Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Eur Urol Focus. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

Eur Urol Focus. 2017 December ; 3(6): 584–589. doi:10.1016/j.euf.2017.01.007.

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

Mark W. Ball[*], **Michael A. Gorin**, **Charles G. Drake**, **Hans J. Hammers**, and **Mohamad E. Allaf**

The James Buchanan Brady Urological Institute & Department of Urology, Johns Hopkins University School of Medicine

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 or stage or survival.

Objective—To investigated 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—The 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.

[*]Corresponding author. The James Buchanan Brady Urological Institute & Department of Urology, Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287, USA. Fax: +1 888 2775726, mark.ball@jhmi.edu (M.W. Ball).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Author contributions: Mark W. Ball had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ball, Allaf.
Acquisition of data: Ball.
Analysis and interpretation of data: Ball, Gorin, Drake, Hammers, Allaf.
Drafting of the manuscript: Ball.
Critical revision of the manuscript for important intellectual content: Ball, Gorin, Drake, Hammers, Allaf.
Statistical analysis: Ball.
Obtaining funding: Allaf.
Administrative, technical, or material support: Allaf.
Supervision: Allaf.
Other: None.

Financial disclosures: Mark W. Ball certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

In this study of eight urologic malignancies, there was correlation between the degree of genomic alteration and pathologic aggressiveness or survival outcomes. As genomic data become more available, the degree of genomic alterations may be useful as a biomarker of biologic aggressiveness.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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.

Keywords

Mutations; Copy number alteration; Genomics; Malignancy; Kidney cancer; Bladder cancer; Prostate cancer

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 the TCGA database.

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 Figure 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 Figure 2. The tumor type with the highest fraction of the genome with CNV was KICH

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

(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) are described below.

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 MC, and there were no pathologic associations with CNV. Survival data were not available for ACC.

3.1.2. Bladder cancer—BLCA had the highest MC and fourth highest CNV. High-grade tumors were associated with higher MC (174 vs 87, $p = 0.001$). There were no other pathologic associations with MC or CNV. There was no association with survival outcomes for MC or CNV.

3.1.3. Chromophobe RCC—KICH had the lowest MC and the highest CNV. Fuhrman grade was not assigned to KICH tumors in the TCGA. There were no associations between MC or CNV and pathologic staging data. In univariate analysis, MC was associated with OS (hazard ratio [HR] 1.003, 95% confidence interval [CI] 1.0004–1.005; $p = 0.021$) and RFS (HR 1.004, 95% CI 1.002–1.007; $p = 0.002$). In multivariable analysis controlling for T stage, MC was independently associated with OS (HR 1.004, 95% CI 1.0006–1.008; $p = 0.022$) and RFS (HR 1.04, 95% CI 1.01–1.07; $p = 0.020$).

3.1.4. Clear cell RCC—KIRC had the fourth lowest MC and the second lowest CNV. There was no association with Fuhrman grade and MC for a four-tier ($p = 0.27$) or a two-tier system; however, CNV was associated with higher Fuhrman grade in both four-tier ($p = 0.0006$) and two-tier ($p = 0.0001$) systems. Higher CNV was also associated with longer RFS (HR 2.46, 95% CI 1.0–6.05; $p = 0.050$). In multivariable analysis controlling for T stage, N stage, and Fuhrman grade, higher CNV (HR 3.13, 95% CI 1.20–8.10; $p = 0.020$) remained independently associated with RFS.

3.1.5. Papillary RCC—KIRP had the third highest MC and fourth lowest CNV. There were no pathologic associations with MC or CNV. Grade data were not available, but KIRP subtype (type 1 and type 2) was available for 124 patients. There was no difference between type 1 and type 2 in MC (70 vs 79; $p = 0.3$) or CNV (0.07 vs 0.08; $p = 0.7$). Higher CNV was associated with both OS (HR 10.3, 95% CI 2.25–47.1; $p = 0.003$) and RFS (HR 9.26, 95% CI1.17–73.3; $p = 0.04$). In multivariable analysis controlling for T stage and N stage, CNV remained independently associated with OS (HR 48.6, 95% CI 7.23–326.6; $p < 0.0001$) and RFS (HR 22.02, 95% CI 2.09–231.98; $p = 0.01$).

3.1.6. Pheochromocytoma and paraganglioma—PCPG had the second lowest MC and the third lowest CNV. There were no stage or grade data to correlate with MC and CNV. There were no deaths or recurrences for which to perform survival analysis.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

3.1.7. Prostate cancer—PRAD had the third lowest MC and the lowest CNV. Higher primary Gleason score was associated with both higher MC ($p = 0.0004$) and higher CNV ($p = 0.0001$). N stage was also associated with higher CNV ($p = 0.0007$). OS was not calculated as there was only one death in the PRAD cohort. Biochemical RFS was not associated with MC or CNV.

3.1.8. Testicular germ cell tumors—TGCT had the fourth highest MC and the third highest CNV. There was no association between MC or CNV and stage or survival outcomes. Grade data were not available.

4. Discussion

Until recently, cancer biology has been studied at the single-gene level. With the availability of large genomic data sets from the TCGA, whole-genome alterations can now be studied. We performed a comprehensive analysis of how genomic changes compare both across genitourinary cancer types and within grades and stages for each malignancy. We found a wide range for somatic MC and CNV between and within tumor types. Moreover, we found that for the majority of malignances, higher levels of MC and CNV changes were associated with advanced pathologic features. Furthermore, the degree of genomic alteration can correlate with survival. These findings give us insight into tumor biology that may have implications for prognosis and therapeutics.

Previous multicancer studies have demonstrated the wide range for somatic MC [12] and CNV [13] across different malignancy types. Our work complements those data by describing pathologic correlation and reporting rates for several malignancies that were not included in earlier multicancer studies. It also supports data reported by Rubin and colleagues [5] that showed increasing CNV and MC across grade groups in prostate cancer.

It has been postulated for some time that genetic instability is associated with poorer clinical outcomes [14]. Genetic instability has largely been studied in terms of microsatellite instability and chromosomal instability, and has been linked to adverse pathology and survival in colon cancer [15]. One theory, described by Kinzler and Vogelstein, is that mutations in “caretaker” genes that maintain the integrity of the genome is an early event in cancer development that accelerates the accumulation of additional mutations that eventually lead to neoplasia [16]. Our data support the role of genetic instability in the progression to higher grade and/or higher stage cancer for some genitourinary malignancies.

High MC has previously been associated with greater response to checkpoint inhibitors in melanoma, non-small cell lung cancer, and renal cell carcinoma [7,8,17,18]. In our study, 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. In addition, MC was independently associated with OS and RFS in KICH.

Global CNV has previously been associated with pathologic features in several non-GU malignancies [19]. In this study, CNV was associated with higher N stage in PRAD, Fuhrman grade in KIRC, and primary Gleason grade in PRAD. In addition, higher CNV was

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

independently associated with inferior RFS for KIRC, as well as inferior OS and RFS for KIRP.

Taken together, these data support the concept that greater genetic variability is correlated with higher pathologic stage and stage in multiple genitourinary malignancies. At the dawn of the era of personalized medicine and affordable personal genomes, genomic data will increasingly complement pathologic data. In fact, schemata already exist for incorporation of sequencing data into clinical practice [20]. Our analysis demonstrates one way in which these two data sources converge.

There are several limitations that should be noted. These data were obtained from publicly available somatic mutation data, but restricted-access germline data were not analyzed. Some individuals are at higher risk of malignancy because of germline features, and these individuals may have different MC and CNV patterns in their genomes. Furthermore, we used provisional data sets for tumors for which the comprehensive analysis was not yet published (ACC, TGCT, PCPG). Mutation calling in these data sets may be prone to a higher false-discovery rate than if a more stringent mutation calling algorithm were used. In addition, the impact of MC and CNV on survival outcomes may be limited by low event frequency. For example, for KIRP the magnitude of the HR estimates and the large confidence intervals probably reflect the small number of OS and RFS events in this data set. Finally, our analysis is limited to only two types of genomic alteration. The degree of epigenetic modification and expression level changes may drive pathologic and clinical behavior as well.

5. Conclusions

Although there is a wide range for somatic MC and CNV between and within genitourinary malignancy types, there was some correlation of genomic alterations with pathologic features and survival outcomes. In the era of personalized medicine, the degree of genomic alterations may serve as a prognostic biomarker.

Acknowledgments

***Funding/Support and role of the sponsor*:** This work was supported by a Buerger Family Scholar grant and NIH P30CA006973. The sponsors played no direct role in the study.

References

1. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. Nature. 2009; 458:719–24. [PubMed: 19360079]
2. Damrauer JS, Hoadley KA, Chism DD, et al. Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology. Proc Natl Acad Sci U S A. 2014; 111:3110–5. [PubMed: 24520177]
3. Pena-Llopis S, Vega-Rubin-de-Celis S, Liao A, et al. BAP1 loss defines a new class of renal cell carcinoma. Nat Genet. 2012; 44:751–9. [PubMed: 22683710]
4. Tryggvadottir L, Vidarsdottir L, Thorgeirsson T, et al. Prostate cancer progression and survival in BRCA2 mutation carriers. J Natl Cancer Inst. 2007; 99:929–35. [PubMed: 17565157]
5. Rubin MA, Girelli G, Demichelis F. Genomic correlates to the newly proposed grading prognostic groups for prostate cancer. Eur Urol. 2016; 69:557–60. [PubMed: 26563871]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

6. Ping Z, Siegal GP, Almeida JS, Schnitt SJ, Shen D. Mining genome sequencing data to identify the genomic features linked to breast cancer histopathology. J Pathol Inform. 2014; 5:3. [PubMed: 24672738]
7. Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med. 2014; 371:2189–99. [PubMed: 25409260]
8. Ball MW, Johnson MH, Gorin MA, et al. Clinical, pathologic, and genomic profiles of exceptional responders to anti-PD1 therapy in renal cell carcinoma. J Clin Oncol. 2016; 34(Suppl 2):625.
9. Cerami E, Gao J, Dogrusoz U, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012; 2:401–4. [PubMed: 22588877]
10. Gao J, Aksoy BA, Dogrusoz U, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal. 2013; 6 pl1.
11. Mermel CH, Schumacher SE, Hill B, Meyerson ML, Beroukhim R, Getz G. GISTIC2.0 facilitates sensitive and confident localization of the targets of focal somatic copy-number alteration in human cancers. Genome Biol. 2011; 12:R41. [PubMed: 21527027]
12. Lawrence MS, Stojanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature. 2013; 499:214–8. [PubMed: 23770567]
13. Zack TI, Schumacher SE, Carter SL, et al. Pan-cancer patterns of somatic copy number alteration. Nat Genet. 2013; 45:1134–40. [PubMed: 24071852]
14. Carter SL, Eklund AC, Kohane IS, Harris LN, Szallasi Z. A signature of chromosomal instability inferred from gene expression profiles predicts clinical outcome in multiple human cancers. Nat Genet. 2006; 38:1043–8. [PubMed: 16921376]
15. Diaz LA Jr. The current clinical value of genomic instability. Semin Cancer Biol. 2005; 15:67–71. [PubMed: 15613290]
16. Kinzler KW, Vogelstein B. Cancer-susceptibility genes. Gatekeepers and caretakers. Nature. 1997; 386:761–3. [PubMed: 9126728]
17. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015; 348:124–8. [PubMed: 25765070]
18. Van Allen EM, Miao D, Schilling B, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science. 2015; 350:207–11. [PubMed: 26359337]
19. Jeon YK, Cheon JE, Kim SK, Wang KC, Cho BK, Park SH. Clinicopathological features and global genomic copy number alterations of pilomyxoid astrocytoma in the hypothalamus/optic pathway: comparative analysis with pilocytic astrocytoma using array-based comparative genomic hybridization. Mod Pathol. 2008; 21:1345–56. [PubMed: 18622384]
20. Gagan J, Van Allen EM. Next-generation sequencing to guide cancer therapy. Genome Med. 2015; 7:1. [PubMed: 25606059]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

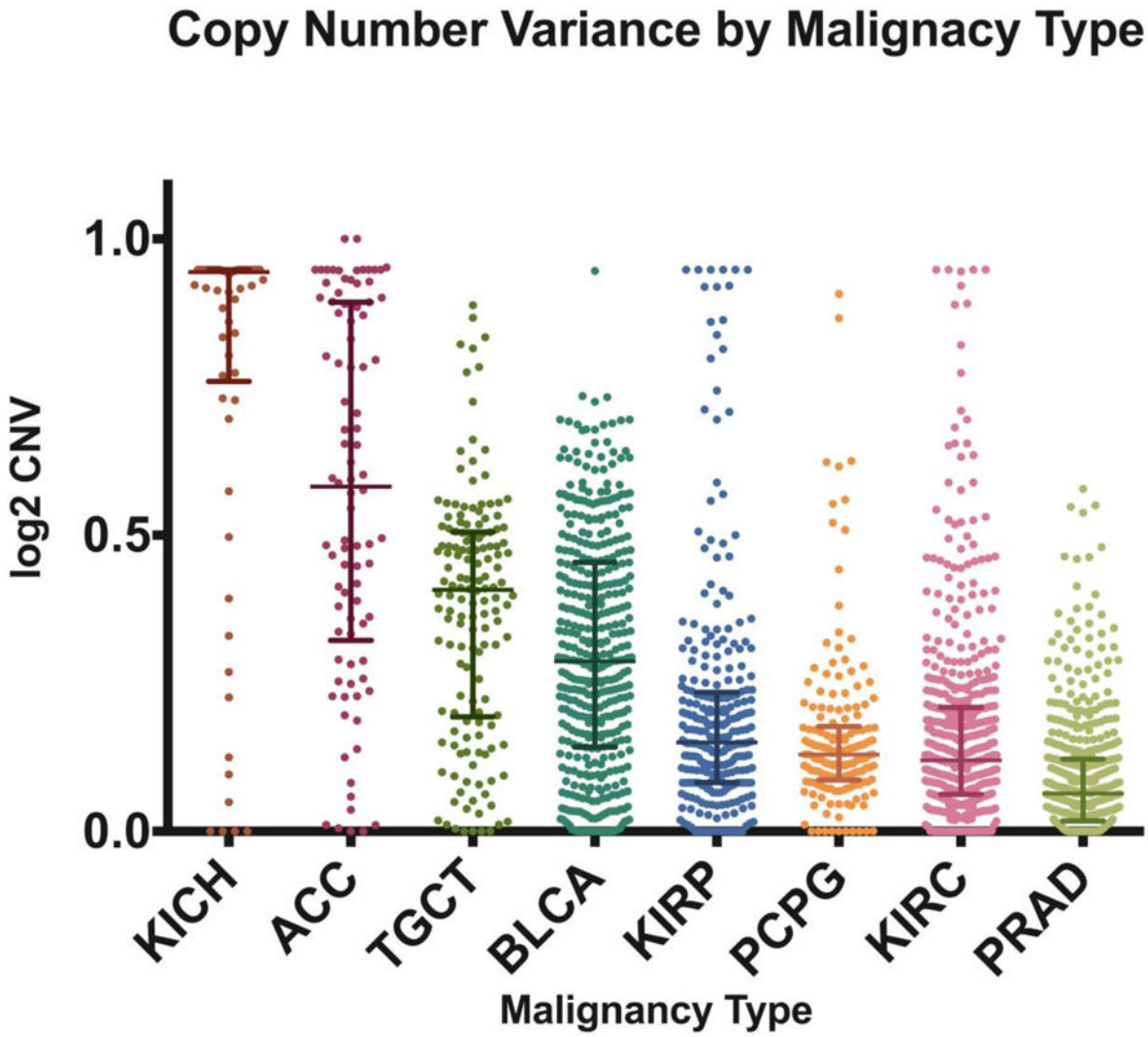

Fig. 1.

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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

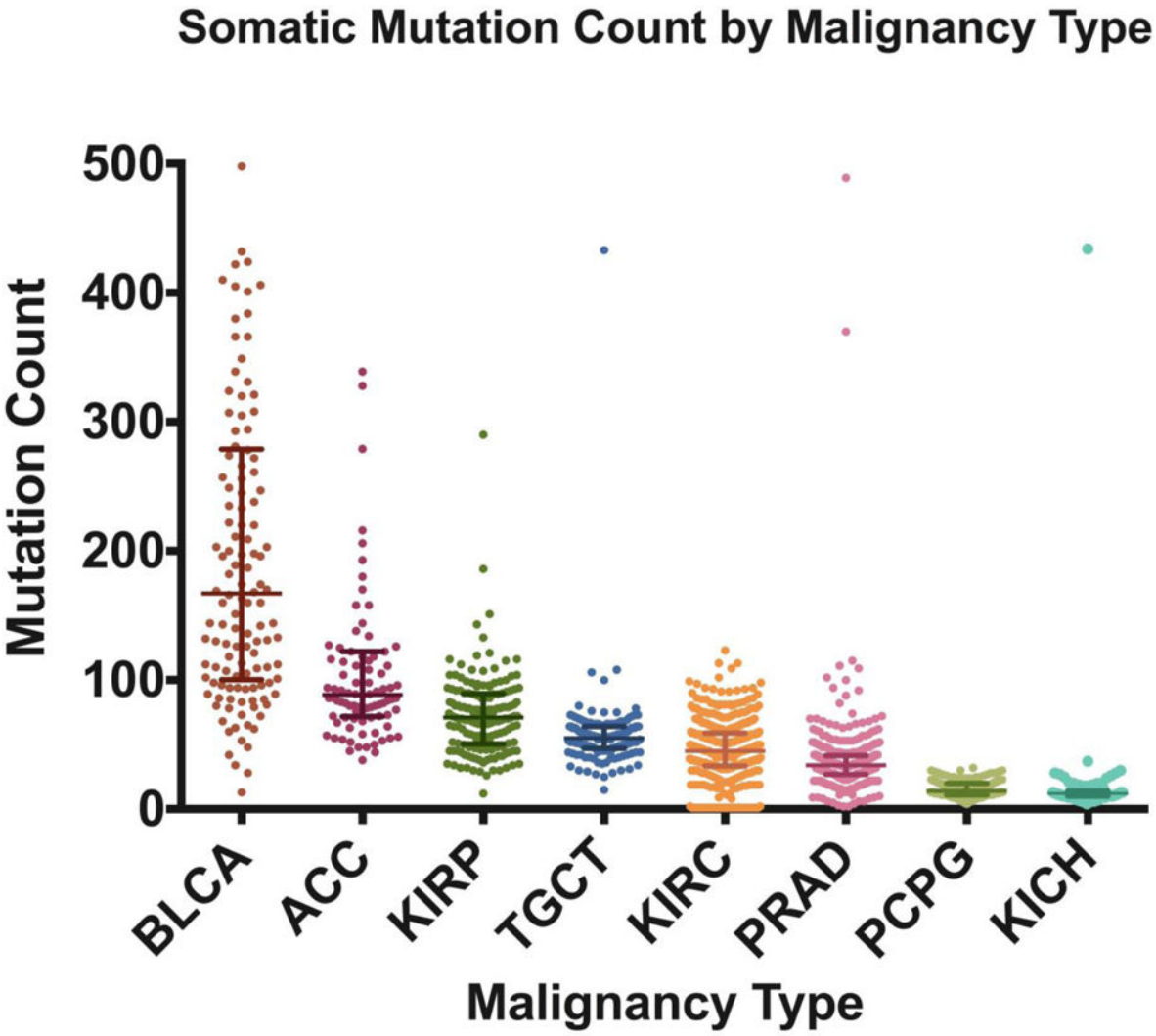

Fig. 2.

Copy number variation (CNV) 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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1

Median somatic MC as a function of stage and grade among genitourinary malignancies

	ACC		BLCA		KIRC		KIRP		KICH		PRAD		TGCT	
	MC	***p* value**	**MC**	***p* value**	**MC**	***p* value**	**MC**	***p* value**	**MC**	***p* value**	**MC**	***p* value**	**MC**	***p* value**
T stage		0.0022		0.62		0.38		0.67		0.17		0.36		0.16
T1	63		NA		43		70		60		NA		57	
T2	84		148		50		77		62		34		52	
T3	92		174		47		69		57		38		62	
T4	119		169		37		72 (NA)		116		42		NA	
N stage		0.81		0.72				0.57		0.0046		0.33		0.086
N0	89		170		49		69		60		37		58	
N1	93		192		49		69		100		36		48	
M stage		0.047		0.12		0.41		0.45		0.12	NA			0.17
M0	85		160		46		67		62				57	
M1	108		194		41		69		77				68	
Grade		0.94		0.001		0.17					NA			
Low	80		87		43									
High	84		174		47									
Stage		0.013		0.72		0.41		0.52		0.052	NA			
I	63		126 (NA)		43		69		60					
II	85		156		47		70		62					
III	92		172		51		76		57					
IV	108		196		42		67		93					
Primary GS												0.0004		
3											32			
4											38			
5											44			

MC = mutation count; ACC = adrenocortical carcinoma; BLCA = bladder cancer; KIRC = clear cell renal cell carcinoma (RCC); KIRP = papillary RCC; PCPG = pheochromocytoma and paraganglioma; PRAD = prostate adenocarcinoma; TGCT = testis germ cell tumor. GS = Gleason score; NA = not available.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2

Median CNV as a function of stage and grade among genitourinary malignancies

	ACC		BLCA		KIRC		KIRP		KICH		PRAD		TGCT	
	CNV	***p* value**	**CNV**	***p* value**	**CNV**	***p* value**	**CNV**	***p* value**	**CNV**	***p* value**	**CNV**	***p* value**	**CNV**	***p* value**
T stage		0.16		0.65		0.068		0.11		0.22		0.12		0.44
T1	0.36		NA		0.11		0.15		0.94		NA		0.42	
T2	0.63		0.29		0.13		0.13		0.95		0.039		0.41	
T3	0.58		0.28		0.13		0.20		0.91		0.063		0.35	
T4	0.67		0.24		0.20		0.30		0.51 (NA)		0.11		NA	
N stage		0.40		0.72		0.39	0.15	0.41		0.48		0.0007		0.42
N0	0.59		0.24		0.13		0.23		0.94		0.048		0.41	
N1+	0.68		0.35		0.09				0.84		0.14		0.42	
M stage		0.20		0.34		0.095		0.16		0.17	NA			0.17
M0	0.58		0.28		0.12		0.17		0.95				0.41	
M1	0.73		0.42		0.14		0.23		0.87				0.47	
Grade		0.29		0.060		0.0006					NA		NA	
Low	0.86		0.12		0.10									
High	0.47		0.29		0.14									
Stage		0.10		0.73		0.068		0.12		0.36	NA		NA	
I	0.19		10 (NA)		0.11		0.16		0.94					
II	0.59		0.27		0.13		0.13		0.95					
III	0.55		0.24		0.13		0.19		0.93					
IV	0.73		0.35		0.14		0.24		0.81					
Primary GS												0.0001		
3											0.031			
4											0.075			
5											0.12			

CNV = copy number variation; ACC = adrenocortical carcinoma; BLCA = bladder cancer; KIRC = clear cell renal cell carcinoma (RCC); KIRP = papillary RCC; PCPG = pheochromocytoma and paraganglioma; PRAD = prostate adenocarcinoma; TGCT = testis germ cell tumor. GS = Gleason score; NA = not available.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3

Survival outcomes as a function of somatic MC and CNV among genitourinary malignances

	Overall survival		Recurrence-free survival	
	HR (95%CI)	***p* value**	**HR (95%CI)**	***p* value**
ACC				
MC	NA		NA	
CNV	NA		NA	
BLCA				
MC	1.8 (0.99–3.30)	0.053	1.94 (0.99–3.82)	0.055
CNV	0.95 (0.26–3.45)	0.94	1.15 (0.65–2.03)	0.63
KICH				
MC	1.003 (1.0004–1.005)	0.021	1.004 (1.002–1.007)	0.002
MC (MV)	1.004 (1.0006–1.008)	0.022	1.04 (1.01–1.07)	0.020
CNV	1.03 (0.086–12.4)	0.98	1.21 (0.10–14.3)	0.88
KIRC				
MC	1.00 (0.99–1.01)	0.55	1.00 (0.99–1.01)	0.28
CNV	1.58 (0.67–3.71)	0.29	2.46 (1.0–6.05)	0.050
CNV (MV)	NA		3.13 (1.20–8.10)	0.020
KIRP				
MC	0.99 (0.98–1.01)	0.93	1.00 (0.98–1.02)	0.76
CNV	10.3 (2.25–47.1)	0.003	9.26 (1.17–73.3)	0.04
CNV (MV)	48.6 (7.23–326.6)	<0.0001	22.02 (2.09–231.98)	0.01
PRAD[a]				
MC	NA		1.01 (0.98–1.06)	0.33
CNV	NA		5.45 (0.02–1437.7)	0.55
PCPH				
MC	NA		NA	
CNV	NA		NA	
TGCT				
MC	0.95 (0.86–1.03)		0.99 (0.97–1.02)	0.54
CNV	0.0045 (1.24e−06–16.531)	0.19	1.45 (0.15–14.3)	0.75

MC = mutation count; CNV = copy number variation; HR = hazard ratio; CI = confidence interval; ACC = adrenocortical carcinoma; BLCA = bladder cancer; KIRC = clear cell renal cell carcinoma (RCC); KIRP = papillary RCC; PCPG = pheochromocytoma and paraganglioma; PRAD = prostate adenocarcinoma; TGCT = testis germ cell tumor; NA = not available; MV = multivariable analysis controlling for stage and grade when available.

[a]Recurrence-free survival for PRAD was measured using biochemical recurrence