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An update on genetic predisposition for prostate cancer: Perspectives and prospects

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ABSTRACT

Prostate cancer (PC) is a heterogeneous disease that kills a significant number of people all over the world. It is the most common cancer in men, especially in the western world, and causes morbidity and mortality. There are several important risk factors known for PC like age, ethnicity, and inherited genetic variants which contribute significantly. The current research studies are endeavoring to identify genetic markers for PC and to understand underlying molecular mechanisms, so that new diagnostic and screening tests based on genetics can be developed for PC. The present review discusses candidate genes such as HOXB13, BRCA1, BRCA2, ATM, MMR gene, RAD51C, CHECK2, etc., and family-based linkage studies which defined the location of loci on chromosomal regions like 1q24-25, 1q42-43, Xq27-28, 1p36, 20q13, 17q21. Furthermore, the major part of the review focuses on important PC susceptible loci (8q24, 10q11, 17q12, 17q24, and 19q13, etc.) and risk variants identified by population-based genome-wide association studies (GWAS).

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Introduction

Prostate cancer (PC) is one of the most common causes of cancer-associated death among men in developed as well as developing countries (1, 2, 3, 4, 5). Among all new cancers diagnosed in the United States in 2020, PC is predicted to make up nearly one-fifth of the total cancer cases (4, 6). Similarly, in other parts of the world, including Asian and Middle Eastern countries, the incidence of the disease has been on the rise due to significant changes in lifestyle (7, 8). PC shows a very high degree of heritability, and epidemiological evidence coming from various study designs (twin, family-based, case-control cohort, etc.) supports the key contributing role of genes in the etiology of PC (9,10, 11, 12). Twin studies have shown a higher risk of developing PC for monozygotic twins than for dizygotic twins when one is diagnosed with PC, thus stressing the role of genetic factors (12). Risk factors like age, ethnicity and positive family history are major determinants of the predisposition to PC (13, 14). For example, compared to men of European Americans, the incidence of PC among African American (AA) and Asian Indian men is higher (15). The incidence and mortality rates for PC are strongly associated with age (16). First-degree relatives of patients with PC have a much higher risk of developing the disease compared to the general population (17). Similarly, the risk to first-degree relatives of patients under the age of 60 years with PC is >4-fold higher than to those without a family history (18). To a lesser degree, factors like diet and lifestyle choices, such as smoking, physical activity, etc. have also been implicated in to the risk for PC development (19, 20).

The genetic component that contributes to the etiology of PC comprises rare variants with moderate- to high penetrance and common variants with low penetrance (2). The rare variants with moderate- to high penetrance have been largely identified through candidate gene approaches or linkage studies in hereditary and familial cases of PC, whereas GWAS were frequently utilized to identify low-risk common genetic variants located in multiple loci throughout the genome of a population (Figure 1). The identification of genetic variants that can be effectively used to predict PC risk with very high confidence has remained difficult due to the heterogeneity involved in PC. Although the prostate-specific antigen (PSA) test is still a standard test for the early detection of PC (21), however, it lacks sensitivity and specificity (22). Furthermore, PSA is not a marker of PC but only a prostate-specific marker (22), thus underlining the need to identify novel biomarkers and molecular targets for the diagnosis, monitoring,

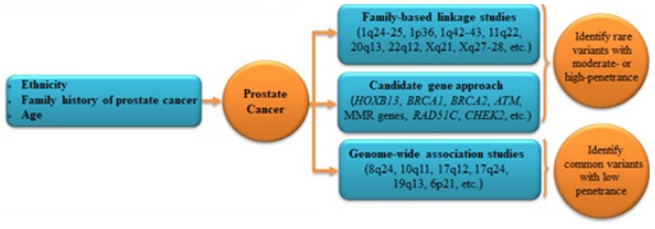

Figure 1. Risk factors for prostate cancer, and approaches for identifying risk loci and genetic variants associated with prostate cancer susceptibility.

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and treatment of the disease (23).

In the present review, we discuss the PC candidate genes, PC susceptible loci found by linkage analysis in family-based settings, and GWAS-identified PC susceptible loci and genetic variants in population-based settings.

Family-based linkage studies and candidate gene approach

The early research into the identification of high penetrant PC susceptible loci was done through linkage studies in hereditary PC cases. A large number of such studies were performed on populations of European descent. PC susceptibility loci obtained from linkage studies were found to be located on chromosomal regions like 1q24-25 (HPC1) (24, 25, 26), 1q42-43 (PCAP) (26, 27), Xq27-28 (HPCX) (28), 1p36 (CAPB) (26, 27), 20q13 (HPC20) (29), 17q21 (HOXB13) (30, 31), etc. Similarly, linkage studies in families of non-European descent also have identified hereditary PC susceptibility loci, namely, 1p36, 1q24-25, 1q42.2-43, 2p16, 2p21, 11q22, 12q24, 17p11, 22q12, Xq21 and Xq27-28 in African American families (32, 33, and 34) and 1p36 in Japanese families (35). Later, fine-mapping of these regions was undertaken for the identification of candidate genes and biological pathways that play important roles in the etiology of PC. The candidate gene approach involves examining single nucleotide polymorphisms (SNPs) within genes that have already been known to be associated with a specific trait or disease. In the hereditary/familial PC context, several moderate- to high-penetrant susceptibility genes have been proposed. Genes belonging to DNA repair, steroid hormone metabolism, carcinogen metabolism, inflammation, and transcription have been proposed as candidate genes for PC.

HOXB13 is one such gene that has emerged as the most widely replicated susceptibility gene for PC risk. A germline missense mutation G84E in the *HOXB13* gene was found in PC families after the screening of hundreds of genes in the region 17q21-22, previously identified in PC linkage studies (36). *HOXB13* is a homeobox transcription factor that interacts with the androgen receptor and plays an important role in the growth and differentiation of normal and cancerous prostate cells (37). Recently, *HOXB13* was recommended by a consensus conference on PC to be included in the panel of genetic testing for suspected hereditary PC (38). Nyberg and group (2019), in a recent meta-analysis study of the PC risk attributed to the *HOXB13* G84E mutation, concluded that the risk of developing PC is in the carrier of this mutation. The presence of the G84E mutation has been reported exclusively in European men, thus suggesting a founder effect (39). Other germline mutations in *HOXB13* have also been reported in different ethnic groups (40, 41, and 42).

Germline alterations in the tumor suppressor genes *BRCA1* and *BRCA2* have also been associated with an increased risk of PC. The *BRCA1*- and *BRCA2*-encoded proteins ascertain genome integrity by playing significant roles in the homologous recombination-mediated DNA repair pathway. In comparison to *BRCA2* mutations that have been reported to result in up to a 5-fold increase in the risk of PC development in the carrier (43, 44), the risk of PC due to a *BRCA1* variant is found to be less pronounced with 1.8-fold to 3.8-fold increase in the relative risk of PC diagnosis by the age of 65 years (45, 46). A recent meta-analysis on the association between *BRCA* mutations and PC risk reported a higher risk of PC for *BRCA2* carriers (2.64-fold) than for *BRCA1* carriers (1.35-fold) (47). The lifetime risk of PC at the age of 80 years in the current study was reported to be between 19–61% for *BRCA2* and 7–26% for *BRCA1* carriers (48). Similar to the *BRCA1* and *BRCA2*, variants in other DNA-repair genes, such as *ATM*, DNA mismatch repair, or MMR genes (*MLH1*, *MLH3*, *MSH2*, *MSH6*), *RAD51C,* and *CHEK2* have also been associated with PC risk (49, 50). Despite the efforts of several studies, the candidate gene approach has been criticized for its lack of replication and lack of statistical power due to a smaller sample size (51, 52). Furthermore, a family gene accounts for only part of the familial cases because an individual in the PC family can develop the disease even in the absence of such germline variants (53). Therefore, the majority of such findings are failed to evolve into recommended genetic testing in clinical practice for the prediction of PC development. Furthermore, the lack of conclusive findings from family-based linkage studies and candidate gene approaches indicate interplay of multiple genes for PC susceptibility. The identification of common loci with low penetrability that predisposes to PC and can explain not only sporadic PC but also familial PC which is highly desirable and remains the focus of many genome-wide association studies (GWAS) (54).

Genome-Wide Association Studies (GWAS)

Whereas linkage studies identify rare genetic variants with moderate- to high penetrance, GWAS can identify common genetic variants with low penetrance. The results of GWAS showed that the majority of the genetic variants associated with PC are located in nonprotein coding regions such as the regulatory regions of genes and RNA-coding regions in the genome (55, 56). More than 200 common variants have been identified as PC risk by GWAS (57). Figure 2 illustrates the distribution described in PC susceptibility.

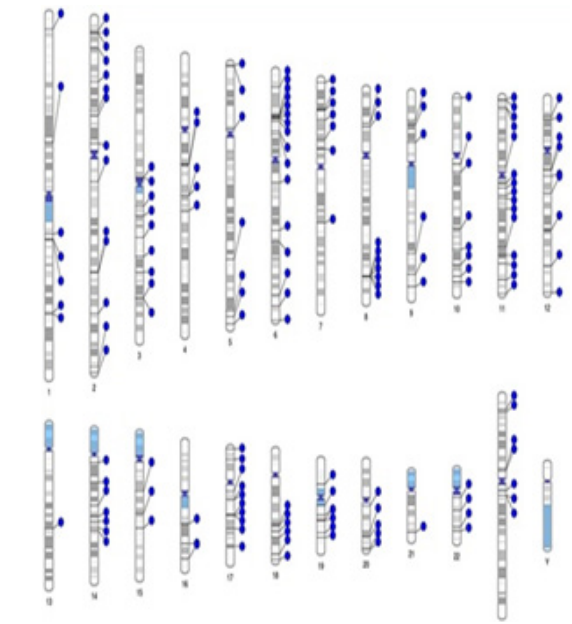

Figure 2. PC risk loci identified by Genome-wide association studies (GWAS). The loci associated with PC risk are represented by circles on different human chromosomes. The data for PC risk loci were obtained from Al Olama et al. (2014) and Schumacher et al. (2018) and plotted using PhenoGram software available online at http://visualization.ritchielab.org/phenograms/plot.

The 8q24 region of the chromosome has emerged as one of the most common risk loci associated with PC in multiple populations, such as European, African, African American, Asian, Latinos, etc. This region was first identified in Icelandic population in a GWAS analysis (58). Authors further replicated the study in the AA population and found that the variant at locus 8q24 confers higher risk of PC for AA men than for men of European ancestry (58). Unlike many other PC susceptible loci that have failed to be replicated, the 8q24 region has been successfully associated with PC in many populations by both recent GWAS and meta-analyses of GWAS (59, 60, 61, and 62). The 8q24 region has been found to harbour many risk variants predisposing to PC. In a meta-analysis and case-control study performed by Cheng and collaborators (2008), three variants (rs10090154, rs16901979, and rs6983267) on 8q24 regions were found to be positively associated with advanced PC. The variant rs72725854 (A>G/T) at locus 8q24 has been reported to contribute to an increased risk for PC development in men of African ancestry (63, 64). Although the PC-susceptibility region within 8q24 is not known to possess protein-coding genes, the presence within it of regulatory elements that regulate the expression of neighboring genes, such as *C-MYC,* has been reported. For example, the risk variant rs72725854 has recently been shown to harbor an enhancer that can regulate the transcription of long noncoding RNAs (lncRNAs) and *MYC* in the 8q24 region via 3D-conformation (65).

The 10q11 region is another chromosomal region that has gained prominence for possessing genetic variants associated with PC risk (66, 67). The association of variants on 10q11 with PC was replicated in different populations such as South African (68), Romanian (69), African American (70), etc. RA report in the Latino population the 10q11 region is the most significant risk region for PC, surpassing the risk associated with the 8q24 region. These authors replicated the findings of other GWAS (71) by reporting a significant association between the risk variant rs10993994, located upstream of *MSMB* at 10q11, and PC risk. The variant rs10993994 is located outside the protein-coding region and found to contribute to PC risk by affecting the expression of nearby genes *MSMB* and *NCOA4* (72). Kim and collaborators (2015) found three additional genetic variants rs7077830, rs2611489, and rs4631830 on 10q11 to be associated with PC risk in the Korean population. The variants at 10q11 have been associated with serum PSA levels in men (73).

The 17q12 is another region that has been implicated as PC susceptibility loci by many studies. Two genetic variants, rs7501939 and rs3760511, on 17q12 were found to be associated with PC risk in the GWAS of 1501 Icelandic men with PC and 11,290 controls (74). The 17q12 region was later also replicated in UK (66) and USA in separate GWAS. The genetic variant rs4430796 located within *HNF1B* gene on 17q12 has been found to be strongly associated with the PC risk in a fine-mapping study (75). 17q12 region contains genes that have been searched for PC association (76).

PC susceptibility locus at 17q24 has also been pinpointed as another risk loci. In a recent meta-analysis of association of the variant rs1859962 with the risk of PC development, the authors found the rs1859962 [G] allele to be significantly associated with the risk of PC (77). The variant rs1859962 has been mapped to enhancer elements looping with oncogene *SOX9* (78).

Several genetic variants in the region 19q13 have been reported to be associated with PC risk in GWAS. The authors conducted the first GWAS in Han Chinese (4484 with PC cases and 8934 controls). The authors identified the variant rs103294, located within the leukocyte immunoglobulin-like receptor (LIR) gene, contributing to PC risk on 1the 9q13.4 region and found the risk allele rs103294[C] to be associated with increased expression of *LILRA3,* a family member of LIR genes known to regulate inflammatory response (79).

The authors performed GWAS in Japanese men (4584 with PC and 8801 controls) and identified five new loci including 6p21 (rs1983891 in *FOXP4*) for PC susceptibility (80). The variant rs1983891 at 6p21 was later also associated with PC risk in European men in a fine-mapping study among men of European ancestry (81).

The authors conducted a GWAS for PC on more than 23,000 Icelandic men and identified common variants, rs5945572 on Xp11.22 and rs721048 on 2p15, associated with PC (73). The variant rs5945572 has been mapped upstream of *NUDT11* gene and was further validated in AA population (82), and in multi-ethnic cohort (AA, European American, Japanese American, Latinos, and Native Hawaiians) (83).

Recently, in a meta-analysis of GWAS, two novel PC susceptibility loci, 13q34 and 22q12, were reported in men of African ancestry (63). Takata and colleagues (2019) identified 12 new susceptible loci for PC in the Japanese population. These loci were found to be located on different chromosomes (1, 2, 3, 8, 10, 12, 15, 20, 22, and X), and most of the loci were also predicted to gene regulatory functions (84).

In spite of the discovery of common loci for PC risk, there are very few genetic variants that have been identified by GWAS to be associated with PC aggressiveness. In a multistage, case-only GWAS of 12,518 PC cases, two new loci, rs35148638 at 5q14.3 and rs78943174 at 3q26.31, were identified and found to be associated with PC aggressiveness as measured by the Gleason score (85). Similarly, identified a novel variant, rs9623117 at 22q13, in two GWAS and reported its association with the aggressive PC risk. Other GWAS-identified loci associated with PC aggressiveness have been reviewed (86).

Challenges and future perspective

Prostate cancer is a heterogeneous disease and genetics has an essential role in its etiology. The advancement in genetic technology and the continuing reduction of sequencing costs have shifted the focus from family-based linkage analysis to population-based association studies that can identify common variants of PC predisposition.

Although GWAS has identified many risk variants and risk loci for PC, being located on non- coding regions has made their biological interpretation in the etiology of PC difficult and uncertain. This provides impetus for research into the functional studies of identified genetic variants, so that the underlying networks of genes and signaling pathways involved in PC can be elucidated and novel targets for the treatment of PC can be emerged.

Secondly, most of the studies for the identification of genetic variants for PC have been done on European populations. This can hamper the genetic risk prediction for PC across the global populations. The generalizability

of these variants in a diverse racial and ethnic population by validation studies is much needed before risk loci can be utilized in PC risk modeling. The individual is generally contributing only a small fraction for the risk of PC development and thus cannot be successfully used to predict the overall risk of PC in an individual. Polygenic risk scores (PRS) that combine the risk scores of many such genetic variants identified in multiple studies have been developed for the stratification of susceptibility to PC. The PRS for PC screening can supplement the drawbacks of PSA testing. However, the use of PRS obtained from one type of population (e.g., European) for the prediction of PC risk in the other under-represented populations is the limiting factor for its worldwide usage (87). Despite much effort, genetic testing for PC susceptibility falls behind other common cancers, like colorectal and breast cancer.

Conclusions

Prostate cancer is heterogeneous sickness and genetics has a crucial position in its etiology. The development in genetic era and the persevering with discount of sequencing expenses has shifted the focal point from family-primarily based totally linkage evaluation to population-primarily based totally affiliation research that may become aware of not unusual place versions of PC predisposition. Similarly, although a number of loci have been identified by GWAS, the genetic variants that discriminate between aggressive and non-aggressive forms of PC are very much desirable because most of the death in PC cases is due to metastatic castration-resistant prostate cancer (a form of advanced PC). The present review discusses candidate gene and family-based linkage studies, each antecedently stylish for the identification of genetic markers for PC. Furthermore, the foremost a part of the review focuses on important PC loci and risk variants known by population-based genome-wide association studies (GWAS). Thus, there are vast opportunities for future replication and validation studies in other populations to elucidate a clear picture of genetic biomarkers involved in PC etiology that can pave the way for the development of individualized screening and prevention strategies.

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Interest conflict

The authors declare that they have no conflict of interest.

Author Contribution

MAE designs the concept and manuscript writing a final draft. BEG helps to write the first draft of the manuscript. AOM helps to write the final draft. AM contributed in interest MT helps to design the concept manuscript and analysis including editing the manuscript.

References

1. Bray F, Ferlay J, Soerjomataram, I, Siegel R L, Torre L A, and Jemal A. Global cancer statistics GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 2018; 68(6), 394-424.
2. Farashi S, Kryza T, Clements J and Batra J. Post-GWAS in prostate cancer: from genetic association to biological contribution. Nat Rev Cancer. 2019; 19(1):46-59.
3. Sultan A, Choudhary V, and Parganiha A. Worsening of rest-activity circadian rhythm and quality of life in female breast cancer patients along progression of chemotherapy cycles. Chronobiol Int. 2017; 34(5), 609-623.
4. Sultan A, Parganiha A, Sultan T, Choudhary V, and Pati A K. Circadian clock, cell cycle, and breast cancer: an updated review. Biol Rhythm Res. 2017; 48(3), 353-369.
5. Sultan A, Pati A K, Choudhary V, and Parganiha A. Hospitalization-induced exacerbation of the ill effects of chemotherapy on rest-activity rhythm and quality of life of breast cancer patients: a prospective and comparative cross-sectional follow-up study. Chronobiol Int. 2018; 35(11), 1513-1532.
6. Siegel R L, Miller K D, and Jemal A. Cancer statistics, CA: a cancer journal for clinicians. 2020; 70(1), 7–30.
7. Salim E I, Moore M A, Al-Lawati J A, Al-Sayyad J, Bazawir A, Bener A, Corbex M, El-Saghir N, Habib O S, Maziak W, Mokhtar H C, Seif-Eldrin I A, and Sobue T. Cancer epidemiology and control in the arab world - past, present and future. Asian Pacific journal of cancer prevention: APJCP. 2009; 10(1), 3-16.
8. Rawla P. Epidemiology of Prostate Cancer. World journal of oncology. 2019; 10(2), 63-89.
9. Lichtenstein P, Holm N V, Verkasalo P K, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, and Hemminki K. Environmental and heritable factors in the causation of cancer analyses of cohorts of twins from Sweden. Denmark, and Finland. The New England journal of medicine. 2000; 343(2), 78–85.
10. Gronberg H. Prostate cancer epidemiology. The Lancet. 2003; 361(9360), 859-864.
11. Schaid D J. The complex genetic epidemiology of prostate cancer. Human molecular genetics. 2004; 13(suppl_1), R103-R121.
12. Mucci L A, Hjelmborg J B, Harris J R, Czene K, Havelick D J, Scheike T, Graff R E, Holst K, Möller S, Unger R H, McIntosh C, Nuttall E, Brandt I, Penney K L, Hartman M, Kraft P, Parmigiani G, Christensen K, Koskenvuo M, Holm N V. Nordic Twin Study of Cancer (NorTwinCan) Collaboration Familial Risk and Heritability of Cancer Among Twins in Nordic Countries. JAMA, 2016; 315(1), 68–76.
13. Pernar C H, Ebot E M, Wilson K M, and Mucci L A. The Epidemiology of Prostate Cancer. Cold Spring Harbor perspectives in medicine. 2018; 8(12), a030361.
14. Taitt H E. Global trends and prostate cancer: A review of incidence, detection, and mortality as influenced by race, ethnicity, and geographic location. American journal of men's health. 2018; 12(6), 1807–1823.
15. Zeigler-Johnson CM, Rennert H, Mittal RD, Jalloh M, Sachdeva R, Malkowicz SB, Mandhani A, Mittal B, Gueye SM, and Rebbeck TR. Evaluation of prostate cancer characteristics in four populations worldwide. The Canadian journal of urology. 2008. 15(3), 4056–4064.
16. Brandt A, Bermejo JL, Sundquist J, and Hemminki K. Age at Diagnosis and Age at Death in Familial Prostate Cancer. Oncologist. 2009; 14, 1209-1217.
17. Goldgar DE, Easton DF, Cannon-Albright L A, and Skolnick M H. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. Journal of the National Cancer Institute. 1994; 86(21), 1600–1608.
18. Lange EM. Identification of genetic risk factors for prostate cancer: analytic approaches using hereditary prostate cancer families. Male Reproductive Cancers. 2010; (pp. 203-228). Springer, New York, NY.
19. Ballon-Landa, E, and Parsons JK. Nutrition, physical activity, and lifestyle factors in prostate cancer prevention. Current Opinion in Urology. 2017; 28(1), 55-61.

20. Peisch SF, Van Blarigan EL, Chan JM, Stampfer MJ, and Kenfield SA. Prostate cancer progression and mortality: a review of diet and lifestyle factors. World journal of urology. 2017; 35(6), 867-874.
21. Roobol MJ. Screening for prostate cancer: are organized screening programs necessary Translational Andrology and Urology. 2018; 7(1): 4-11.
22. Nogueira L, Corradi R, and Eastham JA. Prostatic specific antigen for prostate cancer detection. International braz j urol. 2009; 35(5), 521-531.
23. Zhang JH. Bend the healthcare cost curve without pain? The health outcome after the Medicare reimbursement cut in 1997. The International Journal of Health Planning and Management. 2015; 30(2): 164-172.
24. Cooney KA, McCarthy JD, Lange E, Huang L, Miesfeldt S, Montie JE, Oesterling J E, Sandler H M, and Lange K. Prostate cancer susceptibility locus on chromosome 1q: a confirmatory study. Journal of the National Cancer Institute. 1997; 89 (13), 955–959.
25. Neuhausen SL, Farnham JM, Kort E, Tavtigian SV, Skolnick MH, and Cannon-Albright LA. Prostate cancer susceptibility locus HPC1 in Utah high-risk pedigrees. Human molecular genetics, 1999; 8(13), 2437–2442.
26. Berry R, Schaid DJ, Smith JR, French AJ, Schroeder JJ, McDonnell SK, Peterson BJ, Wang ZY, Carpten JD, Roberts SG, Tester DJ, Blute ML, Trent JM, and Thibodeau SN. Linkage analyses at the chromosome 1 loci 1q24-25 (HPC1), 1q42.2-43 (PCAP), and 1p36 (CAPB) in families with hereditary prostate cancer. American journal of human genetics. 2000A; 66(2), 539–546.
27. Xu J, Zheng SL, Chang B, Smith JR, Carpten JD, Stine OC, Isaacs SD, Wiley K E, Henning L, Ewing C, Bujnovszky P, Bleeker ER, Walsh PC, Trent JM, Meyers D A, and Isaacs WB. Linkage of prostate cancer susceptibility loci to chromosome 1. Human genetics. 2001; 108(4), 335–345.
28. Schleutker J, Matikainen M, Smith J, Koivisto P, Baffoe-Bonnie A, Kainu T, Gillanders E, Sankila R, Pukkala E, Carpten J, Stephan D, Tammela T, Brownstein M, Bailey-Wilson J, Trent J, and Kallioniemi OPA. Genetic epidemiological study of hereditary prostate cancer (HPC) in Finland: frequent HPCX linkage in families with late-onset disease. Clinical cancer research, 2000; 6(12), 4810–4815.
29. Berry R, Schroeder JJ, French AJ, McDonnell SK, Peterson BJ, Cunningham JM, Thibodeau S N, and Schaid DJ. Evidence for a prostate cancer-susceptibility locus on chromosome 20. American journal of human genetics. 2000B; 67(1), 82–91.
30. Breyer J P, Avritt TG, McReynolds KM, Dupont WD, and Smith JR. Confirmation of the HOXB13 G84E germline mutation in familial prostate cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2012; 21(8), 1348–1353.
31. Xu J, Lange EM, Lu L, Zheng SL, Wang Z, Thibodeau SN, Cannon-Albright LA, Teerlink CC, Camp NJ, Johnson AM, Zuhlke KA, Stanford JL, Ostrander EA, Wiley KE, Isaacs SD, Walsh P C, Maier C, Luedeke M, Vogel W, Schleutker J. International Consortium for Prostate Cancer Genetics HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Genetics (ICPCG). Human genetics. 2013; 132(1), 5–14.
32. Ledet EM, Sartor O, Rayford W, Bailey-Wilson JE, and Mandal DM. Suggestive evidence of linkage identified at chromosomes 12q24 and 2p16 in African American prostate cancer families from Louisiana. The Prostate. 2012; 72(9), 938–947.
33. Brown WM, Lange EM, Chen H, Zheng SL, Chang B, Wiley KE, Isaacs SD, Walsh PC, Isaacs WB, Xu J, and Cooney KA. Hereditary prostate cancer in African American families: linkage analysis using markers that map to five candidate susceptibility loci. British journal of cancer. 2004; 90(2), 510–514.
34. Baffoe-Bonnie AB, Kittles RA, Gillanders E, Ou L, George A, Robbins C, Ahaghotu C, Bennett J, Boykin W, Hoke G, Mason T, Pettaway C, Vijayakumar S, Weinrich S, Jones MP, Gildea D, Riedesel E, Albertus J, Moses T, Lockwood E, Carpten JD. Genome-wide linkage of 77 families from the African American Hereditary Prostate Cancer study (AAHPC). The Prostate. 2007; 67(1), 22–31.
35. Matsui H, Suzuki K, Ohtake N, Nakata S, Takeuchi T, Yamanaka H, and Inoue I. Genomewide linkage analysis of familial prostate cancer in the Japanese population. Journal of human genetics. 2004; 49(1), 9–15.
36. Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, Tembe WD, Wiley KE, Isaacs SD, Johng D, Wang Y, Bizon C, Yan G, Gielzak M, Partin AW, Shanmugam V, Izatt T, Sinari S, Craig DW, Zheng, SL, Walsh PC, Cooney KA. Germline mutations in HOXB13 and prostate-cancer risk. The New England journal of medicine. 2012; 366(2), 141–149.
37. Norris JD, Chang CY, Wittmann BM, Kunder RS, Cui H, Fan D, Joseph JD, and McDonnell DP. The homeodomain protein HOXB13 regulates the cellular response to androgens. Molecular cell. 2009; 36(3), 405–416.
38. Giri VN, Knudsen KE, Kelly WK, Abida W, Andriole GL, Bangma CH, Bekelman JE, Benson M C, Blanco A, Burnett A, Catalona WJ, Cooney KA, Cooperberg M, Crawford DE, Den RB, Dicker AP, Eggener S, Fleshner N, Freedman ML, Hamdy FC, Gomella LG. Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2018; 36(4), 414–424.
39. Chen Z, Greenwood C, Isaacs WB, Foulkes WD, Sun J, Zheng SL, Condreay LD, and Xu J. The G84E mutation of HOXB13 is associated with increased risk for prostate cancer: results from the REDUCE trial. Carcinogenesis. 2013; 34(6), 1260–1264.
40. Maia S, Cardoso M, Pinto P, Pinheiro M, Santos C, Peixoto A, Bento MJ, Oliveira J, Henrique R, Jerónimo C, and Teixeira MR. Identification of two novel HOXB13 germline mutations in Portuguese prostate cancer patients. PLoS One. 2015; 10(7), e0132728.
41. Lin X, Qu L, Chen Z, Xu C, Ye D, Shao Q, Wang X, Qi J, Chen Z, Zhou F, Wang M, Wang Z, He D, Wu D, Gao X, Yuan J, Wang G, Xu Y, Wang G, Dong P, Xu J. A novel germline mutation in HOXB13 is associated with prostate cancer risk in Chinese men. The Prostate. 2013; 73(2), 169–175.
42. Hayano T, Matsui H, Nakaoka H, Ohtake N, Hosomichi K, Suzuki K, and Inoue I. Germline variants of prostate cancer in Japanese families. PloS one. 2016; 11(10), e0164233.
43. Thompson D, Easton D. Breast Cancer Linkage Consortium. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. The American Journal of Human Genetics. 2001; 68(2), 410-419.
44. Dias A, Kote-Jarai Z, Mikropoulos C, and Eeles R. Prostate cancer germline variations and implications for screening and treatment. Cold Spring Harbor perspectives in medicine. 2018; 8(9), a030379.
45. Thompson D, and Easton DF. Cancer incidence in BRCA1 mutation carriers. Journal of the National Cancer Institute. 2002; 94(18), 1358-1365.
46. Leongamornlert D, Mahmud N, Tymrakiewicz M, Saunders E, Dadaev T, Castro E, Goh C, Govindasami K, Guy M, O'Brien L, Sawyer E, Hall A, Wilkinson R, Easton D, UKGPCS Collaborators Goldgar D, Eeles R, and Kote-Jarai Z. Germline BRCA1 mutations increase prostate cancer risk. British journal of cancer.

2012; 106(10), 1697–1701.
47. Oh M, Alkhushaym N, Fallatah S, Althagafi A, Aljadeed R, Alsowaida Y, Jeter J, Martin JR, Babiker HM, McBride A, and Abraham I. The association of BRCA1 and BRCA2 mutations with prostate cancer risk, frequency, and mortality: A meta-analysis. The Prostate. 2019; 79(8), 880–895.
48. Lecarpentier J, Silvestri V, Kuchenbaecker KB, Barrowdale D, Dennis J, McGuffog L, Soucy P, Leslie G, Rizzolo P, Navazio AS, Valentini V, Zelli V, Lee A, Amin Al Olama A, Tyrer JP, Southey M, John EM, Conner TA, Goldgar DE, Buys SS and Ottini L. Prediction of Breast and Prostate Cancer Risks in Male BRCA1 and BRCA2 Mutation Carriers Using Polygenic Risk Scores. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017; 35(20), 2240–2250.
49. Benafif S, and Eeles R. Genetic predisposition to prostate cancer. British medical bulletin. 2016; 120(1), 75–89.
50. Brandão A, Paulo P, and Teixeira MR. Hereditary Predisposition to Prostate Cancer: From Genetics to Clinical Implications. International journal of molecular sciences. 2020; 21(14), 5036.
51. Wilkening S, Chen B, Bermejo JL, and Canzian F. Is there still a need for candidate gene approaches in the era of genome-wide association studies? Genomics. 2009; 93(5), 415-419.
52. Patnala R, Clements J, and Batra J. Candidate gene association studies: a comprehensive guide to useful in silico tools. BMC genetics. 2013; 14(1), 1-11.
53. Benafif S, Kote-Jarai Z, Eeles RA, and PRACTICAL Consortium. A Review of Prostate Cancer Genome-Wide Association Studies (GWAS). Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2018; 27(8), 845–857.
54. Alberti C. Hereditary/familial versus sporadic prostate cancer: few indisputable genetic differences and many similar clinicopathological features. European review for medical and pharmacological sciences. 2010; 14(1), 31–41.
55. Wasserman NF, Aneas I, and Nobrega MA. An 8q24 gene desert variant associated with prostate cancer risk confers differential in vivo activity to a MYC enhancer. Genome research. 2010; 20(9), 1191-1197.
56. Huppi K, Pitt JJ, Wahlberg BM, and Caplen NJ. The 8q24 gene desert: an oasis of non-coding transcriptional activity. Frontiers in genetics. 2012; 3, 69.
57. Ni Raghallaigh H, Eeles R. Genetic predisposition to prostate cancer: an update. Familial Cancer. Fam Cancer. 2022; Jan; 21(1):101-114.
58. 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, Stefansson K. A common variant associated with prostate cancer in European and African populations. Nature genetics. 2006; 38(6), 652–658.
59. 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, Haiman CA. African Ancestry Prostate Cancer GWAS Consortium. Human genetics, 2014; 133(5), 509-521.
60. Matejcic M, Saunders EJ, Dadaev T, Brook MN, Wang K, Sheng X, Olama A, Schumacher FR, Ingles SA, Govindasami K, Benlloch S, Berndt SI, Albanes D, Koutros S, Muir K, Stevens VL, Gapstur SM, Tangen CM, Batra J, Clements J, Haiman CA. Germline variation at 8q24 and prostate cancer risk in men of European ancestry. Nature communications. 2018; 9(1), 4616.
61. Tong Y, Yu T, Li S, Zhao F, Ying J, Qu Y, and Mu D. Cumulative evidence for relationships between 8q24 variants and prostate cancer. Frontiers in Physiology. 2018; 9, 915.
62. Du Z, Hopp H, Ingles SA, Huff C, Sheng X, Weaver B, Stern M, Hoffmann TJ, John EM, Van Den Eeden SK, Strom S, Leach RJ, Thompson IM, Jr, Witte JS, Conti DV, and Haiman CAA. Genome-wide association study of prostate cancer in Latinos. International journal of cancer. 2020; 146(7), 1819–1826.
63. Conti DV, Wang K, Sheng X, Bensen JT, Hazelett DJ, Cook MB, Ingles SA, Kittles RA, Strom S S, Rybicki BA, Nemesure B, Isaacs WB, Stanford JL, Zheng W, Sanderson M, John EM, Park J Y, Xu J, Stevens VL, Berndt SI, PRACTICAL/ELLIPSE Consortium. Two Novel Susceptibility Loci for Prostate Cancer in Men of African Ancestry. Journal of the National Cancer Institute. 2017; 109(8), djx084.
64. Darst BF, Wan P, Sheng X, Bensen JT, Ingles SA, Rybicki BA, Nemesure B, John EM, Fowke J H, Stevens VL, Berndt SI, Huff CD, Strom SS, Park JY, Zheng W, Ostrander EA, Walsh PC, Srivastava S, Carpten J, Sellers T A, Haiman CA. A germline variant at 8q24 contributes to familial clustering of prostate cancer in men of African ancestry. European urology. 2020; 78(3), 316–320.
65. Walavalkar K, Saravanan B, Singh AK, Jayani RS, Nair A, Farooq U, Islam Z, Soota D, Mann R, Shivaprasad PV, Freedman ML, Sabarinathan R, Haiman CA, and Notani D. A rare variant of African ancestry activates 8q24 lncRNA hub by modulating cancer associated enhancer. Nature communications. 2020; 11(1), 3598.
66. 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, Easton DF. Multiple newly identified loci associated with prostate cancer susceptibility. Nature genetics. 2008; 40(3), 316–321.
67. 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, Chanock SJ. Multiple loci identified in a genome-wide association study of prostate cancer. Nature genetics. 2008; 40(3), 310–315.
68. Fernandez P, Salie M, du Toit D, and 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.
69. Jinga V, Csiki IE, Manolescu A, Iordache P, Mates IN, Radavoi D, Rascu S, Badescu D, Badea P, and Mates D. Replication study of 34 common SNPs associated with prostate cancer in the Romanian population. Journal of cellular and molecular medicine. 2016; 20(4), 594–600.
70. Wang Y, Ray AM, Johnson EK, Zuhlke KA, Cooney KA, and 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. The Prostate. 2011; 71(3), 225-231.
71. Kote-Jarai Z, Easton DF, Stanford JL, Ostrander EA, Schleutker J, Ingles SA, Schaid D, Thibodeau S, Dork T, Neal D, Donovan J, Hamdy F, Cox A, Maier C, Vogel W, Guy M, Muir K, Lophatananon A, Kedda MA, Spurdle A, Eeles RA. Multiple novel prostate cancer predisposition loci confirmed by an international study: the PRACTICAL Consortium. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2008. 17(8), 2052–2061.
72. 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, and Freedman ML. Analysis of the

10q11 cancer risk locus implicates MSMB and NCOA4 in human prostate tumorigenesis. PLoS genetics. 2010; 6(11), e1001204.

73. Gudmundsson J, Sulem P, Rafnar T, Bergthorsson JT, Manolescu A, Gudbjartsson D, Agnarsson BA, Sigurdsson A, Benediktsdottir KR, Blondal T, Jakobsdottir M, Stacey SN, Kostic J, Kristinsson KT, Birgisdottir B, Ghosh S, Magnusdottir DN, Thorlacius S, Thorleifsson G, Zheng SL, Stefansson K. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. Nature genetics. 2008; 40(3), 281–283.
74. Gudmundsson J, Besenbacher S, Sulem P, Gudbjartsson DF, Olafsson I, Arinbjarnarson S, Agnarsson BA, Benediktsdottir KR, Isaksson HJ, Kostic JP, Gudjonsson SA, Stacey SN, Gylfason A, Sigurdsson A, Holm H, Bjornsdottir US, Eyjolfsson GI, Navarrete S, Fuertes F, Garcia-Prats MD, Stefansson K. Genetic correction of PSA values using sequence variants associated with PSA levels. Science translational medicine. 2010; 2(62), 62ra92
75. Sun J, Zheng SL, Wiklund F, Isaacs SD, Purcell LD, Gao Z, Hsu FC, Kim ST, Liu W, Zhu Y, Stattin P, Adami HO, Wiley KE, Dimitrov L, Sun J, Li T, Turner AR, Adams TS, Adolfsson J, Johansson JE, Xu J. Evidence for two independent prostate cancer risk-associated loci in the HNF1B gene at 17q12. Nature genetics. 2008; 40(10), 1153–1155.
76. Yu DD, Guo SW, Jing YY, Dong YL, and Wei LX. A review on hepatocyte nuclear factor-1beta and tumor. Cell & bioscience. 2015; 5, 58.
77. Ren F, Zhang P, Ma Z, Zhang L, Li G, Huang X, Chang D, and Yu X. Association of 17q24 rs1859962 gene polymorphism with prostate cancer risk: A systematic review and meta-analysis. Medicine. 2020; 99(3), e18398.
78. Zhang X, Cowper-Sal R, Bailey SD, Moore JH, and Lupien M. Integrative functional genomics identifies an enhancer looping to the SOX9 gene disrupted by the 17q24. 3 prostate cancer risk locus. Genome research. 2012; 22(8), 1437-1446.
79. 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, Sun Y. Genome-wide association study in Chinese men identifies two new prostate cancer risk loci at 9q31.2 and 19q13.4. Nature genetics. 2012; 44(11), 1231–1235.
80. Takata R, Akamatsu S, Kubo M, Takahashi A, Hosono N, Kawaguchi T, Tsunoda T, Inazawa J, Kamatani N, Ogawa O, Fujioka T, Nakamura Y, and Nakagawa H. Genome-wide association study identifies five new susceptibility loci for prostate cancer in the Japanese population. Nature genetics. 2010; 42(9), 751–754.
81. Al Olama AA, Kote-Jarai Z, Berndt SI, Conti DV, Schumacher F, Han Y, Benlloch S, Hazelett D J, 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, Haiman CA. A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. Nature genetics. 2014; 46(10), 1103–1109.
82. Hooker S, Hernandez W, Chen H, Robbins C, Torres JB, Ahaghotu C, Carpten J, and Kittles R A. Replication of prostate cancer risk loci on 8q24, 11q13, 17q12, 19q33, and Xp11 in African Americans. The Prostate. 2010; 70(3), 270–275.
83. Waters KM, Le Marchand L, Kolonel LN, Monroe KR, Stram DO, Henderson BE, and Haiman CA. Generalizability of associations from prostate cancer genome-wide association studies in multiple populations. Cancer Epidemiology and Prevention Biomarkers. 2009; 18(4), 1285-1289.
84. Takata R, Takahashi A, Fujita M, Momozawa Y, Saunders EJ, Yamada H, Maejima K, Nakano K, Nishida Y, Hishida A, Matsuo K, Wakai K, Yamaji T, Sawada N, Iwasaki M, Tsugane S, Sasaki M, Shimizu A, Tanno K, Minegishi N, Nakagawa H. 12 new susceptibility loci for prostate cancer identified by genome-wide association study in Japanese population. Nature communications. 2019; 10(1), 4422.
85. Berndt SI, Wang Z, Yeager M, Alavanja MC, Albanes D, Amundadottir L, Andriole G, Beane Freeman L, Campa D, Cancel-Tassin G, Canzian F, Cornu JN, Cussenot O, Divez WR, Gapstur S M, Grönberg H, Haiman CA, Henderson B, Hutchinson A, Hunter DJ, Chanock SJ. Two susceptibility loci identified for prostate cancer aggressiveness. Nature communications. 2015; 6, 6889.
86. Pinto AR, Silva J, Pinto R, and Medeiros R. Aggressive prostate cancer phenotype and genome-wide association studies: where are we now? Pharmacogenomics. 2020; 21(7), 487-503.
87. Duncan L, Shen H, Gelaye B, Meijsen J, Ressler K, Feldman M, Peterson R, and Domingue B. Analysis of polygenic risk score usage and performance in diverse human populations. Nature communications. 2019; 10(1), 1-9.