New and old Hereditary forms of Renal Cell Carcinoma.

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Renal cell carcinoma affects approximately 30,000 individuals per year in the United States and is responsible for close to 12,000 annual deaths. Kidney cancer, is a tumor comprising several histologic subtypes, the molecular hallmarks of which support their classification as distinct entities. While the vast majority of renal tumors occur sporadically, about 4% are found in association with syndromes of a heritable nature. Over the past 15 years considerable insight into the genetic basis of renal cancer has come from studies of renal cancer families. Identification of the genes involved in the hereditary forms of renal cell carcinoma has provided significant information about the genes involved in the common, sporadic (non-hereditary) forms of the disease.

Recognition of this group of tumors is, however, rather important both, clinically and scientifically, because it is now recognized that kidney tumors may occur in familial settings more frequently than previously contemplated. Early detection and diagnosis of these tumors, identification of specific genes that characterize each syndrome and elucidation of mechanisms responsible for the development of tumors, are important in order to establish appropriate therapies as well as for genetic counseling. At the moment, only morphology can assist in identifying and diagnosing some of the newly recognized syndromes.

Hereditary renal syndromes include:

- Von Hippel-Lindau disease,
- Hereditary papillary renal cell carcinoma,
- Birt-Hubb-Dube
- HLRCC
- SDH syndrome
- Tuberous Sclerosis
- Familial Oncocytoma
- Syndromes associated with Wilms’ tumor.

Each syndrome is associated with a specific renal pathology. Clinically, the tumors are more likely to be multifocal and bilateral and with early incipient lesions scattered throughout the adjacent renal parenchyma. The most common form of hereditary kidney cancer is VHL, which is associated with clear cell or conventional renal carcinoma (~75%). This disease has been associated with mutations in the von Hippel-Lindau gene (at 3p25) and loss of heterozygosity at chromosome 3p. Next in frequency is papillary renal cell carcinoma (~10%), associated with trisomies of chromosomes 7 and 17 and losses of chromosome Y. Chromophobe renal cell carcinoma is even more rare (~5%), is associated with numerous specific chromosomal losses (-1, -2, -6, -10, -13, -17, -21) and is seen in patients with BHD.
syndrome. Renal oncocytoma, a benign neoplasm most often without any chromosomal abnormalities, is represented at a frequency of ~3-5%.

**Von Hippel Lindau: The VHL Kidney Cancer Tumor Suppressor Gene**

VHL is an autosomal dominant cancer syndrome in which affected individuals are at risk to develop tumors in a number of organs. The most frequent clinical manifestations are:

- Bilateral, multifocal clear cell renal carcinoma
- CNS Hemangioblastomas (Cerebellum, Spine)
- Pancreatic neuro endocrine tumors
- Pheochromocytomas
- Retinal angiomas

**Pathology**

Tumors identified in VHL patients and kindred’s are frequently bilateral and multifocal. Morphologically, they are similar to sporadic RCC. Grossly the tumors have a yellow color with extensive areas of hemorrhage and necrosis. The tumor cells are large with clear cytoplasm although occasional eosinophilic cells may be identified. A variety of growth patterns, solid, tubular and papillary can be found. Cysts are frequently present in VHL, with a multilocular growth pattern. They vary in sized and are separated by fibrous / hyalinized septa. The cysts are usually lined by a single row of low nuclear grade tumor cells. The *VHL* gene is known to be located in 3p25-p26, but changes have been reported in 5q21+ (70%) and 14q- (41%).
No deleted allele of the VHL gene shows somatic mutations or hypermethylated induced inactivation in 80% of cases; VHL is a tumor suppressor gene that encodes elongin, which inhibits the generation of a transcriptional elongation complex of vascular endothelial growth factor; loss of VHL causes an increase in VEGF, may cause the increased vascularity of these tumors.

Patients with VHL associated tumors have a better prognosis and longer survivals that for sporadic RCC. Sporadic cases 38% die of disease overall and metastases develop in 27-37% of patients.

**Papillary RCC Type I**

Hereditary papillary renal cell carcinoma is an autosomal dominant disease characterized by the development of multifocal renal cell tumors.

Papillary (chromophil) RCC is recognized by the formation of papillary structures lined by cuboidal small cells with scanty basophilic cytoplasm and small indolent nuclei. They can also exhibit focal tubular or solid patterns of growth. The papillae may be filled with foamy macrophages and psammoma bodies are common (type I). Marked nuclear atypia is rare. Papillary RCC as clear cell tumors derives from the proximal tubule. The tumors are multifocal in more that 80% of the cases, and incipient lesions can be found scattered throughout the adjacent renal parenchyma. Tumors stain positive for CK7, negative for CK20.

Hereditary papillary RCC (HPRC) is a rare condition characterized by type 1 papillary RCC and mutations in the tyrosine-kinase domain of the c-MET proto-oncogen on 7q34. Loss of chromosome 7 is the initiating event along with the loss of a sex chromosome.
It is estimated that approximately half the members of affected families will develop tumors by the age of 50 years. The 5-year survival for patients with this type of tumors is about 82-90%, much better than clear cell independent of stage. Metastases can occur to regional lymph nodes and lung.

**Birt Hogg Dubé Syndrome (BHD)**

Several years ago we described families with members affected with multiple renal oncocytomas. We termed this clinical entity “familial renal oncocytoma”. Subsequently, we found that some families with familial renal oncocytoma were also affected with the Birt Hogg Dubé Syndrome (BHD). This syndrome, first described in 1977 by Drs. Birt, Hogg, and Dubé, was initially characterized by a predisposition to develop multiple small papules on the head and neck. These papules are benign tumors of the hair follicles (fibrofolliculomas). We expanded the phenotype of Birt Hogg Dubé syndrome to include and confirm the association of lung cysts and renal carcinoma with the fibrofolliculomas described by Drs. Birt, Hogg and Dubé. Fifteen to thirty five percent of affected BHD individuals develop renal carcinoma. The histologic type of BHD associated renal carcinoma is markedly different from that of either VHL (clear cell RCC) or HPRC (Type I papillary RCC).

BHD patients are at risk to develop chromophobe RCC, oncocytic RCC and oncocytoma. In our analysis of 134 renal tumors in 30 BHD patients from 19 families, we have noted tumors of conventional, chromophobe, papillary, and oncocytoma histologic types, as well as tumors of a hybrid histology not previously linked to a familial syndrome the hybrid and chromophobe RCC predominated, making this the first report of a heritable syndrome conferring a predisposition to tumors with chromophobic elements or of chromophobe histology.
The size of tumors at presentation in the 30-patient subset increased with increasing malignant potential of the histologic type: The hybrid tumors averaged 2.2 cm, the chromophobe RCCs 3.0 cm, and the clear cell RCCs 4.7 cm in diameter.

Morphologically, these hybrid oncocytic tumors had zones classic for oncocytoma (large cells, poorly defined cell borders, finely granular eosinophilic cytoplasm throughout, and large nuclei with homogenous basophilic chromatin) and other zones consistent with chromophobe RCC (well-defined cell borders, “fluffy” eosinophilic cytoplasm, pyknotic nuclei, and perinuclear halos). Cells in the chromophobe zones of these tumors were arranged in the characteristic plant-like distribution of chromophobe RCC. On the other hand, the oncocytoma-like zones lacked the characteristic loose connective tissue background, central scar, and nephroid growth pattern usually seen in oncocytomas. Incipient lesions or oncocitosis, was widespread throughout the renal parenchyma.

The BHD gene has been localized to a 4cm region on the short arm of chromosome 17. The prognosis of patients with these tumors is similar to that of Papillary type I, unless clear cell cancers develop.

**Hereditary Leiomyomatosis Renal Cell Carcinoma (HLRCC)**

In 2001, an autosomal dominant hereditary syndrome involving cutaneous and uterine leiomyomas was reported to be associated with renal cancer in two families. A familial autosomal dominant predisposition to multiple cutaneous leiomyomas had been noted in the 1950’s. In 1965 Mezzadra had suggested the association of uterine leiomyomas with the cutaneous leiomyomas. Subsequent reports have confirmed a dominant familial predisposition to cutaneous and uterine leiomyomas, Multiple Cutaneous Leiomyoma (MCL).

Alam, et. al. performed a genomewide screen of 11 families with this disorder and found linkage to 1q42.3-q43. They reduced the critical region to 14cM, naming the locus as MCUL1 (multiple cutaneous and uterine leiomyomata).

In 2001 Lanonen et. Al reported on the clinical, histopathologic and, molecular features of a cancer syndrome with predisposition to uterine leiomyomas and papillary renal cancer. In the Finnish family studied, 11 members had uterine leiomyomas and 2 had uterine leiomyosarcoma. Seven individuals had a history of cutaneous nodules, two of which were confirmed to be a cutaneous leiomyomatosis. The four kidney cancer cases occurred in young (33-48) year old females and displayed a unique natural history. All these renal tumors were of papillary histology and presented as unilateral solitary lesions that had metastasized at the time of diagnosis. A second smaller family was studied also. Linkage analysis mapped the predisposition gene to chromosome 1q. Losses of the normal chromosome 1q
were observed in tumors that had occurred in the kindred displaying the phenotype. The Finnish group recently reported the finding of mutation of fumarate hydratase (fumarase) in the germline of some of the HLRCC and MCL kindred’s. It is now believed that MCL and HLRCC are the same disorder.

![Image](image.png)

Although the original description of these tumors was that of Papillary type II we have recently described a variety of patterns including tubular, solid and papillary and mixed. The hallmark of these neoplasms is the presence of a large nucleous with perinucleolar halos.

**Hereditary Paraganglioma-Pheochromocytoma syndrome (SDH).**

Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndrome is a disease characterized by the presence of paragangliomas and pheochromocytomas. Extra-adrenal parasympathetic paragangliomas are located predominantly in the head and neck. Pheochromocytomas, which arise from the adrenal medulla, typically hypersecrete catecholamines. Paraganglioma syndrome has been classified genetically into 4 entities, PGL1, PGL2, PGL3, and PGL4. To date, 3 of these 4 entities have been associated with germline mutations in the genes encoding 3 of the subunits of succinate dehydrogenase (SDH), which has a key function in the Krebs cycle and the respiratory chain. Germline mutations in SDHB, SDHC, and SDHD have been found in PGL4, PGL3, and PGL1, respectively. **We have been able to study and the morphologic features of 11 cases of Renal cell carcinoma in patients with SDH. Some cases were know to be part**
of family syndromes but in others, the morphology suggested SDHB disease that was confirmed later after genetic studies. Most of the tumors had a similar appearance to oncocytoma.

**Tuberous Sclerosis**

Tuberous sclerosis (TS) is an autosomal dominant disease characterized by cortical tubers, giant cell astrocytomas, retinal hamartomas, cardiac and renal tumors. The disease is associated with two predisposing genes, \( TSC1 \) at 9q34 and \( TSC2 \) at 16p13. Renal tumors are most frequently angiomyolipomas but clear cell RCC and chromophobe renal tumors have also been described.
References


