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REVIEW ARTICLE

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Hereditary kidney cancer syndromes: Genetic disorders driven by alterations in metabolism and epigenome regulation

Hisashi Hasumi | Masahiro Yao

Department of Urology, Yokohama City University, Yokohama, Japan

Correspondence
Hisashi Hasumi, Department of Urology, Yokohama City University, Yokohama, Japan.
Email: hasumi@yokohama-cu.ac.jp

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Although hereditary kidney cancer syndrome accounts for approximately five percent of all kidney cancers, the mechanistic insight into tumor development in these rare conditions has provided the foundation for the development of molecular targeting agents currently used for sporadic kidney cancer. In the late 1980s, the comprehensive study for hereditary kidney cancer syndrome was launched in the National Cancer Institute, USA and the first kidney cancer-associated gene, *VHL*, was identified through kindred analysis of von Hippel-Lindau (VHL) syndrome in 1993. Subsequent molecular studies on *VHL* function have elucidated that the VHL protein is a component of E3 ubiquitin ligase complex for hypoxia-inducible factor (HIF), which provided the basis for the development of tyrosine kinase inhibitors targeting the *HIF-VEGF/PDGF* pathway. Recent whole-exome sequencing analysis of sporadic kidney cancer exhibited the recurrent mutations in chromatin remodeling genes and the later study has revealed that several chromatin remodeling genes are altered in kidney cancer kindred at the germline level. To date, more than 10 hereditary kidney cancer syndromes together with each responsible gene have been characterized and most of the causative genes for these genetic disorders are associated with either metabolism or epigenome regulation. In this review article, we describe the molecular mechanisms of how an alteration of each kidney cancer-associated gene leads to renal tumorigenesis as well as denote therapeutic targets elicited by studies on hereditary kidney cancer.

KEYWORDS
Birt-Hogg-Dubé syndrome, cancer metabolism, epigenome regulation, hereditary leiomyomatosis renal cell cancer, von Hippel-Lindau syndrome

Abbreviations: AML, angiomyolipoma; AMPK, 5′-AMP-activated protein kinase; BHD syndrome, Birt-Hogg-Dubé syndrome; *CA-IX*, *carbonic anhydrase IX*; CIMP, CpG island methylator phenotype; DENN, differentially expressed in neoplastic vs normal cells; FH, fumarate hydratase; FLCN, folliculin; FNIP1 and FNIP2, folliculin-interacting proteins 1 and 2; GAP, GTPase-activating protein; GEF, guanine nucleotide exchange factor; HGF, hepatocyte growth factor; HIF, hypoxia inducible factor; HLRCC, hereditary leiomyomatosis and renal cell cancer; *HMOX1*, *haem oxygenase 1*; HOCT, hybrid oncocytic/chromophobe tumor; HPRCC, hereditary papillary renal cell carcinoma; KEAP1, kelch-like ECH-associated protein 1; LAM, lymphangioleiomyomatosis; MEF, mouse embryonic fibroblast; mTOR, mammalian target of rapamycin; PDGF, platelet-derived growth factor; PHD, prolyl-hydroxylase; RCC, renal cell carcinoma; SDHB, SDHC and SDHD, succinate dehydrogenase B,C and D; SEGA, subependymal giant cell astrocytoma; *TCEB1*, *transcription elongation factor B polypeptide 1*; TCGA, the Cancer Genome Atlas; TGF-α, transforming growth factor alpha; TKI, tyrosine kinase inhibitor; TSC, tuberous sclerosis; VEGF, vascular endothelial growth factor; VHL syndrome, von Hippel-Lindau syndrome.

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1 | VON HIPPEL-LINDAU (VHL) SYNDROME

von Hippel-Lindau (VHL) syndrome is a rare hereditary neoplastic syndrome, which predisposes patients to develop retinal angioma, hemangioblastoma of the central nervous system, pheochromocytoma, pancreatic cystadenoma and neuroendocrine tumor, and clear cell renal cell carcinoma (RCC) (Figure 1). The gene responsible for the disease, located at chromosome 3p25.3, was identified as *VHL* tumor suppressor by positional cloning method in 1993.[1,2] Subsequent molecular studies have shown that VHL is a component of the E3 ubiquitin ligase complex which specifically recognizes HIF protein for degradation through the ubiquitin proteasome pathway; therefore, *VHL* alteration leads to the accumulation of HIF as well as increased transcription of its downstream genes, *VEGF*, *PDGF* and *TGF-α*, which promote tumor progression.[3] In 2013, independent research groups of The Cancer Genome Atlas (TCGA) project and in the University of Tokyo conducted whole-exosome sequencing of sporadic clear cell RCC using next-generation sequencing technology and elucidated that nearly 90% of sporadic clear cell RCC harbors alterations in *VHL* itself or in *TCEB1*, a component of the VHL complex.[4,5] These findings have provided robust evidence for using antiangiogenic agents or tyrosine kinase inhibitors (TKIs), including bevacizumab, sorafenib, sunitinib, axitinib and pazopanib, which target the VHL-HIF-VEGF/PDGF pathway as standardized therapeutics for sporadic RCC. However, in addition to *VEGF/PDGF*, HIF transcriptionally regulates a variety of genes, including *cyclin D1*, *glut1* and *CA-IX* etc. Thus, this partial inhibition of *HIF* downstream genes may limit the efficacy of TKI for RCC treatment.[6] In this notion, HIF2α antagonist has been developed and its efficacy is under investigation.[7]

2 | BIRT-HOGG-DUBÉ' (BHD) SYNDROME

Birt-Hogg-Dubé (BHD) syndrome is a rare genetic disorder that causes development of lung cysts, fibrofolliculomas, and renal tumors with various histological subtypes, including chromophobe RCC, hybrid oncocytic/chromophobe tumor (HOCT), clear cell RCC, papillary RCC, and oncocytoma[8-12] (Figure 2). In 2002, the responsible gene, *FLCN* was identified and the majority of germline *FLCN* mutations were either nonsense mutations or frameshift mutations with a few exceptions of missense mutations, including H255Y and K508R.[13-15] Folliculin (FLCN) binds to its two interacting partners, folliculin-interacting protein 1 and 2 (FNIP1 and FNIP2), and senses energy through the interaction between FNIPs and 5′AMP-activated protein kinase (AMPK), an important energy-sensing molecule.[16-19] Disruption of FLCN-FNIPs interaction drives upregulated mTORC1-dependent protein synthesis, upregulated *PGC1α*-dependent mitochondrial oxidative metabolism and aberrant kidney cell proliferation.[20-24] Crystallography of FLCN protein exhibited that FLCN has a DENN domain in its C-terminus, suggesting FLCN may act as a modifier for Rab small GTPase family as well as a regulator for membranous trafficking.[25,26] In addition, FLCN shows either GAP activity towards RagC/D GTPases or GEF activity towards RagA/B GTPases, which consequently regulates mTORC1 localization on lysosomes, implying that FLCN may regulate multiple small GTPases.[27,28] These findings highlight that FLCN plays important roles in metabolism, and disruption of metabolism under *FLCN* deficiency may drive aberrant kidney cell proliferation. Kidney-specific *Flcn* knockout mouse develops hyperproliferative polycystic kidney. However, this mouse model dies at 3 weeks of age as a result of renal failure before developing kidney cancer.[23] Therefore, it is suggested that an additional mutation may be necessary for developing kidney cancer in cooperation with *FLCN* deficiency.

3 | HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER (HLRCC)

Hereditary leiomyomatosis and renal cell cancer (HLRCC) predisposes patients to develop leiomyomatosis of skin and uterus with

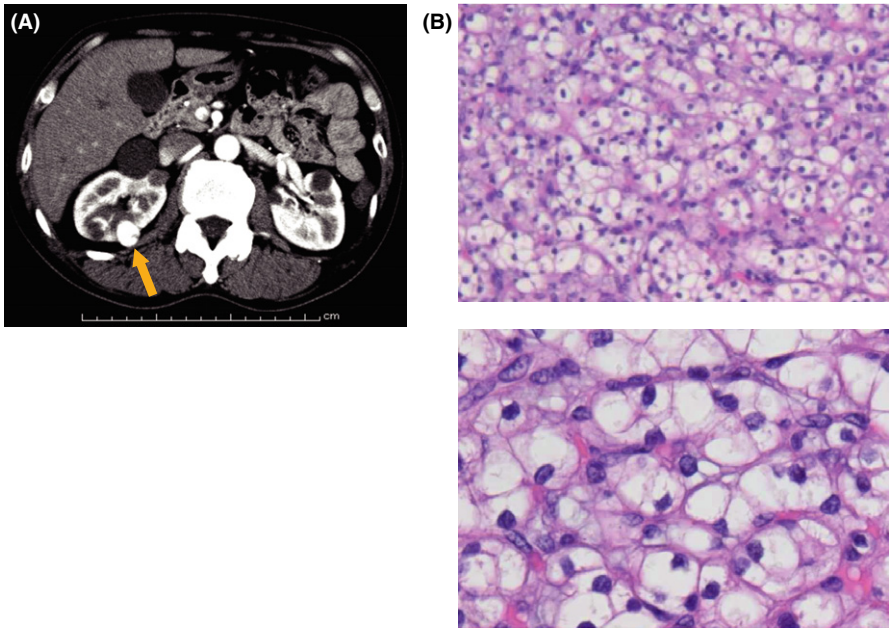

FIGURE 1 von Hippel-Lindau (VHL) syndrome-associated kidney cancer. A, Computed tomography with contrast material of VHL patient shows hypervascular tumor in the right kidney (orange arrow) and multiple cysts in both kidneys. Partial nephrectomy was done to the right kidney. B, Four out of 5 tumors and 1 out of 4 cyst walls exhibited the histology of clear cell renal cell carcinoma. Upper panel shows low magnification and lower panel shows high magnification of H&E staining

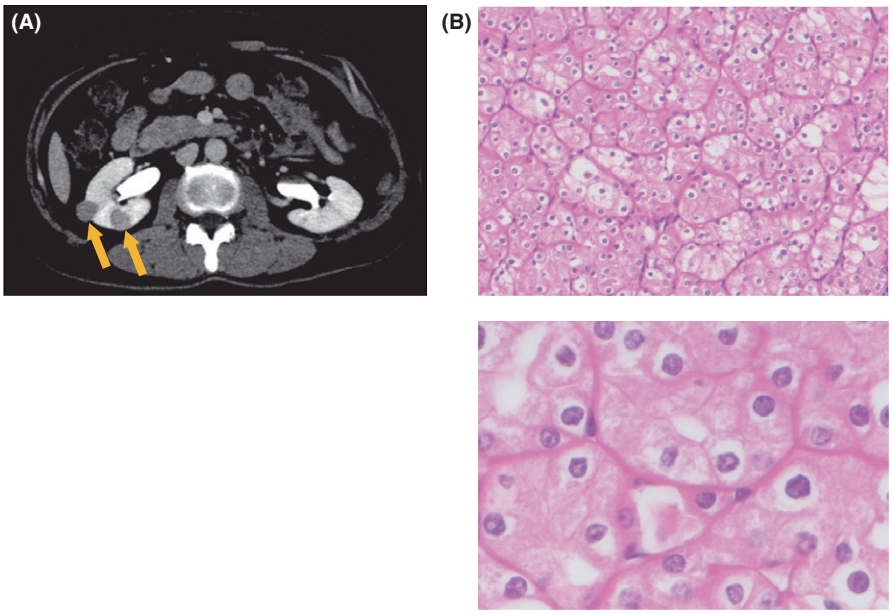

FIGURE 2 Birt-Hogg-Dubé (BHD) syndrome-associated kidney cancer. A, Computed tomography with contrast material of BHD patient shows weakly stained tumors in the right kidney (orange arrows). Partial nephrectomy was done to the right kidney. B, H&E stain shows the most predominant forms of BHD-associated kidney cancer, hybrid oncocytic/chromophobe tumors (HOCT). Low magnification (upper panel) and high magnification (lower panel). Figures are from Hasumi et al[8]

high frequency as well as type 2 papillary RCC in 10%-16% of the affected patients, which presents a very aggressive behavior and metastasizes even from a small-sized tumor, leading to very poor prognosis.[29] In 2002, *FH* was identified as a causative gene for HLRCC.[30] Alteration of *FH* drives the metabolic shift towards glycolysis as well as the accumulation of fumarate, an oncometabolite which inhibits α-ketoglutarate-dependent enzymes, including PHD and DNA demethylases, leading to HIF accumulation or genome-wide methylated status called CpG island methylator phenotype (CIMP).[31-34] In *FH*-deficient cells, KEAP1, E3 ubiquitin ligase for Nrf2 antioxidant transcription factor, is inactivated by its succinylated residues, leading to Nrf2 accumulation and resistance of *FH*-deficient cells to reactive oxygen species.[35] In fact, an inhibitor for *HMOX1*, a downstream target of *Nrf2*, suppressed cell proliferation of *Fh*-deficient mouse embryonic fibroblasts (MEFs).[36]

4 | HEREDITARY PARAGANGLIOMA-PHEOCHROMOCYTOMA SYNDROME

Germline mutations in *SDHB*, *SDHC*, and *SDHD*, genes responsible for hereditary paraganglioma-pheochromocytoma syndrome, cause the development of kidney cancer .[37] Alteration of *SDH* leads to the metabolic shift towards glycolysis as well as to the accumulation of succinate, which drives tumor progression in the same way as does the accumulation of fumarate in *FH*-deficient kidney cells.[38,39]

5 | HEREDITARY PAPILLARY RENAL CELL CARCINOMA (HPRCC)

Hereditary papillary renal cell carcinoma (HPRCC) is a very rare type of hereditary kidney cancer syndrome compared to VHL syndrome, BHD syndrome and HLRCC, and predisposes patients to develop bilateral type 1 papillary RCC. In 1997, activating mutation of *MET* was identified as a responsible genetic alteration. c-MET, encoded by the *MET* gene is a tyrosine kinase receptor for HGF and the constitutive active form of c-MET drives kidney cell proliferation.[40-42] Whole-exosome sequencing of sporadic kidney cancer showed alterations in the c-MET/HGF pathway in 12% of clear cell RCC and in 10% of papillary RCC, indicating that targeting the c-MET/HGF pathway is rational for the treatment of these histological types of kidney cancer and, in fact, the efficacy of cabozantinib which targets both c-MET and VEGFR has been reported.[43,44]

6 | COWDEN SYNDROME

Cowden syndrome predisposes patients to develop intestinal hamartomatous polyps, benign skin tumors and macrocephaly. Patients are also at risk of malignancies in breast, thyroid, uterus and prostate, and 4%-16% of patients develop kidney cancer with various types of histology, including papillary, chromophobe, and clear cell RCC.[45] Alteration of *PTEN*, a causative gene for Cowden syndrome, drives activation of the PI3K-AKT-mTOR pathway.

7 | TUBEROUS SCLEROSIS (TSC)

Tuberous sclerosis (TSC), a hamartoma syndrome with a triad of facial angiofibromas, seizure and developmental delay, predisposes patients to develop subepedymal giant cell astrocytoma (SEGA), angiomyolipoma (AML) in kidney, lymphangioleiomyomatosis (LAM) in lung and kidney cancer in 3% of affected patients. *TSC1* and *TSC2* have been identified as causative genes for TSC.[46] TSC2 is a GTPase activating protein for Rheb GTPase whereas TSC1 regulates stability of TSC2 protein; either *TSC1* or *TSC2* mutation increases GTP-bound Rheb GTPase, leading to constitutive activation of mTORC1

complex.[47] Targeted next-generation sequencing analysis of TSC-associated kidney cancer demonstrated a relatively small number of somatic mutations in addition to *TSC1/2* mutations, suggesting that mutations in *TSC1/2* themselves may be strong driver mutations.[46]

8 | CHROMOSOME 3P TRANSLOCATION-ASSOCIATED KIDNEY CANCER SYNDROME

While sporadic clear cell RCC frequently harbors a large chromosomal deletion at chromosome 3p, hereditary kidney cancer with germline chromosomal 3p translocation has been reported.[48] Chromosomal rearrangement involving chromosome 3p leads to loss of multiple kidney cancer-associated genes including *VHL*, *BAP1*, *PBRM1* and *SETD2*. Single inactivation of either *Vhl*, *Bap1* or *Pbrm1* does not cause development of kidney cancer, whereas double inactivation of *Vhl/Bap1* or *Vhl/Pbrm1* does cause development of kidney cancer, indicating that a large chromosomal deletion involving this locus is a critical event triggering renal tumorigenesis.[49,50]

9 | *BAP1* CANCER SUSCEPTIBILITY SYNDROME

One of the biggest findings in whole-exome sequencing for sporadic kidney cancer using next-generation sequencing technology are the recurrent alterations in chromatin remodeling genes in clear cell and papillary RCC. Among these alterations, *BAP1* mutations were found in 15% of sporadic RCC.[4,5] *BAP1* mutation is a critical driver for renal tumorigenesis as double inactivation of murine *Vhl* and *Bap1* develops malignant lesions in mouse kidney.[50] Interestingly, a later study on hereditary kidney cancer reported that a germline *BAP1* mutation was found in kidney cancer kindred.[51] *BAP1* is a tumor suppressor for multiple organs and germline *BAP1* mutation drives malignant mesothelioma and malignant melanoma in uvea and skin. BAP1 deubiquitinates histone H2A at K119 and chromatin immunoprecipitation and DNA sequencing (ChIP-seq) for BAP1 protein showed that significant BAP1 peaks locate near the transcription start sites of 5731 genes which may include the targets for *BAP1*-deficient kidney cancer.[52]

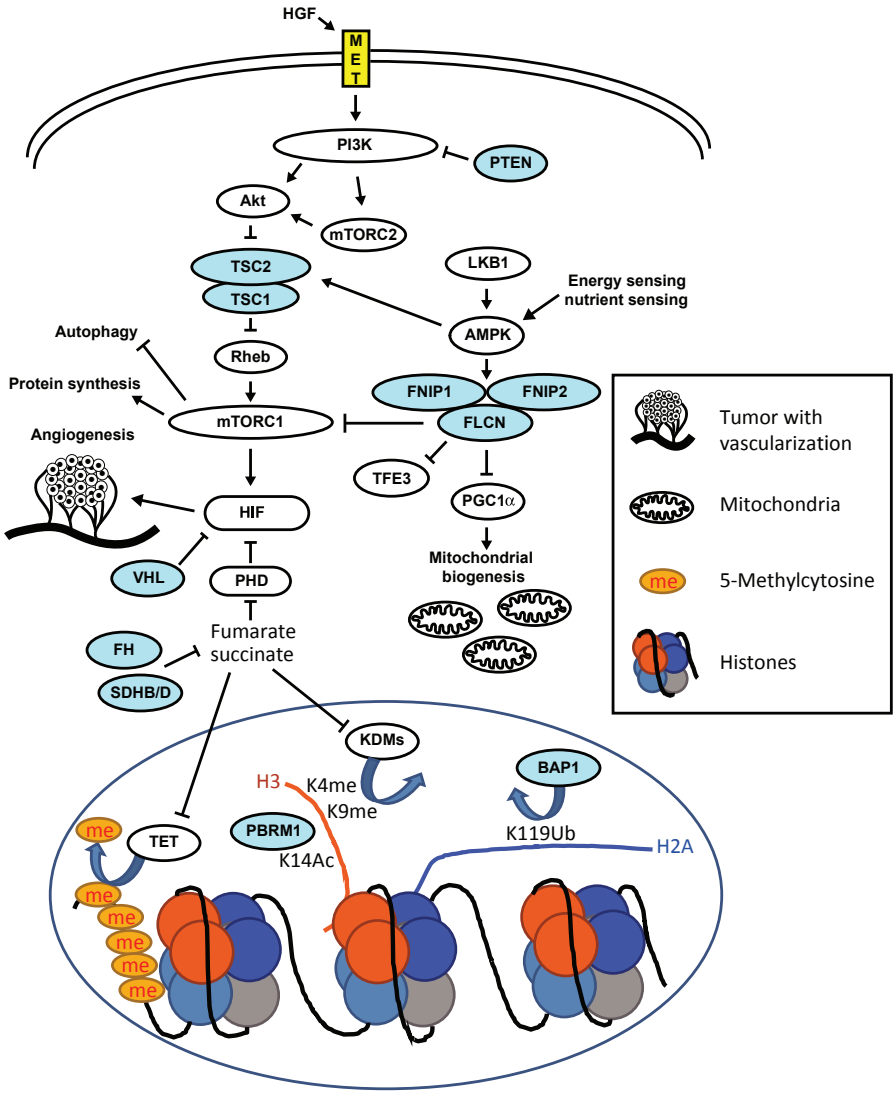

FIGURE 3 Hereditary kidney cancer-associated genes. Blue shows tumor suppressor and yellow shows oncogene. PHD, prolyl hydroxylase; KDMs, lysine demethylases; TET, Ten-eleven translocation methylcytosine dioxygenase

10 | OTHER HEREDITARY KIDNEY CANCERS

Germline *PBRM1* mutation has been reported in a kindred of kidney cancer.[53] PBRM1 remodels chromatin structure as well as regulates other tumor suppressors through its bromodomain interaction with acetylated lysine in histone H3 at K14 or in tumor suppressor proteins.[54] *PBRM1* mutation is an important driver mutation for kidney cancer development as its alteration was found in 40% of sporadic RCC, and double inactivation of murine *Vhl* and *Pbrm1* causes development of kidney cancer in mouse.[4,5,49] Additionally, germline *CDKN2B* mutation was found in kidney cancer kindred.[55] Thus, a subset of genes found to be altered in sporadic kidney cancer by next-generation sequencing analysis may be candidates for causative genes of hereditary kidney cancer. In addition, kindred with multiple germline mutations in cancer-associated genes have been reported: neurofibromatosis type I with BHD syndrome, Li-Fraumeni syndrome with BHD syndrome and Lynch syndrome with BHD syndrome. In these kindred, symptoms that are not observed in each syndrome were observed when the two syndromes occurred together, suggesting that we have to treat these patients with precautions.[56]

11 | CONCLUSION

Although hereditary kidney cancer accounts for approximately five percent of all kidney cancers, mechanistic insight into tumorigenesis of these rare genetic disorders has provided the basis for the development of novel therapeutics for sporadic kidney cancer. Recent genome-wide analysis on sporadic kidney cancer using next-generation sequencing technology has further identified novel kidney cancer-associated genes and later studies showed that some of these genes are altered in kidney cancer kindred at the germline level. Thus, to sort out driver mutations of kidney cancer, it is important to integrate data of genome-wide analysis on sporadic kidney cancer with germline genomic data of patients with hereditary kidney cancer. Notably, most of the kidney cancer-associated genes have roles in either metabolism or chromatin remodeling, suggesting that disruption of metabolism, dysregulation of chromatin remodeling, or loss of crosstalk between metabolism and the epigenome may drive renal tumorigenesis (Figure 3). In conclusion, understanding the metabolic and epigenetic abnormalities underlying deficiencies of kidney cancer-associated genes may lead to the development of novel diagnostic biomarkers, diagnostic imaging modalities and novel therapeutics for kidney cancer.

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CONFLICT OF INTEREST

Authors declare no conflicts of interest for this article.

ORCID

Hisashi Hasumi http://orcid.org/0000-0001-8211-8835

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