Published in final edited form as:

Semin Ultrasound CT MR. 2017 February ; 38(1): 59–71. doi:10.1053/j.sult.2016.10.002.

Hereditary Renal Tumor Syndromes: Update on Diagnosis and Management

Sonia Gaur, BS^{1,2}, Baris Turkbey, MD¹, and Peter Choyke, MD¹

¹Molecular Imaging Program, National Cancer Institute, Bethesda, MD

²Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA

Abstract

Hereditary renal cancers account for about 5–8% of all renal tumors. Over the last two decades a number of syndromes have been identified that predispose patients to early renal cancer development, representing all the major histologic types of tumor pathology. In this review, we describe the current knowledge concerning the cell type, known mechanism of tumor development, other manifestations of the syndrome, imaging findings, genetic screening and imaging surveillance recommendations for each of the major syndromes associated with hereditary renal cancers.

Introduction

Hereditary renal cancers account for 5–8% of human renal cancers. Because genetic associations are not always known in a particular patient and because we do not yet recognize all the genetic factors involved in renal cancer, the percentage of renal tumors that are likely to have a hereditary component is probably higher. The presence of a hereditary tumor has important implications for the patient and the family. For the patient, association with a particular form of hereditary renal cancer has implications for the aggressiveness of the disease, other medical conditions, how frequently surveillance imaging should be performed and how the features of that hereditary condition need to be prioritized. For the family, identification of a genetic cause of renal cancer has practical implications for genetic screening, counseling and family planning.

There are many ways to classify hereditary renal cancers. One can describe them by their frequency, the type of renal tumors they produce, how they are managed, their aggressiveness among others. Here we will take an imaging-centric approach, grouping conditions by their appearance on cross sectional imaging. Of course, in reality there is often more known about the patient than just their imaging, for instance there may be prior

Address Correspondence to: Peter Choyke, MD, Molecular Imaging Program, National Cancer Institute, Building 10, Room B3B69F, Bethesda, MD 20892, pchoyke@nih.gov, T: 301 402 8409, F: 301 402 3191.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

information regarding a patient's family history that would be important for diagnosis. However, for the sake of organization we will focus on imaging features.

Hereditary tumors are recognized by their early onset, their multiplicity, and a history of first and second degree relatives having similar manifestations. We will begin with Von Hippel Lindau (VHL) that presents with multiple solid, cystic, and solid-cystic renal masses, presenting a characteristic imaging appearance for this most common of hereditary renal cancer syndromes. We will proceed to Birt Hogg Dube (BHD) syndrome in which multiple solid lesions are seen. Next, we consider Tuberous Sclerosis Complex (TSC) in which angiomyolipomas are commonly accompanied by non-fatty solid masses, including renal cancer, and cysts. This will be followed by a description of Hereditary Papillary Renal Cancer (HPRC) in which the tumors are poorly enhancing papillary type I tumors. In contrast to this relatively slow growing tumor type, the tumors associated with Hereditary Leiomyoma Renal Cell Carcinoma (HLRCC) are among the most aggressive. They are often also hypoenhancing but contain cystic components. Usually only one tumor is present unlike HPRC. Renal Medullary Carcinoma (RMC) is typically a large tumor seen in young patients with the sickle cell trait. If a renal mass involves the renal pelvis and has a hereditary component, thoughts turn to Hereditary Non Polyposis Colon Cancer (HNPCC) or Lynch syndrome (LS) which is better known for its association with colorectal cancers. If the tumor is solitary and looks like a sporadic renal cancer then consideration should be given to a number of other genetic conditions predisposing to renal cancer. These include Succinate Dehydrogenase Subunit B (SDHB) found in association with paragangliomas and pheochromocytomas, translocation of chromosome 3, Cowden's and Familial Renal Carcinoma (FRC) (Fig. 1).

It is important to use the terms screening and surveillance in a clearly understood manner. Screening usually refers to genetic testing of both affected and non-affected family members. Surveillance usually refers to serial testing with imaging and other serum markers to monitor the progression of the disease in an individual patient.

The discovery of a hereditary renal cancer syndrome in a patient prompts several responses. Consideration should be given to referral of the patient to a center specializing in genetic causes of renal cancer as these conditions are rare and experience can only be accumulated in specialized centers. One of the prime considerations is genetic screening of first degree relatives, either looking for specific mutations found in the proband or by karyotyping depending on the condition. The next consideration is surveillance in the affected individual. This typically is done with imaging and specific serum biomarkers as indicated by the condition. Increasingly, as the quality of body MRI has improved, surveillance is done with this modality as it spares the patient inordinate exposure to ionizing radiation over their lifetime. Low dose CT continues to play an important role as the disease may not be well characterized by MRI in all cases. A policy of alternating CT and MRI on serial surveillance imaging markedly reduces ionizing radiation while benefiting from the complementary nature of CT and MRI. However, it is vital that the tempo of the disease be understood regardless of how the patient is imaged. For instance, surveillance is not recommended for HLRCC, SDHB, RMC, and HNPCC as these tumors are uniformly aggressive. Close

surveillance (every year or every other year) is recommended in VHL, BHD, and TSC, whereas less intense surveillance is warranted in HPRC.

Treatment also varies according to disease. For the aggressive tumor types described above, aggressive loco-regional surgery is recommended as these tumors tend to be locally invasive. Complete resection is the best chance for a long term survival and therefore, radical nephrectomy may be indicated. For the intermediate and low risk tumor types, emphasis is placed on nephron sparing techniques including robotic nephron sparing surgery and focal ablations. In this manner the tumors can be controlled while renal function is maintained for the maximal period. The risks associated with chronic dialysis or transplantation caused by overly aggressive surgical or ablative therapy can be nearly as high as the tumor itself so a balanced approach between treatment and active surveillance is warranted. In this regard, for the syndromes that pose intermediate and low risk, a threshold diameter of 3cm for a solid renal tumor has proven successful in avoiding metastatic disease while spacing out surgical procedures so as to delay loss of renal function. This strategy has proven successful over a variety of hereditary conditions as will be described.

Having discussed the various hereditary renal cancers in a general way, we will now discuss each entity separately considering their genetics, the mechanism by which they form renal cancers, the types and characteristics of the renal cancers, other manifestations of the disease and clinical and screening/surveillance strategies.

Von Hippel Lindau (VHL)

Genetics and mechanism

VHL is caused by a mutation in the VHL gene on 3p25.6 which has 3 exons.¹ Many (~1000) different mutations, splice variants, deletions and complete loss of the gene have been described in VHL. Approximately 75% are point mutations or small deletions/insertions that can be detected by sequence analysis, with the remaining alterations being partial or complete gene deletions that can be detected by duplication/deletion analysis.² The protein VHL is known to normally interact with various hypoxia inducible factors (HIF) so as to encourage their degradation. These proteins are hypoxia responsive and are part of the cell's oxygen sensing mechanism. HIF1 α and HIF1 β are upregulated in hypoxia and become transcription factors for various growth factors including vascular endothelial growth factor (VEGF), epithelial growth factor receptor (EGFR), platelet derived growth factor (PDGF) and glucose transporter (GLUT 1) among others. When VHL is mutated, it no longer performs this vital task of regulating the HIFs, which then accumulate despite normoxic conditions. Whereas the cell might function relatively normally with one disabled copy of VHL, when a second "hit" occurs in the wild type copy of VHL, this can lead to uncontrolled growth. Thus, the cell behaves as if it is chronically hypoxic and produces factors that stimulate growth of tumors. VHL is a truncal gene in clear cell renal cancer and can be found commonly in sporadically occurring renal cancer.²

The VHL syndrome occurs with a frequency of approximately 1:36000 making it the most common hereditary renal cancer. There is 90% penetrance by age 60.³

Renal manifestations

Approximately 25–40% of patients with VHL develop clinical renal cell carcinoma. The cell type associated with VHL is always clear cell carcinoma. It manifests most frequently as a clear cell lining of otherwise benign cysts but also as solid and solid cystic tumors. One common manifestation of VHL cancers is as a sponge-like mass consisting of numerous cysts with solid, clear cell elements forming the enhancing part of the tumor. Many tumors have solid and cystic components. From a clinical viewpoint, the amount of solid disease, not cystic disease, determines whether the lesion should be treated. The risk of metastasis occurring in tumors <3cm in diameter is very low and therefore this diameter is used as the threshold for initiation of therapy.⁴

Based on careful microscopic evaluation of resected kidneys, up to 600 microtumors and 1100 microcysts can be detected in a VHL kidney.³ However, the vast majority of these are slow growing and at any given time most patients have only 2 or 3 tumors near or exceeding 3cm in diameter. Exceptions to this rule can occur rarely.

It is widely quoted that 35–45% of patients with VHL will die of metastatic disease, which may have been true in the past before widespread use of cross sectional imaging. Now, tumors are discovered at an earlier stage and nephron sparing surgery or renal ablations are performed much more expeditiously. Thus, death from metastatic renal cancer in VHL has become less common. Occasionally, so much of the kidney needs to be resected that the patient is rendered functionally or anatomically anephric. When bilateral nephrectomies become inevitable, renal transplantation can be considered after a 1- to 2 year metastasis-free waiting period and as long as transplant immunosuppression does not adversely affect the underlying course of VHL disease.⁵

Appearance on imaging

Contrast enhanced CT or MRI reveals intensely enhancing foci within the tumor on arterial phase imaging (Fig. 2). There is generalized enhancement on the nephrographic phase which expands over the arterial phase enhancement area. Enhancement tends to be heterogeneous either due to cysts or necrosis within the tumor. T2 weighted MRI can demonstrate the extent of cystic disease but often the cystic components are not as bright as simple cysts due to the presence of protein or hemorrhage in the cyst. Fat suppressed T1 weighted contrast enhanced MRI with subtraction can be helpful in differentiating complex cysts from enhancing solid tumor (Fig. 3).⁶

Other manifestations

VHL also affects many organs in the body. In the abdomen the pancreas can contain cysts, serous cystadenomas and solid enhancing tumors known as non-functional pancreatic neuroendocrine tumors (PNET) (Fig. 4). The latter are early enhancing lesions seen only on arterial phase imaging (co-incident with enhancement in clear cell carcinomas. Adrenal and extra-adrenal pheochromocytomas also enhance early. In the posterior fossa of the brain, hemangioblastomas are seen as enhancing solid and cystic masses. They are confined to the cerebellum and brainstem but are also found throughout the spinal column and nerve roots. Similar tumors are found in the retina where they are called retinal angiomas. Early attention

to these lesions can avert blindness. Deafness can be caused by endolymphatic sac tumors (ELST) arising in the inner ear. Other features of VHL include epididymal cystadenomas and cystadenomas of the broad ligament in women.

Genetic Screening

Mutation gene testing should be performed in family members based on the proband's genetic abnormality.

Imaging Surveillance

In affected patients, abdominal ultrasound should be performed every two years up to age of 16.³ Beyond age of 16, annual abdominal MRI or CT should be performed. If CT is used, dose reduction should be employed as patients may eventually have 30 or more cross sectional imaging studies for surveillance alone over the course of their lifetime. Based on the growth rates and specific mutations in an individual patient, the interval and imaging modality may be modified.^{7,8} Intervention should occur when a lesion reaches 3 cm.

Birt Hogg Dubè (BHD)

Genetics and mechanism

Birt Hogg Dube (BHD) syndrome is an autosomal dominant condition caused by a germline inactivating mutation in the suppressor gene called folliculin (FLCN) located on 17p11.2. Defects in FLCN are transmitted in the germline in an autosomal dominant pattern. Loss of FLCN causes an upregulation of mTOR activity which in turn, leads to cell growth especially after a 2nd hit in the normal allele.⁹ FLCN may play a role in the differentiation of renal tubular cells.³ HIF is also stabilized by FLCN mutations, similar to what occurs in VHL, resulting in increased transcription of growth factor genes downstream of HIF.

Renal manifestations

Approximately 13–34% of affected patients have renal tumors. Unlike VHL in which all tumors are clear cell carcinomas, the renal tumors associated with BHD vary in histological type. Approximately 50–67% of tumors are of the hybrid oncocytic-chromophobe type, 23–34% are chromophobe tumors, 7–9% are clear cell, 3–5% are oncocytomas, and approximately 2% are papillary renal cancers.² Angiomyolipomas have also been reported and renal cysts are commonly seen.^{10–12} In 80% of cases there is a discordance of tumor subtype among different tumors in the same patient.

Most BHD renal tumors are of intermediate aggressiveness comparable to VHL. Although it appears that the BHD renal tumors are somewhat less aggressive than several other hereditary RCC syndromes, the disease should not be considered as uniformly indolent since aggressive tumor behavior has been documented.¹³ Hence, BHD tumors are often called oncocytic neoplasia of uncertain malignant potential by pathologists.¹⁴

Appearance on imaging

Oncocytic and Chromophobe RCC and their hybrids exhibit homogeneous enhancement on CT and MR images (Fig. 5, Fig. 6). There is a conspicuous absence of necrosis centrally and

the tumors are notable for their uniformity. The lesions can be large (> 7 cm) and often contain calcifications.¹⁵ Presence of multiple solid, uniform enhancing renal lesions is suggestive of BHD and points away from VHL and other conditions associated with poorly enhancing papillary tumors discussed below.

Other Manifestations

Skin lesions are found in 90% of affected individuals. These lesions are characterized as cutaneous fibrofolliculomas, which are benign tumors of the hair follicle including fibrofolliculomas (2–4 mm pale skin bumps on the face, neck and upper torso) trichodiscomas, and acrochordons (skin tags that occur on the eyelids, neck, and axillae). Pulmonary cysts are common (70–84%) especially in the lower lobes and spontaneous pneumothoraxes are seen in 23%-30% of patients younger than age 40 (Fig. 7).^{2,6,16–19} A number of possible associations with BHD have been made including intestinal polyps, neurothekomas, meningiomas, multinodular goiter, medullary thyroid carcinoma, parathyroid adenomas, and cutaneous lipomas but these are not classically linked to BHD.

Genetic Screening

Germline FLCN testing is recommended beginning at age 21.²

Imaging Surveillance

Annual MRI or low dose CT is recommended beginning at age 20.²⁰ In patients without a renal lesion MRI every 3 years is recommended.²¹

Tuberous Sclerosis Complex (TSC) or Bourneville's Disease

Genetics and mechanism

Tuberous Sclerosis Complex (TSC) is caused by germline mutations in TSC1 which encodes hamartin (9q34) or TSC2 which encodes tuberin (16p13.3).^{22,23} Interestingly, TSC2 is immediately adjacent to the gene for Polycystic Kidney Disease 1 (PKD1) and overlapping genetic syndromes characterized by both TSC and PKD have been observed.²⁴ Mutations in TSC2 are associated with more severe forms of TSC. TSC occurs in 1:6000 to 1:1000 people and the mean age of diagnosis of renal manifestations is 30 years.²⁵

Only 30% of TSC is inherited and most cases are spontaneous mutations. This can delay the diagnosis of TSC because of the absence of a family history.^{6,26}

Hamartin and tuberin form an intracellular complex which interacts with numerous cellular pathways. Most notably the complex negatively regulates mammalian target of rapamycin (mTOR). mTOR is critical to many cellular processes such as cell cycle progression, angiogenesis, transcription, translation, and nutrient uptake. Therefore when either hamartin or tuberin is abnormal, the mTOR pathway is upregulated contributing to tumor formation.²⁷ Like the other syndromes, however, a 2nd hit on the wild type allele is necessary for tumor formation.

Renal manifestations

By far, angiomyolipomas (AML) of the kidney are the most frequent renal tumors in TSC. Approximately 70–90% of TSC patients develop one or more AMLs.^{22,28} Renal involvement with multiple AMLs is a leading cause of death from hemorrhage and renal failure.²⁵ In addition to AMLs, numerous cysts can be seen leading to pain, infection and renal insufficiency particularly in cases associated with PKD1. Epithelioid AML is a very rare subtype of AML and has malignant potential. Epithelioid AML occurs in patients with or without TSC. The imaging findings of epithelioid AMLs are non-specific and therefore difficult to distinguish from renal cancer, but typically demonstrate a complex cystic enhancing mass with solid renal tumor that has an appearance similar to AML but with minimal fat.^{6,29,30} Approximately one third of patients with tuberous sclerosis have non-fatty AMLs. These are typically higher in density on non-contrast CT and enhance uniformly. Both lipid-poor AMLs and renal cancers are avidly enhancing, making it difficult to differentiate the two. In addition, it is important to be aware that AMLs can extend into the inferior vena cava and local lymph nodes, mimicking malignancy.¹⁹

Renal cancer develops in only 1–4% of patients with TSC.^{26,31} The mean age of presentation is 28 years and frequently tumors are bilateral.^{26,32} Cases of renal cancer in children and young adults further point to a genetic link between TSC and renal cancer.^{23,33} The average tumor size for RCC in TSC patients is 2.9cm (with a range of 0.1 to 22cm).²⁵ The tumors are well defined, primarily solid, but with occasional cystic components. Hemorrhage is frequently present, but no tumor necrosis has been reported.²⁵ Both papillary and chromophobe and oncocytoma cell types are seen, and renal cancers in TSC have been subclassified into 3 subsets.^{19,26} The largest subset is termed TSC-associated papillary RCC, the second subset is morphologically similar to a hybrid oncocytic/chromophobe tumor, and includes tumors that display morphologic characteristics of both oncocytoma and chromophobe RCC in varying proportions, reminiscent of hybrid oncocytic/chromophobe tumor.³ The third subset consists of unclassified renal epithelial neoplasms.²⁵ Image guided biopsies of the lesion may be necessary to distinguish a tumor from a non-fatty AML although surveillance studies will also provide an index of the growth rate. Rapidly growing tumors are more suspicious for malignancy.¹⁹ The 3 cm rule also applies for intervention in TSC renal masses.

Appearance on imaging

Non fatty AMLs have homogenous high signal before contrast media injection and exhibit high attenuation on unenhanced CT, T2 signal hypointensity, and increased uniform contrast enhancement.^{34,35} Due to abnormal tumor vascularity, including aneurysms, acute hemorrhage within AMLs may be life threatening. Large (>4 cm) AMLs can be treated successfully with angio-embolization and it is wise to do so before the condition becomes emergent.⁶ Non fatty AMLs may be difficult to distinguish radiographically from renal cancer, and either biopsy or serial follow-up are needed. Clearly biopsy provides a more immediate and definitive answer.

Other Manifestations

TSC is characterized by multiple benign hamartomas especially in the brain such as cortical tubers (80%) and subependymal giant cell astrocytomas (10%) resulting in neurologic manifestations, especially epilepsy and cognitive disability.^{14,36} Retinal hamartomas can cause loss of vision. Hamartomas in the face (facial angiofibromas) are found in 90–100% of TSC patients. Skin (fibrous forehead plaques, shagreen patches) and under the nail bed subungual fibromas are also seen. Another condition with similar genetic abnormalities similar to those of tuberous sclerosis is lymphangioleiomyomatosis (LAM), which is a mosaic form of tuberous sclerosis with associated pulmonary cysts, renal cysts, AMLs, and retroperitoneal and pelvic lymphangiomas.²⁶ LAM is seen in 26–39% of patients with TSC. Cardiac rhabdomyomas are seen in 50–70% of infants with TSC but spontaneously resolve in most cases.^{25,26,37} Additional findings include rectal polyps, bone islands, and thyroid adenomas.³⁸ Many patients have received benefit from systemic drugs such as sirolimus and everolimus which interfere with the mTOR pathway, with responses seen in LAM and AMLs.^{39–42}

Genetic Screening

Affected individuals should be screened for TSC1 or TSC2 mutations. Since many patients are new mutations, a decision needs to be made about whether to screen apparently unaffected family members, a decision that can be made on the basis of a detailed family history.

Imaging Surveillance

Imaging surveillance with abdominal MRI or low dose CT is recommended at least every one to three years both to monitor growth of AMLs and provide early detection of renal tumors.²¹

Hereditary Papillary Renal Cancer (HPRC)

Genetics and mechanism

HPRC is caused by an activating mutation in the MET proto-oncogene located at 7q31.1. It is an autosomal dominant disease with high penetrance. It is a rare disease with an estimated incidence of 1:10 million.^{3,43} Only 30 known families have been described.² Two thirds of affected patients develop papillary renal cancers by age 60 and 90% by age 80, indicating high penetrance.^{3,26,44}

MET encodes a transmembrane protein which is the tyrosine kinase receptor for hepatocyte growth factor (HGF), also known as scatter factor. Mutations in the tyrosine kinase portion of the receptor cause activation leading to cell proliferation, prolonged cell survival, increased cell motility and angiogenesis.⁴⁵ In HPRC, trisomy 7 with duplication of the mutant MET allele can cause the disease.⁴⁶ Again, a second genetic hit is required for tumor formation.

MET mutations, splice variants and MET fusion genes all predicted to activate the MET pathway can be seen in 15% of sporadic Type 1 papillary RCC.⁴⁷

Renal manifestations

HPRC produces papillary type 1 tumors, with as many as 3400 tumors per kidney, although most are microscopic.⁴⁸ Most tumors are too small to be seen without a microscope but macroscopic tumors can also occur and be visible by imaging. Removal of a tumor is recommended at a diameter of 3cm to avoid metastatic disease which, although rare, can occur.

Type I papillary tumors tend to be slow growing and therefore, do not present until 50–70 years during life and frequently only at autopsy.^{19,26}

Appearance on imaging

Type 1 papillary tumors demonstrate mild enhancement (10–30 HU on CT or 15% on contrast enhanced MRI) which is uniform (Fig. 8, Fig. 9). The enhancement may be so low that at first glance, the tumors may be difficult to distinguish from cysts.⁴⁹ On MRI, the lesions are hypointense on T2W MRI and are poorly enhancing.⁴⁹ Sonographically, the lesions may be isoechoic with background making them difficult to see.¹⁹ Therefore, ultrasound is not recommended for their detection or follow-up.

Other Manifestations

No other tumors or manifestations are known to occur in HPRC making it unique among the hereditary renal cancers.

Genetic Screening

At risk family members should be screened for MET mutation analysis at age 21.²

Imaging Surveillance

These tumors are slow growing and usually indolent so do not require frequent surveillance. A policy of imaging every 2–4 years with MRI is recommended in affected family members but may be even less frequent if growth patterns are very slow.

Hereditary Leiomyoma Renal Cell Carcinoma (HLRCC) or Reed Syndrome

Genetics and mechanism

This disease results in a particularly invasive and aggressive renal malignancy, papillary type II renal cancer. It is caused by a mutation in the fumarate hydratase (FH) gene located at 1q42.3-q43.

Mutations in FH causes interruption of the normal Krebs cycle therefore, effectively eliminating oxidative phosphorylation in the cells and causing a metabolic switch to aerobic glycolysis or Warburg physiology.^{50–52} Because fumarate is no longer converted to malate, fumarate accumulates in the cell, acting as a competitive inhibitor of HIF prolyl hydroxylase, thus preventing HIF degradation by VHL.⁵³ Increased intracellular glucose levels, caused by shunting of glucose metabolism away from the Krebs cycle, produce NADPH-mediated reactive oxygen species which also further stabilize HIF.⁹ This has the

effect of creating a pseudohypoxic state similar to VHL which promotes cell growth. Of course, a second hit is required for an actual tumor to develop.⁵⁴

Renal manifestations

HLRCC produces type II papillary renal tumors. Approximately 15–30% of those with an FH mutation develop renal cancer. The mean age of presentation is 36–39 years.²⁶ These tumors have a large nucleus with prominent organophilic or eosinophilic nucleolus surrounded by a clear halo.⁵⁵ They have an aggressive course unlike most other renal cancers.

Appearance on imaging

Unlike other hereditary renal cancers, HLRCC tumors are often solitary and unilateral. They enhance poorly but are aggressive in nature (Fig. 10, Fig. 11).⁶ As the tumors enlarge they tend to become more vascular.^{19,26} Metastases are characterized by local lymphovascular spread of disease so that even small tumors measuring 1cm in diameter can show microscopic invasive features locally and involvement of local lymph nodes (Fig. 12). Peritoneal dissemination is not uncommon. Primary renal HLRCC demonstrates poor enhancement with cystic changes. Metastatic disease is often FDG-PET avid because of the Warburg physiology, making this modality a good method for assessing metastases unlike in most cases of clear cell renal cancer. Metastasis can be found in retroperitoneal and mediastinal lymph nodes, as well as liver and bone.⁵⁶ Metastases are generally incurable and death often results within 5 years.²⁶

Other Manifestations

HLRCC was first discovered in Finland among women with what appeared to be a predisposition to uterine leiomyomas. Indeed uterine fibroids develop at an early age (20–35 years) and often require hysterectomy due to their aggressive growth with symptoms of menorrhagia and pelvic pain. Patients also demonstrate skin leiomyomas which can be painful to pressure or low temperature and are located on the trunk and limbs. These lesions, whether in the skin or uterus, typically remain benign but malignant transformation has been reported.²⁶

Adrenal cortical hyperplasia has been reported in some cases of HLRCC.³

Genetic Screening

Germline FH mutation testing is recommended beginning at age 8 for patients at risk for cutaneous or uterine leiomyomas or type II papillary renal tumors.

Imaging Surveillance

Because of their aggressive behavior, HLRCC tumors are not placed on surveillance. They are treated as soon as they can be verified. Annual MRI testing for patients with no signs of renal disease but a positive gene screen will detect tumors early while they are still curable.^{2,21} Once a tumor is identified for surgical intervention, either by radical nephrectomy or by partial nephrectomy, wide surgical margins are recommended for any HLRCC solid mass.⁵⁷ The 3cm rule does not apply to HLRCC.^{57–59}

Renal Medullary Cancer (RMC) in association with sickle cell trait

Genetics and mechanism

RMC is a highly aggressive type of renal cancer associated with the Sickle Cell Trait. It is caused by a genetic alteration in the germline, which is a single nucleotide polymorphism in the beta-globin gene on chromosome 11.9. In addition to point mutations, monosomy of 11 is seen in 66%.⁶⁰ The crucial genetic abnormality and its mechanism is not understood yet. Clearly millions of people have the sickle cell trait, yet RMC is very uncommon so it is unclear why this disease develops in some individuals and not others.

Renal manifestations

Most patients present in the 3rd decade of life with an age range of 5–39 years.³ These tumors are highly aggressive often resulting in death within 10–15 weeks of diagnosis.

RMC is characterized by a dense desmoplastic response with dense fibrotic stroma.^{14,61,62} The stroma also is highly inflammatory containing numerous neutrophils. Sickled erythrocytes in nearby vessels can be helpful in making the diagnosis.

Appearance on imaging

RMCs are typically large, centrally located and highly infiltrative. They often cause renal obstruction with dilation of the collecting system. Their appearance is heterogeneous with necrosis and intratumoral hemorrhage.⁶³

Other Manifestations

There are no known additional associations with RMC.

Genetic Screening

Since the exact cause of RMC with sickle cell trait is not known there is no specific genetic screening test.

Imaging Surveillance

Given the rarity of RMC in sickle cell trait, there are no recommendations for screening. Once a tumor is discovered it should be treated as soon as possible given the highly aggressive nature of the disease and its very poor prognosis.

Hereditary non-polyposis colorectal cancer syndrome (HNPCC) or Lynch Syndrome

Genetics and mechanism

HNPCC is characterized by colorectal cancers, endometrial and urothelial malignancies of the urinary tract including the renal pelvis. It is an autosomal dominant disease caused by germline mutations in one of four DNA mismatch repair genes including MSH1 (3p21.3), MSH2 (2p21), MSH6 (2p16), and PMS2 (7p22.2) genes.⁶⁴ MSH1 and MSH 2 account for 85% of patients.⁶⁵ As implied by the name, there is an inability to correct spontaneous

mutations in the genome due to failure of these repair genes and this leads to the development of tumors.

Renal manifestations

Urothelial malignancies of the upper tract represent the third most common tumor type in HNPCC after colorectal and uterine malignancies. Urothelial malignancies occur in 2.5–5% of patients with HNPCC. There is an equal male to female ratio, unlike sporadic urothelial tumors that are more frequent in men.⁶⁶ Upper urinary tract urothelial tumor risk is greater in patients with MSH2 mutations than other mismatch gene mutations.⁶⁵

Appearance on imaging

Upper tract urothelial malignancies appear as a filling defect in the renal pelvis or ureter with or without ipsilateral obstruction. The tumors enhance with contrast media but they are not hyperenhancing. The wall of the renal pelvis/ureter may be thickened.^{67,68} The tumor can invade directly into the renal pelvis fat or the renal parenchyma and tends to assume the shape of the kidney rather than creating discrete masses as is the case for renal parenchymal tumors. Thus, typical of urothelial malignancies these tumors have an infiltrative pattern within the renal parenchyma. On MRI, lesions will show restricted diffusion.⁶⁹ The tumor may spread to adjacent nodes and then on to the lung, bone and liver. Diagnosis can be made by image guided percutaneous biopsy or by transureteral biopsy although the latter is more technically challenging. After treatment, there is a substantial risk of recurrence bilaterally so kidney sparing should be considered.^{64,66}

Other Manifestations

Colorectal cancer occurs in 63% of HNPCC patients and endometrial cancer occurs in 9%. Overall HNPCC accounts for 1% to 5% of all colorectal cancers and 2% to 5% of all endometrial cancers.^{64,70}

Other cancers have been implicated including those involving the ovaries, small bowel, stomach, hepatobiliary, skin, brain and bladder, prostate testes. The Muir-Torre syndrome, a variant of HNPCC, is associated with sebaceous carcinoma, a cutaneous cancer.⁷⁰

Genetic Screening

At risk family members should be screened for the appropriate mismatch repair gene in the teenage years. Screening colonoscopy should be initiated early in positive patients. Endometrial ultrasound and pelvic examinations are warranted in affected females.

Imaging Surveillance

There are no established recommendations for surveillance of patients with HNPCC for urothelial malignancy. Certainly, any sign of hematuria warrants an imaging study.⁶⁴ CT Urography is the preferred imaging modality as it is best established, but MR urography and even retrograde pyelography can be helpful in response to any sign of hematuria.⁶⁴

Succinate Dehydrogenase Subunit B (SDHB)

Genetics and mechanism

Succinate dehydrogenase is another Krebs cycle enzyme found in the inner mitochondria membrane that is part of electron transport chain complex II and converts succinate to fumarate. Germline mutations have been reported in the succinate dehydrogenase subunit B (SDHB), C (SDHC) and D (SDHD) but the strongest association with renal tumor is with SDHB.³⁸ SDHA, SDHB, SDHC and SDHD are located on 5p15, 1p36, 1q21 and 11q23 respectively. As with the FH mutation, mutation of SDHB causes a shunt from the Krebs cycle to aerobic glycolysis. The accumulation of succinate causes HIF stabilization due to inhibition of prolylhydroxylase activity similar to VHL. SDHB-tumors are rare with an estimated incidence of 0.1-.2% of all renal cancers.⁷¹

Renal manifestations

Patients present at mean age of 37 (range 14–76 years).⁷¹ SDHB is associated with several subtypes of RCC including clear cell and chromophobe carcinomas. The risk of a renal cancer is 14% by age 70.⁷² Oncocytomas have also been reported.^{26,73} Many patients have bilateral tumors.⁷¹ These tumors can exhibit aggressive behavior and one third of patients developed metastatic disease.⁷¹ Thus SDHB falls into the category of an aggressive renal malignancy along with HLRCC and HNPCC.

Appearance on imaging

The tumors are solid with occasional cystic change.^{71,74} MRI and low dose CT can be used to diagnose the lesions which are not distinctive by imaging (Fig. 13, Fig. 14). The presence of paragangliomas and pheochromocytomas along with renal cancer is a strong sign of SDHB.

Other Manifestations

This family of disorders is associated with a high risk of head and neck paragangliomas and adrenal/extradrenal pheochromocytomas.⁷³ Paragangliomas include carotid body tumors and there is an association with gastrointestinal stromal tumors (GIST).^{21,72}

Genetic Screening

SDH germline mutation is recommended for at risk family members with familial pheochromocytoma and renal cell carcinoma, or if the pathology suggests a SDHB-related pattern.

Imaging Surveillance

Due to the potential for metastatic disease, imaging surveillance is generally not recommended and identified lesions should be treated expeditiously.²

Less well characterized hereditary renal cancers

Here we briefly discuss several rare disorders that are included as hereditary renal cancer syndromes. Knowledge of these disorders is incomplete due to the small numbers of affected patients.

Translocation of Chromosome 3

Genetics and mechanism

Translocations of the third chromosome (3:2, 3:8, 3:11, and 3:6) are associated with tumors that express somatic mutations in the VHL gene.^{19,75} The location of the translocated segment break is the site of a functional mutation which is different from the VHL locus.¹⁹

Renal Manifestations and Imaging

The appearance on CT/MRI demonstrates an avidly enhancing mass. No manifestations of VHL are seen.^{19,26}

Genetic Screening

Karyotype testing is recommended in this disorder.²

Imaging Surveillance

Unless there is a history of translocation and renal cancer annual renal surveillance is not necessary.²⁶ When lesions are found they should be treated.

Familial Renal Cancer (FRC)

Genetics and Mechanism

Familial clear cell RCC is thought to be the result of multigenic inheritance, that is, caused by a combination of multiple genes.²⁶ Therefore, no specific genetic abnormality has been identified.

Renal Manifestations and Imaging

Tumors are typically clear cell carcinomas but other FRCs have been reported and the appearance of these tumors is typical and non-specific.

Genetic Screening

For patients with familial clear cell, it is recommended that genetic testing for VHL, SDHC, BAP1, TSC1 and TSC2 be performed. For familial chromophobe RCC, FLCN, TSC1, TSC2, and sometimes PTEN (depending on the clinical manifestations) are recommended. For early onset familial RCC, SDH and FH germline mutations are recommended testing.²

Imaging Surveillance

There are no specific recommendations for imaging surveillance.

Cowdens/PTEN

Genetics and Mechanism

Cowden's syndrome is a general tumor predisposition syndrome occurring in 1:200,000 individuals. More than 70% of patients with Cowden syndrome have germline mutations in the Phosphatase and Tensin Homologue (PTEN) gene on chromosome 10q22–23.⁷⁶

The PTEN hamartoma- tumor syndrome is associated with germline mutations of the PTEN tumor-suppressor gene which leads to increased cell proliferation and reduced cell death.⁷⁷ Women have PTEN hamartoma tumor syndrome twice as often as men do. This syndrome is associated with Cowden, Bannayan-Riley-Ruvalcaba, and other syndromes

Renal Manifestations and Imaging

The lifetime risk for RCC in individuals with germline PTEN mutations is estimated to be 34% with the typical diagnosis at a mean of 40 years.⁷⁸ Cowden's and PTEN are associated with papillary renal cancer commonly occurring in the 5th decade of life. Other renal tumor types including clear cell, chromophobe, papillary RCC (types 1 and 2), have also been reported.

Other Manifestations

Other tumor types such as multiple hamartomas, and macrocephaly are reported. Such patients are at increased risk for breast, endometrial, and thyroid cancers, as well as dermatologic conditions such as acral keratosis and facial trichilemmomas.⁷⁷

Genetic Screening

Screening for PTEN mutations should be performed in family members.

Imaging Surveillance

There are no specific recommendations for imaging surveillance.

Summary and Conclusion

Hereditary renal cancers represent a diverse group of cancer syndromes that include all the reported cell types of renal cancer. Commonalties among these diseases include onset of renal cancer at an earlier age than normal, multiple lesions, accompanying stereotypical non renal pathology and recommendations for genetic screening of at risk family members as well as imaging surveillance. Many of the tumor syndromes involve the stabilization of HIF resulting in downstream transcription of multiple growth factors. Unique differences among these entities include a widely ranging aggressiveness from relatively indolent to highly aggressive, and differences in the appearance of renal tumors on imaging.

It is likely that the list of possible hereditary renal cancer syndromes will expand in the future with increased use of genomics. While it is unlikely that new autosomal dominant diseases will be discovered, it is highly likely that multiple genes interacting together to cause renal cancer will be discovered and many of these will be heritable. In the meantime it

is important for radiologists to be familiar with this expanding list of hereditary causes of renal cancer.

Acknowledgments

We would like to thank Rabindra Gautam of the Urologic Oncology Branch in the National Cancer Institute, National Institutes of Health for providing the images used throughout this review.

This research was made possible through the National Institutes of Health (NIH) Medical Research Scholars Program, a public-private partnership supported jointly by the NIH and generous contributions to the Foundation for the NIH from the Doris Duke Charitable Foundation, The American Association for Dental Research, the Colgate-Palmolive Company, Genentech and alumni of student research programs and other individual supporters via contributions to the Foundation for the National Institutes of Health. For a complete list, please visit the Foundation website at: <http://fnih.org/work/education-training-0/medical-research-scholars-program>.

References

1. Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. *J Urol*. 2003; 170(6 Pt 1):2163–2172. [PubMed: 14634372]
2. Linehan WM. Evaluation and screening for hereditary renal cell cancers. *Can Urol Assoc J*. 2013; 7(9–10):324–325. [PubMed: 24319510]
3. Adeniran AJ, Shuch B, Humphrey PA. Hereditary Renal Cell Carcinoma Syndromes: Clinical, Pathologic, and Genetic Features. *Am J Surg Pathol*. 2015; 39(12):e1–e18. [PubMed: 26559379]
4. Linehan WM, Srinivasan R, Garcia JA. Non-clear cell renal cancer: disease-based management and opportunities for targeted therapeutic approaches. *Semin Oncol*. 2013; 40(4):511–520. [PubMed: 23972715]
5. Richard S, Gardie B, Couve S, Gad S. Von Hippel-Lindau: how a rare disease illuminates cancer biology. *Semin Cancer Biol*. 2013; 23(1):26–37. [PubMed: 22659535]
6. Kawashima A, Young SW, Takahashi N, King BF, Atwell TD. Inherited renal carcinomas. *Abdom Radiol (NY)*. 2016; 41(6):1066–1078. [PubMed: 27108134]
7. Coleman JA, Russo P. Hereditary and familial kidney cancer. *Curr Opin Urol*. 2009; 19(5):478–485. [PubMed: 19584731]
8. Byler TK, Bratslavsky G. Hereditary renal cell carcinoma: genetics, clinical features, and surgical considerations. *World J Urol*. 2014; 32(3):623–630. [PubMed: 24710684]
9. Sidana A, Srinivasan R. Therapeutic Strategies for Hereditary Kidney Cancer. *Curr Oncol Rep*. 2016; 18(8):50. [PubMed: 27325049]
10. Tobino K, Seyama K. Birt-Hogg-Dube syndrome with renal angiomyolipoma. *Intern Med*. 2012; 51(10):1279–1280. [PubMed: 22687807]
11. Byrne M, Mallipeddi R, Pichert G, Whittaker S. Birt-Hogg-Dube syndrome with a renal angiomyolipoma: further evidence of a relationship between Birt-Hogg-Dube syndrome and tuberous sclerosis complex. *Australas J Dermatol*. 2012; 53(2):151–154. [PubMed: 22571569]
12. Takahashi M, Kahnoski R, Gross D, Nicol D, Teh BT. Familial adult renal neoplasia. *J Med Genet*. 2002; 39(1):1–5. [PubMed: 11826016]
13. Khoo SK, Giraud S, Kahnoski K, et al. Clinical and genetic studies of Birt-Hogg-Dube syndrome. *J Med Genet*. 2002; 39(12):906–912. [PubMed: 12471204]
14. Srigley JR, Delahunt B, Eble JN, et al. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. *Am J Surg Pathol*. 2013; 37(10):1469–1489. [PubMed: 24025519]
15. Adley BP, Smith ND, Nayar R, Yang XJ. Birt-Hogg-Dube syndrome: clinicopathologic findings and genetic alterations. *Arch Pathol Lab Med*. 2006; 130(12):1865–1870. [PubMed: 17149965]
16. van Steensel MA, Verstraeten VL, Frank J, et al. Novel mutations in the BHD gene and absence of loss of heterozygosity in fibrofolliculomas of Birt-Hogg-Dube patients. *J Invest Dermatol*. 2007; 127(3):588–593. [PubMed: 17124507]

17. Zbar B, Alvord WG, Glenn G, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dube syndrome. *Cancer Epidemiol Biomarkers Prev.* 2002; 11(4): 393–400. [PubMed: 11927500]
18. Toro JR, Wei MH, Glenn GM, et al. BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dube syndrome: a new series of 50 families and a review of published reports. *J Med Genet.* 2008; 45(6):321–331. [PubMed: 18234728]
19. Choyke PL, Glenn GM, Walther MM, Zbar B, Linehan WM. Hereditary renal cancers. *Radiology.* 2003; 226(1):33–46. [PubMed: 12511666]
20. Menko FH, van Steensel MA, Giraud S, et al. Birt-Hogg-Dube syndrome: diagnosis and management. *Lancet Oncol.* 2009; 10(12):1199–1206. [PubMed: 19959076]
21. Ho TH, Jonasch E. Genetic kidney cancer syndromes. *J Natl Compr Canc Netw.* 2014; 12(9): 1347–1355. [PubMed: 25190700]
22. Guo J, Tretiakova MS, Troxell ML, et al. Tuberous sclerosis-associated renal cell carcinoma: a clinicopathologic study of 57 separate carcinomas in 18 patients. *Am J Surg Pathol.* 2014; 38(11): 1457–1467. [PubMed: 25093518]
23. 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. [PubMed: 9242607]
24. Martignoni G, Bonetti F, Pea M, Tardanico R, Brunelli M, Eble JN. Renal disease in adults with TSC2/PKD1 contiguous gene syndrome. *Am J Surg Pathol.* 2002; 26(2):198–205. [PubMed: 11812941]
25. Yang P, Cornejo KM, Sadow PM, et al. Renal cell carcinoma in tuberous sclerosis complex. *Am J Surg Pathol.* 2014; 38(7):895–909. [PubMed: 24832166]
26. Verine J, Pluvinage A, Bousquet G, et al. Hereditary renal cancer syndromes: an update of a systematic review. *Eur Urol.* 2010; 58(5):701–710. [PubMed: 20817385]
27. Axwijk PH, Kluijt I, de Jong D, Gille H, Teertstra J, Horenblas S. Hereditary causes of kidney tumours. *Eur J Clin Invest.* 2010; 40(5):433–439. [PubMed: 20534065]
28. Rakowski SK, Winterkorn EB, Paul E, Steele DJ, Halpern EF, Thiele EA. Renal manifestations of tuberous sclerosis complex: Incidence, prognosis, and predictive factors. *Kidney Int.* 2006; 70(10): 1777–1782. [PubMed: 17003820]
29. Froemming AT, Boland J, Cheville J, Takahashi N, Kawashima A. Renal epithelioid angiomyolipoma: imaging characteristics in nine cases with radiologic-pathologic correlation and review of the literature. *AJR Am J Roentgenol.* 2013; 200(2):W178–W186. [PubMed: 23345382]
30. Tsukada J, Jinzaki M, Yao M, et al. Epithelioid angiomyolipoma of the kidney: radiological imaging. *Int J Urol.* 2013; 20(11):1105–1111. [PubMed: 23551572]
31. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet.* 2008; 372(9639):657–668. [PubMed: 18722871]
32. Washecka R, Hanna M. Malignant renal tumors in tuberous sclerosis. *Urology.* 1991; 37(4):340–343. [PubMed: 2014599]
33. Bjornsson J, Short MP, Kwiatkowski DJ, Henske EP. Tuberous sclerosis-associated renal cell carcinoma. Clinical, pathological, and genetic features. *Am J Pathol.* 1996; 149(4):1201–1208. [PubMed: 8863669]
34. Sasiwimonphan K, Takahashi N, Leibovich BC, Carter RE, Atwell TD, Kawashima A. Small (<4 cm) renal mass: differentiation of angiomyolipoma without visible fat from renal cell carcinoma utilizing MR imaging. *Radiology.* 2012; 263(1):160–168. [PubMed: 22344404]
35. Jinzaki M, Tanimoto A, Narimatsu Y, et al. Angiomyolipoma: imaging findings in lesions with minimal fat. *Radiology.* 1997; 205(2):497–502. [PubMed: 9356635]
36. Hansel DE. Genetic alterations and histopathologic findings in familial renal cell carcinoma. *Histol Histopathol.* 2006; 21(4):437–444. [PubMed: 16437389]
37. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med.* 2006; 355(13):1345–1356. [PubMed: 17005952]
38. Gupta S, Kang HC, Ganeshan DM, Bathala TK, Kundra V. Diagnostic approach to hereditary renal cell carcinoma. *AJR Am J Roentgenol.* 2015; 204(5):1031–1041. [PubMed: 25905938]

39. Davies DM, de Vries PJ, Johnson SR, et al. Sirolimus therapy for angiomyolipoma in tuberous sclerosis and sporadic lymphangioleiomyomatosis: a phase 2 trial. *Clin Cancer Res.* 2011; 17(12): 4071–4081. [PubMed: 21525172]
40. Dabora SL, Franz DN, Ashwal S, et al. Multicenter phase 2 trial of sirolimus for tuberous sclerosis: kidney angiomyolipomas and other tumors regress and VEGF- D levels decrease. *PLoS One.* 2011; 6(9):e23379. [PubMed: 21915260]
41. 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. [PubMed: 23312829]
42. Kingswood JC, Jozwiak S, Belousova ED, et al. The effect of everolimus on renal angiomyolipoma in patients with tuberous sclerosis complex being treated for subependymal giant cell astrocytoma: subgroup results from the randomized, placebo-controlled, Phase 3 trial EXIST-1. *Nephrol Dial Transplant.* 2014; 29(6):1203–1210. [PubMed: 24729041]
43. Zbar B, Tory K, Merino M, et al. Hereditary papillary renal cell carcinoma. *J Urol.* 1994; 151(3): 561–566. [PubMed: 8308957]
44. Maher ER. Genetics of familial renal cancers. *Nephron Exp Nephrol.* 2011; 118(1):e21–e26. [PubMed: 21071978]
45. Peruzzi B, Bottaro DP. Targeting the c-Met signaling pathway in cancer. *Clin Cancer Res.* 2006; 12(12):3657–3660. [PubMed: 16778093]
46. Gossage L, Eisen T, Maher ER. VHL, the story of a tumour suppressor gene. *Nat Rev Cancer.* 2015; 15(1):55–64. [PubMed: 25533676]
47. Linehan WM, Spellman PT, et al. Cancer Genome Atlas Research N. Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma. *N Engl J Med.* 2016; 374(2):135–145. [PubMed: 26536169]
48. Ornstein DK, Lubensky IA, Venzon D, Zbar B, Linehan WM, Walther MM. Prevalence of microscopic tumors in normal appearing renal parenchyma of patients with hereditary papillary renal cancer. *J Urol.* 2000; 163(2):431–433. [PubMed: 10647647]
49. Egbert ND, Caoili EM, Cohan RH, et al. Differentiation of papillary renal cell carcinoma subtypes on CT and MRI. *AJR Am J Roentgenol.* 2013; 201(2):347–355. [PubMed: 23883215]
50. Sudarshan S, Sourbier C, Kong HS, et al. Fumarate hydratase deficiency in renal cancer induces glycolytic addiction and hypoxia-inducible transcription factor 1alpha stabilization by glucose-dependent generation of reactive oxygen species. *Mol Cell Biol.* 2009; 29(15):4080–4090. [PubMed: 19470762]
51. Shuch B, Linehan WM, Srinivasan R. Aerobic glycolysis: a novel target in kidney cancer. *Expert Rev Anticancer Ther.* 2013; 13(6):711–719. [PubMed: 23773105]
52. 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. [PubMed: 21398687]
53. Behnes CL, Schlegel C, Shoukier M, et al. Hereditary papillary renal cell carcinoma primarily diagnosed in a cervical lymph node: a case report of a 30-year-old woman with multiple metastases. *BMC Urol.* 2013; 13:3. [PubMed: 23320739]
54. Singer EA, Bratslavsky G, Middleton L, Srinivasan R, Linehan WM. Impact of genetics on the diagnosis and treatment of renal cancer. *Curr Urol Rep.* 2011; 12(1):47–55. [PubMed: 21128028]
55. 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. [PubMed: 17895761]
56. Grubb RL 3rd, 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 9–80. [PubMed: 17509289]
57. Linehan WM. Genetic basis of kidney cancer: role of genomics for the development of disease-based therapeutics. *Genome Res.* 2012; 22(11):2089–2100. [PubMed: 23038766]
58. Pavlovich CP, Grubb RL 3rd, Hurley K, et al. Evaluation and management of renal tumors in the Birt-Hogg-Dube syndrome. *J Urol.* 2005; 173(5):1482–1486. [PubMed: 15821464]

59. 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. [PubMed: 10210376]
60. Choudhary S, Sudarshan S, Choyke PL, Prasad SR. Renal cell carcinoma: recent advances in genetics and imaging. *Semin Ultrasound CT MR.* 2009; 30(4):315–325. [PubMed: 19711643]
61. Przybycin CG, Magi-Galluzzi C, McKenney JK. Hereditary syndromes with associated renal neoplasia: a practical guide to histologic recognition in renal tumor resection specimens. *Adv Anat Pathol.* 2013; 20(4):245–263. [PubMed: 23752087]
62. Gatalica Z, Lilleberg SL, Monzon FA, et al. Renal medullary carcinomas: histopathologic phenotype associated with diverse genotypes. *Hum Pathol.* 2011; 42(12):1979–1988. [PubMed: 21733559]
63. Maxwell PH, Wiesener MS, Chang GW, et al. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature.* 1999; 399(6733):271–275. [PubMed: 10353251]
64. Mork M, Hubosky SG, Roupert M, et al. Lynch Syndrome: A Primer for Urologists and Panel Recommendations. *J Urol.* 2015; 194(1):21–29. [PubMed: 25711197]
65. Goecke T, Schulmann K, Engel C, et al. Genotype-phenotype comparison of German MLH1 and MSH2 mutation carriers clinically affected with Lynch syndrome: a report by the German HNPCC Consortium. *J Clin Oncol.* 2006; 24(26):4285–4292. [PubMed: 16908935]
66. Crockett DG, Wagner DG, Holmang S, Johansson SL, Lynch HT. Upper urinary tract carcinoma in Lynch syndrome cases. *J Urol.* 2011; 185(5):1627–1630. [PubMed: 21419447]
67. Kawashima A, Vrtiska TJ, LeRoy AJ, Hartman RP, McCollough CH, King BF Jr. CT urography. *Radiographics.* 2004; (24 Suppl 1):S35–S54. discussion S5-8. [PubMed: 15486248]
68. Vikram R, Sandler CM, Ng CS. Imaging and staging of transitional cell carcinoma: part 2, upper urinary tract. *AJR Am J Roentgenol.* 2009; 192(6):1488–1493. [PubMed: 19457809]
69. Wehrli NE, Kim MJ, Matza BW, Melamed J, Taneja SS, Rosenkrantz AB. Utility of MRI features in differentiation of central renal cell carcinoma and renal pelvic urothelial carcinoma. *AJR Am J Roentgenol.* 2013; 201(6):1260–1267. [PubMed: 24261365]
70. Roupert M, Yates DR, Comperat E, Cussenot O. Upper urinary tract urothelial cell carcinomas and other urological malignancies involved in the hereditary nonpolyposis colorectal cancer (lynch syndrome) tumor spectrum. *Eur Urol.* 2008; 54(6):1226–1236. [PubMed: 18715695]
71. Gill AJ, Hes O, Papathomas T, et al. Succinate dehydrogenase (SDH)-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients. *Am J Surg Pathol.* 2014; 38(12):1588–1602. [PubMed: 25025441]
72. Ricketts CJ, Forman JR, Rattenberry E, et al. Tumor risks and genotype-phenotype-proteotype analysis in 358 patients with germline mutations in SDHB and SDHD. *Hum Mutat.* 2010; 31(1): 41–51. [PubMed: 19802898]
73. Ricketts C, Woodward ER, Killick P, et al. Germline SDHB mutations and familial renal cell carcinoma. *J Natl Cancer Inst.* 2008; 100(17):1260–1262. [PubMed: 18728283]
74. Williamson SR, Eble JN, Amin MB, et al. Succinate dehydrogenase-deficient renal cell carcinoma: detailed characterization of 11 tumors defining a unique subtype of renal cell carcinoma. *Mod Pathol.* 2015; 28(1):80–94. [PubMed: 25034258]
75. van Kessel AG, Wijnhoven H, Bodmer D, et al. Renal cell cancer: chromosome 3 translocations as risk factors. *J Natl Cancer Inst.* 1999; 91(13):1159–1160. [PubMed: 10393725]
76. Nelen MR, Padberg GW, Peeters EA, et al. Localization of the gene for Cowden disease to chromosome 10q22-23. *Nat Genet.* 1996; 13(1):114–116. [PubMed: 8673088]
77. Mester JL, Zhou M, Prescott N, Eng C. Papillary renal cell carcinoma is associated with PTEN hamartoma tumor syndrome. *Urology.* 2012; 79(5):1187, e1–e7. [PubMed: 22381246]
78. 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. [PubMed: 22252256]

Fig. 1. Hereditary renal cancer syndromes. Genetic syndromes with their most common manifestations are listed in each box.

Fig. 2. Single renal mass in a VHL patient. Axial contrast enhanced CT of a VHL patient demonstrates a left-sided sponge-like renal mass with both solid and cystic components. The solid components show contrast enhancement (arrow).

Fig. 3.

Bilateral solid-cystic renal masses in a VHL patient. Axial T2W MRI of a VHL patient shows solid-cystic masses in both kidneys (arrows) (A); whereas axial fat saturated contrast enhanced T1W MRI at the same level reveals better differentiation of cystic versus solid components within these masses (arrows) (B).

Fig. 4.

Renal and extra-renal manifestations of VHL. Axial contrast enhanced CT of a VHL patient demonstrates a dominantly solid lesion in the right kidney (long white arrow), a cystic lesion within the left kidney (asterisk), several cysts within the body and tail of the pancreas (short white arrows), additionally noted is an enhancing lesion within the spinal column suggestive of a hemangioblastoma (red arrow).

Fig. 5. Bilateral renal tumors in a BHD patient. Axial contrast enhanced CT of a BHD patient demonstrates multiple homogeneously enhancing tumors (arrows). Within these tumors, some higher density calcifications can be seen.

Fig. 6. MRI findings of renal involvement in BHD. Axial contrast-enhanced T1W MRI of a BHD patient showing a uniformly appearing hypointense tumor in the left kidney (arrow).

Fig. 7.
CT findings of pulmonary involvement in BHD. Axial contrast-enhanced lung CT of a BHD patient showing multiple pulmonary cysts (asterisks). These cysts have the potential of leading to spontaneous pneumothorax.

Fig. 8. Bilateral renal involvement in HPRC. Axial contrast-enhanced abdominal CT of a HPRC patient demonstrating tumors with uniform mild enhancement (arrows). This appearance is typical of type 1 papillary tumors and may sometimes resemble cystic lesions on imaging.

Fig. 9. Bilateral type I papillary renal tumors in HPRC. Axial contrast-enhanced fat-saturated T1 MRI of HPRC patient demonstrating the uniform hypointense appearance of type I papillary renal tumors, present in this patient bilaterally (arrows).

Fig. 10. Papillary type II tumor in HLRCC. Axial contrast enhanced CT scan of a HLRCC patient, demonstrating an enhancing large solitary tumor in the left kidney (arrows). This poor enhancement is characteristic of the appearance of renal papillary type II tumors. Some cystic change can also be seen within this tumor.

Fig. 11. MRI findings of renal involvement in HLRCC. Axial contrast enhanced fat saturated T1W MRI of HLRCC patient demonstrating a solitary, poorly enhancing, cystic-appearing type II papillary tumor in the left kidney (arrow).

Fig. 12.

Local tumor invasion in HLRCC. Axial contrast enhanced abdominal CT scan in a HLRCC patient demonstrating the aggressive nature of the papillary type II renal tumors associated with this syndrome. The tumor in this patient shows local invasion into the adjacent left abdominal wall (arrows).

Fig. 13. Renal involvement in SDH-B deficiency. Axial contrast enhanced CT scan of SDH-B deficiency patient, demonstrating both solid and cystic components within tumor in the left kidney (arrows). The appearance of these tumors varies, as there are several solid-cystic subtypes seen in this disease.

Fig. 14.

MRI findings of renal involvement in SDH-B deficiency. Axial contrast enhanced T1W MRI of SDH-B deficiency patient demonstrating 2 tumors in the left kidney, that are non-uniform in appearance and not particularly distinctive by imaging (arrows). The more hypointense tumor appears to contain more cystic component, while the other tumor appears less hypointense and predominantly solid.