Genome Medicine

REVIEW

Prostate cancer genomics: can we distinguish between indolent and fatal disease using genetic markers?

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Abstract

Prostate cancer is one of the most heritable cancers in men, and recent genome-wide association studies have revealed numerous genetic variants associated with disease. The risk variants identified using case-control designs that compared unaffected individuals with all types of patients with prostate cancer show little or no ability to discriminate between indolent and fatal forms of this disease. This suggests different genetic components are involved in the initiation as compared with the prognosis of prostate cancer. Future studies contrasting patients with more and less aggressive disease, and exploring association with disease progression and prognosis, should be more effective in detecting genetic risk factors for prostate cancer outcome.

Prostate cancer

Prostate cancer constitutes a major health burden, being the most common non-cutaneous malignancy among men in developed countries. In 2007, almost 800,000 new cases of prostate cancer and 250,000 deaths from this disease were estimated to have occurred worldwide [1]. The highest incidence of prostate cancer is observed in the USA, with 192,280 new cases and 27,360 deaths expected in 2009, thereby being the second most common cause of cancer-related death [2]. Prostate cancer is a heterogeneous disease and its natural history is not completely understood. Early autopsy studies have shown a high prevalence of clinically undetected prostate cancer at time of death. In the USA, more than one in three men over 50 years of age had histologic evidence of prostate cancer at autopsy and this prevalence was observed to increase with age, with more than 67% of men aged over 80 years having prostate cancer at time of death [3]. These findings indicate that a high proportion of prostate tumors are clinically insignificant and will never lead to a lethal outcome. Furthermore, the introduction and widespread application of prostate-specific antigen (PSA) testing has led to increased detection of early-stage, low-volume, non-palpable tumors. This has in turn raised concerns of increased overdiagnosis and unnecessary treatment of indolent disease [4,5]. To this end, new strategies to help clinicians distinguish between lethal and indolent prostate cancer are urgently needed. Prostate cancer is one of the most heritable cancers in men and recent studies have revealed numerous genetic variants associated with this disease. This review will give an overview of the current knowledge of prostate cancer genetics, with a special focus on the ability of genetic variants to predict more aggressive forms.

Prostate cancer susceptibility variants

A family history of prostate cancer is one of the strongest risk factors, and twin studies suggest that as much as 42% of the disease risk is explained by heritable factors [6]. Attempts to decipher the heritable component of prostate cancer based on candidate gene association studies and genome-wide linkage studies in multiple case families have suggested numerous prostate cancer susceptibility genes and loci. However, an inability to replicate reported linkage and association findings suggest that prostate cancer is genetically complex with multiple common low-penetrance genes involved in prostate cancer predisposition [7]. Recently, genome-wide association studies (GWAS) have emerged as a powerful method to identify genomic low-risk susceptibility regions for complex diseases, including cancer [8]. Through genotyping platforms that explore hundreds of thousands of single nucleotide polymorphisms (SNPs) simultaneously, it is possible to screen the complete genome for common genetic variation associated with the disease of interest. In 2006 the first prostate cancer susceptibility region was identified at chromosome 8q24.

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This region was initially identified through linkage analysis in Icelandic families with prostate cancer, followed up by association analysis in three independent case-control populations [9], and separately through admixture mapping in African Americans [10]. Subsequent GWAS and region-focused studies have revealed five distinct linkage disequilibrium blocks harboring prostate cancer susceptibility alleles at 8q24 [11-17]. The 8q24 region has also been shown to harbor susceptibility alleles for breast cancer [18], colorectal cancer [19], bladder cancer [20], and ovarian cancer [14]. The 1.2 Mb sequence at 8q24 containing all observed risk alleles does not code for any known genes, and the biologic mechanisms underlying these associations are unknown. The oncogene c-*Myc* is the closest distal gene to this region and it has been suggested that the observed associations reflect long-range control of *Myc* expression; however, further functional studies are needed to reveal the role that these variants play in cancer susceptibility. To date, 29 distinct genetic loci harboring prostate cancer risk alleles have been identified and consistently replicated (Table 1). In general, the effect of variants in these regions on prostate cancer risk is modest, with odds ratios typically ranging between 1.1 and 1.3. It has been estimated [21] that hitherto identified variants together explain approximately 22% of the familial risk of prostate cancer, and it is anticipated that many more prostate cancer susceptibility variants will be identified in the future.

Prostate cancer susceptibility variants and disease aggressiveness

To date there is no reliable way of predicting whether prostate cancer will be an aggressive, fast-growing disease or a non-aggressive, slow-growing type of cancer. In general, a combination of tumor staging (using the tumor, node, metastasis staging system [22]), tumor grading (using the Gleason scoring system [23]) and diagnostic PSA serum levels are used to classify patients into different prognostic risk groups to guide clinicians in treatment decisions. In genetic association studies, patients with prostate cancer are commonly classified as having a more aggressive form of the disease if they fulfill any of the following criteria: (1) disease spread outside of the prostate gland, or presence of cancer in the lymph nodes or other metastatic sites; (2) presence of poorly differentiated cancer as indicated by a high Gleason score (that is, 4 + 3 = 7 or higher); or (3) a serum PSA level associated with a high likelihood of extensive disease (that is, >20 ng/ml).

Several studies have explored the capacity of established prostate cancer risk variants to distinguish between less aggressive and more aggressive disease [9-13,24-46]. Overall, results are inconclusive, with some studies reporting stronger associations for some of these variants among patients with more aggressive prostate cancer, while others did not. In a large replication study from the PRACTICAL (Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome) consortium, which evaluated genetic variants at chromosome 3p12, 6q25, 7q21, 10q11, 11q13, 19q13 and Xp11 among 7,370 prostate cancer cases and 5,742 controls, no association with tumor grade was observed for any of the explored variants [45]. Fitzgerald and coworkers assessed the same seven variants and an additional six variants at chromosome 7p15, 8q24, 10q26, and 17q12 in a population-based study comprising 1,308 cases and 1,267 controls for association with family history and clinical features of more aggressive disease [46]. No association was observed between any of the evaluated risk variants and a composite measure of disease aggressiveness; however, two variants, rs10993994 at 10q11 (P = 0.02) and rs5945619 at Xp11 (P = 0.03), were nominally significantly associated with Gleason score.

Most of the published studies exploring established risk variants with respect to prostate cancer aggressiveness have had several limitations, including small sample size, heterogeneous definition of aggressive disease across multiple study populations, and reliance on clinical grading and staging of tumors. To address these limitations, Kader and coworkers evaluated 20 established risk variants in 17 distinct genomic regions among 5,895 patients with prostate cancer who were of European descent and who underwent radical prostatectomy for treatment of prostate cancer [47]. Based on the entire prostate gland, each tumor was uniformly graded and staged using the same protocol. Tumors with pathologic Gleason scores of 4+3 or higher, or pathologic stage of T3b or higher, or non-organ confined disease, were defined as more aggressive disease (N = 1,253); tumors with organ confined disease, pathologic Gleason score of 3+4 or lower, and pathologic stage of T2 were classified as less aggressive disease (N = 4,233). For 18 of the 20 variants explored, no significant difference was observed in risk allele frequencies between patients with more aggressive and less aggressive disease. Two variants were significantly associated with disease aggressiveness: SNP rs2735839 downstream of the kallikrein 3 gene (*KLK3*; $P = 8.4 \times 10^{-7}$), which is the gene coding for PSA; and SNP rs10993994 in the microseminoprotein β gene (*MSMB*; P = 0.046). To reduce the possible impact of heterogeneity in the definition of aggressive disease, risk variants were also tested for association with Gleason score and pathological stage separately. SNP rs2735839 in the *KLK3* gene ($P = 7.7 \times 10^{-6}$) and SNP rs10993994 in the *MSMB* gene (P = 0.02) were the only variants associated with Gleason score. For tumor stage, only SNP rs2735839 in the *KLK3* gene was significant ($P = 1.9 \times 10^{-4}$). Of note,

Table 1. Established prostate cancer susceptibility alleles

dbSNP number	Chromosome	Gene[a]	Risk allele[b]	Study
rs1465618	2p21	*THADA*	A	Eeles *et al*. 2009 [21]
rs721048	2p15	*EHBP1*	A	Gudmundsson *et al*. 2008 [27]
rs12621278	2q31.1	*ITGA6*	A	Eeles *et al*. 2009 [21]
rs4857841	3q21.3	*EEFSEC*	A	Gudmundsson *et al*. 2009 [57]
rs12500426	4q22.3	*PDLIM5*	A	Eeles *et al*. 2009 [21]
rs17021918	4q22.3	*PDLIM5*	C	Eeles *et al*. 2009 [21]
rs7679673	4q24	*FLJ20032*	C	Eeles *et al*. 2009 [21]
rs9364554	6q25.3	*SLC22A3*	T	Eeles *et al*. 2008 [28]
rs10486567	7p15.2	*JAZF1*	G	Thomas *et al*. 2008 [26]
rs6465657	7q21.3	*LMTK2*	C	Eeles *et al*. 2008 [28]
rs1512268	8p21.2	*NKX3-1*	T	Eeles *et al*. 2009 [21]
rs12543663	8q24.21		C	Al Olama *et al*. 2009 [16]
rs10086908	8q24.21		T	Al Olama *et al*. 2009 [16]
rs1016343	8q24.21		T	Al Olama *et al*. 2009 [16]
rs13252298	8q24.21		A	Al Olama *et al*. 2009 [16]
rs6983561	8q24.21		C	Al Olama *et al*. 2009 [16]
rs16901979	8q24.21		A	Gudmundsson *et al*. 2007 [11]
rs16902094	8q24.21		G	Gudmundsson *et al*. 2009 [57]
rs445114	8q24.21		T	Gudmundsson *et al*. 2009 [57]
rs620861	8q24.21		C	Al Olama *et al*. 2009 [16]
rs6983267	8q24.21		G	Al Olama *et al*. 2009 [16]
rs1447295	8q24.21		A	Amundadottir *et al*. 2006 [9]
rs10993994	10q11.23	*MSMB*	T	Eeles *et al*. 2008 [28]
rs4962416	10q26.13	*CTBP2*	C	Thomas *et al*. 2008 [26]
rs7127900	11p15.5		A	Eeles *et al*. 2009 [21]
rs12418451	11q13.2		A	Zheng *et al*. 2009 [34]
rs11228565	11q13.2		A	Gudmundsson *et al*. 2009 [57]
rs10896449	11q13.2		G	Thomas *et al*. 2008 [26]
rs11649743	17q12	*HNF1B*	G	Sun *et al*. 2008 [30]
rs4430796	17q12	*HNF1B*	A	Gudmundsson *et al*. 2007 [11]
rs1859962	17q24.3		G	Gudmundsson *et al*. 2007 [11]
rs8102476	19q13.2	*PPP1R14A*	C	Gudmundsson *et al*. 2009 [57]
rs2735839	19q13.33	*KLK3*	A	Eeles *et al*. 2008 [28]
rs9623117	22q13.1	*TNRC6B*	C	Sun *et al*. 2009 [31]
rs5759167	22q13.2	*BIK*	G	Eeles *et al*. 2009 [21]
rs5945619	Xp11.22	*NUDT11*	C	Eeles *et al*. 2008 [28]

[a]Genes within the linkage-disequilibrium block defined by the associated variant: *BIK*, BCL2-interacting killer; *CTBP2*, C-terminal binding protein 2 isoform 2; *EEFSEC*, elongation factor for selenoprotein translation; *EHBP1*, EH domain binding protein 1; *FLJ20032*, hypothetical protein LOC54790; *HNF1B*, hepatocyte nuclear factor 1 homeobox B; *ITGA6*, integrin alpha chain 6; *JAZF1*, juxtaposed with another zinc finger gene 1; *KLK3*, kallikrein 3; *LMTK2*, lemur tyrosine kinase 2; *MSMB*, β-microseminoprotein isoform a precursor; *NKX3-1*, NK3 transcription factor related locus 1; *NUDT11*, nudix-type motif 11; *PDLIM5*, PDZ and LIM domain 5 isoform d; *PPP1R14A*, protein phosphatase 1 regulatory inhibitor; *SLC22A3*, solute carrier family 22 member 3; *SLC25A37*, mitochondrial solute carrier protein; *THADA*, thyroid adenoma associated isoform 1; *TNRC6B*, trinucleotide repeat containing 6B isoform 2. [b]Risk alleles as defined from published data cited in the column.

for both of these variants, the alleles that are associated with increased risk for prostate cancer were more frequent in patients with less aggressive disease. Since these risk alleles have been shown to strongly associate with higher PSA levels among population controls [28,48,49], it is possible that the observed association with aggressive disease may partly reflect a PSA detection bias.

It should be noted that the lack of association between established prostate cancer risk variants and disease aggressiveness does not imply non-existence of such genetic variants in the genome. All susceptibility variants identified to date were discovered using case-control designs comparing unaffected individuals with all types of patients with prostate cancer. It has been argued that a more effective design to identify genetic variants associated with aggressive disease should involve a case-case design contrasting patients with more and less aggressive disease. Support for this idea was recently provided in a study including 4,829 patients with more aggressive disease and 12,205 patients with less aggressive disease from seven study populations [50]. Initially, publicly available genotype data for approximately 27,000 genetic variants across the genome were explored for association with disease severity among patients with prostate cancer from four populations examined in the Cancer Genetic Markers of Susceptibility study using a case-case design. A subset of variants (n = 74), showing association within each Cancer Genetic Markers of Susceptibility study, and where the direction of association was consistent among all four studies, was selected for further evaluation in an additional three study populations from Sweden and the USA. This revealed one genetic variant (rs4054823 at 17p12) for which the TT genotype was consistently higher among patients with more aggressive compared with less aggressive disease in each of the seven populations studied (overall $P = 2.1 \times 10^{-8}$ under a recessive genetic model). If confirmed in independent study populations, this finding is of great importance, not because of immediate clinical utility, but as a proof of principle that genetic variants predisposing to more aggressive prostate cancer exist.

Prostate cancer susceptibility variants and disease progression and prognosis

In contrast to exploring inherited genetic variants associated with aggressiveness of disease at time of diagnosis, only a few studies have assessed the importance of established risk variants on prostate cancer progression and prognosis.

Only one study has explored confirmed risk variants in relation to prostate cancer progression. Among 320 patients who were recruited from three hospitals in Taiwan where they were treated with radical prostatectomy, Huang and co-workers explored association between 20 prostate cancer risk variants and biochemical failure defined by recurrence of PSA [51]. During a mean follow-up of 38.5 months, biochemical failure occurred in 113 (35%) of the patients. In univariate analysis, three risk variants (rs1447295 at 8q24, and rs7920517 and rs10993994 at 10q11) were associated with PSA recurrence. Interestingly, these associations remained significant after adjusting for established prognostic factors such as age, preoperative PSA level, tumor stage, Gleason score, and surgical margin, suggesting that these variants may improve prediction of PSA recurrence among patients treated with radical prostatectomy. Further studies are required to validate these findings.

Penney and co-workers [52] explored eight genetic variants at chromosome 8q24, 17q12, and 17q24.3 for association with prostate cancer mortality in three US prostate cancer study populations comprising a total of 6,460 patients of which 493 died as a result of prostate cancer during follow-up. None of the explored variants was associated with prostate cancer mortality, neither in analysis contrasting lethal cases with long-time survivors (alive over 10 years after diagnosis), nor in survival analysis among all patients. The total number of risk alleles was also not associated with prostate cancer mortality.

A prospective population-based cohort study of Swedish patients with prostate cancer explored the association between 16 established risk variants and prostate cancer mortality [52]. In total, 2,875 patients diagnosed between 2001 and 2003 were followed up for prostate cancer mortality through January 2008. Overall, 626 (21%) of the patients died during follow-up and of those 440 (15%) had prostate cancer classified as their underlying cause of death. No association between any of the explored variants and prostate cancer mortality was observed, either in exploring individual variants or in assessing the cumulative effect of all variants.

Additional studies in large populations are needed to comprehensively explore possible associations, although current evidence suggests that established risk variants are not risk factors for prostate cancer outcome.

Future clinical use of genetic factors

Recent GWAS studies have been successful in identifying many low-penetrant susceptibility alleles for prostate cancer, and it is anticipated that many more variants will be detected through combined analysis across existing studies, new generations of larger studies, and increasing size of replication studies. Individually, each risk variant has a modest effect on disease risk and they will clearly not be useful for individualized risk prediction. However, risk profiles based on a combination of risk variants lead to an appreciable increased risk of disease [35] and there is potential for the predictive power to increase considerably as more risk variants are detected [53]. This may have important implications for targeted prevention and screening programs for prostate cancer through identification of high-risk groups.

Since there is considerable co-morbidity associated with curative treatment of prostate cancer (surgery or radiotherapy), there is clear clinical utility in detecting

genetic markers that can improve discrimination between those patients that will follow a benign course from those with tumors that carry a poor prognosis and for whom curative therapy is indicated. In addition, inherited genetic markers, in contrast to measurement of a tumor-derived product, can be informative at an earlier stage when the disease is potentially curable. However, it is evident that hitherto identified prostate cancer risk variants provide little or no discriminative capacity between indolent and aggressive forms of prostate cancer. Large GWAS among affected men contrasting more and less aggressive cases, and exploring association with disease progression and prostate cancer mortality, are clearly needed to detect inherited genetic variants associated with aggressive forms of prostate cancer. Initial findings indicate that genetic variants predisposing to more aggressive disease exist [50] and this is also supported by recent epidemiological studies proposing a genetic component in cancer prognosis [54,55].

The detection of inherited genetic markers capable of discriminating between indolent and fatal forms of prostate cancer holds promise to improve detection and clinical management of this disease in several ways. A genetic-based, targeted PSA screening strategy may reduce both overdiagnosis and mortality by identifying those men at risk for fatal prostate cancer at a curable stage. In addition, extended tools to guide clinicians in treatment decisions are critical to improve disease prognosis and decrease treatment-induced morbidity.

Abbreviations

GWAS, genome-wide association study; PSA, prostate-specific antigen; SNP, single-nucleotide polymorphism.

Competing interests

The author declares that he has no competing interests.

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