Chromosome 13q deletion and lethal prostate cancer: Biomarker to cancer therapeutics

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Background: A significant portion of early prostate cancers (PC) do not progress to metastatic and lethal mCRPC, creating a clinical dilemma in early management, often leading to both overtreatment and undertreatment. Thus, understanding the molecular characteristics of aggressive primary PC is critical for developing more effective treatment strategies, enabling early risk stratification, and potentially reducing healthcare costs and the morbidity associated with overtreatment. Chromosome 13 (Chr13) is the largest acrocentric chromosome in humans, yet it has the lowest gene density among autosomes. Cytogenetic studies, conducted decades ago, identified allelic loss of Chr13q as an early marker of aggressive PC. A study involving 7,375 PC cases found that 21% of localized cases exhibited Chr13q deletion, which correlated with advanced tumor stages and early biochemical recurrence (BCR). However, the biological mechanisms and phenotypic impact of Chr13q deletion in PC progression remain poorly understood.

Methodology and results: We analyzed sequencing data from the TCGA and MSK-IMPACT cohort samples and found that a significant fraction of localized prostate cancers (PCs) and mCRPC harbor co-deletions of the Chr13q genes BRCA2 and RB1. The mRNA expression of Chr13q genes is significantly lower in PC patients who harbored the BRCA2-RB1 co-deletion (mostly heterozygous) compared to patients with unaltered Chr13q, indicating that 13q deletion in PC is typically not limited to the BRCA2-RB1 region of the chromosome. We developed 3-colored FISH probes and showed that human PC cells and mCRPC organoids that harbor single-copy deletion of BRCA2 also exhibit deletion of RB1 and demonstrate higher sensitivity to PARP inhibitors. Importantly, our 3-color FISH method not only successfully detected BRCA2-RB1 co-deletion in paraffin-embedded prostatectomy tissue samples but also demonstrated the ploidy of Chr13 and heterogeneity of Chr13q loss in primary prostate tissue. In the TCGA cohort, we observed that among patients with primary PC, those harboring both high polyploidy (ploidy score ≥3) and BRCA2-RB1 co-deletion exhibit more aggressive disease (shorter BCR survival) compared to those with high polyploidy but wildtype BRCA2 and RB1, and those with diploid (ploidy score ≤2) patients. (p_{trends}>0.0001).

Conclusion: Our study aims to systematically evaluate how Chr13q deletion impacts the progression of PC and its susceptibility to treatment. We anticipate that our study will establish a solid foundation of knowledge that can be used to identify aggressive primary PC and the related risk of progressing to lethal CRPC. This will help develop more effective treatments for patients with aggressive and lethal PC, particularly those with Chr13q..

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Conflicts of Interest Disclosure Statement

GC has served as a scientific consultant for GuidePoint and received consultation fees.

PWK has investment interest in Convergent Therapeutics, Context Therapeutics LLC, Candel Therapeutics and ESSA Pharma. He is a company board member for Convergent Therapeutics, Context Therapeutics, and Essa Pharma. He is a consultant/scientific advisory board member for ImmunisAI, Candel Therapeutics and PrognomIQ.

Patent application: GC and PWK. Methods for predicting responsiveness of prostate cancer patients to PARP inhibitors. US patent application SK2018-066-02.