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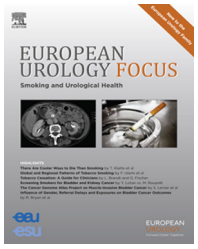

From Lab to Clinic

The Landscape of Whole-genome Alterations and Pathologic Features in Genitourinary Malignancies: An Analysis of the Cancer Genome Atlas

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Abstract

Background: The accumulation of somatic genetic alterations drives carcinogenesis. Little is known, however, about how the level of genetic alteration across an entire cancer genome affects tumor grade, stage or survival.
Objective: To investigate the influence of somatic mutation count (MC) and copy number variation (CNV) on pathologic and oncologic outcomes in patients with genitourinary malignancies in The Cancer Genome Atlas (TCGA).
Design, setting, and participants: TCGA data sets for adrenocortical carcinoma (ACC), bladder urothelial carcinoma (BLCA), chromophobe renal cell carcinoma (RCC; KICH), clear cell RCC (KIRC), papillary RCC (KIRP), pheochromocytoma and paraganglioma (PCPG), prostate adenocarcinoma (PRAD), and testis germ cell tumor (TGCT) were accessed via cBioportal.
Outcome measurements and statistical analysis: Median MC and CNV were compared among and within each tumor type. Patients were stratified by grade and stage, and differences in MC and CNV were compared. Correlation of MC and CNV with overall survival (OS) and recurrence-free survival (RFS) was analyzed when these data were available.
Results and limitations: Among the tumor types analyzed, BLCA had the highest MC at 167, followed by ACC (89), KIRP (71), TGCT (55), KIRC (45), PRAD (34), PCPG (14), and KICH (12). The tumor type with the highest fraction of the genome with CNV was KICH (0.94), followed by ACC (0.58), TGCT (0.41), BLCA (0.29), KIRP (0.15), PCPG (0.13), KIRC (0.12), and PRAD (0.06). MC was associated with higher T stage in ACC, N stage in KIRC, M stage in ACC, grade in BLCA, and primary Gleason score in PRAD, and was associated with OS and RFS in KICH. CNV was associated with higher N stage in PRAD, grade in KIRC, and Gleason grade in PRAD. In addition, higher CNV was independently associated with inferior RFS for KIRC, as well as inferior OS and RFS for KIRP.
Conclusions: MC and CNV vary greatly among tumor types.
Patient summary: Cancers with higher levels of genomic alterations are associated with worse pathologic features and survival. The degree of genomic alterations could serve as a useful marker of disease aggressiveness.

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1. Introduction

Stepwise accumulation of somatic genetic alterations is the basis for cancer. These genetic changes include base insertions, deletions, substitutions, translocation events, and copy number alterations [1]. A major focus of cancer research over the last several decades has been identifying these alterations in single genes, and this approach has led to critical discoveries in cancer biology. Much less is known about how the level of genetic alteration across an entire cancer genome affects the natural history of an individual malignancy.

At the tissue level, tumor biology is driven by stage and grade, and these data are the backbone of prognostic information used to counsel patients and plan treatments. While some studies have shown clustering of mutations that are associated with grade and stage [2–5], the effect that genomic alterations have on tumor grade and stage on histopathologic analysis has not been fully elucidated.

With the publication of whole cancer genomes as part of The Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium, the association of whole-genome alterations such as mutation count (MC) and copy number variation (CNV) can now be correlated with clinicopathologic characteristics, survival outcomes, and therapeutic response [6]. For example, higher MC and downstream protein changes underlie the genetic basis of the CTLA-4 response in the treatment of metastatic melanoma [7] and may play a role in response to nivolumab in clear cell kidney cancer [8]. The effect, if any, of whole-genome alterations on the natural history of genitourinary malignancies has not yet been evaluated.

In this study, we hypothesized that higher MC and CNV would be associated with advanced pathologic features including tumor grade and stage and survival outcomes among patients with genitourinary malignancies in TCGA.

2. Materials and methods

Data sets for adrenocortical carcinoma (ACC), bladder urothelial carcinoma (BLCA), chromophobe renal cell carcinoma (RCC; KICH), clear cell RCC (KIRC), papillary RCC (KIRP), pheochromocytoma and paraganglioma (PCPG), prostate adenocarcinoma (PRAD), and testis germ cell tumor (TGCT) were accessed via the cBioPortal for Cancer Genomics data portal (www.cbioportal.org). cBioPortal is a web-based TCGA data mining tool developed by investigators at Memorial Sloan-Kettering Cancer Center and includes data from published TCGA reports as well as provisional data sets for all non-embargoed TCGA tumors types [9,10]. All cases available as of January 1, 2016 were included in analysis. The number of cases available for analysis were 92 ACC; 408 BLCA for CNV and 130 for MC; 66 KICH; 518 KIRC; 292 KIRP; 184 PCPG; 400 PRAD; and 156 TGCT.

MC and CNV data were derived from cBioPortal. MC was defined as the number of nonsynonymous mutations per genome. Copy number changes were identified using the GISTIC 2.0 algorithm [11]. CNV was calculated as the fraction of the genome exhibiting copy number alterations by summing all segments with log 2 copy number >0.2 compared to the reference, divided by the total number of segments (maximum score 1.0). Median MC and CNV were assessed for tumor grade, T stage, N stage, and M stage for samples with available information. Grade was analyzed as a dichotomous variable (low grade vs high grade); for KIRC, Fuhrman grades 1 and 2 were analyzed as low grade, and Fuhrman grades 3 and 4 as high grade. For tumors types with substaging (eg, T2a and T2b in BLCA), substages were combined for analysis. Wilcoxon rank-sum and Kruskal-Wallis tests were used to compare differences in median MC and CNV across malignancies and between groups. When survival data were available, survival analysis was performed. Univariate Cox regression was used to test the association of MC and CNV with overall survival (OS) and recurrence-free survival (RFS) when these data were available. Significant associations were further evaluated using multivariable regression. All statistical analysis was performed using Stata 13.1 (StataCorp, College Station, TX, USA). Two-sided p values <0.05 were considered significant.

3. Results

3.1. Analysis of MC and CNV across malignancies

A comparison of MC for each cancer type is shown in Fig. 1. BLCA had the highest MC at 167 (interquartile range [IQR] 101–278), followed by ACC (89, IQR 72–22), KIRP (71, IQR 51–89), TGCT (55, IQR 47–64), KIRC (45, IQR 34–59), PRAD (34, IQR 27–41), PCPG (14, IQR 11–20), and KICH (12, IQR 9–18). The CNV for each malignancy is shown in Fig. 2. The tumor type with the highest fraction of the genome with CNV was KICH (0.94, IQR 0.77–0.95), followed by ACC (0.58, IQR 0.33–0.89), TGCT (0.41, IQR 0.20–0.51), BLCA (0.29, IQR 0.14–0.45), KIRP (0.15, IQR 0.08–0.23), PCPG (0.13, IQR 0.09–0.18), KIRC (0.12, IQR 0.06–0.21), and PRAD (0.06, IQR 0.02–0.12). The associations between pathologic features for each type malignancy and MC (Table 1) and CNV (Table 2). Survival correlations are summarized in Table 3.

3.1.1. Adrenal cortical carcinoma

ACC had the second highest MC and second highest CNV. Higher T stage was associated with higher MC ($p = 0.0022$), and M1 patients had higher MC than M0 patients (108 vs 85, $p = 0.047$). There were no other pathologic associations with

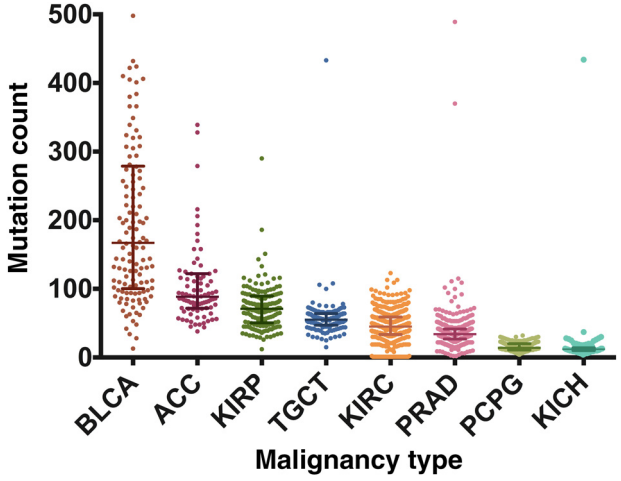

Fig. 1 – Somatic mutation count by malignancy type. BLCA = bladder urothelial carcinoma; ACC = adrenocortical carcinoma; KICH = chromophobe renal cell carcinoma (RCC); KIRC = clear cell RCC; KIRP = papillary RCC; PCPG = pheochromocytoma and paraganglioma; PRAD = prostate adenocarcinoma; TGCT = testis germ cell tumor.

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