

GENETIC SYNDROMES ASSOCIATED WITH RENAL CELL CARCINOMA – A REVIEW

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Aims. A review of recent knowledge on hereditary syndromes related to renal cell carcinoma.

Methods. Aim of this review was to summarize the recent knowledge of genetic syndromes associated with renal cell carcinoma.

Results. Summary of incidence and factors modulating risk of hereditary renal cell carcinoma development.

Conclusions. Hereditary forms of RCC are relatively rare. Their study is beneficial in many ways. In individuals at a higher risk of a hereditary syndrome, the knowledge of hereditary forms may help to significantly decrease the impact of the hereditary disease. In the general population, knowledge acquired by the study of hereditary forms of RCC may in the future contribute to both diagnosis and treatment of sporadic tumours.

INTRODUCTION

Kidney cancer belongs to 16 most frequent malignancies in the Czech Republic and globally. In 2008, a total of 265,731 persons were diagnosed with this type of cancer and 113,315 people died (IARC) (ref.¹). And the incidence continues to rise.

Renal cell carcinoma (RCC) is not a single entity but rather a group of tumours originating from kidney epithelium². RCC originates from the tubular structures of the kidney and is classified into 4 main histological types. The most common type, accounting for 75% (ref.^{3–5}) of all RCC cases, is clear cell renal cell carcinoma (ccRCC).

The others are papillary (10–15%) (ref.^{4,6}), chromophobe (3–5%) (ref.^{4–6}), oncocytoma (5–9%) (ref.^{4,5}) and collecting duct (1%) RCC (ref.^{5,6}) (Table 1).

CHARACTERISTICS OF HEREDITARY FORMS OF RCC

Approximately 4% of all RCC are hereditary^{2,7}.

Men are twice as likely as women to become affected. The incidence of sporadic forms of RCC begins to increase after 30 years of age, with cases occurring most rapidly after the age of 45 and peaking after 70 years. This

Table 1. Classification schema for kidney epithelial neoplasias.

Histological type	Cell origin	Genes implicated	Chromosomal abnormalities	% of all RCC tumors (ref. ^{4–6})
Clear cell RCC	Proximal tubule	VHL, BHD	-3p, +5q, -Y, -9p, -14q, t(3;5) (p;q)	75 %
Papillary RCC	Proximal tubule	MET, FH, HRPT2	+7, +17, -Y, +12, +16, +20 t(X;1) (p11.2;q21.2) t(X;17) (p11.2;q25.3)	Type 1: <5% Type 2: <10%
Chromophobe RCC	Intercalated cell Cortical collecting duct	BHD	-1, -2, -6, -10, -13, -17, -21	3–5%
Oncocytoma	Intercalated cell Cortical collecting duct	BHD	-1, -Y t(5;11) (q35;q13) t(9;11) (p23;q13)	5–9%
Collecting duct (Bellini's duct) RCC	Medullary collecting duct	FH	-7q32, -6p, -8p, -21q	<1%

Adapted from Valladares-Ayerbes M, 2008 (ref.⁵)

Table 2. Hereditary cancer syndromes in RCC.

Syndrome	Causative gene, location	Renal manifestation	Other manifestations	Gene product	Pathway involvement	Incidence	Penetrance	Gene type	Average age of tumour detection
Von Hippel-Lindau (VHL)	VHL, 3p25	Clear cell RCC	Retinal and CNS haemangioblastomas; pheochromocytomas; pancreatic cysts, neuroendocrine tumours; epididymal tumours; endolymphatic sac tumours; broad ligament and broad ligament cystadenomas	VHL protein	Hypoxia-inducible factor (HIF)	1:35,000 (ref. ¹⁴) - 1:36,000 (ref. ¹⁵)	Highly penetrant >90% under 65 years of age (ref. ¹²) RCC occurs in 24-45% of VHL patients (ref. ¹²)	Tumour suppressor	39 (ref. ¹²)
Hereditary papillary renal carcinoma (HPRC)	MET, 7q31	Papillary RCC type 1	None	Tyrosine kinase receptor (ref. ^{48,49})	HGF/c-MET	As yet unknown (ref. ¹²)	Highly penetrant (ref. ^{3,12})	Proto-oncogene (ref. ²⁴)	5th to 6th decade (ref. ¹²)
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)	FH, 1q42-43	Papillary RCC type 2, collecting duct RCC	Uterine leiomyomas and leiomyosarcomas; cutaneous nodules (leiomyomas)	Fumarate hydratase (FH)	The tricarboxylic acid cycle (Krebs cycle), causing overexpression of HIF	From 2-6% (ref. ¹⁰) to 15% (ref. ³⁴); up to 32% (ref. ¹⁸) in families with germline mutation	Low penetrance	Tumour suppressor	36-39 (ref. ^{13,14,55})
Birt-Hogg-Dubé (BHD)	FLCN (previously known as BHD), 17q11.2	Hybrid oncocytoma RCC, chromophobe RCC, clear cell RCC, oncocytoma	Cutaneous papules (fibrofolliculomas); lung cysts, spontaneous pneumothorax, possibly colon polyps	Folliculin	Regulation of AMPK and mTOR (ref. ^{13,21,24})	Prevalence of 1:200,000 (ref. ²⁸)	Renal tumours in 25-35% of BHD patients (ref. ^{13,28})	Tumour suppressor	50 (ref. ^{24,14})
Hyperparathyroidism-jaw tumour (HPT-JT)	HRPT2, 1q25-31	Mixed epithelial and stromal tumours, papillary RCC, cysts, Wilms' tumour, renal hamartoma, RCC, renal cortical adenoma, multiple renal cysts (ref. ^{29,30,56})	Parathyroid tumours (carcinomas), fibro-osseous mandibular and maxillary tumours, uterine tumours	Parafibromin (ref. ³⁷)	Suppresses expression of MYC which encodes the c-MYC proto-oncogene	About 50 families with HPT-JT syndrome have been reported (ref. ³⁰)	Highly penetrant. Renal abnormalities in about 15% of HPT-JT patients (ref. ³⁰)	Tumour suppressor	-

Table 2. (continued)

Syndrome	Causative gene, location	Renal manifestation	Other manifestations	Gene product	Pathway involvement	Incidence	Penetrance	Gene type	Average age of tumour detection
Constitutional chromosome 3 translocation	Unknown gene, candidates are many genes on chromosome 3 (incl. FHIT, TRC8, DIRC1, DIRC2, DIRC3, HSBAP1, LSAMP, RASSF5, KCNIP4 and FBW7, SETD2, JARID1C, HNF1B and HNF1A)	Clear cell RCC	None	-	-	-	-	-	-
Familial papillary thyroid cancer (FPTC)	Unknown gene, 1q21	Papillary RCC, oncocytoma	Papillary thyroid cancer, nodular thyroid disease	-	-	-	-	-	-
Familial (clear cell) RCC of as yet unknown genetic cause	-	ccRCC	-	-	-	-	Low	-	50-70 (ref. ¹⁴)
Tuberous sclerosis (TS)	TSC1 9q34 TSC2 16p13.3	Renal angioliopoma, cysts, oncocytoma, RCC (ref. ⁴²)	Hamartomas in various organs, angiofibromas, fibromas; rhabdomyomas and angiomyolipomas; epilepsy (ref. ^{11,46})	Hamartin tuberin (ref. ⁴²)	Hamartin and tuberin form a heterodimer and inhibit pathways downstream of mTOR (ref. ⁴²)	Incidence is not higher than in the normal population but the tumours occur at a younger age.	In the hereditary form, almost complete penetrance, variable expressivity (ref. ^{14,43,44}) 1:27,000 by some estimates (ref. ³⁸)	Tumour suppressor (ref. ⁴²)	28 (ref. ⁴⁶)
SDHB-associated hereditary paraganglioma/pheochromocytoma	SDHB, 1p36 SDHC, 1q21 SDHD, 11q23 (ref. ^{11,59})	Clear cell RCC chromofobe RCC oncocytoma (ref. ^{47,48})	Paraganglioma Pheochromocytoma (ref. ⁵⁹)	-	-	-	-	-	Before the age of 30 (ref. ^{11,47})
Familial renal oncocytoma (FRO)	Unknown gene, possible overlap with BHD (ref. ⁴)	Oncocytoma	No extrarenal manifestations	-	-	Low prevalence, unknown incidence	-	-	55.8 years (ref. ⁶⁰)

is due to accumulation of genetic and epigenetic changes in the cells of ageing individuals and failing repair and defence mechanisms. However, this is not true for hereditary forms of RCC. Hereditary RCC is rather rare and specific. Hereditary forms of RCC typically occur at a younger age. More frequently, hereditary RCC is multifocal and bilateral. Most of the known forms of hereditary RCC are linked to syndromes (with the exception of balanced translocations of chromosome 3).

The study of hereditary RCC has led to identification of hereditary syndromes in RCC.

Pavlovich and Schmidt listed 7 hereditary syndromes associated with RCC, in 5 of which genes causing the syndromes had been revealed². The presented article expands the list to 11 syndromes and more than 10 genes associated with the development of these syndromes.

Renal cell carcinoma is not a single disease but an entire collection of different types of cancer, each of which is caused by a different gene and has a different histology and clinical course. Each of the genes (VHL, MET, FLCN, TSC1, TSC2, FH and SDH) is, in a way or another, involved in pathways responding to metabolic stress or nutrient stimulation.

Mutations in each of these genes result in dysregulation of metabolic pathways involved in oxygen, iron, energy or nutrient sensing, suggesting that RCC is a disease of cell metabolism⁸.

Hereditary forms of RCC usually have a typical structure and occur at a much younger age as compared with sporadic forms. Since hereditary RCC is usually a tumour syndrome, besides renal manifestation, there are other – extrarenal – manifestations of the syndrome. Frequently, extrarenal manifestations may prevail and RCC develops in only a small proportion of patients suffering from a particular syndrome.

Hereditary syndromes associated with increased or earlier development of RCC are summarized in (Table 2). Hereditary RCC occurs at a younger age whereas in the normal population, RCC is seen between the ages of 60 and 70. More frequently, hereditary RCC is multifocal and bilateral. Moreover, unlike sporadic RCC that is twice as frequent in males, the gender distribution is equal^{9,10}.

If a hereditary type of tumour is suspected, tumour histology and possibly extrarenal symptoms may be helpful in the differential diagnosis to rule out sporadic forms¹¹.

All the listed syndromes are autosomal dominant, with the exception of RCC associated with involvement of chromosome 3 (ref.¹¹).

SYNDROMES ASSOCIATED WITH RCC

Von Hippel-Lindau (VHL) syndrome

In VHL syndrome, an increased incidence of ccRCC is observed.

VHL syndrome results from a mutation in the VHL tumour suppressor gene. The disease is autosomal dominant and highly penetrant (80–90% penetrance²). Approximately 24–45% (ref.¹²) patients with VHL syn-

drome develop ccRCC, typically between 25 and 60 years (a mean of about 39 years¹²). Histologically, the cases are almost exclusively ccRCC. The tumours are usually solid or cystic, very often multifocal and bilateral^{2,11,13,14}.

The extrarenal manifestations of VHL syndrome include retinal and CNS haemangioblastomas, pheochromocytomas, pancreatic cysts and neuroendocrine tumours, endolymphatic sac tumours, and epididymal and broad ligament cystadenomas^{2,11,14}.

The incidence of VHL syndrome is reported as between 1/35,000 (ref.¹⁴) and 1/36,000 (ref.¹⁵).

Hereditary papillary renal carcinoma (HPRC)

Families with HPRC syndrome suffer from type 1 papillary RCC. The syndrome is caused by mutation of the MET (mesenchymal-epithelial transition factor) proto-oncogene^{2,11,14}. The mutation is typical for familial papillary RCC.

Apart from type 1 papillary carcinoma, neither other typical manifestations nor the exact incidence of this hereditary RCC are known. HPRC typically develops between the 5th and 6th decade of life. The disorder is highly penetrant. Persons affected by HPRC syndrome have a 90% (ref.^{16,17}) likelihood of developing RCC by the age of 80 years^{8,18}.

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)

Individuals affected by HLRCC syndrome are at increased risk of type 2 papillary RCC. This type is rarer but more aggressive^{18,19}.

HLRCC syndrome is caused by mutations in the fumarate hydratase (FH) gene on chromosome 1q42-43.

In addition to renal involvement, it is common for patients with HLRCC to have uterine leiomyomas, leiomyosarcomas and cutaneous leiomyomas^{2,11,13,14,20}.

(Some families, however, are only affected by cutaneous and uterine leiomyomas, rarely with RCC. In such cases, the syndrome is called multiple cutaneous and uterine leiomyomatosis²).

HLRCC usually occurs at a young age (the youngest known case was at the age of 16 years¹³, with a median incidence at the age of 39 years¹⁴).

Birt-Hogg-Dubé (BHD) syndrome

The gene mutated in Birt-Hogg-Dubé syndrome is FLCN, previously known as BHD. Mutations in the FLCN gene are found especially in hereditary forms of RCC (ref.^{9,21–24}).

About 25–35% (ref.¹³) of patients with BHD syndrome develop various types of renal tumours^{13,25–27}.

Histologically, the tumours are hybrid chromophobe/oncocytoma (50%), chromophobe (34%), ccRCC (9%) and oncocytoma (5%) (ref.²).

Various histological types of RCC may be present within a single family affected by BHD syndrome, in a single patient or even in the same kidney^{28,13}.

Tumour lesions may be solitary or bilateral and multifocal.

Members of families affected by BHD syndrome have a 7-fold increased risk of RCC as compared with the normal population²⁶.

In addition to RCC, the BHD manifestations include cutaneous papules (fibrofolliculomas, most commonly on the head, neck and anterior trunk) in about 85% (ref.¹³) of BHD patients and lung cysts in more than 80% (ref.¹³) of patients. About 25% (ref.¹³) of patients have a history of spontaneous pneumothorax. Although some families were found to have a higher prevalence of colon cancer it is not known yet whether this may be considered a BHD syndrome manifestation²⁸.

The prevalence of BHD syndrome is 1:200,000 (ref.²⁸).

In BHD syndrome, RCC typically occurs around the age of 50 (ref.^{14,24,28}).

Hyperparathyroidism-jaw tumour (HPT-JT)

In some families, hereditary HPT-JT syndrome increases the prevalence of kidney neoplasms – nephroblastomas, hamartomas and Wilms' tumour and renal cysts^{27,29,30}.

Approximately 95% (ref.²⁹) of persons with HPT-JT develop hyperparathyroidism, 5% (ref.²⁹) of patients develop parathyroid carcinoma and about half of the patients are known to have fibro-osseous mandibular and maxillary tumours.

HPT-JT is associated with mutations in the HRPT2 (hyperparathyroidism 2) tumour suppressor gene. Since only about 50 families have been reported so far, the exact incidence has not been determined³⁰.

Constitutional chromosome 3 translocation

Balanced chromosome 3 translocations are a rare cause of ccRCC (OMIM 603046 and 144700)^{31,32,14}. A total of 13 different constitutional translocations involving chromosome 3 have been described, of which 7 are associated with familial kidney cancer and the remaining 6 were not found to run in families^{33,34}.

The candidates are many genes on chromosome 3 (incl. FHIT, TRC8, DIRC1, DIRC2, DIRC3, HSBAP1, LSAMP, RASSF5, KCNIP4 and FBW7 (ref.^{33,34}); SETD2 and JARID1C (ref.³⁵); Rebouissou suggested that the impact of germline mutations HNF1B and HNF1A may predispose to RCC (ref.³⁶)).

At present, little is known about RCC caused by constitutional chromosomal translocations. The only clue is the presence of chromosome 3 translocation and multifocal and bilateral ccRCC.

The search for other genes responsible for hereditary forms of kidney cancer/renal cell carcinoma has not been completed. Several other genetic abnormalities will likely be associated with familial kidney cancer.

Familial papillary thyroid cancer (FPTC)

Persons affected by the syndrome have higher rates of papillary RCC and renal oncocytoma. In addition to tumours of the kidney, they develop papillary thyroid cancer and nodular thyroid disease. Of all cases of papillary thyroid cancer, only 5% (ref.²) are of hereditary origin.

The FPTC phenotype has been linked to 1q21 (ref.³⁷), indicating a new RCC-associated gene could be responsible for this syndrome¹⁴.

Familial RCC of as yet unknown genetic cause

Familial ccRCC is defined as the development of ccRCC in two or more members of the same family, in whom VHL disease and constitutional chromosome 3 translocation have been ruled out^{38,39,7,14}. This type of tumour is associated with a very low frequency (over 70 families have been reported). In those families, first-degree relatives have a 2–3-fold increased risk of RCC than the normal population⁴⁰. As the cause remains unknown, the multigenetic mechanism of inheritance is assumed².

Tuberous sclerosis (TS)

This hereditary syndrome is associated with mutations in the TSC1 and TSC2 genes^{41,42}.

As much as 70% (ref.¹⁴) of TS cases are caused by spontaneous germline mutation and only 30% (ref.¹⁴) are hereditary. (The hereditary form is characterized by almost complete penetrance but variable expressivity.)

Renal lesions are seen in 50–80% (ref.¹⁴) of TS patients (angiomyolipomas, cysts, oncocytomas, RCC). Renal angioliipomas may be life-threatening if bleeding occurs¹¹.

Between 1% and 4% (ref.^{43,44}) of patients with TS syndrome develop RCC.

Although the incidence is consistent with sporadic forms of RCC, they develop at a young age – 28 years of age on average⁴⁵. Most frequent is ccRCC but chromophobe RCC, papillary RCC and oncocytomas were also reported⁴⁶.

A total of 90% (ref.¹¹) of TS patients suffer from epilepsy. Only 30% (ref.¹¹) of cases have the classical triad of epilepsy, mental retardation and sebaceous adenoma. Skin manifestations include hypomelanotic macules, facial angiofibromas, shagreen patches and fibrous plaques. In the mouth, gingival fibromas may be found. Other potential extrarenal manifestations are periventricular hamartomas, cardiac rhabdomyomas and retinal hamartomas. As many as 75% (ref.¹¹) of patients are found to have renal asymptomatic angiomyolipomas.

Hereditary paraganglioma/pheochromocytoma

Originally, two families with hereditary paragangliomas were found to have a higher prevalence of ccRCC. In those persons, three out of four genes encoding succinate dehydrogenase, a Krebs cycle enzyme, were mutated (SDHB, SDHC, SDHD) (ref.⁴⁷). Later research revealed bilateral, multifocal ccRCC or chromophobe RCC with a very early onset⁴⁸.

Other – extrarenal – tumours include paragangliomas and pheochromocytomas. The patients are diagnosed with kidney cancer before the age of 30. As the disease is rare, the prevalence is as yet unknown.

Familial renal oncocytoma (FRO)

The syndrome is usually associated with solitary, multifocal and bilateral oncocytomas. As of now, FRO

syndrome is only known to be autosomal dominant but the particular gene has not been identified. Potential overlap with BHD is being studied⁴⁹. On average, persons with FRO develop kidney cancer at the age of 55.8 years⁵⁰. Apart from kidney cancer, no other manifestations are known.

Due to the low frequency (only about 20 cases are known), the exact prevalence of the syndrome has not been determined.

DISCUSSION

The importance of the study of hereditary forms of RCC is in identifying pathways involved in the particular type of tumours. Subsequently, the pathways are also studied in sporadic forms of the tumour. The knowledge of the development and mechanism of involvement of genetic pathways leads us to the metabolic effect resulting from the genetic disorder and gives us a chance to distinguish various forms of the same histological type of cancer. As a result, the so-called tailored therapy may be applied in each individual patient.

The exact mechanism of the development of hereditary RCC is still not completely known. The key steps are activation of the cell proliferation cascade and prevention of apoptosis^{2,21,51}. Impaired regulation of proliferation and angiogenesis are two main components of carcinogenesis in the kidneys²¹.

The findings may also be applied in prevention of kidney cancer in families affected by any of the syndromes. The question is how to tell that an individual has a hereditary form of RCC.

A hereditary form of RCC should be suspected if:

- 1) the patient has a personal or family history of RCC,
- 2) there is bilateral or/multifocal RCC,
- 3) there is early-onset RCC (under 50 years of age^{2,52,53}).

Additionally, RCC should be suspected if the patient or his/her relatives has any of extrarenal manifestations typical for certain forms of syndromes, such as fibrofolliculomas or pneumothorax¹⁴.

According to Axwijk et al., screening should be recommended to¹¹:

- 1) patients with a mutation in one of the mentioned genes, associated with a RCC syndrome,
- 2) patients and first-degree relatives from a family with a suspected RCC syndrome, which could not be confirmed by genetic analysis,
- 3) patients and first-degree relatives in a family with two or more first- or second-degree relatives with RCC,
- 4) individuals with RCC before the age of 50 and their first-degree relatives.

For diagnosis and secondary prevention, ultrasound and CT are the examination of choice in persons with kidney disease manifestations. At present, however, these preventive (screening) measures can mostly be applied in

persons with an increased risk of developing this serious condition.

CONCLUSION

Although hereditary forms of RCC are relatively rare, their study is beneficial in many ways. In individuals at a higher risk of a hereditary syndrome, the knowledge of hereditary forms may help to significantly decrease the impact of the hereditary disease. In the general population, knowledge acquired by the study of hereditary forms of RCC may in the future contribute to both diagnosis and treatment of sporadic tumours.

The latest genetic tests are increasingly used for identification of patients with a particular genetic abnormality potentially underlying RCC. However, due to financial and organizational reasons, screening of increasing numbers of patients at risk may be a serious economic problem in the future. Therefore, it is essential to identify various strategies according to the severity of a risk increase in a particular individual.

ABBREVIATIONS

BHD, Birt-Hogg-Dubé; ccRCC, Clear cell RCC; c-Met (MET), Protooncogene coding hepatocyte growth factor receptor (HGFR); c-MYC, Protooncogene; CNS, Central nervous system; CT, Computer tomography; DIRC1, Disrupted in renal carcinoma 1; DIRC2, Disrupted in renal carcinoma 2; DIRC3, Disrupted in renal carcinoma 3; FBW7, F-box and WD repeat domain containing 7; FH, Fumarate hydratase; FHIT, Gene coding fragile histidine triad protein; FLCN, Folliculin, previously known as BHD gene; FPTC, Familial papillary thyroid cancer; FRO, Familial renal oncocytoma; HGF, Hepatocyte growth factor; HIF, Hypoxia inducible factor; HLRCC, Hereditary leiomyomatosis and renal cell carcinoma; HNF1A, HNF1 homeobox A; HNF1B, HNF1 homeobox B; HPRC, Hereditary papillary renal carcinoma; HPT-JT, Hyperparathyroidism-jaw tumour; HRPT2, Hyperparathyroidism 2, tumour suppressor gene; HSPBAP1, Heat-shock 27-kD protein-associated protein 1; IARC, The International Agency for Research on Cancer; JARID1C, Jumonji, AT rich interactive domain 1C (known also like KDM5C - lysine (K)-specific demethylase 5C); KCNIP4, Kv channel interacting protein 4; LSAMP, Gene coding limbic system-associated membrane protein; MET, Mesenchymal-epithelial transition factor, proto-oncogene; MRI, Magnetic resonance imaging; mTOR, Mammalian target of rapamycin; RASSF5, Ras association (RalGDS/AF-6) domain family member 5; RCC, Renal cell carcinoma; SDH, Succinate dehydrogenase, a Krebs cycle enzyme; SDHB, SDHC, SDHD, genes encoding succinate dehydrogenase subunits; SETD2, SET domain containing; TRC8, Translocation in renal carcinoma, chromosome 8 gene; TS, Tuberous sclerosis; TSC1, Gene coding tuberous sclerosis protein 1;

TSC2, Gene coding tuberous sclerosis protein 2; VHL, Von Hippel-Lindau.

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