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REVIEW

Clinical genomics of renal epithelial tumors

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Kidney and upper urinary tract cancers account for approximately 54,000 cases every year in the United States, and represent about 3.7% of adult malignancies, with more than 13,000 annual deaths. Classification of renal tumors is typically based on histomorphologic characteristics but, on occasion, morphologic characteristics are not sufficient. Each of the most common histologic subtypes harbors specific recurrent genetic abnormalities, such as deletion of 3p in conventional clear cell carcinoma, trisomy 7 and 17 in papillary renal cell carcinoma, multiple monosomies in chromophobe renal cell carcinoma, and a nearly diploid genome in benign oncocytomas. Knowledge of this information can provide diagnostic support and prognostic refinement in renal epithelial tumors. Identification of the specific subtype of a renal tumor is critical in guiding surveillance for recurrence and the appropriate use of targeted therapies. Cytogenomic arrays are increasingly being used as a clinical tool for genome-wide assessment of copy number and loss of heterozygosity in renal tumors. In addition, the improved understanding of the hereditary causes of renal tumors and their role in sporadic malignancies has led to the development of more effective targeted therapies. This review summarizes the genetic and genomic changes in the most common types of renal epithelial tumors and highlights the clinical implications of these aberrations.

Keywords Renal cell carcinoma, diagnosis, prognosis, genetics, chromosomal imbalances, cytogenomic array, cytogenetics, SNP array, virtual karyotype

Kidney and upper urinary tract cancers account for approximately 54,000 cases every year in the United States, and represent about 3.7% of adult malignancies, with more than 13,000 annual deaths (1,2). Renal cell carcinoma (RCC) is the most common renal malignancy, with three common subtypes representing about 95% of all renal tumors: clear cell (ccRCC, 75% of RCC), papillary (pRCC, 10%), and chromophobe (chRCC, 5%). The fourth most common renal epithelial tumor is oncocytoma (OC, 5%), a benign neoplasm (Figure 1) (3). Although the majority of renal tumors occur in a sporadic fashion, approximately 2–4% occur in the setting of hereditary predisposition syndromes (4). There are four main hereditary cancer syndromes involving the renal epithelium: von Hippel Lindau (VHL) syndrome, which predisposes to development of ccRCC; hereditary papillary renal cell carcinoma (HPRCC); Birt-Hogg-Dubé syndrome (BHDS), which predisposes to development of chRCC and OC; and hereditary leiomyomatosis and renal cell carcinoma (HLRCC), which predispose to pRCC and collecting duct carcinomas (3).

Categorization of renal tumors can typically be done on the basis of histomorphologic characteristics. The correct determination of histologic subtype is critical because each has a distinct biologic behavior and therapeutic indications (5–7). However, morphologically challenging cases do occur. Even with generous sampling of large resection specimens, some tumors may have non-specific characteristics or overlap in morphologic features between tumor types. These morphologically challenging tumors are usually termed “unclassified renal cell carcinomas,” “renal cell carcinoma not otherwise specified,” or “eosinophilic renal carcinoma” in surgical pathology reports (3). Non-specific diagnoses confound efforts of the clinical team to predict tumor behavior, define appropriate follow up strategies, and guide therapeutic decisions. Difficulty in the morphologic assessment of renal tumors is compounded when evaluating scant tissue obtained from biopsy, or when architectural

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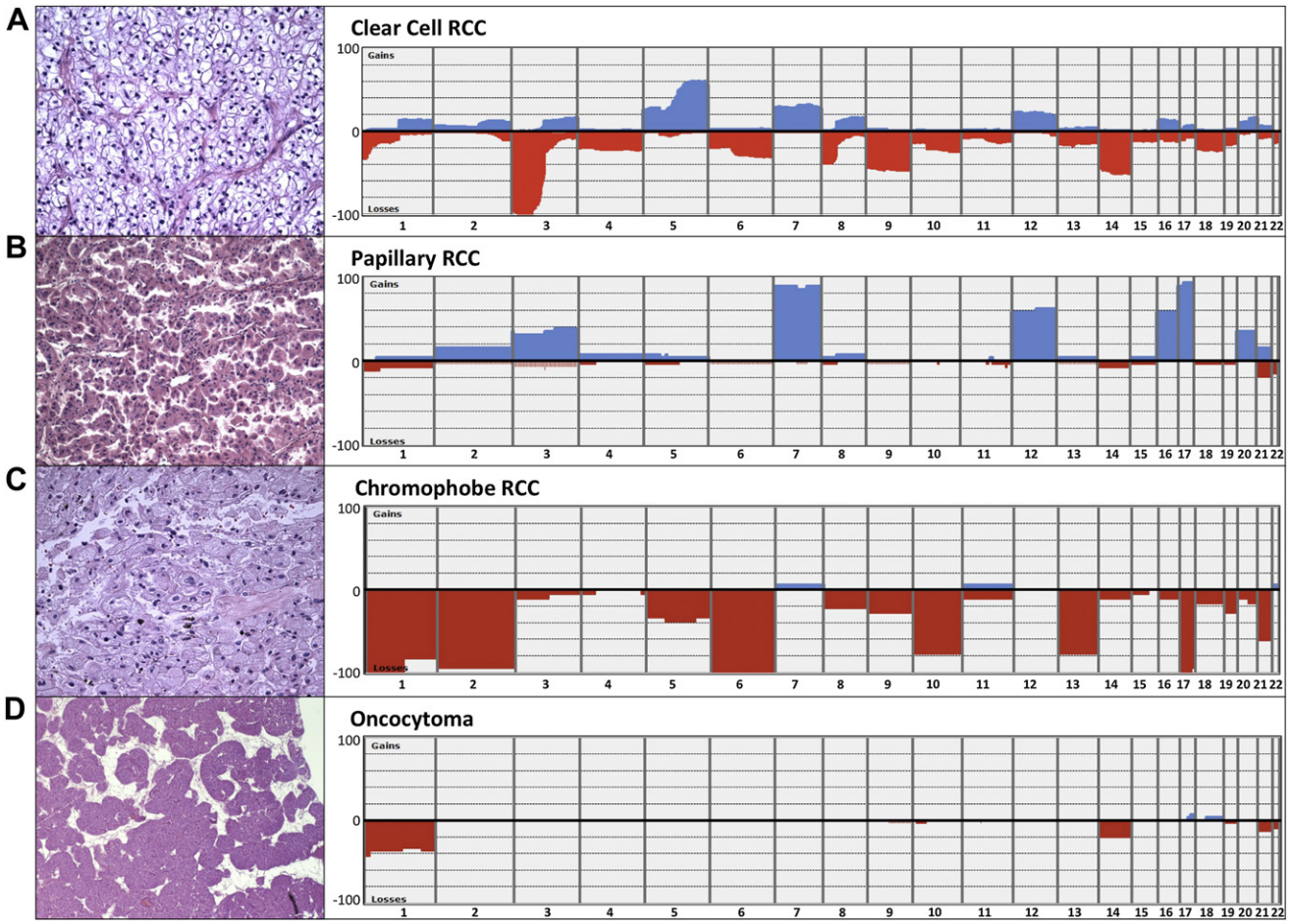

Figure 1 Morphology and genomic profiles for the most common renal epithelial tumors. Each renal epithelial tumor has morphologic (left column) and chromosomal copy number profiles (right column) that are characteristic to each subtype (red, loss; blue, gain; red stripes, aUPD). (A) Clear cell RCC, $n = 130$, with characteristic loss of 3p and frequent imbalances in chromosomes 5, 7, 9, and 14. (B) Papillary RCC, $n = 26$, with characteristic gain of chromosomes 7 and 17 and frequent imbalances in chromosomes 3 (including aUPD), 12, 16, and 20. (C) Chromophobe RCC, $n = 18$, note hypodiploid complement with frequent losses of chromosomes 1, 2, 6, 10, 13, 17, and 21. (D) Oncocytoma, $n = 30$, with majority of tumors showing normal chromosomal complement and frequent complete or partial loss of chromosome 1.

context is lost, as in fine needle core biopsy specimens (8,9). Immunohistochemical (IHC) profiles can help categorize morphologically challenging tumors (10), but sometimes overlapping phenotypes or non-specific staining profiles render IHC unsuccessful in resolving the differential diagnostic dilemmas.

Other laboratory studies, such as conventional cytogenetics, cytogenomic arrays, fluorescence in situ hybridization (FISH), or microsatellite polymerase chain reaction to assess loss of heterozygosity (LOH) can further aid in classification. These assays are able to assess copy number changes directly or by inference (LOH), either in a global or targeted approach. They are useful for classification of renal epithelial tumors because each of the most common subtypes harbors specific recurrent genomic abnormalities, as described below (Table 1, Figure 1) (11). Each assay has inherent strengths and weaknesses that should be considered when evaluating published data and when selecting the appropriate methods for clinical diagnostics (12). Cytogenomic arrays, such as array comparative genomic hybridization (aCGH) and single-nucleotide polymorphism (SNP) arrays, have been used to classify RCC on the basis of the specific genomic profiles for each subtype (Figure 1) (13,14). Cytogenomic arrays can provide not only diagnostic support, but also identify additional genomic changes, some of which are associated with outcome in specific subtypes.

Although most patients with renal epithelial tumors have an excellent prognosis, 30% of patients with initially organ-confined ccRCC will develop metastases. In addition, due to the paucity of overt clinical manifestations of localized disease, up to 30% of patients will present with metastases at the time of initial diagnosis (2). Treatment for advanced or metastatic kidney cancer is a formidable challenge with the traditional therapies currently available. Investigation of the Mendelian single-gene syndromes, such as von Hippel Lindau syndrome (VHL: *VHL* gene), hereditary papillary renal cell carcinoma (HPRCC: *MET* gene), Birt-Hogg-Dubé (BHD: *BHD* gene), and hereditary leiomyomatosis renal cell carcinoma (HLRCC: *FH* gene), however, have provided an opportunity to develop pathway-specific therapies (6).