Novel epidemiological and computational genomic approaches to explore the missing heritability of primary and metastatic prostate cancer

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PC is also one of the most heritable cancers. Several twin and family studies have shown that up to 60% of PC risk can be attributed to inherited genetic defects. Over the last decades, several Mendelian PC predisposition genes, such as *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *NBN*, *PALB2*, and *HOXB13*, were described. However, germline mutations in these PC risk genes explain the cancer risk in under 5% and 10% of primary and metastatic PC patients respectively, clearly indicating the presence of additional undiscovered inherited PC susceptibility defects. In this study, we explore the "missing heritability" of PC by using robust epidemiological and computational genomic approaches to identify novel PC susceptibility genes and pathways. First, we leverage the concept of allelic genetic drift to dissect the inherited genomic alterations in a large cohort of Arab primary and secondary PC patients. Being genetically very distinct from the European populations, analyzing the germline genomic architecture of the Arab PC patients provides a unique opportunity to explore novel population-specific genetic defects driving PC susceptibility and progression in such populations. In addition to characterizing novel PC susceptibility genes using population genetics, we here explore the utility of novel integrative computational frameworks that uses paired germline DNA and RNA sequencing data to infer the functional impact of splice-site variants as well as non-coding intronic and epigenetic alterations, which are currently categorized as variants of unknown significance (VUSs). Such analysis approach aims to overcome the well-recognized limitation of the DNA-based molecular testing to identify pathogenic germline alterations that are not currently captured by standard testing pipelines. Overall, this study aims to use novel epidemiological and computational approaches to expand what is known about the heritability of primary and metastatic PC and to identify novel inhered genomic determinants of PC initiation, progression, and chemoresistance. By delineating PC susceptibility in Arab PC patients, we will have the ability to explore new mechanisms for PC risk and tumorigenesis, which can potentially provide new avenues to implement PC screening and prevention strategies. Furthermore, this study, through integrative analysis of DNA sequencing and RNA expression data, would substantially improve our ability to identify patients with clinically-actionable pathogenic defects in the PC risk genes that are not currently captured by standard DNA-based clinical testing. Collectively, identification of novel inherited PC risk alleles is expected to improve the diagnostic yield of genetic testing and capture more individuals and families with high inherited cancer risk where enhanced PC screening and prevention measures can be implemented.

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