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Single Nucleotide Polymorphisms in Prostate Cancer: A Comprehensive Review

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Abstract

Prostate cancer (PCa) is a major global health concern, with significant genetic contributions to its aetiology. Single nucleotide polymorphisms (SNPs) are pivotal genetic variations influencing PCa susceptibility, progression, and therapeutic outcomes. This review synthesises current knowledge on SNPs in PCa, exploring their role in disease risk, molecular mechanisms, and clinical implications. It covers the historical context of PCa, its epidemiology in Indian, Asian, and global populations, and the interplay between genetic and environmental factors. Additionally, the review addresses benign prostatic hyperplasia (BPH) and its genetic overlap with PCa, current research trends, and future directions for leveraging SNPs in precision medicine. By integrating findings from genome-wide association studies (GWAS) and functional analyses, this review aims to provide a holistic understanding of SNPs in PCa and their potential in improving diagnosis and treatment strategies.

Keywords: Prostate cancer, PCa, SNP, epidemiology, GWAS, Global, India

1. Introduction

Prostate cancer (PCa) is the second most common malignancy among men globally, with approximately 1.4 million new cases reported in 2020 [1]. The occurrence of prostate cancer differs notably among ethnic groups, being more common in Western populations but steadily increasing in Asian countries like India [2]. Genetic factors, especially small changes in DNA called single nucleotide polymorphisms (SNPs), play a significant part in a person's risk for developing prostate cancer—accounting for about 60% of inherited susceptibility [3]. These SNPs are subtle, single-letter differences in the genetic code that can

affect how genes are expressed and how proteins function, ultimately shaping an individual's likelihood of getting the disease. SNPs, defined as single-base-pair variations in the genome, influence gene expression, protein function, and disease risk. Recent advances in genome-wide association studies (GWAS) have revealed over 400 genetic variants, called single nucleotide polymorphisms (SNPs), that are associated with an increased risk of prostate cancer. These discoveries have significantly deepened our understanding of the genetic factors underlying the disease [4]. This review delves into how these SNPs contribute to prostate cancer, the biological processes they influence, and their potential impact on diagnosis and treatment—highlighting differences across populations and outlining areas for future research.

2. History of Prostate Cancer

The earliest documented cases of prostate cancer date back to the 19th century, with initial reports describing it as a rare malignancy [5]. The introduction of prostate-specific antigen (PSA) testing in the late 1980s marked a significant turning point in prostate cancer detection. While the PSA protein was discovered and characterised throughout the 1970s, its clinical use as a blood test to monitor treatment response and detect recurrence began in the mid-1980s. By the late 1980s and early 1990s, PSA testing started being used for early detection and screening efforts, gaining approval for this purpose by health authorities in the early 1990s [6]. This advancement dramatically increased the number of prostate cancer diagnoses and remains a key tool in urology today. However, the PSA test has limited specificity, as elevated levels can also result from non-cancerous conditions such as benign prostatic hyperplasia (BPH), leading to concerns about overdiagnosis and unnecessary treatments [7]. Over time, improvements in imaging technology, biopsy methods, and molecular genetics have significantly enhanced the management of prostate cancer. The advent of GWAS in the 2000s identified SNPs as key contributors to PCa risk, shifting the focus toward personalised medicine to improve risk stratification and treatment outcomes [8].

3. Epidemiology of Prostate Cancer

3.1 Indian Scenario

In India, prostate cancer is the second most common cancer among men, with an age-standardised incidence rate of 7.5 per 100,000 [9]. Urbanisation, improved screening, and lifestyle changes have driven rising incidence, particularly in metropolitan areas like Delhi and Mumbai [2]. Genetic research involving Indian populations has pinpointed variations in genes like VDR and CYP17 that are linked to an increased risk of prostate cancer [10]. Unfortunately, challenges such as limited access to advanced diagnostic tools and cultural barriers to screening often lead to late-stage diagnosis, emphasising the urgent need for genetic studies tailored to specific regions [11].

3.2 Asian Scenario

Compared to Western countries, PCa cases across Asia are significantly lower. However, recent studies have shown that PCa incidence is increasing rapidly, particularly in East Asian countries like Japan and China [12]. In Japan, the incidence rate is approximately 30 per 100,000, driven by ageing populations and Westernised diets [13]. SNPs in genes like FGF23 and VDR have been linked to PCa risk in Asian cohorts [14]. Ethnic-specific genetic variations, such as those at the 8q24 locus, show differential risk associations compared to other populations [15]. These findings emphasise the importance of tailored genetic screening in Asian populations.

3.3 Worldwide Perspective

Globally, PCa incidence is highest among African-American men (179 per 100,000) and lowest in South-Central Asia (3.1 per 100,000) [1]. African-American men also face higher mortality rates, suggesting a role for genetic predisposition and aggressive disease phenotypes [16]. Genome-wide association studies (GWAS) have discovered more than 450 single nucleotide polymorphisms (SNPs) that are linked to an increased risk of developing prostate cancer. Notably, regions such as the KLK3 gene and the 8q24 locus have shown consistent associations with prostate cancer across different ethnic backgrounds [3]. Factors like diet

and smoking can also interact with these genetic variants, shaping an individual's overall risk for the disease [17]. Considering the significant global impact of prostate cancer, it is increasingly important to conduct research that brings together both genetic and environmental perspectives to better understand and address this health challenge.

4. Single Nucleotide Polymorphisms (SNPs)

SNPs are single base-pair substitutions occurring at a frequency greater than 1% in a population [18]. They are the most common form of genetic variation, occurring approximately every 300 base pairs in the human genome [19]. Single nucleotide polymorphisms (SNPs) may occur within the parts of genes that directly code for proteins, potentially changing how those proteins work, or in non-coding regions that regulate gene activity. In prostate cancer, these SNPs are typically discovered through genome-wide association studies (GWAS), which compare genetic differences between affected individuals and healthy controls [8]. Some of these SNPs, like those found in the KLK3 gene that produces prostate-specific antigen (PSA), impact disease risk by altering gene expression or the function of the encoded protein [20].

5. SNPs Associated with Prostate Cancer

Conti et al. [4] in their study, through GWAS, reported that more than 400 SNPs are associated with PCa risk, which is approximately 42.6% of familial risk. Gudmundsson et al. [21] found that the SNPs located in the 8q24 regions (rs16901979) have different impacts across ethnic groups, as this SNP has much stronger risk effects documented among African-American men. One important genetic variant, rs17632542 in the KLK3 gene, has been shown by Eeles et al. [22] to decrease the overall risk of developing prostate cancer. Nevertheless, this genetic variant is also shown to increase the likelihood of the cancer spreading to other parts of the body [22]. Non-coding SNPs may often be present in regulatory regions, altering transcription factor binding and gene expression [23-24]. For example, rs60464856 in RUVBL1 enhances PCa cell proliferation by upregulating cell-cycle pathways [24]. Huynh-Le et al. [25] in a study on prostate cancer in the Cohort of Swedish Men have shown that combined SNPs in polygenic risk scores (PRS) help in risk prediction, particularly for early-onset and aggressive PCa.

6. Benign Prostatic Hyperplasia (BPH)

Benign prostatic hyperplasia (BPH) is a common, non-cancerous enlargement of the prostate gland that affects more than half of men over the age of 60 [26]. While BPH itself is not a direct cause of prostate cancer, both conditions share some genetic risk factors, particularly certain variations in the CYP17 and VDR genes [27]. For example, the CYP17 rs743572 C allele is linked to a roughly 1.58 times higher likelihood of developing BPH in Asian populations. BPH may contribute to PCa progression through inflammation, a key event in prostate carcinogenesis [28]. Genetic screening for BPH-associated SNPs could aid in early risk stratification [29].

7. Gene Association Studies

Research focused on genetic links has identified particular gene variants that contribute to prostate cancer risk. Key genes among these include MSMB, ITGA6, and KLK3, which are recognised as important biomarkers [30]. For example, specific changes in the MSMB gene can reduce how much of the gene is expressed, which in turn raises an individual's likelihood of developing prostate cancer [31]. Research in Asian populations has also confirmed connections between prostate cancer and genes like VDR and FGF23 [14]. Moreover, comprehensive studies—such as those examining specific SNPs in the 8q24 region within Iranian cohorts—are refining potential genetic markers for clinical application [32]. These findings highlight the complex, polygenic nature of prostate cancer, where numerous SNPs together influence an individual's overall risk.

8. Gene-Environment Interactions

Environmental factors such as diet, smoking, and obesity interact with genetic variations to influence the risk of developing prostate cancer. For example,

consuming a high-fat diet can increase the risk associated with specific SNPs in the 8q24 region [33]. Similarly, smoking can worsen the effects of XRCC1 gene variants by promoting oxidative stress and DNA damage [34]. In Asian populations, insufficient selenium intake has been shown to amplify the risk linked to variations in the VDR gene. These complex interactions underscore the importance of developing comprehensive models that combine both genetic and environmental factors to predict prostate cancer risk more accurately [35].

9. Current Studies

Current research focuses on the functional characterisation of PCa-associated SNPs using high-throughput technologies like SNP-seq [36]. Studies are exploring expression quantitative trait loci (eQTLs) to link SNPs with gene expression changes, identifying 88 genes associated with 51 risk loci [37]. In Asian populations, PRS models are being developed to predict early-onset PCa [29]. Additionally, CRISPR-based screening has prioritised regulatory SNPs, such as rs60464856, for their role in PCa progression. These efforts aim to translate genetic findings into clinical tools for risk assessment and therapy.

10. Future Studies

Future research should prioritise functional validation of SNPs in diverse populations, particularly in understudied regions like India [2]. Integrating multi-omics data (e.g., genomics, transcriptomics, proteomics) will elucidate SNP-driven molecular pathways (Haffner et al., 2021). Developing ethnic-specific PRS models will enhance risk prediction [38]. Moreover, long-term studies that examine how genes and environmental factors interact are essential to developing practical prevention approaches. Technological innovations such as CRISPR gene-editing and artificial intelligence-driven data analysis are significantly advancing our capacity to identify the crucial genetic variants that contribute to prostate cancer. These technological strides are paving the way toward highly personalised medical approaches tailored to individual genetic profiles [39].

11. Conclusion

SNPs are pivotal in understanding PCa susceptibility and progression, with over 400 variants identified through GWAS. Their role in modulating gene expression and protein function underscores their potential as biomarkers. Regional variations, particularly in India and Asia, highlight the need for ethnic-specific research. The interplay between SNPs and environmental factors further complicates PCa risk, necessitating integrated approaches. Ongoing and future studies leveraging advanced technologies will enhance the clinical utility of SNPs, improving PCa diagnosis, risk stratification, and personalised treatment.

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