# Hereditary Kidney Cancer Syndromes

Naomi B. Haas and Katherine L. Nathanson

**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

*From Department of Medicine, Division of Hematology/Oncology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; and Department of Medicine, Division of Translational Medicine and Human Genetics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA.*

*N.B.H. and K.L.N. report no conflicts of interest.*

*Address correspondence to Katherine L. Nathanson, MD, Department of Medicine, Division of Translational Medicine and Human Genetics, Perelman School of Medicine at the University of Pennsylvania, 351 BRB 2/3, 421 Curie Blvd., Philadelphia, PA 19104. E-mail: knathans@exchange.upenn.edu*



*1548-5595/$36.00*

*http://dx.doi.org/10.1053/j.ackd.2013.10.001*

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

**Table 1. Inherited Cancer Susceptibility Syndromes Associated With an Increased Risk of Kidney Cancer**

| Syndrome | Gene | Protein | Kidney Cancer Type | Other Cancers | Non-Neoplastic Findings |
|---|---|---|---|---|---|
| BAP1 mutant disease | *BAP1* | BRCA-associated protein | Clear cell | Melanoma<br>Uveal melanoma<br>Mesothelioma | Epithelioid atypical Spitz tumors |
| Birt-Hogg-Dubé syndrome | *FLCN* | Folliculin | Oncocytic, chromophobe | – | Fibrofolliculomas<br>Lung cysts, pneumothorax |
| Familial clear cell kidney cancer with chromosome 3 translocation | Translocation chromosome 3 | | Clear cell | – | – |
| Hereditary leiomyomatosis and kidney cell cancer | *FH* | Fumarate hydratase | Papillary type 2 | – | Cutaneous leiomyomas<br>Uterine leiomyomas |
| Hereditary papillary kidney cancer | *MET* | c-MET | Papillary type 1 | – | – |
| PTEN hamartoma syndrome | *PTEN* | PTEN | Clear cell | Breast cancer<br>Thyroid cancer | Mucocutaneous papules, hamartomas, lipomas, macrocephaly |
| SDH-associated kidney cancer | *SDHB*<br>*SDHC*<br>*SDHD* | Succinate dehydrogenase subunits B, C, D | Clear cell, chromophobe, oncocytoma | Paraganglioma<br>Pheochromocytoma | – |
| Tuberous sclerosis complex | *TSC1*<br>*TSC2* | Hamartin<br>Tuberin | Angiomyolipoma<br>Epitheliod angiomyolipoma | Angiomyolipomas<br>Subependymal giant cell astrocytomas | Facial angiofibroma<br>Hypomelanotic macule<br>Connective tissue nevus<br>Forehead plaque<br>Ungal and periungal fibromas |
| Von Hippel Lindau disease | *VHL* | pVHL | Clear cell | CNS: hemangioblastoma (brain, spine, retina)<br>Adrenal: pheochromocytoma<br>Inner ear: endolymphatic sac tumors<br>Pancreas: neuroendocrine tumors | Pancreatic, kidney cysts |

Abbreviations: CNS, central nervous system; PTEN, phosphatase and tensin homolog; SDH, succinate dehydrogenase.

(96%) retained both kidneys. Of the 71 patients (66%) that required intervention for interval growth of lesions larger than 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 kidney tumors, a nephron-sparing approach was successfully used 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 renal cell carcinoma (RCC) have been inconsistent. Choueiri and colleagues examined *VHL* status as a predictive biomarker in 123 patients treated with various VEGF inhibitors; they suggested that loss-of-function mutations in *VHL* were associated with treatment response.[39] There are ongoing clinical trials specifically using the current VEGF-tyrosine kinase inhibitors in patients with VHL (http://www.clinicaltrials.gov). Because these patients often have hemangioblastomas in extrarenal sites, the goals of these therapies are not only to control malignant disease but also to temper symptoms of the 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 ccRCC are ongoing. A pilot study was recently conducted that tested the feasibility of vaccinating advanced RCC patients with the corresponding mutant VHL peptides.[40] A mutant VHL peptide vaccine was administered to 6 patients with *VHL*-mutant RCC. Four of 5 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 and median progression-free survival were 30.5 and 6.5 months, respectively.

In addition, because the *VHL* gene is functionally lost through hypermethylation in up to 19% of sporadic clear cell RCC cases, re-expressing VHL silenced by methylation in ccRCC cells using a hypomethylating agent may be an approach to treatment in patients with this type of cancer. A pilot experiment was conducted in mouse xenografts using 2 hypomethylating agents to re-express VHL in cell culture and in mice bearing human ccRCC to evaluate the effects of re-expressed VHL in these models.[41] Real-time reverse transcription polymerase chain reaction was used to evaluate the ability of zebularine and 5-aza-2′-deoxycytidine (5-aza-dCyd) to re-express VHL in 4 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 in culture and in xenografted murine tumors. Well-described phenotypic changes of VHL expression including decreased invasiveness into Matrigel and decreased VEGF 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 RCCs.[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 kidney cancers. Families with inherited mutations in *MET* leading to multifocal papillary kidney cancer (type 1) are quite rare, much more so than VHL and most of the other described inherited kidney cancer syndromes, including HLRCC and Birt-Hogg-Dubé (BHD) disease.

#### Hereditary Leiomyomatosis and Kidney 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 kidney cancer.[49,50] Papillary type 2 kidney cancer is the pathological type most commonly associated with HLRCC and tends to have an early age of onset, be of high grade, and have an aggressive course.[51] The mean age of kidney cancer diagnosis is 40 years, but metastatic kidney cancer can present in the teens. Other types of kidney cancers also can occur, including collecting duct and clear cell cancers.[50,52,53] Independent of underlying architecture, cells in the kidney cancers associated with HLRCC have a characteristic pathological appearance with large nuclei with inclusion-like orangiophilic or eosinophilic nucleoli surrounded by a clear halo, which can be recognized by knowledgeable pathologists.[51]

The gene fumarate hydratase (*FH*), which encodes the enzyme that 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 of 337) in the *FH* mutation database (http://chromium.liacs.nl/lovd_sdh/home.php?select_db=FH).[55] The lower fumarate hydratase (FH) 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, similar 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* behaves as a tumor suppressor gene because loss of the wild-type allele is observed in kidney cancer from individuals with *FH* mutations. Patients with biallelic mutations (homozygous or compound heterozygotes) develop FH deficiency, 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 1 mutation can go on to develop papillary type 2 kidney cancer. Mutations have not been observed in sporadic RCC, but in part the lack of observation may arise because of the limited number of papillary type 2 tumors included in the screening series.[57]

In kidney cancers with *FH* mutations, HIF accumulation increases when high levels of fumarate inhibit the HIF proline hydroxylases 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 RCC. Two studies have demonstrated that FH loss results in activation of Nrf2-dependent activation of antioxidant pathways.[66,67] NRF2 (NFE2L2, nuclear factor, erythroid 2-like 2), 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 and colleagues and Adam and colleagues 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. In addition, diminished 5′-AMP-activated protein kinase is found in FH-deficient kidney cancer, which facilitates increased fatty acid and protein biosynthesis because of decreased iron and increased HIF-1α levels.[69]

Immunohistochemistry for FH is not a reliable marker to detect kidney papillary type 2 tumors associated with HLRCC, which contain missense mutations in *FH*, because these leave stable but inactive protein. Fumarate reacts spontaneously with cysteine sulphydryl groups to chemically modify proteins in a process termed succination. Therefore, immunohistochemistry for *S*-(2-succinyl) cysteine 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 has been done to characterize FH-deficient kidney cancers. Loss of chromosome 1q was found as expected, consistent with the tumor suppressor role of *FH*, as were gains of chromosomes 2, 7, and 17 and losses of 13q12-q21.1, 14, 18, and X, suggesting a distinct genetic profile for these kidney 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 nonrenal manifestation of HLRCC and develop in 75% to 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 1 series.[53,75] The histopathology of the uterine leiomyomas associated with HLRCC appear to be quite similar to the kidney 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% to 100% of individuals with a mean age of presentation of 25 years (range 10-47 years), but they can develop later into the 40s.[77]

### *Other Tumor Manifestations*

Wilm's tumor has been reported in 2 pediatric patients with *FH* mutations, suggesting a possible associated predisposition.[54,78] Leydig cell tumors also have been reported in patients 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, 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 1 and 2 papillary kidney cancers, including foretinib, cabozantinib, and arq 197, have been completed or are underway (www.clinicaltrials.govv).[82] A Phase II trial of 2 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 endpoint was overall response rate. The presence of a germline *Met* mutation was highly predictive of a response (5 of 10 vs 5 of 57 patients with and without germline *Met* mutations, respectively). The most frequent adverse events (AEs) 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-tyrosine kinase inhibitor was evaluated in histologically confirmed, advanced, or metastatic papillary RCC in which the overall response rate was 11% (5 of 45 patients; 95% confidence interval [CI] 3-24%), and the disease control rate was 64% (ie, 5 partial response and 24 stable disease).[84] The median overall survival time was 27 months (95% CI, 13-36 months). The probability of freedom from treatment failure at 6 months was 29% (95% CI, 17% to 42%). There was 1 Grade 5 AE of pneumonitis, 1 Grade 4 AE of thrombosis, and 9 other Grade 3 AEs.

## Birt-Hogg-Dube Disease

Patients with BHD disease have an autosomal-dominant syndrome characterized by the development of fibrofolliculomas (dysplastic hair follicles), lung cysts and spontaneous pneumothorax, and kidney cancer.[85,86] This syndrome occurs in approximately 1 of 200,000 people and is underdiagnosed because of its variable, and often mild, presentation. The gene for BHD maps to 17p12q11.2 and was identified through linkage in affected families; thus, it was named folliculin (*FLCN*).[87] Point mutations and large genomic rearrangements have been found in *FLCN* and are causative of Birt-Hogg-Dube (BHD).[88] The folliculin (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 negatively regulates ribosomal RNA synthesis.[89-91] A wide spectrum of kidney cancers (papillary RCC, ccRCC, mixed, and oncocytomas) has been observed in patients with BHD, even within the same kidney.[92] The kidney parenchyma surrounding the kidney 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 kidney cancers, although this is not common.[93,94]

Criteria for the diagnosis of BHD have been proposed and include major criteria of (1) at least 5 fibrofolliculomas, at least 1 histologically confirmed, of adult onset, or (2) pathogenic *FLCN* mutation. Minor criteria for the diagnosis of BHD include (1) multiple lung cysts—bilateral basally located lung cysts with no other apparent cause, with or without spontaneous pneumothorax; (2) kidney cancer—early onset (<50 years), multifocal or bilateral kidney cancer, or kidney cancer of mixed chromophobe and oncocytic histology; and (3) a first-degree relative with BHD.[95] Patients should have 1 major or 2 minor criteria for diagnosis. BHD is vastly underdiagnosed.

### *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 target KIT mutations, are active.

### *Other Inherited Syndromes With an Increased Risk of Kidney Cancer*

#### BAP1 (BRCA-Associated Protein-1) Mutations and Familial Kidney Cancer

Somatic mutations in *BAP1* (BRCA-associated protein-1 gene) were identified through whole exome sequencing studies.[97] *BAP1* mutations have been associated with a higher tumor grade and decreased overall survival as compared with those with *PBRM1* mutations, which are negatively correlated.[98] In the massively parallel sequencing of clear cell kidney cancer, germline mutations also were identified. Two recent studies have suggested that *BAP1* mutations predispose to familial clear cell kidney 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 multifocal clear cell kidney cancer is thought to be loss of the rearranged chromosome during mitosis, which requires a quadrivalent (4 chromosomes coming together), leading to greater errors during chromosomal segregation. Because multiple genes involved in the pathogenesis of clear cell kidney cancer are located on chromosome 3p, including *VHL*, *PBRM1*, *BAP1*, and *SETD2*,[107] it is not surprising that a mechanism of increased loss of 1 allele leads to an increased risk of clear cell kidney cancer.

### PTEN Hamartoma Tumor Syndrome (Cowden Disease)

PTEN hamartoma tumor syndrome 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 disease are very common, seen in essentially all patients by their 30s, and include trichilemmomas, papillomatous papules, and acral and plantar keratoses.[109] Clear cell kidney cancer has been reported in patients with Cowden disease, with recent estimates suggesting a standardized incidence ratio of 30.6 (95% CI 17.8, 49.4), however this number may be an overestimate due to ascertainment bias.[110-112] One study has shown the loss of the wild-type *PTEN* allele in a kidney cancer from a Cowden disease patient.[111] A study of sporadic kidney cancers and cell lines has shown that mutations in *PTEN* are present, particularly in late-stage and clear cell kidney cancers.[113]

### Succinate-Dehydrogenase-Associated Paraganglioma/Pheochromocytoma

Mutations in 3 of the 4 genes (succinate dehydrogenase [*SDH*] *B*/*C*/*D*) comprising the succinate dehydrogenase (SDH) complex, which participates in the Krebs cycle, converting fumarate to succinate, and as mitochondrial respiratory chain complex II, have been associated with an increased risk of kidney 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 with 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 various RCCs including clear cell, chromophobe, and oncocytomas.[117-119] These kidney tumors recently have been reported to be particularly aggressive.[120]

### Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is an 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, kidney angiomyolipomas (AMLs), 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 germline mutations in 70% of cases; patients with *TSC2* mutations are more severely affected with greater kidney involvement among other features.[125] The 50% to 80% of patients with TSC who develop kidney lesions can have AMLs, cysts, oncocytomas, and RCCs. Of affected TSC patients, 75% to 80% develop AMLs and less than 5% develop kidney cancer (with precise estimates varying across studies).[126] Patients can develop epitheliod AMLs, and the other more common types of kidney 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 1 of the genes translating these proteins leads to upregulation of the HIF pathway. mTOR inhibitors including rapamycin and analogs such as everolimus, temsirolimus, and dual mTOR inhibitors have been used to treat patients with TSC and lymphangiomyomatosis. Everolimus was recently approved by the U.S. Food and Drug Administration to treat AMLs (and subependymal astrocytomas) on the basis of a double-blinded placebo controlled trial showing a response rate of 42% (95% CI 31, 55%) as compared with 0% in patients treated with placebo.[127] This study forms the basis of the recommendation that TSC patients with multiple AMLs be treated with everolimus.

## Conclusion

The identification of genes associated with inherited susceptibility to kidney cancer has led to a greatly increased understanding of kidney tumor pathogenesis. Because mutations in each gene tend to be associated with specific pathological subtypes of kidney cancer, examining the 2 in conjunction has allowed a more precise definition of each, thus both refining our understanding of kidney tumors and associated cancer susceptibility syndromes. Patients with inhered cancer susceptibility syndromes including kidney 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. In addition, these advances in knowledge have further delineated aberrantly activated pathways so that cancer therapeutics can be appropriately targeted in each subtype of kidney cancer.

## References


1. Von Hippel E. Uber eine sehr seltene Erkanung der netzhaut. *Graefes Arch Clin Exp Opthalmol.* 1904;59(1):83-106. (German)
2. Lindau A. Studien ber kleinbirncysten bau: pathogenese und beziehungen zur angiomatosis retinae. *Acta Radiol Microbiol Scandinavica.* 1926;1(suppl):1-128.
3. Richards FM, Crossey PA, Phipps ME, et al. Detailed mapping of germline deletions of the von Hippel-Lindau disease tumour suppressor gene. *Hum Mol Genet.* 1994;3(4):595-598.
4. Richards FM, Maher ER, Latif F, et al. Detailed genetic mapping of the von Hippel-Lindau disease tumour suppressor gene. *J Med Genet.* 1993;30(2):104-107.
5. Richards FM, Phipps ME, Latif F, et al. Mapping the Von Hippel-Lindau disease tumour suppressor gene: identification of

germline deletions by pulsed field gel electrophoresis. *Hum Mol Genet.* 1993;2(7):879-882.
6. Latif F, Tory K, Gnarra J, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science.* 1993; 260(5112):1317-1320.
7. Maher ER, Bentley E, Yates JR, et al. Mapping of the von Hippel-Lindau disease locus to a small region of chromosome 3p by genetic linkage analysis. *Genomics.* 1991;10(4):957-960.
8. Maher ER, Webster AR, Richards FM, et al. Phenotypic expression in von Hippel-Lindau disease: correlations with germline VHL gene mutations. *J Med Genet.* 1996;33(4):328-332.
9. Ong KR, Woodward ER, Killick P, Lim C, Macdonald F, Maher ER. Genotype-phenotype correlations in von Hippel-Lindau disease. *Hum Mutat.* 2007;28(2):143-149.
10. Zbar B, Kishida T, Chen F, et al. Germline mutations in the Von Hippel-Lindau disease (VHL) gene in families from North America, Europe, and Japan. *Hum Mutat.* 1996;8(4):348-357.
11. Hes F, Zewald R, Peeters T, et al. Genotype-phenotype correlations in families with deletions in the von Hippel-Lindau (VHL) gene. *Hum Genet.* 2000;106(4):425-431.
12. Chen F, Kishida T, Yao M, et al. Germline mutations in the von Hippel-Lindau disease tumor suppressor gene: correlations with phenotype. *Hum Mutat.* 1995;5(1):66-75.
13. Brauch H, Kishida T, Glavac D, et al. Von Hippel-Lindau (VHL) disease with pheochromocytoma in the Black Forest region of Germany: evidence for a founder effect. *Hum Genet.* 1995;95(5):551-556.
14. Maher ER, Iselius L, Yates JR, et al. Von Hippel-Lindau disease: a genetic study. *J Med Genet.* 1991;28(7):443-447.
15. Maher ER, Yates JR, Harries R, et al. Clinical features and natural history of von Hippel-Lindau disease. *Q J Med.* 1990;77(283): 1151-1163.
16. Crossey PA, Foster K, Richards FM, et al. Molecular genetic investigations of the mechanism of tumourigenesis in von Hippel-Lindau disease: analysis of allele loss in VHL tumours. *Hum Genet.* 1994;93(1):53-58.
17. Murgia A, Martella M, Vinanzi C, Polli R, Perilongo G, Opocher G. Somatic mosaicism in von Hippel-Lindau Disease. *Hum Mutat.* 2000;15(1):114.
18. Sgambati MT, Stolle C, Choyke PL, et al. Mosaicism in von Hippel-Lindau disease: lessons from kindreds with germline mutations identified in offspring with mosaic parents. *Am J Hum Genet.* 2000;66(1):84-91.
19. Vortmeyer AO, Lubensky IA, Fogt F, Linehan WM, Khettry U, Zhuang Z. Allelic deletion and mutation of the von Hippel-Lindau (VHL) tumor suppressor gene in pancreatic microcystic adenomas. *Am J Pathol.* 1997;151(4):951-956.
20. Tse JY, Wong JH, Lo KW, Poon WS, Huang DP, Ng HK. Molecular genetic analysis of the von Hippel-Lindau disease tumor suppressor gene in familial and sporadic cerebellar hemangioblastomas. *Am J Clin Pathol.* 1997;107(4):459-466.
21. Lubensky IA, Gnarra JR, Bertheau P, Walther MM, Linehan WM, Zhuang Z. Allelic deletions of the VHL gene detected in multiple microscopic clear cell renal lesions in von Hippel-Lindau disease patients. *Am J Pathol.* 1996;149(6):2089-2094.
22. Mandriota SJ, Turner KJ, Davies DR, et al. HIF activation identifies early lesions in VHL kidneys: evidence for site-specific tumor suppressor function in the nephron. *Cancer Cell.* 2002;1(5):459-468.
23. Kibel A, Iliopoulos O, DeCaprio JA, Kaelin WG Jr. Binding of the von Hippel-Lindau tumor suppressor protein to Elongin B and C. *Science.* 1995;269(5229):1444-1446.
24. Kishida T, Stackhouse TM, Chen F, Lerman MI, Zbar B. Cellular proteins that bind the von Hippel-Lindau disease gene product: mapping of binding domains and the effect of missense mutations. *Cancer Res.* 1995;55(20):4544-4548.
25. Stebbins CE, Kaelin WG Jr, Pavletich NP. Structure of the VHL-ElonginC-ElonginB complex: implications for VHL tumor suppressor function. *Science.* 1999;284(5413):455-461.
26. Ohh M, Takagi Y, Aso T, et al. Synthetic peptides define critical contacts between elongin C, elongin B, and the von Hippel-Lindau protein. *J Clin Invest.* 1999;104(11):1583-1591.
27. Cockman ME, Masson N, Mole DR, et al. Hypoxia inducible factor-alpha binding and ubiquitylation by the von Hippel-Lindau tumor suppressor protein. *J Biol Chem.* 2000;275(33): 25733-25741.
28. Kim W, Kaelin WG Jr. The von Hippel-Lindau tumor suppressor protein: new insights into oxygen sensing and cancer. *Curr Opin Genet Dev.* 2003;13(1):55-60.
29. Banks RE, Tirukonda P, Taylor C, et al. Genetic and epigenetic analysis of von Hippel-Lindau (VHL) gene alterations and relationship with clinical variables in sporadic renal cancer. *Cancer Res.* 2006;66(4):2000-2011.
30. Dondeti VR, Wubbenhorst B, Lal P, et al. Integrative genomic analyses of sporadic clear cell renal cell carcinoma define disease subtypes and potential new therapeutic targets. *Cancer Res.* 2012;72(1): 112-121.
31. Gordan JD, Lal P, Dondeti VR, et al. HIF-alpha effects on c-Myc distinguish two subtypes of sporadic VHL-deficient clear cell renal carcinoma. *Cancer Cell.* 2008;14(6):435-446.
32. Richards FM, Webster AR, McMahon R, Woodward ER, Rose S, Maher ER. Molecular genetic analysis of von Hippel-Lindau disease. *J Intern Med.* 1998;243(6):527-533.
33. Li L, Zhang L, Zhang X, et al. Hypoxia-inducible factor linked to differential kidney cancer risk seen with type 2A and type 2B VHL mutations. *Mol Cell Biol.* 2007;27(15):5381-5392.
34. Clifford SC, Cockman ME, Smallwood AC, et al. Contrasting effects on HIF-1alpha regulation by disease-causing pVHL mutations correlate with patterns of tumourigenesis in von Hippel-Lindau disease. *Hum Mol Genet.* 2001;10(10):1029-1038.
35. Knauth K, Bex C, Jemth P, Buchberger A. Renal cell carcinoma risk in type 2 von Hippel-Lindau disease correlates with defects in pVHL stability and HIF-1alpha interactions. *Oncogene.* 2006; 25(3):370-377.
36. Goldfarb DA, Neumann HP, Penn I, Novick AC. Results of renal transplantation in patients with renal cell carcinoma and von Hippel-Lindau disease. *Transplantation.* 1997;64(12):1726-1729.
37. Walther MM, Choyke PL, Glenn G, et al. Renal cancer in families with hereditary renal cancer: prospective analysis of a tumor size threshold for renal parenchymal sparing surgery. *J Urol.* 1999; 161(5):1475-1479.
38. Duffey BG, Choyke PL, Glenn G, et al. The relationship between renal tumor size and metastases in patients with von Hippel-Lindau disease. *J Urol.* 2004;172(1):63-65.
39. Choueiri TK, Plantade A, Elson P, et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. *J Clin Oncol.* 2008;26(1):127-131.
40. Rahma OE, Ashtar E, Ibrahim R, et al. A pilot clinical trial testing mutant von Hippel-Lindau peptide as a novel immune therapy in metastatic renal cell carcinoma. *J Transl Med.* 2010;8:8.
41. Alleman WG, Tabios RL, Chandramouli GV, et al. The in vitro and in vivo effects of re-expressing methylated von Hippel-Lindau tumor suppressor gene in clear cell renal carcinoma with 5-aza-2′-deoxycytidine. *Clin Cancer Res.* 2004;10(20):7011-7021.
42. Zbar B, Glenn G, Lubensky I, et al. Hereditary papillary renal cell carcinoma: clinical studies in 10 families. *J Urol.* 1995;153(3 Pt 2):907-912.
43. Zbar B, Tory K, Merino M, et al. Hereditary papillary renal cell carcinoma. *J Urol.* 1994;151(3):561-566.
44. Schmidt L, Duh FM, Chen F, et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. *Nat Genet.* 1997;16(1): 68-73.
45. Schmidt L, Junker K, Nakaigawa N, et al. Novel mutations of the MET proto-oncogene in papillary renal carcinomas. *Oncogene.* 1999;18(14):2343-2350.

46. Lubensky IA, Schmidt L, Zhuang Z, et al. Hereditary and sporadic papillary renal carcinomas with c-met mutations share a distinct morphological phenotype. *Am J Pathol.* 1999;155(2):517-526.
47. Lindor NM, Dechet CB, Greene MH, et al. Papillary renal cell carcinoma: analysis of germline mutations in the MET proto-oncogene in a clinic-based population. *Genet Test.* 2001;5(2):101-106.
48. Dharmawardana PG, Giubellino A, Bottaro DP. Hereditary papillary renal carcinoma type I. *Curr Mol Med.* 2004;4(8):855-868.
49. Toro JR, Nickerson ML, Wei MH, et al. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. *Am J Hum Genet.* 2003;73(1):95-106.
50. Alam NA, Rowan AJ, Wortham NC, et al. Genetic and functional analyses of FH mutations in multiple cutaneous and uterine leiomyomatosis, hereditary leiomyomatosis and renal cancer, and fumarate hydratase deficiency. *Hum Mol Genet.* 2003;12(11):1241-1252.
51. Merino MJ, Torres-Cabala C, Pinto P, Linehan WM. The morphologic spectrum of kidney tumors in hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. *Am J Surg Pathol.* 2007;31(10):1578-1585.
52. Grubb RL III, Franks ME, Toro J, et al. Hereditary leiomyomatosis and renal cell cancer: a syndrome associated with an aggressive form of inherited renal cancer. *J Urol.* 2007;177(6):2074-2079. discussion 2079-80.
53. Wei MH, Toure O, Glenn GM, et al. Novel mutations in FH and expansion of the spectrum of phenotypes expressed in families with hereditary leiomyomatosis and renal cell cancer. *J Med Genet.* 2006;43(1):18-27.
54. Smit DL, Mensenkamp AR, Badeloe S, et al. Hereditary leiomyomatosis and renal cell cancer in families referred for fumarate hydratase germline mutation analysis. *Clin Genet.* 2011;79(1):49-59.
55. Bayley JP, Launonen V, Tomlinson IP. The FH mutation database: an online database of fumarate hydratase mutations involved in the MCUL (HLRCC) tumor syndrome and congenital fumarase deficiency. *BMC Med Genet.* 2008;9:20.
56. Pithukpakorn M, Wei MH, Toure O, et al. Fumarate hydratase enzyme activity in lymphoblastoid cells and fibroblasts of individuals in families with hereditary leiomyomatosis and renal cell cancer. *J Med Genet.* 2006;43(9):755-762.
57. Gardie B, Remenieras A, Kattygnarath D, et al. Novel FH mutations in families with hereditary leiomyomatosis and renal cell cancer (HLRCC) and patients with isolated type 2 papillary renal cell carcinoma. *J Med Genet.* 2011;48(4):226-234.
58. Vahteristo P, Koski TA, Naatsaari L, et al. No evidence for a genetic modifier for renal cell cancer risk in HLRCC syndrome. *Fam Cancer.* 2010;9(2):245-251.
59. Gellera C, Uziel G, Rimoldi M, et al. Fumarase deficiency is an autosomal recessive encephalopathy affecting both the mitochondrial and the cytosolic enzymes. *Neurology.* 1990;40(3 Pt 1):495-499.
60. Bourgeron T, Chretien D, Poggi-Bach J, et al. Mutation of the fumarase gene in two siblings with progressive encephalopathy and fumarase deficiency. *J Clin Invest.* 1994;93(6):2514-2518.
61. Coughlin EM, Christensen E, Kunz PL, et al. Molecular analysis and prenatal diagnosis of human fumarase deficiency. *Mol Genet Metab.* 1998;63(4):254-262.
62. Bonioli E, Di Stefano A, Peri V, et al. Fumarate hydratase deficiency. *J Inherit Metab Dis.* 1998;21(4):435-436.
63. Maradin M, Fumic K, Hansikova H, et al. Fumaric aciduria: mild phenotype in a 8-year-old girl with novel mutations. *J Inherit Metab Dis.* 2006;29(5):683.
64. Ottolenghi C, Hubert L, Allanore Y, et al. Clinical and biochemical heterogeneity associated with fumarase deficiency. *Hum Mutat.* 2011;32(9):1046-1052.
65. Linehan WM, Rouault TA. Molecular pathways: fumarate hydratase-deficient kidney cancer–targeting the warburg effect in cancer. *Clin Cancer Res.* 2013;19(13):3345-3352.
66. Adam J, Hatipoglu E, O'Flaherty L, et al. Renal cyst formation in Fh1-deficient mice is independent of the Hif/Phd pathway: roles for fumarate in KEAP1 succination and Nrf2 signaling. *Cancer Cell.* 2011;20(4):524-537.
67. Ooi A, Wong JC, Petillo D, et al. An antioxidant response phenotype shared between hereditary and sporadic type 2 papillary renal cell carcinoma. *Cancer Cell.* 2011;20(4):511-523.
68. Giudice A, Arra C, Turco MC. Review of molecular mechanisms involved in the activation of the Nrf2-ARE signaling pathway by chemopreventive agents. *Methods Mol Biol.* 2010;647:37-74.
69. Tong WH, Sourbier C, Kovtunovych G, et al. The glycolytic shift in fumarate-hydratase-deficient kidney cancer lowers AMPK levels, increases anabolic propensities and lowers cellular iron levels. *Cancer Cell.* 2011;20(3):315-327.
70. Bardella C, El-Bahrawy M, Frizzell N, et al. Aberrant succination of proteins in fumarate hydratase-deficient mice and HLRCC patients is a robust biomarker of mutation status. *J Pathol.* 2011;225(1):4-11.
71. Maxwell PH. Seeing the smoking gun: a sensitive and specific method to visualize loss of the tumour suppressor, fumarate hydratase, in human tissues. *J Pathol.* 2011;225(1):1-3.
72. Koski TA, Lehtonen HJ, Jee KJ, et al. Array comparative genomic hybridization identifies a distinct DNA copy number profile in renal cell cancer associated with hereditary leiomyomatosis and renal cell cancer. *Genes Chromosomes Cancer.* 2009;48(7):544-551.
73. Launonen V, Vierimaa O, Kiuru M, et al. Inherited susceptibility to uterine leiomyomas and renal cell cancer. *Proc Natl Acad Sci U S A.* 2001;98(6):3387-3392.
74. Tomlinson IP, Alam NA, Rowan AJ, et al. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. *Nat Genet.* 2002;30(4):406-410.
75. Stewart L, Glenn GM, Stratton P, et al. Association of germline mutations in the fumarate hydratase gene and uterine fibroids in women with hereditary leiomyomatosis and renal cell cancer. *Arch Dermatol.* 2008;144(12):1584-1592.
76. Garg K, Tickoo SK, Soslow RA, Reuter VE. Morphologic features of uterine leiomyomas associated with hereditary leiomyomatosis and renal cell carcinoma syndrome: a case report. *Am J Surg Pathol.* 2011;35(8):1235-1237.
77. Alam NA, Barclay E, Rowan AJ, et al. Clinical features of multiple cutaneous and uterine leiomyomatosis: an underdiagnosed tumor syndrome. *Arch Dermatol.* 2005;141(2):199-206.
78. Badeloe S, van Spaendonck-Zwarts KY, van Steensel MA, et al. Wilms tumour as a possible early manifestation of hereditary leiomyomatosis and renal cell cancer? *Br J Dermatol.* 2009;160(3):707-709.
79. Carvajal-Carmona LG, Alam NA, Pollard PJ, et al. Adult Leydig cell tumors of the testis caused by germline fumarate hydratase mutations. *J Clin Endocrinol Metab.* 2006;91(8):3071-3075.
80. Lamba M, Verma S, Prokopetz R, Pierscianowski TA, Jabi M, Moyana T. Multiple cutaneous and uterine leiomyomas associated with gastric GIST. *J Cutan Med Surg.* 2005;9(6):332-335.
81. Matyakhina L, Freedman RJ, Bourdeau I, et al. Hereditary leiomyomatosis associated with bilateral, massive, macronodular adrenocortical disease and atypical Cushing syndrome: a clinical and molecular genetic investigation. *J Clin Endocrinol Metab.* 2005;90(6):3773-3779.
82. Eder JP, Shapiro GI, Appleman LJ, et al. A phase I study of foretinib, a multi-targeted inhibitor of c-Met and vascular endothelial growth factor receptor 2. *Clin Cancer Res.* 2010;16(13):3507-3516.
83. Choueiri TK, Vaishampayan U, Rosenberg JE, et al. Phase II and biomarker study of the dual MET/VEGFR2 inhibitor foretinib in patients with papillary renal cell carcinoma. *J Clin Oncol.* 2013;31(2):181-186.
84. Gordon MS, Hussey M, Nagle RB, et al. Phase II study of erlotinib in patients with locally advanced or metastatic papillary histology renal cell cancer: SWOG S0317. *J Clin Oncol.* 2009;27(34):5788-5793.

85. Khoo SK, Bradley M, Wong FK, Hedblad MA, Nordenskjold M, Teh BT. Birt-Hogg-Dube syndrome: mapping of a novel hereditary neoplasia gene to chromosome 17p12-q11.2. *Oncogene.* 2001;20(37): 5239-5242.
86. Schmidt LS, Warren MB, Nickerson ML, et al. Birt-Hogg-Dube syndrome, a genodermatosis associated with spontaneous pneumothorax and kidney neoplasia, maps to chromosome 17p11.2. *Am J Hum Genet.* 2001;69(4):876-882.
87. Nickerson ML, Warren MB, Toro JR, et al. Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dube syndrome. *Cancer Cell.* 2002;2(2):157-164.
88. Benhammou JN, Vocke CD, Santani A, et al. Identification of intragenic deletions and duplication in the FLCN gene in Birt-Hogg-Dube syndrome. *Genes Chromosomes Cancer.* 2011;50(6):466-477.
89. Luijten MN, Basten SG, Claessens T, et al. Birt-Hogg-Dube syndrome is a novel ciliopathy. *Hum Mol Genet.* 2013;22(21):4383-4397.
90. Medvetz DA, Khabibullin D, Hariharan V, et al. Folliculin, the product of the Birt-Hogg-Dube tumor suppressor gene, interacts with the adherens junction protein p0071 to regulate cell-cell adhesion. *PLoS One.* 2012;7(11):e47842.
91. Gaur K, Li J, Wang D, et al. The Birt-Hogg-Dube tumor suppressor Folliculin negatively regulates ribosomal RNA synthesis. *Hum Mol Genet.* 2013;22(2):284-299.
92. Pavlovich CP, Grubb RL III, Hurley K, et al. Evaluation and management of renal tumors in the Birt-Hogg-Dube syndrome. *J Urol.* 2005;173(5):1482-1486.
93. Khoo SK, Kahnoski K, Sugimura J, et al. Inactivation of BHD in sporadic renal tumors. *Cancer Res.* 2003;63(15):4583-4587.
94. da Silva NF, Gentle D, Hesson LB, Morton DG, Latif F, Maher ER. Analysis of the Birt-Hogg-Dube (BHD) tumour suppressor gene in sporadic renal cell carcinoma and colorectal cancer. *J Med Genet.* 2003;40(11):820-824.
95. Menko FH, van Steensel MA, Giraud S, et al. Birt-Hogg-Dube syndrome: diagnosis and management. *Lancet Oncol.* 2009;10(12): 1199-1206.
96. Linehan WM, Pinto PA, Bratslavsky G, et al. Hereditary kidney cancer: unique opportunity for disease-based therapy. *Cancer.* 2009;115(suppl 10):2252-2261.
97. Pena-Llopis S, Vega-Rubin-de-Celis S, Liao A, et al. BAP1 loss defines a new class of renal cell carcinoma. *Nat Genet.* 2012;44(7): 751-759.
98. Kapur P, Pena-Llopis S, Christie A, et al. Effects on survival of BAP1 and PBRM1 mutations in sporadic clear-cell renal-cell carcinoma: a retrospective analysis with independent validation. *Lancet Oncol.* 2013;14(2):159-167.
99. Farley MN, Schmidt LS, Mester JL, et al. A novel germline mutation in BAP1 predisposes to familial clear-cell renal cell carcinoma. *Mol Cancer Res.* 2013;11(9):1061-1071.
100. Popova T, Hebert L, Jacquemin V, et al. Germline BAP1 mutations predispose to renal cell carcinomas. *Am J Hum Genet.*, http://dx.doi.org/10.1016/j.ajhg.2013.04.012.
101. Bodmer D, Eleveld M, Ligtenberg M, et al. Cytogenetic and molecular analysis of early stage renal cell carcinomas in a family with a translocation (2;3) (q35;q21). *Cancer Genet Cytogenet.* 2002;134(1):6-12.
102. Bonne AC, Bodmer D, Schoenmakers EF, van Ravenswaaij CM, Hoogerbrugge N, van Kessel AG. Chromosome 3 translocations and familial renal cell cancer. *Curr Mol Med.* 2004;4(8):849-854.
103. Eleveld MJ, Bodmer D, Merkx G, et al. Molecular analysis of a familial case of renal cell cancer and a t(3;6) (q12;q15). *Genes Chromosomes Cancer.* 2001;31(1):23-32.
104. Foster RE, Abdulrahman M, Morris MR, et al. Characterization of a 3;6 translocation associated with renal cell carcinoma. *Genes Chromosomes Cancer.* 2007;46(4):311-317.
105. Kanayama H, Lui WO, Takahashi M, et al. Association of a novel constitutional translocation t(1q;3q) with familial renal cell carcinoma. *J Med Genet.* 2001;38(3):165-170.
106. Koolen MI, van der Meyden AP, Bodmer D, et al. A familial case of renal cell carcinoma and a t(2;3) chromosome translocation. *Kidney Int.* 1998;53(2):273-275.
107. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature.* 2013;499(7456):43-49.
108. Liaw D, Marsh DJ, Li J, et al. Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. *Nat Genet.* 1997;16(1):64-67.
109. Gustafson S, Zbuk KM, Scacheri C, Eng C. Cowden syndrome. *Semin Oncol.* 2007;34(5):428-434.
110. Zbuk KM, Eng C. Cancer phenomics: RET and PTEN as illustrative models. *Nat Rev Cancer.* 2007;7(1):35-45.
111. Lynch ED, Ostermeyer EA, Lee MK, et al. Inherited mutations in PTEN that are associated with breast cancer, Cowden disease, and juvenile polyposis. *Am J Hum Genet.* 1997;61(6):1254-1260.
112. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res.* 2012;18(2):400-407.
113. Kondo K, Yao M, Kobayashi K, et al. PTEN/MMAC1/TEP1 mutations in human primary renal-cell carcinomas and renal carcinoma cell lines. *Int J Cancer.* 2001;91(2):219-224.
114. Letouze E, Martinelli C, Loriot C, et al. SDH mutations establish a hypermethylator phenotype in paraganglioma. *Cancer Cell.* 2013;23(6):739-752.
115. Astuti D, Latif F, Dallol A, et al. Gene mutations in the succinate dehydrogenase subunit SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma. *Am J Hum Genet.* 2001;69(1):49-54.
116. Amar L, Baudin E, Burnichon N, et al. Succinate dehydrogenase B gene mutations predict survival in patients with malignant pheochromocytomas or paragangliomas. *J Clin Endocrinol Metab.* 2007;92(10):3822-3828.
117. Ricketts C, Woodward ER, Killick P, et al. Germline SDHB mutations and familial renal cell carcinoma. *J Nat Cancer Inst.* 2008;100(17):1260-1262.
118. Vanharanta S, Buchta M, McWhinney SR, et al. Early-onset renal cell carcinoma as a novel extraparaganglial component of SDHB-associated heritable paraganglioma. *Am J Hum Genet.* 2004;74(1):153-159.
119. Morris MR, Maina E, Morgan NV, et al. Molecular genetic analysis of FIH-1, FH, and SDHB candidate tumour suppressor genes in renal cell carcinoma. *J Clin Pathol.* 2004;57(7):706-711.
120. Ricketts CJ, Shuch B, Vocke CD, et al. Succinate dehydrogenase kidney cancer: an aggressive example of the Warburg effect in cancer. *J Urol.* 2012;188(6):2063-2071.
121. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med.* 2006;355(13):1345-1356.
122. European Chromosome 16 Tuberous Sclerosis Consortium. Identification and characterization of the tuberous sclerosis gene on chromosome 16. *Cell.* 1993;75(7):1305-1315.
123. Kozlowski P, Roberts P, Dabora S, et al. Identification of 54 large deletions/duplications in TSC1 and TSC2 using MLPA, and genotype-phenotype correlations. *Hum Genet.* 2007;121(3-4):389-400.
124. van Slegtenhorst M, de Hoogt R, Hermans C, et al. Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. *Science.* 1997;277(5327):805-808.
125. Dabora SL, Jozwiak S, Franz DN, et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. *Am J Hum Genet.* 2001;68(1):64-80.
126. Dixon BP, Hulbert JC, Bissler JJ. Tuberous sclerosis complex renal disease. *Nephron Exp Nephrol.* 2011;118(1):e15-e20.
127. Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet.* 2013; 381(9869):817-824.