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Single Nucleotide Polymorphisms: A New Paradigm in Predicting the Risk of Prostate Cancer

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Abstract

Prostate cancer (PC) is a most important health care problem because of its high prevalence, health-related costs, and mortality. Even though most patients have clinically localized and indolent tumors at diagnosis, worldwide, this disease still holds second place in the leading causes of cancer deaths. Research on susceptibility genes is one of hot issues in risk factors of prostate cancer. Nevertheless, the confirmation of prostate cancer susceptibility genes has been challenging. Thus focusing on the increasing number of single nucleotide polymorphisms (SNPs) that have been suggested to be implicated in the development and progression of PC. While individual SNPs are only moderately associated with PC risk, in combination, they have a stronger association. Therefore, identification of numerous variations in genes and analysis of their effects may lead to a better understanding of their impact on gene function and health of an individual. This improved knowledge may provide a starting point for the development of new useful SNP markers for medical testing and a safer individualized medication to treat the most common devastating disorders. This will revolutionize the medical field in the future. To illustrate the effect of SNPs on gene function and phenotype, this review focuses on genetic susceptibility of prostate cancer and role of single nucleotide polymorphism and revealing the impact of SNPs on the development and progression of prostate cancer.

Keywords: Prostate cancer; Genetic susceptibility; Single nucleotide polymorphism

Introduction

Prostate Cancer (PC) has become a major health problem in industrialized world during the last decades of the 20th century. It is now the most commonly diagnosed solid tumor among men in developed countries [1,2]. This cancer has a complex, multi-factorial etiology with an estimated 45% of disease variation being attributed to genetic factors and 50% to environmental/lifestyle factors [3]. One of the strongest risk factors for this disease is family history of PC; having a first-degree relative diagnosed with PC is associated with a two- to three-fold elevation in the relative risk, and both early age at diagnosis and multiple affected family members are important predictors of risk in relatives [4,5]. Taken together, these results suggest an important inherited component to disease risk. Nevertheless, interpreting the genetic basis for PC has been challenging, particularly since unique high-risk genetic mutations have not been identified. Single nucleotide polymorphism (SNP) is the simplest form of DNA variation among individuals. These simple changes can be of transition or transversion type and they occur throughout the genome at a frequency of about one in 1,000 bp. They may be responsible for the diversity among individuals, genome evolution, the most common familial traits such as curly hair, inter-individual differences in drug response, and complex and common diseases such as cancer, cardiovascular, Parkinson's , diabetes, obesity, hypertension, and psychiatric disorders. SNPs may change the encoded amino acids (non-synonymous) or can be silent (synonymous) or simply occur in the noncoding regions. They may influence promoter activity, messenger RNA (mRNA) conformation, and subcellular localization of mRNAs and proteins and hence may produce disease. Therefore, identification of numerous variations in genes and analysis of their effects may lead to a better understanding of their impact on gene function and health of an individual. The most promising results have emerged from genome-wide association studies (GWAS) of PC, which have identified numerous highly replicated and independent SNPs distributed throughout the human genome [6-14]. These SNPs individually confer modest risks of PC with Odds ratio (ORs of 1.05-1.30) and only a subset has been associated with aggressive metastatic PC [15]. In addition, some risk alleles affect serum prostate specific antigen (PSA) levels which may impact PC screening. The set of currently characterized SNPs identified through large GWAS, however, do not explain the majority of the familial/hereditary risk for PC [16-19].

There has been an increasing focus on the role of single nucleotide polymorphisms in the development and progression of PC but also on their role in diagnostics and risk prediction. A SNP is a DNA sequence variation occurring when a single nucleotide (A, T, C, or G) in the genome differs from the normally expected nucleotide. These SNPs are known to underlie differences in our susceptibility to diseases. SNPs need to be determined only once and are easy to determine, making them interesting biomarkers. The rising interest in the role of SNPs in PC development and progression is illustrated by the number of studies being published on SNPs in the PC field. Further, research has focused on identifying the genetic foundations of prostate cancer. It has been recognized that a number of forms of genetic changes coupled with epigenetic and gene expression changes can increase the prediction to develop prostate cancer. Identifying relevant genetic changes offers the ability to develop novel biomarkers to allow early and accurate detection of prostate cancer as well as provide risk stratification of patients following their diagnosis. In connection to the diagnosis, the concept of personalized or individualized medicine has gained significant attention. Over the past twenty years, the scientific community has come to believe that carcinogenesis is the result of genetic and/or epigenetic changes to protein-coding oncogenes and tumor suppressor genes. In the case of solid-organ malignancies such as prostate cancer,

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these result typically from somatic genetic events. However, in addition to these somatic genetic changes, it has also become clear that many cancers, including prostate, exhibit loss of function of tumor suppressor genes due to epigenetic changes in expression. Epigenetic mechanisms include biochemical modification of histones supporting DNA, modification of the DNA itself and expression of non-coding RNAs, including miRNAs. Despite the high prevalence of prostate cancer, little is known about its cause. Many genes have been implicated in the development of both sporadic and particularly hereditary prostate. Unfortunately, attempts at identifying a reliable biomarker have thus far proved unsuccessful due in large part to the highly variable disease, multiple implicated epidemiological factors and advanced patient age at diagnosis [20,21]. Therefore, a better understanding of the genetic and molecular characteristics distinguishing indolent from lethal prostate cancers is necessary to understand the genetic polymorphisms and metabolic pathways underlying prostate cancer development offers the opportunity to explore new therapeutic interventions with the possibility of offering patient-specific targeted therapy. Therefore, it is interesting to determine the role of these SNPs in the clinical field.

Molecular genetics of prostate cancer

Evidence of a genetic contribution to the susceptibility to PC has been established through familial aggression, segregation and twin studies. Besides age and race, family history is the only well-established risk factor for PC [22-24]. Over the years, genetic epidemiological research has accrued much evidence in favor of a significant hereditary element for PC susceptibility. Familial aggregation of prostate cancer i.e., the occurrence of more than one PC case among first-degree relatives, has been recognized as early as the 1950s. Since then, epidemiological studies have shown that first-degree relatives of PC patients have a 2- to 3-fold increased risk of developing PC [25]. The highest risks of PC have been observed in men having multiple affected relatives, or relatives diagnosed at an early age. This familial risk of prostate cancer has been observed in multiple ethnic populations (Americans, Australians, Europeans, Asian-Americans, Caucasians, Asian Pacific and African-Americans decedents) [26]. The increasing rate of PC has been compared between monozygotic and dizygotic twins, making it possible to assess genetic and environmental factors. Such studies from Nordic countries and the USA consistently show a high increasing rate in monozygotic twins. From a meta-analysis of three twin registries in Sweden, Denmark, and Finland, the estimated heritability for PC was found to be 42%, which was the highest of all studied cancers. Family studies and twin studies may strongly suggest a genetic component in PC, but cannot be used to conclude the specific genetic mode of transmission. Several segregation studies have been performed to reveal the mode of inheritance of PC within families. Three studies from the USA and one Swedish study have showed a Mendelian autosomal dominant inheritance for familial aggregation of PC. While segregation analyses of Australian PC families observed that a dominantly inherited risk contributed to early-onset PC specifically, late-onset PC was mainly due to a recessive inheritance pattern. A more recent study by Gong et al. found that a multi-factorial model explained the segregation of PC better than did the previous research regarding Mendelian models. Since 1996, genome wide scans have yielded several loci that were believed to harbor PC susceptibility genes [27]. Smith et al. were the first to report a PC susceptibility locus linked to 1q24-25, designated HPC1 (hereditary prostate cancer 1), in a population of 91 high-risk PC families from the US and Sweden [28].

The mapping of HPC loci at 1q42.2-43 (PCP), Xq27-28 (HPCX), 1p36 (CAPB), 20q13 (HPC20), 8p22-23 and 17p11 followed and three genes have been successfully cloned within the linked loci (RNASEL at 1q24-25, MSR1 at 8p22-23, and HPC2/ELAC2 at 17p11). However, these genes are thought to only explain a small proportion of the occurrence of HPC. The failure to identify highly-penetrant loci has led to the hypothesis that susceptibility to common cancers is polygenic, that is due to a large number of variants each conferring a small increase in risk. In an attempt to explain the hereditary basis of PC, focused candidate gene studies have varied in their success. Some have been successful in detecting multiple associations with PC, while most of have been poorly replicated [29]. Association studies, which compare frequencies of genetic polymorphisms between cases and controls, offer a powerful approach to identify low-penetrant variants. Early association studies were based on studying limited numbers of polymorphisms in candidate genes that were suspected to be important in carcinogenesis. Technological advancements have allowed researchers to move pass hunts for candidate genes and now allow hundreds of thousands of single nucleotide polymorphism to be genotyped simultaneously. Such genome-wide association studies (GWAS) have identified over 30 germ line loci for PC [30]. The most notable PC region identified is 8q24. The most striking finding is that at least five distinct loci within chromosome 8q24 harbor germ line variants associated with PC. However, GWAS have revealed an association between particular single nucleotide polymorphisms and prostate cancer risk (2p15, 3p12, 6q25, 7p15, 7p21, 8q24, 9q33, 10q11, 10q26, 11q13, 17q12, 17q24.3, 19q13, and Xp11). In the early stages of cellular transformation, gene expression changes in MYC (v-myc myelocytomatosis viral oncogenes), MET (met proto-oncogene), TERT (telomerase reverse transcriptase), AMACR (alpha-methyl acyl-CoA racemase) and cell cycle regulators such as CDKN1B (cyclin-dependent kinase inhibitor 1B, p27Kip1) are among the most common. The most prominent epigenetic modification observed in disease initiation is hyper methylation of the GSTP1 promoter, rendering this gene silent. In patients with clinically diagnosed prostate cancer, TP53 (tumor protein p53) is the most commonly mutated gene, along with a host of other less prevalent genetic alterations including BCL2 (B-cell CLL/lymphoma 2), PTEN, RB1, CDKN2A (cyclin-dependent kinase inhibitor 2A, p16), and TGFB1. In stages of more advanced and hormone-refractory disease, mutated and amplified AR is the most consistent change observed both at the genetic as well as at the protein level. Fusion of the TMPRSS2 gene with members of the ETS family (ETS, ERG, ETV1, and ETV4) is also commonly seen in prostate cancer [31-33].

Prostate cancer is currently considered to be a complex multifactorial disease with the vast majority of familial clustering attributed to the interaction of multiple shared moderate to low penetrance susceptibility genes as well as shared environmental factors. However, even with these findings, there is no clear evidence that variants associated with PC risk are also associated with cancer aggressiveness or mortality.

Role of single nucleotide polymorphism

Single nucleotide Polymorphisms are minute variations in the DNA sequence that are passed on from parents to children. They are the most common type of genetic variation in humans. Formally, an allele, that is, a variation in DNA sequence, is defined to be polymorphic if it occurs in at least one percent of a population [34]. Therefore, although overall humans are very similar at the DNA sequence level, because the genome is large there is substantial latitude for individual genetic variation. SNPs occur about once in every 800 base pairs [35]. The Human Genome Project and advances in related technologies have supported the investigation of the relationship between genetic variation and many health outcomes, including prostate cancer.

Since 2001, about 1,000 publications have reported associations between prostate cancer and SNPs and other genetic variants. The vast majority of the studies have related to candidate genes, in which the genes and variants, usually SNPs, have been specifically selected for investigation based on biological and physiological information regarding the involvement of gene products in early developmental pathways, biochemical and cellular process of progression, and/or clinical manifestations. For prostate cancer, the most intensively investigated associations have related to genes in the following pathways: adhesion molecules (CDH1); androgen metabolism (AR, ESR2, SRDA2,); angiogenesis (VEGF) angiotensin conversion (ACE); base-excision repair (XRCC1); inflammation and immune response (IL8, IL10, MSR1, PTGS2, TNF); inhibition of cell growth (FGFR4, TGFB1, TGFBR1); insulin-like growth factor metabolism (IGF1, IGFBP3); one carbon metabolism (MTHFR, diverse genes139); oxidative response (MnSOD, hOGG1); substrate metabolism (CYP1A1, CYP3A4, CYP17, GSTM1, GSTT1, GSTP1, NAT1 and NAT2, UGT2B17); vitamin D metabolism (VDR); and, common variants of genes for which rare mutations are associated with increased cancer risk (ELAC/HPC2, RNASEL, TP53, MDM2,) [36-50]. In general, the results of candidate gene studies have been inconclusive, for reasons discussed in many interpretations [51,52].

There has been a cumulative focus on the role of single nucleotide polymorphisms in the development and progression of PC but also on their role in diagnostics and risk prediction. A SNP is a DNA sequence variation occurring when a single nucleotide (A, T, C, or G) in the genome differs from the normally expected nucleotide. These SNPs are known to underlie differences in our susceptibility to diseases. SNPs need to be determined only once and are easy to determine, making them interesting biomarkers. The rising interest in the role of SNPs in PC development and progression is exemplified by the number of studies being reported on SNPs in the PC field. In 2008, an extensive genome-wide association study compared SNPs between PC cases and controls. Since then, numerous GWAS studies have been conducted which elucidates approximately 40% of the familial risk. With ongoing GWAS, we could anticipate that more genetic variants will be found, explaining more of the PC familial risk. However, the question has been raised whether finding more PC risk associated SNPs will have added value over the currently known ones [53]. Advances in high-throughput genotyping, together with the completion of the HapMap and Human Genome Projects, have enabled the performance of GWAS and, even more recently, detailed whole-exome and whole genome sequencing studies. These genetic studies have generally been designed as case control studies involving relatively large cohorts of patients that evaluate associations between the frequencies of SNPs and disease status. The SNPs identified in GWAS are believed to be surrogates for the true causative locus within a linkage imbalance block that is biologically responsible for the association GWAS of PC have rapidly progressed after the identification of the 8q24 locus [54-56]. In fact, there are now more than 80 altered SNPs associated with increased PC risk identified by GWAS on 20 different chromosomes (Table 1). In general, the relative increased risk of developing PC based on any

Locus	Nearby Genes	SNP	Reference Allele	Risk Allele	Per Allele OR	(95% CI)
1q21	KCNN3	rs1218582	A	G	1.06	(1.03–1.09)
1q32	MDM4, PIK3 C2B	rs4245739	A	C	0.91	(0.88–0.95)
2p11	GGCX/VAMP8	rs10187424	A	G	0.92	(0.89–0.94)
2p15	EHBP1	rs721048	G	A	1.15	(1.10–1.21)
2p21	THADA	rs1465618	G	A	1.08	(1.03–1.12)
2p24	C2orf43	rs13385191	A	G	1.15	(1.10–1.21)
2p25	TAF1B:GRHL1	rs11902236	G	A	1.07	(1.03–1.10)
2q31	ITGA6	rs12621278	A	G	0.75	(0.70–0.80)
2q37	MLPH	rs2292884	A	G	1.14	(1.09–1.19)
2q37	FARP2	rs3771570	G	A	1.12	(1.08–1.17)
3p11	Unknown	rs2055109	T	C	1.2	(1.13–1.29)
3p12	Unknown	rs2660753	C	T	1.18	(1.06–1.31)
3q13	SIDT1	rs7611694	A	C	0.91	(0.88–0.93)
3q21	EEFSEC	rs10934853	C	A	1.12	(1.08–1.16)
3q23	ZBTB38	rs6763931	C	T	1.04	(1.01–1.07)
3q26	CLDN11/SKIL	rs10936632	A	C	0.9	(0.88–0.93)
4q13	AFM, RASSF6	rs1894292	G	A	0.91	(0.89–0.94)
4q22	PDLIM5	rs17021918	C	T	0.9	(0.87–0.93)
4q22	PDLIM5	rs12500426	C	A	1.08	(1.05–1.12)
4q24	TET2	rs7679673	C	A	0.91	(0.88–0.94)
5p12	FGF10	rs2121875	T	G	1.05	(1.02–1.08)
5p15	TERT	rs2736098	G	A	0.87	(0.84–0.90)
5p15	IRX4	rs12653946	C	T	1.26	(1.20–1.33)
5p15CL	CLPTM1	rs401681	G	A	1.07	(0.86–1.33)
5q35	FAM44B (BOD1)	rs6869841	G	A	1.07	(1.04–1.11)
6p21	CCHCR1	rs130067	T	G	1.05	(1.02–1.09)
6p21	FOXP4	rs1983891	C	T	1.15	(1.09–1.21)
6p21	NOTCH4	rs3096702	G	A	1.07	(1.04–1.10)
6p21	ARMC2, SESN1	rs2273669	A	G	1.07	(1.03–1.11)
6q22	RFX6	rs339331	C	T	1.22	(1.15–1.28)
6q25	SLC22A3	rs9364554	C	T	1.17	(1.08–1.26)
6q25	RSG17	rs1933488	A	G	0.89	(0.87–0.92)

7p15	JAZF1	rs10486567	A	G	0.74	(0.66–0.83)
7p21	SP8	rs12155172	G	A	1.11	(1.07–1.15)
7q21	LMTK2	rs6465657	T	C	1.12	(1.05–1.20)
8p21	SLC25A37	rs2928679	C	T	1.05	(1.01–1.09)
8p21	NKX3.1	rs1512268	G	A	1.18	(1.14–1.22)
8p21	EBF2	rs11135910	G	A	1.11	(1.07–1.16)
8q24	Unidentified	rs188140481	G	A	2.90	(2.44–3.44)
8q24	Unidentified	rs1447295	C	A	1.62	(1.20–1.93)
8q24	Unidentified	rs6983267	T	G	1.26	(1.13–1.41)
8q24	Unidentified	rs16901979	C	A	1.79	(1.36–2.34)
8q24	Unidentified	rs10086908	T	C	0.87	(0.81–0.94)
8q24	Unidentified	rs16902094	G	A	1.21	(1.15–1.26)
8q24	Unidentified	rs445114	C	T	1.22	(1.12–1.32)
8q24	Unidentified	rs12543663	A	C	1.08	(1.00–1.16)
8q24	Unidentified	rs620861	C	T	0.9	(0.84–0.96)
9q31	RAD23B-KLF4	rs817826	T	C	1.41	(1.29–1.54)
9q33	DAB21P	rs1571801	C	A	1.27	(1.10–1.48)
10q11	MSMB	rs10993994	C	T	1.25	(1.17–1.34)
10q24	TRIM8	rs3850699	A	G	0.91	(0.89–0.94)
10q26	CTBP2	rs4962416	T	C	1.2	(1.07–1.34)
10q26	Unidentified	rs2252004	T	G	1.16	(1.10–1.22)
11p15	Unidentified	rs7127900	G	A	1.22	(1.17–1.27)
11q12	FAM111A	rs1938781	T	C	1.16	(1.11–1.21)
11q13	TPCN2-MYEOV	rs11228565	G	A	1.23	(1.16–1.31)
11q13	TPCN2-MYEOV	rs10896450	A	G	1.16	(1.06–1.27)
11q13	Unidentified	rs12418451	G	A	1.15	(1.06–1.24)
11q13	Unidentified	rs7931342	G	T	0.84	(0.79–0.90)
11q22	MMP7	rs11568818	A	G	0.91	(0.88–0.94)
12q13	TUBA1C/PRPH	rs10875943	T	C	1.07	(1.04–1.10)
12q13	KRT8	rs902774	G	A	1.17	(1.11–1.24)
12q24	TBX5	rs1270884	G	A	1.07	(1.04–1.10)
13q22	Unidentified	rs9600079	G	T	1.18	(1.12–1.24)
14q22	FERMT2	rs8008270	G	A	0.89	(0.86–0.93)
14q24	RAD51L1	rs7141529	A	G	1.09	(1.06–1.12)
17p13	VPS53, FAM57A	rs684232	A	G	1.1	(1.07–1.14)
17q12	HNF1B	rs4430796	G	A	1.22	(1.15–1.30)
17q12	HNF1B	rs11649743	A	G	1.28	(1.07–1.52)
17q21	HOXB13	rs138213197	G	A	20.1	(3.5–803.3)
17q21	ZNF652	rs7210100	A	G	1.51	(1.35–1.69)
17q21	SPOP, HOXB13	rs11650494	G	A	1.15	(1.09–1.22)
17q24	Unidentified	rs1859962	T	G	1.2	(1.14–1.27)
18q23	SALL3	rs7241993	G	A	0.92	(0.89–0.95)
19q13	KLK3	rs2735839	G	A	0.83	(0.75–0.91)
19q13	Unidentified	rs8102476	T	C	1.12	(1.08–1.15)
19q13	Unidentified	rs11672691	G	A	1.12	(1.03–1.21)
19q13	LILRA3	rs103294	T	C	1.28	(1.21–1.36)
20q13	GATAS, CABLES2	rs2427345	G	A	0.94	(0.91–0.97)
20q13	ZGPAT	rs6062509	A	C	0.89	(0.66–0.92)
22q13	TNRC6B	rs9623117	A	C	1.18	(1.11–1.26)
22q13	BIL/TTLL1	rs5759167	G	T	0.86	(0.83–0.88)
Xp11	NUDT11	rs5945572	T	C	1.23	(1.16–1.30)
Xp22	SHROOM2	rs2405942	A	G	0.88	(0.83–0.92)
Xq12	AR	rs5919432	A	G	0.94	(0.89–0.98)

Abbreviations: CI: Confidence Interval; OR: Odds Ratio; SNP: Single-nucleotide Polymorphism.
Source: Data retrieved from multiple genome wide association studies [57-63].

Table 1: List of Single nucleotide polymorphisms associated with significantly increased risk of prostate cancer.

individual SNP is small, ranging from 1.02 to 1.5 fold [57-63]. However, this risk appears to be cumulative and increases with the number of risk alleles that an individual carries. Together with family history, it has been assessed that SNPs can explain approximately 30% of the familial risk of PC in men of various ethnic populations around the globe [58]. Several genome-wide association studies have identified close to 100 PC susceptibility variants, primarily in populations of European ancestry, to a lesser extent in African American men and recently, in African

men. Even though many of these associations exceeded or were close to genome-wide significance levels, it remains necessary to confirm these findings in multiple independent populations to rule out false positive results, thereby improving the likelihood that they represent true associations. However, the SNPs detected through GWAS studies are mostly limited to "index SNPs," excluding other SNPs which are in linkage disequilibrium. Clearly, these index SNPs are not necessarily the SNPs causative for its associated phenotype [62,63]. Consequently, molecular analyses will be essential to recognize the exact SNP within each linkage dominion which is the relevant SNP. SNPs that lie within an open reading frame can lead to changes in messenger RNA stability or translation efficiency, as well as changes in structure of the encoded proteins. However, most SNPs are located outside of the genes and are suspected to affect gene expression levels and genome organization. Therefore, with advances in genotyping and sequencing technologies at a fraction of the cost, continued discovery of novel SNPs associated with disease initiation, progression, it is interesting to determine the role of these SNPs in the clinical field and response to treatment is anticipated in the future. Translation of these discoveries into routine clinical diagnostic tests and screening tools that provide personalized medicine should be possible. Ultimately prospective, large clinical trials involving multi-institutional collaborations will be required to validate the usefulness of these SNPs and genetic markers in the management of PC. In the meantime, continued genetic studies that identify novel genetic variations in all forms of PC are critical to advancing our knowledge of the genetic basis of the disease.

Conclusion

The purpose of this review was to establish the evidence base behind using single nucleotide polymorphism in prostate cancer risk assessment, which includes risk stratification, screening for undiagnosed disease, and assessing prognosis. The high incidence of prostate cancer, the problems associated with current test methods particularly prostate-specific antigen screening in asymptomatic men, the difficulty of determining prognosis in many affected men, and the lack of clarity on the utility of different therapeutic approaches, mean that other avenues need to be explored with some energy. Even fairly modest improvements in risk classification could translate into large health gains in absolute terms. It is of crucial conceptual importance to recognize that this review is based on a framework of risk prediction, as distinct from pivotal inference. In the situation of risk prediction, it is relevant to compare models that include standard risk factors with models that include the same risk factors together with single nucleotide polymorphisms. This contrasts with the situation of pivotal inference in which the SNP status of an individual is assigned at birth. In a clinically-oriented, test evaluation approach such concerns are secondary to assessing performance as a predictor of a particular outcome.

Furthermore, ever since the definition of the human genome, the basis for genetic variations that can lead to individual risks for diseases has become more and more clear. Genome-wide association studies have defined groups of SNPs which partially predict increased risk for PC. As suggested in this review, SNPs have a great potential in predicting patients' risk for PC and therapy response, which could have an important impact in every day clinic. Although many authors have suggested that genetic information can improve risk prediction and therefore be useful in clinical practice, there are several studies showing contradicting results, limiting their current clinical use. These contradicting results could be explained by multiple reasons. First, studies performed on small, heterogeneous populations might result in high rates of false positive and negative data. Secondly, most conducted studies are based on SNPs which have been correlated with PC in GWAS studies. Since PC phenotypes are probably determined by a spectrum of genetic variation, with possible interdependencies of SNPs, GWAS studies are probably not sufficient to develop a full understanding of these variations in PC. Throughout this review, it has become clear that some challenges still remain for translational research on the role of SNPs in PC. Firstly, clinical studies on SNPs should be performed in well-powered studies, which could give more conclusive results. Secondly, the important challenge for further basic research is to identify the causative SNPs within each linkage equilibrium. Hopefully, these SNPs will not only function as predictors but also give evidences to important pathways in PC development, which could be therapeutic targets. It will only be after the enrichment of GWAS data by detailed SNP mapping and functional SNP testing that the most relevant SNPs can be analyzed in clinical research. Taken together, therefore, benefits from improvements in prostate cancer risk prediction, screening, and prognostic stratification will depend to a large extent on clearer evidence that surveillance, diagnostic, and treatment strategies in themselves lead to reductions in morbidity and mortality. In the future, we expect them to become critical to interpret individualized PC risk, inter-individual biomarker variation, and therapeutic response.

References

1. (2012) American Cancer Society Cancer Facts and Figures. Atlanta Georgia.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. (2011) Global cancer statistics. CA Cancer J Clin 61: 69-90.
3. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, et al. (2000) Environmental and heritable factors in the causation of cancer-analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 343: 78-85.
4. Bruner DW, Moore D, Parlanti A, Dorgan J, Engstrom P (2003) Relative risk of prostate cancer for men with affected relatives: systematic review and meta-analysis. Int J Cancer 107: 797-803.
5. Zeegers MP, Jellema A, Ostrer H (2003) Empiric risk of prostate carcinoma for relatives of patients with prostate carcinoma: a meta-analysis. Cancer 97: 1894-1903.
6. Kiciaski M, Vangronsveld J, Nawrot TS (2011) An epidemiological reappraisal of the familial aggregation of prostate cancer: a meta-analysis. PLoS One 6: e27130.
7. Amundadottir LT, Sulem P, Gudmundsson J, Helgason A, Baker A, et al. (2006) A common variant associated with prostate cancer in European and African populations. Nat Genet 38: 652-658.
8. Gudmundsson J, Sulem P, Manolescu A, Amundadottir LT, Gudbjartsson D, et al. (2007) Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. Nat Genet 39: 631-637.
9. Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, et al. (2007) Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet 39: 645-649.
10. Freedman ML, Haiman CA, Patterson N, McDonald GJ, Tandon A, et al. (2006) Admixture mapping identifies 8q24 as a prostate cancer risk locus in African-American men. Proc Natl Acad Sci U S A 103: 14068-14073.
11. Haiman CA, Patterson N, Freedman ML, Myers SR, Pike MC, et al. (2007) Multiple regions within 8q24 independently affect risk for prostate cancer. Nat Genet 39: 638-644.
12. Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G, et al. (2007) Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nat Genet 39: 977-983.
13. Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, et al. (2008) Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet 40: 316-321.
14. Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, et al. (2008) Multiple loci identified in a genome-wide association study of prostate cancer. Nat Genet 40: 310-315.

15. Hsu FC, Sun J, Wiklund F, Isaacs SD, Wiley KE, et al. (2009) A novel prostate cancer susceptibility locus at 19q13. Cancer Res 69: 2720-2723.

16. Zheng SL, Sun J, Wiklund F, Smith S, Stattin P, et al. (2008) Cumulative association of five genetic variants with prostate cancer. N Engl J Med 358: 910-919.

17. Wiklund FE, Adami HO, Zheng SL, Stattin P, Isaacs WB, et al. (2009) Established prostate cancer susceptibility variants are not associated with disease outcome. Cancer Epidemiol Biomarkers Prev 18: 1659-1662.

18. Witte JS (2009) Prostate cancer genomics: towards a new understanding. Nat Rev Genet 10: 77-82.

19. Waters KM, Le Marchand L, Kolonel LN, Monroe KR, Stram DO, et al. (2009) Generalizability of associations from prostate cancer genome-wide association studies in multiple populations. Cancer Epidemiol Biomarkers Prev 18: 1285-1289.

20. Klein RJ, Hallden C, Gupta A, Savage CJ, Dahlin A, et al. (2012) Evaluation of multiple risk-associated single nucleotide polymorphisms versus prostate-specific antigen at baseline to predict prostate cancer in unscreened men. Eur Urol 61: 471-477.

21. Bao BY, Pao JB, Huang CN, Pu YS, Chang TY, et al. (2011) Polymorphisms inside MicroRNAs and MicroRNA target sites predict clinical outcomes in prostate cancer patients receiving androgen deprivation therapy. Clin Cancer Res 17: 928-936.

22. Cunningham GR, Ashton CM, Annegers JF, Souchek J, Klima M, et al. (2003) Familial aggregation of prostate cancer in African-Americans and white Americans. Prostate 56: 256-262.

23. Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC (1992) Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci USA 89: 3367-3371.

24. Grönberg H, Damber L, Damber JE, Iselius L (1997) Segregation analysis of prostate cancer in Sweden: support for dominant inheritance. Am J Epidemiol 146: 552-557.

25. Grönberg H, Damber L, Damber JE (1994) Studies of genetic factors in prostate cancer in a twin population. J Urol 152: 1484-1487.

26. Gong G, Oakley-Girvan I, Wu AH, Kolonel LN, John EM, et al. Segregation Analysis of Prostate Cancer in 1719 White, African-American and Asian-American Families in the United States and Canada. Cancer Causes and Control 13: 471-482.

27. Smith JR, Freije D, Carpten JD, Grönberg H, Xu J, et al. (1996) Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. Science 22: 1371-1374.

28. Varghese JS, Easton DF (2010) Genome-wide association studies in common cancers--what have we learnt? Curr Opin Genet Dev 20: 201-209.

29. Kader AK, Sun J, Isaacs SD, Wiley KE, Yan G, et al. (2009) Individual and cumulative effect of prostate cancer risk-associated variants on clinico pathologic variables in 5,895 prostate cancer patients. Prostate 1: 1195-1205.

30. Penney KL, Salinas CA, Pomerantz M, Schumacher FR, Beckwith CA, et al. (2009) Evaluation of 8q24 and 17q risk loci and prostate cancer mortality. Clin Cancer Res 15: 3223-3230.

31. Shen MM, Abate-Shen C (2010) Molecular genetics of prostate cancer: new prospects for old challenges. Genes Dev 24: 1967-2000.

32. Elo JP, Visakorpi T (2001) Molecular genetics of prostate cancer. Ann Med 33: 130-141.

33. Cavalli-Sforza LL, Bodmer WF (1971) The Genetics of Human Populations, San Francisco: WH Freeman and Company 118.

34. Feero WG, Guttmacher AE, Collins FS (2010) Genomic medicine--an updated primer. N Engl J Med 362: 2001-2011.

35. Qiu LX, Li RT, Zhang JB, Zhong WZ, Bai JL, et al. (2009) The E-cadherin (CDH1)--160 C/A polymorphism and prostate cancer risk: a meta-analysis. Eur J Hum Genet 17: 244-249.

36. Zeegers MP, Kiemeney LA, Nieder AM, Ostrer H (2004) How strong is the association between CAG and GGN repeat length polymorphisms in the androgen receptor gene and prostate cancer risk? Cancer Epidemiol Biomarkers Prev 13: 1765-1771.

37. Gu M, Dong X, Zhang X, Niu W (2012) The CAG repeat polymorphism of androgen receptor gene and prostate cancer: a meta-analysis. Mol Biol Rep 39: 2615-2624.

38. Chen YC, Kraft P, Bretsky P, Ketkar S, Hunter DJ, et al. (2007) Sequence variants of estrogen receptor beta and risk of prostate cancer in the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. Cancer Epidemiol Biomarkers Prev 16: 1973-1981.

39. Li J, Coates RJ, Gwinn M, Khoury MJ (2010) Steroid 5-{alpha}-reductase Type 2 (SRD5a2) gene polymorphisms and risk of prostate cancer: a HuGE review. Am J Epidemiol 171: 1-13.

40. Li X, Huang Y, Fu X, Chen C, Zhang D, et al. (2011) Meta-analysis of three polymorphisms in the steroid-5-alpha-reductase, alpha polypeptide 2 gene (SRD5A2) and risk of prostate cancer. Mutagenesis 26: 371-383.

41. Hong TT, Zhang RX, Wu XH, Hua D (2012) Polymorphism of vascular endothelial growth factor -1154G>A (rs1570360) with cancer risk: a meta-analysis of 16 case-control studies. Mol Biol Rep 39: 5283-5289.

42. Ruiter R, Visser LE, Van Duijn CM, Stricker BH (2011) The ACE insertion/deletion polymorphism and risk of cancer, a review and meta-analysis of the literature. Curr Cancer Drug Targets 11: 421-430.

43. Zhang Y, He J, Deng Y, Zhang J, Li X, et al. (2011) The insertion/deletion (I/D) polymorphism in the Angiotensin-converting enzyme gene and cancer risk: a meta-analysis. BMC Med Genet 12: 159.

44. Geng J, Zhang Q, Zhu C (2009) XRCC1 genetic polymorphism Arg399Gln and prostate cancer risk: A meta-analysis. Urol 74: 648-653.

45. Wei B, Zhou Y, Xu Z, Ruan J, Zhu M, et al. (2011) XRCC1 Arg399Gln and Arg194Trp polymorphisms in prostate cancer risk: a meta-analysis. Prostate Cancer Prostatic Dis 14: 225-231.

46. Zou YF, Wang F, Feng XL, Tian YH, Tao JH, et al. (2011) Lack of association of IL-10 gene polymorphisms with prostate cancer: evidence from 1,581 subjects. Eur J Cancer 47: 1072-1079.

47. Shao N, Xu B, Mi YY, Hua LX (2011) IL-10 polymorphisms and prostate cancer risk: a meta-analysis. Prostate Cancer Prostatic Dis 14: 129-135.

48. Wang N, Zhou R, Wang C, Guo X, Chen Z, et al. (2012) -251 T/A polymorphism of the interleukin-8 gene and cancer risk: a HuGE review and meta-analysis based on 42 case-control studies. Mol Biol Rep 39: 2831-2841.

49. Sun J, Hsu FC, Turner AR, Zheng SL, Chang BL, et al. (2006) Meta-analysis of association of rare mutations and common sequence variants in the MSR1 gene and prostate cancer risk. Prostate 66: 728-737.

50. Xu B, Tong N, Chen SQ, Hua LX, Wang ZJ, et al. (2011) FGFR4 Gly388Arg polymorphism contributes to prostate cancer development and progression: a meta-analysis of 2618 cases and 2305 controls. BMC Cancer 11: 84.

51. Xu B, Tong N, Li JM, Zhang ZD, Wu HF (2010) ELAC2 polymorphisms and prostate cancer risk: a meta-analysis based on 18 case-control studies. Prostate Cancer Prostatic Dis 13: 270-277.

52. Li H, Tai BC (2006) RNASEL gene polymorphisms and the risk of prostate cancer: a meta-analysis. Clin Cancer Res 12: 5713-5719.

53. Choudhury AD, Eeles R, Freedland SJ, Isaacs WB, Pomerantz MM, et al. (2012) The role of genetic markers in the management of prostate cancer. Eur Urol 62: 577-587.

54. Meyer KB, Maia AT, O'Reilly M, Ghoussaini M, Prathalingam R, et al. (2011) A functional variant at a prostate cancer predisposition locus at 8q24 is associated with PVT1 expression. PLoS Genet 7: e1002165.

55. Eeles RA, Olama AA, Benlloch S (2013) Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. Nat Genet 45: 385-391.

56. Foulkes WD (2008) Inherited susceptibility to common cancers. N Engl J Med 359: 2143-2153.

57. Sun J, Chang BL, Isaacs SD, Wiley KE, Wiklund F, et al. (2008) Cumulative effect of five genetic variants on prostate cancer risk in multiple study populations. Prostate 68: 1257-1262.

58. Al Olama AA, Kote-Jarai Z, Giles GG, Guy M, Morrison J, et al. (2009) Multiple loci on 8q24 associated with prostate cancer susceptibility. Nat Genet 41: 1058-1060.

59. Eeles RA, Kote-Jarai Z, Al Olama AA, Giles GG, Guy M, et al. (2009) Identification of seven new prostate cancer susceptibility loci through a genome-wide association study. Nat Genet 41: 1116-1121.

60. Kote-Jarai Z, Olama AA, Giles GG, Severi G, Schleutker J, et al. (2011) Seven prostate cancer susceptibility loci identified by a multi-stage genome-wide association study. Nat Genet 43: 785-791.

61. Van den Broeck T, Joniau S, Clinckemalie L, Helsen C, Prekovic S, et al. (2014) The role of single nucleotide polymorphisms in predicting prostate cancer risk and therapeutic decision making. Biomed Res Int p: 627510.

62. Fernandez P, Salie M, du Toit D, Van der Merwe A (2015) Analysis of Prostate Cancer Susceptibility Variants in South African Men: Replicating Associations on Chromosomes 8q24 and 10q11. Prostate cancer pp: 1-7.

63. Thibodeau SN, French AJ, McDonnell SK, Cheville J, Middha S, et al. (2015) Identification of candidate genes for prostate cancer-risk SNPs utilizing a normal prostate tissue eQTL data set. Nat Commun 6: 8653.