

Genetic determinants of cancer hallmark activities predict prostate cancer risk and aggressiveness

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Background

Improved risk stratification for prostate cancer, a highly heritable malignancy, is required to optimize clinical decision-making. Current genetic risk models based on common variants lack specificity for disease severity and do not account for the coordinated effects of variants that converge on shared functional mechanisms.

Methods

Here, by quantifying the convergence of thousands of common genetic variants onto cancer hallmark gene sets, we developed germline-driven activity scores that estimate inherited activity of cancer hallmark mechanisms and linked them to prostate cancer risk and outcomes.

Results

In the UCLA ATLAS Biobank, germline-driven androgen response activity was associated with increased prostate cancer risk and elevated PSA levels, whereas PI3K–AKT–mTOR activity was associated with reduced metastatic risk. Using ICGC, we identified a previously unrecognized form of mechanistic germline–somatic interactions, linking the adipogenesis activity to somatic genomic instability.

Conclusions

These findings reveal that inherited risk for prostate cancer is shaped by the collective impact of genetic variation on convergent biological mechanisms underlying cancer susceptibility, lethality, and tumor evolution.

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Conflicts of Interest Disclosure Statement

Paul T. Spellman is or has been a consultant for Natera, Laboratory Corp, Foundation Medicine, Tempus, Illumina, Twist Bioscience, and Foresight. Paul T. Spellman holds an equity position in Convergent Diagnostics. All other authors declare no competing interests.