The long tail of significantly mutated genes in prostate cancer

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Background:
The mutational landscape of primary and metastatic prostate cancers have been robustly assessed through whole exome sequencing (WES) of tumors. These studies have identified multiple recurrently mutated genes that typically alter the functions of established cancer pathways, including androgen signaling, DNA repair, Wnt signaling, and PI3K signaling. Other pathways, such as splicing or SWI/SNF, have not been typically associated with prostate cancer from a somatic mutation perspective. This may be partially explained by the low mutational burden of prostate cancer. We hypothesized that mutation analysis of a uniformly analyzed large cohort of prostate cancer would reveal new significantly mutated genes and pathways.

Methods:
We assembled and uniformly analyzed a cohort of 1035 tumor and matched germline primary and metastatic prostate cancers from various sources, and performed mutational significance analysis to determine which pathways and new genes are altered recurrently but at lower frequencies in prostate cancer.

Results:
Our approach identifies previously known genes that are mutated in prostate cancer (SMGs), including SPOP, TP53, PTEN, FOXA1, APC, ATM, CDK12, CTNNB1, CDKN1B, BRCA2, RB1, PIK3CA, CHD1 and, exclusive to the metastatic subset, AR. Additional significantly mutated genes were observed that have been previously implicated in cancer, including epigenetic modifiers such as KMT2C, KMT2D, and KDM6A. Among the novel genes are SPEN (spen family transcriptional repressor), a hormone-dependent tumor suppressor, which has been implicated in breast cancer, where it acts as estrogen receptor cofactor mediating drug responsiveness. Our approach uncovers cancer pathways that were not previously addressed to play a role in prostate cancer tumorigenesis. Among these we identified frequent truncating mutations in key regulators of the SWI/SNF complex such as SMARCA1, ARID1A, ARID1B and ARID2. Moreover, we discovered a novel potential role of the splicing pathway in prostate cancer with driver mutations in SF3B1 and U2AF1. Moreover, our analysis reveals that the tail of significantly mutated genes in prostate cancer contains driver mutations in clinically actionable genes, with oncogenic mutations in BRAF, KRAS, HRAS, AKT1, PIK3CB, and inactivating mutations in PIK3R1.

Conclusions:
Through aggregation, uniform genomic analysis, and integrative molecular interpretation, we present a broader perspective of the somatic alteration landscape in prostate cancer, identify established cancer pathways not previously associated with prostate cancer as being relevant, and nominate new mutated genes as significantly mutated in this disease. This long tail of mutation highlights the diversity of prostate tumor oncogenesis.

Conflict of Interest Statement:

No conflict of interest

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