer, along with uveal and cutaneous melanoma and mesothelioma.[99,100]

Chromosome 3 translocations

Multiple families with inherited susceptibility due to balanced translocations involving chromosome 3 have been described.[101–106] The mechanism behind the increased risk of multi-focal clear cell renal cancer is thought to be loss of the rearranged chromosome during mitosis, which requires a quadrivalent (four chromosomes coming together), leading to greater errors during chromosomal segregation. As multiple genes involved in the pathogenesis of clear cell renal cancer are located on chromosome 3p, including *VHL*, *PBRM1*, *BAP1*, and *SETD2*,[107] it is not surprising that a mechanism of increased loss of one allele leads to an increased risk of clear cell renal cancer.

PTEN hamartoma tumor syndrome (Cowden disease)

PTEN is associated with an increased risk of benign and malignant tumors of the thyroid, breast and endometrium caused by mutations in *PTEN*.[108] Dermatological manifestations of Cowden syndrome are very common, seen in essentially all patients by their 30s, and include trichilemmomas, papillomatous papules, and acral and plantar keratoses.[109] Clear cell renal cancer has been reported as a observed in patients with Cowden syndrome, with recent estimates suggesting a standardized incidence ratio of 30.6 (95% CI 17.8, 49.4).[110–112] One study has shown the loss of the wild type *PTEN* allele in a renal cancer from a Cowden syndrome patient.[111] A study of sporadic renal cancers and cell lines have shown that mutations in PTEN are present, particularly in late stage and clear cell renal cancers.[113]

SDH- associated paraganglioma/pheochromocytoma

Mutations in three of the four proteins (*SDHB*/*C*/*D*)comprising the succinate dehydrogenase complex, which participates in both the Krebs cycle, converting fumarate to succinate and as mitochondrial respiratory chain complex II, have been associated with an increased risk of renal cancer.[114] Patients with mutations in the SDH genes have an increased risk of developing tumors of the autonomic nervous system - pheochromocytomas and paragangliomas, both head and neck, and in the thorax and abdomen.[115] Germline *SDHB* mutations are associated with increased risk of metastatic disease as compared to mutations in the other genes of the SDH complex, all of which are associated with an increased risk of pheochromocytomas and paragangliomas.[116] Patients can develop a variety of RCCs including clear cell, chromophobe, and oncocytomas.[117–119] These renal tumors recently have been reported to be particularly aggressive.[120]

Tuberous Sclerosis Complex

Tuberous Sclerosis Complex (TSC) is a autosomal dominant genetic disorder characterized by the formation of hamartomas in multiple organs, including brain, kidney, skin and lung. The formation of hamartomas leads to neurologic disorders, including epilepsy, mental retardation, and autism as well as dermatologic manifestations such as facial angiofibromas, renal angiomyolipomas, and pulmonary lymphangiomyomatosis.[121] Inactivating mutations in *TSC1* (chromosome 9q34) encoding hamartin, or *TSC2* (chromosome 16p13.3) encoding tuberin are responsible for the phenotype.[122–124] The mutations occur as spontaneous germ-line mutations in 70% of cases; patients with TSC2 mutations are more severely affected with greater renal involvement among other features.[125] The 50 to 80% of patients with TSC who develop renal lesions can have angiomyolipomas (AMLs), cysts, oncocytomas, and renal cell carcinomas. Of affected TSC patients, 75–80% develop AMLs and less than 5% develop renal cancer (with precise estimates varying across studies)[126]. Patients can develop epitheliod angiomyolipomas, and the other more common types of renal cancer have been reported.

Hamartin and tuberin are proteins that heterodimerize and inhibit downstream pathways of mammalian target of rapamycin (mTOR).[121] Thus, inactivation of one of the genes translating these proteins leads to upregulation of the HIF pathway. mTor inhibitors including rapamycin, analogs such as everolimus, temsirolimus and dual TOR inhibitors have been used to treat patients with TSC and lymphangiomyomatosis. Recently, everolimus was FDA approved to treat angiomyolipomas (and subependymal astrocytomas) based on a double-blinded placebo controlled trial showing a response rate of 42% (95% CI 31, 55%) as compared to 0% in patients treated with placebo.[127] This study forms the basis of the recommendation that TSC patients with multiple angiomyolipomas be treated with everolimus.

Conclusion

The identification of genes associated with inherited susceptibility to renal cancer has led to a greatly increased understanding of renal tumor pathogenesis. As mutations in each gene tend to be associated with specific pathological sub-types of renal cancer, examining the two in conjunction has allowed a more precise definition of each, thus both refining our understanding of renal tumors and associated cancer susceptibility syndromes. Patients with inhered cancer susceptibility syndromes including renal cancer are being increasingly recognized by physicians and referred for specialist evaluation, leading to improved clinical outcomes with medical management guidelines targeted for those diseases. Additionally, these advances in knowledge have further delineated aberrantly activated pathways so that cancer therapeutics can be appropriately targeted in each sub-type of renal cancer.

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Clinical Summary

- Currently there are ten inherited cancer susceptibility syndromes which are associated with an increased risk of renal tumors, of varying pathological types.
- Therapeutic options for the treatment of renal tumors associated with cancer susceptibility syndromes are expanding, and are discussed herein.

Table 1

Inherited cancer susceptibility syndromes associated with an increased risk of renal cancer

Syndrome	Gene	Protein	Renal cancer type	Other cancers	Non-neoplastic findings
BAP1 mutant disease	*BAP1*	BRCA associated protein	Clear cell	Melanomoa Uveal melanoma Mesothelioma	Epithelioid atypical Spitz tumours
Birt-Hogg-Dubé syndrome	*FLCN*	folliculin	Oncocytic, chromophobe	---	Fibrofolliculomas Lung cysts, pneumothorax
Familial clear cell renal cancer with chromosome 3 translocation	Translocation chr 3		Clear cell	---	---
Hereditary Leiomyomatosis and Renal Cell Cancer	*FH*	fumarate hydratase	Papillary type 2	---	Cutaneous leiomyomas Uterine leiomyomas
Hereditary papillary renal cancer	*MET*	c-MET	Papillary type 1	---	---
PTEN hamartoma syndrome	*PTEN*	PTEN	Clear cell	Breast cancer Thyroid cancer	Mucocutaneous papules, hamartomas, lipomas, macrocephaly
SDH associated renal cancer	*SDHB* *SDHC* *SDHD*	succinate dehydrogenase subunits B, C, D	Clear cell, chromophobe, oncocytoma	Paraganglioma Pheochromocytoma	---
Tuberous Sclerosis Complex	*TSC1* *TSC2*	hamartin tuberin	Angiomyolipoma Epitheliod angiomyolipoma	Angiomyolipomas Subependymal giant cell astrocytomas	Facial angiofibroma Hypomelanotic macule Connective tissue nevus Forehead plaque Ungal and peri-ungal fibromas
Von Hippel Lindau disease	*VHL*	pVHL	Clear cell	CNS - hemangioblastoma (brain, spine, retina) Adrenal - pheochromocytoma Inner ear - endolymphatic sac tumors Pancreas - neuroendocrine tumors	Pancreatic, renal cysts

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