Hereditary Kidney Cancer Syndromes

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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 kidney cancer, which are reviewed herein. Clear cell kidney cancer is associated with von Hippel Lindau disease, chromosome 3 translocations, PTEN hamartomatous syndrome, and mutations in the BAP1 gene as well as several of the genes encoding the proteins comprising the succinate dehydrogenase complex (*SDHB/C/D*). Type 1 papillary kidney cancers arise in conjunction with germline mutations in *MET* and type 2 as part of hereditary leiomyomatosis and kidney cell cancer (fumarate hydratase [*FH*] mutations). Chromophone and oncocytic kidney cancers are predominantly associated with Birt-Hogg-Dubé syndrome. Patients with Tuberous Sclerosis Complex (TSC) commonly have angiomyolipomas and rarely their malignant counterpart epithelioid angiomyolipomas. The targeted therapeutic options for the kidney cancer associated with these diseases are just starting to expand and are an area of active clinical research.

Key Words: von Hippel Lindau disease, Birt-Hogg-Dube disease, Kidney cancer, Genetic susceptibility, Genetic disease

Introduction

Hereditary kidney cancer accounts for 3% to 5% of all kidney cancer; however, this number is likely underestimated. Ten inherited cancer susceptibility syndromes are currently associated with an 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 of kidney cancer has and will lead to the discovery of mutated genes 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 heterogeneous. Herein, we describe the most prevalent of these syndromes. Many of the genes identified through the study of familial kidney cancer have also proven to be important in sporadic kidney cancers, with von Hippel Lindau (VHL) disease 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 the causality and aggressive behavior related to the inherited genetics of kidney cancer.

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 kidney cysts; and neuroendocrine tumors, endolymphatic sac tumors, and pheochromocytomas. Some but not all patients develop clear cell kidney cancer, presenting as bilateral and sometimes hundreds of lesions within the kidney.

The first patients with this syndrome were described in 1860, and it was recognized as a familial by Von Hippel some 30 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 mutated gene responsible for these families and VHL disease, *VHL*, was found through the study of multiple case families to be located at 3p25-26.[3-6]

There is significant variation in phenotype in VHL disease that was observed before gene identification.[7] Subsequent to the identification of *VHL*, a strong genotype-phenotype correlation was seen with a mutation type that was predictive of disease.[8] Patients with type 1 mutations (in general, truncating mutations) have a decreased incidence of pheochromocytoma as compared with 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 clear cell renal cell carcinoma (ccRCC; type 2B), and 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

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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, leading to more than one child with 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, kidney cysts, and clear cell kidney cancer from patients with VHL.[19-22] The wild-type allele of *VHL* is lost consistently in kidney cysts in VHL patients, suggesting that loss of that allele is an important initiating event in tumorigenesis.[22] pVHL (VHL protein) contains 2 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 substrates of which are the hypoxia-inducible factors (HIFs), which are transcription factors that regulate a broad program of hypoxia-responsive genes including vascular endothelial growth factor (VEGF).[27] Inactivation of *VHL* results in upregulation of HIF-1α and -2α, which drive angiogenesis and proliferation and 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 the University of Pennsylvania further identified 2 subgroups of VHL-inactivated clear cell cancers: 1 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 kidney carcinoma.

CLINICAL SUMMARY

- There are currently 10 inherited cancer susceptibility syndromes that are associated with an increased risk of kidney tumors of varying pathological types.
- Therapeutic options for the treatment of kidney tumors associated with cancer susceptibility syndromes are expanding and are discussed herein.

Frameshift and nonsense mutations in *VHL* are associated with a high penetrance of clear cell kidney cancer, with a risk at age 50 of 70%.[9] Full and partial gene deletions of *VHL* confer a lower risk of clear cell kidney cancer at age 50 of 40%. As discussed above, type 2A missense mutations also confer a high risk of kidney cancer, whereas other missense mutations, including types 2B and 2C, do not appear to be associated with kidney 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, whereas type 2A mutations do not impair binding but are within the HIF-binding site (β-domain).[34] Knauth and colleagues showed that *VHL* type 2A mutations had higher stability and higher ubiquitin ligase activity with respect to HIF-1α as compared with type 2B mutations.[35] Li and colleagues demonstrated that type 2A mutations retain their ability to regulate HIF-1α and HIF-2α.[33] In contrast, type 2A mutations are associated with the retention of HIF-2α activity and increased growth in contrast to type 2B mutations. These data implicate a biological difference accounting for the variable risk of kidney cancer associated with different types of kidney 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. Because these patients present with multifocal disease at an early age and the tumors vary in aggressiveness, every effort should be made to preserve kidney function through nephron-sparing approaches (partial nephrectomy, thermal ablative therapies, or observation) in patients with disease limited to the kidneys. However, in patients with locally advanced disease, the likelihood of recurrent disease and ESRD is much higher; thus, bilateral resection of the kidneys followed by kidney transplantation is a more accepted approach.[36] In a contemporary series, 85% to 90% of VHL patients are now diagnosed with kidney masses less than 6 cm, and only 11% of patients have progressed to distant metastases.[37] Given the low reported rate of metastasis among patients with sporadic kidney cortical neoplasms less than 3 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 and colleagues reported no evidence of metastatic disease progression and no need for kidney 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 and colleagues confirmed the safety of this approach.[38] Over a median follow-up of 41 months, all 108 patients with lesions less than 3 cm in size remained free of distant metastases, all avoided kidney transplantation and dialysis, 37 (34%) remained on observation without intervention, and 104