Review

Current progress and questions in germline genetics of prostate cancer

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Abstract Dramatic progress has been made in the area of germline genetics of prostate cancer (PCa) in the past decade. Both common and rare genetic variants with effects on risk ranging from barely detectable to outright practice-changing have been identified. For men with high risk PCa, the application of genetic testing for inherited pathogenic mutations is becoming standard of care. A major question exists about which additional populations of men to test, as men at all risk levels can potentially benefit by knowing their unique genetic profile of germline susceptibility variants. This article will provide a brief overview of some current issues in understanding inherited susceptibility for PCa.

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1. Introduction

While over 1,111,700 men are diagnosed with prostate cancer (PCa) each year worldwide, fortunately a much smaller number (307,500) eventually die from this disease [1]. Understanding the role played by inherited factors in the progression of PCa to lethal disease has important translational impact on the detection, diagnosis and prognosis of this common cancer. Specifically, being able to predict which men are more likely to develop a lethal PCa vs. an indolent one is currently an unmet clinical need.

Twin studies indicate that PCa is among the most heritable of all common cancers [2,3]. The past 10–12 years have seen dramatic progress in elucidating molecular factors affecting PCa susceptibility, with both common, single-nucleotide polymorphisms (SNPs) and rare genetic variants (high penetrance genes) playing fundamental roles.

2. Genetic risk score (GRS) and PCa

Since 2007, many PCa risk-associated SNPs have been identified through genome-wide association studies.
(GWAS). To date, more than 163 SNPs have been consistently associated with risk of PCA [4]. SNPs are among the primary inherited determinants affecting gene expression and causal PCA risk SNPs, like those associated with other cancers, or other traits in general, are typically located in regulatory elements, e.g. gene promoters and enhancers, and can act as on-off or dimmer switches for individual gene expression levels and regulation.

Each SNP has a very modest individual effect on disease risk odds ratios (ORs: 1.05–1.20) but together they have a much stronger effect [5]. This cumulative effect can be measured using a GRS, a type of polygenic risk score, based upon one’s genotype for a panel of risk associated SNPs [6]. GRS is weighted by the ORs of each SNP and is population-standardized, and making it accurate and easy to interpret. For example, GRS can be interpreted as a relative risk (RR) for the general population regardless of how many SNPs are used for the GRS calculation. A GRS of 1 indicates average risk. A GRS less than 1 and a GRS greater than 1 indicate lower risk and higher risk than the general population, respectively.

The clinical validity of GRS, i.e., the ability of GRS to accurately stratify risk, has been consistently established in many well-designed studies, including large case–control studies with samples sizes over 100 000 subjects [4,7], clinical trial populations [8–11], clinical prostate biopsy cohorts [12,13], and prospective studies [14]. In the largest genetic association study performed to date [4], GRS was significant associated with PCA risk among 140 000 subjects. Compared to men in the 25th and 75th percentile of GRS, men in the 90th–99th percentile and top 1 percentile have RRs of 2.69 (95% confidence interval (CI): 2.55–2.82) and 5.71 (95% CI: 5.04–6.48), respectively.

There are several important clinical utilities of GRS. First, GRS can supplement family history information and the presence of mutations in high(er)-penetrance genes (HPGs) such as breast cancer susceptibility genes (BRCA2), ataxiatelangietasia mutated (ATM), and homeobox b13 (HOXB13), to identify high-risk men for prostate-specific antigen (PSA) screening. In fact, more high-risk men in the general population can be identified through GRS than by family history and HPGs [11]. Second, GRS has a strong impact on PCA penetrance for HPG carriers. For example, in a large study of 933 male BRCA2 carriers, the penetrance for PCA by age 85 was 40% among all the carriers but was 70% and 24% if their GRS was at top and bottom 5 percentile, respectively [15]. Third, GRS can also be used to supplement clinical variables such as PSA, PSA density, and digital rectal examination for decision making of prostate biopsy [8–13]. These results emphasized the compelling rationale for the translation of the use of GRS profiling to identify men most likely to benefit from PCA disease screening.

3. Genetic risk factors for lethal disease

As mentioned above, the most recent discoveries from Schumacher et al. [4] and Dadaev et al. [16] bring the number of common PCA risk SNPs to over 160, explaining an ~28% of familial relative risk for PCAs. A major limitation of these markers, however, is that few if any of these germline sequence variants can, individually or in combination, differentiate risk for an aggressive from indolent form of PCAs [4,17]. Does this mean that inherited genetic variants specifically associated with aggressive PCAs do not exist? To the contrary, study designs used in the past where a majority of patients studied have less aggressive disease undoubtedly presented a major barrier to discovery of genetic determinants of an aggressive PCA phenotype. In other words, quite simply, in order to find genetic risk factors for lethal PCAs, one must study lethal PCAs. Surprisingly, until recently, there have been very few large-scale sequencing studies of men with metastatic/lethal PCAs.

Most previous studies searching for germline variants predisposing to more aggressive disease have been limited by the relatively small numbers of men with lethal or metastatic castrate resistant prostate cancer (mCRPC) that have been available for analysis. Indeed, most large study cohorts of PCA patients that have been available for study are derived from men undergoing surgical treatment for PCA (i.e., clinically localized disease), or are population-based, being composed of a representative distribution of patients in terms of tumor stage and grade. Since in the era of PSA screening most PCAs diagnosed is well differentiated and clinically localized with very few lethal events, these cohorts are largely composed of cases that are understood to be de-enriched in men carrying significant germline risk factors for aggressive disease. This “dilution” factor has also been a major barrier to the success of studies using family history to enrich for genetic factors for PCAs, since, again in the PSA era, many PCAs families selected only on the basis of a PCA diagnosis, irrespective of disease stage or grade, are clusters of men with the form of PCA which is present at a very high frequency in the population, that is, small volume, organ confined, well differentiated disease. This form of PCA is highly likely to be indolent, and by virtue of its occurrence in the majority of aged men, highly unlikely to be driven by rare high penetrance cancer susceptibility genes.

A major reason for these suppositions comes from multiple recently reported sequencing studies of germline DNA of a particularly important segment of the PCA patient population, that is, men with mCRPC. Two landmark papers are of particular importance in this regard. Robinson et al. [18] identified mutations in three DNA repair genes, BRCA1, BRCA2, and ATM, at a surprisingly high rate in men unselected for age at diagnosis or family history, but rather for aggressive disease. Of 19 patients with biallelic inactivation of BRCA2, half had inherited a mutated inactive copy, a frequency 4 to 5 times higher than observed in previous studies of PCA patients. Subsequently, Pritchard et al. [19] demonstrated an elevated rate of germline mutations in a number of DNA repair genes in men with metastatic PCAs. Importantly, the combined frequency of pathogenic mutations in a set of genes including BRCA2 and ATM was higher than that reported in either the Exome Aggregation Consortium (ExAC) database of 53 000 unselected individuals or in the Cancer Genome Atlas (TCGA) database of men with clinically localized PCAs.

Many previous studies had indicated that BRCA2 was an important gene for PCA susceptibility. In 1997, Sigurdsson et al. [20] described the association of a deleterious founder mutation in BRCA2 with aggressive PCAs in Icelandic
families. Subsequently, multiple studies confirmed the link between PCs and BRCA2 emphasizing BRCA2 as a strong risk factor [21–23]. Castro et al. [25] and others have described and characterized BRCA2 as an important prognostic factor for aggressive PCs [24–29]; however, the mutation frequency was low and most estimates suggested that BRCA2 accounted for a very small fraction of PCs (1%–2%), even when early onset family history, positive cases were examined [30–32].

The studies by Robinson et al. [18], Pritchard et al. [19], and other similar studies, for the first time, provide strong evidence that inherited mutations may contribute to a substantial fraction of lethal PCa etiology and that such mutations can be exploited for differentiating risk for aggressive from indolent PCa [33]. Additional, critically important aspects of these findings are the therapeutic implications that arise as a result of PCs patients harboring drug-sensitizing mutations in DNA repair genes (e.g., the use of poly ADP-ribose polymerase [PARP] inhibitors to create a synthetic lethality in cancer cells deficient in homologous recombination repair due to deleterious mutations in BRCA2 and other homologous recombination repair genes), as described by Mateo et al. [34], and the far reaching implications that inherited pathogenic mutations can have for family members [35].

While promising, largely due to mutation rarity, larger studies are urgently needed to better catalog germline pathogenic mutations in lethal PCa patients. More importantly, in-depth studies of large, well annotated patient populations are needed to establish associations between these mutations and lethal PCa, and to assess whether they can differentiate risk of lethal/aggressive PCa from indolent PCa.

4. Interaction of somatic and inherited genetic alterations to lethal/aggressive PCa

While somatic mutations play a required role in carcinogenesis, it is upon the fixed background of one’s inherited genotype that these somatic mutations arise and contribute to the carcinogenic and tumor progression process. As such, the inherited genotype can have an impact on the spectrum of somatic alterations that lead to cancer development and behavior. To what extent genetic factors affect overall PCa aggressiveness is still debatable.

Epidemiological data provide support for heritability of aggressiveness of PCs. For example, PCa patients are found to be more likely to die of the disease if their father died of PCa [36]. Using a population-based database that includes ~3 million families to analyze the relationship of survival between sons and their fathers, Lindström et al. [36] found an increased hazard ratio of 2.07 (95% CI:1.13–3.79) for death from PCa in sons with poor father survival compared with those with good father survival, suggesting a genetic susceptibility for lethal PCa.

4.1. Somatic mutations

Intensive efforts have been devoted to identifying and characterizing somatic mutations in prostate tumors. Indeed, a wide array of DNA copy number alterations [37–48], fusion genes [37,49–62], and point mutations [18,44,63–75] have been discovered. A recent study documented over 100 genes which were mutated at significant rates in PCs, marking the first time a comprehensive catalog of mutations in both localized and metastatic PCs is readily available [76]. Excitingly, somatic DNA alterations in TP53, PTEN, CDK12, RB1, BRCA2, MYC and AR, have clearly emerged as being among the most common and important drivers of metastatic/lethal vs. indolent disease.

4.2. Inherited mutations may influence susceptibility to somatic alterations via variations in DNA repair ability

Although somatic alterations may occur in cancer cells as a response to internal or external stress, the inherited genome can modulate the degree and types of these somatic alterations. A clear example of this is microsatellite instability resulting from mismatch repair defects in cancer cells which have mutations in mismatch repair genes including MLH1, MSH2, MSH6, and PMS2. Cancer cells with bi-allelic inactivation of these genes through either inherited or somatic loss of function (LOF) mutations, loss of heterozygosity (LOH) or both are characterized by hundreds to thousands of point mutations and small indels throughout the genome. Clinically, due to the high number of neoantigens generated by this hypermutation phenotype, patients with mismatch repair defects are prime candidates for checkpoint blockade and other evolving immunotherapies [77]. Intriguingly, genomic rearrangements associated with somatic CDK12 mutations may elicit similar therapeutically relevant immunogenic neoantigens [78].

In PCs the genetic instability incurred when critical DNA repair genes and pathways are inactivated may drive tumor progression to a more lethal phenotype, possibly by direct mutational inactivation of genes suppressing invasion or other aspects of the metastatic process.

Similarly, the inability to repair double strand breaks by virtue of inactivating mutations in homologous recombination repair genes can generate specific genomic signatures of copy number changes, and other mutational events [79]. In this context, the survival and clonal expansion of cancer cells with increased genetic instability due to DNA repair defects reflects a balance between decreased fitness as a result of compromised ability to repair DNA and the selective prosurvival, proproliferation states afforded by inactivation of genes involved in apoptosis/tumor suppressor/checkpoint inhibition and deregulated growth promoting pathways.

5. Summary and conclusions

It is becoming apparent that stratification of men at all risk levels is possible using germline genetic markers: Men undiagnosed for PCs can benefit from knowing their risk of any PCa diagnosis as determined by common genetic variants, as well as their risk of aggressive/lethal disease, as conferred by rare pathogenic mutations in genes like BRCA2 and ATM. Men diagnosed with low risk PCs can be informed of their suitability for treatment by active surveillance [80], and men diagnosed with high risk disease can benefit by...
identification of optimal treatment regimens. Using a combination of common and rare genetic variants, a personalized program of disease screening before diagnosis, and disease management and treatment after diagnosis can be designed.

Some of the recent progress in the area of PCa genetics is summarized below:

- Loss of function mutations in DNA repair genes are present in ~5%–20% of lethal PCa cases. The repair genes most frequently sequenced are derived largely from the breast ovarian cancer (BROCA) panels used for genetic testing in breast and ovarian cancers. These panels typically include *BRCA1* and *BRCA2*, **ATM**, **BARD1**, **BLM**, **BRIP1**, **CHEK2**, **ERCC2**, **FANC** genes, **MSH2**, **MSH6**, **NBN**, **PALB2**, **PMS2**, **PTEN**, **RAD51B**, and **RAD51C**, **TP53**, and **WRN**. These genes represent the major DNA repair pathways, with emphasis on homologous recombination and mismatch repair pathways. The variation of frequencies of mutations reported in different studies is the result of 1) different sets and different numbers of DNA repair genes being assayed, and 2) differing numbers of carriers of founder mutations, particularly in *BRCA2* (e.g. S1982fs Ashkenazi founder mutation) in different study populations. These founder mutations can substantially alter the mutation frequencies observed in different study populations.

- In virtually all published series of genetic testing in men with advanced PCa (CRPC) *BRCA2* is consistently observed to be the most frequently mutated gene, followed by **ATM** and **CHEK2**. Mutations in *BRCA2* and **ATM** are the only genes which are consistently observed to be more common in cases with lethal disease vs. indolent disease; possibly **CHEK2**, **PALB2** and **MSH2** also may distinguish risk for more aggressive disease but more data are needed.

- Somewhat surprisingly, the likelihood of inherited mutations in DNA repair genes in an individual is largely unrelated to family history of PCa [19]. A family history of other adenocarcinomas, particularly of the breast, pancreas, and/or colon, is just as predictive, if not more so, than a family history positive for PCa. This is likely not the case for individuals having multiple family members with advanced PCa, particularly at young age.

- A critical characteristic of common variants is their ability to affect the penetrance of *BRCA2* and most likely other high penetrance genes.

- Much more whole exome sequencing data are needed to identify novel genes associated with susceptibility and/or treatment sensitivity. So far, **HOXB13** is the only non-DNA repair genes discovered that is consistently associated with inherited risk for PCa [80].

### 6. Questions

When and who to screen with germline genetic testing?

Should all men be tested?

What variants should be tested for?

Which genes are most prognostic? Are there genes other than *BRCA2* and **ATM** which are consistently associated with high risk disease, and if so how can we find them? Currently only 15% or less of men with advanced disease harbor a pathogenic germline DNA repair gene mutation.

Do common variants affect the penetrance of all high penetrance genes?

What is the spectrum of high penetrance gene mutations in African Americans? Can these genes explain any of the high incidence and mortality rates from PCa in this understudied high risk population?

### Author contributions

**Study design:** William B. Isaacs, Jianfeng Xu.

**Drafting of the manuscript:** William B. Isaacs, Jianfeng Xu.

**Critical revision of the manuscript:** William B. Isaacs.

### Conflicts of interest

The authors declare no conflict of interest.

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