Review article

Genetic analysis of the principal genes related to prostate cancer: A review

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Abstract

Prostate cancer is one of the most common leading causes of cancer death in men. Attributable to many genetic linkage and genome-wide association studies (GWAS) around the world, several high-penetrance genetic variants have been identified. Many polymorphisms in genes, such as ELAC2 (locus HPC2), RNase L (locus hereditary prostate cancer 1 gene [HPC1]), and MSR1 have been recognized as important genetic factors that confer an increased risk of developing prostate cancer in many populations. A review of the literature was then performed analyzing the roles of these and other genes in prostate cancer. Our main challenge is optimizing the role of these genes in prostate cancer development, even trying to use these genes as general biomarkers. The principal aim of this review is to determine the most important variants in the principal genes related to prostate cancer and examine the differences among populations. The concept of individualized or personalized targeted cancer therapy has gained significant attention throughout oncology. In prostate cancer, the creation of a personalized panel of single-nucleotide polymorphisms (SNP) biomarkers may be important for the early and accurate detection of this cancer. As a result, the need for a good biomarker is required to detect prostate cancer earlier and to provide tools to follow patients during the early stages of the cancer. At present, prostate cancer continues to have an unclear etiology, which is a combination of genetic and numerous environmental factors. Among genetic factors, no variants of the RNase L, ELAC2, or MSR1 genes have been detected with similar expression patterns in different populations all around the world. © 2013 Elsevier Inc. All rights reserved.

Keywords: RNase L; ELAC2; HPC2; MSR1; Biomarker; Prostate cancer

1. Introduction

The genetic influence of some regions of the genome in different cancers is not a new field of research. Genes, such as BRCA1 and 2 are known to influence the progression of breast cancer and have been considered high-penetrance genes for the development of breast cancer since 1994.

This review focuses on prostate cancer, 1 of the 6 most common cancers in the world. However, the incidence rates of prostate cancer vary due not only to genetic factors but also due to ethnicity [1], geographic residence area [2], age, socioeconomic standing [3,4], and other environmental factors, such as lifestyle [5], place of work, and dietary habits [2,6]. Thus, the differences in the rates of prostate cancer are a combination of genetic susceptibility factors and external risk factors. These varying contributions to prostate cancer incidence are reflected in the many differences in the rates of prostate cancer around the world. Asiatic countries, such as China, have the lowest rates. The highest rates are found in North America, especially in the African-American population [7].

There are 2 general types of prostate cancer, familial and sporadic. Familial prostatic disease is chiefly recognized because the cancer appears at early ages (<55 years old) in the affected members of the same family. However, in sporadic prostate cancer, the genetic material is damaged by external ambient exposure during the life of the indi-
individual. Both types of cancers have different incidence rates; in familial or hereditary cancer, the rates reach 15%, whereas in sporadic carcinoma, the rates approach values of 80 or 90% [8]. The goal of this review is to determine the most important variants in the principal genes related to prostate cancer and examine the differences among the populations.

1.1. The need for new predictive biomarkers

Tumor biomarkers are used to detect some cancers and to detect, treat, and diagnose the disease in its early stages [9]. It is possible to detect prostate cancer early due to the presence of positive tumor biomarkers, such as prostate-specific antigen (PSA), by screening. PSA levels are routinely checked, and correlation of PSA levels with the likelihood of cancer is well defined. PSA values of 4 ng/ml in the blood are considered the threshold for a prostatic biopsy. However, values below 10 ng/ml exhibit low specificity for prostate cancer detection [10]. The fact that PSA is not only produced by malignant cells is one of the predominant shortcomings of this biomarker, and it is possible to obtain false positive or false negative results. Cases with high levels of PSA in benign prostatic hyperplasia or other types of prostatitis have been described [11]. In addition, there are some reports of men whose PSA values are below 4 ng/ml but who suffer from aggressive prostate cancer (with Gleason scores above 7) [12].

Nevertheless, there are no other biomarkers used at the moment for the detection of prostate cancer. However, there are many studies for finding alternatives biomarkers, such as PCA3 (prostate cancer antigen 3) [13], TMPRSS2: ETS (transmembrane protease, serine 2: transcription factor ETS-related gene) [14], GSTP1 (glutation-S-transferase enzyme) [15], and C-reactive protein [16] among others, but they still need to be evaluated in clinical trials. These biomarkers can be detected in urine; PCA3 by quantification of mRNA, TMPRSS2: ETS by Southern blot hybridization; in tissue, GSTP1 by DNA mutilation assays; or in plasma, C-reactive protein by agglutination assays. Furthermore, some studies in the inactivation PTEN (phosphatase and tensin homolog) by the resulting of proteomic profiles were analyzed by machine learning to build predictive regression models for tissue PTEN status and diagnosis and grading of this cancer. What’s it will guide path to biomarker discovery may hold the promise for the realization of personalized cancer medicines [17]. Also, recent studies analyze copy number aberrations (CNAs) data on risk of relapse relative to transcriptome profiling and its utility in integrated prostate oncogene data set [18]. Latest studies performed in 2012, have discovered a new mutation named as G84E (rs138213197) in HOXB13 gene, which has been cataloged as the first major genetic variant associated with inherited prostate cancer [19].

1.2. Genetic factors

Although the incidence of prostate cancer is high in select populations, its cause remains unknown. What is clear, however, is that prostate cancer is a heterogeneous disease with multiple genetic and environmental factors involved in its etiology. Many genes are responsible for the development of sporadic and, in particular, hereditary prostate cancer, including hereditary prostate cancer 1 gene (HPC1) (1q24–25), CAPB (1p36), PCAP (1q42–43), HPC2 (17p12), HPC20 (20q13), and HPCX (Xq27–28) [20]. Nonetheless, the high variability of the disease, the many epidemiologic factors, and the advanced age at diagnosis has made the identification of a good biomarker for prostate cancer very difficult [21].

Genetic biomarkers have been used previously for the detection and diagnosis of breast and ovarian cancer. Mutations in BRCA1 and BRCA2 confer a high risk for the development of these cancers [22]. Apart from prostate and breast cancer, similar studies are being performed in bladder cancer using BCLA4 (specific protein for the nuclear matrix in bladder cancer) [23]; and in colorectal cancer using serum carcinoembryonic antigen (CEA) as well as genetic biomarkers, such as microsatellite instability (MSI), MutL homolog 1 (MLH1) (colon cancer, nonpolyposis type 2 [E. coli]), and adenomatous polyposis coli gene (APC) [24]. However, few positive results have been achieved in either case. The most relevant candidate genes for prostate cancer are RNase L (HPC1), located at chromosome 1q22; MSR1, with a linkage region on chromosome 8p; and ELAC2 (HPC2), on chromosome 17p11 [21, 25]. These 3 genes have been identified as hereditary tumor suppressor genes in prostate cancer [26].

2. Materials and methods

We performed a systematic literature search between September 2007 and May 2012. Studies on the use of genetic markers in relation to prostate cancer were identified by searching the PubMed, Science Direct, and Scopus electronic databases. The search strategy included terms used to describe prostate cancer, its etiology and screening, and genetic analysis. In a first step, the search performed global information about prostate etiology, prostate cancer, biomarkers, and genes in prostate cancer. In a second phase, it was delimited to the main genes ELAC2 – HPC2, RNase L – HPC1, and MSR1, its variants, and prostate cancer. For further relevant studies, this search was supplemented by reviewing the bibliographies of key papers. The search was limited to publications in the English language. No manual search of meeting abstracts was performed.

2.1. HPC1 or RNase L gene

RNase L is an endoribonuclease located on chromosome 1q22 and is the effector of the 2–5-A system, a major
enzymatic pathway involved in interferon activity. This ribonuclease plays an important role in the antiviral activities of interferons and is related to innate immunity. RNase L is part of the innate immune system that responds to a pathogen-associated molecular pattern (PAMP) to induce degradation of viral and cellular RNAs, thereby blocking viral infections [27]. RNase L is also involved in cellular proliferation and apoptosis in response to viral infections and other external stimuli. Further, RNase L plays an important role as a tumor suppressor gene [28].

In 1996, Smith et al. identified a region on chromosome 1,1q24–25, as a susceptibility locus in familial prostate cancer [29]. Since then, this gene has been widely studied. Many variants within the RNase L gene have been described, especially in exons 1 and 3. The most common mutations are E265X, R462Q, 471delAAAG, I97L, M111, G59F, S113S, I221V, E262X, S406F, Y530C, and D541E. Some of these mutations have been identified in several studies as related to hereditary or sporadic prostate cancer, although some of the studies presented inconclusive results [30,31]. The 471delAAAG is a null mutation associated with an increased risk of prostate cancer in Ashkenazi Jew males [32]. However, this finding remains controversial because studies by Dagan et al. reported low rates of the 471delAAAG mutation in the Ashkenazi population that rejected the consideration as a major factor of cancer susceptibility in this population [30].

The main mutations in the RNase L gene related to prostate cancer are 3 missense mutations: D541E, R462Q, and I97L [31,33,34]. R462Q and D541E are non-synonymous variants showing a reduction in the enzymatic activity of RNase L [26]. I97L is a missense mutation located in the third and seventh repetition site of the ankyrin domain [35].

The R462Q or Arg462Gln variant is associated with an increased risk in prostate cancer in familial cases in the Finnish population [36], among American Caucasians [30], and among Japanese men [25]. In the population in the south of Spain, the genotype A/A is associated with a worse prognosis [37]. Several other studies, including a population-based study conducted in Swedish population [38] and in the German population [25], have found no association between the Arg462Gln polymorphism and sporadic prostate cancer. In vitro studies have indicated that the Gln variant results in the decreased enzyme activity of RNase L, which allow tumor cells to escape the apoptotic pathway, mainly, because RNase L acts as a true tumor suppressor [39].

D541E or Asp541Glu increase the risk of prostate cancer in some Japanese men [40]. However, in other analyses, such as the ones performed in European populations, no correlation is described between D541E and prostate cancer [36,41,42].

With respect to I97L or Ile97Leu, although denoted as a major mutation in prostate cancer, most of the studies do not shown a clear correlation between this mutation and the risk of prostate cancer [33].

However, some reports of other mutations in prostate cancer, such as E265X, a truncation protein motif, or M111, a missense mutation in the start codon are also described in individuals of African-American ancestry [43,44].

2.2. HPC2 or ELAC2 gene

Hereditary prostate cancer gene 2 (HPC2) is also known as ELAC2 gene (elaC homolog 2, Escherichia coli) [45]. Some mutations in this gene are related to a 2%–5% increased risk of prostate cancer [46].

ELAC2 is located on chromosome 17p. It encodes a gene product that exhibits similarity to a family of DNA interstrand crosslink repair proteins [47] with a potential role in cancer susceptibility. ELAC2 encodes an unfamiliar but essential enzyme for tRNA biosynthesis known as tRNA 3’ processing endoribonuclease (3’ tRNase). Its main function is the removal of a 3’ trailer from precursor tRNA (pre-tRNA), which is transcribed in a larger form than the final product [48,49].

The main mutations in the ELAC2 gene related to prostate cancer are missense changes, such as Ser217Leu and Ala541Thr [50]. However, there are others, including 1641insG, Arg781His, and Glu622Val. It has been suggested that missense mutations Ser217Leu, Ala541Thr, and Arg781His do not affect the enzyme/substrate complex formation, the chemical cleavage step, and the substrate release process [48,51]. However, genes with mutation 1641insG encode for a protein that do not show the enzymatic activity at all [48]. Otherwise, Glu622Val is proposed to affect the protein function but it is not still known how [52]. The Ser217Leu mutation varies in different ethnic groups. In Asiatic and European populations, the Leu217 allele is related to an increased predisposition for prostate cancer [53]. The Thr541 allele is linked to an increased risk for prostate cancer in comparison with the Ala541 allele in Asiatic populations [53].

As in the case of RNase L gene, there are controversial results with respect to the relationship between the major variants of the ELAC 2 genes (Ser217Leu and Ala541Thr) and prostate cancer. Some studies report an important effect of the missense mutations Ser217Leu and Ala541Thr in prostate cancer. However, other studies performed in UK do not find this correlation [51,54].

2.3. MSR1 gene

The MSR1 gene is located at the 8p22 region [45] and encodes the macrophage scavenger receptors type A. Some linkage studies performed by Xu et al [45,55] relate this gene to prostate cancer and to some pathologies, such as Alzheimer disease and atherosclerosis [56]. Previous studies have described some mutations linked to prostate cancer, including Arg293X, Asp175Tyr, His441Arg, Val113Ala, and Ile54Val. Arg293X, a truncating protein mutation, was first described by Xu et al in familial studies in individuals of European descen-
dent with prostate cancer [57]. Asp175Tyr is a missense mutation also described by Xu et al in African-American individuals [57]. There is little information concerning the His441Arg, Val113Ala, and Ile54Val mutations apart from their possible effect on the development and progression in prostate cancer.

There are also regions in the MSR1 gene that seem to play a role in prostate cancer. Rs12718376, in the terminal 3’ regions of gene MSR1, was characterized as linked to an increased risk of prostate cancer in the Caucasian population [26]. There are others regions that seem to interact with prostate cancer, such as rs918 (UTR 3’), rs1904577 (intron region), rs2127565 (intron region), and Pro275Ala, but little information is available.

2.4. Environmental factors

As previously mentioned, one of the major characteristics of prostate cancer is the high variability in incidence rates due to differences in race, geographic area or age as well as differences in environmental factors, such as place of work, nutrition and lifestyle (Fig. 1). Environmental factors are one of the causes of the different incidence rates of different cancers worldwide [74]. In prostate cancer, it is normal to distinguish between epidemiologic endogenous factors (e.g., race, hormonal factors, familial information, age, etc.) and exogenous factors (e.g., diet, environmental factors, and lifestyle) [75].

Among the studies, there is a notable difference in the incidence of prostate cancer within the same ethnic group living in different geographic areas and exposed to different external factors. The highest prevalence rates as well as the youngest deaths in prostate cancer are found in African American populations [76]. The lowest incidence of prostate cancer has been observed in Asiatic populations [75]. Median incidence rates are noted in Hispanic and European populations [76]. Among Europeans, the highest incidence rates are observed in Northern European populations, such as Iceland, and the lowest rates are found in Italy, Spain, and France [77,78].

2.5. Genome-Wide Association Studies (GWAS) database

Here, we present a systematic review of published studies of single-nucleotide polymorphisms (SNPs) in populations around the world and some GWAS analyses performed mainly in European populations.

Among all the GWAS in prostate cancer, those performed in European populations that included data about the RNase L, MSR1, and ELAC2 genes were eligible for inclusion in our review. GWAS studies on Americans of North European descent revealed significant associations between prostate cancer and RNase L, EZH2 (7q36–rs2302427), and NKX3–1 (8p21–rs1567669) [61]. Breyer et al performed a series of case-control studies in Caucasian populations compounded by 523 independent familial prostate cancer cases and 523 age-matched controls without a personal or family history of prostate cancer and found interesting results in RNase L and ELAC2 genes. SNPs within four regions associated with sporadic prostate cancer in published genome-wide association studies were selected for assay. With respect to the RNase L gene, in R462Q, the minor allele (A) heterozygote exhibited a significant association (P = 0.031) and an increased risk of prostate cancer (OR, 1.34; P = 0.031). However, D541E in homozygotes (T) was associated with a reduced risk of prostate cancer (OR 0.64, P = 0.018). In the ELAC2 gene at rs4792311 (S217L), the minor allele A has not been linked to a significant association (P = 0.56) or to an increased risk of prostate cancer (OR 1.13; P = 0.60) [61].

Beuten et al have genotyped 41 tagged SNPs, selected using Haploview, covering the RNase L, ELAC2, and MSR1 genes in a case-control cohort, which included 1,436 (596 cases, 840 controls) Caucasians, 648 (194 cases, 454 controls) Hispanics, and 270 (82 cases, 188 controls) African-Americans. Their study confirmed that although these genes are significantly associated with an increased risk of prostate cancer, there are differences among the 3 ethnic groups. In Hispanics, variants in RNase L rs627928 (Asp541Glu) (OR, 1.72; 95% CI, 1.05–2.81; P = 0.030), rs486907 (Arg462Gln) (OR, 3.92; 95% CI, 1.54–9.96; P = 0.0040), and rs682585 (OR, 0.58; 95% CI, 0.38–0.86; P = 0.007) had the strongest effects on prostate cancer risk. Further, in this population group, 1 SNP (rs12114368) within MSR1 was found to be significantly associated with prostate cancer risk (O.R: 0.64; 95% CI, 0.43–0.95; P = 0.029). In African-Americans, single SNPs (rs433601 and rs351572) within MSR1 were significantly associated with prostate cancer risk (P values 0.039–0.024). In Caucasians, variants within MSR1 (rs12718376, rs17484273, rs351572) and ELAC2 (rs17552022, rs11545302) are most likely to confer prostate cancer risk. rs11545302 (ELAC2) exhibited a major effect independent of other significant SNPs (P = 2.03 × 10−5). The strongest associations with prostate cancer risk were seen with rs12718376 in MSR1 (OR, 0.32; 95% CI, 0.12–0.90; P = 0.031) and rs11545302 in ELAC2.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Replication study design</th>
<th>Population</th>
<th>Risk allele</th>
<th>Association test OR (95% CI)</th>
<th>( P )</th>
<th>Reference</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNase L - (HPC1) 1q24–25</td>
<td>471delAAAG</td>
<td>Population-based case study (979 cases and 1,251 controls)</td>
<td>Ashkenazi Jewish men</td>
<td>delAAAG allele = 0.89 (0.74–1.68)</td>
<td>0.80</td>
<td>Agalliu et al 2010 [58]</td>
<td>No association between the deletion and prostate cancer.</td>
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<td>Glu265X (E265X)</td>
<td></td>
<td>Case-control (116 families HPC, 492 patients PC, 223 BPH and 566 controls)</td>
<td>Finnish families STOP codon</td>
<td>OR (STOP codon) = 4.56 (1.07–19.42)</td>
<td>0.04</td>
<td>Rökman et al 2002 [36]</td>
<td>The median age at disease onset for carriers was 11 years younger than noncarriers in HPC.</td>
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<tr>
<td>rs486907</td>
<td>Arg462Gln (R462Q)</td>
<td>Family-based case–control study (423 cases and 454 sibling controls)</td>
<td>Caucasians A</td>
<td>OR (A allele) = 2.29 (1.25–4.21)</td>
<td>0.007</td>
<td>Casey et al 2002 [41]</td>
<td>AA genotype was found to increase prostate cancer risk over 4-fold compared with the GG genotype. This variant may be involved in a substantial percentage of prostate cancer cases regardless of family history.</td>
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<td></td>
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<td>Case-control study (68 cases and 146 controls)</td>
<td>African Americans A</td>
<td>OR (A allele) = 10.41 (2.62–41.40)</td>
<td>0.001</td>
<td>Shook et al 2007 [44]</td>
<td>AA genotype was found to increase prostate cancer risk over 10-fold when compared to GG genotype. Significant increase in prostate cancer risk.</td>
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<tr>
<td></td>
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<td>Case-control study (194 cases and 454 controls)</td>
<td>Hispanic Caucasians A</td>
<td>OR (A allele) = 3.68 (1.54–9.96)</td>
<td>0.004</td>
<td>Beuten et al 2010 [26]</td>
<td>Increased risk of familial PC associated with the Arg allele. The AA genotype was associated with a decreased risk of prostate cancer. The Arg462Gln variant had no association with advanced or aggressive tumors but an inverse association with less aggressive tumors and with tumors identified in younger men.</td>
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<td>Case-control study (438 FPC cases and 510 controls)</td>
<td>Caucasian A</td>
<td>OR (A allele) = 0.54 (0.32–0.91)</td>
<td>0.02</td>
<td>Wang et al 2002 [42]</td>
<td>AA genotype was found to increase prostate cancer risk to a significant degree.</td>
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<td>Case-control study (101 FPC cases and 105 controls)</td>
<td>Japanese A</td>
<td>OR (A allele) = 0.93 (0.35–2.44)</td>
<td>0.014</td>
<td>Nakazato et al 2003 [40]</td>
<td>Gln genotype was not observed in cases and reduced prostate cancer risk to a significant degree.</td>
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<tr>
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<td></td>
<td>Population-based case study (979 cases and 1,251 controls)</td>
<td>Ashkenazi Jewish men</td>
<td>OR (A allele) = 0.86 (0.63–1.19)</td>
<td>0.08</td>
<td>Agalliu et al 2010 [58]</td>
<td>AA genotype of RNase L rs486907 had a 35%–50% reduction in the risk of prostate cancer in comparison with men with the GG genotype, which was significant in men diagnosed at younger ages (&lt;65 years) and among those with a first-degree family history of prostate cancer.</td>
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<td></td>
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<td>Case-control study (231 SPC cases and 100 controls)</td>
<td>Spanish A</td>
<td>n.d.</td>
<td>From 0.047 to 0.0001</td>
<td>Alvarez-Cubero et al 2011 [37]</td>
<td>AA genotype was observed in younger ages and more aggressive clinical parameters (Gleason 8–10; stages 3 and 4; PSA 20 ng/ml). Marked association with familial prostate cancer risk.</td>
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<td>Case-control study (101 FPC cases and 105 controls)</td>
<td>Japanese G</td>
<td>OR (G allele) = 6.94 (3.98–12.10)</td>
<td>0.0009</td>
<td>Nakazato et al 2003 [40]</td>
<td>The GG and TT genotypes were associated with an increased risk for prostate cancer Two copies of the glutamic acid was associated with an increased risk of advanced disease</td>
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<td>Case-control study (150 cases and 170 controls)</td>
<td>European-American G</td>
<td>OR (G allele) = 1.68 (1.04–2.70)</td>
<td>0.045</td>
<td>Noonan-Wheeler et al 2006 [60]</td>
<td>The GG and TT genotypes were associated with an increased risk for prostate cancer Two copies of the glutamic acid was associated with an increased risk of advanced disease</td>
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<td>Case-control study (1247 SPC cases and 801 controls)</td>
<td>Swedish Caucasian G</td>
<td>OR (G allele) = 0.77 (0.59–1.00)</td>
<td>0.03</td>
<td>Wiklund et al 2004 [38]</td>
<td>Under a recessive genetic model, provided marginally significant evidence for association with sporadic prostate cancer for homozygous carriers compared with homozygous non-carriers.</td>
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<tr>
<td>Gene</td>
<td>Variant</td>
<td>Replication study design</td>
<td>Population</td>
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<td>Case-control study (194 cases and 454 controls)</td>
<td>Hispanic</td>
<td>G</td>
<td>OR (G allele) = 1.72 (1.02–2.81)</td>
<td>0.030</td>
<td>Beuten et al 2010</td>
<td>The GG and TT genotypes were associated with an increased risk for prostate cancer.</td>
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<td></td>
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<td>Case-control study (362 cases and 519 controls)</td>
<td>Caucasian</td>
<td>G</td>
<td>OR (G allele) = 0.5 (0.2–0.9)</td>
<td>0.040</td>
<td>Robbins et al 2008</td>
<td>Significant protective effect for the RNase L 541-D allele.</td>
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<td>Case-control study (553 cases and 553 controls)</td>
<td>African</td>
<td>T</td>
<td>OR (T allele) = 0.64 (0.44–0.92)</td>
<td>0.018</td>
<td>Breyer J.P. et al 2009</td>
<td>Homozygotes for the minor allele (T) had a significantly reduced risk of prostate cancer.</td>
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<td>Case-control study (231 SPC cases and 100 controls)</td>
<td>Americans of northern European</td>
<td>G</td>
<td>n.d.</td>
<td>From 0.021 to &lt;0.001</td>
<td>Alvarez-Cubero et al 2011 [37]</td>
<td>GG genotype was observed in younger ages and more aggressive clinical parameters (Gleason 8–10; stages 3 and 4; PSA 20 ng/ml). Individuals with this genotype are considered to have the worst prognoses.</td>
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<tr>
<td></td>
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<td>Case-control study (362 cases and 519 controls)</td>
<td>Hispanic</td>
<td>G</td>
<td>n.d.</td>
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<td>Beuten et al 2010</td>
<td>Significant association with prostate cancer risk.</td>
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<tr>
<td>G50S</td>
<td></td>
<td>Caso-control (116 families HPC, 492 patients PC, 223 BPH and 566 controls)</td>
<td>Finnish families</td>
<td>A</td>
<td>n.d.</td>
<td></td>
<td>Rökman et al 2002 [36]</td>
<td>Frequencies were significantly different in the patients with HPC than in the controls. G50S frequencies were significantly different in the patients with HPC than in the controls because of the complete linkage disequilibrium with E265X.</td>
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<td>ELAC2 - (HPC2) 17p11</td>
<td>Hispanic</td>
<td>G</td>
<td>OR (G allele) = 0.58 (0.38–0.86)</td>
<td>0.004</td>
<td>Beuten et al 2010</td>
<td>Significant association with prostate cancer risk.</td>
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<tr>
<td>rs682585</td>
<td>5’ UTR</td>
<td>Case-control study (194 cases and 454 controls)</td>
<td>Caucasian</td>
<td>T</td>
<td>OR (T allele) = 1.12 (1.00–1.25)</td>
<td>0.045</td>
<td>Xu et al 2010</td>
<td>Evidence for the association between the Leu217 vs. Ser217 polymorphism and prostate cancer risk.</td>
</tr>
<tr>
<td>rs4792311</td>
<td>Ser217Leu</td>
<td>Case-control study (3,318 cases and 3,299 controls)</td>
<td>Caucasian</td>
<td>T</td>
<td>OR (T allele) = 2.09 (1.07–4.05)</td>
<td>0.134</td>
<td>Xu et al 2010</td>
<td>Evidence for the association between the Leu217 vs. Ser217 polymorphism and prostate cancer risk.</td>
</tr>
<tr>
<td>Ala541Thr</td>
<td></td>
<td>Case-control study (814 cases and 950 controls)</td>
<td>Asian</td>
<td>T</td>
<td>OR (T allele) = 1.54 (0.99–2.41)</td>
<td>0.034</td>
<td>Noonan-Wheeler, et al 2006 [60]</td>
<td>The presence of at least one copy of the leucine 217 allele was associated with an increased risk of advanced disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case-control study (150 cases and 170 controls)</td>
<td>European-American</td>
<td>T</td>
<td>OR (T allele) = 4.44 (1.84–10.69)</td>
<td>0.944</td>
<td>Xu et al 2010</td>
<td>Associated with increased prostate cancer risk.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case-control study (805 cases and 553 controls)</td>
<td>Asian</td>
<td>A</td>
<td>OR (A allele) = 1.54 (0.99–2.41)</td>
<td>0.909</td>
<td>Robbins et al 2008</td>
<td>Minor allele frequency was &lt;1% in both cases and controls; therefore it was not possible to accurately assess risk.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case-control study (362 cases and 519 controls)</td>
<td>African</td>
<td>A</td>
<td>OR (A allele) = 1.0 (0.2–5.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs11545302</td>
<td></td>
<td>Case-control study (596 cases and 840 controls)</td>
<td>Caucasian</td>
<td>G</td>
<td>OR (G allele) = 9.1 × 10⁻⁶</td>
<td>9.1 × 10⁻⁶</td>
<td>Beuten et al 2010</td>
<td>Strong association with PC risk.</td>
</tr>
<tr>
<td>Thr520Thr</td>
<td>rs17558088</td>
<td>Case-control study (596 cases and 840 controls)</td>
<td>Caucasian</td>
<td>G</td>
<td>OR (G allele) = 1.73 (1.36–2.22)</td>
<td>0.018</td>
<td>Beuten et al 2010</td>
<td>Strong association with PC risk.</td>
</tr>
<tr>
<td>Thr631Thr</td>
<td>1641insG</td>
<td>Linkage disequilibrium analysis (127 pedigree)</td>
<td>Utah</td>
<td>n.d.</td>
<td></td>
<td>n.d.</td>
<td>Tavtigian et al 2001</td>
<td>Found in one pedigree of high-risk prostate cancer families.</td>
</tr>
<tr>
<td>Arg781His</td>
<td>Linkage disequilibrium analysis (127 pedigree)</td>
<td>Utah</td>
<td>A</td>
<td>n.d.</td>
<td>n.d.</td>
<td>Tavtigian et al 2001</td>
<td>It is thought to contribute to the phenotype conferred by the triple missense allele Leu217, Thr541 and His781.</td>
<td></td>
</tr>
<tr>
<td>Glu216X</td>
<td></td>
<td>Case-control study (473 cases and 502 controls)</td>
<td>—</td>
<td>STOP codon</td>
<td></td>
<td>n.d.</td>
<td>Wang et al 2001</td>
<td>Found in 2 of 3 affected men in a single family.</td>
</tr>
<tr>
<td>Glu622Val</td>
<td>(E622V)</td>
<td>Case-control study (107 families HPC, 467 patients PC, 223 BPH and 568 controls)</td>
<td>Finnish</td>
<td>T</td>
<td>OR (T allele) = 2.94 (1.05–8.23)</td>
<td>n.d.</td>
<td>Rökman et al 2001</td>
<td>3-Fold increased risk of PC in carriers of the Val622 mutation compared to non-carriers.</td>
</tr>
<tr>
<td>Gene</td>
<td>Variant</td>
<td>Replication study design</td>
<td>Population</td>
<td>Risk allele</td>
<td>Association test OR (95% CI)</td>
<td>P</td>
<td>Reference</td>
<td>Remarks</td>
</tr>
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<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>MSR1</td>
<td>8p22</td>
<td>Case-control study</td>
<td>Caucasian</td>
<td>A</td>
<td>OR (A allele) = 0.64 (0.48-0.86)</td>
<td>0.004</td>
<td>Beuten et al 2010</td>
<td>Noncoding intronic SNPs play a role in determining susceptibility to PC.</td>
</tr>
<tr>
<td></td>
<td>rs12718376</td>
<td>(596 cases and 840 controls)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3'UTR</td>
<td>Case-control study</td>
<td>African American</td>
<td>C</td>
<td>OR (C allele) = 1.59 (1.06-2.39)</td>
<td>0.024</td>
<td>Beuten et al 2010</td>
<td>Noncoding intronic SNPs play a role in determining susceptibility to PC.</td>
</tr>
<tr>
<td></td>
<td>rs4333601</td>
<td>(82 cases and 188 controls)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>3'UTR</td>
<td>Case-control study</td>
<td>African American</td>
<td>G</td>
<td>OR (G allele) = 1.90 (1.09-3.32)</td>
<td>0.025</td>
<td>Beuten et al 2010</td>
<td>Noncoding intronic SNPs play a role in determining susceptibility to PC.</td>
</tr>
<tr>
<td>HPCX</td>
<td>Xq27–28</td>
<td>Population-based case study</td>
<td>Ashkenazi Jewish men</td>
<td>Allele 135</td>
<td>OR (allele 135) = 1.77 (1.15-2.71)</td>
<td>0.01</td>
<td>Agalliu et al 2010</td>
<td>Positive association with PC and positively associated with the risk of low Gleason score.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(979 cases and 1,251 controls)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Population-based case study</td>
<td>Ashkenazi Jewish men</td>
<td>Allele 188</td>
<td>OR (allele 188) = 1.65 (1.08-2.54)</td>
<td>0.02</td>
<td>Agalliu et al 2010</td>
<td>Positive association with PC and positively associated with the risk of low Gleason score.</td>
</tr>
<tr>
<td>BRCA-2</td>
<td>999del5</td>
<td>Case study (30 carriers of the mutation and 497 non-carriers)</td>
<td>Icelandic population</td>
<td>del5</td>
<td>n.d.</td>
<td>0.0-0.007</td>
<td>Tryggvadóttir et al 2007 [68]</td>
<td>Mutation carriers had a lower mean age at diagnosis, more advanced tumor stage, higher tumor grade and shorter median survival time. The mutation is strongly associated with the development of lethal disease.</td>
</tr>
</tbody>
</table>
Table 1  
(Continued)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Replication study design</th>
<th>Population</th>
<th>Risk allele</th>
<th>Association test OR (95% CI)</th>
<th>P</th>
<th>Reference</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>5’ UTR G202A</td>
<td>Case study (257 cases)</td>
<td>Caucasian</td>
<td>A</td>
<td>n.d.</td>
<td>0.51</td>
<td>Agalliu et al 2007 [69]</td>
<td>An estimation that &lt;1% of early-onset prostate cancers in the general US Caucasian population can be attributed to these rare disease-associated BRCA2 mutations.</td>
<td></td>
</tr>
<tr>
<td>6174delIT</td>
<td>Case-control study (246 cases and 640 controls)</td>
<td>Utah</td>
<td>A</td>
<td>n.d.</td>
<td>n.d.</td>
<td>Allen-Brady et al 2009 [70]</td>
<td>High-risk prostate cancer pedigrees observed in Utah. Cases were significantly more likely than controls to harbor the mutation. BRCA2 mutation-associated survival advantage for patients with prostate cancer, leading to an over representation of the 6174delIT allele</td>
<td></td>
</tr>
<tr>
<td>5369delATTT</td>
<td>Family study</td>
<td>Spanish</td>
<td>delATTT</td>
<td>n.d.</td>
<td>n.d.</td>
<td>Salgado et al 2010 [72]</td>
<td>This mutation, which generates an aberrant stop codon at position 1723, could affect important BRCA2 functions because it causes the absence of BRCA2 C-terminal conserved region, which is necessary for DSS1 and DNA binding processes. Not many replications of numerical data.</td>
<td></td>
</tr>
<tr>
<td>A1342CHis372Asn</td>
<td>Case-control study (246 cases and 640 controls)</td>
<td>Utah</td>
<td>n.d.</td>
<td>n.d.</td>
<td>Allen-Brady et al 2009 [70]</td>
<td>High-risk prostate cancer pedigrees observed in Utah.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ser455SerS455S</td>
<td>Case-control study (246 cases and 640 controls)</td>
<td>Utah</td>
<td>C</td>
<td>n.d.</td>
<td>0.004</td>
<td>Agalliu et al 2007 [69]</td>
<td>Significant difference between Caucasian and African-American patients.</td>
<td></td>
</tr>
<tr>
<td>Ser2414Ser S2414S</td>
<td>Case study (24 cases from 16 HPC families)</td>
<td>Jewish</td>
<td>G</td>
<td>n.d.</td>
<td>0.04</td>
<td>Agalliu et al 2007 [69]</td>
<td>Significant difference between Caucasian and African-American patients.</td>
<td></td>
</tr>
</tbody>
</table>

BC = breast cancer; BPH = benign prostatic hyperplasia; del = deletion; FPC = familiar prostate cancer; HPC = hereditary prostate cancer; n.d. = no data; OC = ovarian cancer; PC = prostate cancer; SPC = sporadic prostate cancer; HPC1 = hereditary prostate cancer 1 gene; PSA = prostatic specific antigen.
(OR, 2.19; 95% CI, 1.25–3.82; \(P = 0.006\)). Haplotype analysis of SNPs within the RNase L, ELAC2 and MSR1 genes revealed a major haplotype (39%), G-A-G-C-G, for the SNPs rs918-rs1904577-rs2127565-rs12718376-rs3747531-rs351572 within MSR1 that significantly increased the risk for prostate cancer in Caucasians under the dominant model (OR, 1.58; 95% CI, 1.23–2.04; \(P = 4.02 \times 10^{-4}\)). In the ELAC2 gene, this study also identified 2 synonymous SNPs (rs11545302/Thr520Thr in exon 17 and rs17552022/Thr631Thr in exon 20) that conferred significant risk effects on prostate cancer [26].

Other GWAS analyses have identified more than 30 potential prostate cancer susceptibility variants, primarily in the 8q24 chromosomal region and on chromosomes 3, 7, 17, 22, and X [79]. The analyses performed by Hindorff et al have identified 4 SNPs that are significantly associated with prostate cancer among men of African descent (rs10486567, rs5945572, rs5945619, and rs7931342) [79].

3. Conclusions

The combination of genetic tools and clinical information has led to the generation of a new focus in medicine: personalized cancer medicine. This new goal involves not only changing the tools for detecting cancer with new, more specific biomarkers but also in improving the efficiency of genetic tools and new generation sequencing technologies for cancer patients and their relatives. These new approaches will offer the possibility of the earlier detection of the pathology and a different or specific treatment depending on an individual’s genotype. Using genetic biomarkers, such as RNase L in prostate cancer and the clinical information about patients, stratification among patients could be determined based on the aggressiveness of the pathology [37], and also signatures reflecting tissue PTEN status may aid in selecting suitable patients and provide proof of target modulation [17]. Alterations of androgen receptor (AR) through mutation, gene amplification, and/or overexpression are common in metastatic samples [18]. Some splice variants, such as AR3 (which mainly regulates genes like AKT1) has been recently related as a prognosis marker to predict patient outcome in response to hormonal therapy [80]. Combination markers, such as fusion of the TMPRSS2 gene with the ERG oncogene and aberrant DNA methylation patterns are commonly found in prostate cancer. Updated analysis has suggested that the relationship between ERG expression, DNA methylation of CYP26A1, TBX15, HOXD3, and clinicopathologic features of prostate cancer are associated with ERG expression and clinicopathologic variables, which suggests that the incorporation of these markers could be useful in a pre- and post-treatment clinical setting [81]. Thus, a cancer genetics-guided path to biomarker discovery may hold the promise for the realization of personalized cancer medicines [17]. Information about CNA-based test might guide treatment choice in men with newly diagnosed prostate cancer, distinguishing low-risk from high-risk disease, but only if these data add to the prognostic impact currently provided by the histology-based Gleason score [18]. However, it is still being tested and adding to studies in transcriptome analysis [18,82]. The combination of this information will allow medical professionals to establish different medicine protocols in more aggressive cancers and offer the possibility of performing preliminary controls in families considered at risk. Although many significant steps in the treatment of prostate cancer have been taken with respect to clinical matters and genetic information, there is still a long way to go (Table 1).

References


