Genomic Hallmarks and Structural Variation in Metastatic Prostate Cancer

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BACKGROUND
While mutations affecting protein-coding regions have been examined across many cancers, structural variants at the genome-wide level are still poorly defined. Genomic structural variants (SVs) present in metastatic castration-resistant prostate cancer (mCRPC) include genomic deletions, insertions, tandem duplications, inversion rearrangements, and inter-chromosomal translocations. Gene fusions involving the E26 transformation-specific (ETS) family of transcription factors have been identified in 40-60% of mCRPC cases, and fusions joining androgen-sensitive genes to oncogenes have been described. However, the majority of SVs involve intergenic or intronic noncoding regions of the genome and are not captured by exome sequencing or transcriptome analysis.

METHODS
To comprehensively investigate the genomic drivers of mCRPC, we interrogated the whole genomes and transcriptomes of mCRPC samples from over 100 patients at a mean depth of 109X in tumors, a depth 2-3 times greater than that achieved in previous large WGS studies in cancer.

RESULTS
Deep sequencing of a large patient cohort permitted us to discover novel recurrent SVs and define the prevalence of these variations in mCRPC. Notably, we observed amplification of an intergenic enhancer region 624 kilobases upstream of the androgen receptor (*AR*) in 81% of patients, correlating with increased *AR* expression. Our data support the model that amplification at the putative enhancer locus results in increased *AR* expression, acting in an additive fashion with, and independently of, amplification of *AR* itself. In total, 85% of patients had either enhancer amplification or a pathogenic activating *AR* mutation. Tandem duplication hotspots also occur near *MYC*, in lncRNAs associated with post-translational *MYC* regulation. Classes of structural variations were linked to distinct DNA repair deficiencies, suggesting their etiology, including associations of *CDK12* mutation with tandem duplications and *BRCA2* inactivation with deletions. We observed chromothripsis in 23% of mCRPC patients and demonstrated that chromothripsis was significantly associated with *TP53* alterations. This observation supports the proposed but unproven mechanistic association between *TP53* alteration and chromothripsis.

CONCLUSIONS
Our study demonstrates the utility of whole genome analysis across a clinically relevant metastatic tumor cohort, as our analysis led to multiple discoveries that eluded existing exome-centric genomic investigations in the advanced disease setting. We have provided the first landscape of structural variants in mCRPC, a substantial mutational class in this disease that will serve as a repository for other researchers to continue exploring their biological and clinical significance. Together, these observations provide a comprehensive view of how structural variations affect critical regulators in metastatic prostate cancer.

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