Genetic Kidney Cancer Syndromes

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Abstract

Hereditary forms of renal cell carcinoma (RCC) have yielded clues regarding the molecular pathogenesis of sporadic RCC. The discovery of germline mutations in chromatin-modulating enzymes also defined a new hereditary RCC syndrome. Although histologically distinct RCC subtypes exist, emerging themes shared between hereditary and sporadic RCC include dysregulation of the von Hippel-Lindau tumor suppressor protein/hypoxia inducible factor axis, defective ciliogenesis, and aberrant tumor metabolism. This article describes the most common hereditary RCC syndromes and associated extrarenal manifestations. Recent evidence supports developing screening guidelines for early-onset RCC to identify persons with germline mutations in the absence of secondary clinical manifestations. (J Natl Compr Canc Netw 2014;12:1347–1355)

Hereditary renal cell carcinoma (RCC) has been estimated to account for 5% to 8% of all RCC cases, and extrarenal manifestations may present as early as 3 years of age (Table 1).1,2 RCC is a diverse set of cancers that originate from the renal parenchyma. Histologic classifications include clear cell, papillary, chromophobe, and translocation; rare subtypes include renal medullary and collecting duct. Hereditary familial RCC syndromes have yielded clues regarding the molecular pathogenesis of sporadic RCC and have served as a framework for the development of targeted therapies. With diverse presentations and incomplete penetrance of RCC, establishing screening guidelines for detecting early-onset RCC may help identify persons with germline mutations who have an increased risk of developing RCC.

von Hippel-Lindau Disease

von Hippel-Lindau (VHL) disease is an autosomal dominant disorder caused by germline mutations in the VHL gene, a tumor suppressor found on chromosome 3p25.3 Patients inherit a nonfunctional VHL allele from a parent, or have a de novo germline VHL mutation.4 A stochastic secondary inactivation of the other allele leads to the development of renal cysts and tumors. The most common sporadic RCC histologic type (75%) is clear cell RCC (ccRCC), which is also associated with loss of VHL function. Mechanisms of biallelic VHL inactivation in sporadic ccRCC include loss of heterozygosity at the VHL locus, somatic VHL mutations, and VHL hypermethylation.5 The VHL gene product, pVHL, acts as an oxygen sensor that regulates degradation of the hypoxia-inducible factors (HIFs) (Figure 1). The HIF family contains 3 subunits: HIF-1α, HIF-2α, and HIF-3α. HIFs bind hypoxia-related elements to transactivate target genes, such as vascular endothelial growth factor (VEGF), involved in cellular adaptation to hypoxia. pVHL acts as the substrate recognition component of the ubiquitin E3 ligase complex.6 Recognition by pVHL requires the hydroxylation of HIF-1α and HIF-2α by an oxygen-dependent prolyl hydroxylase, and in normoxia, pVHL targets HIF-1α and HIF-2α for proteasomal degradation.7 Conversely, in hypoxic conditions or in pVHL-deficient cells, HIF-1α and HIF-2α bind to HIF-1β, forming a transcription factor leading to expression of hypoxia-responsive genes.8 In the setting of pVHL loss, inhibition of HIF-2α is sufficient to suppress tumor formation.9 pVHL loss is also associated with Aurora
kinase A overexpression and formation of visceral cysts, a common feature shared with other ciliopathies.

VHL disease is characterized by an increased risk of kidney cysts, ccRCC, pheochromocytomas, and central nervous system hemangioblastomas (Table 1 and Figure 2). The mean age of RCC onset is 35 years, and RCC is the leading cause of death in persons affected by VHL disease. In a trial evaluating the use of sunitinib in VHL-associated lesions, responses were noted in renal lesions but not hemangioblastomas. Activation of the fibroblast growth factor (FGF) pathway may mediate escape from VEGF inhibition and a trial of dovitinib, an inhibitor of VEGF and FGF signaling, is underway in VHL (ClinicalTrials.gov identifier: NCT01266070), but results are not yet available. Other potential therapeutic interventions include Aurora kinase A inhibitors to restore primary cilia formation, but whether restoring cilia would reduce tumorigenesis in renal cyst mice models is unknown.

**Tuberous Sclerosis Complex**

Tuberous sclerosis complex is caused by germline mutations in the TSC1/2 genes, located on chromosomes 9q34 and 16p13, respectively. The mTOR complex 1 (mTORC1) signaling cascade is regulated by a heterodimer of TSC1 (hamartin) and TSC2 (tuberin), which function as tumor suppressors (Figure 1). Inactivation of TSC1/2 results in a derepression of mTORC1 inhibition. The mTOR pathway responds to both external and internal stimuli to regulate a diverse set of processes, including cell proliferation, nutrient abundance, protein synthesis, and cytoskeletal rearrangements.

Persons who inherit TSC1/2 mutations may develop hamartomas, angiomyolipomas, pulmonary lymphangioleiomyomatosis, subependymal giant cell astrocytomas, and RCC (Figure 3). Similar to those with VHL disease, persons with TSC1/2 mutations have kidney cysts that are associated with ciliary dysfunction. Angiomyolipomas cause morbidity through spontaneous hemorrhage, invasion of adjacent renal parenchyma, and chronic kidney disease. The identification of mTORC1 activation caused by TSC1/2 mutations led to clinical trials using sirolimus, an mTOR inhibitor (ClinicalTrials.gov identifier: NCT00457808), in patients with tuberous sclerosis complex. Everolimus was approved by the FDA for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis after a phase III trial showed a response rate of 42%, defined as a reduction in angiomyolipoma volume of 50%. In the study, 78% of the patients had bilateral angiomyolipomas and 40% had prior invasive procedures, suggesting that everolimus is
### Table 1  Hereditary Renal Cancer Carcinoma Syndromes

<table>
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<tr>
<th>Syndrome</th>
<th>Pattern of Inheritance</th>
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<th>RCC Histologic Characteristic</th>
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<th>Possible RCC Therapies and Drug Trials</th>
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<td>VHL</td>
<td>AD</td>
<td>VHL</td>
<td>pVHL</td>
<td>ccRCC</td>
<td>Hemangioblastomas&lt;br&gt;Pheochromocytomas&lt;br&gt;Endolymphatic sac tumors&lt;br&gt;Paragangliomas&lt;br&gt;Cystadenomas of epididymis&lt;br&gt;Visceral cysts</td>
<td>At age ≥15 y: Annual ophthalmologic examination&lt;br&gt;Annual plasma metanephrine, normetanephrine, chromogranin testing&lt;br&gt;Annual abdominal imaging&lt;br&gt;Annual audiometry&lt;br&gt;MRI of CNS q2y&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Sunitinib&lt;sup&gt;15&lt;/sup&gt; Pazopanib (ClinicalTrials.gov identifier: NCT01486227) Verdutinib (ClinicalTrials.gov identifier: NCT01266070) Vandetanib (ClinicalTrials.gov identifier: NCT00566995)</td>
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<tr>
<td>Tuberous sclerosis complex</td>
<td>AD</td>
<td>TSC1/TSC2</td>
<td>Hamartin/tuberin</td>
<td>Angiomyolipoma, RCC</td>
<td>Angiomyolipomas&lt;br&gt;Subependymal giant cell astrocytomas&lt;br&gt;Hamartomas&lt;br&gt;Cutaneous fibromas&lt;br&gt;Autism spectrum disorder&lt;br&gt;Pulmonary lymphangioleiomyomatosis</td>
<td>MRI abdomen q1–3y&lt;br&gt;CT chest (with lung cysts) q2–3y&lt;br&gt;Annual dermatologic examination&lt;br&gt;Dental exam q6mo&lt;br&gt;Echocardiography q1–3y based on symptoms&lt;br&gt;Annual ophthalmologic examination&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Temsirolimus, everolimus&lt;sup&gt;16,17&lt;/sup&gt;</td>
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<td>PTEN hamartoma syndrome</td>
<td>AD</td>
<td>PTEN</td>
<td>PTEN</td>
<td>ccRCC</td>
<td>Breast cancer&lt;sup&gt;19&lt;/sup&gt; Follicular thyroid carcinoma&lt;br&gt;Endometrial cancer&lt;br&gt;Mucocutaneous papules&lt;br&gt;Autism spectrum disorder&lt;br&gt;Macrocephaly&lt;br&gt;Lhermitte-Duclos disease</td>
<td>Adults: annual thyroid ultrasound and dermatologic examination, colonoscopy (age ≥35 y), abdominal imaging q2y (age ≥40 y) Women (age ≥30 y): annual breast screening, gynecologic ultrasound Consider screening 5–10 y before youngest age of diagnosis in family&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Temsirolimus, everolimus&lt;sup&gt;16&lt;/sup&gt;</td>
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<td>Hereditary papillary RCC, type I papillary kidney cancer</td>
<td>AD</td>
<td>MET</td>
<td>c-MET</td>
<td>Papillary type I</td>
<td>No reported extrarenal manifestations</td>
<td>Annual abdominal imaging&lt;sup&gt;26&lt;/sup&gt; Cabozantinib (ClinicalTrials.gov identifier: NCT01885747) INC280 (ClinicalTrials.gov identifier: NCT02019693) Fotereinib&lt;sup&gt;27&lt;/sup&gt;</td>
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<td>Hereditary leiomyomatosis and RCC, type II papillary kidney cancer</td>
<td>AD</td>
<td>FH</td>
<td>FH</td>
<td>Papillary type II</td>
<td>Cutaneous leiomyomas&lt;br&gt;Uterine leiomyomas&lt;br&gt;Renal cysts</td>
<td>Dermatologic examinations q1–2y&lt;br&gt;Annual MRI to evaluate for renal lesions&lt;br&gt;Annual gynecologic ultrasound&lt;sup&gt;25,34&lt;/sup&gt;</td>
<td>Bevacizumab/erlotinib (ClinicalTrials.gov identifier: NCT0130519)</td>
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<td>SDH-associated kidney cancer</td>
<td>AD</td>
<td>SDH</td>
<td>SDH subunits B/C/D</td>
<td>ccRCC, chromophobe, oncocytoma</td>
<td>Paraganglioma&lt;br&gt;Pheochromocytoma&lt;br&gt;Gastrointestinal stromal tumors</td>
<td>Abdominal imaging&lt;sup&gt;26&lt;/sup&gt; MRI of the paraganglial system</td>
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<td>Birt-Hogg-Dubé</td>
<td>AD</td>
<td>FLN</td>
<td>Folliculin</td>
<td>Mixed oncocytic/chromophobe</td>
<td>Fibrofolliculomas&lt;br&gt;Pulmonary cysts&lt;br&gt;Trichodiscomas&lt;br&gt;Acrochordons</td>
<td>Age ≥20 y: Annual abdominal imaging or q36mo in persons without renal lesions (MRI preferable)&lt;br&gt;Baseline chest imaging&lt;sup&gt;26,28&lt;/sup&gt;</td>
<td></td>
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<td>BAP1 predisposition to familial ccRCC</td>
<td></td>
<td>BAP1</td>
<td>BRCA1-associated protein-1</td>
<td>ccRCC</td>
<td>Uveal melanoma&lt;br&gt;Melanoma&lt;br&gt;Mesothelioma</td>
<td>Not established, consider annual abdominal imaging</td>
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an alternative for patients with multifocal disease or those ineligible for surgical intervention. Multiple renal cysts and angiomyolipomas develop, and renal disease is the leading cause of death in persons affected by tuberous sclerosis complex.\(^18\) Other causes of death include pulmonary lymphangioleiomyomatosis and subependymal giant cell astrocytomas.

**Phosphatase and Tensin Homolog Hamartoma Syndrome**

Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome is linked to inactivating germ-line mutations in *PTEN*, located on chromosome 10q23.\(^19\) Loss of PTEN function leads to a potent derepression of the phosphoinositide 3-kinase/AKT pathway, which stimulates cell growth and survival (Figure 1).\(^20\) PTEN mutations occur in approximately 5% of sporadic ccRCC cases, and a decrease in PTEN protein expression occurs in a significant number of sporadic RCCs.\(^21\)

The lifetime risk of RCC in persons with germ-line PTEN mutations is estimated to be as high as 34%, with typical onset of RCC at age 40 years.\(^22\) PTEN hamartoma tumor syndrome is also associated with a spectrum of clinical manifestations, including breast cancer, endometrial cancer, follicular thyroid cancer, hamartomas, and mucocutaneous lesions (Figure 4).\(^19\) Although ascertainment bias may overestimate the risks, the age-related penetrance estimates reveal lifetime risks of 85%, 35%, 28%, 9%, and 6% for female breast cancer, thyroid cancer, endometrial cancer, colon cancer, and melanoma, respectively.\(^22\) Targeting the mTOR pathway in the context of PTEN deficiency has been proposed in PTEN hamartoma tumor syndrome–associated cancers, to exploit this potential vulnerability. A trial of sirolimus was completed in persons with PTEN hamartoma tumor syndrome (ClinicalTrials.gov identifier: NCT00971789), but the results are not available.

**Hereditary Papillary RCC, Type I Papillary Kidney Cancer**

Originally described as an inherited RCC that was histologically distinct from VHL disease, hereditary papillary RCC (HPRC) is an autosomal dominant cancer syndrome characterized by mutations in the proto-oncogene *MET* on chromosome 7q31 (Figure 1).\(^23\) Type I papillary RCCs occur in sporadic and hereditary forms, and somatic MET mutations are also found in approximately 10% of sporadic papillary kidney cancer.\(^24\) *MET* encodes the cell surface receptor for hepatocyte growth factor that promotes
migration, invasion, proliferation, and angiogenesis. Unlike sporadic ccRCC and VHL disease, these RCC tumors lack 3p alterations but exhibit trisomy 7, leading to multiple copies of MET and tumorigenesis initiated by the combination of a MET mutation and duplication of the mutated allele.25

Persons affected by this cancer syndrome can have bilateral involvement with more than 1000 tumors per kidney, suggesting the presence of microscopic precursors that may not be apparent on routine imaging.25 Extrarenal manifestations have not been reported. The presence of MET pathway activation or germline MET mutations was recently associated with responses to foretinib, a multikinase inhibitor targeting MET/VEGF receptor 2.27 A risk-adapted approach of observing patients with small tumors (<3 cm), independent of location or number of tumors, was developed to guide surveillance based on a 10-year follow-up study of parenchymal-sparing surgery in hereditary RCC.28 Papillary RCC is hypoechoic and can be missed by ultrasound.29 Active surveillance with CT/MRI is recommended until a kidney tumor reaches 3 cm to mitigate the risk of metastatic disease and preserve renal function.

Focused Review
Genetic Kidney Cancer Syndromes

Hereditary Leiomyomatosis and RCC, Type II Papillary Kidney Cancer

Hereditary leiomyomatosis and RCC (HLRCC) is characterized by a germline mutation in FH (fumarate hydratase), found on chromosome 1q42.30 FH is a Krebs cycle enzyme that converts fumarate to malate, and FH inactivation causes a metabolic shift to aerobic glycolysis in FH-deficient kidney cancer.31 The buildup of fumarate inhibits prolyl hydroxylase (PHD), interferes with the recognition of HIF-1α and HIF-2α by pVHL, and leads to an increase in VEGF-mediated angiogenesis (Figure 1).32

Affected persons can present with cutaneous leiomyomas, uterine leiomyomas, and type II papillary RCC (Figure 5).32,33 Systemic therapy specific for patients with HLRCC has yet to be fully developed. Expression profiling of an Fh1-deficient mouse model and HLRCC cell lines shows a common pathway of dysregulated glycolytic genes, suggesting that FH deficiency may sensitize cells to glycolytic inhibitors.31 For example, the glycolytic inhibitor 2-deoxy-D-glucose was used to treat a patient with HLRCC after experiencing disease progression while receiving an mTOR inhibitor, and although the patient experienced hypoglycemia consistent with inhibition of glycolysis, no antitumor effect occurred.33 The median age of onset for the development of papillary RCC is 37 years, and individuals in approximately 15% of families with HLRCC develop disease.1,29 Although a 3-cm threshold is used to guide management of RCC in other hereditary syndromes, immediate surgical management of any identified HLRCC-associated renal tumors is suggested because of aggressive growth and a propensity for early metastases.34 Papillary RCC is hypoechoic, can be missed by ultrasound, and is best screened with CT/MRI imaging.29 Uterine leiomyomas also develop earlier in women affected by cutaneous leiomyomas compared with the general population.34 Because of symptomatic leiomyomas, women affected by HLRCC have higher rates of hysterectomy and undergo hysterectomy at a younger age, indicating a need for family planning counseling.

Succinate Dehydrogenase–Associated Kidney Cancer

Succinate dehydrogenase (SDH)–associated kidney cancer is linked to a germline mutation in genes that
encode for subunits of the tricarboxylic acid cycle enzyme, SDH. SDH genes include SDHA (chromosome 5p15), SDHB (chromosome 1p36), SDHC (chromosome 1q23), and SDHD (chromosome 11q23). Mutations in SDH cause accumulation of succinate and, similar to fumarate in HLRCC, also inhibit prolyl hydroxylation of HIF-1α and HIF-2α (Figure 1).

RCC may be the only clinical presentation in persons with germline SDHB, SDHC, or SDHD mutations. Extrarenal manifestations include pheochromocytomas, paragangliomas, carotid body tumors, and gastrointestinal stromal tumors. Because of the rarity of these tumors, no established screening guidelines have been developed. Mutations in Krebs cycle enzymes shift the cells toward increased glucose uptake, aerobic glycolysis, and fatty acid synthesis. The increased dependence on glycolytic pathways suggests that inhibitors of glucose uptake, glycolysis, and fatty acid synthesis could exploit the vulnerability of these tumors. Among the SDH subunit mutations, SDHB and SDHD carriers are more likely to develop RCC, with a median age of onset of 30 years. Symptoms related to pheochromocytomas and paragangliomas may present as early as 3 years of age in germline carriers, supporting a role for germline testing of SDHB and SDHD at initial presentation. Subsequent surveillance for renal masses and extrarenal manifestations is likely warranted in this population.

**Birt-Hogg-Dubé Syndrome**

Birt-Hogg-Dubé (BHD) is an autosomal dominant syndrome caused by mutations of the FLCN gene, located on chromosome 17p11. The FLCN gene encodes for folliculin, a downstream target of both adenosine monophosphate–dependent protein kinase and mTORC1 signaling; folliculin also localizes to cilia (Figure 1). Loss of folliculin function leads to mTORC1 activation and dysregulation of ciliogenesis.

Clinically, BHD is characterized by fibrofolliculomas, pulmonary cysts, and early-onset RCC, commonly with mixed oncocytoma and chromophobe histologic characteristics. Similar to the VHL and tuberous sclerosis complex disease syndromes, the BHD-associated pulmonary cysts share characteristics consistent with a ciliopathy. The risk of developing RCC at age 70 years has been estimated to be 16% in patients with BHD, with characteristic hybrid histologic characteristics of chromophobe RCC and oncocytomas. Similar to VHL disease and HPRC, active surveillance is recommended for the management of renal lesions less than 3 cm. When adjusted for age, persons with BHD have a 50-fold increased risk of pneumothorax. Pulmonary consultation is recommended for those at risk of ambient atmospheric pressure changes, and smoking cessation may reduce morbidity associated with pulmonary cysts. mTOR inhibitors have prolonged survival of folliculin-deficient mice and have been proposed to treat the clinical manifestations of BHD. A trial of topical rapamycin to treat BHD-associated fibrofolliculomas did not reduce the size or number of cutaneous lesions.

**BRCA1-Associated Protein-1 Predisposition to Familial ccRCC**

Systematic sequencing of sporadic ccRCC identified loss-of-function mutations in histone-modulating enzymes, such as the BRCA1-associated protein-1 (BAP1) (5%–15%) gene on chromosome 3p21.1. BAP1 functions as a nuclear deubiquitinase that interacts with polycomb group (PcG) proteins at open

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**Figure 5** Clinical manifestations of hereditary leiomyomatosis and renal cell carcinoma (HLRCC). HLRCC is an autosomal dominant hereditary cancer syndrome in which affected persons have germline inactivating mutations of FH. Affected persons are at increased risk for tumor development of skin, uterus, and kidney. Abbreviation: RCC, renal cell carcinoma.
chromatin and promotes double-strand break repair (Figure 1). After the discovery of BAP1 mutations in sporadic ccRCC, germline mutations were linked with familial ccRCC syndromes. Germline BAP1 mutations are also associated with uveal melanomas and mesotheliomas. However, the BAP1 syndrome is rare, making it difficult to assess its prevalence in the general population and estimate tumor risks to guide surveillance. The use of general guidelines for early-onset kidney screening may be considered based on age of initial presentation.

Overlapping Mechanisms Between Hereditary and Sporadic ccRCC

The overlap of gene mutations in VHL, TSC1, MTOR, PTEN, and BAP1 in both hereditary and sporadic ccRCC has increased the understanding of tumorigenesis. The 4 most frequently mutated genes (VHL, ≈52%; polybromo-1, ≈33%; SETD2, ≈12%; and BAP1, ≈10%) are located on chromosome 3p, a region that is deleted in more than 90% of sporadic ccRCCs, supporting a mechanism of biallelic inactivation of these tumor suppressors. In parallel with the clinical benefit seen with mTOR inhibitors in the tuberous sclerosis complex syndrome, a subset of patients with sporadic ccRCC and TSC1 inactivation or MTOR mutations may experience a durable response to mTOR inhibitors. PTEN (≈4%) and PIK3CA (≈3%) mutations occur in approximately 4% of sporadic ccRCC cases, supporting a phenotypic convergence on the PI3K/mTOR axis (Figure 1). An integrated analysis of molecular pathways identified a common metabolic phenotype of increased glycolysis between sporadic ccRCC and HLRCC. Krebs cycle mutations in HLRCC and SDH-associated kidney cancer stabilize HIF and shift metabolism to increased reliance on aerobic glycolysis, characterized as “the Warburg effect,” by mobilizing nutrients (nucleotides, amino acids, lipids) for cell proliferation. Similarly, in sporadic ccRCC, biallelic inactivation of VHL leads to HIF stabilization, and tumors with metabolic shifts toward aerobic glycolysis are associated with a worse survival.

Establishing a Role for Early-Onset Kidney Cancer Screening

The median age of patients with sporadic RCC was 64 years in an analysis of the SEER 17 registry program, which was considerably older than the median age of 37 years in a cohort of patients with hereditary kidney cancer. At the NCI Urologic Oncology Branch, patients with VHL, BHD, HLRCC, HPRC, and SDHB syndromes had median ages of onset ranging from 35 to 50 years. Because the median age of presentation for hereditary RCC is 27 years younger than that for RCC observed in the general population, patients with RCC who are 46 years old or younger should consider ge-

**Figure 6** Germline testing of selected genes based on renal cell carcinoma (RCC) histology: (A) clear cell, (B) papillary type I, (C) papillary type II, and (D) chromophobe. Persons with RCC aged 46 years or younger should be considered for genetic counseling and germline mutations testing, even in the absence of secondary clinical manifestations. The RCC histologic characteristics may guide which germline mutations to test. (Hematoxylin and eosin stain; original magnification x10 and x40 [inset]) Courtesy of Dr. Melissa L. Stanton, Mayo Clinic Arizona.
netic counseling and germline mutation testing even in the absence of secondary clinical manifestations. The histology of early-onset RCC may guide which germline mutations to test (Figure 6).

Conclusions
 Patients with hereditary RCC syndromes provide the clinician with unique diagnostic, surveillance, and therapeutic challenges. Many of the described syndromes demonstrate highly distinct phenotypes, allowing clinical findings to guide genetic testing. Once a hereditary RCC syndrome is identified, careful adherence to surveillance strategies, appropriate management of the renal and extrarenal disease manifestations, and attention to at-risk family members will lead to improvement in patient outcome.

The hereditary drivers of several nonsyndromic RCC cohorts have long eluded investigators. Advances in genomewide sequencing technologies have led to the identification of additional mutations in RCC and to the discovery of the most recently described BAP1 familial RCC syndrome.

Despite the complexity of networks involved in hereditary and sporadic RCC, these alterations share a common dysregulation of the HIF-VEGF axis and aberrant tumor metabolism. The identification of genes linked to RCC syndromes has led to the development of clinical trials selecting for patients affected by hereditary syndromes (Table 1). Additional drug targets may exist outside the mTOR and VEGF pathways, such as proteins that influence metabolic sensitivity or chromatin remodeling proteins. Ultimately, the identification of new druggable targets for sequential or combination therapies may provide a more robust form of therapy for patients who have sporadic and hereditary RCC.

The observed early onset of hereditary RCC indicates that primary preventative strategies are more likely to increase life expectancy in affected persons than administering targeted therapies in the metastatic setting. Persons affected with RCC at age 46 years or younger should be considered for genetic counseling and germline mutational testing, even in the absence of secondary clinical manifestations. As life expectancy increases, additional clinical manifestations in hereditary RCC syndromes will undoubtedly become apparent, and clinicians and families must maintain vigilant and report new findings.

References

Genetic Kidney Cancer Syndromes


