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Marker Genes of Clear Cell Renal Cell Carcinoma

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Abstract

An analysis was conducted on marker genes indicating the induction of clear cell renal cell carcinoma (ccRCC) and their role in the pathogenesis of this oncological disease.

The diagnostic and therapeutic approaches for ccRCC are evolving with the identification of marker genes. The use of molecular biology methods has enabled the detection of somatic mutations in RCC marker genes like VHL, BAP1, OGG1, FLCN, MDM2, TP53, and RNF139. Targeted drugs like sorafenib, sunitinib, bevacizumab, pazopanib, axitinib, everolimus, and temsirolimus are being utilized in the treatment of RCC metastases. The diagnostic value of specific alleles in marker genes like rs1642742 and rs779805 of the VHL gene, rs1052133 of the OGG1 gene, rs2279744 of the MDM2 gene, and rs1597368777 of the TP53 gene has been confirmed in detecting ccRCC. Mutations in these marker genes play a significant role in the pathogenesis of ccRCC and are associated with the development and progression of the disease.

The identification of these mutations can aid in the diagnosis, prognosis, and treatment of ccRCC.

Marker genes are essential in understanding the molecular mechanisms underlying ccRCC. Mutations in genes like VHL, BAP1, OGG1, FLCN, MDM2, TP53, and RNF139 are key drivers of ccRCC pathogenesis. The diagnostic and therapeutic implications of these mutations are significant in the management of ccRCC. Further research into the role of

marker genes in ccRCC is essential for developing targeted therapies and improving patient outcomes.

Keywords: clear cell renal cell carcinoma, marker genes

Introduction

Renal cell carcinoma (RCC) is a cancer that originates in the tubular epithelium of the kidney. It accounts for >90% of renal cancer cases. The disease covers about 10 histological and molecular subtypes, of which clear cell renal cell carcinoma (ccRCC) is the most common. Localized RCC can be successfully treated with surgery, while metastatic RCC is refractory to traditional chemotherapy in the vast majority of cases. The risk of metastasis in ccRCC is 83-88% (Hsieh J.J. et al., 2018).

It should be noted that RCC is among the 10 most common cancers worldwide. However, it is a heterogeneous group of malignant neoplasms of the kidney and includes such main subtypes as clear cell RCC (ccRCC), papillary RCC (pRCC)8 and chromophobe RCC (chRCC). At the same time, there is a predominance of metastasis (83-88%) in ccRCC (Hsieh J.J. et al., 2018).

The use of molecular biology methods has provided significant progress in the development of diagnostic and treatment methods for this group of diseases. Firstly, the OMIM database contains a diagnostic panel of somatic mutations of RCC marker genes: VHL, TRC8, OGG1, FLCN and BAP1. Meanwhile, according to some authors, in hereditary kidney cancer syndromes, the risk of the disease may be due to mutations in a wider range of genes (Hsieh J.J. et al., 2018). Secondly, new methods for treating RCC metastases based on the use of targeted drugs are being introduced into clinical practice: sorafenib, sunitinib, bevacizumab, pazopanib and axitinib (inhibitors of vascular endothelial growth factor (VEGF) and its receptor (VEGFR)), as well as everolimus and temsirolimus, which are inhibitors of the mTOR-1 complex.

Clear cell renal cell carcinoma (ccRCC)

ccRCC, depending on the population, accounts for 70 to 90% of malignant kidney tumors. In most cases, this type of tumor is caused by mutations in the von Hippel–Lindau tumor suppressor gene (VHL), localized on chromosome 3.

In the diagnosis of ccRCC, an important role is given to molecular biology methods aimed at identifying marker genes of the disease and clarifying the pathogenesis at the molecular level. In particular, most authors of publications in this area recognize the relevance of VHL gene mutations in the pathogenesis of ccRCC (Cancer Genome Atlas Research Network., 2013; Li F. et al., 2021). The authors express the opinion that the main cause of ccRCC is the genetic or epigenetic loss of VHL, which leads to dysregulation of hypoxia-inducible factor (HIF) signaling. The protein encoded by the VHL gene is a component of the E3 ligase complex that ubiquitinates HIF-1α and HIF-2α for further proteasomal degradation (Warren A.Y., Harrison D., 2018; Moch H. et al., 2016; 2022; Li F. et al., 2021). The most common forms of VHL gene mutations are point mutations, duplications or loss of 3p25, as well as epigenetic (promoter methylation) mechanisms of gene expression regulation (Hsieh J.J. et al., 2018). However, VHL is not the only gene whose mutations are associated with the pathogenesis of ccRCC.

GENES – MARKERS OF CLEAR CELL KIDNEY CARCINOMA

VHL GENE in the pathogenesis of ccRCC

In normal renal parenchyma, the VHL gene encodes the protein pVHL (von Hippel-Lindau tumor suppressor protein, acting as an E3 ubiquitin ligase) binds to HIF (hypoxia induced factor) and stimulates its degradation in the proteasome. The gene locus is located 3p25.3 ((GRCh38): 3:10,141,778-10,153,667). According to Nordstrom-O'Brien M. et al. (2010), the VHL gene includes 3 exons and is involved in the synthesis of two proteins: a full-length protein weighing 30 kDa (p30, 213) and a protein weighing 19 kDa (p19, 160 amino acids), which is generated by alternative translation initiation in the internal methionine at position 54. According to the authors, both protein isoforms (p30 and p19) have tumor suppressor properties. In ccRCC tumor cells, a mutant VHL gene is present and the protein

encoded by it loses its function, thus, ccRCC cells experience a deficiency of the pVHL protein. As a result, a rapid increase in the level of HIF protein in ccRCC tumor cells is observed. Therefore, HIF1a and HIF2a proteins are also considered as relevant marker proteins in the therapy of RCC tumors (Li F. et al., 2021). Loss of VHL gene expression results in abnormal accumulation of HIF proteins despite normoxia, which through activation of HIF target genes stimulates angiogenesis and glycolysis, and also causes disruption of the cell mitotic cycle, initiating its malignancy (Arai E., Kanai Y., 2011).

At the same time, experimental studies have shown that loss of Vhl in mice does not lead to the development of ccRCC. The authors of the cited publication suggest that additional genetic or epigenetic events are necessary for the induction of ccRCC (Hsieh J.J. et al., 2018). According to modern studies, both familial and sporadic ccRCC are most often characterized by loss of heterozygosity, i.e. deletion of one VHL allele in the small arm of chromosome 3, while the remaining allele acquires an inactivating mutation, which is accompanied by a complete loss of the functional protein (Szegedi K. et al., 2023). A summary of modern experience in diagnosing ccRCC indicates that various scales of deletion of the small arm of chromosome 3 are a widespread phenomenon in this pathology, which makes the cytogenetic method quite relevant in the study of tumor tissue (Williamson S.R. et al., 2020).

The diagnostic value of the rs779805 and rs1642742 alleles of the VHL gene in detecting ccRCC has been confirmed (Chrabańska M. et al., 2023). The results of clinical studies confirm the high information value of rs1642742 of the VHL gene in diagnosing ccRCC in various human populations (Wang W.-C. et al., 2014). The authors of the cited publication also note the loss of heterozygosity for the VHL gene in most patients with ccRCC carrying a single rs1642742 allele. According to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/variation/342407/), rs1642742 is caused by the VHL c.-294G>A polymorphism, localized in the 3'UTR region of the gene. It is reported that the rs1642742 allele can disrupt the interaction between microRNA and target mRNA, changing the regulation of gene expression, participating in the pathogenesis of a number of oncological diseases, including hepatocellular carcinoma (Chen X. et al., 2021) and ccRCC (Gilyazova I.R. et al., 2020). According to clinical observations (Verbiest A. et al., 2018), the presence of the rs1642742 allele in the patient's genotype was associated with an unfavorable outcome of ccRCC.

According to ClinVar, the rs779805 mutation is caused by the VHL c.-195 G>A/G>C polymorphism

(https://www.ncbi.nlm.nih.gov/clinvar/variation/342397/?oq=((291569[AlleleID]))&m=NM_000551.3(VHL):c.-195G%3EA). There is evidence that the rs779805 mutation promotes promoter DNA methylation and gene inactivation (Moore L.E. et al., 2011; Remenyi G. et al., 2021). An opinion is expressed about the high diagnostic value of rs1642742 and rs779805 in detecting clear cell renal cell carcinoma (Wang W.-C. et al., 2014). At the same time, as a result of population studies, Qin C. et al. (2012) did not find reliable differences in the frequency of occurrence of the wild-type allele and the rs779805 allele of the VHL gene between practically healthy subjects of the control group and the group of patients with ccRCC. At the same time, the authors confirm a significant correlation of the presence of the rs779805 allele in the genotype with a negative prognosis for the course of the disease, concluding that rs779805 may be useful not so much as an inducer of the pathogenesis of the disease, but as a prognostic biomarker in patients with ccRCC.

BAP1 Gene in the Pathogenesis of ccRCC

The BAP1 gene encodes BRCA1-ASSOCIATED PROTEIN-1.

The gene locus is located on the small arm of chromosome 3, 3p21.1 ((GRCh38): 3:52 401 008-52 410). The BAP1 protein is a nuclear ubiquitin carboxyterminal hydrolase and belongs to one of several classes of enzymes responsible for deubiquitination processes. The BAP1 protein binds to the RING finger of the BRCA1 protein and enhances BRCA1-mediated cell growth suppression. In addition, BAP1 interacts with ASXL1 to form the Polycomb group deubiquitinase complex. This complex deubiquitinates histone H2A (H2Aub1) and is involved in the repression of target genes through epigenetic modification of chromatin. According to the literature, BAP1 mutations weaken the gene-mediated suppression of cell proliferation. It is reported that BAP1 gene mutation occurs in 5-15% of ccRCC cases and is associated with an unfavorable prognosis of the disease (Diez-Calzadilla N.A. et al., 2021). It has been established that BAP1 protein deficiency is associated with clear cell renal cell carcinoma and is characterized by higher tumor growth rates (Ball M.W. et al., 2020). It is believed that suppression of BAP1 expression was associated with a high degree of malignancy of ccRCC tumors (Peña-Llopis S. et al., 2012). Inactivation of the BAP1 gene in RCC causes changes in chromatin architecture, a response to DNA damage, and disruption of the cell cycle regulation (Maher E.R., 2018). As noted above, deletions of

the small arm of chromosome 3 are a common occurrence in ccRCC, with about 90% of ccRCC tumor cells carrying a deletion of chromosome 3 (Battaglia A., 2014; Williamson S.R. et al., 2020). Consequently, this event can lead to the loss of not only the VHL gene, but also the BAP1 gene, the loci of which are located quite close (Weaver C. et al., 2022). Currently, a number of different pathological mutations of the BAP1 gene have been identified. In particular, rs372586694, c.121G>A (missense mutation with substitution of amino acid residues in the Gly41Ser protein), rs123598 (c.444C>T). It has been established that rs375129361 (c.277A>G; p.Thr93Ala) (Popova T. et al., 2013), as well as c.41T>A (p.Leu14His) (Farley M.N. et al., 2013), are associated with renal cell carcinoma. It is believed that rs375129361 can be considered as one of the causes of familial clear cell renal cell carcinoma with early onset of the disease (before 40 years) due to disruption of the deubiquitinating activity of the BAP1 protein (Popova T. et al., 2013). On the other hand, the c.41T>A (p.Leu14His) mutation can disrupt the enzymatic properties of the BAP1 protein due to the rearrangement of a highly conserved region in the catalytic domain. A study of ccRCC tumor tissue samples revealed a large number of mutations in the BAP1 gene (Battaglia A., 2014); however, subsequent review publications highlight c.41T>A and c.277A>G as the main markers of pathology (Testa U. et al., 2020). It is assumed that the somatic mutation of the BAP1 gene c.535C>T (p.Arg179Trp) may be the cause of the disease in ccRCC, biliary tract cancer, and lung cancer (Bell H.N. et al., 2022).

OGG1 GENE in the pathogenesis of ccRCC

The OGG1 gene encodes the 8-OXOGUANINE DNA GLYCOSYLASE protein. The gene locus is located 3p25.3 ((GRCh38): 3:9 749 952-9 783 108). The function of the 8-OXOGUANINE DNA GLYCOSYLASE protein is to excise 8-oxoguanine (8-oxoG) bases from DNA oxidized by reactive oxygen species. The literature suggests that, firstly, cells lacking OGG1 gene activity may have an increased likelihood of becoming malignant, thus leading to the development of ccRCC. Secondly, cytogenetic abnormalities of human chromosome 3p leading to loss of heterozygosity are observed with high frequency in ccRCC (Audebert M. et al., 2000; Battaglia A., 2014; Williamson S.R. et al., 2020). Loss of heterozygosity for the OGG1 allele located on chromosome 3p25 was found in 85% of 99 examined samples of human clear cell renal cell carcinoma (Habib S.L., 2009). According to clinical studies for residents of the PRC, an important marker of the risk of developing kidney

carcinoma is rs1052133, caused by a missense mutation, a substitution of amino acid residues in the OGG protein (C> G / C> T; p.Ser326Cys) (Zhao H. et al., 2011). However, according to the ClinVar database https://www.ncbi.nlm.nih.gov/snp/rs1052133#frequency_tab the frequency of occurrence of this pathological allele is quite high all over the world. It has been shown that the substitution of the amino acid residue from serine to cytosine in the OGG1 protein caused by rs1052133 leads to a significant decrease in the reparative activity of the enzyme (Yamane A. et al., 2004; Collins A.R., Gaivão I., 2007).

The important role of rs1052133 in the pathogenesis of renal cell carcinomas is confirmed by the modern development of methods for targeted therapy of these diseases (Chang W.-S. et al., 2020). There is evidence that this pathological allele can cause various types of cancer, including renal cell carcinomas (Tsai C.-W. et al., 2012; Chang W.-S. et al., 2020) and hepatocellular carcinoma (Mahmoud A.A. et al., 2019). Detection of rs1052133 in patients with renal cell carcinoma was carried out using PCR (Chang W.-S. et al., 2020). According to the authors, the sequences of the forward and reverse primers for genotyping hOGG1 rs1052133 were 5'-ACTGTCACTAGTCTCACCAG-3' and 5'-GGAAGGTGGGAAGGTG-3', respectively.

FLCN GENE in ccRCC pathogenesis

The gene encodes the FOLLICULIN protein. Alternative names for the FLCL gene

BHD gene. Gene locus 17p11.2 ((GRCh38): 17:17,212,212-17,237,330). The protein is a tumor suppressor. According to the literature, two main variants of the FLCL gene transcript on chromosome 17p11.2 have been identified. At the same time, variant 1 of the gene transcript (3723 bp, 14 exons) encodes at least 2 isoforms of the protein. Isoform 1 of folliculin includes 579 amino acid residues with a mass of 64 kDa. Published studies are based on transcript variant 1 and isoform 1 of the FLCN protein (Schmidt L.S., Linehan W.M., 2018). Suppression of FLCN gene expression is accompanied by activation of the effect of the HIF2α protein on the PI3K/mTORC2 signaling pathway, which, in turn, leads to an increase in the number of downstream target genes Cyclin D1, MMP9, etc. (Zhao X. et al., 2020). Therefore, in kidney tumors with FLCN deficiency, activation of mTOR and AKT is observed. Mutations in the gene are considered as the main cause of the development of Birt-Hogg-

Dubé syndrome, a hereditary disease accompanied by multiple lung cysts, recurrent pneumothorax, skin lesions and kidney tumors (Daccord C. et al., 2020). According to the authors of the cited review, about 200 gene mutations have been identified that cause protein shortening, as well as frameshifts (small deletions or insertions), nonsense mutations, or splice site mutations that may be accompanied by a loss of folliculin function. However, the most common types of gene mutation in families with Birt-Hogg-Dubé syndrome are a cytosine insertion (c.1733insC) or deletion (c.1733delC) in a mononucleotide tract of eight cytosines (c.1733–1740) in exon 11 (Schmidt L.S. et al., 2005). Patients with Birt-Hogg-Dubé syndrome have a high risk of developing renal tumors, including chromophobe RCC, renal oncocytoma, ccRCC, and papillary RCC (Schmidt L.S. et al., 2005; Kuroda N. et al., 2014). Birt-Hogg-Dubé syndrome (BHDS; MIM135150) is an autosomal dominant disorder that predisposes to the development of fibrofolliculomas, pulmonary cysts, pneumothorax, and renal neoplasia. It is emphasized that the risk of developing renal cancer in patients with Birt-Hogg-Dubé syndrome is 7 times higher and FLCN mRNA levels were reduced in renal tumors from patients with Birt-Hogg-Dubé syndrome (Kuroda N. et al., 2014). It has been shown that induction of mutations in the Bhd gene in rats, in order to develop an experimental model of Birt-Hogg-Dubé syndrome, dramatically increases the risk of developing ccRCC in animals (Okimoto K. et al., 2004).

There is evidence in the literature that the nature and frequency of mutations in the FLCN gene generally do not differ significantly in the populations of North America, Europe, and China (Liu Y. et al., 2017).

At the same time, according to Furuya M. et al. (2015), mutations in exon 11 (c.1285dupC) and in exon 12 (c.1347_1353 dupCCACCCT) are associated with clear cell renal cell carcinoma. Moreover, the FLCN variant c.1285dupC (p.His429ProfsX27; rs80338682) leads to the formation of a premature termination codon, which, according to predictions, can cause truncation of the encoded protein or the absence of the protein. According to modern literature reviews, this gene variant should be considered as the most common mutation, quite widespread in different human populations (Liu K. et al., 2019).

MDM2 GENE in ccRCC pathogenesis

The locus is located at 12q15 ((GRCh38): 12:68,808,172-68,850,686). Alternative gene names: MOUSE DOUBLE MINUTE 2 HOMOLOG

p53-BINDING PROTEIN MDM2, ONCOPROTEIN MDM2, HDM2.

The MDM2 protein is an E3 ubiquitin ligase that targets the tumor suppressor protein p53. Ubiquitination of p53 promotes its proteasomal degradation. According to the literature, the oncogenic effects of MDM2 can be caused not only by inhibition of p53 function. It has been reported that in some types of carcinomas, high MDM2 expression correlates with low E-cadherin expression, promoting metastasis processes (Noon A.P. et al., 2010). It is believed that SNP in the promoter region of MDM2 (rs2279744) can lead to abnormal expression of MDM2 protein, which is accompanied by enhanced inactivation of p53 (Yu M. et al., 2022). It was shown that rs2279744 (SNP309) in the intronic p53-sensitive promoter of the MDM2 gene is accompanied by an increase in the level of MDM2 mRNA and protein (Lalonde M.-E. et al., 2012). Genotyping of MDM2-SNP309 (rs2279744, c.14+309T>G) single nucleotide polymorphisms (SNPs) in 200 human RCC samples compared with samples from 200 age/sex-matched healthy subjects (followed by direct DNA sequencing) showed that RCC patients had a significant increase in the MDM2-SNP309 GG genotype compared with healthy controls. The analysis revealed that the MDM2-SNP309 GG genotype is associated with poor prognosis and the survival of patients carrying the GG genotype was significantly worse than that of RCC patients with homozygous wild-type or heterozygous (TG + TT) genotypes (Hirata H. et al., 2007; Li F. et al., 2021). Meanwhile, according to Shi B. et al. (2021), the diagnostic value of MDM2 for detecting ccRCC is not so significant due to the low frequency of gene mutations. It is noteworthy that the pathological allele rs2279744 is considered a factor predisposing to the development of hepatocellular carcinoma (Zhang C. et al., 2020) and, possibly, to distant metastases of breast cancer (Bartnykaitė A. et al., 2021).

On the other hand, it has been suggested that ccRCC may be associated with a sharp increase in mTOR activity, which in turn activates the MDM2 protein, which is accompanied by accelerated degradation of the p53 tumor suppressor (Dell'Atti L. et al., 2022). Thus, dysfunction of MDM2 is caused not only by a mutation in the gene encoding this protein, but also by activation of the PI3K-Akt-mTOR signaling system. There is evidence that inhibition of MDM2 helps suppress tumor cell growth in ccRCC in vitro and in vivo models (Dell'Atti L. et al., 2022). The literature suggests a set of primers used to identify rs2279744 in the MDM2 gene by PCR-RFLP using restriction enzymes followed by electrophoresis in agarose

gel, when the T-allele is represented by a 157 bp fragment, and the G-allele is represented by 109+48 bp fragments.

MDM2 rs2279744 F 5'-CGCGGGAGTTCAGGGTAAAG-3'

R 5'-CTGAGTCAACCTGCCCACTG-3'

Endonuclease MspA1I 37 °C for 1 hour

(Cited in Bartnykaitė A. et al., 2021).

TP53 GENE in the pathogenesis of ccRCC

The TP53 gene encodes the p53 tumor suppressor protein. Alternative names for the P5 protein, TRANSFORMATION-ASSOCIATED PROTEIN 53. Gene locus 17p13.1 ((GRCh38): 17: 7 668 421-7 687 490).

In RCC, mutations in the p53 gene can contribute to the acquisition of metastatic potential by tumor cells (Uhlman D.L. et al., 1994). There is evidence that a decrease in the role of the p53 tumor suppressor in ccRCC cells may be due not to mutations in the TP53 gene, but to functional inactivation of the p53 protein, the mechanisms of which require more in-depth study (Diesing K. et al., 2021).

It is reported that in ccRCC tumors, as in some other malignant tumors, intratumor heterogeneity of cancer cells can be observed, when areas with granular eosinophilic cytoplasm are found in some of them (Nilsson H. et al., 2020). According to the authors of the cited publication, mutations of the tumor suppressor TP53 (all TP53 mutations occurred in the region of the DNA-binding domain and led to the loss of function of the encoded protein) and increased mTORC1 activity were recorded exclusively in eosinophilic ccRCC cells. Based on the data obtained, it is concluded that the identified mutations of the TP53 gene are associated with the eosinophilic phenotype of ccRCC tumor cells, which, in turn, is associated with a higher degree of malignancy and clinically more aggressive tumors.

According to the literature, the TP53 mutation c.579T>A (p.His193Gln; rs1597368777,) may play an important role in the pathogenesis of clear cell renal cell carcinoma; this variant is located in the DNA-binding domain of the p53 protein (Bandoh N. et al., 2023). It is believed that the TP53 mutation (c.818G>A; p.R273H; rs28934576) in clear cell renal cell carcinoma may increase tumor resistance to the therapeutic effects of HIF-2 inhibitors (Courtney K.D. et al., 2020). This mutation causes changes within the functionally critical DNA-binding domain of the protein. It has been established that this pathogenic

variant of TP53 has a fairly high frequency of occurrence in European populations (1/5000-1/20000) and may be associated with the pathogenesis of Li-Fraumeni syndrome, and is also associated with several oncological diseases, including soft tissue sarcomas, breast cancer, brain tumors, adrenocortical carcinomas, and leukemia (Olfson E. et al., 2015).

RNF139 GENE

(Alternative names TRC8 and HRCA1) encodes the protein RING FINGER PROTEIN 139. The gene locus is located in the large arm of chromosome 8 8q24.13 ((GRCh38): 8:124,474,880-124,488,618). The RNF139 protein (TRC8) is an E3 ubiquitin ligase that functions in the endoplasmic reticulum and is involved in the regulation of sterol biosynthesis. At the same time, the translocation of chromosomes 3;8, t(3;8)(p14.2;q24.1) is considered as one of the causes of hereditary renal cell carcinoma (Gimelli S. et al., 2009). According to Gemmill R.M. (1998) showed that in the 3:8 translocation, the TRC8 gene (chromosome 8) merges with the FHIT gene (chromosome 3) and is disrupted in the sterol-sensitive domain. Further studies showed that this chromosomal rearrangement associated with the development of RCC is caused by the breakpoint of chromosome 8 located in the region of palindromic AT-rich repeats in the first intron of the RNF139 gene (TRC8), while the breakpoint of chromosome 3 is located in the AT-rich palindromic sequence in intron 3 of the FHIT gene (PATRR3) (Kato T. et al., 2014). The protein product of the gene can be effectively detected in tissues by immunohistochemistry (Gimelli S. et al., 2009).

Summary

Marker genes play a crucial role in the pathogenesis of clear cell renal cell carcinoma (ccRCC). RCC is a common cancer originating in the kidney, with ccRCC being the most prevalent subtype. Mutations in marker genes like VHL, BAP1, OGG1, FLCN, MDM2, TP53, and RNF139 are associated with the development and progression of ccRCC. The VHL gene, located on chromosome 3, is a key player in ccRCC pathogenesis due to its role in regulating HIF signaling. Mutations in VHL lead to dysregulation of HIF, promoting angiogenesis and glycolysis in ccRCC tumor cells. The BAP1 gene, located on chromosome 3, is linked to ccRCC development, with mutations in BAP1 associated with higher tumor growth rates. The OGG1 gene, located on chromosome 3, is involved in DNA repair and its mutations can

contribute to the development of ccRCC. The FLCN gene, located on chromosome 17, is a tumor suppressor gene and mutations in FLCN are associated with Birt-Hogg-Dubé syndrome and ccRCC. The MDM2 gene, located on chromosome 12, is an E3 ubiquitin ligase that targets the tumor suppressor p53. Mutations in MDM2 can lead to abnormal p53 inactivation, promoting tumor growth in ccRCC. The TP53 gene, located on chromosome 17, encodes the p53 tumor suppressor protein and mutations in TP53 can contribute to the metastatic potential of ccRCC tumor cells. The RNF139 gene, also known as TRC8, is an E3 ubiquitin ligase involved in sterol biosynthesis and its disruption due to chromosomal translocations can lead to hereditary renal cell carcinoma.

The diagnostic and therapeutic approaches for ccRCC are evolving with the identification of marker genes. The use of molecular biology methods has enabled the detection of somatic mutations in RCC marker genes like VHL, BAP1, OGG1, FLCN, MDM2, TP53, and RNF139. Targeted drugs like sorafenib, sunitinib, bevacizumab, pazopanib, axitinib, everolimus, and temsirolimus are being utilized in the treatment of RCC metastases. The diagnostic value of specific alleles in marker genes like rs1642742 and rs779805 of the VHL gene, rs1052133 of the OGG1 gene, rs2279744 of the MDM2 gene, and rs1597368777 of the TP53 gene has been confirmed in detecting ccRCC. Mutations in these marker genes play a significant role in the pathogenesis of ccRCC and are associated with the development and progression of the disease. The identification of these mutations can aid in the diagnosis, prognosis, and treatment of ccRCC.

Marker genes are essential in understanding the molecular mechanisms underlying ccRCC. Mutations in genes like VHL, BAP1, OGG1, FLCN, MDM2, TP53, and RNF139 are key drivers of ccRCC pathogenesis. The diagnostic and therapeutic implications of these mutations are significant in the management of ccRCC. Further research into the role of marker genes in ccRCC is essential for developing targeted therapies and improving patient outcomes.

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