**Supplementary Methods**

**Targeted capture and sequence analysis**

Formalin-fixed paraffin embedded (FFPE) sections were obtained and reviewed by a genitourinary pathologist to assess for tumor content and viability. To enrich for tumor purity, macrodissection of tumor regions was performed whenever necessary prior to nucleic extraction. The average estimated tumor purity from histologic review was 46% for the UTUC cohort and 42% for the UCB cohort. DNA was extracted from formalin-fixed, paraffin-embedded tumor tissue as previously described (1). Protein-coding exons of a panel of at least 230 and up to 468 cancer-associated genes (Supplementary Table S1) were sequenced for all samples, using an institutional capture-based next generation sequencing platform (Memorial Sloan Kettering – Integrated Molecular Profiling of Actionable Cancer Targets [MSK-IMPACT]) (2). MSK-IMPACT has been extensively validated and has been optimized to detect single nucleotide variants (SNVs), indels, copy number variants (CNVs) and structural variants in genes that are functionally relevant to cancer. Matched normal DNA was available for all samples and was analyzed simultaneously to identify and filter out germline single nucleotide polymorphisms (SNPs).

Specific details on the panel design, capture protocol, sequencing, quality control, read alignment, and bioinformatic pipeline for variant calling with MSK-IMPACT have been validated and described in depth previously (2). In brief, DNA from tumor and matched normal specimens for each patient were extracted and normalized to yield 50-250ng of DNA. Specimens with low DNA yield (<50ng) following DNA extraction were deemed insufficient for sequencing. DNA was then sheared for the creation of an equimolar pool of bar-coded libraries and was subjected to targeted exon capture using custom hybrid oligonucleotides capture technology (Nimblegen SeqCap EZ library custom oligo). Deep sequencing on an Illumina HiSeq 2500 (Illumina Inc, San Diego, CA, USA) was performed for all protein-coding exons and selected introns for 230 to 468 cancer genes (Supplementary Table S1).

Sequence reads were aligned to the reference human genome (hg19) around indels to reduce alignment artifacts using the Burrows-Wheeler Alignment tool and the Genome Analysis Toolkit. Single-nucleotide variants were called using MuTect. Insertions and deletions (indels) were called using the Somatic Indel Detector tool. Copy number alterations were identified using an in-house developed algorithm, and structural variants were detected using Delly. Germline variants were eliminated through the use of patient-matched germline DNA. Each alteration identified by the pipeline was manually reviewed. Missense mutations were deemed putative drivers or passengers based on the OncoKB annotation (3). Mutational burden was calculated using the total number of non-synonymous mutations over the total number of megabases sequenced.

To determine allelic configurations, total and allele-specific copy number states were inferred using FACETS (version 0.5.6) (4). We utilized a two-pass implementation whereby a low-sensitivity run (cval = 100) first determines the purity and log-ratio corresponding to diploidy. The copy number state of individual genes is determined by a run with higher sensitivity for focal events (cval = 50).

**Microsatellite instability and mutational signature decomposition**

The proportions of instable microsatellites were identified using MSIsensor algorithm (version 0.2) (5). MSIscore was defined as the percentage of unstable microsatellite sites divided by total number of microsatellite sites tested.

Signature decomposition analysis (6,7) was performed for all tumor samples with 10 or more single nucleotide somatic mutations. From the somatic mutations in an individual tumor sample, contributions were inferred from known mutational signatures, which are probability distributions over the nucleotide change and flanking 5’ and 3’ nucleotide context of each mutation. Each mutation in the sample is viewed as a random draw from the following random process: first a mutational signature is chosen at random according to its contribution, or degree of exposure, then a mutation type is chosen at random according to that signature. This gives a mixture model, a weighted combination of signatures where the weights are unknown and sum to one, with each weight indicating the proportion of mutations in the sample attributed to that signature. These weights are inferred using an optimization algorithm that maximizes a log-likelihood function derived from this random model. Confidence intervals and quasi p-values were calculated via resampling with replacement from the observed set of mutations and performing mutational signature decomposition for all iterations. The quasi *P*-value for a particular signature was calculated as the fraction of samples with a signature proportion greater than a pre-calculated noise threshold (1 x 10-5). Signatures representing at least 15% mutations and with a significant quasi p-value (<0.05) were plotted.

**Data Availability**

Genomic and associated clinicopathologic data are publicly available through the MSKCC cBioPortal for Cancer Genomics (8).

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