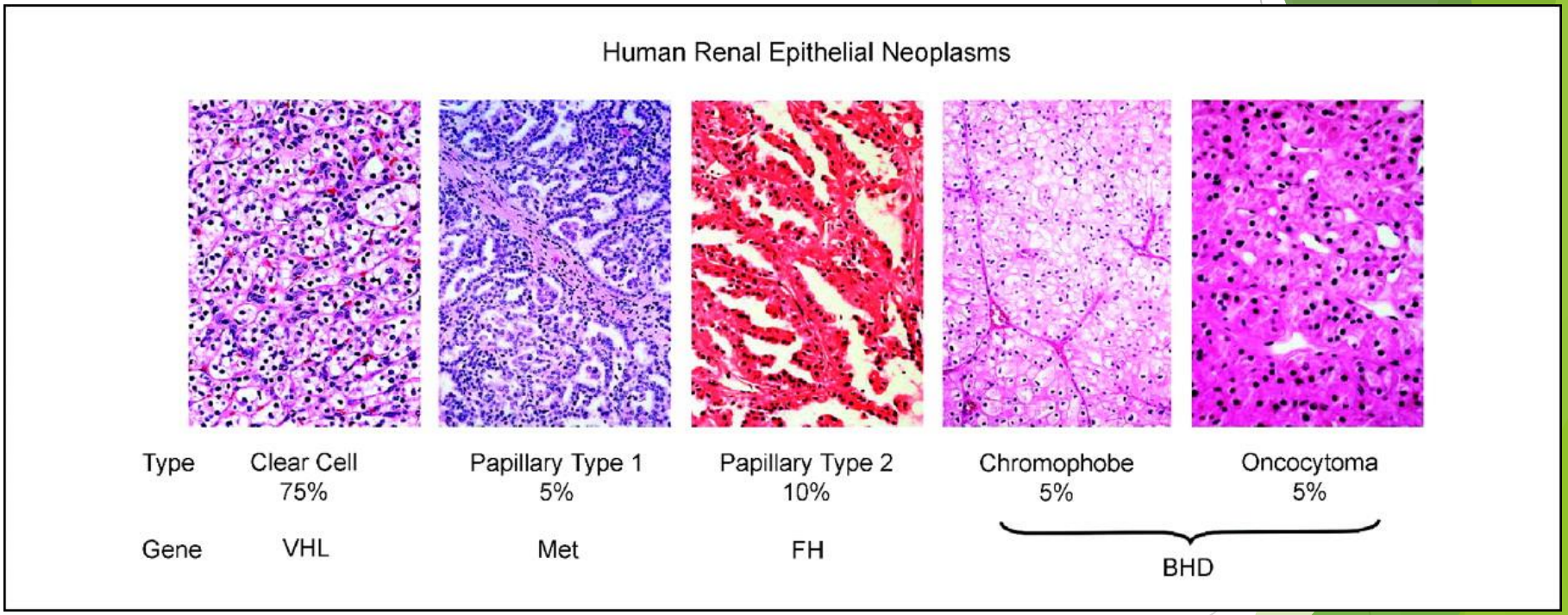
Hereditary Kidney Cancer Syndromes

Tue Nguyen, MD

Kidney cancer is not a single disease; it is made up of a number of different types of cancer that occur in the kidney, each with different histologic types, having a different clinical course, and associated with alteration of a different gene.



W. Marston Linehan et al. Clin Cancer Res 2007;13:671s-679s

Clinical Cancer Research
AACR American Association for Cancer Research

Familial Renal Cell Carcinoma

Syndrome	Mechanism	Clinical Manifestations
Von-Hippel Lindau (VHL)	*VHL* tumor suppressor gene (3p25-26)	Clear cell or cystic RCC Retinal angiomas CNS hemangioblastomas Pancreatic cysts and islet tumors Epididymal cystadenomas Pheochromocytomas
Hereditary Papillary RCC (HPRCC)	*MET* proto-oncogene (7q31)	Type I papillary RCC
Hereditary Leiomyoma RCC (HLRCC)	*Fumurate hydratase (FH)* tumor suppressor gene (1q42-44)	Type II papillary RCC (aggressive) Cutaneous leiomyomas Uterine fibroids
Birt-Hogg-Dube (BHD)	*Folliculin* tumor suppressor gene (17p11.2)	Chromophobe RCC or oncocytomas Fibrofolliculomas of head and neck Pulmonary cysts and spontaneous pneumothoraces
BAP1 tumor predisposition syndrome	BRCA1 Associated Protein 1 (3p21.1)	Clear cell RCC or other Uveal and cutaneous melanomas Mesothelioma
Hereditary Paraganglioma-Pheochromocytoma Syndromes	Succinate Dehydrogenase Complex	SDH-deficient RCC Paragangliomas Pheochromocytoma GIST

Hereditary Kidney Cancer Syndromes

- Von Hippel-Lindau Syndrome (VHL)
- Hereditary Papillary Renal Cell Carcinoma (HPRCC)
- Hereditary Leiomyoma Renal Cell Carcinoma (HLRCC)
- Birt-Hogg-Dube Syndrome (BHD)
- BAP1 tumor predisposition syndrome
- Hereditary Paraganglioma-Pheochromocytoma Syndromes
- Tuberous sclerosis

Von Hippel-Lindau Syndrome (VHL)

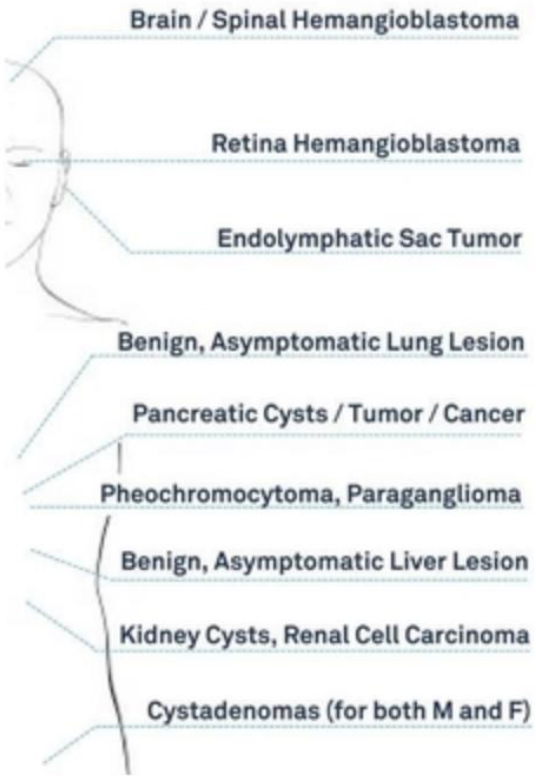
- Clear cell RCC develops with early age of onset (3rd - 5th decade)
- Often bilateral and multifocal (approximately 50% penetrance)
- Clinical manifestations include retinal angiomas, endolymphatic sac tumors, benign CNS hemangioblastomas, pancreatic cysts and islet tumors, epididymal cystadenomas, and pheochromocytomas
- A mutated *VHL* tumor suppressor gene, located at chromosome 3p25-26, is unable to form the E3 ubiquitin ligase complex which regulates the degradation of regulatory proteins, including Hypoxia Inducible Factor (HIF)
  - results in upregulation of vascular endothelial growth factor (VEGF) and other regulatory proteins

- Von Hippel Lindau – VHL gene on 3p25 and encodes for the VHL protein
- The VHL complex targets hypoxia-inducible factors (HIFs) for proteosomal degradation through ubiquitination.
- Virtually all tumors of VHL patients lose the remaining allele, most commonly through loss of heterozygosity (LOH)
- Inactivation of VHL leads to accumulation of HIF-1 and HIF-2 and their downstream targets, which include vascular endothelial growth factor (VEGF), glucose transporter-1, platelet derived growth factor-b, and transforming growth factor-a, which likely leads to the development of RCC.

Von Hippel Lindau

- Autosomal Dominance
- Risk of pheochromocytomas is associated with missense mutations,
  - Subset into type 1 and type 2 based on likelihood of pheochromocytoma
- Nonsense or Frameshift mutations - earlier age of onset of RCC, and higher risks of RCC and retinal angiomas (vs deletions or missense mutations)
- Renal Malignancy with very high penetrance (70% develop RCCs, Median age 45)
- Presentation rarely is Renal Masses

VHL – other Manifestations



Renal Manifestations

- Multiple Cystic and Solid lesions throughout kidneys bilaterally
- Typically exhibit low nuclear grade and stage

- Treatment – OBSERVATION UNTIL 3 CM – then clean them out

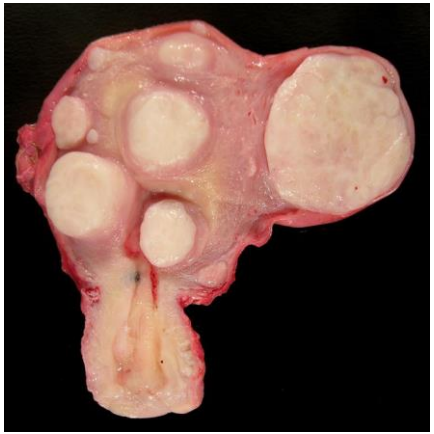
Hereditary Papillary Renal Cell Carcinoma (HPRCC)

- Characterized by bilateral and multifocal Type I papillary RCC
- Least common syndrome, and there are no extrarenal findings
- Missense mutation of the *c-MET* proto-oncogene at 7q31

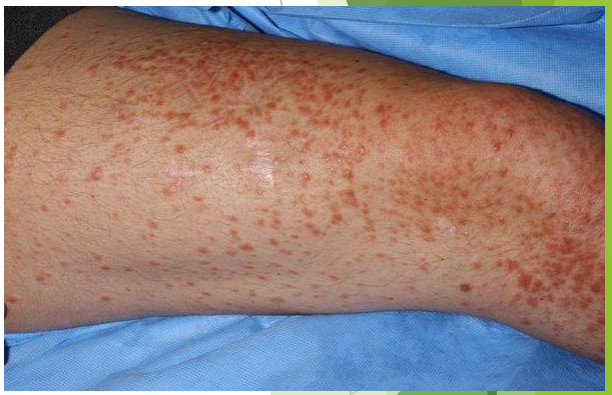
Hereditary Leiomyoma Renal Cell Carcinoma (HLRCC)

- Characterized by papillary type II RCC (20% penetrance) with an aggressive clinical behavior necessitating early surgical intervention with wide resection. Metastatic progression is not uncommon.
- Other clinical manifestations include painful cutaneous and uterine leiomyomas
- The HLRCC locus has been mapped to 1q42-44, the site of the *Fumarate Hydratase* (*FH*) tumor suppressor gene

HLRCC



- Uterine/leiomyomomas – Almost 100 % Penetrance
  - Skin leiomyomas – Very painful
  - Often women with early hysterectomies
- Renal Manifestations – 2-20%
- **NO 3cm Rule**



Birt-Hogg-Dube Syndrome (BHD)

- Characterized by bilateral, multifocal, chromophobe RCC, oncocytomas, or hybrid renal tumors (20-40% penetrance)
- Other clinical manifestations include fibrofolliculomas of the head and neck, pulmonary cysts, and spontaneous pneumothorax
- The *BHD* gene has been mapped to 17p11.2, which encodes the tumor suppressor gene product *Folliculin*

Birt-Hogg-Dube (BHD)

- BHD is caused by mutations in the FLCN tumour suppressor gene. 17p11.2
- Concomitant LOH or somatic mutations in the wild-type allele are frequently observed.
- FLCN mutations in sporadic chromophobe RCC have not been observed to our knowledge.
- The recent TCGA analysis, did not find any FLCN mutations, although whole chromosome 17 loss was common.
- Primarily hybrid or chromophobe histological type

Birt-Hogg-Dube (BHD)

- Fibrofolliculomas (benign, smooth papules that predominantly occur in the face and upper torso) from the 3rd decade
- Bilateral pulmonary cysts and concomitant risk for pneumothorax are also common.
- About one third of BHD patients develop renal tumors

BAP1 (BRCA Associated Protein 1) tumor predisposition syndrome

- Typically, unifocal ccRCC, but other histologies recently reported
- Other associated cancers include uveal and cutaneous melanomas and mesotheliomas
- BAP1 gene has been mapped to 3p21.1 and somatic loss is common in sporadic ccRCC and associated with high nuclear grade and more aggressive outcomes.

BAP1 tumor predisposition syndrome

- BAP1, located on 3p21.1, encodes for a multifunctional protein that was initially found to bind to the BRCA1 RING finger and enhance BRCA1-mediated cell growth suppression
- Has role in chromatin remodeling as well
- Autosomal dominant
- BAP1 alterations are seen in about 10–15% of sporadic ccRCCs.
- Risk of RCC in BAP1 carriers is estimated at 10%
- increased risks of melanoma and mesothelioma
- Somatic ccRCC with BAP1 mutations is associated with a higher tumor grade and decreased survival,

Hereditary Paraganglioma-Pheochromocytoma Syndromes

- Generally, unifocal tumors, characterized by neoplastic cells with vacuolated cytoplasm and cytoplasmic inclusions that contain pale eosinophilic fluid of flocculent material
- Loss of SDHB on IHC is a sensitive and specific marker for these neoplasms and should prompt genetic assessment (recognized WHO histology)
- Other associated tumors include paragangliomas, pheochromocytomas and gastrointestinal stromal tumors
- Succinate dehydrogenase is a mitochondrial enzyme complex made up of four protein subunits (SDHA, SDHB, SDHC, SDHD)

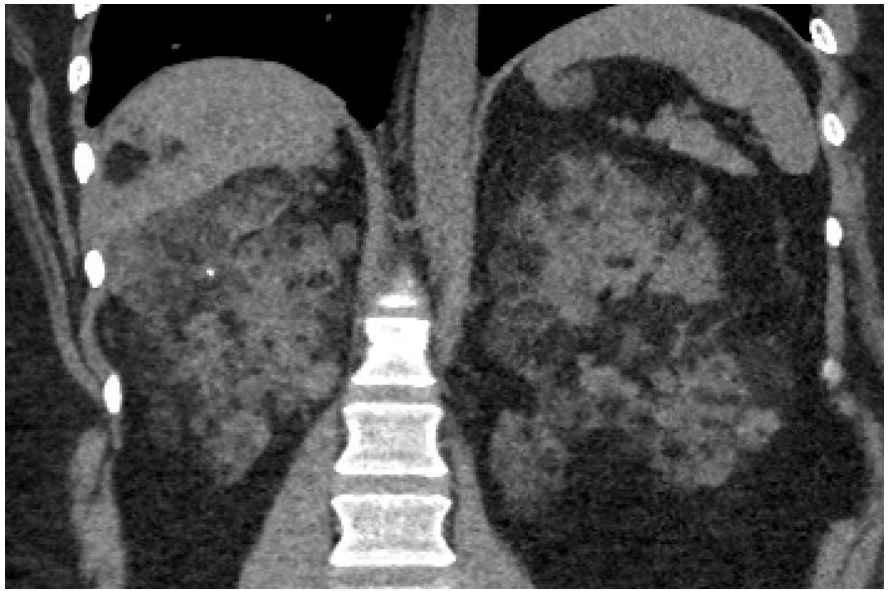
Hereditary paraganglioma-pheochromocytoma syndromes

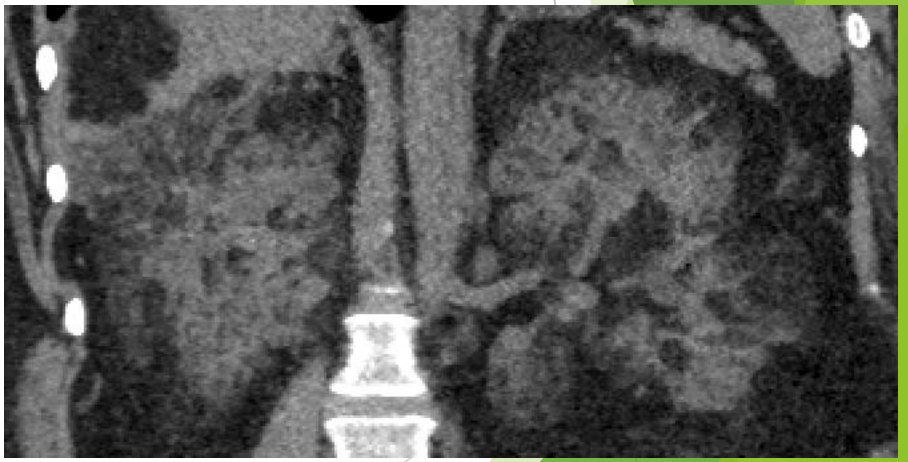
- Pathogenic variants in the SDH genes (SDHA, SDHB, SDHC, SDHD, and SDHAF2) are associated with the development of paragangliomas, pheochromocytomas, gastrointestinal stromal tumors, and RCCs
- SDH is a mitochondrial enzyme complex made up of four protein subunits (SDHA, SDHB, SDHC, and SDHD). The enzyme catalyses the oxidation of succinate to fumarate in the Krebs cycle. Mutations in Krebs cycle enzymes shift the cells towards increased glucose uptake, aerobic glycolysis, and fatty acid synthesis

Tuberous sclerosis complex (TSC)

- Tuberous sclerosis complex (TSC) is an autosomal dominant condition characterized by abnormalities of the skin, neurocognitive deficits and brain lesions, renal tumors, and other conditions.
- heterozygous germline pathogenic variants in TSC1 or TSC2
- About two thirds of individuals with TSC have de novo mutations

TSC Kidneys





TSC Associated symptoms

- Skin findings, including hypopigmented macules, facial angiofibromas, and periungual fibromas very common
- Most individuals have CNS lesions (including cortical dysplasia, subependymal nodules, and, at a lesser frequency, subependymal giant cell astrocytomas).
- Associated neurological conditions include seizures and autism spectrum disorder.
- Other manifestations include lymphangio- leiomyomatosis (LAM) of the lung (which primarily affects women), cardiac rhabdomyomas, and retinal hamartomas

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