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Characterization of Clinical Cases of Advanced Papillary Renal Cell Carcinoma via Comprehensive Genomic Profiling

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Abstract

Background: Papillary renal cell carcinoma (PRCC) is a rare subset of RCC. The Cancer Genome Atlas (TCGA) data largely reflect localized disease, and there are limited data for advanced PRCC.
Objective: To characterize the frequency of genomic alterations (GAs) in patients with advanced PRCC for whom comprehensive genomic profiling (CGP) was performed in the context of routine clinical care.
Design, setting, and participants: Formalin-fixed, paraffin-embedded tissue was obtained for 169 consecutive patients with confirmed PRCC. DNA was extracted and comprehensive genomic profiling was performed in a certified central laboratory.
Measurements: Hybrid-capture, adaptor ligation-based libraries of up to 315 genes were sequenced to a median coverage of 648×. All classes of GAs were identified, including substitutions, insertions/deletions, copy number alterations, and rearrangements.
Results and limitations: From 169 patients, either primary tumor tissue (102 patients, 60%) or metastatic tissue (67 patients, 40%) was collected. In patients with type 1 PRCC, commonly altered genes were *MET* (33%; 8 activating mutations, 5 amplifications at > 6 copies), *TERT* (30%), *CDKN2A/B* (13%), and *EGFR* (8%). In patients with type 2 PRCC, commonly altered genes were *CDKN2A/B* (18%), *TERT* (18%), *NF2* (13%), and *FH* (13%); *MET* GAs (5 mutations, 3 amplifications) were observed in 7% of type 2 cases. Notable differences from TCGA data include higher frequencies of *MET*, *NF2*, and *CDKN2A/B* GAs,

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association of alterations in SWI/SNF complex genes with type 2 PRCC, and observation of frequent *CDKN2A/B* alterations in both type 1 and type 2 disease.
Conclusions: Both the current study and the TCGA experience represent similarly sized cohorts of patients with PRCC. Key differences in GA frequency probably underscore the marked difference in stage distribution between these data sets. These results may inform planned precision medicine trials for metastatic PRCC.
Patient summary: Papillary renal cell carcinoma (PRCC) is a rare subtype of kidney cancer, and understanding of the biology of advanced PRCC is limited. This report highlights some of the unique biologic features of PRCC that may inform on future use of targeted therapies for the treatment of metastatic disease.

1. Introduction

Papillary renal cell carcinoma (PRCC) accounts for approximately 15–20% of cases of RCC [1]. For patients with advanced PRCC, treatment options unfortunately remain limited, and current guidelines emphasize enrollment in clinical trials. While VEGF- and mTOR-directed therapies have led to dramatic improvements in clinical outcome for patients with metastatic clear-cell RCC (ccRCC) over the past decade, the efficacy of these targeted agents appears to be more modest in metastatic PRCC [2,3]. Progression-free survival (PFS) estimates for first-line VEGF-directed agents such as sunitinib typically range from 9 to 12 mo in patients with metastatic ccRCC, whereas published series indicate PFS ranging from 1.6 to 6.6 mo for metastatic PRCC in the same setting [4–9].

The discordant response to VEGF-directed agents among RCC types can probably be explained by the distinct biology of PRCC compared to ccRCC. It is generally accepted that ccRCC is driven by alterations in *VHL* leading to upregulation of HIF and subsequently VEGF [10]. By contrast, PRCC appears to have distinct oncogenic drivers with different aberrant pathways that vary by papillary subtype. The Cancer Genome Atlas (TCGA) experience for PRCC has recently been reported, and offers characterization of 161 patients [1]. Type 1 PRCC was characterized by alterations in the *MET* proto-oncogene, while type 2 PRCC has been linked to alterations in *CDKN2A*, *SETD2*, and *TFE3*. A subset of type 2 disease (designated CpG island methylator phenotype, or CIMP) appears to have particularly poor survival, and several of these patients have alterations in the *FH* gene.

One limitation of the TCGA experience is that 73% of patients were characterized as having M0 disease at diagnosis. In fact, only 3% of the TCGA patients were characterized as having M1 disease (for the remainder, stage was unknown). With this in mind, it is challenging to predicate clinical trial designs of targeted therapy for advanced PRCC on this data set. In the current study, we assess the frequency of GAs in a cohort of PRCC patients with predominantly advanced disease for whom comprehensive genomic profiling (CGP) was performed in the context of routine clinical care.

2. Patients and methods

Previously published methods were used to perform CGP for 169 consecutive patients with PRCC sequenced between 2012 and 2016 [11,12]. Samples from patients were submitted by clinicians in the course of clinical care with limited accompanying information including age, gender, stage, and disease site. In brief, formalin-fixed, paraffin-embedded (FFPE) tissues were obtained [13]. Central pathology review arbitrated by two board-certified pathologists (E.Y., S.M.A.) was used to determine type 1 versus type 2 designation for 147 cases. Cases with discordant assessment of subtype between the two pathologists were arbitrated via mutual discussion; ultimately, a consensus was reached for designation of each case. Pathology for the 22 cases that were determined locally (3 cases of type 1, 10 of type 2, 9 unspecified) were designated "unclassified." For all cases in the current series, DNA was extracted from 40 μm of FFPE sections with at least 20% tumor cells. Targeted next-generation sequencing was performed on hybridization-captured, adaptor ligation-based libraries in a laboratory with Clinical Laboratory Improvement Amendments certification and College of American Pathologists accreditation (Foundation Medicine, Cambridge, MA, USA). In total, up to 315 cancer-related genes were assessed along with select introns from 31 genes frequently rearranged in cancer [14]. Captured libraries were sequenced to a median exon coverage depth of 648×. Base substitutions, short insertions, deletions, copy number changes (homozygous deletions and amplifications), and gene fusions and rearrangements were assessed using previously published methods [12,15].

Wholly deidentified data were used for the current analysis. Approval for the study, including a waiver of informed consent and a Health Insurance Portability and Accountability Act waiver of authorization, was obtained from the Western Institutional Review Board (Protocol No. 20152817). Data from the TCGA Papillary Renal Cell Carcinoma study were accessed using cBioPortal (February 2017); analysis of the TCGA dataset in cBioPortal was restricted to the 161 published cases by using the patient barcodes from the appendix of the TCGA publication [1,16]. Descriptive statistics were used to compare the frequency of GAs in the current data set and the TCGA report [1]. Fisher's exact test (two-tailed) was used to compare the frequency of GAs in primary versus metastatic samples, and in type 1 versus type 2 disease; p values are unadjusted.

3. Results

3.1. Patient characteristics

Of the 169 patients with PRCC identified, 129 patients were male and 40 were female, with a median age of 60 yr (range 19–88; Table 1). After central pathologic review, 39 patients were classified as type 1 and 108 patients as type 2; 22 patients were designated as unclassified. The distributions for age and gender were similar across these subtypes. The majority of patients were stage IV (103 patients, 61%). A total of 36 patients (21%) were stage III, and only 22 patients had stage I or II disease (13%). In

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