Editorial Commentary

Better screened than sorry!—an informed panel of inherited DNA repair gene variants for prostate cancer screening and prognostication

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DNA repair gene (DRG) alterations have been established as an emerging class of biomarkers and targets for cancer therapies. Although mutations interfering with specific DNA repair pathways have been characterized and exploited mainly in breast and ovarian cancers, the recent identification of a fraction of primary and metastatic prostate cancer (PCa) patients harboring similar defects has opened up for testing DRG mutation-induced vulnerabilities also for this disease (1,2). Enthusiasm was especially triggered by seminal work by Mateo *et al.*, which highlighted the clinical efficacy of exploiting DRG alterations by reporting preferential positive response to PARP inhibition in metastatic castration resistant prostate cancer (mCRPC) patients (3). Altogether this suggested a novel class of biomarkers to molecularly stratify mCRPC patients and increased the interest in the identification of additional DRG alterations in PCa patients.

PCa represents a common and clinically heterogeneous disease entity, one of the most heritable of human cancers and a leading cause of cancer-related death in males worldwide (4,5). Nearly all PCa patients are diagnosed with adenocarcinomas that show a broad range of clinical behaviours, from relatively indolent to metastatic progression and lethality. Even though most of PCa patients are successfully treated with surgery or radiation therapy, a fraction of men relapses and progresses to an incurable metastatic stage.

The identification of markers to distinguish indolent from aggressive disease at time of diagnosis together with the characterization of markers for treatment stratification at time of androgen deprivation therapy resistance are among the biggest challenges in the setting of PCa translational research.

Given the strong hereditary component of PCa (4), the identification of genetic markers for disease development and progression have been studied over the last two decades. The recent advances in high-throughput, genome-wide profiling technologies have further enabled the discovery and characterization of genetic variants associated with PCa predisposition, including inherited mutations in several genes involved in DNA damage repair. Accordingly, early studies associated germline mutations of *BRCA2* with the development of an aggressive form of PCa and with poor survival (6,7). In 2016 Pritchard and colleagues reported an increase in the prevalence of germline DRG mutations (in a panel of 20 DRGs) in mCRPC patients (11.8%) compared to localized PCa patients (4.6%), arguing that germline DRG variants are associated with a more aggressive disease (8). Supporting this association, further studies comparing aggressive and indolent PCa patients provided evidence that germline variants within a restricted list of DRGs (involved mainly in the homologous recombination

repair pathway) contribute to metastatic PCa predisposition (9,10). However, following data of mCRPC patients from a prospective study suggested that only *BRCA2* germline mutations are prognostic factors and that there is no significant association between other DRG germline variants and patients outcome (11). Nevertheless, the debate concerning the association between other DRG mutations and PCa is still ongoing.

In this scenario, Leongamornlert *et al.* recently reported the results of a screening of 167 genes involved in 8 DNA damage response and repair pathways within a UK-based cohort of 1,281 young-onset PCa cases and 1,160 controls selected for either no family history for the disease or low PSA level (12,13). By performing targeted sequencing of exonic regions of a total of 175 genes using healthy cells DNA (final target regions consisted of about 1.5 Mbp), the study identified a total of 233 protein truncating variants, including frameshift indels, stop gain, and splice variants. Of those, 80 are part of the BROCA panel of cancer predisposition genes (http://web.labmed.washington.edu/tests/genetics/BROCA_VERSIONS) (14). Among the identified inherited variants, 6 variants in the *XPC* gene (Xeroderma pigmentosum, complementation group C) were associated with aggressive phenotype (defined as Gleason score ≥8) and a single nucleotide variant in *NBN* (Nibrin) was established in the gene-level case-control analysis as associated with PCa predisposition, together with marginally associated variants in *HOXB13* and in *POLL*. The gene-set-level analysis performed with adaptive combination of P values (ADA) led to the definition of two gene-sets: one predisposition panel (Predis18: *RNASEL*, *BRCA2*, *POLE*, *POLM*, *CHEK2_1100del*, *RECQL4*, *MSH5*, *ATM*, *CHEK2_non1100del*, *BLM*, *ERCC3*, *GEN1*, *NHEJ1*, *PARP2*, *POLD1*, *CDC25C*, *MSH2*, *NEIL2*, *TDP1*, *LIG4* and *BRCA1*) with significant enrichment among PCa cases compared to controls, and one aggressive panel (Agg4: *BRCA2*, *MSH2*, *ERCC2*, *CHEK2_non1100del*), whose carriers showed significant association with clinical variables denoting aggressive disease (higher PSA, Gleason score ≥8, higher tumor stage, and nodal spread). When testing association with overall survival and disease-specific survival, carriers of the Agg4 panel demonstrated significantly worse clinical behaviour.

The study of Leongamornlert *et al.* confirmed previous results related to an enrichment for *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *GEN1* variants [genes already identified by Pritchard *et al.* (8)] in PCa cases compared to controls and, additionally, provided an extended list of DRGs that could be potential candidates for clinical screening and risk profiling.

There are several features empowering the findings of this work. First, the use of a large cohort including more than one thousand PCa cases and controls matched for genetic ancestry and with comparable age, and the selection of the control set with absence of PCa family history or low PSA levels (<0.5 ng/mL) significantly improve the statistical power of the study allowing for the detection of rare variants. Second, the selection of a young-onset (diagnosed at ≤60 yr) PCa patients' cohort provides a great opportunity to identify novel variants associated with increased risk for this disease. Indeed, young men diagnosed with PCa have greater genetic risk compared to older patients (15). Furthermore, high-grade early-onset PCa patients showed worse prognosis compared to late-onset PCa (16,17). Third, compared to previous studies in which only highly selected genes were analysed, the work of Leongamornlert *et al.* includes a large panel of genes (167 genes) involved in several DNA repair pathways and in cell cycle regulation. Additionally, 8 PCa related genes and predisposition candidates (such as *AR*, *HOXB13* and *SPOP*) were included in the analyses. Finally, the long follow up time of the patients represents an additional value of the study.

While the study from Leongamornlert *et al.* presents the most comprehensive design in the setting of DRG variants, additional work would augment its relevance and, more broadly, the understanding of the role of DRG mutations in PCa aggressiveness and in the response to different treatments. For instance, since the disease risk varies substantially based on ethnicity (18), DRG variants incidence should be evaluated across ancestries; germline and somatic variants should be jointly assessed to fully understand DRG role in aggressive disease, as the frequency of DRG alterations significantly increases when both components are considered (19-21). Additionally, the response of DRG mutation carriers to PCa specific treatments should be eventually investigated in large cohorts to clarify the role of DRG mutations as predictive biomarkers.

Studies as the one of Leongamornlert *et al.* represent a unique opportunity to identify rare genetic variants to be used for PCa screening and prognostication. On one side, these data can inform on PCa susceptibility and aggressiveness leading to earlier diagnosis and driving patient enrolment either in active surveillance or

therapeutic intervention programs. On the other, they could contribute to the molecular stratification of PCa patients for personalized therapy and expose additional vulnerabilities expanding PCa therapeutic opportunities.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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