Prostate International 8 (2020) 135–145

Contents lists available at ScienceDirect

Prostate International

journal homepage: https://www.journals.elsevier.com/prostate-international

Review Article

A review of studies examining the association between genetic biomarkers (short tandem repeats and single-nucleotide polymorphisms) and risk of prostate cancer: the need for valid predictive biomarkers

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ARTICLE INFO

Article history:
Received 10 September 2019
Received in revised form
22 October 2019
Accepted 8 November 2019
Available online 2 December 2019

Keywords:
Human genetics
Prostate cancer
Short tandem repeats
Single-nucleotide polymorphisms
X-chromosome
Y-chromosome

ABSTRACT

Prostate cancer (PCa) is a challenging polygenic disease because the genes that cause PCa remain largely elusive and are affected by several causal factors. Consequently, research continuously strives to identify a genetic marker which could be used as an indicator to predict the most vulnerable (i.e., predisposed) segments of the population to the disease or for the gene which may be directly responsible for PCa. To enhance the genetic etiology of PCa, this research sought to discover the key studies conducted in this field using data from the main journal publication search engines, as it was hoped that this could shed light on the main research findings from these studies, which in turn could assist in determining these genes or markers. From the research highlighted, the studies primarily used two kinds of markers: short tandem repeats or single-nucleotide polymorphisms. These markers were found to be quite prevalent in all the chromosomes within the research carried out. It also became apparent that the studies differed in both quantity and quality, as well as being conducted in a variety of societies. Links were also determined between the degree and strength of the relationship between these markers and the occurrence of the disease. From the studies identified, most recommended a larger and more diverse survey for the parameters which had not been studied before, as well as an increase in the size of the community (i.e., the population) being studied. This is an indication that work in this field is far from complete, and thus, current research remains committed toward finding genetic markers that can be used clinically for the diagnosis and screening of patients with PCa.

1. Introduction

Because of its polygenic nature, prostate cancer (PCa) is considered to be among the most complex diseases to be fully understood. This has created a degree of uncertainty to professionals involved in this field, as well as to the patients themselves and their families. Although there has been significant improvement in the treatment and diagnosis of PCa over the last twenty years, along with an accumulation of knowledge linked to its risk factors, there is still a gap in understanding the genetic

Abbreviations: PCa, Prostate cancer; STRs, Short tandem repeats; SNPs, Single-nucleotide polymorphisms; NRY, Nonrecombining Y; BPH, Benign prostatic hyperplasia; PSA, Prostate-specific antigen; ARE, Androgen response element; GWAS, Genome-wide association studies.

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https://doi.org/10.1016/j.prnil.2019.11.003
p2287-8882 e2287-903X/

background of the disease, an area which would improve the lives of patients with PCa.[7]

Most men especially who are older than 40 years will eventually develop some kind of disease related to the prostate, such as benign prostate hyperplasia (BPH), prostatitis, and PCa.[1] Moreover, the epidemiological studies indicate that about 11% of men will be diagnosed with PCa during a period of their lives.[6,22] Therefore, PCa ranks as the second category of cancers which affects men worldwide.[17] In every racial and ethnic group in the United States, PCa among men and breast cancer among women were the most frequent incident cancers.[13] Moreover, when patients develop such diseases, there are typically no easy solutions or interventions.[34]

Although PCa is a common cancer and there are important signs of a genetic effect in its etiology, the nature of the genetic role in cancer remains complex.[28] When some family members have been exposed to PCa, this significantly increases the risk factor for others within the family of being afflicted with the same condition by twofold or threefold if the father or brother has the disease, respectively.[11,52,55] Although studies of twins and families have shown a genetic component of the disease, the detection of genes or genetic variants responsible for the disease is still difficult to ascertain because many genes are involved in causing the disease; in other words, this disease has a polygenic inheritance.[51] The hereditary effect or characteristic of PCa may be considered as being the highest among all other types of cancer.[53,54]

The detection of the genetic basis of PCa makes it possible to find more accurate methods of screening, diagnosis, and therapy. Gaining more knowledge of the genetic basis of the disease will aid in the disclosure of the effect of modifiable factors in the incidence of the disease through advanced studies that focus on the interaction between the environment and genetic background. [7]

Owing to the characteristics of the short tandem repeats (STRs) such as high polymorphism, pervasive presence, and common sequences, these can all assist in helping to identify individuals who are most susceptible to PCa.[39] The information obtained from lineage markers such as STRs or other markers which have low mutation rates are perhaps from among the best sources available in helping to identify inheritance scenarios.[56,57] Consequently, many studies have been carried out to verify the relationship between the phenotype and genotype of people using STRs which can determine the lineage of the Y-chromosome.[11,12,36,38,58] The role of the Y-chromosome in the incidence of PCa has been identified through cytogenetic and gene expression studies.[38]

This review has sought to present a brief history of previous empirical work that has assessed the relationship between genetic biomarkers such as STRs and single-nucleotide polymorphisms (SNPs) and the incidence of PCa among male population, with a view to focusing on those studies' results and conclusions which have been summarized in this review. It has also presented the biomarkers identified for prediction, diagnosis, or screening of PCa, as well as the possibility of classifying exposure of men to PCa according to their genetic background.

2. Brief history of PCa

The prostate is a gland that helps to produce semen that carries sperm, which physically surrounds the male urethra.[1] PCa is a malignant tumor that occurs in the prostate gland, and in many cases, it does not cause any symptoms and may remain dormant or undetected without any development or complications. However, the other type of PCa does not remain in the prostate but spreads to other places, such as the bones and lymph nodes, this is referred to as metastatic PCa.[2,59]

In most countries, there has been a steady increase in the incidence of PCa, documented in epidemiological studies.[60,61] PCa stands as a serious challenge to the health community as it is the most common malignancy among men; it accounts for 33% of cancers affecting men.[62] Furthermore, although some countries may have a low incidence of PCa, they suffer from high mortality rates for those afflicted with the disease. One such example is Middle African countries, in which the PCa incidence rate of 16.4 per 100,000 people is reported; however, the mortality rate is 13.4 per 100,000 people. In contrast, the lowest incidence and mortality rates for PCa in the world have been recorded in Eastern Asian countries.[7]

Because of the high incidence rate compared with other solid tumors, it is one of the most serious cancerous diseases that can affect men. At present, PCa incidence rate is the second after lung cancer and the deaths caused by PCa are the 4th highest in the world among men, after lung, liver, stomach cancer.[63,64]

Although, the disease risk factors such as aging, race, and heredity are among the most prominent factors affecting patients with PCa, the exact cause of the disease is still unknown. For instance, many studies have suggested that PCa is closely linked to age because the possibility of developing PCa increases with every decade of life; also, in general, two-thirds of people diagnosed with cancer are between 60 and 79 years old, and cancer deaths occur in about 80% of patients older than 70 years, specifically, the average age of PCa diagnosis is between 60 and 70 years old.[2,65]

Furthermore, a second factor associated with PCa is the geographic location, involved in the development of PCa through its effect on population behavior in diet and physical activity, as well as the percentage of environmental pollution in that region.[66] It is important to identify a clinically efficient genetic test to identify PCa susceptibility, beyond modifiable external risk factors such as those discussed previously.[67]

The regulation of some modifiable risk factors which are associated with PrCa such as lifestyle habits, diet, anthropometric characters, and sexual behavior could participate in lowering the incidence of the disease.[68,69]

There is a growing debate about the development of PCa, and it is centered on the molecular aspects, including genetic changes in somatic and germ line levels. Therefore, the greater the knowledge of the molecular and genetic basis of PCa, the better might be the prediction of this disease's progression, particularly if significant developments are made in this area.[65] Owing to its appearance and prevalence, many diagnostic methods have been developed. It has also been confirmed in the literature that it can be affected by many causes and the involvement of more than one gene in its occurrence.[70] Currently, the research findings around the world have not yet reached clinical applicable novel markers for predicting PCa progression.[71]

3. The role of Y-chromosome in PCa incidence

There is a distinction for each group of Y-haplogroup according to its geographic origin, so men belonging to a particular ethnic group have a different Y lineage from other races and therefore a different susceptibility to develop PCa.[11] Ewis et al[16] reported that they had studied Japanese patients with PCa and matched them to the controls, who were Japanese men from similar geographical regions, to exclude any opportunity for ethnic differences. This is because the ethnic composition of the groups under study is vital when thinking about the specific alleles in a specific location or the individual pattern that is predisposed to the development of a particular disorder.[16] The theory of the effect of race on the incidence of PCa is supported by different incidence rate between races, with rates being higher in the African–American population followed by Caucasians, but lower among Japanese men.[11] The role of the Y-chromosome has been suggested in PCa, primarily because

the deletion of the Y-chromosome is the most dominant chromosomal alteration noticed in PCa tissues.[10,25] Furthermore, cytogenetic research in primary prostate malignancy has indicated that the loss of the Y-chromosome is the most widespread chromosomal abnormality observed.[10]

Evidence supports potential liability for the Y-chromosome in PCa development, but there is controversy [11]; whereas, the study of Elfving et al[15] showed that the Y-chromosome was lost in healthy tissues of older men. Other studies found that they had observed the loss of the Y-chromosome in the malignant prostate tissue, and moreover, it had not been noticed in the nearby apparently normal tissue.[4,25]

Individuals who are born with a (p arm) but without the (q arm) of the Y-chromosome are men, whereas individuals born with the long arm of the Y-chromosome with the short arm lost are women.[18] A patient with PCa shares the same genetic background with his father and male siblings, especially the Y-chromosome, which is transmitted exclusively from fathers to male children without any events of recombination. The male siblings are genetically closer if they receive the same X-chromosome from the mother. For men who have a father or brother with PCa, their risk is higher. Higher risk has been observed once more if more than one member of an individual's family has developed PCa. Moreover, it is also higher if the cancer is diagnosed at an early age.[2]

The results of the analysis of the genetic expression in the PCa tissues have shown an abnormal pattern of certain genes in the Y-chromosome;[30] specifically, in the sex-determining gene (SRY) because it has shown a down regulation in the PCa tissue. Research has found that the SRY gene is a negative regulator of the androgen receptor (AR), showing that the AR activity increases if the SRY gene is lost, thus stimulating cancer growth.[38,49] This effect happens because the process of development and incidence of PCa is affected by androgen, as the effect of the androgen is demonstrated through the mediator that is the androgen receptor, a transcription factor that depends on the ligand. In addition, it is worth noting that testosterone and dihydrotestosterone regulate the activity of the AR gene monohuman copy in the X-chromosome.[3]

Based on in vivo studies, researchers have reported that the Y-chromosome has a more protective role than its susceptible role in PCa. They have found that the addition of the Y-chromosome inhibits cancerous tumors in the cell lines of human prostate cells, leading to the claim that this chromosome contains a gene(s) with a tumor suppression function.[44] Another study by Wang et al[45] found weak but consistent evidence of a protective effect of haplogroup E1b1b1c in chromosome Y in all studies with a nominally significant metaanalysis. This points to additional efforts being required to study this haplogroup in detail, and the Y-chromosome in general, within the same community and within broader societies.

4. Studies conducted on Y-SNPs

Different Y-chromosomes could be classified by binary markers into haplogroups organized by a tree of phylogeny.[45] More than 300 haplogroups lie under 20 major clades constituted by the Y-chromosome tree. In relation to their findings, Paracchini et al[38] findings showed a significant contribution of Y-chromosome factor in PCa development in Japanese men , where they found a significant association exclusively present in the lineage O3. The increase in risk is associated with the increase in difficulty of disease and elder age.

Similarly, any mutation increased susceptibility to, or protection from, PCa would be in full linkage disequilibrium with all other binary markers such as SNPs and would fall on a particular haplogroup of the Y phylogeny, unrelated to the physical distance between the markers. Consequently, lineages that carry a protective or predisposing factor will be found at a superior frequency between patients or healthy controls, respectively.[38]

Men belonging to haplogroups O2b* and O2b1 in the study by Ewis et al were the least likely to develop PCa, whereas the male haplogroup DE had a higher susceptibility to the disease.[16] These results highlighted that the Y-chromosome carries the tumor genes and/or tumor suppressor genes, which work at different stages of the tumor. Consequently, it can be interpreted that Japanese men with haplogroup O2b* and O2b1 have different Y-chromosomes from those found in DE haplogroups and those untagged. In addition, men from O2b* and O2b1 may have genes or DNA sequences acting as tumor inhibitors, making them resistant to the development of this male cancer. On the other hand, susceptible haplogroups could lack a locus or sequence which may exist on the Y-chromosomes of DE haplogroups and untagged with an oncogenic-like activity, making DE and untagged haplogroups more likely to develop PCa. Thus, the creation of human cancer, especially male organ cancers, such as testicular and prostate cancer, may be the result of various Y-chromosome lineage showing different levels of resistance or susceptibility.[16]

In the Korean population, Kim et al[26] attempted to confirm Y-chromosomal lineage role in PrCa development. They observed 11 different Y-chromosome strains (C-RPS4X, K-M9, N-M214, O-M175, O-M119, O- O-LINE1, O-M134), identified through 14 biomarkers in cancer cases and control samples, most of which were the predominant haplogroups expected in East Asia. Within this Korean population, there was a high frequency of the haplogroup O-M175 (and subgene) in both groups of patients with PCa (84.0%) and normal controls (76.3%). There were no statistically significant differences ($p = 0.05$) in the distribution of Y-chromosomal haplogroup frequencies between the case and control groups. Moreover, the authors compared their results per each significant lineage with previous studies of Ewis et al[16] and Paracchini et al[38], but did not find significant differences in the comparison with their results. They refer variations between their findings and previous studies to the reflection of false-positive associations or to genetic predisposition expressed by the Japanese living in a different environment. The cases studied by Paracchini et al[38] were the Japanese who lived in the United States, whereas the cases studied by Kim et al [26] were from Korea. Although both populations were from East Asia, they lived in different environments which may have caused the differences in the results between these studies.

The presence of a limited role of inherited Y-chromosome variations in PCa etiology in European populations was suggested by Wang et al.[45] Based on their comparison of haplogroup frequencies between studies, they noted the presence of matches among those accomplished in the United States and France (R1 group). Their study suggested that genetic variation in Y-chromosomes have a partial function in PCa etiology in European people, while recommending follow-up in additional large and distinct studies of a multitude of ethnic populations. In addition, they found weak but consistent evidence for the protective effect of haplogroup E1b1b1c in all studies with metaanalysis of nominal significance. Thus, they recommended an additional increased effort for this haplogroup in people of Jewish and European Ashkenazi origin. The authors concluded that they could not exclude the role of all groups of Y-haplogroups in PCa development, and their study had a strong ability to detect common alleles with relatively large effects. Therefore, they recommend the establishment of additional research to test a comprehensive collection of markers of Y-chromosome haplogroups in future studies.[45]

The independent effect of chromosome Y in increasing the risk of PCa apart from other autosomes was indicated by the results of Cannon-Albright et al[11] in which there was a significant excess in

the incidence of PCa among the Y-chromosome id sharing male offspring of the founder in comparison with all descendants (empirical $p < 0.05$). Therefore, they concluded that a study of this particular societal group could allow identification of genes or variants which could protect against PCa. Ewis et al[58] have hypothesized that the genes found in the Y-chromosome and loci can help to identify the most vulnerable group of men to PCa. Consequently, Y-chromosome can be involved in the identification of the group or subgroup of men who are more susceptible than others to this genetic risk; therefore, this could decrease the mortality rate in this category of the population, furthermore decreasing the percentage of men who are subjected to biopsies or harsh procedure for diagnosis.[51]

5. Studies examining the association between STRs markers and exposure to PCa

An analysis of the STR markers could provide a means to quickly examine the genome at known or unknown loci to test predisposition to certain diseases.[12,43] Microsatellite-based trials may add more information about resistance or susceptibility to PCa.[12] Because STRs are generally considered to be selectively neutral (not affected by natural selection), they are affected instead by gene flow, genetic drift, and mutations, and thus are useful in the definition of population and the estimation of differences among populations.[20] Therefore, the study by Riley and Krieger[39] proposed to scan the Xq11, 13 regions by STRs of genetic loci. This inquiry provided rapid analysis to compare between large groups of patients with PCa and healthy controls.

There is no doubt that progress in genotyping technology has led to a steady increase in knowledge of genomic disorders of complex diseases such as PCa. Since predicting those elements of the population that are susceptible to any hereditary disease is one of the main pathways of human genetics. Therefore, many studies have attempted to find any link between the biomarkers and the susceptibility of PCa. Consequently, discovering a diagnostic biomarker to identify men with clinically significant PCa will be of immeasurable assistance in helping to lower the mortality rate of this disease.[7]

It is apparent that a study conducted by researchers of Johns Hopkins University was the first published study to report a significant linkage between familial PCa with the genetic loci located in region 1q 24-25, termed hereditary prostate cancer1.[41] The findings of Ewis et al[58] support their hypothesis regarding the different susceptibility or resistance of male descendants from different Y-chromosomal origins to develop PCa (as a male-specific cancer).

Concurrently, a proportion of research has investigated the relationships between PCa and family hereditary or/and Y-chromosome allele;[11] some of these studies have revealed that there is an association between Y lineages and incidence of PCa;[12,36,38,58], while other studies correlate between X-chromosome and PCa.[3,19,39,72] However, there also exists research reporting no association or only a weak association between PCa and selected genetic biomarkers highlighting the clear contention in the field.[26,32]

Androgen receptor (AR) is a transactivation factor which depends on the binding of the steroid hormone. This factor is very important in the proliferation and differentiation of prostate cells. The polymorphic variations of the AR gene region, where polymorphism shows the highest variation in the number of repeats for the sequences (CAG and GGC), may alter transcriptional activity for the future.[33]

The study by Neto et al[72] has reported an increase in PCa incidence by 2.44 times in people with CAG repeat less than or equal to 21 bp length. In addition, when they combined both forms, the risk of CAG and GGC was found to be higher when their length was less than or equal to 37 bp; therefore, the authors pointed out that the cutoff indicated the existence of a subset population who were at the greatest risk of developing PCa. Although their conclusion confirmed the above mentioned findings, there is still some controversy in proving the relationship between AR gene polymorphism and PCa. At the same time, they assumed that the shorter repeats are associated with increased transcriptional activity; consequently, this could be related to a higher risk of PCa because these polymorphisms exist in the transcriptional area of the gene. There are also studies indicating that variations in the single polymorphic region can affect the function of gene because of their linkage association.[50] On the other hand, when considering the long CAG repeats, a small study by Alptekin et al [3] has reported that there are statistically significant differences ($P = 0.03$; $P < 0.05$) between controls and BPH, as well as controls and adenocarcinoma, respectively.

The results of this abovementioned study imply that longer CAG repeats may be related to the higher level of receptor transactivation, as the number of CAG repeats rises in patients with BPH and adenocarcinoma compared with the controls with the highest increase in patients with adenocarcinoma. However, these results may be owing to a small size sample that was present in their study.[3] These incompatibilities may refer to the deficiency of a uniform model of analysis and different cutoff points for these studies, resulting in difficulty in drawing direct comparisons.

Gsur et al[19] reported that one possible limitation of their study was that the control group of patients with BPH did not adequately represent that group because the polymorphisms in the AR and prostate-specific antigen (PSA) genes in that group may be related to prostate size or BPH etiology.

Another study of note conducted by Neto et al[72] found an increase in risk to PCa in their population when they considered the sum of two polymorphisms CAG and GGC repeats length together. Therefore, the authors concluded that these findings might reflect the activity of transcriptional and regulatory status of the genes in exon 1. They adopted the previous proposal of Nelson and Witte[37] which indicated that the conflicting results in previous studies in the function of these polymorphisms in PCa could be attributed to the requirement of gathering either environmental or genetic factors which increase the incidence of PCa.

The results of the study conducted by Neto et al[72] on the genetic polymorphism of CAG repeat alone or along with the GGC repeat in the AR gene showed a link between these repeats and the increased risk of PCa development. Based on this, the authors concluded that it could serve as a clinically useful tool to identify people with high susceptibility to this disease. In comparison, the study by Biolchi et al[9] which examined two cutoff points of repeats 21 and 22 did not find any link between CAG repeat length in AR gene and the risk of BPH in Brazilian men. As previously mentioned, the studies conducted to find a link between CAG polymorphisms alone or with GGC polymorphism and the increased risk of developing PCa have demonstrated conflicting results.

The data from the Y-haplotype are relatively inexpensive and direct, and risk estimates from a single assay may be helpful for numerous people.[11] A study conducted on Malaysian society

showed the effect of genetic elements of the Y-chromosome on PCa. The authors stated that the DYS388 loci and less likely DYS439 loci, as well as haplotypes models that include DYS388, DYS435, DYS437, and DYS439, appear to have the ability to be used as a screening method to predict susceptibility to PCa.[36]

6. The location of the genes and genetic biomarkers (STRs or SNPs) in the human genome

It is known that PCa is not transmitted from parents to sons, but inherited genes can cause it or can protect against it. Many inherited genes that appear to raise the risk of PCa have been identified.[2] The polygenic nature of PCa has led to identify numerous genetic changes. This happens during the multiple trials to obtain PCa susceptible loci and genes that share the same molecular means of development and progression.[16] Genome-wide association studies (GWAS), conducted in the form of scans of the entire human genome, have revealed a number of susceptible genetic loci which are found on different chromosomes and distributed on most chromosomes, particularly X–Y, as well as chromosomes 1, 7, 8, 9, 10, 12, 18, and 20.[8,16] Fig. 1 demonstrates the distribution of loci associated with PCa risk identified by GWAS.

For 13 genes in the androgen pathways and 12 genes in the estrogen pathway, Cunningham et al[14] conducted a systematic investigation for 46 polymorphisms (34 SNPs, 10 STRs, and 2 null alleles). Their investigation aimed to test the possible associations between the common genetic variants of the enzymes involved in the metabolic pathways of androgen and estrogen and increased risk of intermittent and familial prostate disease. Although most studies used one type of polymorphic marker SNPs or STRs; the study by Cunningham et al[14] from the few studies used two kinds of genetic variants (SNPs and STRs markers) together to examine the presence of association. To cover all expected markers (SNPs and STRs) which related to PCa, Cunningham et al[14] included all known nonsynonymous coding SNPs in the genes selected for analysis. In addition, they also selected further frequently investigated synonymous coding SNPs, STRs, or SNPs in the promoter region.

Because the Xq1 and Xq13 region of the X chromosome is involved in familial PCa and other diseases and the phosphoglycerate kinase (PGK1) STR is the most polymorphic locus described in the Xq11-Xq13 interval; Riley and Krieger[39] have examined the human PGK1 gene STR polymorphisms within that region. It is worth mentioning that the X-chromosome is directly transferred from fathers to their daughters without any changes except the pseudoautosomal region. During maternal stage the rate of recombination varying inside the chromosome; some regions did not experience any recombination, which means that it is transferred as it is from grandfathers to siblings in maternal pedigree without any changes; therefore, it can be used as a lineage marker.

In the present review, PCa linkage studies are summarized and listed in Table 1, according to their publishing year, inspected chromosome, and location of susceptible locus on these chromosomes. These studies have concentrated on the Y-chromosome and ignored X-chromosome markers as lineage markers; even though, lineage markers in the X- and Y-chromosome can be used to identify relatives in paternity cases and can be used for genealogies.[73,74]

Kommu et al[27] have addressed why there are many conflicting reports in favor or rejection of the existence of the links in many regions of the genome and why the genetic predisposition of PCa is so complex, making an understanding of the genetic basis of the disease so challenging. They referred primarily to the involvement of many predisposing genes. Their study revealed that in a high ratio of families with an elevated risk of the disease, this may not be due to one gene only. Moreover, the authors concluded that the traditional association studies may not be the best means to

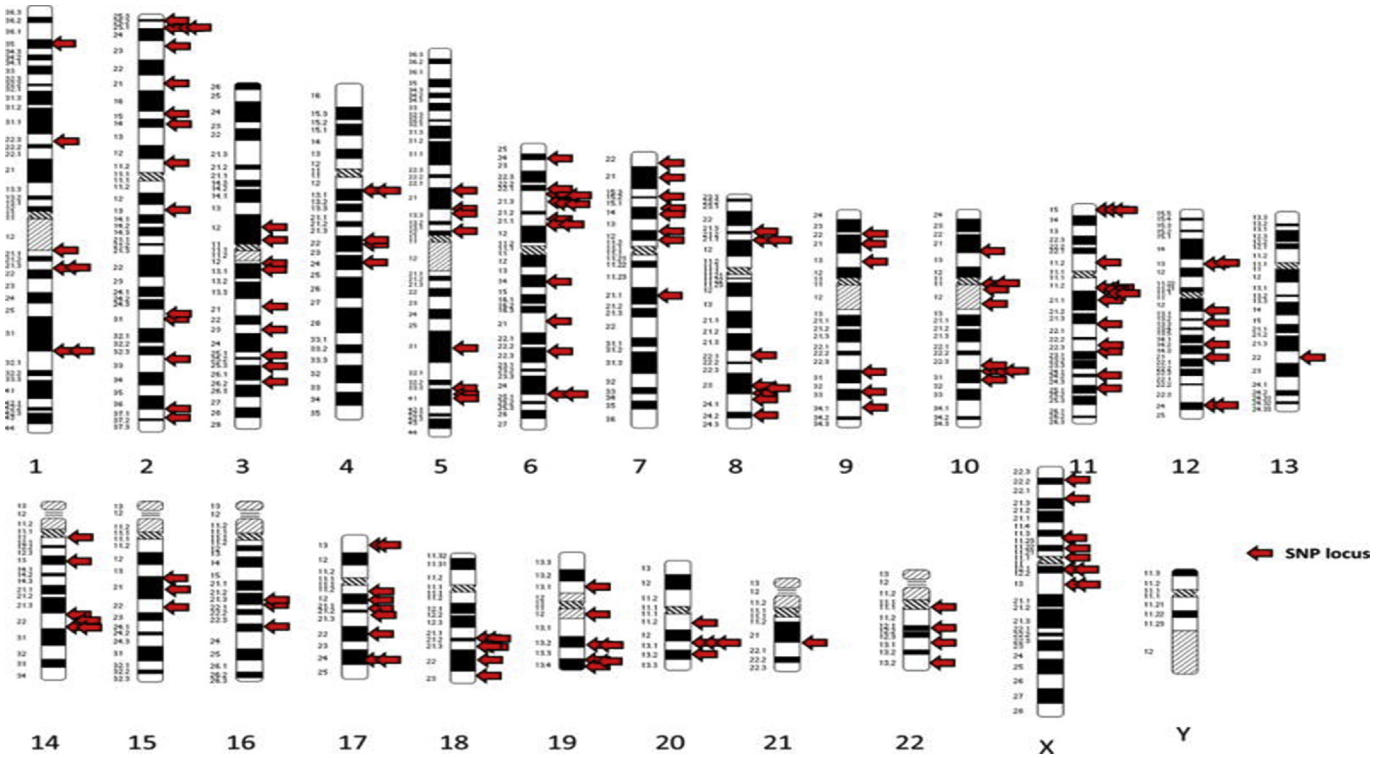

Fig. 1. Demonstrates the distribution of loci associated with prostate cancer risk identified by GWAS studies (each red arrow represents an individual SNP), adopted from [8]. SNP, single-nucleotide polymorphism; GWAS, genome-wide association studies.

identify the genes that predispose to PCa because of genetic heterogeneity, as different family clusters are owing to different genes.

Because the PCa is a massively polygenic disease, as described previously, some researchers have used the polygenic risk score (PRS) modeling as a tool that could aid in assessing patients' tendency for PCa.[5,21,35,46] These studies explore the discriminative ability of the PRS and evaluate whether there is significant information added to the overall risk prediction of PCa by these scores.

This tool was first proposed by the study of Lande and Thompson[29] under the term marker-assisted selection, followed by several studies which confirmed PRS feasibility for certain complex diseases.[23,24,31,47]

Based on PRS performance in some studies, the values of the PRS may have prominent clinical utility by its ability to detect patients with PCa at heightened genetic risk.[5,21,46] Moreover, patients susceptible to PCa could be assessed more effectively, and a personalized smarter screening plan can be implemented by sorting men who need to be screened regularly and excluding others.[21]

For those with increased PRS value and who have a family history (FH), screening can be suggested at an early age and performed more frequently. Similarly, for those who have a low PRS and a FH, screening could be lagged or performed less frequently.[21] The study by Helfand et al [21] has shown that the value of the PRS exceeds the impact of FH on the prediction of population at risk.

The use of this approach is promising to overcome the dilemma of complex diseases that are affected by multiple genetic loci or by the surrounding environment. In addition, it could be a valuable tool for evaluating large-scale genomic studies.[46] However, its current formula needs further development to be more sensitive and specific to the susceptible population. To achieve this, for instance, Yang et al[48] applied a linear mixed model method which uses all markers to estimate the additive genetic contribution to a trait including significant and nonsignificant markers also does not split data into training and test sets. Furthermore, advanced analytical techniques will be crucial to isolate genetic markers of the disease from GWAS,[35] along with global cooperation to increase sample sizes and to ensure the diversity of population included in these studies.

7. Number of loci used in the association studies

In PCa association studies, the number of examined genetic variants (STRs or SNPs loci) was varied and fluctuated from one study to another. Because the low number of loci comprised in earlier studies was one of the main disadvantages of these studies, some studies have been keen to increase the number of loci or to use two kinds of genetic variants to overcome this drawback and to scan the suspected area in human genome for significant alleles that influence the correlated PCa.[14,45]

Over the past 23 years, the number of genetic loci used in PCa association studies have been increased dramatically, from 9 loci used in the study by Smith et al[41] to 163 loci identified by Schumacher et al [40]; owing to the recent tremendous progress in molecular genetics by the integration of next-generation sequencing technologies.

These advanced technologies have led the GWAS and fine-mapping efforts to discover this large number of susceptible loci; these PCa variants were related to different inherited background populations, most of which are from European ancestry.[40] In addition to this enormous quantity of loci, the study by Takata et al[42] found 12 novel loci associated with PCa risk in Japanese population.

8. Research methodology and population size of association studies

A review of the relevant empirical data indicated that majority of studies adopted a case-control methodology in their investigations of the association between genotyping and phenotyping of patients with PCa because it is the most appropriate one for comparison in this kind of diseases. These studies have investigated the relationship between genetic markers in whole genome comprising sex chromosomes and PCa risk, with inconsistent conclusions.

Mostly the researchers use a research methodology based on cases and controls because they cannot perform it by the cohort method. The characteristics of each society depend on the type of

Table 1
Studies according to the chromosome and the physical location of susceptible locus in the chromosome.

Chromosome no.	Chromosomal location of loci	STR/SNP marker	Authors
1	1q24-25	Hereditary PCA 1 (HPCA1)	41
19	Prostate-specific antigen (PSA) gene is located at the 19q13.41 chromosome 19	the A/G polymorphism at the ARE I the promoter region of the PSA gene	3
X	Xq11Xq13 Region	PGK1 STR Allele	39
	Xq11-12 in exon 1 of the AR gene	Polymorphic CAG repeats in exon 1.	19
	Xq11-12 in exon 1 of the AR gene	CAG and GGC repeats	72
	In the exon 1 of the androgen receptor (AR) gene at the Xq11.2-q12 chromosome X.	CAG and GGC repeats	3
	In the exon 1 of the androgen receptor (AR) gene at the Xq11.2-q12 chromosome X.	Polymorphic CAG repeat in the androgen receptor (AR).	9
Y	DYS19	DYS19	58
	four haplogroups DE, O2b*, O2b1, and untagged	four haplogroups DE, O2b*, O2b1, and untagged	16
	M253, M223, M46 (Tat), M17, and M269. M46 failed in genotyping	I1a*, R1a1, N3 K* P* R1a*, R1b3, I1c,	32
	Region Yp11.2 (DYS393, DYS456, DYS458 and DYS19)	Allele 12 of DYS393 and allele 19 of DYS458 (protective). Allele 13 of DYS393 (increased risk).	12
	Y-chromosome	Y-linked STR MultiPlex PCAR, DYS388, DYS435, DYS437, DYS439	36
	34 binary Y chromosome markers (the E1b1b1c haplogroup in the last intron of the taxilin gamma 2 pseudogene (*TXLNG2P)* on chromosome Yq11.222)	34 chromosome Y markers genotyped, 26 were observed, and 28 haplogroups including three combined groups (R1b1b + R1b*, R1a + R1*, and I2b + I2c), as the leaf nodes of the NRY tree	45
	Y-chromosome	17 Y-STR (A commercial kit Y filer™ PCR amplification kit (Applied Biosystems, Foster City, CA).	75

NRY, nonrecombining Y; STR, short tandem repeat; SNP, single-nucleotide polmorphism; PCR, polymerase chain reaction; CAG, nucleotides sequence; GGC, nucleotides sequence; AR, androgen receptor.

study and the variables to be disclosed. Cunningham et al[14] have designed a study based on cases of patients with cancer with a strong FH of familial prostate cancer (FPC) with cases and controls for patients with sporadic prostate cancer (SPC) who have a negative FH of PCa.

Paracchini et al[38] conducted the cohort study on the Hawaiian and Californian population for 930 cases of PCa and 1208 control cases belonging to four ethnic groups, where they tested the distribution of 116 Y lineages. The population size was varied, ranging between 90 and 275,543 individuals. One clear limitation in most of the studies which investigated the association and susceptibility to PCa was the size of population. In Table 2, this research has included the size of the populations for the aforementioned studies.

Since Riley and Krieger [39] found that half of their population's known alleles were presented in their study with a percentage less than 5% of known alleles, they stated that in future studies, it would be necessary to use a larger population to assess the probable correlation of these alleles with PCa.

Regarding the studies which have given false-positive results or inconsistent findings, it may be concluded that this occurred because of the very low frequency of the haplogroup in the population or because of lack of differentiation between ethnic groups inside the two arms of healthy and patient groups. It is therefore recommended to avoid the low frequency haplogroups and to find the subgroups (branches) inside each ethnic population to reduce the prevalence of false-positive research findings.

9. Association between genetic STRs/SNPs variations and the risk of PCa

To identify an association, the studies used two kinds of polymorphic genotyping: STRs and/or SNPs. Generally, studies which used STRs apply these polymorphisms on the X-chromosome;[3,19,39,72] meanwhile, some studies are applied on Y-chromosome;[12,36,38,58]. On the other hand, SNPs have been used in the majority of previous studies on Y-chromosome or other autosomes, Table 2;[14,16,26,32,38,45]. Depending on the nature of polymorphism distributed on the chromosome or certain gene, the selection of genetic marker (STR or SNP) is performed. These ideas have originated from researchers' beliefs that as much as they succeeded in being able to screen the human genome with possible markers, this has also led to an increased chance of identifying a significant associated marker. Some researchers try to use both types of genetic markers (STRs and SNPs) in one study such as those performed by Cunningham et al[14] and Wang et al.[45]

The recognition of specific Y-haplotypes associated with increased PCa risk may represent many men, so its results represent more than one genetic test. This is because the presence of risky Y-chromosome represents a potential risk to all men who own the same chromosome in the family pedigree.[11] The study of Riley and Krieger [39] was one of the first of its kind conducted on the association between X-chromosome genetic variations and PCa. Their study results showed that the allele 13 divided patients with PCa in terms of age, where patients with a 13 allele were older than others who lacked this allele ($p < 0.005$);while, in terms of PCa incidence, the allele 12 (PGK1 STR) was more common among patients, with a statistically significant difference ($p = 0.03$) between patients and controls group. However, their study did not find any significant associations in the comparison based on the other allele which have 9 repeats.[39]

In another piece of research conducted by Gsur et al[19], the authors studied the effect of change on the level of single nucleotide on PCa. Their findings showed that men with at least one G allele had a 63% lower risk of cancer. The G allele was associated with the more advanced disease at the time of diagnosis. In addition, they found a significant trend in the odds ratio from genotype A/A to genotype G/G between low-grade disease and high-grade disease. Moreover, the authors found an important effect of polymorphism PSA−androgen response element PSA on PCa risk. However, it is worth noting that their data did not give evidence of a correlation between the length of the CAG repeat and PCa.

Table 2
Population studies examine the association between STRs/SNPs markers and PCa.

S.	Authors, year	Place/country/area	Number of volunteers
1	39	University of Washington Medical Center	PCa = 103, HC = 299.
2	19	Austrian Caucasians (newly diagnosed)	PCa = 190, HC = 190 control men with BPH.
3	58	Japan (Tokushima, Kawasaki)	PCa = 90, HC = 99.
4	38	Four ethnic groups in Hawai and California	PCa = 930, HC = 1208.
5	16	Japan	PCa = 92, HC = 109
6	26	Korea	PCa = 106, HC = 110.
7	14	Hispanic ancestry, 3 African American, and 5 other types of ancestry.	FPC = 438 cases from 178 families (One family had Hispanic ancestry; the remainder had non-Hispanic Caucasian ancestry) and SPCa = 499 (491 reported non-Hispanic Caucasian ancestry, 3 African American, and 5 other types of ancestry). HC = 493 were derived from a population-based collection (490 reported non-Hispanic Caucasian ancestry and 3 reported Hispanic ancestry).
8	32	Swedish population	PCa = 1,447, HC = 983.
9	72	Universidade Federal do Rio Grande do Sul in Brazil.	PCa = 49, HC = 51.
10	12	Porto, Portugal	PCa = 281, HC = 175.
11	36	Malaysia	PCa = 84, HC = 91.
12	45	Population of European and Ashkenazi Jewish ancestry.	PCa = 3,995. HC = 3,815. From four studies, Total = 7,810 men.
13	3	Urology Department at Çukurova University, Çukurova region, Adana, Turkey.	PCa = 44, HC = 22, BPH = 33.
14	9	The Urology outpatient clinic at the Hospital de Clínicas de Porto Alegre	Total = 214 subjects; (BPH = 126, HC = 88).
15	11	Utah, Utah Population Database (UPDB).	PCa = 18,291, HC = 257,252 YIDs two at least showed the Y-chromosome, Genealogy data.
16	75	Iraq (Middle and South area).	PCa = 100, HC = 100

PCa, prostate cancer; STRs/SNPs, single tandem repeats/sinle-nucleotide polymorphisms; SD, standard deviation; FPC, familial prostate cancer; SPC, sporadic prostate cancer; YIDs,Y-chromosome id; HC, healthy control; BPH, benign prostatic hyperplasia.

In male-only cancers, Ewis et al[16] concluded that men from various Y-chromosome lineages might have diverse vulnerability to oncogenesis. Certain men are at high risk, whereas others may exhibit resistance. Therefore, the degree of susceptibility to human cancer may vary according to Y-chromosome structures.[16]

Although there is a strong correlation in their large population (more than 2,000 subjects), Lindström et al[32] declared that they did a follow-up experiment to confirm their previous findings, but they were unable to reproduce these results. This follow-up study demonstrates that false-positive outcomes also occur in large groups of well-powered populations and that repetition is always required to prove a real relationship. However, they chose a few SNPs to do their own link study which had five binary markers, i.e., M253, M223, M9, M17, and M269 for genotyping in the screening group representing more than 95% of male Swedish lineages. The limitation in Lindström et al[32] study is the failure to analyze the M46 binary marker, which resulted in collapsing four specific lineages into one haplogroup. They suggested further studies on non-European populations on the grounds that these studies are necessary to further explore the presumed role of chromosome Y in PCa.

Given the evidence supporting the presence of several PCa susceptibility genes on autosomal chromosomes from association and linkage studies as shown in Table 2, in addition to the potential presence of environmental risk factors and the possibility of overdiagnosis of PCa based on PSA testing, it is not surprising that it is difficult to conclusively test the hypothesis of chromosome Y.[11]

Moreover, Fig. 2 showed that even the female descendants who share their father's X-chromosome have an affected male offspring not marked with "+", thus confirming the attribution of X-chromosome in PCa.

The analysis of Cannon-Albright et al[11] presented a strong evidence of Y-chromosome involvement in PCa and identified a strong source for individuals and pedigrees to examine these high-risk Y-chromosomes to identify and characterize predisposing genes or variants. Identifying specific Y-chromosomes associated with increased risk is difficult and was only possible here because the Utah Population Database has decades of data related to genealogy and cancer. However, even with genealogy and cancer data in extended pedigrees, it is not always possible to distinguish between autosomal or X-chromosome potential versus Y-chromosome contribution in the development of PCa.[11] Hence, the activation of the genes in the X-and Y-chromosome are affected by both chromosomes; therefore, it was inferred that both chromosomes could have a complementary role in cancer development. This idea originated from the fact that many of the genes on Y-chromosome have homologs on the X-chromosome.[76]

10. The assessment of PSA as a current biomarker for PCa prediction

The PSA test is one such diagnostic test used as a diagnostic tool for patients who may have PCa. This test is based on the PSA ratio in the blood. A second diagnostic test is the digital rectal exam (DRE), which is used as add-on to increase the power of the medical diagnostic procedure in conjunction with the PSA test.[71] Although the over diagnosed cases detected by PSA screening varied from one model to another, the results indicated that 23% to 42% of the cases diagnosed by PSA as cancer cases were over diagnosed.[77] The benefit of screening is that a very early diagnosis of PCa means that the disease does not necessarily require active treatment. It has been viewed that detection of this disease in its earliest stages is vital to effective treatment.[2]

Despite its widespread use for early detection and monitoring of patients with cancer, the physiological nature of the role of PSA in the prostate tissue is still unclear, because it appears to have different functions, including pathogenic and other protection from PCa.[19]

For all reasons aforementioned, there is an urgent need for vital predictive biomarkers to identify subjects with clinically significant PCa.[7] This has led to the discovery of many PCa biomarkers over the last decade.[78] Among these are some STR markers in X- and Y-chromosomes. [3,58] These biomarkers need to be carefully evaluated in a framework for clinical application.[67] Furthermore, in the search for novel prognostic genetic biomarkers for PrCa, many tumor markers have been proposed. The number of articles published on this subject has increased substantially in the last decade. However, PSA, prostate cancer antigen 3 (PCA3), and circulating tumour cells (CTCs) are still the only markers used in clinical practice. Many published results on novel PrCa biomarkers were not reproducible in subsequent studies and thus may never attain the Food and Drug Administration–approved status.[7]

There is ongoing debate about the ability of the PSA test to detect early PCa accurately. This is because the PSA level associated with clinical progress is contentious, having been confirmed by only some of the research studies.[79] Despite this, a change in the threshold for the diagnosis of the disease and the recurrence of screening, as well as the inclusion of other biomarkers has the potential to reduce the overdiagnosis associated with the PSA test.[67] Several promising new biomarkers for people with high levels of PSA or who have been diagnosed with PCa are likely to aid in distinguishing between men who need cancer treatment and those who do not.[67]

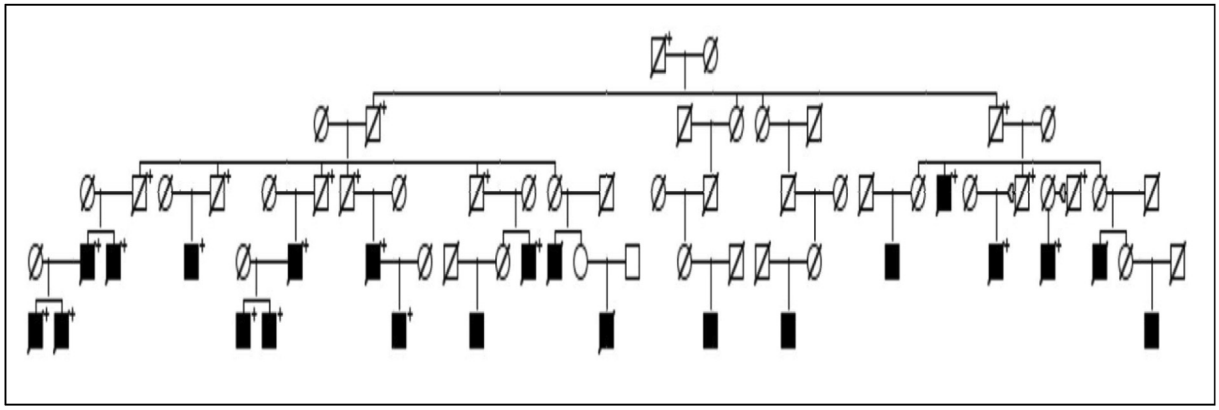

Fig. 2. Example pedigree with significant excess of PCa among Y-chromosome–sharing men. Those male descendants who share the founder's Y-chromosome are marked with "+" (Adopted from [11]). PCa, prostate cancer.

There are many debates regarding the use of the PSA test alone; so, Catalona et al[80] and Raaijmakers et al[81] propose the addition of some useful supplements test for screening PCa. To make the PSA measurement more efficient, some factors have been added to this test, such as the ratio of various PSA isoforms (pro-, free, complexed, and B), measurement of the PSA over time (doubling time or velocity of PSA), and prostate size (density of PSA) to use the unique characteristics of these additional factors, as well as the addition of other biomarkers such as the Kallikrein panel.

To enhance the accuracy of the PSA test, it has been suggested that new PCa biomarkers be added such as PCA3 score, Prostate Health Index, the four-Kallikrein panel, and transmembrane serine protease 2-erythroblast transformation specific related gene (MTPRSS2-ERG) assays as this will lead to a more accurate assessment of prostate conditions.[82] However, these promising biomarkers need further evaluation to be labeled as vital indicators used in screening procedures for PCa. In addition, the identification of subgroups in a uniformed and precise way is the challenge by which this category of patients can be managed. Therefore, it is crucial to develop and validate new markers of aggression, especially in men with Gleason 6 and PSA less than 10 ng/ml.[67] Although the PSA test may be prostate specific, it is not specific to PCa. Therefore, continued research into alternative prostate-specific markers is required.[83]

11. Conclusion

In contrast to other types of cancer, PCa susceptible genes are distributed along the entire chromosomes, from chromosomes 1 to X and Y; moreover, a specific confirmed biomarker for PCa has not yet been discovered until now. This situation calls for perhaps a different approach to think in a manner that differs from previous studies, which have concentrated on SNPs as markers to identify associations but have often found little significant differences or have given a weak association between healthy controls and the PCa group. Therefore, it is recommended that future research using different population groups and comparing patients with PCa with carefully selected controls will help to confirm or deny previous findings.

On the other hand, the main researches, which analyzed this disease genetically, focused on precise genetic biomarkers that will detect the most serious cases of PCa. Therefore, a number of promising potential methods such as urinary biomarkers have been identified but need further development, also need to focus on the modifiable factors that are associated with more aggressive PCa.[67] In a similar vein, the less aggressive prostate diseases also require unique biomarkers, as this will help to reduce the cost of treatment and suffering of patients because of unnecessary tests and harsh medication. Furthermore, because the latent nature of this disease, early detection is beneficial as this can facilitate treatment with appropriate medication or interventions.[82]

Finally, owing to the complex nature of this disease and the lack of a clear consensus on its identification, it is not possible to provide a comprehensive range of information from all the studies that have been conducted to find a relationship between the phenotype and genotype of individuals afflicted with PCa. However, it is hoped that this review elaborated the nature of genetic biomarkers (STRs, SNPs) and the studies which link them to PCa, thus providing the reader with an appreciation of the current state of knowledge in this field, and highlighting where future efforts may be more fruitfully directed.

Author contribution

M.H.A. contributed to study design and concepts, manuscript and figure preparation, and editing of the manuscript. Y.R. and S.A. contributed to editing manuscript and revising. P.B.I. contributed to final approval and editing manuscript. C.P.P., K.A.B.M.G, and R.V. contributed to revising manuscript and final approval.

Conflicts of interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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