Structural alterations in castration-resistant prostate cancer revealed by linked-read genome sequencing

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Background: Nearly all prostate cancer deaths are from metastatic castration-resistant prostate cancer (mCRPC), but there have been few whole genome sequencing (WGS) studies of this state compared with localized disease. Thus, we have an incomplete picture of alterations within the noncoding genome that may drive mCRPC.

Methods: We performed linked-read whole genome sequencing (WGS) on 23 mCRPC biopsy specimens, including 12 collected after progression on next-generation androgen pathway inhibitors. We analyzed cell-free DNA sequencing data from 86 patients with mCRPC. In addition, we analyzed paired whole exome sequencing (WES)/transcriptome sequencing(RNA) data from the PCF/SU2C cohort.

Results: In addition to frequent rearrangements affecting known prostate cancer genes, we observed diverse structural rearrangements that resulted in *AR* gain and that disrupted negative regulators of *AR*. In several cases, the *AR* locus became progressively rearranged upon progression on androgen pathway inhibitors, indicating persistent selective pressure on the *AR* axis in this setting. Unexpectedly, we observed highly recurrent tandem duplications involving a novel, mCRPC-specific enhancer of the *AR*, reminiscent of alterations seen in enhancers of other driver oncogenes and consistent with persistent addiction to AR signaling in mCRPC. Duplications involving this *AR* enhancer were observed in a majority of mCRPC cases (70-87% of mCRPC cases compared with only 2% of primary prostate cancers). Similar alterations were seen involving a putative enhancer of *MYC*. A subset of these cases displayed enhancer duplication in the context of a *CDK12*-associated genome-wide tandem duplicator phenotype, analogous to that previously observed in breast, ovarian, and localized prostate cancers. This TDP, which was also detectable in whole exome sequencing data and in whole genome sequencing of cfDNA from patients with mCRPC, was associated with biallelic inactivation of *CDK12* and mutually exclusive with rearrangements involving ETS factors.

Conclusions: Our findings highlight the complex structural genomic landscape of mCRPC, nominate new alterations that may inform precision medicine approaches, and suggest that additional recurrent events in the noncoding mCRPC genome may yet to be discovered.

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