Hereditary kidney cancer syndromes

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INTRODUCTION

Hereditary kidney cancer syndromes were originally described based on clinical observations that defined the disease phenotype. Family studies and advances in molecular genetics have provided important insights into the molecular pathways underlying the pathogenesis of these syndromes, as well as new insights into sporadic renal cell carcinoma (RCC) [1,2]. Each of these syndromes has its own molecular alteration, and these are often reflected in distinctive histologic features and clinical course. Fewer than 5 percent of all RCC cases are thought to be due to a hereditary syndrome [3,4].

The inherited kidney cancer syndromes are summarized and reviewed here (table 1). Other topics provide more general discussions of RCC and its management. (See "Clinical manifestations, evaluation, and staging of renal cell carcinoma" and "Epidemiology, pathology, and pathogenesis of renal cell carcinoma" and "Prognostic factors in patients with renal cell carcinoma".)

POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease is a common disorder, occurring in approximately 1 in every 400 to 1000 live births. It is estimated that fewer than one-half of these cases are diagnosed during an individual's lifetime, since the disease is often clinically silent. (See "Autosomal dominant polycystic kidney disease (ADPKD): Genetics of the disease and mechanisms of cyst growth" and "Autosomal dominant polycystic kidney disease (ADPKD):

Treatment" and "Autosomal dominant polycystic kidney disease (ADPKD): Kidney manifestations", section on 'Renal cancer'.)

The incidence of renal cell carcinoma (RCC) in patients with polycystic kidney disease does not appear to be increased compared with the general population [5,6]. However, the tumors are more often bilateral at presentation (12 versus 1 to 4 percent in sporadic RCC in the general population), multicentric (28 versus 6 percent), and sarcomatoid in type (33 versus 1 to 5 percent).

HEREDITARY PAPILLARY RENAL CARCINOMA

Hereditary papillary renal carcinoma (HPRC) is a familial cancer syndrome in which affected individuals are at risk for the development of type 1 papillary renal cell carcinomas [7]. (See "Epidemiology, pathology, and pathogenesis of renal cell carcinoma", section on 'Papillary carcinomas'.)

HPRC is a highly penetrant, autosomal dominant condition. Both early and late-onset forms of HPRC have been described [8,9]. HPRC is manifested primarily by the development of papillary renal tumors, which are often multifocal and bilateral. On imaging studies, the lesions are relatively hypovascular and grow slowly [10].

Genetic linkage analyses found that the *HPRC* gene (the *MET* protooncogene) is located on the long arm of chromosome 7 [11]. This gene codes for a membrane-bound receptor for hepatocyte growth factor (HGF) and has an intracellular tyrosine kinase domain. Pathogenic variants in *MET* constitutively activate the tyrosine kinase domain of this protein in patients with HPRC [12].

Most patients have bilateral, multifocal tumors. As such, nephron-sparing procedures such as partial nephrectomy are preferred to maintain renal function while minimizing the risk of distant metastases [13]. Patients with tumors less than 3 cm generally are managed with observation. (See "Diagnostic approach, differential diagnosis, and management of a small renal mass" and "Definitive surgical management of renal cell carcinoma", section on 'Partial nephrectomy'.)

The treatment of patients with distant metastases or unresectable disease, including agents targeting the *MET* pathway, is being discussed separately. (See "The treatment of advanced non-clear cell renal carcinoma", section on 'Papillary renal cell carcinoma'.)

Analysis of germline *MET* pathogenic variants is recommended for patients with HPRC. Techniques are being developed to detect carriers of germline pathogenic variants in family members of patients with HPRC [9,11].

KIDNEY CANCER ASSOCIATED WITH GERMLINE PATHOGENIC VARIANTS OF THE TRICARBOXYLIC ACID CYCLE

Inherited pathogenic variants involving enzymes of the tricarboxylic acid (Krebs) cycle are associated with aggressive forms of renal cell carcinoma (RCC) that have a propensity to metastasize even at a small size (<1 cm). Therefore, early surgical intervention is warranted, even for very small tumors. To date, two enzyme pathogenic variants have been characterized: fumarate hydratase, which causes hereditary leiomyomatosis and RCC, and succinate dehydrogenase, which is associated with hereditary paraganglioma and pheochromocytoma, and rarely, RCC. (See "Clinical presentation and diagnosis of pheochromocytoma" and "Pheochromocytoma and paraganglioma in children".)

Hereditary leiomyomatosis and renal cell cancer syndrome

Molecular pathogenesis — Hereditary leiomyomatosis and renal cell cancer (HLRCC) is a syndrome in which affected family members have cutaneous and uterine leiomyomas, and/or type 2 papillary RCCs. This syndrome is also called the multiple cutaneous and uterine leiomyomatosis syndrome (MCUL1) or Reed's syndrome. (See "Epidemiology, pathology, and pathogenesis of renal cell carcinoma", section on 'Papillary carcinomas' and "The treatment of advanced non-clear cell renal carcinoma", section on 'Papillary renal cell carcinoma' and "Uterine fibroids (leiomyomas): Variants and smooth muscle tumors of uncertain malignant potential", section on 'Fumarate hydratase deficiency'.)

Family studies have linked HLRCC to molecular alterations in the fumarate hydratase (*FH*) gene, which is located on the long arm of chromosome 1 [14]. *FH* is part of the mitochondrial Krebs or tricarboxylic acid cycle. The mechanism by which alterations in *FH* lead to HLRCC is not completely understood, although it may involve increased cellular dependence on glycolysis and pseudohypoxia [15,16]. One study showed that an antioxidant response element-controlled gene, the aldo-keto reductase family 1 member B10 (*AKR1B10*), is upregulated in *FH* knockdown and *FH* null cell lines [17]. Other experiments have found that inactivating pathogenic variants of *FH* appear to result in the generation of reactive oxygen species and stabilization of hypoxia-inducible factor 1 alpha (HIF1A), which is necessary for the generation of pseudohypoxia [18]. (See "Molecular biology and pathogenesis of von Hippel-Lindau disease", section on 'Hypoxia-inducible factor 1 and 2' and "Epidemiology, pathology, and pathogenesis of renal cell

carcinoma", section on 'Fumarate hydratase-deficient RCC and hereditary leiomyomatosis and renal cell cancer associated RCC'.)

HLRCC is transmitted in an autosomal dominant fashion, and the *FH* gene is thought to act as a tumor suppressor gene. Germline alterations that have been identified include missense, nonsense, insertion, deletion, and splice-site mutations [19].

Clinical presentation — The most striking clinical feature of the disease is the occurrence of severely symptomatic uterine fibroids among affected women, often requiring hysterectomy at a young age due to uterine bleeding or discomfort [20]. Transformation of leiomyomas to leiomyosarcomas has been reported in rare cases [21].

Cutaneous leiomyomas are common among individuals with HLRCC. These leiomyomas typically develop on the trunk and extremities and are quite apparent and symptomatic. In a few cases, patients may have only subtle skin findings [20,22]. (See "Hereditary leiomyomatosis and renal cell cancer (HLRCC)" and "Hereditary leiomyomatosis and renal cell cancer (HLRCC)", section on 'Cutaneous leiomyomas'.)

Renal tumors occur in 20 to 30 percent of patients [14,22]. These renal carcinomas tend to be aggressive, with rapid nodal and distant dissemination, even if the primary tumor is relatively small and contained. As an example, in a French series of 182 patients with HLRCC, the median age at diagnosis was 40 years old, and 82 percent had metastatic disease at diagnosis [23]. Skin leiomyosarcomas were rare, and most histologies were consistent with type 2 papillary RCC. Median survival for metastatic disease was 18 months.

Management — Patients with HLRCC syndrome should undergo regular surveillance imaging for renal carcinoma, with early intervention upon diagnosis. Details on surveillance are discussed separately. (See "Hereditary leiomyomatosis and renal cell cancer (HLRCC)", section on 'Surveillance for renal cancer'.)

A multidisciplinary approach is required for optimal management of patients with HLRCC, including referrals to gynecology, dermatology, urology, medical oncology, and genetic counseling.

Patients with HLRCC and locally advanced RCC should be offered prompt surgical management with wide surgical margins and consideration of retroperitoneal lymph node dissection, due to the high risk of metastatic disease. (See "Definitive surgical management of renal cell carcinoma" and "Hereditary leiomyomatosis and renal cell cancer (HLRCC)", section on 'Surveillance for renal cancer'.)

For patients with unresectable or metastatic disease, systemic targeted therapy with bevacizumab and erlotinib has demonstrated particular efficacy in patients with HLRCC based on preliminary data from one nonrandomized phase II trial (NCT01130519) [24]. In patients with HLRCC, tumorigenesis is driven by genetic alterations to glucose metabolism [14-16,25,26]. The combination of bevacizumab and erlotinib (inhibitors of vascular endothelial growth factor [VEGF] and epidermal growth factor receptor [EGFR], respectively) is hypothesized to inhibit effective glucose delivery to tumor cells, presenting a logical therapeutic approach to this disease [25]. Further studies are needed to confirm the efficacy and toxicity of this approach.

In the above phase II study, among all 83 patients with advanced papillary RCC treated with bevacizumab plus erlotinib, the objective response rate (ORR) was 54 percent [24]. The ORR was higher among the 43 patients with HLRCC compared to the 40 patients with sporadic papillary RCC (72 versus 35 percent, respectively), and was independent of International Metastatic RCC Database Consortium (IMDC) risk group (table 2) or prior therapy. For patients with HLRCC, median progression-free survival (PFS) was approximately 21 months. (See "The treatment of advanced non-clear cell renal carcinoma", section on 'Papillary renal cell carcinoma'.)

Data are limited and have mixed results for the efficacy of checkpoint inhibitor immunotherapy in patients with HLRCC. While one case report showed no responders to checkpoint inhibitor therapy among eight treated patients with metastatic HLRCC [27], another case report demonstrated a complete response to the combination of nivolumab and ipilimumab [28].

Succinate dehydrogenase deficiency — This enzyme deficiency is associated with an autosomal dominant condition called hereditary paraganglioma and pheochromocytoma. The syndrome is characterized by paragangliomas involving the head and neck region, thorax, abdomen, pelvis, and/or urinary bladder. Paragangliomas typically develop in patients in their thirties. However, rarely, an aggressive variant of RCC is also seen with this syndrome. Succinate dehydrogenase (*SDH*) is comprised of four subunits (*SDHA*, *SDHB*, *SDHC*, and *SDHD*), and each subunit has been associated with cases of RCC [29]. *SDH*-associated RCC presents at an early age [29], although the age at diagnosis ranges from 24 to 73 years [30,31]. The histologic type of kidney cancer varies, although in most cases, pathologic analysis showed either a clear cell or chromophobe type RCC [30,31]. Cases of metastatic *SDH*-associated RCC responding to sunitinib or pazopanib have been reported [32,33]. (See "Epidemiology, pathology, and pathogenesis of renal cell carcinoma", section on 'Succinate dehydrogenase–deficient renal cell carcinoma'.)

Testing for pathogenic variants in *SDH* is advised in patients with early onset kidney cancer (ie, age <45 years), bilateral or multifocal tumors, and a family history of pheochromocytoma or paraganglioma and kidney cancer [29,34]. (See "Pheochromocytoma in genetic disorders".)

BIRT-HOGG-DUBÉ SYNDROME

Birt-Hogg-Dubé (BHD) syndrome is an inherited syndrome in which affected individuals are at risk for the development of bilateral, multifocal kidney cancer, as well as various dermatologic and pulmonary lesions [35]. (See "Birt-Hogg-Dubé syndrome".)

BHD syndrome is caused by pathogenic variants in the folliculin (*FLCN*) gene (also known as the BHD gene), which is localized to the short arm of chromosome 17 [36,37]. Pathogenic variants in the germline of affected individuals have been identified in 90 percent of affected families [38]. DNA sequencing of renal tumors from patients with germline *FLCN* pathogenic variants has identified somatic pathogenic variants in the wild-type copy of the gene, suggesting that *FLCN* is a loss-of-function tumor suppressor gene [39].

The *FLCN* gene may be involved in energy, metabolism, and nutrient sensing through the mammalian target of rapamycin (mTOR) pathway. The folliculin-interacting protein (FNIP1) interacts with 5' AMP-activated protein kinase (AMPK), a key molecule for energy sensing to negatively regulate mTOR activity [40].

The penetrance of renal cancer in patients with BHD is up to 30 percent [41,42]. In one series, the risk of renal tumors was 27 percent at a mean age of 50 years [41]. However, the incidence of renal tumors may vary in different families, and BHD may be underdiagnosed in patients with variable skin findings. One series that included 115 *FLCN* carriers estimated penetrance for renal cancer and pneumothorax to be 16 and 29 percent, respectively, at 70 years of age [42].

The histology of renal tumors in patients with BHD syndrome varies. Tumors containing a mixed pattern of chromophobe and oncocytic renal cancer are typical, but other histologies may be present [35,41].

Dermatologic manifestations of BHD syndrome include skin lesions called fibrofolliculomas, which are benign hamartomatous tumors of hair follicles [35]. These whitish papules are most common on the nose and cheeks, and typically are first observed around age 20 years.

Approximately 80 percent of patients with BHD have multiple pulmonary cysts that can be identified by computed tomography (CT) of the lungs [35]. Spontaneous pneumothorax may be seen in up to one-fourth of patients [43-45].

The kidney cancers observed in patients with BHD syndrome tend to be bilateral or multifocal in more than one-half of cases and are usually slow growing. Thus, the recommended management approach includes observation of tumors less than 3 cm; when surgery is

recommended, all visible tumors should be removed [46]. As with hereditary papillary renal carcinoma, nephron-sparing surgery is preferred to radical nephrectomy [35,47]. Follow-up in patients undergoing nephron-sparing surgery is important given the high risk of disease recurrence in the ipsilateral kidney.

An animal model of BHD has been developed to provide a model for the evaluation of therapeutic approaches to this syndrome [48]. In this model, treatment with the mTOR inhibitor rapamycin led to tumor shrinkage.

TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis complex (TSC; also called tuberous sclerosis) is a hereditary condition that is due to pathogenic variants in one of two interacting tumor suppressor gene products, hamartin (TSC1) or tuberin (TSC2). The clinical manifestations include bilateral, multifocal renal lesions, which typically are angiomyolipomas. (See "Tuberous sclerosis complex: Genetics, clinical features, and diagnosis".)

The predominant management issue for patients with TSC is the risk of growth and bleeding from the renal angiomyolipoma. These issues are discussed separately. (See "Renal manifestations of tuberous sclerosis complex", section on 'Angiomyolipomas'.)

Fewer than 5 percent of patients with TSC develop renal cell carcinoma [49]. In one series, the TSC-associated RCC tumors occurred at a younger age than sporadic tumors and occurred primarily in women [50]. Most tumors displayed clear cell histology. Four of the six patients died of metastatic disease.

OTHER CLEAR CELL RCC HEREDITARY SYNDROMES

Von Hippel-Lindau disease — Von Hippel-Lindau (VHL) disease is an inherited, autosomal dominant syndrome manifested by a variety of benign and malignant tumors, including clear cell carcinoma of the kidney. The pathogenesis of VHL syndrome and the management of patients with VHL are discussed separately. Familial, non-VHL, clear cell renal cell carcinoma (RCC) may also be associated with chromosome 3 translocations [51]. (See "Clinical features, diagnosis, and management of von Hippel-Lindau disease" and "Molecular biology and pathogenesis of von Hippel-Lindau disease" and "Epidemiology, pathology, and pathogenesis of renal cell carcinoma", section on 'Von Hippel-Lindau gene'.)

Hereditary BAP-1-associated renal cell carcinoma — A germline pathogenic variant in the breast cancer susceptibility 1 (*BRCA1*)-associated protein 1 (*BAP1*) gene predisposes to familial clear cell RCC [4,52]. Further details about this syndrome are discussed separately. (See "Epidemiology, pathology, and pathogenesis of renal cell carcinoma", section on 'BAP1 gene'.)

Other tumors associated with *BAP1* germline pathogenic variants include familial uveal melanoma, cutaneous melanoma, and mesothelioma [53]. (See "Inherited susceptibility to melanoma", section on 'BAP1 gene' and "Malignant peritoneal mesothelioma: Epidemiology, risk factors, clinical presentation, diagnosis, and staging", section on 'Inherited susceptibility'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cancer of the kidney and ureters".)

SUMMARY

- **Recognizing hereditary kidney cancer syndromes –** Recognizing clinical features associated with hereditary renal cell carcinoma (RCC) is the most important step in establishing the diagnosis. These initial clinical findings and the patient's family history continue to be effective means for identifying affected individuals and family members. (See 'Introduction' above.)

- **Genetic testing –** The identification of genetic risk factors for renal cell carcinoma in a patient or family member may be an indication for a treatment strategy that can minimize or prevent disease-related morbidity. Discussions about the risks and benefits of genetic screening should involve a trained genetic counselor who can review any issues with patients prior to proceeding with genetic testing. (See "Genetic testing".)

- **Polycystic kidney disease –** For patients with polycystic kidney disease who develop RCC, tumors are more often bilateral, multicentric, and of sarcomatoid histology at presentation compared to those who develop sporadic RCC in the general population. (See 'Polycystic kidney disease' above.)

- **Hereditary leiomyomatosis and renal cell cancer –** Hereditary leiomyomatosis and renal cell cancer (HLRCC), a syndrome linked to molecular alterations in the fumarate hydratase

(*FH*) gene, is associated with papillary type 2 RCCs. (See 'Hereditary leiomyomatosis and renal cell cancer syndrome' above.)

- For patients with unresectable or metastatic HLRCC, bevacizumab plus erlotinib is an effective systemic treatment option. (See 'Management' above.)

- **Other hereditary clear cell RCC syndromes –** Other syndromes associated with hereditary clear cell RCC include von Hippel-Lindau disease and pathogenic variants in the breast cancer susceptibility 1 (*BRCA1*)-associated protein 1 (*BAP1*) gene. (See 'Other clear cell RCC hereditary syndromes' above.)

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GRAPHICS

Clinical and molecular characteristics of the most common hereditary kidney cancer syndromes

Syndrome	Gene/protein	Chromosomal locus	Potential pathway	Clinical features
Hereditary papillary renal cancer	c-MET	7q31	HGFR	Papillary type I renal cell carcinoma
Hereditary leiomyomatosis renal cell carcinoma	Fumarate hydratase	1q42	Krebs cycle/HIF1	Papillary type II renal cell carcinoma/skin carcinoma, and uterine leiomyoma
Birt-Hogg-Dube	Folliculin	17p11	mTOR	Chromophobe, oncocytic, hybrid, and clear cell renal cell carcinoma, fibrofolliculoma, pulmonary cysts, pneumothorax
Hereditary paraganglioma and pheochromocytoma	Succinate dehydrogenase	5p15	Krebs cycle/hypoxia	Clear cell, chromophobe renal cell carcinoma, pheochromocytoma, paragangliomas
Tuberous sclerosis complex (TSC)	TSC1 TSC2	9q34 16p13	mTOR	Clear cell renal cell carcinoma, angiomyolipoma
von Hippel-Lindau (VHL)	VHL gene	3p25	HIF-1	Clear cell renal cell carcinoma, hemangioblastomas, retinal angiomas, pheochromocytomas, endolymphatic sac tumors of the middle ear

HGFR: hepatocyte growth factor receptor (also known as c-MET); HIF-1: hypoxia-inducible factor 1; mTOR: mammalian target of rapamycin.

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International Metastatic Renal Cell Carcinoma Database Consortium criteria

Karnofsky performance status score <80
Time from original diagnosis to initiation of targeted therapy <1 year
Hemoglobin less than the lower limit of normal
Serum calcium greater than the upper limit of normal
Neutrophil count greater than the upper limit of normal
Platelet count greater than the upper limit of normal

- Favorable risk: None of the above risk factors present.
- Intermediate risk: 1 or 2 of the above risk factors present.
- Poor risk: 3 or more risk factors present.

Adapted from: Heng DYC, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal Cell Carcinoma Database Consortium prognostic model: A population-based study. Lancet Oncol 2013; 14:141.

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Contributor Disclosures

Toni K Choueiri, MD Equity Ownership/Stock Options: Pionyr [Oncology]; Tempest [Oncology]; Osel [Oncology]. Grant/Research/Clinical Trial Support: BMS [Oncology]; Pfizer [Genitourinary cancer]; Exelixis [Genitourinary cancer]; Roche [Genitourinary cancer]; Eisai [Genitourinary cancer]; Merck [Genitourinary cancer]; AstraZeneca [Genitourinary cancer]; Novartis [Genitourinary cancer]. Consultant/Advisory Boards: Pfizer [Genitourinary cancer]; Bristol-Myers Squibb [Genitourinary cancer]; Merck [Genitourinary cancer]; Novartis/GlaxoSmithKline [Genitourinary cancer]; Exelixis/Ipsen [Genitourinary cancer]; Eisai [Genitourinary cancer]; EMD Serono [Genitourinary cancer]; Lilly Oncology [Genitourinary cancer]; Infinity [Genitourinary cancer]; IQVA [Genitourinary cancer]; Calithera [Genitourinary cancer]; Surface Oncology [Genitourinary cancer]; Janssen [Genitourinary cancer]; Aveo [Genitourinary cancer]. Other Financial Interest: KidneyCan [Board of Directors, unpaid]; Aravive [member of DMC]. All of the relevant financial relationships listed have been mitigated. **Michael B Atkins, MD** Equity Ownership/Stock Options: Pyxis [Immunotherapy];Werewolf Therapeutics [Immunotherapy]. Grant/Research/Clinical Trial Support: AstraZeneca [RCC];Bristol Myers Squibb [Melanoma and RCC];Merck [Melanoma and RCC]. Consultant/Advisory Boards: Adagene [Melanoma, RCC, immunotherapy];Agenus [Melanoma, RCC, immunotherapy];Apexigen [Melanoma, RCC, immunotherapy];Asher Bio [Melanoma, RCC, immunotherapy];AstraZeneca [Melanoma, RCC, immunotherapy];Aveo [Melanoma, RCC, immunotherapy];Bristol Myers Squibb [Melanoma, RCC, immunotherapy];Eisai [Melanoma, RCC, immunotherapy];Exelixis [Melanoma, RCC, immunotherapy];Fathom [Melanoma, RCC, immunotherapy];Idera [Melanoma, RCC, immunotherapy];Iovance [Melanoma, RCC, immunotherapy];Leads [Melanoma, RCC, immunotherapy];Merck [Melanoma, RCC, immunotherapy];Novartis [Melanoma, RCC, immunotherapy];PACT [Melanoma, RCC, immunotherapy];Pfizer [Melanoma, RCC, immunotherapy];Pneuma [Melanoma, RCC, immunotherapy];Roche [Melanoma, RCC, immunotherapy];SAB Bio [Melanoma, RCC, immunotherapy];SeaGen [Melanoma, RCC, immunotherapy];Simcha [Melanoma, RCC, immunotherapy];Surface [Melanoma, RCC, immunotherapy];Symphogen [Melanoma, RCC, immunotherapy];Takeda [Melanoma, RCC, immunotherapy]. All of the relevant financial relationships listed have been mitigated. **Sonali Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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