Chapter 10

Genetic Association Studies on Prostate Cancer

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Abstract

The modern research on molecular basis of prostate cancer (PCa) development includes studies aiming to identify potential genetic markers which could be used in diagnostics and/or monitoring of PCa. Genome-wide association studies (GWASs) have identified over 75 variants associated with PCa risk. One of the major PCa-related regions identified through GWASs is found to be a segment of 8q24. Other important PCa-susceptibility regions are 17q12, 17q24, 10q11, and 19q13. Candidate-gene based approach has also provided evidence of association between PCa risk and genetic variants located in functionally significant genes (both protein-coding and noncoding RNA genes) involved in normal prostatic cell growth, malignant transformation, or in the development of metastases. Nevertheless, the success of these studies is questionable, since numerous candidates for PCa-susceptibility variants were identified, but these results failed to replicate. The main aim of both types of genetic association studies on PCa is the identification of potential PCa genetic markers which could be used for constructing reliable algorithms for evaluating the risk for PCa development and/or PCa progression.

Keywords: prostate cancer, association study, GWAS, candidate gene, validation study, replication study

1. Introduction

Alarming statistics on prostate cancer (PCa) incidence and mortality, as well as the results of epidemiological studies, have led to focusing research efforts on discovering molecular mechanisms underlying its onset and progression [1]. Still, molecular basis of PCa pathogenesis remains largely unknown, while the results of studies in this area of research suggest that

PCa is one of the most genetically and molecularly heterogeneous malignant tumors [2]. Among PCa cases, most are sporadic, while a significantly smaller percent represents familial type, including hereditary cases. High-penetrability PCa-related loci are not common in populations and are found to be associated with hereditary PCa. Since PCa represents a multifactorial disease with polygenic basis, and sporadic cases are much more frequently diagnosed, most of the research in the area of PCa molecular genetics has focused on genetic variants with low penetrability [3].

The modern research on molecular basis of PCa development includes studies aiming to identify potential genetic markers which could be used in diagnostics and/or monitoring of PCa [1]. This is of utmost importance, since one of the major issues in clinical practice related to PCa is a large percent of latent PCa among newly diagnosed [4]. The overdiagnosis of PCa in early diagnosed cases, due to indolent forms, leads to unnecessary morbidity because of application of invasive therapeutic procedures [5]. This led to focusing the research efforts on discovering genetic markers that could be used for assessing the biological potential of early diagnosed PCa. Therefore, the use of these genetic markers, together with standard prognostic parameters of PCa progression, which include initial serum PSA level, Gleason score, and clinical stage, could greatly improve the current clinical protocols by being implemented in algorithms for evaluating the patient's risk of PCa and/or PCa aggressiveness [1].

Studies aiming to identify potential PCa-related loci are designed as case-control or case-only studies, which evaluate the differences in genotype distributions between cases and controls, as well as between different groups of patients, classified according to clinical characteristics. The most validated loci associated with PCa risk were identified through Genome-wide association studies (GWAS) [6]. Nevertheless, numerous PCa-related genetic variants were found in studies based on selected candidate genes [7].

2. Linkage analyses and high-penetrability loci

Linkage analyses have led to identification of the first high-penetrability PCa susceptibility loci [1]. These studies were based on analyses in hereditary PCa, which is a less frequent type of PCa, and yielded high or moderate-penetrability loci, such as HPC1 (eng. *Hereditary Prostate Cancer 1*, HPC1) mapped in chromosomal region 1q24-25 [8], PCAP (eng. *Predisposing for Cancer Prostate*, PCAP) mapped in 1q42.2-43 [9] and HPCX (eng. *Hereditary Prostate Cancer on X Chromosome*, HPCX) located in 1q42.2-43 [10]. Later on, additional linkage studies identified several other loci primarily associated with familial PCa and rarely found to be altered in sporadic type [1, 3]. Fine-mapping of these regions has led to identifying several candidate genes, such as *RNASEL* or *ELAC2* [11, 12]. Nevertheless, since the major percent of PCa is sporadic types, numerous studies have focused on identifying low-penetrability loci associated with not only sporadic PCa, but also potentially contributing to the risk of developing familial type of disease [3]. These studies were not designed as linkage, but instead as genetic association studies with case–control matched groups.

3. Genome-wide association studies

The *Human genome project* was critical for making high-throughput genome-wide analyses possible. Not only that this project yielded DNA sequence information but also provided basis for development of methodology, including high-throughput genotyping assays, as well as software tools for analyzing large amount of genetic data [13]. Therefore, sequencing of human DNA provided basis for GWASs, including those on PCa [14].

To date (February 2016), GWASs have identified over 75 variants associated with prostate cancer risk, predominantly in populations of European ancestry (**Figure 1**) [15, 16]. The first GWASs were conducted in 2007, for which a large collection of samples were obtained from PCa patients and healthy controls, as well as databases that included clinical data of patients were constructed [17–19]. The necessity of a large number of subjects for this type of study was obvious even in this early period of conducting GWASs.

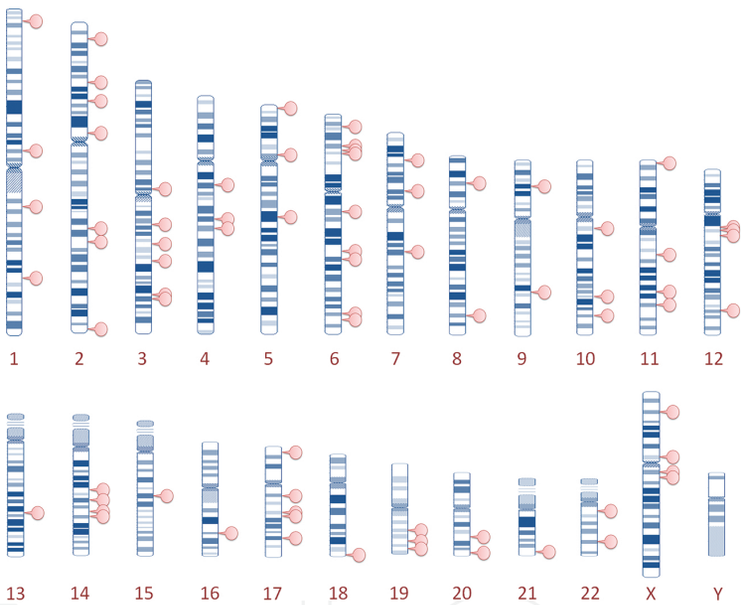

Figure 1. Ideograms of human chromosomes with marked PCa susceptibility loci identified through GWASs. Ideograms were obtained from NCBI Map Viewer, while GWAS hits were found in NHGRI-EBI GWAS catalog.

As in other complex diseases, PCa GWASs are usually designed in a multistage manner, with the whole set of tag-single nucleotide polymorphisms (tag-SNPs) being evaluated in the first phase, and only subsets of the most significant SNP being replicated in much larger groups of patients and controls in next phases [20, 21]. Thus, repeating the tests yields the most significant results [20].

The results of initial GWASs showed that most of the PCa-associated genetic variants are located in so-called "gene-deserts". The lack of protein-coding genes in these regions was explained by the supposed presence of regulatory sequences of major proto-oncogenes and tumor-suppressive genes [22, 23]. Today, another explanation is also the presence of genes encoding regulatory RNA molecules within PCa-risk regions [24].

3.1. 8q24 region

One of the major PCa-related regions was found to be 8q24. Within approximately 1 million base pairs segment of 8q24 reside multiple variants associated with PCa [25]. This region was first identified as associated with PCa susceptibility in a genome-wide linkage study conducted in Icelandic population [26]. Later on, the association of genetic variants within this region with PCa risk was shown in initial GWASs from 2007. Gudmunsson et al., Haiman et al. and Yeager et al. have shown the association between previously reported rs1447295 and PCa risk [17–19]. Also, these first GWASs identified other PCa susceptibility variants within 8q24, rs6983267, and rs16901979. Afterward, GWASs have provided evidence for association of other single-nucleotide genetic variants (SNVs) from 8q24 with PCa risk, such as rs4242382, rs7017300, and rs7837688 [27, 28]. In the recent years, by implementing clinical data and by using case-only design, both GWASs and validation studies have provided evidence for an association of several loci within 8q24 with PCa aggressiveness or survival [29–32].

PCa-susceptibility region within 8q24 was defined as *gene desert*, since no known protein-coding genes were located within it. Nevertheless, the possible biological explanation for the effect of genetic variants located in 8q24 on PCa risk was their influence on the regulation of the expression of nearby genes, mainly *C-MYC*. It was suggested that regulatory sequences controlling the transcription rate of *C-MYC* gene were located in 8q24, and that functional genetic variants which are in strong linkage disequilibrium (LD) with PCa susceptibility locus or several loci effect the sequence and therefore the function of regulatory elements [23]. Previous studies on molecular mechanisms of PCa pathogenesis have shown the functional significance of *C-MYC*, both by analyzing mutational signatures of malignant prostate tissue and by conducting functional analyses in cell cultures, which included stimulation or silencing of *C-MYC* expression [33]. Other than prostate cancer, several other malignancies were associated with 8q24, including breast and colorectal cancer. Some of the subregions of 8q24 associated with these cancers are found to overlap with those related to PCa, while others differ (**Figure 2**) [34].

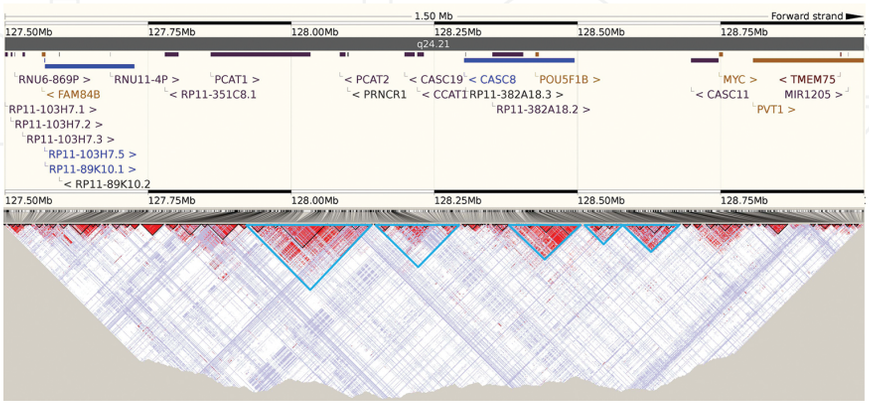

Figure 2. PCa risk-associated regions within 8q24. Lower part of the figure represents Haploview output for a segment of 8q24 (ch8:127500000..129000000) with marked subregions associated with PCa in GWASs. The upper part of the figure is a representation of genes located in the region of interest obtained from Ensembl genome browser (GRCh37).

3.2. 17q12

17q12 is another PCa susceptibility region identified through initial GWAS. Two of the genetic variants located in 17q12, rs7501939 and rs3760511, were found to be associated with the risk of developing PCa in the study by Gudmundsson et al. conducted in 2007 [35]. In this GWAS, minor alleles of these two single nucleotide genetic variants were found to confer the increased risk of PCa in cohorts of participants from Iceland, Netherlands, and the USA, while in the group of Hispanics this genetic association was not shown [35]. The results of this GWAS were further validated in multiple populations, mostly of European origin [36–43]. Validation studies were even conducted in Africans in which genetic association studies on PCa are scarce [37, 44–47]. The most recent meta-analysis of both GWASs and validation studies has also shown the association of these genetic variants with PCa risk [43].

SNVs rs7501939 and rs3760511 are located in the first intron of the hepatocyte nuclear factor 1 β(*HNF1β*) or transcription factor 2 (*TCF2*) which is a transcription factor showing tissue-specific expression pattern. Therefore, the association of genetic variants located in 17q12 with PCa risk could be explained by the effect of functional genetic variants on *HNF1β* function or expression [41].

3.3. 17q24

Another PCa-susceptibility region on chromosome 17 is 17q24. Genetic variants located within this region which were found to be associated with PCa are intergenic variants. Similar to 8q24 genetic variants, those located in 17q24 are found in a gene desert, probably harboring multiple regulatory sequences controlling the expression of surrounding genes [48]. One of the most proximal genes is *SOX9*, which is an important proto-oncogene in prostatic tissue. Recent findings have shown the location of PCa-associated genetic variants in an enhancer looping to *SOX9* gene [48]. Among these genetic variants is a tag-SNP previously identified through GWAS, as well as potentially functional genetic variants found by deep sequencing of PCa-susceptibility region [35, 48].

3.4. 10q11

Two out of the three GWASs, which were published in 2008 in the same issue of *Nature Genetics*, have identified PCa-associated genetic variants in the region 10q11 [27, 36]. Afterward, other studies have provided additional evidence to support the association between 10q11 and PCa susceptibility, including both GWASs and validation studies [49–55]. One of these PCa risk-associated genetic variants was located in the close proximity of the transcription start site of the gene Microseminoprotein B (*MSMB*) which encodes a tumor-suppressor, and was, therefore, even considered as potentially functional. For the risk allele of this genetic variant, it was further shown to affect the expression of *MSMB* gene in a negative manner [56, 57]. The other gene in proximity to this genetic variant is *Nuclear receptor coactivator 4* (*NCOA4*). NCOA4 protein interacts with androgen receptor (AR) and acts as corepressor of androgen-responding genes. Therefore, functional genetic variants in LD with GWAS hits could

potentially contribute to PCa risk by affecting the expression of these two genes, or others in proximity [58].

3.5. 19q13

Region 19q13 harboring kallikrein genes *KLK2* and *KLK3* was found to be associated with PCa susceptibility through GWASs [59]. Several genetic variants associated with PCa risk were located in *KLK3* gene, such as missense SNV rs17632542 identified by fine-mapping of PCa-associated subregion 19q13.33. These genes encode serine-proteases, one of which is PSA, used for PCa diagnosis and disease monitoring. Therefore, the association of PCa-risk genetic variants with serum PSA level was evaluated, yielding statistically significant results for potentially functional SNV rs17632542 [15, 59].

Another subregion associated with PCa risk is 19q13.4 in which a GWASs hit is in strong LD in Chinese population with germline deletion affecting *LILRA3* gene, involved in inflammatory pathways [60].

4. Candidate gene-based approaches

Even before GWASs, the necessity of conducting association studies in order to identify low and moderate penetrability genetic variants that contribute to PCa risk was obvious. Therefore, numerous candidate genes were analyzed for genetic variants associated with PCa, with questionable success due to false discoveries and the lack of replication [61]. Candidates were selected based on their potential functional significance in normal prostatic cell growth, malignant transformation, or in the development of metastases. Therefore, among these candidate genes are those encoding proteins involved in androgen signaling, cell-cycle control mechanisms, major tumor-suppressors, or proto-oncogenes, as well as those involved in cellular adhesion or communication with surrounding cellular or matrix components of prostate epithelium [62, 63]. This implies the need for previous knowledge when designing case-control studies using candidate gene approach [64].

Even though these studies were common before GWASs, they are still conducted in numerous populations, aiming to confirm previously found associations, or to identify new ones by analyzing other candidates, selected by using modern research results, such as those involved in regulatory functions of non-coding RNAs [65].

4.1. Protein-coding genes

4.1.1. Androgen signaling

Since androgen signaling is essential for growth and survival of prostate epithelial cells, genes involved in androgen biosynthesis, signal reception and transduction, as well as in androgen metabolism have emerged as candidates for case–control studies [63]. Most of these studies involved Androgen receptor (AR), as the major component of androgen signaling and

regulation of expression of androgen-responding genes. Among these studies, major percentage relied on analyzing the potential association of the length of CAG repeat string with exon 1 which encodes a poly-glutamine tract of AR with PCa risk [66]. This homopolymeric tract is located in N-terminal domain of AR, which possesses transactivational properties and its length is inversely correlated with transactivation function [67]. Even though initial results were promising, the supposed association was not confirmed in a large percentage of later studies, and the effect sizes were not large enough to support the substantial biological role. Therefore, the association of this genetic variant with PCa risk remains controversial [68–70].

Another three-nucleotide (GGN) repeat string, encoding polyglycine tract in AR, was analyzed for potential association between its length and PCa risk. This repeat string is also located in exon 1, but less studied than the CAG repeat tract, possibly due to technical problems in amplifying GC-rich DNA regions [71]. The effect of the length of GGN repeat string on transactivational properties of AR is still unclear, and the other proposed mechanism of potential functional significance is the effect on AR translation [72]. Studies on the potential association of this microsatellite on PCa risk and progression yielded contrasting results [73–79].

Mixed results were also found for *SRD5A2* (type II steroid 5α-reductase), which is the major enzyme converting testosterone to dihydrotestosterone. Similarly, studies analyzing genetic variants within *CYP17*, *CYP19A*, *HSD17B*, and *HSD3B* have shown initial promising results, lacking consistent validation [63, 80].

4.1.2. Carcinogen metabolism

Among genes involved in cell detoxification, those encoding glutathione-S-transferases have been mostly analyzed. Nevertheless, most of these studies yielded insignificant results on association with PCa risk [81]. Other frequently analyzed genes involved in metabolism of carcinogens are *PON1*, *CYP1A1, CYP1B1*, and *CYP3A4* [80, 82–85].

Two genetic variants within *PON1* have been analyzes in multiple populations, L55M and Q129R. The results to date are inconclusive, but the meta-analysis conducted in 2012 suggested the association of L55M missense variant with PCa risk [82]. Also, a recent meta-analysis on only three PCa studies and Q129R showed statistically significant association for several genetic models of association [83].

The most commonly analyzed SNVs in *CYP1A1* are missense variants rs1048943 (p.Ile462Val) and rs4646903, which are also called MspI polymorphisms, since they alter the recognition site for MspI restriction enzyme. Numerous studies and also the recent meta-analyses showed the association between these SNVs and PCa risk [84–86].

The results obtained for genetic variants in *CYP1B1* and *CYP3A4* are controversial, with the recent meta-analyses suggesting the association of L432V, N453S, and A119S polymorphisms of *CYP1B1* and A392G in *CYP3A4* with PCa susceptibility [87, 88].

4.1.3. DNA repair, cell cycle control, and apoptosis

Dysfunctions of DNA repair pathway, apoptosis regulation, and cell cycle control mechanisms alter the cells response to DNA damage and lead to uncontrolled proliferation, progression and metastasis of malignant diseases. Also, genetic variants in genes involved in these processes could potentially attribute to cancer susceptibility and/or progression risk [62].

Among the genes analyzed for association between genetic variants and prostate cancer risk or aggressiveness are *XRCC1* and *XRCC3* (X-ray repair cross-complementing proteins 1 and 3), *ERCC1* and *ERCC2* (Excision repair cross-complementing rodent repair deficiency, complementation group 1 and 2), *LIG4* (Ligase IV), *ATM* (Ataxia telangiectasia mutated), *XPD* (Xeroderma pigmentosum group D), *MDM2* (Human mouse double-minute 2 protein), *CDKN1A*, and *CDKN1B* (Cyclin-Dependent Kinase Inhibitors 1A, and 1B), *CCND1* (Cyclin D1) as well as *BCL2* (B-cell lymphoma 2) and *TP53* (tumor protein p53) [89–102]. Genetic variants within most of these genes were found to be associated with PCa aggressiveness or response to therapy. Nevertheless, these results were seldom replicated in multiple populations.

The most common SNVs in *XRCC1* studied in case–control studies on cancer risk are rs1799782 (p.Arg194Trp), rs25489 (p.Arg280His), and rs25487 (p.Arg399Gln) [89, 103]. These genetic variants were also analyzed for their potential association with PCa risk in numerous studies, but the obtained results were inconsistent [89, 90]. For rs25489, association with radiation-induced late toxicity in PCa patients was also shown [104]. Similarly, rs861539 (p.Thr241Met) in *XRCC3* was found to be associated with early adverse effects induced by radiotherapy, based on quantitative data synthesis of 6 studies [105].

A recent study conducted in Spain showed the association of rs11615 in *ERCC1* and rs17503908 in *ATM* with PCa aggressiveness [93]. Genetic variants in the same chromosomal region as *ERCC1* were previously analyzed in a large study that provided opposing results. Nevertheless, this previous study was designed as to include subjects from multiple populations, and its results could therefore be influenced by genetic backgrounds of study participants [93, 106].

Among genetic variants located in *MDM2*, missense variant SNP309 in the promoter region was most frequently analyzed. This SNV was found to be associated with both PCa risk and aggressiveness in multiple studies [107, 108]. The first study on this subject yielded no evidence of the supposed association [109]. Nevertheless, results obtained in several later studies suggested the association of SNP309 with the risk of PCa progression to the more advanced stage, or the statistical trend of significance was reached [108].

Numerous studies conducted on a potential association between *CCND1* genetic variant rs603965 (p.Ala870Gly) and PCa risk, yielding inconsistent results [99]. This SNV was found to affect alternative splicing and thus alter the C-terminal domain. Other genetic variants within this gene were shown to be associated with the risk of PCa biochemical reoccurrence after radical prostatectomy [110].

The most extensively analyzed SNV located in *TP53* gene is rs1042522 (p.Arg72Pro). This genetic variant was found to be associated with PCa risk, especially among Caucasians [102]. When it comes to *BCL2*, encoding the founding member of apoptosis regulatory proteins,

promoter SNV c.-938C > A was associated with PCa risk, although lacking replication, as well as with disease-free survival and biochemical recurrence of PCa after radical prostatectomy [100, 101, 111].

4.1.4. Vitamin D signaling

Vitamin D signaling in PCa has stimulatory effect on apoptosis, as well as inhibitory effect on the progression of cell cycle. Therefore, multiple genetic variants within the gene encoding the receptor for vitamin D (*VDR*) were analyzed for their potential association with PCa risk and/or progression. Most of them are loci named FokI, BsmI, ApaI, and T I, according to restriction enzyme used for genotyping, Cdx2 in promoter region and polyA microsatellite, which were most frequently tested [112–114].

Even though the initial results on these loci were promising, in multiple populations, they were not replicated [113, 115]. The association of these genetic variants with PCa progression parameters and the disease outcome also remains inconclusive [113, 116].

4.1.5. Chronic inflammation and angiogenesis

Numerous genes involved in chronic inflammation have been studies for association of genetic variants that reside within them with PCa risk and/or progression [117]. Also, the importance of vascular support to cancer growth stimulated the association studies on PCa analyzing genetic variants located in angiogenesis-related genes [62]. Since these processes are codependent, numerous genes primarily found to be involved in chronic inflammation are also discussed as angiogenesis-related genes, and vice versa.

Among the most important factors of chronic inflammation are *TGF-β*, *COX2*, *TNF-α*, and *IL-1-β*, as well as *PPAR-γ*. To date, several SNVs in *TGF-β1* have been identified as PCa-susceptibility variants, some of them also associated with PCa aggressiveness [118–123]. The studies on the most of the chronic inflammation-related genes provided conflicting results [117].

There have been various PCa case–control studies involving *Vascular endothelial growth factor* (*VEGF*) gene, encoding the important proangiogenic growth factor, as well as genes encoding Interleukin 8 (IL-8) and Interleukin 10 (IL-10) [96, 124–128] for genetic variant rs1570360 [c.-1154G > A] located in the promoter region of *VEGF*, statistically significant association with PCa risk was shown in several studies [126]. Most other *VEGF* genetic variants analyzed for potential association with PCa risk and/or progression are also located in the promoter region [126, 129–131]. These SNVs could be associated with transcription rate of *VEGF* [132], which is positively correlated with tumor stage, Gleason score, as well as with shorter period of disease-free survival [133].

Candidates for this type of studies were also genes encoding transcription factors which regulate the expression of *VEGF*, such as Hypoxia inducible factor 1 (*HIF1A*), Epidermal growth factor (*EGF*), and Lymphotoxin *α* (*LTA*). Nevertheless, except for *HIF1A*, association of genetic variants within these genes with PCa risk was not shown, or was mostly found in small sample studies and poorly replicated [62, 125, 126, 134].

Some of the key regulators of angiogenesis are also fibroblast growth factors (*FGF*s). Therefore, receptor *FGFR4* gene has been analyzed for genetic variants associated with PCa risk and/or progression. The most commonly tested SNV is a missense variant rs351855 (p.Gly388Arg), found to be associated with PCa risk and aggressiveness in a relatively small number of studies [135].

Among the most extensively analyzed candidate genes in PCa-related case-control studies are *NOS3* and *NOS2A*, encoding nitric oxide synthases [136]. Both endothelial and inducible nitric oxide synthases, encoded by these genes, are enzymes that catalyze the production of NO from L-arginine and L-citrulline amino acids [137]. Being the major producer of NO in endothelial cells, eNOS, encoded by *NOS3*, is involved in the control of vascular tone and angiogenesis, which is essential for tumor growth and the development of metastases. Yet, the synthesis of NO is associated with apoptosis, which has the opposing effect on carcinogenesis [138]. Numerous genetic variants within these genes, especially *NOS3*, have been analyzed for potential association with PCa risk and/or progression [136]. Most commonly analyzed SNVs are -786 T > C (rs2070744) and 894G > T (rs1799983) [139–147], while several studies included insertion-deletion polymorphism 4a4b located in intron 4 of *NOS3* [140, 146, 148, 149]. For rs1799983, which is a missense genetic variant, it was hypothesized to affect NOS3 stability [150]. The other common SNV, rs2070744, affects promoter activity by allele C creating a binding site with validation protein 1A (RPA1) [151].

Angiogenesis process and tumor invasion also require degradation of extracellular matrix and basal membranes, which are catalyzed by matrix metalloproteinases. Among the genes encoding this class of enzymes, *MMP2* and *MMP9* are analyzed for genetic variants associated with PCa risk, and also for disease aggressiveness, due to their functional significance in tumor invasiveness [139, 152–156]. Commonly analyzed genetic variant in *MMP2* promoter is rs243865. For minor allele of this SNV it was shown to be associated with reduced transcription rate of *MMP2* [157].

4.1.6. Cellular adhesion

Among genes involved in cellular adhesion, *CDH1* encoding E-cadherin was the candidate gene for the most case-control studies on PCa. Since aberrant expression of this gene is correlated with the increased metastatic potential of PCa, genetic variants in its promoter region were analyzed for potential association with PCa risk and progression [158, 159]. Most extensively studied SNV−160C > A was found to affect *CDH1* expression and was identified as PCa susceptibility genetic variant in multiple populations [158, 160].

Only few studies also included genetic variants in genes encoding intercellular adhesion molecules (ICAMs), proteins involved in cellular adhesion and signaling. The analyzed genetic variants are those located in *ICAM-1*, *ICAM-4*, and *ICAM-5* genes and need a further evaluation for potential association with PCa risk and/or progression [161, 162].

4.2. Long noncoding RNA genes

The potential involvement of long noncoding RNAs (lncRNAs) in prostate carcinogenesis was suggested not only by the results of expression analyses that showed several known oncogenic and/or tumor-suppressive lcnRNAs to be aberrantly expressed in malignant prostatic tissue or plasma samples from patients with PCa but also by the identification of several PCa-specific lncRNAs [163, 164].

Several SNVs in lncRNA genes were identified as PCa susceptibility variants in case–control studies on PCa. In their study published in 2011, Jin et al. have stated that eight SNVs identified to that time through GWAS are located in lncRNA intervals [165]. They also identified a SNV in a putative lncRNA which was not later experimentally confirmed as a PCa-susceptibility variants [165]. In a study published in 2013, Xue et al. have shown the association between two tag-SNPs in Prostate cancer gene expression marker 1 (*PCGEM1*) and PCa risk in Chinese population [166]. Genetic variant in another PCa-specific gene, prostate cancer associated 3 (*PCA3*), was analyzed for the length of a TAAA repeat string in the promoter region. This genetic variant was also found to be associated with PCa risk [167]. In a GWAS published in 2014, Cook et al. have identified rs7918885 in *RP11-543 F8.2* gene as a PCa-susceptibility SNV in West African men, although GWAS statistical significance threshold was not reached [168]. Also, by using fine-mapping and resequencing of PCa-susceptibility subregion of 8q24, *lncRNA* gene prostate cancer noncoding RNA 1 (*PRNCR1*) was found to be located between the most significantly associated genetic variant [169].

4.3. *MicroRNA* genes

Dysregulation of diverse regulatory mechanisms based on microRNA activity has been implicated in prostate carcinogenesis. Therefore, possibly functional genetic variants located in *microRNA* genes emerged as potential PCa-associated loci. Among these genetic variants are those that potentially influence microRNA biogenesis, stability of mature microRNAs, efficiency of target gene regulation, as well as target specificity. By affecting these features of microRNA regulatory mechanisms, microRNA SNVs could be associated with aberrant expression of various important PCa-related oncogenes or tumor-suppressive genes [170–172].

MicroRNA genetic variants have been analyzed for their potential association with PCa in only a few studies conducted in Asian populations and in a single population of European origin. These studies have provided discordant results on the effects of genetic variants in rs2910164 in *hsa-miR-146a* [173–176], *hsa-miR-196a2* [174, 176, 177], and rs3746444 in *hsa-miR-499* gene on PCa risk [174, 177]. In a recent study, rs4705342 located in *hsa-miR-143* gene promoter was found to be associated with the risk of developing PCa [178]. Since the number of conducted studies is small, additional findings from multiple populations are needed in order to make further conclusions.

Another SNV, rs895819 located in a gene encoding miR-27a, which is androgen-regulated and stimulates the androgen signalization in a positive feedback loop, was found to be associated with PCa risk, as well as with the development of distant metastases. Nevertheless, these

results are derived from a single study on PCa risk and rs895819 conducted relatively recent and needs further validation [177].

5. Replication, validation studies, and Meta-analyses

Differences in genetic backgrounds are an important issue in genetic association studies. Therefore, interpretation of data requires discussing the potential differences between populations. Therefore, in order to analyze such differences, multiple validation analyses are conducted in various population and ethnicities. These studies are designed so that they resemble as much as possible to the original study that yielded genetic associations, or the lack of it. The ratio for conducting such studies is the possible lack of association between identified PCa-susceptibility variants with PCa risk in certain populations, or the differences in effect sizes [179]. Replication studies, conducted in confirmation group of participants from the same population in which the initial results were found, is a method of checking reproducibility and evaluating possible false positives and effect overestimation [179, 180].

Currently, replications and validations are conducted for both GWASs results, as well as for results from candidate gene-based studies. Of utmost importance is conducting replication and validation analyses of hits from studies with relatively small sample sizes, as well as with poorly clinically characterized cases with the lack of data on possible confounders, or questionable recruitment of controls [180]. Also, an important issue in case–control studies on PCa is the type of control group, which is in some cases healthy controls, while in others group of patients with benign prostatic hyperplasia (BPH). Furthermore, classification systems for patients with PCa which are used for evaluating potential genetic associations with PCa progression differ between studies, which together with small sizes of patient groups, calls for replication of acquired statistically significant data.

All of these issues are a potential reason for the opposing results on the association of the most of genetic variants analyzed in multiple studies with PCa risk and progression. Therefore, in order to elucidate the effect of these genetic variants, meta-analyses of eligible studies are frequently conducted. Combining the results from smaller studies through data synthesis in meta-analysis could result in increased statistical power [181]. Therefore, meta-analyses could provide more precise estimations, as well as the insight in the potential effect of confounders [182], such as ethnicity, participant recruitment strategy, or study size.

6. Future perspectives

The main aim of genetic association studies on PCa is the identification of potential PCa genetic markers which could be used for constructing reliable algorithms for evaluating the risk for PCa development and/or PCa progression [1]. Therefore, it is important not only to identify these PCa-related genetic variants, but also to precisely characterize their effect sizes. In order to do that, ethnic differences need to be taken into account [179]. Other important issues in

interpreting results of association studies are gene–gene and gene-environment interactions. Therefore, future research and designing such algorithms require integration of knowledge on genetic associations, cellular pathways, and statistical epistasis in which real biological interaction could be reflected.

Since the major problem in clinical practice related to PCa is the overdiagnosis and monitoring of patients [4], additional studies on PCa aggressiveness with clinically well characterized groups of PCa patients are needed to identify genetic variants associated with PCa progression risk. The later implementation of algorithms based on these genetic variants could greatly improve clinical protocols in monitoring and treating PCa.

7. Conclusion

The efforts for improving clinical protocols in PCa diagnostics, monitoring and treatment resulted in conducting genetic association studies on PCa. These studies aim to identify potential PCa genetic markers and characterize their association with PCa risk and/or progression through measuring effect sizes. The identified and validated genetic markers could then be used for constructing reliable algorithms for evaluating the risk for PCa development and, more importantly, for PCa progression. Implementing such algorithms in clinical practice is expected to improve the distinction between early diagnosed PCa cases that require aggressive treatment and latent PCa cases which remain indolent during patient's lifetime.

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References

[1] Goh CL, Eeles RA. Germline genetic variants associated with prostate cancer and potential relevance to clinical practice. In: Cuzick J, Thorat MA, editors. Prostate Cancer Prevention. Heidelberg, Germany: Springer; 2014. pp. 9–26. (Recent Results in Cancer Research; vol 202).

[2] Boyd LK, Mao X, Lu YJ. The complexity of prostate cancer: genomic alterations and heterogeneity. Nat Rev Urol. 2012; 9(11):652–64. doi: 10.1038/nrurol.2012.185.

[3] Alberti C. Hereditary/familial versus sporadic prostate cancer: few indisputable genetic differences and many similar clinicopathological features. Eur Rev Med Pharmacol Sci. 2010; 14(1):31–41.

[4] Mühlberger N, Kurzthaler C, Iskandar R, Krahn MD, Bremner KE, Oberaigner W, et al. The ONCOTYROL Prostate Cancer Outcome and Policy Model: Effect of Prevalence Assumptions on the Benefit-Harm Balance of Screening. Med Decis Making. 2015; 35(6):758–72.

[5] Klotz L. Active surveillance for favorable-risk prostate cancer: background, patient selection, triggers for intervention, and outcomes. Curr Urol Rep. 2012;13(2):1539.

[6] Chen R, Ren S, Sun Y. Genome-wide association studies on prostate cancer: the end or the beginning? Protein Cell. 2013; 4(9):677–86.

[7] Cartwright R, Mangera A, Tikkinen KA, Rajan P, Pesonen J, Kirby AC, Thiagamoorthy G, Ambrose C, Gonzalez-Maffe J, Bennett PR, Palmer T, Walley A, Järvelin MR, Khullar V, Chapple C. Systematic review and meta-analysis of candidate gene association studies of lower urinary tract symptoms in men. Eur Urol. 2014 Oct;66(4):752–68. doi: 10.1016/j.eururo.2014.01.007.

[8] Smith JR, Freije D, Carpten JD, Grönberg H, Xu J, Isaacs SD, Brownstein MJ, Bova GS, Guo H, Bujnovszky P, Nusskern DR, Damber JE, Bergh A, Emanuelsson M, Kallioniemi OP, Walker-Daniels J, Bailey-Wilson JE, Beaty TH, Meyers DA, Walsh PC, Collins FS, Trent JM, Isaacs WB. Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. Science. 1996; 274(5291):1371–4.

[9] Berthon P1, Valeri A, Cohen-Akenine A, Drelon E, Paiss T, Wöhr G, Latil A, Millasseau P, Mellah I, Cohen N, Blanché H, Bellané-Chantelot C, Demenais F, Teillac P, Le Duc A, de Petriconi R, Hautmann R, Chumakov I, Bachner L, Maitland NJ, Lidereau R, Vogel W, Fournier G, Mangin P, Cussenot O, et al. Predisposing gene for early-onset prostate cancer, localized on chromosome 1q42.2-43. Am J Hum Genet. 1998; 62(6): 1416–24.

[10] Xu J, Meyers D, Freije D, Isaacs S, Wiley K, Nusskern D, Ewing C, Wilkens E, Bujnovszky P, Bova GS, Walsh P, Isaacs W, Schleutker J, Matikainen M, Tammela T, Visakorpi T, Kallioniemi OP, Berry R, Schaid D, French A, McDonnell S, Schroeder J, Blute M, Thibodeau S, Grönberg H, Emanuelsson M, Damber JE, Bergh A, Jonsson BA, Smith J, Bailey-Wilson J, Carpten J, Stephan D, Gillanders E, Amundson I, Kainu T, Freas-Lutz D, Baffoe-Bonnie A, Van Aucken A, Sood R, Collins F, Brownstein M, Trent J. Evidence for a prostate cancer susceptibility locus on the X chromosome. Nat Genet. 1998; 20(2):175–9.

[11] Carpten J, Nupponen N, Isaacs S, Sood R, Robbins C, Xu J, Faruque M, Moses T, Ewing C, Gillanders E, Hu P, Bujnovszky P, Makalowska I, Baffoe-Bonnie A, Faith D, Smith J, Stephan D, Wiley K, Brownstein M, Gildea D, Kelly B, Jenkins R, Hostetter G, Matikainen M, Schleutker J, Klinger K, Connors T, Xiang Y, Wang Z, De Marzo A, Papadopoulos N, Kallioniemi OP, Burk R, Meyers D, Grönberg H, Meltzer P, Silverman

R, Bailey-Wilson J, Walsh P, Isaacs W, Trent J. Germline mutations in the ribonuclease L gene in families showing linkage with HPC1. Nat Genet. 2002; 30(2):181–4

[12] Tavtigian SV, Simard J, Teng DH, Abtin V, Baumgard M, Beck A, Camp NJ, Carillo AR, Chen Y, Dayananth P, Desrochers M, Dumont M, Farnham JM, Frank D, Frye C, Ghaffari S, Gupte JS, Hu R, Iliev D, Janecki T, Kort EN, Laity KE, Leavitt A, Leblanc G, McArthur-Morrison J, Pederson A, Penn B, Peterson KT, Reid JE, Richards S, Schroeder M, Smith R, Snyder SC, Swedlund B, Swensen J, Thomas A, Tranchant M, Woodland AM, Labrie F, Skolnick MH, Neuhausen S, Rommens J, Cannon-Albright LA. A candidate prostate cancer susceptibility gene at chromosome 17p. Nat Genet. 2001; 27(2):172–80.

[13] Hood L, Rowen L. The Human Genome Project: big science transforms biology and medicine. Genome Med. 2013; 5(9):79.

[14] Shen H. Progress of cancer genomics. Thorac Cancer. 2015; 6(5):557-60. doi: 10.1111/1759-7714.12281.

[15] Sullivan J, Kopp R, Stratton K, Manschreck C, Corines M, Rau-Murthy R, Hayes J, Lincon A, Ashraf A, Thomas T, Schrader K, Gallagher D, Hamilton R, Scher H, Lilja H, Scardino P, Eastham J, Offit K, Vijai J, Klein RJ. An analysis of the association between prostate cancer risk loci, PSA levels, disease aggressiveness and disease-specific mortality. Br J Cancer. 2015; 113(1):166-72. doi: 10.1038/bjc.2015.199.

[16] Al Olama AA, Kote-Jarai Z, Berndt SI, Conti DV, Schumacher F, Han Y, Benlloch S, Hazelett DJ, Wang Z, Saunders E, Leongamornlert D, Lindstrom S, Jugurnauth-Little S, Dadaev T, Tymrakiewicz M, Stram DO, Rand K, Wan P, Stram A, Sheng X, Pooler LC, Park K, Xia L, Tyrer J, Kolonel LN, Le Marchand L, Hoover RN, Machiela MJ, Yeager M, Burdette L, Chung CC, Hutchinson A, Yu K, Goh C, Ahmed M, Govindasami K, Guy M, Tammela TL, Auvinen A, Wahlfors T, Schleutker J, Visakorpi T, Leinonen KA, Xu J, Aly M, Donovan J, Travis RC, Key TJ, Siddiq A, Canzian F, Khaw KT, Takahashi A, Kubo M, Pharoah P, Pashayan N, Weischer M, Nordestgaard BG, Nielsen SF, Klarskov P, Røder MA, Iversen P, Thibodeau SN, McDonnell SK, Schaid DJ, Stanford JL, Kolb S, Holt S, Knudsen B, Coll AH, Gapstur SM, Diver WR, Stevens VL, Maier C, Luedeke M, Herkommer K, Rinckleb AE, Strom SS, Pettaway C, Yeboah ED, Tettey Y, Biritwum RB, Adjei AA, Tay E, Truelove A, Niwa S, Chokkalingam AP, Cannon-Albright L, Cybulski C, Wokołorczyk D, Kluźniak W, Park J, Sellers T, Lin HY, Isaacs WB, Partin AW, Brenner H, Dieffenbach AK, Stegmaier C, Chen C, Giovannucci EL, Ma J, Stampfer M, Penney KL, Mucci L, John EM, Ingles SA, Kittles RA, Murphy AB, Pandha H, Michael A, Kierzek AM, Blot W, Signorello LB, Zheng W, Albanes D, Virtamo J, Weinstein S, Nemesure B, Carpten J, Leske C, Wu SY, Hennis A, Kibel AS, Rybicki BA, Neslund-Dudas C, Hsing AW, Chu L, Goodman PJ, Klein EA, Zheng SL, Batra J, Clements J, Spurdle A, Teixeira MR, Paulo P, Maia S, Slavov C, Kaneva R, Mitev V, Witte JS, Casey G, Gillanders EM, Seminara D, Riboli E, Hamdy FC, Coetzee GA, Li Q, Freedman ML, Hunter DJ, Muir K, Gronberg H, Neal DE, Southey M, Giles GG, Severi G; Breast and Prostate Cancer Cohort Consortium (BPC3); PRACTICAL

(Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome) Consortium; COGS (Collaborative Oncological Gene-environment Study) Consortium; GAME-ON/ELLIPSE Consortium, Cook MB, Nakagawa H, Wiklund F, Kraft P, Chanock SJ, Henderson BE, Easton DF, Eeles RA, Haiman CA. A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. Nat Genet. 2014; 46(10):1103–9, doi: 10.1038/ng.3094.

[17] Gudmundsson J, Sulem P, Manolescu A, Amundadottir LT, Gudbjartsson D, Helgason A, Rafnar T, Bergthorsson JT, Agnarsson BA, Baker A, Sigurdsson A, Benediktsdottir KR, Jakobsdottir M, Xu J, Blondal T, Kostic J, Sun J, Ghosh S, Stacey SN, Mouy M, Saemundsdottir J, Backman VM, Kristjansson K, Tres A, Partin AW, Albers-Akkers MT, Godino-Ivan Marcos J, Walsh PC, Swinkels DW, Navarrete S, Isaacs SD, Aben KK, Graif T, Cashy J, Ruiz-Echarri M, Wiley KE, Suarez BK, Witjes JA, Frigge M, Ober C, Jonsson E, Einarsson GV, Mayordomo JI, Kiemeney LA, Isaacs WB, Catalona WJ, Barkardottir RB, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. Nat Genet. 2007; 39(5):631–7.

[18] Haiman CA, Patterson N, Freedman ML, Myers SR, Pike MC, Waliszewska A, Neubauer J, Tandon A, Schirmer C, McDonald GJ, Greenway SC, Stram DO, Le Marchand L, Kolonel LN, Frasco M, Wong D, Pooler LC, Ardlie K, Oakley-Girvan I, Whittemore AS, Cooney KA, John EM, Ingles SA, Altshuler D, Henderson BE, Reich D. Multiple regions within 8q24 independently affect risk for prostate cancer. Nat Genet. 2007; 39(5):638-44.

[19] Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, Minichiello MJ, Fearnhead P, Yu K, Chatterjee N, Wang Z, Welch R, Staats BJ, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cancel-Tassin G, Cussenot O, Valeri A, Andriole GL, Gelmann EP, Tucker M, Gerhard DS, Fraumeni JF Jr, Hoover R, Hunter DJ, Chanock SJ, Thomas G. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet. 2007; 39(5):645-9.

[20] Witte JC. Genome-Wide Association Studies and Beyond. Annu Rev Public Health. 2010; 31:9-20. doi: 10.1146/annurev.publhealth.012809.103723.

[21] Lange EM, Salinas CA, Zuhlke KA, Ray AM, Wang Y, Lu Y, Ho LA, Luo J, Cooney KA. Early onset prostate cancer has a significant genetic component. Prostate. 2012; 72(2): 147-56. doi: 10.1002/pros.21414. Epub 2011 May 2. PubMed PMID: 21538423; PubMed Central PMCID: PMC3784829.

[22] Schierding W, Cutfield WS, O'Sullivan JM. The missing story behind Genome Wide Association Studies: single nucleotide polymorphisms in gene deserts have a story to tell. Front Genet. 2014; 5:39. doi: 10.3389/fgene.2014.00039.

[23] Wasserman NF, Aneas I, Nobrega MA. An 8q24 gene desert variant associated with prostate cancer risk confers differential in vivo activity to a MYC enhancer. Genome Res. 2010; 20(9):1191-7. doi: 10.1101/gr.105361.110.

[24] Huppi K, Pitt JJ, Wahlberg BM, Caplen NJ. The 8q24 gene desert: an oasis of non-coding transcriptional activity. Front Genet. 2012; 3:69. doi: 10.3389/fgene.2012.00069.

[25] Li Q, Liu X, Hua RX, Wang F, An H, Zhang W, Zhu JH. Association of three 8q24 polymorphisms with prostate cancer susceptibility: evidence from a meta-analysis with 50,854 subjects. Sci Rep. 2015; 5:12069. doi: 10.1038/srep12069.

[26] Amundadottir LT, Sulem P, Gudmundsson J, Helgason A, Baker A, Agnarsson BA, Sigurdsson A, Benediktsdottir KR, Cazier JB, Sainz J, Jakobsdottir M, Kostic J, Magnusdottir DN, Ghosh S, Agnarsson K, Birgisdottir B, Le Roux L, Olafsdottir A, Blondal T, Andresdottir M, Gretarsdottir OS, Bergthorsson JT, Gudbjartsson D, Gylfason A, Thorleifsson G, Manolescu A, Kristjansson K, Geirsson G, Isaksson H, Douglas J, Johansson JE, Bälter K, Wiklund F, Montie JE, Yu X, Suarez BK, Ober C, Cooney KA, Gronberg H, Catalona WJ, Einarsson GV, Barkardottir RB, Gulcher JR, Kong A, Thorsteinsdottir U, Stefansson K. A common variant associated with prostate cancer in European and African populations. Nat Genet. 2006; 38(6):652–8.

[27] Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, Yu K, Chatterjee N, Welch R, Hutchinson A, Crenshaw A, Cancel-Tassin G, Staats BJ, Wang Z, Gonzalez-Bosquet J, Fang J, Deng X, Berndt SI, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cussenot O, Valeri A, Andriole GL, Crawford ED, Tucker M, Gerhard DS, Fraumeni JF Jr, Hoover R, Hayes RB, Hunter DJ, Chanock SJ. Multiple loci identified in a genome-wide association study of prostate cancer. Nat Genet. 2008; 40(3):310–5. doi: 10.1038/ng.91.

[28] Zheng SL, Sun J, Cheng Y, Li G, Hsu FC, Zhu Y, Chang BL, Liu W, Kim JW, Turner AR, Gielzak M, Yan G, Isaacs SD, Wiley KE, Sauvageot J, Chen HS, Gurganus R, Mangold LA, Trock BJ, Gronberg H, Duggan D, Carpten JD, Partin AW, Walsh PC, Xu J, Isaacs WB. Association between two unlinked loci at 8q24 and prostate cancer risk among European Americans. J Natl Cancer Inst. 2007; 99(20):1525–33.

[29] Cussenot O, Azzouzi AR, Bantsimba-Malanda G, Gaffory C, Mangin P, Cormier L, Fournier G, Valeri A, Jouffe L, Roupret M, Fromont G, Sibony M, Comperat E, Cancel-Tassin G. Effect of genetic variability within 8q24 on aggressiveness patterns at diagnosis and familial status of prostate cancer. Clin Cancer Res. 2008; 14(17):5635–9. doi: 10.1158/1078-0432.CCR-07-4999.

[30] Suzuki M, Liu M, Kurosaki T, Suzuki M, Arai T, Sawabe M, Kasuya Y, Kato M, Fujimura T, Fukuhara H, Enomoto Y, Nishimatsu H, Ishikawa A, Kume H, Homma Y, Kitamura T. Association of rs6983561 polymorphism at 8q24 with prostate cancer mortality in a Japanese population. Clin Genitourin Cancer. 2011; 9(1):46–52. doi: 10.1016/j.clgc.2011.04.004.

[31] Bensen JT, Xu Z, Smith GJ, Mohler JL, Fontham ET, Taylor JA. Genetic polymorphism and prostate cancer aggressiveness: a case-only study of 1,536 GWAS and candidate SNPs in African-Americans and European-Americans. Prostate. 2013; 73(1):11–22. doi: 10.1002/pros.22532.

[32] Grin B, Loeb S, Roehl K, Cooper PR, Catalona WJ, Helfand BT. A rare 8q24 single nucleotide polymorphism (SNP) predisposes North American men to prostate cancer and possibly more aggressive disease. BJU Int. 2015; 115(1):101–5. doi: 10.1111/bju.12847.

[33] Koh CM, Bieberich CJ, Dang CV, Nelson WG, Yegnasubramanian S, De Marzo AM. MYC and Prostate Cancer. Genes Cancer. 2010; 1(6):617–28. doi: 10.1177/1947601910379132.

[34] Ahmadiyeh N, Pomerantz MM, Grisanzio C, Herman P, Jia L, Almendro V, He HH, Brown M, Liu XS, Davis M, Caswell JL, Beckwith CA, Hills A, Macconaill L, Coetzee GA, Regan MM, Freedman ML. 8q24 prostate, breast, and colon cancer risk loci show tissue-specific long-range interaction with MYC. Proc Natl Acad Sci U S A. 2010; 107(21):9742–6. doi: 10.1073/pnas.0910668107.

[35] Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G, Manolescu A, Rafnar T, Gudbjartsson D, Agnarsson BA, Baker A, Sigurdsson A, Benediktsdottir KR, Jakobsdottir M, Blondal T, Stacey SN, Helgason A, Gunnarsdottir S, Olafsdottir A, Kristinsson KT, Birgisdottir B, Ghosh S, Thorlacius S, Magnusdottir D, Stefansdottir G, Kristjansson K, Bagger Y, Wilensky RL, Reilly MP, Morris AD, Kimber CH, Adeyemo A, Chen Y, Zhou J, So WY, Tong PC, Ng MC, Hansen T, Andersen G, Borch-Johnsen K, Jorgensen T, Tres A, Fuertes F, Ruiz-Echarri M, Asin L, Saez B, van Boven E, Klaver S, Swinkels DW, Aben KK, Graif T, Cashy J, Suarez BK, van Vierssen Trip O, Frigge ML, Ober C, Hofker MH, Wijmenga C, Christiansen C, Rader DJ, Palmer CN, Rotimi C, Chan JC, Pedersen O, Sigurdsson G, Benediktsson R, Jonsson E, Einarsson GV, Mayordomo JI, Catalona WJ, Kiemeney LA, Barkardottir RB, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nat Genet. 2007 Aug; 39(8):977–83.

[36] Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, Jugurnauth SK, Mulholland S, Leongamornlert DA, Edwards SM, Morrison J, Field HI, Southey MC, Severi G, Donovan JL, Hamdy FC, Dearnaley DP, Muir KR, Smith C, Bagnato M, Ardern-Jones AT, Hall AL, O'Brien LT, Gehr-Swain BN, Wilkinson RA, Cox A, Lewis S, Brown PM, Jhavar SG, Tymrakiewicz M, Lophatananon A, Bryant SL; UK Genetic Prostate Cancer Study Collaborators; British Association of Urological Surgeons' Section of Oncology; UK ProtecT Study Collaborators, Horwich A, Huddart RA, Khoo VS, Parker CC, Woodhouse CJ, Thompson A, Christmas T, Ogden C, Fisher C, Jamieson C, Cooper CS, English DR, Hopper JL, Neal DE, Easton DF. Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet. 2008; 40(3):316–21. doi: 10.1038/ng.90.

[37] Sun J, Purcell L, Gao Z, Isaacs SD, Wiley KE, Hsu FC, Liu W, Duggan D, Carpten JD, Grönberg H, Xu J, Chang BL, Partin AW, Walsh PC, Isaacs WB, Zheng SL. Association between sequence variants at 17q12 and 17q24.3 and prostate cancer risk in European and African Americans. Prostate. 2008; 68(7):691–7. doi:10.1002/pros.20754.

[38] Zheng SL, Sun J, Wiklund F, Smith S, Stattin P, Li G, Adami HO, Hsu FC, Zhu Y, Bälter K, Kader AK, Turner AR, Liu W, Bleecker ER, Meyers DA, Duggan D, Carpten JD, Chang BL, Isaacs WB, Xu J, Grönberg H. Cumulative association of five genetic variants with prostate cancer. N Engl J Med. 2008; 358(9):910–9. doi:10.1056/NEJMoa075819.

[39] Levin AM, Machiela MJ, Zuhlke KA, Ray AM, Cooney KA, Douglas JA. Chromosome 17q12 variants contribute to risk of early-onset prostate cancer. Cancer Res. 2008; 68(16): 6492–5. doi: 10.1158/0008-5472.CAN-08-0348.

[40] Stevens VL, Ahn J, Sun J, Jacobs EJ, Moore SC, Patel AV, Berndt SI, Albanes D, Hayes RB. HNF1B and JAZF1 genes, diabetes, and prostate cancer risk. Prostate. 2010; 70(6): 601–7. doi: 10.1002/pros.21094.

[41] Berndt SI, Sampson J , Yeager M, Jacobs KB, Wang Z, Hutchinson A, Chung C, Orr N, Wacholder S, Chatterjee N, Yu K, Kraft P, Feigelson HS, Thun MJ, Diver WR, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Cancel-Tassin G, Cussenot O, Valeri A, Andriole GL, Crawford ED, Haiman C, HendersonB, Kolonel L, Le Marchand L, Siddiq A, Riboli E, Travis RC, KaaksR, Isaacs W, Isaacs S, Wiley KE, Gronberg H, Wiklund F, Stattin P, Xu J, Zheng SL, Sun J, Vatten LJ, Hveem K, Njølstad I, Gerhard DS, Tucker M, Hayes RB, Hoover RN, Fraumeni JF Jr, Hunter DJ, Thomas G, Chanock SJ. Large-scale fine mapping of the HNF1B locus and prostate cancer risk. Hum Mol Genet. 2011; 20(16):3322–9. doi: 10.1093/hmg/ddr213.

[42] Kim HJ, Bae JS, Lee J, Chang IH, Kim KD, Shin HD, Han JH, Lee SY, Kim W, Myung SC. HNF1B polymorphism associated with development of prostate cancer in Korean patients. Urology. 2011 Oct;78(4):969.e1–6. doi: 10.1016/j.urology.2011.06.045.

[43] Nikolić ZZ, Branković AS, Savić-Pavićević DL, Preković SM, Vukotić VD, Cerović SJ, Filipović NN, Tomović SM, Romac SP, Brajušković GN. Assessment of association between common variants at 17q12 and prostate cancer risk-evidence from Serbian population and meta-analysis. Clin Transl Sci. 2014; 7(4):307–13. doi:10.1111/cts.12130.

[44] Chang BL, Spangler E, Gallagher S, Haiman CA, Henderson B, Isaacs W, Benford ML, Kidd LR, Cooney K, Strom S, Ingles SA, Stern MC, Corral R, Joshi AD, Xu J, Giri VN, Rybicki B, Neslund-Dudas C, Kibel AS, Thompson IM, Leach RJ, Ostrander EA, Stanford JL, Witte J, Casey G, Eeles R, Hsing AW, Chanock S, Hu JJ, John EM, Park J, Stefflova K, Zeigler-Johnson C, Rebbeck TR. Validation of genome-wide prostate cancer associations in men of African descent. Cancer Epidemiol Biomarkers Prev. 2011; 20(1): 23–32. doi: 10.1158/1055-9965.EPI-10-0698.

[45] Haiman CA, Chen GK, Blot WJ, Strom SS, Berndt SI, Kittles RA, Rybicki BA, Isaacs WB, Ingles SA, Stanford JL, Diver WR, Witte JS, Hsing AW, Nemesure B, Rebbeck TR, Cooney KA, Xu J, Kibel AS, Hu JJ, John EM, Gueye SM, Watya S, Signorello LB, Hayes

RB, Wang Z, Yeboah E, Tettey Y, Cai Q, Kolb S, Ostrander EA, Zeigler-Johnson C, Yamamura Y, Neslund-Dudas C, Haslag-Minoff J, Wu W, Thomas V, Allen GO, Murphy A, Chang BL, Zheng SL, Leske MC, Wu SY, Ray AM, Hennis AJ, Thun MJ, Carpten J, Casey G, Carter EN, Duarte ER, Xia LY, Sheng X, Wan P, Pooler LC, Cheng I, Monroe KR, Schumacher F, Le Marchand L, Kolonel LN, Chanock SJ, Van Den Berg D, Stram DO, Henderson BE. Genome-wide association study of prostate cancer in men of African ancestry identifies a susceptibility locus at 17q21. Nat Genet. 2011; 43(6):5703. doi: 10.1038/ng.839.

[46] Hooker S, Hernandez W, Chen H, Robbins C, Torres JB, Ahaghotu C, Carpten J, Kittles RA. Replication of prostate cancer risk loci on 8q24, 11q13, 17q12, 19q33, and Xp11 in African Americans. Prostate. 2010; 70(3):270-5. doi:10.1002/pros.21061.

[47] Chornokur G, Amankwah EK, Davis SN, Phelan CM, Park JY, Pow-Sang J, Kumar NB. Variation in HNF1B and obesity may influence prostate cancer risk in African American men: a pilot study. Prostate Cancer. 2013; 2013:384594. doi:10.1155/2013/384594.

[48] Zhang X, Cowper-Sal lari R, Bailey SD, Moore JH, Lupien M. Integrative functional genomics identifies an enhancer looping to the SOX9 gene disrupted by the 17q24.3 prostate cancer risk locus. Genome Res. 2012; 22(8):1437-46. doi:10.1101/gr.135665.111.

[49] Camp NJ, Farnham JM, Wong J, Christensen GB, Thomas A, Cannon-Albright LA. Replication of the 10q11 and Xp11 prostate cancer risk variants: results from a Utah pedigree-based study. Cancer Epidemiol Biomarkers Prev. 2009; 18(4):1290-4. doi: 10.1158/1055-9965.EPI-08-0327.

[50] Takata R, Akamatsu S, Kubo M, Takahashi A, Hosono N, Kawaguchi T, Tsunoda T, Inazawa J, Kamatani N, Ogawa O, Fujioka T, Nakamura Y, Nakagawa H. Genome-wide association study identifies five new susceptibility loci for prostate cancer in the Japanese population. Nat Genet. 2010; 42(9):751-4. doi: 10.1038/ng.635.

[51] Wang Y, Ray AM, Johnson EK, Zuhlke KA, Cooney KA, Lange EM. Evidence for an association between prostate cancer and chromosome 8q24 and 10q11 genetic variants in African American men: the Flint Men's Health Study. Prostate. 2011; 71(3):225–31. doi: 10.1002/pros.21234.

[52] Jin G, Lu L, Cooney KA, Ray AM, Zuhlke KA, Lange EM, Cannon-Albright LA, Camp NJ, Teerlink CC, Fitzgerald LM, Stanford JL, Wiley KE, Isaacs SD, Walsh PC, Foulkes WD, Giles GG, Hopper JL, Severi G, Eeles R, Easton D, Kote-Jarai Z, Guy M, Rinckleb A, Maier C, Vogel W, Cancel-Tassin G, Egrot C, Cussenot O, Thibodeau SN, McDonnell SK, Schaid DJ, Wiklund F, Grönberg H, Emanuelsson M, Whittemore AS, Oakley-Girvan I, Hsieh CL, Wahlfors T, Tammela T, Schleutker J, Catalona WJ, Zheng SL, Ostrander EA, Isaacs WB, Xu J; International Consortium for Prostate Cancer Genetics. Validation of prostate cancer risk-related loci identified from genome-wide association studies using family-based association analysis: evidence from the International Consortium for Prostate Cancer Genetics (ICPCG). Hum Genet. 2012; 131(7):1095–103. doi: 10.1007/s00439-011-1136-0.

[53] Teerlink CC, Thibodeau SN, McDonnell SK, Schaid DJ, Rinckleb A, Maier C, Vogel W, Cancel-Tassin G, Egrot C, Cussenot O, Foulkes WD, Giles GG, Hopper JL, Severi G, Eeles R, Easton D, Kote-Jarai Z, Guy M, Cooney KA, Ray AM, Zuhlke KA, Lange EM, Fitzgerald LM, Stanford JL, Ostrander EA, Wiley KE, Isaacs SD, Walsh PC, Isaacs WB, Wahlfors T, Tammela T, Schleutker J, Wiklund F, Grönberg H, Emanuelsson M, Carpten J, Bailey-Wilson J, Whittemore AS, Oakley-Girvan I, Hsieh CL, Catalona WJ, Zheng SL, Jin G, Lu L, Xu J; International Consortium for Prostate Cancer Genetics, Camp NJ, Cannon-Albright LA. Association analysis of 9,560 prostate cancer cases from the International Consortium of Prostate Cancer Genetics confirms the role of reported prostate cancer associated SNPs for familial disease. Hum Genet. 2014; 133(3):347–56. doi:10.1007/s00439-013-1384-2.

[54] Fernandez P, Salie M, du Toit D, van der Merwe A. Analysis of prostate cancer susceptibility variants in South African men: replicating associations on chromosomes 8q24 and 10q11. Prostate Cancer. 2015; 2015:465184. doi:10.1155/2015/465184.

[55] Jinga V, Csiki IE, Manolescu A, Iordache P, Mates IN, Radavoi D, Rascu S, Badescu D, Badea P, Mates D. Replication study of 34 common SNPs associated with prostate cancer in the Romanian population. J Cell Mol Med. 2016. doi:10.1111/jcmm.12729.

[56] Yeager M, Deng Z, Boland J, Matthews C, Bacior J, Lonsberry V, Hutchinson A, Burdett LA, Qi L, Jacobs KB, Gonzalez-Bosquet J, Berndt SI, Hayes RB, Hoover RN, Thomas G, Hunter DJ, Dean M, Chanock SJ. Comprehensive resequence analysis of a 97 kb region of chromosome 10q11.2 containing the MSMB gene associated with prostate cancer. Hum Genet. 2009; 126(6):743-50. doi:10.1007/s00439-009-0723-9.

[57] Lou H, Yeager M, Li H, Bosquet JG, Hayes RB, Orr N, Yu K, Hutchinson A, Jacobs KB, Kraft P, Wacholder S, Chatterjee N, Feigelson HS, Thun MJ, Diver WR, Albanes D, Virtamo J, Weinstein S, Ma J, Gaziano JM, Stampfer M, Schumacher FR, Giovannucci E, Cancel-Tassin G, Cussenot O, Valeri A, Andriole GL, Crawford ED, Anderson SK, Tucker M, Hoover RN, Fraumeni JF Jr, Thomas G, Hunter DJ, Dean M, Chanock SJ. Fine mapping and functional analysis of a common variant in MSMB on chromosome 10q11.2 associated with prostate cancer susceptibility. Proc Natl Acad Sci U S A. 2009; 106(19):7933-8. doi: 10.1073/pnas.0902104106.

[58] Pomerantz MM, Shrestha Y, Flavin RJ, Regan MM, Penney KL, Mucci LA, Stampfer MJ, Hunter DJ, Chanock SJ, Schafer EJ, Chan JA, Tabernero J, Baselga J, Richardson AL, Loda M, Oh WK, Kantoff PW, Hahn WC, Freedman ML. Analysis of the 10q11 cancer risk locus implicates MSMB and NCOA4 in human prostate tumorigenesis. PLoS Genet. 2010; 6(11):e1001204. doi:10.1371/journal.pgen.1001204.

[59] Parikh H, Wang Z, Pettigrew KA, Jia J, Daugherty S, Yeager M, Jacobs KB, Hutchinson A, Burdett L, Cullen M, Qi L, Boland J, Collins I, Albert TJ, Vatten LJ, Hveem K, Njølstad I, Cancel-Tassin G, Cussenot O, Valeri A, Virtamo J, Thun MJ, Feigelson HS, Diver WR, Chatterjee N, Thomas G, Albanes D, Chanock SJ, Hunter DJ, Hoover R, Hayes RB, Berndt SI, Sampson J, Amundadottir L. Fine mapping the KLK3 locus on chromosome

19q13.33 associated with prostate cancer susceptibility and PSA levels. Hum Genet. 2011; 129(6):675–85. doi:10.1007/s00439-011-0953-5.

[60] Xu J, Mo Z, Ye D, Wang M, Liu F, Jin G, Xu C, Wang X, Shao Q, Chen Z, Tao Z, Qi J, Zhou F, Wang Z, Fu Y, He D, Wei Q, Guo J, Wu D, Gao X, Yuan J, Wang G, Xu Y, Wang G, Yao H, Dong P, Jiao Y, Shen M, Yang J, Ou-Yang J, Jiang H, Zhu Y, Ren S, Zhang Z, Yin C, Gao X, Dai B, Hu Z, Yang Y, Wu Q, Chen H, Peng P, Zheng Y, Zheng X, Xiang Y, Long J, Gong J, Na R, Lin X, Yu H, Wang Z, Tao S, Feng J, Sun J, Liu W, Hsing A, Rao J, Ding Q, Wiklund F, Gronberg H, Shu XO, Zheng W, Shen H, Jin L, Shi R, Lu D, Zhang X, Sun J, Zheng SL, Sun Y. Genome-wide association study in Chinese men identifies two new prostate cancer risk loci at 9q31.2 and 19q13.4. Nat Genet. 2012; 44(11):1231–5. doi: 10.1038/ng.2424.

[61] Hsing AW, Chokkalingam AP. Prostate cancer epidemiology. Front Biosci. 2006; 11:1388-413.

[62] Dianat SS, Margreiter M, Eckersberger E, Finkelstein J, Kuehas F, Herwig R, Ayati M, Lepor H, Djavan B. Gene polymorphisms and prostate cancer: the evidence. BJU Int. 2009; 104(11):1560-72. doi: 10.1111/j.1464-410X.2009.08973.x.

[63] Sissung TM, Price DK, Del Re M, Ley AM, Giovannetti E, Figg WD, Danesi R. Genetic variation: effect on prostate cancer. Biochim Biophys Acta. 2014; 1846(2):446-56. doi: 10.1016/j.bbcan.2014.08.007.

[64] Chang CQ, Yesupriya A, Rowell JL, Pimentel CB, Clyne M, Gwinn M, Khoury MJ, Wulf A, Schully SD. A systematic review of cancer GWAS and candidate gene meta-analyses reveals limited overlap but similar effect sizes. Eur J Hum Genet. 2014; 22(3):402-8. doi: 10.1038/ejhg.2013.161.

[65] Slaby O, Bienertova-Vasku J, Svoboda M, Vyzula R. Genetic polymorphisms and microRNAs: new direction in molecular epidemiology of solid cancer. J Cell Mol Med. 2012; 16(1):8-21. doi: 10.1111/j.1582-4934.2011.01359.x.

[66] Lindström S, Ma J, Altshuler D, Giovannucci E, Riboli E, Albanes D, Allen NE, Berndt SI, Boeing H, Bueno-de-Mesquita HB, Chanock SJ, Dunning AM, Feigelson HS, Gaziano JM, Haiman CA, Hayes RB, Henderson BE, Hunter DJ, Kaaks R, Kolonel LN, Le Marchand L, Martínez C, Overvad K, Siddiq A, Stampfer M, Stattin P, Stram DO, Thun MJ, Trichopoulos D, Tumino R, Virtamo J, Weinstein SJ, Yeager M, Kraft P, Freedman ML. A large study of androgen receptor germline variants and their relation to sex hormone levels and prostate cancer risk. Results from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. J Clin Endocrinol Metab. 2010; 95(9):E121-7. doi: 10.1210/jc.2009-1911.

[67] Chamberlain NL, Driver ED, Miesfeld RL. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. Nucleic Acids Res. 1994; 22:3181-6. 10.1093/nar/22.15.3181.

[68] Price DK, Chau CH, Till C, Goodman PJ, Baum CE, Ockers SB, English BC, Minasian L, Parnes HL, Hsing AW, Reichardt JK, Hoque A, Tangen CM, Kristal AR, Thompson IM, Figg WD. Androgen receptor CAG repeat length and association with prostate cancer risk: results from the prostate cancer prevention trial. J Urol. 2010; 184(6): 2297-302. doi: 10.1016/j.juro.2010.08.005.

[69] Gu M, Dong X, Zhang X, Niu W. The CAG repeat polymorphism of androgen receptor gene and prostate cancer: a meta-analysis. Mol Biol Rep. 2012; 39(3):2615-24. doi: 10.1007/s11033-011-1014-9.

[70] Sun JH, Lee SA. Association between CAG repeat polymorphisms and the risk of prostate cancer: a meta-analysis by race, study design and the number of (CAG)n repeat polymorphisms. Int J Mol Med. 2013; 32(5):1195-203. doi:10.3892/ijmm.2013.1474.

[71] Hsing AW, Gao YT, Wu G, Wang X, Deng J, Chen YL, Sesterhenn IA, Mostofi FK, Benichou J, Chang C. Polymorphic CAG and GGN repeat lengths in the androgen receptor gene and prostate cancer risk: a population-based case-control study in China. Cancer Res. 2000; 60(18):5111-6.

[72] Brockschmidt FF, Nöthen MM, Hillmer AM. The two most common alleles of the coding GGN repeat in the androgen receptor gene cause differences in protein function. J Mol Endocrinol. 2007; 39(1):1-8.

[73] Zeegers MP, Kiemeney LA, Nieder AM, Ostrer H. 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. 2004; 13(11 Pt 1):1765-71.

[74] Vijayalakshmi K, Thangaraj K, Rajender S, Vettriselvi V, Venkatesan P, Shroff S, Vishwanathan KN, Paul SF. GGN repeat length and GGN/CAG haplotype variations in the androgen receptor gene and prostate cancer risk in south Indian men. J Hum Genet. 2006; 51(11):998-1005.

[75] Mittal RD, Mishra DK, Thangaraj K, Singh R, Mandhani A. Is there an inter-relationship between prostate specific antigen, kallikrein-2 and androgen receptor gene polymorphisms with risk of prostate cancer in north Indian population? Steroids. 2007; 72(4): 335-41.

[76] Mittal RD, Mishra D, Mandhani AK. Role of an androgen receptor gene polymorphism in development of hormone refractory prostate cancer in Indian population. Asian Pac J Cancer Prev. 2007; 8(2):275-8.

[77] Lange EM, Sarma AV, Ray A, Wang Y, Ho LA, Anderson SA, Cunningham JM, Cooney KA. The androgen receptor CAG and GGN repeat polymorphisms and prostate cancer susceptibility in African-American men: results from the Flint Men's Health Study. J Hum Genet. 2008; 53(3):220-6. doi: 10.1007/s10038-007-0240-4.

[78] Rodríguez-González G, Cabrera S, Ramírez-Moreno R, Bilbao C, Díaz-Chico JC, Serra L, Chesa N, Cabrera JJ, Díaz-Chico BN. Short alleles of both GGN and CAG repeats at the exon-1 of the androgen receptor gene are associated to increased PSA staining and

a higher Gleason score in human prostatic cancer. J Steroid Biochem Mol Biol. 2009; 113(1–2):85-91. doi: 10.1016/j.jsbmb.2008.11.010.

[79] Akinloye O, Gromoll J, Simoni M. Variation in CAG and GGN repeat lengths and CAG/GGN haplotype in androgen receptor gene polymorphism and prostate carcinoma in Nigerians. Br J Biomed Sci. 2011; 68(3):138-42.

[80] Li J, Mercer E, Gou X, Lu YJ. Ethnical disparities of prostate cancer predisposition: genetic polymorphisms in androgen-related genes. Am J Cancer Res. 2013; 3(2):127-51.

[81] Cai Q, Wang Z, Zhang W, Guo X, Shang Z, Jiang N, Tian J, Niu Y. Association between glutathione S-transferases M1 and T1 gene polymorphisms and prostate cancer risk: a systematic review and meta-analysis. Tumour Biol. 2014; 35(1):247–56. doi: 10.1007/s13277-013-1030-6.

[82] Fang DH1, Fan CH, Ji Q, Qi BX, Li J, Wang L. Differential effects of paraoxonase 1 (PON1) polymorphisms on cancer risk: evidence from 25 published studies. MolBiol Rep. 2012; 39(6):6801–9.

[83] Zhang M, Xiong H, Fang L, Lu W, Wu X, Huang ZS, Wang YQ, Cai ZM, Wu S. Paraoxonase 1 (PON1) Q192R gene polymorphism and cancer risk: a meta-analysis based on 30 publications. Asian Pac J Cancer Prev. 2015; 16(10):4457-63.

[84] Ding G, Xu W, Liu H, Zhang M, Huang Q, Liao Z. CYP1A1 MspI polymorphism is associated with prostate cancer susceptibility: evidence from a meta-analysis. Mol Biol Rep. 2013; 40(5):3483-91.

[85] Wu B, Liu K, Huang H, Yuan J, Yuan W, Wang S, Chen T, Zhao H, Yin C.MspI and Ile462Val polymorphisms in CYP1A1 and overall cancer risk: a meta-analysis. PLoS One. 2013; 8(12):e85166.

[86] Ou C, Zhao Y, Liu JH, Zhu B, Li PZ, Zhao HL. Relationship Between Aldosterone Synthase CYP1A1 MspI Gene Polymorphism and Prostate Cancer Risk. Technol Cancer Res Treat. 2016 Jan 13. pii: 1533034615625519. [Epub ahead of print]

[87] Zhang H, Li L, Xu Y. CYP1B1 polymorphisms and susceptibility to prostate cancer: a meta-analysis. PLoS One. 2013; 8(7):e68634. doi:10.1371/journal.pone.0068634.

[88] He XF, Liu ZZ, Xie JJ, Wang W, Du YP, Chen Y, Wei W. Association between the CYP3A4 and CYP3A5 polymorphisms and cancer risk: a meta-analysis and meta-regression. Tumour Biol. 2014; 35(10):9859-77. doi:10.1007/s13277-014-2241-1.

[89] Feng YZ, Liu YL, He XF, Wei W, Shen XL, Xie DL.Association between the XRCC1 Arg194Trp polymorphism and risk of cancer: evidence from 201 case-control studies. Tumour Biol. 2014; 35(11):10677-97.

[90] Chen Y, Li T, Li J, Mo Z.X-ray repair cross-complementing group 1 (XRCC1) Arg399Gln polymorphism significantly associated with prostate cancer. Int J Biol Markers. 2015; 30(1):e12-21.

[91] Xuan G, Hui Y, Fang H. The association of XRCC3 Thr241Met genetic variant with risk of prostate cancer: a meta-analysis. Afr Health Sci. 2015; 15(1):117-22. doi: 10.4314/ahs.v15i1.16.

[92] Barry KH, Koutros S, Andreotti G, Sandler DP, Burdette LA, Yeager M, Beane Freeman LE, Lubin JH, Ma X, Zheng T, Alavanja MC, Berndt SI. Genetic variation in nucleotide excision repair pathway genes, pesticide exposure and prostate cancer risk. Carcinogenesis. 2012; 33(2):331-7. doi: 10.1093/carcin/bgr258.

[93] Henríquez-Hernández LA, Valenciano A, Foro-Arnalot P, Álvarez-Cubero MJ, Cozar JM, Suárez-Novo JF, Castells-Esteve M, Fernández-Gonzalo P, De-Paula-Carranza B, Ferrer M, Guedea F, Sancho-Pardo G, Craven-Bartle J, Ortiz-Gordillo MJ, Cabrera-Roldán P, Herrera-Ramos E, Rodríguez-Gallego C, Rodríguez-Melcón JI, Lara PC. Single nucleotide polymorphisms in DNA repair genes as risk factors associated to prostate cancer progression. BMC Med Genet. 2014;15:143.

[94] Meyer A, Coinac I, Bogdanova N, Dubrowinskaja N, Turmanov N, Haubold S, Schürmann P, Imkamp F, von Klot C, Merseburger AS, Machtens S, Bremer M, Hillemanns P, Kuczyk MA, Karstens JH, Serth J, Dörk T. Apoptosis gene polymorphisms and risk of prostate cancer: a hospital-based study of German patients treated with brachytherapy. Urol Oncol. 2013; 31(1):74-81. doi:10.1016/j.urolonc.2010.09.011.

[95] Ma Q, Qi C, Tie C, Guo Z. Genetic polymorphisms of xeroderma pigmentosum group D gene Asp312Asn and Lys751Gln and susceptibility to prostate cancer: a systematic review and meta-analysis. Gene. 2013; 530(2):309-14. doi:10.1016/j.gene.2013.08.053.

[96] Chen Y, Zhong H, Gao JG, Tang JE, Wang R. A systematic review and meta-analysis of three gene variants association with risk of prostate cancer: an update. Urol J. 2015; 12(3):2138-47.

[97] Kibel AS, Jin CH, Klim A, Luly J, A Roehl K, Wu WS, Suarez BK. Association between polymorphisms in cell cycle genes and advanced prostate carcinoma. Prostate. 2008; 68(11):1179-86. doi: 10.1002/pros.20784.

[98] Wei F, Xu J, Tang L, Shao J, Wang Y, Chen L, Guan X. p27(Kip1) V109G polymorphism and cancer risk: a systematic review and meta-analysis. Cancer Biother Radiopharm. 2012; 27(10):665-71. doi: 10.1089/cbr.2012.1229.

[99] Zheng M, Wan L, He X, Qi X, Liu F, Zhang DH. Effect of the CCND1 A870G polymorphism on prostate cancer risk: a meta-analysis of 3,820 cases and 3,825 controls. World J Surg Oncol. 2015;13:55.

[100] Hirata H, Hinoda Y, Kikuno N, Suehiro Y, Shahryari V, Ahmad AE, Tabatabai ZL, Igawa M, Dahiya R. Bcl2 -938C/A polymorphism carries increased risk of biochemical recurrence after radical prostatectomy. J Urol. 2009; 181(4):1907-12. doi: 10.1016/j.juro.2008.11.093.

[101] Bachmann HS, Heukamp LC, Schmitz KJ, Hilburn CF, Kahl P, Buettner R, Nückel H, Eisenhardt A, Rübben H, Schmid KW, Siffert W, Eggert A, Schramm A, Schulte JH.

Regulatory BCL2 promoter polymorphism (-938C>A) is associated with adverse outcome in patients with prostate carcinoma. Int J Cancer. 2011; 129(10):2390–9. doi: 10.1002/ijc.25904.

[102] Lu Y, Liu Y, Zeng J, He Y, Peng Q, Deng Y, Wang J, Xie L, Li T, Qin X, Li S. Association of p53 codon 72 polymorphism with prostate cancer: an update meta-analysis. Tumour Biol. 2014; 35(5):3997–4005. doi:10.1007/s13277-014-1657-y.

[103] Hodgson ME, Poole C, Olshan AF, North KE, Zeng D, Millikan RC.Smoking and selected DNA repair gene polymorphisms in controls: systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2010;19(12): 3055–86.

[104] Langsenlehner T, Renner W, Gerger A, Hofmann G, Thurner EM, Kapp KS, Langsenlehner U. Association between single nucleotide polymorphisms in the gene for XRCC1 and radiation-induced late toxicity in prostate cancer patients. Radiother Oncol. 2011; 98(3):387–93.

[105] Song YZ, Han FJ, Liu M, Xia CC, Shi WY, Dong LH. Association between single nucleotide polymorphisms in XRCC3 and radiation-induced adverse effects on normal tissue: a meta-analysis. PLoS One. 2015; 10(6):e0130388.

[106] Kote-Jarai Z, Easton DF, StanfordJL, Ostrander EA, Schleutker J, Ingles SA, Schaid D, Thibodeau S, Dörk T, Neal D, Donovan J, Hamdy F, Cox A, Maier C, Vogel W, Guy M, Muir K, Lophatananon A, Kedda MA, Spurdle A, Steginga S, John EM, Giles G, Hopper J, Chappuis PO, Hutter P, Foulkes WD, Hamel N, Salinas CA, Koopmeiners JS, Karyadi DM, Johanneson B, Wahlfors T, Tammela TL, Stern MC, Corral R, McDonnell SK, Schürmann P, Meyer A, Kuefer R, Leongamornlert DA, Tymrakiewicz M, Liu JF, O'Mara T, Gardiner RA, Aitken J, Joshi AD, Severi G, English DR, Southey M, Edwards SM, Al Olama AA, PRACTICAL Consortium, Eeles RA. Multiple novel prostate cancer predisposition loci confirmed by an international study: the PRACTICAL Consortium. Cancer Epidemiol Biomarkers Prev. 2008; 17(8):2052–61.

[107] Chen T, Yi SH, Liu XY, Liu ZG. Meta-analysis of associations between the MDM2-T309G polymorphism and prostate cancer risk. Asian Pac J Cancer Prev. 2012; 13(9): 4327–30.

[108] Yang J, Gao W, Song NH, Wang W, Zhang JX, Lu P, Hua LX, Gu M. The risks, degree of malignancy and clinical progression of prostate cancer associated with the MDM2 T309G polymorphism: a meta-analysis. Asian J Androl. 2012; 14(5):726–31. doi: 10.1038/aja.2012.65.

[109] Stoehr R, Hitzenbichler F, Kneitz B, Hammerschmied CG, Burger M, Tannapfel A, Hartmann A. Mdm2-SNP309 polymorphism in prostate cancer: no evidence

for association with increased risk or histopathological tumour characteristics. Br J Cancer. 2008; 99(1):78–82. doi: 10.1038/sj.bjc.6604441.

[110] Yu CC, Lin VC, Huang CY, Liu CC, Wang JS, Wu TT, Pu YS, Huang CH, Huang CN, Huang SP, Bao BY. Prognostic significance of cyclin D1 polymorphisms on prostate-specific antigen recurrence after radical prostatectomy. Ann Surg Oncol. 2013; 20 Suppl 3:S492–9.

[111] Kidd LR, Coulibaly A, Templeton TM, Chen W, Long LO, Mason T, Bonilla C, Akereyeni F, Freeman V, Isaacs W, Ahaghotu C, Kittles RA. Germline BCL-2 sequence variants and inherited predisposition to prostate cancer. Prostate Cancer Prostatic Dis. 2006; 9(3):284–92.

[112] Yin M, Wei S, Wei Q. Vitamin D Receptor genetic polymorphisms and prostate cancer risk: a meta-analysis of 36 published studies. Int J Clin Exp Med. 2009; 2(2):159–75.

[113] Zhang Q, Shan Y. Genetic polymorphisms of vitamin D receptor and the risk of prostate cancer: a meta-analysis. J BUON. 2013; 18(4):961–9.

[114] Huang J, Yang J, Wang H, Xiong T, Zhang H, Ma Y, Wang X, Huang J, Du L. The association between the poly(A) polymorphism in the VDR gene and cancer risk: a meta-analysis. Tumour Biol. 2013 Jun;34(3):1833–8. doi:10.1007/s13277-013-0724-0.

[115] Guo Z, Wen J, Kan Q, Huang S, Liu X, Sun N, Li Z. Lack of association between vitamin D receptor gene FokI and BsmI polymorphisms and prostate cancer risk: an updated meta-analysis involving 21,756 subjects. Tumour Biol. 2013; 34(5):3189–200. doi: 10.1007/s13277-013-0889-6.

[116] Pao JB, Yang YP, Huang CN, Huang SP, Hour TC, Chang TY, Lan YH, Lu TL, Lee HZ, Juang SH, Huang CY, Bao BY. Vitamin D receptor gene variants and clinical outcomes after androgen-deprivation therapy for prostate cancer. World J Urol. 2013; 31(2):281–7. doi: 10.1007/s00345-011-0813-x.

[117] Tindall EA, Hayes VM, Petersen DC. Inflammatory genetic markers of prostate cancer risk. Cancers (Basel). 2010; 2(2):1198–220. doi:10.3390/cancers2021198.

[118] Cai Q, Tang Y, Zhang M, Shang Z, Li G, Tian J, Jiang N, Quan C, Niu Y. TGFβ1 Leu10Pro polymorphism contributes to the development of prostate cancer: evidence from a meta-analysis. Tumour Biol. 2014; 35(1):667–73. doi: 10.1007/s13277-013-1092-5.

[119] Wei BB, Xi B, Wang R, Bai JM, Chang JK, Zhang YY, Yoneda R, Su JT, Hua LX. TGFbeta1 T29C polymorphism and cancer risk: a meta-analysis based on 40 case-control studies. Cancer Genet Cytogenet. 2010; 196(1):68–75. doi:10.1016/j.cancergencyto.2009.09.016.

[120] Ewart-Toland A, Chan JM, Yuan J, Balmain A, Ma J. A gain of function TGFB1 polymorphism may be associated with late stage prostate cancer. Cancer Epidemiol Biomarkers Prev. 2004; 13(5):759–64.

[121] Faria PC, Saba K, Neves AF, Cordeiro ER, Marangoni K, Freitas DG, Goulart LR. Transforming growth factor-beta 1 gene polymorphisms and expression in the blood of prostate cancer patients. Cancer Invest. 2007; 25(8):726–32.

[122] Brand TC, Bermejo C, Canby-Hagino E, Troyer DA, Baillargeon J, Thompson IM, Leach RJ, Naylor SL. Association of polymorphisms in TGFB1 and prostate cancer prognosis. J Urol. 2008; 179(2):754–8.

[123] Teixeira AL, Ribeiro R, Morais A, Lobo F, Fraga A, Pina F, Calais-da-Silva FM, Calais-da-Silva FE, Medeiros R. Combined analysis of EGF+61G>A and TGFB1+869T>C functional polymorphisms in the time to androgen independence and prostate cancer susceptibility. Pharmacogenomics J. 2009; 9(5):341–6. doi:10.1038/tpj.2009.20.

[124] Hong TT, Zhang RX, Wu XH, Hua D. Polymorphism of vascular endothelial growth factor -1154G>A (rs1570360) with cancer risk: a meta-analysis of 16 case-control studies. Mol Biol Rep. 2012; 39(5):5283–9. doi: 10.1007/s11033-011-1326-9.

[125] Chen GQ, Luo JB, Wang GZ, Ding JE. Assessment of the associations between three VEGF polymorphisms and risk of prostate cancer. Tumour Biol. 2014; 35(3):1875–9. doi: 10.1007/s13277-013-1250-9.

[126] Chen Y, Li T, Yu X, Xu J, Li J, Luo D, Mo Z, Hu Y. The RTK/ERK pathway is associated with prostate cancer risk on the SNP level: a pooled analysis of 41 sets of data from case-control studies. Gene. 2014; 534(2):286–97. doi:10.1016/j.gene.2013.10.042.

[127] Shao N, Xu B, Mi YY, Hua LX. IL-10 polymorphisms and prostate cancer risk: a meta-analysis. Prostate Cancer Prostatic Dis. 2011; 14(2):129–35. doi:10.1038/pcan.2011.6.

[128] Yu Z, Liu Q, Huang C, Wu M, Li G. The interleukin 10 -819C/T polymorphism and cancer risk: a HuGE review and meta-analysis of 73 studies including 15,942 cases and 22,336 controls. OMICS. 2013; 17(4):200–14. doi: 10.1089/omi.2012.0089.

[129] Xu Y, Zhu S. Associations between vascular endothelial growth factor polymorphisms and prostate cancer risk: a meta-analysis. Tumour Biol. 2014; 35(2):1307–11. doi: 10.1007/s13277-013-1173-5.

[130] Sfar S, Saad H, Mosbah F, Chouchane L. Combined effects of the angiogenic genes polymorphisms on prostate cancer susceptibility and aggressiveness. Mol Biol Rep. 2009; 36(1):37–45.

[131] Jain L, Vargo CA, Danesi R, Sissung TM, Price DK, Venzon D, Venitz J, Figg WD. The role of vascular endothelial growth factor SNPs as predictive and prognostic markers for major solid tumors. Mol Cancer Ther. 2009; 8(9):2496–508. doi: 10.1158/1535-7163.MCT-09-0302.

[132] Orlandi P, Fontana A, Fioravanti A, Di Desidero T, Galli L, Derosa L, Canu B, Marconcini R, Biasco E, Solini A, Francia G, Danesi R, Falcone A, Bocci G. VEGF-A polymorphisms predict progression-free survival among advanced castration-resistant prostate cancer patients treated with metronomic cyclophosphamide. Br J Cancer. 2013; 109(4): 957–64. doi:10.1038/bjc.2013.398.

[133] Roberts E, Cossigny DA, Quan GM. The role of vascular endothelial growth factor in metastatic prostate cancer to the skeleton. Prostate Cancer. 2013; 2013:418340. doi: 10.1155/2013/418340.

[134] Ye Y, Wang M, Hu S, Shi Y, Zhang X, Zhou Y, Zhao C, Wang G, Wen J, Zong H. Hypoxia-inducible factor-1α C1772T polymorphism and cancer risk: a meta-analysis including 18,334 subjects. Cancer Invest. 2014; 32(4):126–35. doi: 10.3109/07357907.2014.883527.

[135] Xu B, Tong N, Chen SQ, Hua LX, Wang ZJ, Zhang ZD, Chen M. FGFR4 Gly388Arg polymorphism contributes to prostate cancer development and progression: a meta-analysis of 2618 cases and 2305 controls. BMC Cancer. 2011; 11:84. doi: 10.1186/1471-2407-11-84.

[136] Nikolić ZZ, Pavićević DLj, Romac SP, Brajušković GN. Genetic variants within endothelial nitric oxide synthase gene and prostate cancer: a meta-analysis. Clin Transl Sci. 2015; 8(1):23–31. doi: 10.1111/cts.12203.

[137] Forstermann U, Boissel JP, Kleinert H. Expressional control of the 'constitutive' isoforms of nitric oxide synthase (NOS I and NOS III) FASEB. J. 1998; 12:773–90.

[138] Burke AJ, Sullivan FJ, Giles FJ, Glynn SA. The yin and yang of nitric oxide in cancer progression. Carcinogenesis. 2013; 34(3):503–12. doi:10.1093/carcin/bgt034.

[139] Jacobs EJ, Hsing AW, Bain EB, Stevens VL, Wang Y, Chen J, Chanock SJ, Zheng SL, Xu J, Thun MJ, Calle EE, Rodriguez C. Polymorphisms in angiogenesis-related genes and prostate cancer. Cancer Epidemiol Biomarkers Prev. 2008; 17(4):972–7.

[140] Medeiros R, Morais A, Vasconcelos A, Costa S, Pinto D, Oliveira J, Lopes C. Endothelial nitric oxide synthase gene polymorphisms and genetic susceptibility to prostate cancer. Eur J Cancer Prev. 2002; 11(4):343–50.

[141] Medeiros RM, Morais A, Vasconcelos A, Costa S, Pinto D, Oliveira J, Ferreira P, Lopes C. Outcome in prostate cancer: association with endothelial nitric oxide synthase Glu-Asp298 polymorphism at exon 7. Clin Cancer Res. 2002;8(11): 3433–7.

[142] Marangoni K, Neves AF, Cardoso AM, Santos WK, Faria PC, Goulart LR. The endothelial nitric oxide synthase Glu-298-Asp polymorphism and its mRNA expression in the peripheral blood of patients with prostate cancer and benign prostatic hyperplasia. Cancer Detect Prev. 2006;30(1): 7–13.

[143] Marangoni K, Araújo TG, Neves AF, Goulart LR. The -786T>C promoter polymorphism of the NOS3 gene is associated with prostate cancer progression. BMC Cancer. 2008; 8:273.

[144] Lee KM, Kang D, Park SK, Berndt SI, Reding D, Chatterjee N, Chanock S, Huang WY, Hayes RB. Nitric oxide synthase gene polymorphisms and prostate cancer risk. Carcinogenesis. 2009; 30(4):621–5.

[145] Ziaei SA, Samzadeh M, Jamaldini SH, Afshari M, Haghdoost AA, Hasanzad M. Endothelial nitric oxide synthase Glu298Asp polymorphism as a risk factor for prostate cancer. Int J Biol Markers. 2013;28(1): 43–8.

[146] Safarinejad MR, Safarinejad S, Shafiei N, Safarinejad S. Effects of the T-786C, G894T, and Intron 4 VNTR (4a/b) polymorphisms of the endothelial nitric oxide synthase gene on the risk of prostate cancer. Urol Oncol. 2013;31(7): 1132–40.

[147] Branković A, Brajušković G, Nikolić Z, Vukotić V, Cerović S, Savić-Pavićević D, Romac S. Endothelial nitric oxide synthase gene polymorphisms and prostate cancer risk in Serbian population. Int J Exp Pathol. 2013; 94(6):355–61.

[148] Medeiros R, Morais A, Vasconcelos A, Costa S, Carrilho S, Oliveira J, Lopes C. Endothelial nitric oxide synthase gene polymorphisms and the shedding of circulating tumour cells in the blood of prostate cancer patients. Cancer Lett. 2003; 189(1):85–90.

[149] Sanli O, Kucukgergin C, Gokpinar M, Tefik T, Nane I, Seckin S. Despite the lack of association between different genotypes and the presence of prostate cancer, endothelial nitric oxide synthase a/b (eNOS4a/b) polymorphism may be associated with advanced clinical stage and bone metastasis. Urol Oncol. 2011; 29(2):183–8.

[150] Senthil D, Raveendran M, Shen YH, Utama B, Dudley D, Wang J, Wang XL. Genotype-dependent expression of endothelial nitric oxide synthase (eNOS) and its regulatory proteins in cultured endothelial cells. DNA Cell Biol. 2005; 24(4):218–24.

[151] Miyamoto Y, Saito Y, Nakayama M, Shimasaki Y, Yoshimura T, Yoshimura M, Harada M, Kajiyama N, Kishimoto I, Kuwahara K, Hino J, Ogawa E, Hamanaka I, Kamitani S, Takahashi N, Kawakami R, Kangawa K, Yasue H, Nakao K. Replication protein A1 reduces transcription of the endothelial nitric oxide synthase gene containing a -786T-->C mutation associated with coronary spastic angina. Hum Mol Genet. 2000; 9(18): 2629–37.

[152] Dos Reis ST, Pontes J Jr, Villanova FE, Borra PM, Antunes AA, Dall'oglio MF, Srougi M, Leite KR. Genetic polymorphisms of matrix metalloproteinases: susceptibility and prognostic implications for prostate cancer. J Urol. 2009; 181(5):2320–5. doi: 10.1016/j.juro.2009.01.012.

[153] dos Reis ST, Villanova FE, Andrade PM, Pontes J Jr, de Sousa-Canavez JM, Sañudo A, Antunes AA, Dall'oglio MF, Srougi M, Moreira Leite KR. Matrix metalloproteinase-2

polymorphism is associated with prognosis in prostate cancer. Urol Oncol. 2010; 28(6): 624–7. doi: 10.1016/j.urolonc.2008.10.012.

[154] Srivastava P, Lone TA, Kapoor R, Mittal RD. Association of promoter polymorphisms in MMP2 and TIMP2 with prostate cancer susceptibility in North India. Arch Med Res. 2012; 43(2):117–24. doi: 10.1016/j.arcmed.2012.02.006.

[155] Yaykaşli KO, Kayikçi MA, Yamak N, Soğuktaş H, Düzenli S, Arslan AO, Metın A, Kaya E, Hatıpoğlu ÖF. Polymorphisms in MMP-2 and TIMP-2 in Turkish patients with prostate cancer. Turk J Med Sci. 2014; 44(5):839–43.

[156] Adabi Z, Mohsen Ziaei SA, Imani M, Samzadeh M, Narouie B, Jamaldini SH, Afshari M, Safavi M, Roshandel MR, Hasanzad M. Genetic Polymorphism of MMP2 Gene and Susceptibility to Prostate Cancer. Arch Med Res. 2015; 46(7):546–50. doi:10.1016/j.arcmed.2015.08.004.

[157] Price SJ, Greaves DR, Watkins H. Identification of novel, functional genetic variants in the human matrix metalloproteinase-2 gene: role of Sp1 in allele-specific transcriptional regulation. J Biol Chem. 2001; 276(10):7549–58.

[158] Chang Z, Zhou H, Liu Y. Promoter methylation and polymorphism of E-cadherin gene may confer a risk to prostate cancer: a meta-analysis based on 22 studies. Tumour Biol. 2014; 35(10):10503–13. doi: 10.1007/s13277-014-2323-0.

[159] Li HC, Albert JM, Shinohara ET, Cai Q, Freyer A, Cai H, Cao C, Wang Z, Kataoka N, Teng M, Zheng W, Lu B. E-cadherin promoter polymorphisms are not associated with the aggressiveness of prostate cancer in Caucasian patients. Urol Oncol. 2006; 24(6): 496–502.

[160] Li LC, Chui RM, Sasaki M, Nakajima K, Perinchery G, Au HC, Nojima D, Carroll P, Dahiya R. A single nucleotide polymorphism in the E-cadherin gene promoter alters transcriptional activities. Cancer Res. 2000; 60(4):873–6.

[161] Kammerer S, Roth RB, Reneland R, Marnellos G, Hoyal CR, Markward NJ, Ebner F, Kiechle M, Schwarz-Boeger U, Griffiths LR, Ulbrich C, Chrobok K, Forster G, Praetorius GM, Meyer P, Rehbock J, Cantor CR, Nelson MR, Braun A. Large-scale association study identifies ICAM gene region as breast and prostate cancer susceptibility locus. Cancer Res. 2004; 64(24):8906–10

[162] Chen H, Hernandez W, Shriver MD, Ahaghotu CA, Kittles RA. ICAM gene cluster SNPs and prostate cancer risk in African Americans. Hum Genet. 2006; 120(1):69–76.

[163] Walsh AL, Tuzova AV, Bolton EM, Lynch TH, Perry AS. Long noncoding RNAs and prostate carcinogenesis: the missing "linc?" Trends Mol Med. 2014; 20(8):428–36. doi: 10.1016/j.molmed.2014.03.005.

[164] Fatima R, Akhade VS, Pal D, Rao SM. Long noncoding RNAs in development and cancer: potential biomarkers and therapeutic targets. Mol Cell Ther. 2015; 3:5. doi: 10.1186/s40591-015-0042-6.

[165] Jin G, Jielin S, Isaacs SD, Wiley KE, Kim S-T, Chu LW, et al. Human polymorphisms at long non-coding RNAs (lncRNAs) and association with prostate cancer risk. Carcinogenesis 2011; 32: 1655–9.

[166] Xue Y, Wang M, Kang M, Wang Q, Wu B, Chu H, Zhong D, Qin C, Yin C, Zhang Z, Wu D. Association between lncrna PCGEM1 polymorphisms and prostate cancer risk. Prostate Cancer Prostatic Dis. 2013; 16(2):139–44, S1. doi:10.1038/pcan.2013.6.

[167] Zhou W, Tao Z, Wang Z, Hu W, Shen M, Zhou L, Wen Z, Yu Z, Wu X, Huang K, Hu Y, Lin X. Long noncoding RNA PCA3 gene promoter region is related to the risk of prostate cancer on Chinese males. Exp Mol Pathol. 2014; 97(3):550–3. doi:10.1016/j.yexmp.2014.11.005.

[168] Cook MB, Wang Z, Yeboah ED, Tettey Y, Biritwum RB, Adjei AA, Tay E, Truelove A, Niwa S, Chung CC, Chokkalingam AP, Chu LW, Yeager M, Hutchinson A, Yu K, Rand KA, Haiman CA; African Ancestry Prostate Cancer GWAS Consortium, Hoover RN, Hsing AW, Chanock SJ. A genome-wide association study of prostate cancer in West African men. Hum Genet. 2014; 133(5):509–21. doi: 10.1007/s00439-013-1387-z.

[169] Chung S, Nakagawa H, Uemura M, Piao L, Ashikawa K, Hosono N, Takata R, Akamatsu S, Kawaguchi T, Morizono T, Tsunoda T, Daigo Y, Matsuda K, Kamatani N, Nakamura Y, Kubo M. Association of a novel long non-coding RNA in 8q24 with prostate cancer susceptibility. Cancer Sci. 2011; 102(1):245–52. doi:10.1111/j.1349-7006.2010.01737.x.

[170] Mishra PJ, Bertino JR. MicroRNA polymorphisms: the future of pharmacogenomics, molecular epidemiology and individualized medicine. Pharmacogenomics. 2009; 10(3):399–416.

[171] Sun G, Yan J, Noltner K, Feng J, Li H, Sarkis DA, et al. SNPs in human miRNA genes affect biogenesis and function. RNA 2009; 15:1640–51.

[172] Ryan BM, Robles AI, Harris CC. Genetic variation in microRNA networks: the implications for cancer research. Nature Reviews Cancer 2010; 10:389–402.

[173] Xu B, Feng NH, Li PC, Tao J, Wu D, Zhang ZD, Tong N, Wang JF, Song NH, Zhang W, Hua LX, Wu HF. A functional polymorphism in Pre-miR-146a gene is associated with prostate cancer risk and mature miR-146a expression in vivo. Prostate. 2010; 70(5):467–72.

[174] George GP, Gangwar R, Mandal RK, Sankhwar SN, Mittal RD. Genetic variation in microRNA genes and prostate cancer risk in North Indian population. Mol Biol Rep. 2011; 38(3):1609-15.

[175] Nikolić ZZ, Savić Pavićević DLj, Vukotić VD, Tomović SM, Cerović SJ, Filipović N, Romac SP, Brajušković GN. Association between genetic variant in hsa-miR-146a gene and prostate cancer progression: evidence from Serbian population. Cancer Causes Control. 2014; 25(11):1571-5.

[176] Parlayan C, Ikeda S, Sato N, Sawabe M, Muramatsu M, Arai T. Association analysis of single nucleotide polymorphisms in miR-146a and miR-196a2 on the prevalence of cancer in elderly Japanese: a case-control study. Asian Pac J Cancer Prev. 2014; 15:2101-2107.

[177] Chu H, Zhong D, Tang J, Li J, Xue Y, Tong N, Qin C, Yin C, Zhang Z, Wang M. A functional variant in miR-143 promoter contributes to prostate cancer risk. Arch Toxicol. 2016; 90(2):403-14. doi: 10.1007/s00204-014-1396-2.

[178] Nikolić Z, Savić Pavićević D, Vučić N, Cidilko S, Filipović N, Cerović S, Vukotić V, Romac S, Brajušković G. Assessment of association between genetic variants in microRNA genes hsa-miR-499, hsa-miR-196a2 and hsa-miR-27a and prostate cancer risk in Serbian population. Exp Mol Pathol. 2015; 99(1):145-50. doi: 10.1016/j.yexmp. 2015.06.009.

[179] König IR. Validation in genetic association studies. Brief Bioinform. 2011; 12(3):253–8. doi: 10.1093/bib/bbq074.

[180] Chanock SJ, Manolio T, Boehnke M, Boerwinkle E, Hunter DJ, Thomas G, Hirschhorn JN, Abecasis G, Altshuler D, Bailey-Wilson JE, Brooks LD, Cardon LR, Daly M, Donnelly P, Fraumeni JF Jr, Freimer NB, Gerhard DS, Gunter C, Guttmacher AE, Guyer MS, Harris EL, Hoh J, Hoover R, Kong CA, Merikangas KR, Morton CC, Palmer LJ, Phimister EG, Rice JP, Roberts J, Rotimi C, Tucker MA, Vogan KJ, Wacholder S, Wijsman EM, Winn DM, Collins FS. NCI-NHGRI Working Group on Replication in Association Studies. Replicating genotype-phenotype associations. Nature. 2007; 447(7145):655–60.

[181] Garg AX, Hackam D, Tonelli M. Systematic review and meta-analysis: when one study is just not enough. Clin J Am Soc Nephrol. 2008; 3(1):253-60. doi:10.2215/CJN.01430307.

[182] Weed DL. Interpreting epidemiological evidence: how meta-analysis and causal inference methods are related. Int J Epidemiol. 2000; 29(3):387-90.

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