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# Genetic characteristics of the non-clear cell renal cancer

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*Renal cancer (RC) is one of the most frequent diseases in oncological urology; the most common form of RC is the dear cell carcinoma. However, percentage of less-studied non-clear cell RC (nccRC) reaches up to 25 % of cases suggesting further studying, improvement of diagnosis and treatment of these tumors. The key events of carcinogenesis are genetic alterations including chromosomal aberrations and point mutations in proto-oncogenes and tumor suppressor genes. This review describes cytogenetic aberrations in the context of nccRC diversity according to the current ISUP classification. Translocation variants of nccRC (MiT-RC) were characterized separately as particular cases of the chromosome rearrangements involving MiT gene family (TFE3, TFEB, M1TF). In addition, the main nccRC hereditary» forms caused by germinal mutations in the genes FLCN, FH, and MET, as well as recent studies of sporadic tumors with using the next generation sequencing techniques were reviewed. These experiments were designed to search for somatic mutations throughout the tumor genome or exome and revealed the different mutational profiles of I/II papillary RC subtypes, chromophobe carcinoma versus oncocytoma. The review may be informative for oncologists, urologists, geneticists and specialists in related sciences.*

**Key words:** *non-clear cell renal cancer, mutation, sequencing, exome, DNA-diagnostics*

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### Heterogeneity of non-clear cell renal cell carcinoma (nccRCC)

Today malignant kidney tumors are among the most frequent cancers in the general structure of cancer in Russia. Among men aged 30–59 years, kidney cancer (KC) takes the 4th place after lung cancer, stomach, and skin cancer [1]. About 95 % of all KC cases are presented by renal cell carcinomas (RCC), while the remaining 5 % KC cases are presented by tumors of the renal pelvis and ureter. RCCs develop from the epithelium of the renal tubules, but despite common origin they present morphologically heterogeneous group of tumors. The main types of RC are clear cell, papillary, chromophobe, rare and non-classified forms [2, 3]. Most molecular biology and clinical studies focus on the most common form of RCC – clear cell renal carcinoma, comprising 75 % of clinical cases. *VHL* gene inactivation is a typical feature of this type of RCCs which leads to hyperexpression of hypoxia-inducible HIF factor and its target genes [4, 5]. Non-clear cell renal cancer (nccRCC) is a rarer study object than clear cell renal cancer. However, it comprises about 20–25 % of all RCCs, which is a clinically significant amount. Currently, the International Society of Urological Pathology (ISUP) recommends the Vancouver classification for description of nccRCC.

**1. Papillary RCC**. Papillary renal cell carcinoma comprises 10–15 % of all RCC cases. In turn, they are divided into type I (characterized by a more favorable prognosis) and type II tumors. Immunohistochemistry profile includes expression of SK7 (more common in type I, than in type II), AMACR, CD10, and RCC–Ma. On the cytogenetic level papillary RCC is characterized by an increase in the number of copies of chromosomes 7 and 17, loss of the Y chromosome.

**2. Chromophobe RCC**. Chromophobe carcinomas comprise up to 5 % of all RCCs. Cells of this type of nccRCC are diffusely positive for SK7, negative for CD9/10. In cases of chromophobe carcinomas, loss of portions or whole chromosomes 1, 2, 6, 10, 13, 17, and 21 is often observed.

**3. Collecting duct carcinoma (Bellini duct carcinoma)**. This type of tumor is less than 1 % of RCC cases, it is characterized by rapid progression. Collecting duct carcinoma does not have any specific patterns of chromosomal aberrations.

**4. Mucinous tubular and spindle cell carcinoma**. Cells have positive staining for CD 10 and SK7, loose chromosomes 1, 4, 6, 13–15, and 22 [6, 7].

**5. MiT family translocation RCC**. This is a translocation type of KC. It occurs mainly in children and adolescents, rarely at a later age, and accounts for only 1 % of RCC cases in adults. At the genetic level, this type of RCC is caused by translocations involving the Xq 11.2 region and formation of chimeric genes involving *TFE3* gene and, rarely, other genes of the MiT family. On immunohistochemical level there is positive staining for AMACR, CD10, and RCC–Ma. However, expression of the C-terminal domain of TFE3 factor is the main immunohistochemical marker used in the routine diagnosis.

**6. Tubulocystic RCC**. Cytological and genetic characteristics (aberrations in chromosomes 7, 17, Y, and expression profile) of this type of renal cancer are close to those of papillary RCC. Its immunohistochemistry profile is characterized by staining for CK8, CK18, SK19, CD10, and AMACR.

**7. Acquired polycystic kidney disease associated with RCC**. This type of RCC is usually a multifocal tumor; at

cytogenetic level aberrations of 1–3,6, 7, 16, Y chromosomes were described.

**8. Clear cell papillary carcinoma**. This type is characterized by positive immunohistochemical staining for CK7 and CA9, negative staining for CD10 and AMACR, accounts for about 1 % of RCC cases. In contrast to clear cell RCC, *VHL* gene deletions aren»t typical for this carcinomas.

There are several additional types of RCCs: medullary RCC associated with *SDHB* gene mutations (RCC with succinate deficiency), KC in patients with hereditary leiomyomatosis, hybrid oncocytoma, and chromophobe RCC, which is common in patients with multiple renal oncocytomas and in patients with the Birt-Hogg-Dubé syndrome, as well as RCC with formation of the *VCL*: *ALK* chimeric oncogene [8–10]. In the last 3 cases, certain genetic disorders may serve as classifying symptoms and diagnostic criteria.

#### Translocation (MiT) renal cancer

In the new ISUP classification significant changes were made concerning translocation RCC variants involving genes of the MiT-family. The family of MiT transcription factors include TFE3, TFEB, TFEC, and MiTF, active mainly in the regulation of differentiation of osteoclasts and melanocytes. However, their expression is observed in other cell types. MiT factors have DNA-binding and activation domains that can form functional heterodimers between different members of the MiT family. The MiT-family genes are involved in intragenic changes described in various tumor types (Table 1). Basically, breakpoint affects the Hr11.2 region [10]. The prevalence of MiT family translocation RCC in children is up to 50 % of all cases of RCC, but in adults it drops down to 1 %. Translocation RCC in adults has a worse prognosis than in children [8]. Morphologically MiT family translocation RCC is heterogeneous. For example, *ASPSCR1: TFE3* chimera is associated with large tumor cells, which have colorless or eosinophilic cytoplasm, and agglomerate in the areas with alveolar and papillary structure. In case of the *PRCC: TFE3* gene, tumor cells have a smaller amount of cytoplasm, usually they contain psammomatous bodies or hyaline nodules.

Accurate differential diagnosis of MiT tumors from other types of RCC is difficult without the use of immunohistochemistry or genetic methods. FISH or immunohistochemistry detection of the relevant TFE3 domain are used as routine diagnostic methods. In some patients MiT tumors with t (6; 11) (p21; q12) translocation were described accompanied by the *alpfa: TFEB* chimera formation. Since the breakpoint is located in the promoter, tumors overexpress native TFEB; FISH or immunohistochemistry are also used in order to detect this adjustment. However, in most cases, TFE3 or TFEB serve as main markers in the differential diagnosis of MiT RCC. CA9, pan-cytokeratins, epithelial membrane antigen, and protease cathepsin K, and melanocyte factors HM-45 and Melan-A, whose expression is stimulated by MiT family members, can also be used for diagnosis [6, 12]. MiT tumors often overexpress MET, which indicates the possibility of using MET inhibitors as antitumor agents. Some of new MiT translocations were detected by sequencing of the transcriptome (RNAseq) in nccRCC samples (*RBM10: TFE3*, *DVL2: TFE3*, *COL21Al: TFEB*, *CLTC: TFEB*, *ACTG1: MITF*) while searching for somatic mutations, which also suggested overexpression of anti-apoptotic factor BIRC7 as a possible target for drugs [13, 14]. This indicates a more significant role of MiT translocations in carcinogenesis than it was thought previously.

#### Rare hereditary forms of non-clear cell renal carcinoma

Non-clear cell renal cell carcinomas are caused by germinal mutations (inherited in a series of generations or *de novo*) and are manifestations of hereditary oncological syndromes. Their fraction in the overall structure of nccRCCs does not exceed several percent, but this pathology has a number of clinical (early manifestation, bilaterality and/or multifocal lesions, pathological changes in other target organs) and molecular genetic features.

*Hereditary leiomyomatosis and renal cell carcinoma* (HLRCC, OMIM: 150800) manifest at the average age of 25 years as multiple leiomyomas of skin and uterus (sometimes leiomyosarcoma) and nccRCC, which occurs in 15–20 % of patients with HLRCC, and can be accompanied by kidney cysts. Malignant neoplasms of the kidneys in this carcinoma family are more often represented by papillary type II carcinomas, in some cases tumors have tubular or tubule-papillary structure. In case of HLRCC, renal tumors are usually solitary, unilateral, but characterized by rapid progression and early metastasis, so the tactics of surgical treatment for this disease does not differ from that in patients with sporadic RCC. Development of HLRCC mutations is associated with the *FH* gene localized in the lq42 region and coding fumarate hydratase, one of the enzymes of the Krebs cycle. About 90 % of them are missense mutations without significant «hot spots», although among representatives of the Caucasian race there is a local maximum in the frequency of occurrence in 190th codon [15]. Inactivation of the second allele in the tumor occurs according to the Knudsen two-hit model, which characterizes *FH* as a tumor suppressor. Inactivation of *FH* leads to the so-called Warburg effect, i. e. switching to glycolysis as the main pathway for the production of adenosine triphosphate (ATP) which is typical for malignant cells, as well as accumulation of the hypoxia-inducible factor (HIF) in cells and overexpression of its target genes [16]. DNA diagnosis of HLRCC involves sequencing of 10 exons of the *FH* gene [17].

*Type I hereditary papillary renal carcinoma* (HPRC, OMIM: 605074) is an autosomal dominant disease characterized by development of type I renal cell papillary carcinomas. Furthermore, both bilateral and multifocal tumors are diagnosed. This type of hereditary RCC is caused by

**Table 1.** *Characteristics of translocations involving the MiT family genes at cytological and genetic levels*

| Translocation | Chimeric gene | Tumor type |
|---|---|---|
| t(X;17)(p11.2;q25) | *ASPSCR1:TFE3* | MiT translocation RCC |
| t(X;1)(p11.2;q21) | *PRCC:TFE3* | MiT translocation RCC |
| der(17)(X;17)(p11.2q25) | *ASPSCR1:TFE3* | Alveolar soft part sarcoma |
| t(X;1)(p11.2;q34) | *SFPQ:TFE3* | MiT translocation RCC |
| t(X;17)(p11.2;q23) | *CLTC:TFE3* | MiT translocation RCC |
| t(X;11)(p11.2;q13) | *YAP1:TFE3* | Epithelioid hemangioma |
| inv(X)(p11.2;q12) | *NonO:TFE3* | MiT translocation RCC |
| t(X;3)(p11.2;q23), t(X;10)(p11.2;q23) | Not identified | MiT translocation RCC |
| t(6;11)(p21;q12) | *alpfa:TFEB* | MiT translocation RCC |
| Not identified | *RBM10:TFE3, DVL2:TFE3, COL21A1:TFEB ACTG1:MITF* | Papillary RCC |
| Not identified | *CLTC:TFEB* | MiT translocation RCC |

activating mutations in proto-oncogene *MET* located at 7q31. *MET* mutations in HPRC lead to constitutional activation of the receptor»s cytoplasmic domain and stimulation of cell division. DNA diagnostic direct methods involve identification of mutations in exons 15–21 of the *MET* gene coding the receptor»s cytoplasmic domain [2, 18].

*Birt–Hogg–Dubé syndrome* (BHDS, OMIM: 135150) is an autosomal dominant disease. It manifests as multiple fibrofolliculomas located predominantly on the face, neck and upper body. About 80 % of patients develop pulmonary cysts. Number and diameter of the cysts can increase in time, which in 10–30 % of cases leads to spontaneous pneumothorax. In 35 % of patients with BHDS kidney tumors develop. In this syndrome, tumors are usually multifocal, bilateral, of different pathological and morphological types, but the most common are hybrid oncocytoma/chromophobe and chromophobe carcinomas. BHDS is caused by germinal mutations in the *FLCN* suppressor gene located at 17p11.2 and coding folliculin. Notably, biallelic inactivation of *FLCN* in the tumor leads to activation of the AKT-mTOR signaling pathway, the same way as in other nncRCCs. Genetic lab diagnostics of BHDS involve analysis of *FLCN* mutations (sequencing of exons 4–14). Germinal mutations of *FLCN* are mostly loss of function mutations: insertions, deletions, and duplications with frameshift, complex mutations, nonsense mutations, mutations of splicing sites; missense mutations are very rarely identified. The *FLCN* gene contains a mutagenesis hot spot: a mononucleotide tract C8 located at exon 11. About 50 % of families carry a germinal mutation in the form of single-nucleotide deletion/insertion in this tract, so it»s practical to start the search from exon 11 [19, 20]. Investigation of *FLCN* for the presence of point mutations in exons can be complemented by the MLPA method for identification of deletions. It was shown that the promotor area of *FLCN* is characterized by increased rate of deletions relative to the coding part. Combination of direct sequencing and MLPA allows to increase clinical sensitivity of the molecular and genetic analysis of families with BHDS from 80 % to 95 % [21].

In total, about 10 forms of hereditary RCC were described, nccRCC is more common in 3 of them. Identification of a pathological germinal mutation in these cases plays a crucial role in diagnosis and treatment [2, 4]. Until recently, stand-alone molecular and genetic studies of sporadic nccRCC didn»t have practical use, but development of whole-genome sequencing increased our insight into the role of point mutations in nccRCC.

### Genetic differences between chromophobe carcinoma and oncocytoma

Microarray-based comparative genomic hybridization has shown that the main types of kidney tumors have their own specific copy number variation (CNV) patterns in different parts of the genome [22]. This observation holds true for CNV differences between a malignant tumor – chromophobe carcinoma – and a benign tumor – oncocytoma. Unfortunately, use of histological and immunohistochemical tests for differential diagnosis of these tumors is challenging.

Differences between CNVs were also confirmed in a comparative study of deletions and amplifications in chromophobe RCC and oncocytoma using copy number determination of genome fragments with SNP-microarray Affymetrix 100K SNP. Results of these studies mostly agree with each other and show that deviations from diploid

chromosome set 2, 6, 10, 13q, 17, and, to lesser extent, 1 and 21q collectively can serve as a criterion for differential diagnosis between chromophobe RCC and oncocytoma [23]. Taking into account these data, other authors have developed a panel of STR markers (D1S2142, D1S3465, D2S1782, GAAT3A06, D10S2469, D13S634, D13S742, D17S1298, D21S1411, and D21S11) located in the areas with the most significant CNV differences between chromophobe RCC and oncocytoma. In conjunction with polymerase chain reaction and fragment analysis in capillary sequencer, this panel allowed to distinguish these tumors in informative cases with 90 % accuracy [24].

However, the main events of carcinogenesis are somatic driver mutations. Only the development of next generation sequencing (NGS) allowed to identify these mutations on the scale of tumor genome. In one study, whole-genome sequencing of 66 chromophobe carcinomas was performed. In total, 142 somatic mutations with various levels of heteroplasmy were identified in the mitochondrial genome, among them 35 mutations – in more than 50 % of mitochondrial DNAs (mtDNA) – were in the *ND5* gene and others. Among point mutations of the nuclear genome, the highest rates were observed in *TP53* and *PTEN*: 32 and 9 % respectively. Despite the fact that most of mtDNA mutations potentially can alter mitochondrial function, on the level of gene expression these mutations didn»t affect the oxidative phosphorylation chain. Firstly, this suggests that in chromophobe RCC the Warburg effect is canceled out by other mechanisms. Secondly, in at least 10 % of chromophobe RCCs, activating mutations in the telomerase gene *TERT* were identified. Moreover, the *C228T* point mutation which was previously described in urothelial carcinoma and melanoma and which leads to formation of an additional binding site for transcription factors, caused only a twofold increase in *TERT* expression. Newly identified chromosomal rearrangements with breakpoints in the *TERT* promotor which sometimes spread over to the *NEK5* gene on chromosome 13 have a bigger effect on the increase in *TERT* expression [25, 26]. Whole-genome sequencing of 12 oncocytomas has shown that they contain point mutations frequently observed in chromophobe RCCs (*TP53* and *PTEN*); considering other mutations, they can be divided into 2 groups: 1st contains rearrangements involving the *CCND1* gene without other aberrations, 2nd – CNVs of chromosomes 1, 14, 21, X, and/or Y. Mutations in mtDNA are observed at early stages, and in the 2nd group they are associated with accumulation of a large number of defective mitochondria, inhibition of their autophagy, and activation of the *TP53* gene. According to one hypothesis, accumulation of defective organelles and *TP53* activation «save» oncocytoma cells from malignant transformation, but if during clonal evolution they acquire inactivating mutations in *TP53*, *PTEN*, and rearrangement in *TERT* they can serve as a source of the eosinophilic variant of chromophobe RCC [27].

### Molecular genetics of sporadic papillary renal carcinoma

Even though activating germinal missense mutations of *MET* cause HPRC which leads to type I papillary carcinomas, similar somatic mutations of this gene are observed in type I sporadic papillary RCC in at most 20 % of cases (in most studies this value is 10 % or less). At the same time, amplification of the 7q31 locus containing *MET* takes place in 45 % of cases, and *MET* hyperexpression – in 90 % of cases of type I papillary RCCs. This makes *MET* a front-runner for targeted drugs [28]. Several targeted drugs – synthetic *MET* inhibitors foretinib (XL880), tivantinib (ARQ197), volitinib (HMPL-504), and a monoclonal antibody against HGF (a receptor coded by *MET*) rilotumumab – are currently in phase II clinical trials. Potentially, nccRCC clinical trials would be performed for cabozantinib (XL184) and ALK/MET/ROS/RET inhibitor crizotinib [29, 30]. Also, possible application of papillary RCC targeted therapy using VEGFR2 inhibitors (sunitinib, sorafenib), mTOR inhibitors (temsirolimus, everolimus), and combination therapy with MET and EGFR inhibitors is considered [31]. Turned out, early results of traditional cytogenetics concerning an increase in chromosomes 7, 17 copy number, and *MET* amplification mostly apply to type I papillary RCCs, whereas type II is characterized by the loss of chromosomes 8, 11, 18, which was determined by comparative genomic hybridization [30, 32].

So far, several large-scale studies of papillary RCC by NGS were published. One of them involves complex genetic examination of 161 papillary RCC samples, including exome sequencing, DNA methylation analysis, and proteomic analysis. As expected, *MET* mutations were identified in 17 % of type I tumors. Moreover, 3 of 17 mutations were germinal instead of somatic, which once again suggests that HPRC diagnostics in young patients with papillary RCC is advisable. Multifactor analysis allowed to classify type II tumors into 3 subgroups with different clinical characteristics. One of the groups was characterized by *SETD2* mutations, another had a unique set of hypermethylated loci and *FH* mutations. Interestingly, in 8 cases tumors with MiT translocations and formation of chimeric genes were observed. In 4 cases, these were previously described chimeras *PRCC: TFE3* and *SFPQ: TFE3*, but the rest were new variants of MiT translocations: *RBM10: TFE3*, *DVL2: TFE3*, *COL21A1: TFEB*, and *TFEB: CADM2*. Most of them were identified in type II tumors with total rate of 12 %.

In both clear cell and papillary RCC, a high rate of mutations in chromatin remodeling genes was observed for type I and II tumors. Mutations in the *SMARCB1* and *PBRM1* genes which participate in SWI/SNF complex formation, *SETD2*, *KDM6A*, *BAP1* genes and other chromatin modifiers were identified in papillary RCCs in 20–38 % of cases. Supposedly, mutations in genes affecting chromatin state increase genome instability and can be considered initiating driver mutations acting at the early stages of car-

**Table 2.** *Genetic characteristics of non-clear cell renal cell carcinoma*

| Type | Chromosomal aberrations | Point mutations |
|---|---|---|
| Papillary | +7, +17 (subtype I); +8, +11, +18 (subtype II); +3q, +16, +20, – Y | *MET* (subtype I), *FH* (subtype II); *SETD2*, *KDM6A*, *BAP1*, *ARID2*, and other chromatin remodeling genes (up to 38 % of cases in total) |
| MiT family translocation RCC | Translocations with transfer of Xp11.2 and 6p21 to other chromosomes | Formation of chimeric genes with the 3'-part consisting of *TFE3* and *TFEB* genes |
| Chromophobe | – 1, – 2, – 6, – 10, – 13, – 17, and –21 | *FLCN* (in BHDS); point mutations in mitochondrial DNA (50 % of alleles), *TP53* and *PTEN* mutations (9–32 % of cases) |

cinogenesis, the same way as rare driver mutations of *PTEN*, *TP53*, *TSC2*, *NRAS*, *KRAS*, and some other oncogenes and suppressor genes act in papillary RCC [14, 33].

In another study, mutation patterns of 19 genes were determined. These patterns were different for types I and II of papillary RCC: mutations and amplification of the *ERBB2* gene were identified in some cases of type II tumors, though in general its activating mutations are not common for RCCs [34]. In another study, exomes of 31 papillary RCC samples were sequenced, where driver mutations were alterations in genes affecting chromatin remodeling: *SETD2*, *BAP1*, and *ARID2* (coding histone methyltransferase, deubiquitinase, and a component of *PBAF* chromatin-remodeling complex, respectively). Some samples in this study were taken as a series of tissue pieces from multifocal tumors or from different areas of the same tumor. It was shown that about 20 % of somatic mutations are characterized by intratumor heterogeneity caused by clonal evolution. Moreover, for early stage tumors «classical» divergent evolution trees were constructed, but for late stage tumors examples of convergent evolution were observed (e. g. independent acquisition of secondary mutations in *SETD2*, changes in CNV of chromosome 3 fragments), similar to clear-cell RCCs [35].

It should be noted, that a separate type of nccRCC according to the ISUP classification – clear cell tubule-papillary carcinoma – on one hand combines characteristics of clear cell and papillary RCCs (for example, a tumor can contain somatic *MET* and *VHL* mutations), but on the other hand it has specific attributes, in particular, hyperexpression of microRNA of the miR-200 family which is unlike both clear cell and papillary RCCs [36]. Genetic differences between papillary RCC subtypes directly influence the search for new targeted drugs. Activation of the *MET* gene and identification of HGF inhibitors are important for type I tumors. Type II papillary RCC with fumarate hydratase deficiency due to *FH* inactivation clearly demonstrates the Warburg effect. In light of this, it was suggested that in this type of nccRCC metabolic pathways should be targeted as opposed to signaling pathways.

Increased fumarate concentration caused by KEAP1 factor stabilizes nuclear factor E2-related factor-2 (NRF2) and increases expression of genes with antioxidant-sensitive elements in their promotors. Currently, compounds affecting NRF2 are being studied [37]. Moreover, all main targeted drugs used in treatment of metastatic RCCs were clinically tried for nccRCCs: mTOR inhibitors temsirolimus and everolimus, multikinase inhibitors sunitinib and sorafenib, pazopanib, and some others [7]. The greatest objective response rate of targeted therapy for nccRCCs was observed for sunitinib and temsirolimus, and the last one is effective independently of the number of previous therapy lines [38, 39]. In general at the current level of our knowledge about kidney tumors, the main cytological, molecular, and genetic characteristics of the most common types of nccRCC can be summarized (Table 2).

## Conclusion

Therefore, nccRCCs are a group of morphologically and genetically diverse tumors, represented by both hereditary and sporadic cases. Algorithms of DNA diagnostics of the main forms of hereditary nccRCCs were developed. Lately, the main focus is on sequencing of nccRCC exome which allows to determine the whole profile of somatic mutations. As a result of these studies, a high rate of mutations in genes responsible for chromatin remodeling was shown for papillary RCC. Moreover, the role of chimeric genes in development of nccRCCs was expanded. Products of genes containing activating somatic mutations can serve as targets for drug therapy.

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