Convergent evolution of complex structural variants drives therapy resistance in metastatic prostate cancer

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BACKGROUND
Targeted therapy prolongs the lives of men with metastatic castration resistant prostate cancer (mCRPC), but mCRPC is ultimately lethal. DNA copy gains that amplify the Androgen Receptor gene locus are a key driver of resistance to targeted therapy in mCRPC. Our group has recently shown that extra-chromosomal DNA (ecDNA) frequently drives this amplification. We hypothesized that ecDNA and other complex structural variants (cSV) also affect other drivers of therapy resistance and continue to evolve during over time.

METHODS
To test this hypothesis we reconstructed cSV profiles in 192 mCRPC tumors using transcriptome, deep whole genome, and Hi-C sequencing.

RESULTS
We identified extra-chromosomal DNA (ecDNA) in more than half of mCRPC biopsies and show it frequently amplifies both driver genes such as *AR* and *MYC* and their non-coding enhancers. The presence of ecDNA was significantly associated with whole genome doubling, chromothripsis, and with inactivating *TP53* alterations. Deep WGS analysis of 53 rapid autopsy samples showed cSV amplifying *AR* can arise independently within distinct tumors in a single patient. Phylogenetic analysis of tumor evolution implicates these cSV as an early event during metastatic spread. Paired analysis of mCRPC as patients developed resistance to AR signaling inhibitor (ARSI) therapy demonstrated cSV evolve in response to ARSI and can be detected in both solid and liquid biopsies.

CONCLUSIONS
We conclude that cSV*,* particularly ecDNA, are a pervasive contributor to intra-patient heterogeneity in late-stage mCRPC and a key driver of targeted therapy resistance.

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CONFLICTS OF INTEREST
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