Analysis of germline modifiers of aggressive prostate cancer using cross-species variation and systems genetics

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Although prostate cancer (PC) is the most common non-cutaneous malignancy in men, the means of assessing prognosis at the time of diagnosis are inaccurate. Accordingly, there is a need to improve the molecular characterization of PC. Our goal is to identify germline modifiers of aggressive PC by breeding the C57BL/6-Tg(TRAMP)8247Ng/J (TRAMP) mouse model of neuroendocrine PC to Diversity Outbred (J:DO) mice, which are a genetically diverse outbred population. Modifier locus mapping in a cohort of 493 (TRAMP x J:DO) F1 males revealed one locus spanning 3.3Mb on Chromosome 8 associated with distant metastasis (LOD=8.42, P=5.3x10-6). Eleven candidate genes within this locus were identified by integrating trait-correlation and expression quantitative trait locus data derived from RNA-seq analysis of 195 (TRAMP x J:DO) F1 tumors. The relevance of these eleven genes to aggressive human PC was investigated via in silico validation, which included three independent PC gene expression datasets and two PC genome-wide association studies (GWAS), encompassing data from over 5,300 PC patients. Three genes (RWDD4, CENPU, and CASP3) harbored variants associated with aggressive PC in GWAS analyses, and had expression levels associated with survival in all PC gene expression datasets. Dysregulation of RWDD4 and CENPU increased in vivo and in vitro aggressiveness of two human PC cell lines. Transcriptomic analysis of these cell lines revealed dysregulation of multiple tumor progression-associated pathways. This study demonstrates the utility of systems genetics as a means to define novel hereditary modifiers of aggressive PC.

Conflicts of Interest: None

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