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Systematic evaluation of underlying defects in DNA repair as an approach to case-only assessment of familial prostate cancer

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Abstract

Risk assessment for prostate cancer is challenging due to its genetic heterogeneity. In this study, our goal was to develop an operational framework to select and evaluate gene variants that may contribute to familial prostate cancer risk. Drawing on orthogonal sources, we developed a candidate list of genes relevant to prostate cancer, then analyzed germline exomes from 12 case-only prostate cancer patients from high-risk families to identify patterns of protein-damaging gene variants. We described an average of 5 potentially disruptive variants in each individual and annotated them in the context of public databases representing human variation. Novel damaging variants were found in several genes of relevance to prostate cancer. Almost all patients had variants associated with defects in DNA damage response. Many also had variants linked to androgen signaling. Treatment of primary T-lymphocytes from these prostate cancer patients versus controls with DNA damaging agents showed elevated levels of the DNA double strand break (DSB) marker ?H2AX ($p < 0.05$), supporting the idea of an underlying defect in DNA repair. This work suggests the value of focusing on underlying defects in DNA damage in familial prostate cancer risk assessment and demonstrates an operational framework for exome sequencing in case-only prostate cancer genetic evaluation.

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Keywords

Case-only study, DNA damage response, Familial prostate cancer, Genetic susceptibility to prostate cancer, Whole exome sequencing