Review Article

Chromosomal aberrations in renal cell carcinoma: An overview with implications for clinical practice

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Abstract

Chromosomal instability and aberrations are known in many cancers including renal cell carcinoma. Detailed understanding of these changes has led to an improved drug discovery and continued developments in other therapeutic options. Chromosomal aberrations have a potential to be used to monitor disease including prognostication. There has been a growing experience in cytogenetic techniques and gap between clinic and laboratory has narrowed significantly in the recent past. Nevertheless, more work on validation of these techniques, establishing threshold and interobserver agreement needs to be carried out for these diagnostic/prognostic tests before utilizing them in clinics as a part of "personalized medicine" care. The review presented here is a summary of common genetic disorders in renal cancer and some of acquired genetic changes which can be used as biomarkers. The review also describes basics of commonly used genetic techniques for wider clinical community involved in the management of renal cancer.

Keywords: Chromosome, clear-cell carcinoma, genetics, head and neck cancer, head and neck squamous cell carcinoma, intensity modulated radiotherapy, radiotherapy kidney, renal cell cancer, three-dimensional conformal radiotherapy, toxicity, xerostomia

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INTRODUCTION

Kidney cancer is the twelfth most common cancer in the world (joint position with pancreatic cancer), with 338,000 new cases diagnosed in 2012 (Ferlay *et al.* 2012).[1] Renal cell cancer is [t] the eighth most common cancer in the UK and is the second most common urological malignancy. It accounts for 2% of all the cancer deaths in the UK. It represents 3% of all new cancer cases in adults in the Western world (Landis *et al.*, 1999).[2] Rising trends in renal cancer rates across all age groups have been observed. The widespread use of imaging resulted in an increased detection of asymptomatic renal tumors; however, it also coincides with a rise in the incidence of advanced renal cancer. These findings suggest that the detection of asymptomatic tumors by imaging alone cannot fully explain the increase seen for renal cancer overall (Tate *et al.*, 2003).[3] The classification of renal cell tumors has recently been revised and published in the 2016 World Health Organization (WHO) classification (Inamura *et al.* 2017).[4,5]

Cancer cells are known to have a range of cytogenetic abnormalities and aberrations at chromosomal levels

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are being identified through genome-wide studies (Albertson *et al.* 2003).[6] With improved detection of these changes, possibility of better understanding of carcinogenesis and treatment strategies is emerging in many cancers. Alterations in chromosomes in cancers can be structural changes or a numerical alteration (copy number variations [CNVs]). Specific focus is drawn on CNV, which is a form of structural variation of the DNA sequence, including multiplication and deletions of a particular segment of DNA (>1 kb) (Stratton *et al*., 2009).[7]

These changes were notoriously difficult to study using conventional cytogenetic techniques, however, with combined genomic hybridization and fluorescent-labeled probes, possibility of detailed identification of both the changes has emerged (Albrecht *et al.* 2004).[8] Latest technology of next-generation sequencing (NGS) has allowed these alterations to be studied at the resolution of a single nucleotide. With the arrival of NGS technologies (Metzker *et al.* 2010),[9] sequence-based CNV detection has rapidly emerged as a viable option to identify CNVs with higher resolution and accuracy (Ku *et al.* 2010).[10]

GENETIC BASIS OF CANCER

The genetic basis of cancer is a very complex process and involves a sheer number of genetic aberrations that have not been fully understood or characterized. Cancer is the clonal expansion of genetically aberrant cells. Genetic instability innately affects cell birth or death (Lengauer *et al*., 1998).[11] In renal cancer, the hereditary forms allowed to identify the gatekeeper genes that predispose to sporadic forms. However, the mechanisms by which a tumor becomes more aggressive and underlying genetic changes have not been fully understood. In general, the main mechanism involves either proto-oncogene or tumor suppressor genes, which control normal cell growth or programmed cell death. This is never straightforward and very few cancers can be linked to one particular gene dysfunctions. Chromosomal aberrations can vary from vast number of chromosomes seen in some tumor karyotypes on large scale to undetectable changes. These small changes can involve only a couple of base pairs, occurring as deletions or insertions (Lengauer *et al*., 1998).[10] Aneuploidy is defined as chromosome number that is not an exact multiple of the usually haploid number. While polyploidy is defined as having a chromosome number that is a multiple greater than two of the haploid number. Segmental aneuploidy is the loss or gain of part of chromosome (Torres *et al*., 2008).[12] Translocation of chromosomes occurs frequently, and parts of one chromosome can be found joined to another (Lengauer *et al*., 1998).[11] These can be balanced or unbalanced, depending on the presence of all 23 pairs of homologous chromosomes even in different segments or loss of one part of a chromosome, respectively.

In this review, we discuss chromosomal aberrations, that is, structural and copy number alterations, in renal cell carcinoma with focus on abilities of these changes to be used for effective diagnostic and prognostic investigations.

CLASSIFICATION AND SUBTYPES

Renal cancer occurs both in hereditary and sporadic forms. Although renal cancer has many genetic predispositions, the hereditary form accounts only for 3%–4% of cases. The current major subtypes of renal cell tumors in the 2016 WHO classification are briefly summarized in Table 1, with a focus on their molecular pathological epidemiology.[3,4] Common genetic changes and hereditary syndromes are summarized in Table 2.

In addition to above syndromes, chromosome 3p translocation (Cohen *et al*.,),[13] tuberous sclerosis, and succinate dehydrogenase gene mutation (Ricketts *et al*., 2008)[14] predispose to rare forms of early-onset hereditary renal cancer. Five genes that have well-known associations with renal cancer were shown to be mutated in a substantial proportion of the clear-cell renal cell carcinoma (ccRCC) samples (Gwangwu *et al.* 2012),[15] including promoters *VHL1* (altered in 27% of the 98 ccRCCs), *TP53* (altered in 6%), and genes involved in chromatin modification, such as polybromo-1 (*PBRM1)* (altered in 21%), lysine-(K-) specific demethylase 5C *(KDM5C*3) (altered in 9%), and SET domain-containing 2 (*SETD2)* (altered in 4%), along with two tumor suppressor genes, BRCA1-associated protein-1 (*BAP1)* (mutated in 8% of the 98 ccRCCs) and *TSC1* (mutated in 3%).

In ccRCC, the *VHL* tumor suppressor gene is the most frequently mutated gene (Creighton *et al.* 2013)[16] and its complete loss through genetic (point mutations, insertions and deletions (indels), and 3p25 loss) and/or epigenetic (promoter methylation) mechanisms constitute the earliest, truncal oncogenic driving event (Hakimi *et al*., 2013).[17] VHL is the substrate recognition component of an E3 ligase complex that ubiquitylates HIF1α and HIF2α for proteasome-mediated degradation (Masson *et al*., 2014).[18] Large-scale cancer genomic projects have been undertaken and have revealed several novel prevalent mutations in ccRCC, including *PBRM1 (*29%–41% of tumor samples), *SETD2 (*8%–12%), *BAP1 (*6%–10%), *KDM5C* (4%–7%), and *MTOR* (5%–6%) (Xu *et al*., 2016).[19] Sporadic ccRCC

Table 1: Current major subtypes of renal cell tumors in the 2016 World Health Organization classification

Renal cell tumor subtypes	Clinical features	Morphological/immunohistochemical features	Molecular features	Putative genes
ccRCC	65%-70% of adult RCCs	Clear/eosinophilic cells with thin-walled, staghorn-shaped vasculature; positive for CAIX and CD10, negative for CK7, and AMACR	Loss of function of VHL, chromosome 3p deletion, inappropriate stabilization of HIFs, genetic mutations in PI3K/AKT pathway, mutations of SETD2, BAP1, and MTOR, aggressive ccRCC demonstrating a metabolic shift	VHL, SETD2, BAP1, MTOR
pRCC	15%-20% of adult RCCs, type 1 shows a better prognosis than type 2	Papillary structure, foamy macrophages; type 1: scanty cytoplasm; type 2: abundant eosinophilic cytoplasm; positive for CD10, CK7, and AMACR, negative for CAIX	Gain of chromosome 7 and/or chromosome 17, loss of chromosome Y; type 1: MET alteration; type 2: CDKN2A silencing, SETD2 mutation; three subtypes according to the TCGA, including CIMP-associated aggressive subtype with an FH mutation	MET, CDKN2A, SETD2, FH
chRCC	5%-7% of adult RCCs, favorable prognosis, BHD syndrome with an FLCN mutation	Prominent cell membrane, irregular nuclei, perinuclear halo, pale to eosinophilic cytoplasm; positive for KIT and CK7, negative for CAIX, and CD10	Loss of chromosomes 1, 2, 6, 10, 13, and 17, somatic mutation in mitochondrial DNA, mutations of TP53 and PTEN, ICD, high-TERT expression by DNA rearrangement within the TERT promoter region with kataegis	TP53, PTEN, TERT

RCC: Renal cell carcinoma, ccRCC: Clear-cell RCC, chRCC: Chromophobe RCC, CIMP: CpG island methylator phenotype, HIF: Hypoxia-inducible factor, pRCC: Papillary RCC, TCGA: The Cancer Genome Atlas, VHL: Von Hippel–Lindau, FLCN: Folliculin, ICD: Imbalanced chromosome duplication, FH: Fumarate hydratase, BHD: Birt–Hogg–Dubé, SETD2: SET domain-containing 2, BAP1: BRCA1-associated protein-1, CAIX: Carbonic anhydrase inhibitor, AMACR: Alpha-methylacyl-CoA racemase, AKT: Aphakia thymoma, MTOR: Mammalian transcript of rapamycin, MET: Methionine, PTEN: Phosphatase and tensin, TERT: Telomerase reverse transcriptase, KIT: Tyrosine kinase

Table 2: Common hereditary syndromes predisposing to renal cancer

Hereditary syndromes	Mode of inheritance	Responsible genes/location	RCC subtype	Clinical manifestation
VHL	Autosomal dominant	VHL gene-3p25	Clear cell	Hemangioblastoma, pheochromocytoma, pancreatic and hepatic cysts
Hereditary papillary renal cell cancer	Autosomal dominant	c-Met proto-oncogene-7q31.1-35	Papillary type I	Associated with breast, pancreas, and lung cancer
Hereditary leiomyomatosis and RCC	Autosomal dominant	FH-1q42.3-q43	Papillary type II	Cutaneous leiomyomata, uterine fibroids
BHD syndrome	Autosomal dominant	BHD gene-17p11.2 Germline mutation of folliculin gene	50% are hybrid chromophobe-oncocytoma, clear cell, or papillary	Spontaneous pneumothorax, hair follicle tumor

RCC: Renal cell carcinoma, VHL: Von Hippel–Lindau, FH: Fumarate hydratase, BHD: Birt–Hogg–Dubé

has been characterized by loss of chromosome 3p in 90% of cases (Junker *et al.*, 2003).[20] Papillary RCC is characterized by trisomy of chromosome 7 and 17 and loss of Y chromosome (Kovacs *et al.*, 1997).[21] Chromophobe RCC (chRCC) exhibits multiple numerical deletions of chromosomes 1, 2, 6, 10, and 17 (Brunelli *et al.*, 2010).[22] Collecting duct carcinoma shows a wide variety of aberrations involving chromosomes 1, X, Y with either translocations or deletions. Furthermore, chromosomes 13 and 22 are affected (Antonelli *et al.*, 2003).[23]

Much research in recent years investigated the role of molecular markers in predicting prognosis and response to treatment in renal cancer. However, none of these markers has been translated into clinical practice or been proven to improve the predictive accuracy of existing prognostic models. Therefore, none of them is recommended for use in routine clinical practice (Tan *et al.*, 2013).[24] This gap in research and clinical practice could be explained by reasons such as methodological differences introducing bias, poor study design including small samples, lack of standardization of the assay employed, and unsuitable statistical analysis (McShane *et al.*, 2005).[25] In the 2016 WHO classification,[4,5] seven new subtypes were adopted as shown in Table 3.[5] The features of their molecular pathological epidemiology are briefly summarized in Table 4.[4]

Several nomograms to predict the prognosis in RCC relying on clinical and pathological parameters have been

developed and externally validated. The integration of molecular or cytogenetic biomarker besides pathological and clinical parameters has been attempted to improve the prognostication of these nomograms (Karakiewics *et al*., 2007, Kim *et al*., 2005, Klatte *et al*., 2009).[26-28] The predictive accuracy of these nomograms ranged between 68% and 90%. The only cytogenetic marker added to a prognostic nomogram for all stages of ccRCC following nephrectomy, including TNM stage and Fuhrman grade, was the loss of chromosome 9p based on karyotyping, reaching predictive accuracy of 89% (Klatte *et al*., 2009a).[28]

Table 3: Classification of renal cell tumors according to the 2016 World Health Organization classification

Current renal cell tumor subtypes	New renal cell tumor subtypes
Clear-cell RCC	Multilocular cystic renal neoplasm of low malignant potential
Papillary RCC	MiT family translocation RCC
Chromophobe RCC	Tubulocystic RCC
Collecting duct carcinoma	Acquired cystic disease-associated RCC
Renal medullary carcinoma	Clear-cell papillary RCC
Mucinous tubular and spindle cell carcinoma	Succinate dehydrogenase-deficient RCC
RCC, unclassified	Hereditary leiomyomatosis and RCC-associated RCC
Papillary adenoma	-
Oncocytoma	-

MiT: Microphthalmia transcription factor, RCC: Renal cell carcinoma

COMMON METHODS USED TO DETECT ABERRATIONS

- Karyotyping [Figure 1] or classical cytogenetics using banding methods plays an important role in the characterization of different type of chromosomal abnormalities. Karyotyping examines chromosomes in cells to help identify aberrations as the cause of a disease. Although it detects big changes such as loss or gain of an entire or portions of a chromosome and translocations, many of the changes that cause disease are very small and require other methods to detect
- Fluorescence *in situ* hybridization (FISH) [Figure 2] analysis began when conventional cytogenetics was with combined with recombinant DNA technology to form a new discipline called molecular cytogenetics. It is the most widely employed adjunct molecular genetic tool by 66% of the pathologists who responded to the questionnaire in the International Society of Urological Pathology consensus meeting in Vancouver 2012 (Tan *et al*., 2013).[24] Fish involves binding, or annealing, of fluorescence labeled, target-specific nucleic acid probes to their complementary DNA sequences, and the subsequent visualization of these probes within cells in the tissue examined. FISH technology has greatly benefited cancer cytogenetics. The technique is ideal as it is rapid and can be performed on any tissue (fresh,

Table 4: New subtypes of renal cell tumors in the 2016 World Health Organization classification

New renal cell tumor subtypes	Clinical features	Morphological/immunohistochemical features	Molecular features
Multilocular cystic renal neoplasm of low malignant potential	Excellent prognosis	Numerous cysts lined by clear cells; positive for CAIX and CK7	VHL mutation, chromosome 3p deletion
MiT family TRCC	Pediatric to young adult patients, mean age of 30 years	Papillary pattern, psammoma bodies, large epithelioid cells, and small cells; positive for TFE3 or TFEB	Xp11 TRCC: TFE3 rearrangement, t (6;12) RCC: TFEB rearrangement
Tubulocystic RCC	Male predominance, mean age of 60 years, indolent	Dilated tubules with a single layer of cells	Gain of chromosomes 7 and 17, loss of chromosome Y
ACD-associated RCC	End-stage renal disease or ACD, indolent	Eosinophilic cytoplasm, sieve-like pattern, intratumoral oxalate crystals; positive for AMACR and CD10, negative for CK7	Gain of chromosomes 3, 16, and Y
CCPRCC	3%-4% of renal tumors, indolent, end-stage renal disease, VHL disease	Clear cytoplasm, papillary pattern, apical-oriented nuclei; positive for CK7 and CAIX, negative for CD10	Lack of the genomic alterations observed in ccRCC/pRCC
SDH-deficient RCC	0.05%-0.2% of renal carcinomas, mean age of 37 years, good prognosis, germline mutation in one of the SDH genes	Cytoplasmic vacuoles and inclusion-like spaces; negative for SDHB, KIT, and CK7	Double-hit inactivation of one of the SDH genes, most commonly SDHB, no mutations in VHL, PIK3CA, AKT, MTOR, MET, or TP53
HLRCC-associated RCC	HLRCC syndrome, aggressive	Large nuclei with inclusion-like eosinophilic nucleoli and perinuclear clearing, abundant eosinophilic cytoplasm, papillary/tubular pattern; positive for 2SC, negative for FH, CK19, 34betaE12, and CK7	Germline mutation in FH, metabolic shift to aerobic glycolysis, increased fumarate and HIF1A

RCC: Renal cell carcinoma, ACD: Acquired cystic disease, CCPRCC: Clear-cell papillary RCC, ccRCC: Clear-cell RCC, HLRCC: Hereditary leiomyomatosis and RCC, SDH: Succinate dehydrogenase, TRCC: Translocation RCC, VHL: Von Hippel–Lindau, FH: Fumarate hydratase, 2SC: S-(2-succino)-cysteine, CAIX: Carbonic anhydrase inhibitor, AMACR: Alpha-methylacyl-CoA racemase, SDHB: Succinate dehydrogenase subunit B, KIT: Tyrosine kinase, AKT: Aphakia thymoma, MTOR: Mammalian transcript of rapamycin, MET: Methionine

frozen, or formalin-fixed paraffin embedded), touch preps, or cell cultures

- Comparative genomic hybridization (CGH) [Figure 3] allows genome-wide screening for CNVs in solid tumors. Conventional CGH relied on two genomes, a test and a control, which are differentially labeled and competitively hybridized to metaphase chromosomes. In an attempt to improve the resolution of traditional CGH, scientists have developed a more advanced technique that combines CGH with microarrays technology. Array CGH relies on slides arrayed with small segments of DNA called probes as the targets of analysis instead of using metaphase chromosomes (Lucito *et al.*, 2003).[29] The main advantage of array CGH (aCGH) is its ability to identify aneuploidies, deletions, gains including duplications or amplifications of any locus represented on an array simultaneously
- Microsatellites [Figure 4] are short tandem repeats of DNA sequences that are made of units of 1–4 nucleotides. The units can be repeated at variable rates at a given microsatellite leading to genetic polymorphism. Microsatellite analysis has been widely employed for mapping, to trace allelic inheritance, and to investigate the somatic loss of heterozygosity (LOH). Using paired control (blood or normal renal tissue) and tumor DNA, microsatellite analysis is a sensitive technique for detecting LOH in tumors. It is fast and inexpensive and can be performed on degraded DNA extracted from formalin-fixed paraffin-embedded tissue. Moreover, in comparison to aCGH and I-FISH, microsatellite typing can detect copy number neutral LOH
- NGS: As mentioned previously, the high demand for low-cost sequencing has driven the development of high-throughput sequencing, which also goes by the term NGS. In imageguided biopsy of renal masses, performance of a custom NGS panel was evaluated for diagnostic and prognostic utility and it was found that targeted NGS can robustly detect genomic alterations requiring only limited DNA (Gowrishankar *et al.*, 2016).[30]

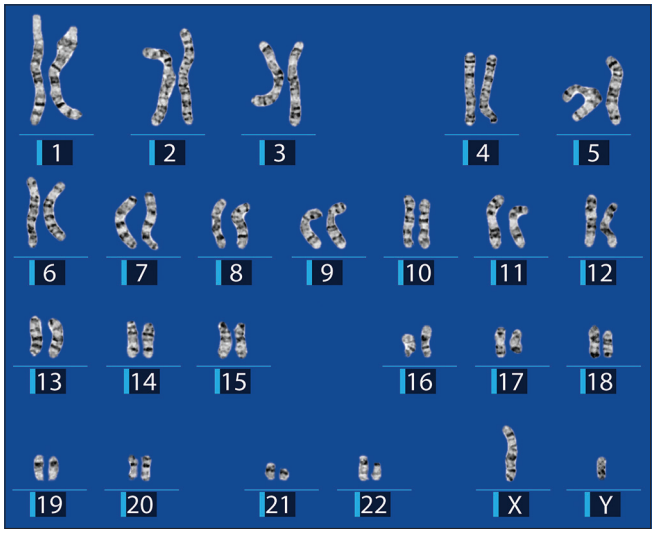

Figure 1: Karyotyping

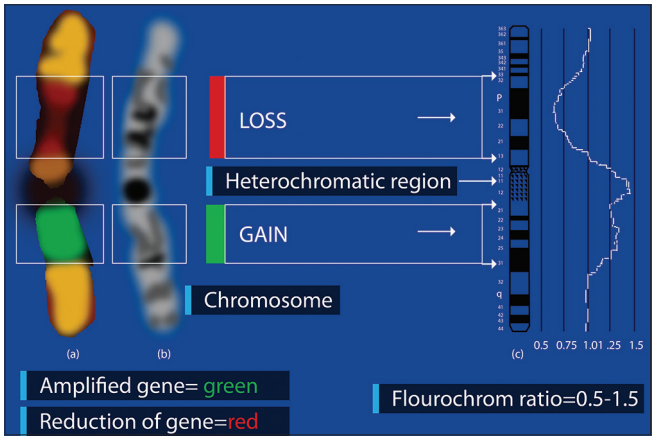

Figure 3: Comparative genomic hybridization

CYTOGENETICS IN SPORADIC RENAL CELL CARCINOMA-DISCUSSION

Many cytogenetic studies have investigated aberrations of chromosomes in relation to pathological parameters and clinical outcomes. The focus was mainly the most common subtypes of RCC: clear cell and papillary. Loss

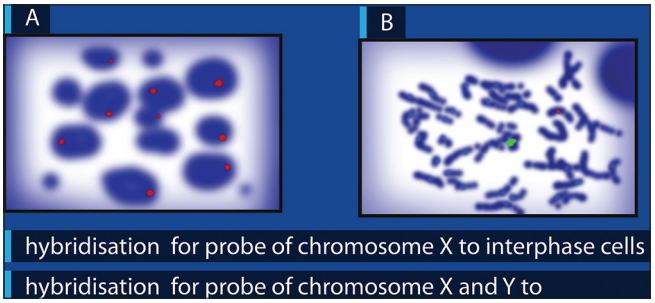

Figure 2: Fluorescence *in situ* hybridization

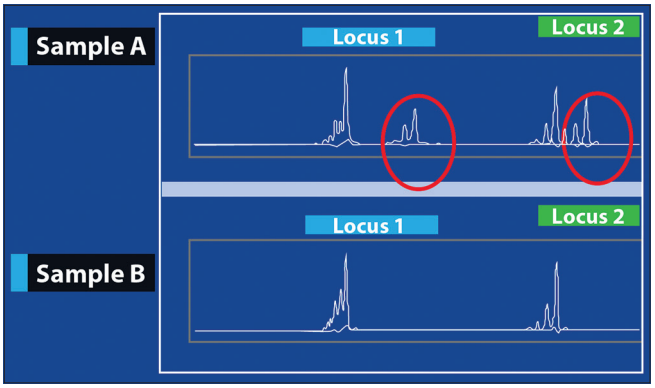

Figure 4: Microsatellite analysis showing loss of heterozygosity

of short arm of chromosome 3 is the most frequent chromosomal CNV in ccRCC, reported in more than 70% of sporadic cases. It distinguishes ccRCC from other subtypes and is associated with better survival in patients affected with it (Kroeger *et al*., 2013).[31] The gain of region 5q31 was associated with prolonged survival in high-grade ccRCC (Gunawan *et al*., 2001).[32] On the other hand, loss of chromosomes 4p, 14q, and 9p are associated with poor prognosis. However, 9p deletion was the only aberration that retained its prognostic significance in multivariate analysis (Klatte *et al*., 2009a).[28] In addition, deletion of Y chromosome is a common nonrandom CNV observed in ccRCC (Kovacs and Frisch, 1989).[33] The loss of Y chromosome was associated with distant metastasis in ccRCC and some other adverse histological features. Trisomy of chromosome 7 is a frequent aberration in ccRCC (Klatte *et al*., 2009a).[28] It has no known prognostic value in ccRCC. The gain of chromosome 8q which harbors the c-MYC oncogene was observed in 28 out of 336 tumors studied by karyotyping. This aberration was found to be associated with metastatic disease and risk of cancer-specific death, and on multivariate analysis was confirmed to be an independent prognostic factor (Klatte *et al*., 2012),[34] summarized in Table 5.

The vast majority of papillary RCCs are sporadic with two recognized, histologically and cytogenetically different subtypes. The sporadic forms show frequently trisomy of chromosome 7 and loss of Y (Brown *et al*., 1997)[41] which are commonly occurring also in the clear-cell subtype. Trisomy of chromosome 17 is present in 80% of papillary RCC, predominantly in Type I (Corless *et al*., 1996).[42] Furthermore, loss of chromosome 9p has been reported and was associated with the more aggressive type II papillary RCC (Klatte *et al*., 2009, Sanders *et al*., 2002),[38,43] summarized in Table 5.

Table 5: Chromosomal aberrations found in renal cell carcinoma subtypes

RCC subtype	Chromosome	Aberration	Prognosis	Study
ccRCC	3p21	Missense	Worse	Hakimi *et al*. 2013[35]
	1p36	Copy number loss	Worse	Lichner *et al*. 2013[36]
	5q31	Copy number gain	Better	Gunawan *et al*. 2001[32]
	9p	LOH	Worse	de Oliveira *et al*. 2014[37]
pRCC	17	Polysomy	Better	Klatte *et al*. 2009[38]
	X	Loss	Worse	Jiang *et al*. 1998[39]
	3p	Loss	Worse	Klatte *et al*. 2009[38]
chRCC	1, 2, 6, 10, 13, 17, 21	Loss	Worse	Yap *et al*. 2015[40]
Oncocytoma	1/1p, 14	Loss	No change	Yap *et al*. 2015[40]

LOH: Loss of heterozygosity, RCC: Renal cell carcinoma, ccRCC: Clear-cell RCC, pRCC: Papillary RCC, chRCC: Chromophobe RCC

CGH was used to detect specific alterations in each of RCC subtypes, in which clear-cell RCC showed − 3p, +5/5q, −8p, −9, −14, −18; papillary (chromophilic) RCC gains of chromosomes 7, 17, 16, 3, 12; chRCC loss of chromosomes 1, 2, 6, 10, 13, 17, 21; renal oncocytomas (Ros) loss of chromosomes 1/1p and 14. Furthermore, for clear-cell RCC, it was possible to define alterations which are associated with metastatic disease: Loss of 9, 10, 14 (Junker *et al*. 2003).[20] Microphthalmia-associated transcription (MiT) family translocation RCC is an RCC subtype characterized by early onset. The MiT family of transcription factors–including MiTF, TFE3, TFEB, and TFEC–shares a basic helix-loop-helix DNA-binding domain and similar target genes (Kentaru *et al*. 2017).[44]

The discovery of the VHL gene in familial and sporadic ccRCC has revolutionized treatment for advanced RCC. Targeted therapy aiming at suppressing angiogenesis through vascular endothelial growth factor (VEGF) or platelet-derived growth factor-mediated pathways has replaced immunotherapy such as interferon alpha and interleukin-2 as treatment for metastatic RCC. The current Food and Drug Administration approved targeted therapy drugs for RCC which are the tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib, and axitinib), monoclonal antibody to VEGF (bevacizumab), and the *MTOR* inhibitors (temsirolimus and everolimus) (Yap *et al*. 2015, Fishman *et al*. 2013).[40,45] Targeted therapy has improved treatment outcome as the overall and cancer-specific survival of metastatic RCC patients has improved in the targeted therapy era compared to the immunotherapy era (Yap *et al*. 2015, Soerenson *et al*. 2014, Nelson *et al*. 2013).[40,46,47]

NGS or exome sequencing studies have discovered several novel genes involved in chromatin modification which are mutated in ccRCC (Duns *et al*. 2012).[48] The newly identified genes are PBRM1, AT-rich interactive domain-containing protein 1A, BAP1, SETD2, and KDM5C.[40,48] PBRM1 mutations are found in up to 41% of ccRCC, making it the second most mutated gene after VHL (Veral *et al*. 2011).[49] The roles of these chromatin modification genes and their proteins products are not fully understood yet, but various studies have shown that the mutational status of these genes may possess prognostic influence on ccRCC. Other genetic aberrations of interest, such as changes at chromosome regions 5q, 8p, 9p, and 14, may affect the prognosis of ccRCC. Copy number gains at 5q conferred a favorable

prognosis whereas a loss had an adverse effect (Nagao *et al.* 2002).[50] LOH in 8p, 9p, and 14q has been associated with higher grade, stage, unfavorable prognosis, and tumor recurrence (Presti *et al.* 2002).[51] Potential candidate genes include CDK2NA (cyclin-dependent kinase inhibitor 2A) at 9p21 and HIF1A at 14q23.2 (Yap *et al.* 2015, Grady *et al.* 2001).[40,52]

Papillary RCCs frequently display gains of chromosomes 7 and 17 (Balint *et al.* 2009).[53] Trisomies 7 and 17 discovered in small papillary renal cell neoplasia indicate that these genetic alterations may be involved in initial tumor development (Brunelli *et al.* 2003).[54] At present, only one gene on chromosome 7 has been positively identified and linked to papillary RCC (pRCC). Hereditary pRCC associated with Type 1 tumors is caused by the mutation of the MET proto-oncogene at 7q31. An activating missense mutation of the MET gene and duplication of chromosome 7 along with the mutated MET gene were postulated to increase the oncogenic effect of MET (Fischer *et al.* 1998).[55] MET mutation associated hereditary pRCC and sporadic pRCC are typically low grade, bilateral tumors with multiple lesions (Yap *et al.* 2015, Duns *et al.* 2012).[40,48]

Hereditary chRCC is found in individuals with Birt–Hogg–Dubé syndrome (BHD). Renal tumors of different histologies such as ccRCC, pRCC, chRCC, and oncocytoma have been reported in BHD sufferers with chRCC and oncocytomas being the predominant types (Pavlovich *et al.* 2005).[56] Germline mutation of the BHD or folliculin gene was discovered and mapped to chromosome 17p11.2 in families with BHD syndrome (Schmidt *et al.* 2005).[57] Common genetic alterations found in sporadic chRCC are the LOH at chromosomes 1, 2, 6, 10, 13, 17, and 21 (Brunelli *et al.* 2010).[22] There is no difference in chromosomal loss pattern between eosinophilic and classic variants of chRCC Brunelli *et al.* 2005).[58] One frequently mutated candidate gene identified in sporadic chRCC is TP53 at 17p13.1 (Gad *et al.* 2007).[59] chRCC and RO pose a diagnostic challenge as both tumors have morphological overlaps. Correct diagnosis is important because RO is largely benign while chRCC is malignant. Losses of chromosomes 2, 6, 10, 13, 17, and 21, found in up to 93% of chRCCs, are not features of ROs and could be used to differentiate the two tumor types (Yap *et al.* 2015, Yusenko *et al.* 2009, and Tan *et al.* 2010).[40,60,61]

CONCLUSION

Each RCC subtype has a distinctive pattern of genetic aberrations, although there are some overlaps in chromosomal and genetic changes. These genetic changes may play an important role in tumorigenesis and affect the progression or prognosis of the tumor. Hence, detection of genetic or chromosomal changes could be a useful diagnostic or prognostic tool as adjunct to conventional immunohistochemistry and histology. Identification of frequently mutated genes and affected signaling pathways also allows for the development of new therapeutic targets or personalized-targeted therapy for better management of advanced RCC.

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Conflicts of interest

There are no conflicts of interest.

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