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Platinum Priority – Brief Correspondence

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Genomic Predictors of Survival in Patients with High-grade Urothelial Carcinoma of the Bladder

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Abstract

Urothelial carcinoma of the bladder (UCB) is genomically heterogeneous, with frequent alterations in genes regulating chromatin state, cell cycle control, and receptor kinase signaling. To identify prognostic genomic markers in high-grade UCB, we used capture-based massively parallel sequencing to analyze 109 tumors. Mutations were detected in 240 genes, with 23 genes mutated in ≥5% of cases. The presence of a recurrent phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) mutation was associated with improved recurrence-free survival (RFS) (hazard ratio [HR]: 0.35; $p = 0.014$) and improved cancer-specific survival (CSS) (HR: 0.35; $p = 0.040$) in patients treated with radical cystectomy (RC). In multivariable analyses controlling for pT and pN stages, *PIK3CA* mutation remained associated with RFS (HR: 0.39; $p = 0.032$). The most frequent alteration, *TP53* mutation (57%), was more common in extravesical disease (69% vs 32%, $p = 0.005$) and lymph node–positive disease (77% vs 56%, $p = 0.025$). Patients with cyclin-dependent kinase inhibitor 2A (*CDKN2A*)–altered tumors experienced worse RFS (HR: 5.76; $p < 0.001$) and worse CSS (HR: 2.94; $p = 0.029$) in multivariable analyses. Mutations in chromatin-modifying genes were highly prevalent but not associated with outcomes. In UCB patients treated with RC, *PIK3CA* mutations are associated with favorable outcomes, whereas *TP53* and *CDKN2A* alterations are associated with poor outcomes. Genomic profiling may aid in the identification of UCB patients at highest risk following RC.

Patient summary: Using next-generation sequencing, we identified genomic subsets of high-grade urothelial bladder cancer associated with favorable and unfavorable outcomes. These findings may aid in the selection of patients most likely to benefit from novel combined modality approaches.

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Despite multimodality treatment, patients with bladder cancer who undergo radical cystectomy (RC) remain at high risk for recurrence. We hypothesized that the significant variability in outcomes of patients with urothelial carcinoma of the bladder (UCB) partly results from differences in the genetic changes mediating UCB development and progression [1–4]. With the goal of identifying prognostic genomic alterations, we used capture-based next-generation sequencing to analyze high-grade UCB tumors for somatic mutations in cancer-associated genes.

Tissue samples and matched germline blood from 109 patients with high-grade UCB were sequenced using MSK-IMPACT, as previously described (details in Supplemental Materials and Methods) [5]. Cohort characteristics are listed in Supplemental Table 1. Average sequence coverage was 579× across all targeted exons. An average of 10 mutations was detected per tumor (range: 0–46). Mutations were detected in 240 genes, with 23 genes mutated in ≥5% of cases (Fig. 1). As validation, we reanalyzed all samples using an orthogonal sequencing platform including all coding exons of *STAG2*, *KDM6A*, *ARID1A*, and *KMT2D* (also known as *MLL2*). Using this method, the vast majority of mutations in these genes identified by MSK-IMPACT (99.3%) were confirmed.

We analyzed mutations and copy number alterations independently and in the context of cancer-related pathways. The most common alteration was *TP53* mutation, identified in 62 patients (57%) (Supplemental Fig. 1a). Alterations in genes that regulate entry into the S phase of the cell cycle were also prevalent (46%) (Supplemental Fig. 1b). Consistent with previous reports, mutations in chromatin-modifying genes (CMGs) were highly prevalent, occurring in 83% of patients (Supplemental Fig. 1c) [1–3]. *KDM6A* was mutated in 45 patients (41%), with 41 of 45 truncating mutations. *ARID1A* alterations (28%), similarly enriched for truncating mutations (30 of 31), were mutually exclusive with *SMARCA4* alterations, suggesting potential overlapping functionality. The histone acetyltransferase genes *CREBBP* and *EP300* also exhibited a pattern of mutually exclusive truncating mutations (13% and 15%, respectively).

Alterations in the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/Akt signaling pathway, mutationally activated in many cancers, are potential therapeutic targets in UCB [4]. We identified PI3K/Akt pathway alterations in 38 patients (35%) (Supplemental Fig. 2a) Recurrent missense mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*), which encodes the α subunit of PI3-kinase, were detected in 23 patients (21%); the vast majority of the mutations were functionally validated activating helical domain mutations (Supplemental Fig. 2b). Additional recurrently mutated PI3K/Akt pathway genes included *PTEN* (6%), *AKT1* (2%), and *TSC1* (6%).

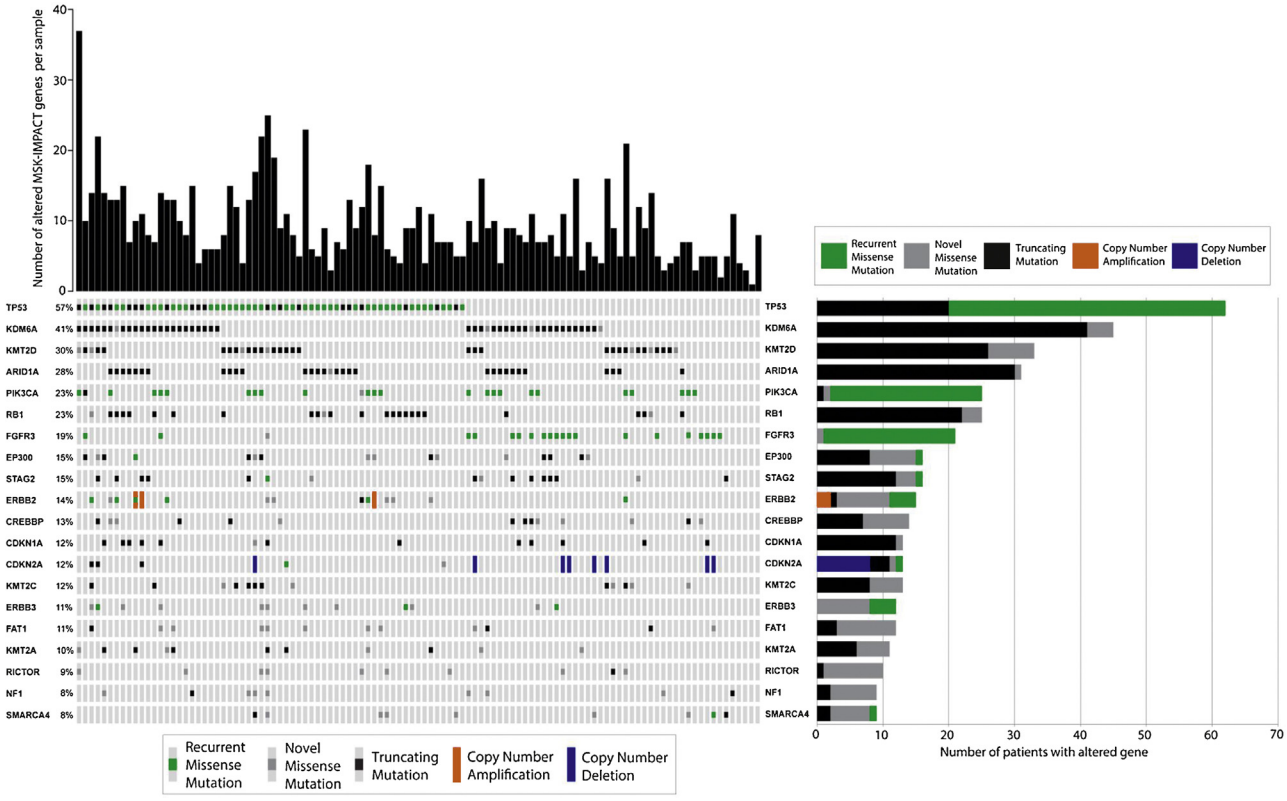

Fig. 1 – Most commonly altered genes in 109 high-grade urothelial carcinoma of the bladder tumors analyzed by MSK-IMPACT. The number of patients with alterations is depicted on the right. Alterations were categorized by type, as recurrent missense mutations, novel missense mutations, truncating mutations (frameshift, nonsense, and splice site), and copy number amplifications or deletions. The oncoprint shows the distribution of alterations across the sequenced samples. The top bar graph illustrates the number of MSK-IMPACT gene alterations per sample.