



Major Candidate Genes Associated with Risk of Hereditary and Sporadic Prostate Cancer

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Authors' contributions

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ABSTRACT

Prostate cancer risk factors gain more awareness in the world nowadays, due to the increasing incidents, which vary among different ethnic groups. Researches about genetic risk factors might help for more understanding of the initiation and development of prostate cancer and estimating risk values among individuals, and develop multi-perspective therapy approaches. Many efforts were achieved to study and evaluate high-risk variants associated with prostate tumors; through different populations. This evaluation depended on the high frequencies of these variants and the role of such variants in cell cycle and DNA repairing system. In this review, we highlighted the major candidate genes and molecular events of prostate cancer: BRCA, CHEK2, HOXB13, ELAC2, SPOP, PTEN, TMPRSS2-ERG Fusion and other less effective variants, in an attempt to explore the molecular seriousness and relative risk of suspected variants associated with hereditary and sporadic prostate cancer. The definition of particular groups of genes that lead prostate cancer prognosis is a difficult task, since the genetic and proteomic studies detected numerous susceptibility alleles complicated with risk of prostate tumors. The estimation of high-risk variants may be a key issue regarding prostate cancer diagnosis and therapy.

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1. INTRODUCTION

Prostate cancer (PCa) is the most common cancer diagnosed among men in most western countries; about 75% of patients are diagnosed after 65 years. The incidence of prostate cancer varies between countries and between different ethnic groups, the highest incidence rates have been observed in North America especially among African-Americans, and in the Scandinavia region, whereas the lowest rates have been observed in India, China, and Japan. However, there is a general increase in incidences in most countries [1,2]. Recently, identifying genetic risk factors for prostate cancer is an active area of medical research, as inherited variations in dozens of genes have been considered as possible risk factors for prostate cancer work as tumor suppressors through different cellular pathways. Alterations in these genes probably contribute to overall prostate cancer risk. But many cases of prostate cancer are not related to inherited gene changes, these cancers are associated with somatic mutations that occur only in certain cells in the infected organ. Tumor suppressor genes negatively regulate normal cell growth; they are involved in the inhibition of cell proliferation, regulation of the cell cycle and apoptosis, cell adhesion and transcriptional regulation and repair DNA damages [3,4]. This review aimed to describe the major candidate genes of prostate cancer intensively investigated in few last decades, with a short focus on the original function of the gene, the pathway as tumor suppressor gene, and the risk susceptibility in different ethnic groups.

2. BRCA1 and BRCA2

The potential association between BRCA1 and BRCA2 mutations and the progression of prostate cancer after diagnosis have been discussed for decades. BRCA mutations might be associated with aggressive prostate disease since the relative risk of developing prostate cancer in BRCA1 and BRCA2 mutation carriers reach 1.8 times and 7–23 times, respectively [5]. The families with deleterious mutations in BRCA1 and BRCA2 had an increased number of prostate cancer infections compared with families without known inherited predisposition. The risk of developing prostate cancer is increased if BRCA1 or BRCA2 mutations are

present [6]. Furthermore, males BRCA2 mutation carriers who develop prostate cancer (PCa) may have a shorter disease-specific life expectancy than men with PCa in the general population [7]. Furthermore, BRCA2 mutation carriers have a five to seven-fold increase in risk [8]. Whilst a family history of early-onset breast cancer/ovarian cancer is a strong predictor of BRCA2 mutation positivity; the ascertainment by the early onset of PCa is the greatest predictor of BRCA2 mutation positivity concerning PCa susceptibility. The BRCA1 gene or breast cancer gene 1 is a tumor suppressor gene, which expressed in the cells, where it can repair damaged DNA as a protein complex, or destroys cells if DNA cannot be repaired in certain mechanisms. BRCA1 along with other tumor suppressors, sensors and signal transducers form protein complex called BRCA1-associated genome surveillance complex (BASC); Involved in the repair of chromosomal damage with an important role in the error-free repair of DNA double-strand breaks [9].

The human BRCA1 gene is located on chromosome 17 and contains 27 exons distributed over about 70 kb of genomic DNA and gives rise to a transcript of 10.4 kb, coding for a protein of 3418 amino acids. The four major BRCA1 protein domains; the Znf C3HC4- RING domain, the BRCA1 serine domain, and two BRCT domains, encode approximately 27% of BRCA1 protein [10]. BRCA1 is part of a protein complex that repairs DNA errors during cell cycle. Double strand breaks occur after the cross-links are removed. The double-strand repair mechanism in which BRCA1 participates in homologous recombination, which depends on utilizing a template of the identical homologous intact sequence from a sister chromatid, forming a homologous chromosome, or forming the same chromosome. DNA repair takes place with the DNA in the cell nucleus, wrapped around the histone, several proteins, including BRCA1, arrive at the histone-DNA complex for this repair [11]. Of course, the defective BRCA1 protein is unable to help to fix DNA damage leading to mutations in other genes. Such mutations can accumulate and may allow cells to divide abnormally to initiate a tumor. Thus, BRCA1 inactivating mutations lead to a predisposition for cancer. In addition to prostate cancer; mutations in the BRCA1 gene also increase the risk of

ovarian, precancerous lesions (dysplasia), leukemias and lymphomas [12].

As same as BRCA1, BRCA2 cancer type 2 susceptibility proteins are responsible for repairing DNA [13]. Genetic characterization has shown that BRCA2 is involved in the maintenance of chromosomal stability and that it has an important role in recombination-mediated double-strand DNA break repair. Thirty-nine amino acid repeats of BRCA2 binding to RAD51 (a key protein in DNA recombinational repair) and resistance to methyl methanesulphonate treatment. The BRCA2 consists of a four-helix cluster core (alpha 1, alpha 8, alpha 9, alpha 10) and two successive beta-hairpins: beta 1 to beta 4 [14]. BRCA2 participates in repairing the DNA process by binding the single-strand DNA and directly interacts with the recombinase RAD51 to stimulate strand invasion, a vital step of homologous recombination [11]. Researchers have identified hundreds of mutations in the BRCA2 gene, many of which cause an increased risk of cancer. BRCA2 mutations are usually insertions or deletions of a small number of DNA base pairs in the gene [12,15]. In addition to prostate cancer, mutations in BRCA2 also lead to an increased risk of ovarian, fallopian tube, pancreatic cancers, malignant melanoma, and ovarian cancer, as well as breast cancer in men and women. There is a piece of evidence for loss of heterozygosity of the BRCA2 region in prostate cancer, particularly those at an advanced stage. The relative risk of developing prostate cancer by age 56 years from a deleterious germline BRCA2 mutation was 23-fold, in some studies. This confirms that BRCA2 is a high-risk prostate cancer susceptibility gene [6]. It's not reported that whether mutations in BRCA1 are related to BRCA2 in the same cells or one patient case, this hypothesis should be examined due to the confident relation of their proteins participating in the DNA repairing mechanism.

3. CHEK2

Human gene Checkpoint kinase 2 (CHEK2) is a tumor suppressor gene that encodes the protein CHK2, a serine-threonine kinase. CHK2 operates in an intricate network of proteins to elicit DNA repair, cell cycle arrest or apoptosis in response to DNA damage [16]. Three deletion variants in the kinase domain in exon 10 and a missense mutation in the FHA domain in exon 3 were linked to inherited susceptibility of the lung, colon, kidney, thyroid cancers, certain brain

tumors, osteosarcoma as well as prostate. Certainly variants: CHEK2 1100delC mutation, and I157T missense mutation through many demographic or ethnic backgrounds [17,18]. Those two mutations have been mentioned widely, to my knowledge regarding hereditary prostate cancer; no reports about other important CHEK2 variants. The exact mechanism of CHEK2 participation in the DNA damage repairing system is unknown. Nevertheless, several mechanisms have been suggested the role of TTK/hMps1, STRAP, p21, and p53 genes in such mechanism [19].

4. ELAC2

The elac ribonuclease Z 2 (ELAC2) gene encodes a protein that is 92 kDa in size and is localized to the mitochondrion [20]. ELAC2 involves in hereditary and sporadic prostate cancer. Multiple mutations including truncation and missense mutations are known to cause prostate cancer [21]. Two ELAC2 missense variants (Ser217Leu and Ala541Thr) were reported as risk variants of developing prostate cancer with different risk profiles, were also observed when cases were stratified by disease aggressiveness. And neither variant was associated with more aggressive prostate cancer phenotypes. Such reports estimated the Ser217Leu genotype may account for approximately 14% of less aggressive prostate cancer cases, and 9% of all sporadic cases in the general United States population of white men <age 65 years [22]. Another finding of a nonsense mutation in the ELAC2 gene confirms its potential role in genetic susceptibility to prostate cancer [23]. However, other results cannot rule out the possibility of a highly penetrate prostate cancer gene at (Ser217Leu and Ala541Thr) locus [24]. There are shortages observed regarding ELAC2 mechanism researches instead of hereditary prostate cancer development or other subtypes of prostate tumors.

5. HOXB13

Homeobox transcription factor gene HOXB13, a checkpoint kinase Gene and other genes, form a gene cluster on chromosome 17 in the 17q21-22 region forming homeobox proteins family [25]. Germline mutation G84E of HOXB13 was reported in hereditary prostate cancer. This mutation associated with an elevated risk of prostate cancer in men of European descent and European-American men [26]. One percent of

the population carrying the variant (rs138213197: G84E of HOXB13). But at the same time, it's associated with a 3 to 5 fold increased risk of prostate cancer. In a statistical conclusion: one-third of G84E carriers will be diagnosed with prostate cancer. This risk is even higher among cases with an early age (≤ 55 years) or a family history of the disease [27]. However, the role of this variant plays in PCa development still uncertain. But it's thought that The G84E variant likely modulates the interaction between the HOXB13 protein and the androgen receptor and affecting FOXA1. Furthermore, the expression of HOX genes likely up or down-regulated in human tumors including colon, lung, and prostate cancer [25,28]. In the case of HOXB13 G84E alterations; it is beneficial to explore other variants that might affect the structure and function of the transcription factor that belongs to the homeobox gene family, in parallel with a deep understanding of HOXB genes mechanism in prostate tissues. And a very important matter to understand is the HOXB13 role in vertebrate embryonic development.

6. SPOP

Speckle type BTB/POZ protein SPOP gene (17q21.33), encodes a protein that modulates the transcriptional repression functions of death-associated protein 6 (DAXX). The SPOP gene contains three domains: an N-terminal MATH domain that recruits substrates, an internal BTB domain, and a C-terminal nuclear localization sequence [29]. Several mutations in SPOP lead to a type of hereditary prostate tumor which involved 10-14.4% of all prostate tumors in various populations, there is no correlation between SPOP mutations with ethnicity, clinical, or pathologic parameters. The expression and mutational status of SPOP, defining a new biotype of prostate cancer associated with a worse prognosis according to accumulated shreds of evidence [30]. Recently the substitutions missense variants Y87N, F133V, G111E, and F102C, suggested as pathogenic. Other findings consider other variants as pathogenic instead of prostate cancer, namely: S14L, N296I, and P133L [31]. When we reviewed the SPOP mutation databases including SNPs, nonsense and missense variants; there are a series of variants that have been recorded to be risky through valued epidemiological and clinical researches, this database could form a driving base to explore the real structural and functional effects on the related protein [32].

7. PTEN

Phosphatase and tensin homolog (PTEN), a tumor suppressor located at chromosome 10, the protein encoded by this gene is a phosphatidylinositol-3, 4, 5-trisphosphate 3-phosphatase. PTEN is a phosphatase that dephosphorylates phosphatidylinositol (3, 4, 5) triphosphate (PtdIns-3, 4, 5-P3), an important intracellular second messenger, lowering its level within the cell. PtdIns-3, 4, 5-P3 is necessary for the activation of Akt, a serine/threonine kinase involved in cell growth and survival. PTEN act to block the Akt, this permits cell cycle goes correctly, same as other critical translations and apoptosis [33]. Mutations of this gene are a step in the development of many cancers, as this gene was identified mutated in a large number of cancers at high frequencies. Indeed, up to 70% of men with prostate cancer are estimated to have lost a copy of the PTEN gene at the time of diagnosis. Furthermore, loss of PTEN function is a common event in glioblastoma, melanoma, endometrial carcinoma, prostate adenocarcinoma, renal cell carcinoma, and head and neck squamous carcinoma. Due to the vital role of PTEN in the regulation of metabolic pathways and cell motility, many studies tried to reveal the PTEN variants involved loss its function related to tumor progressions [84,85].

8. TMPRSS2-ERG GENE FUSION

Transmembrane protease serine 2 (TMPRSS2) related confidentially with androgenic hormones. Fusions of the TMPRSS2 prostate-specific gene with the ERG transcription factor; consider an oncogenic event, which commonly found in prostate tumors. The ERG over-expression induced by TMPRSS2-ERG gene fusion contributes to the development of prostate cancer, which can be easily detected in urine [34]. A fusion between the prostate-specific androgen-regulated TMPRSS2 gene and the ETS genes ERG, ETV1, or ETV4; has been described in clinical prostate tumors, and occurs at a high frequency: approximately 50% of prostate cancers. In a study by Magi-Galluzzi, et al. [36], TMPRSS2-ERG gene fusion translocation, deletion, or both, it was present in 50% (21/42) of Caucasians, 31.3% (20/64) of African-Americans, and 15.9% (7/44) of Japanese [35,36]. Other studies distinguish between TMPRSS2/ERG and TMPRSS2/ETV1 fusion genes with different subtypes that exist in the tissues of prostate cancer. TMPRSS2/ERG and TMPRSS2/ETV1 fusion genes may be used

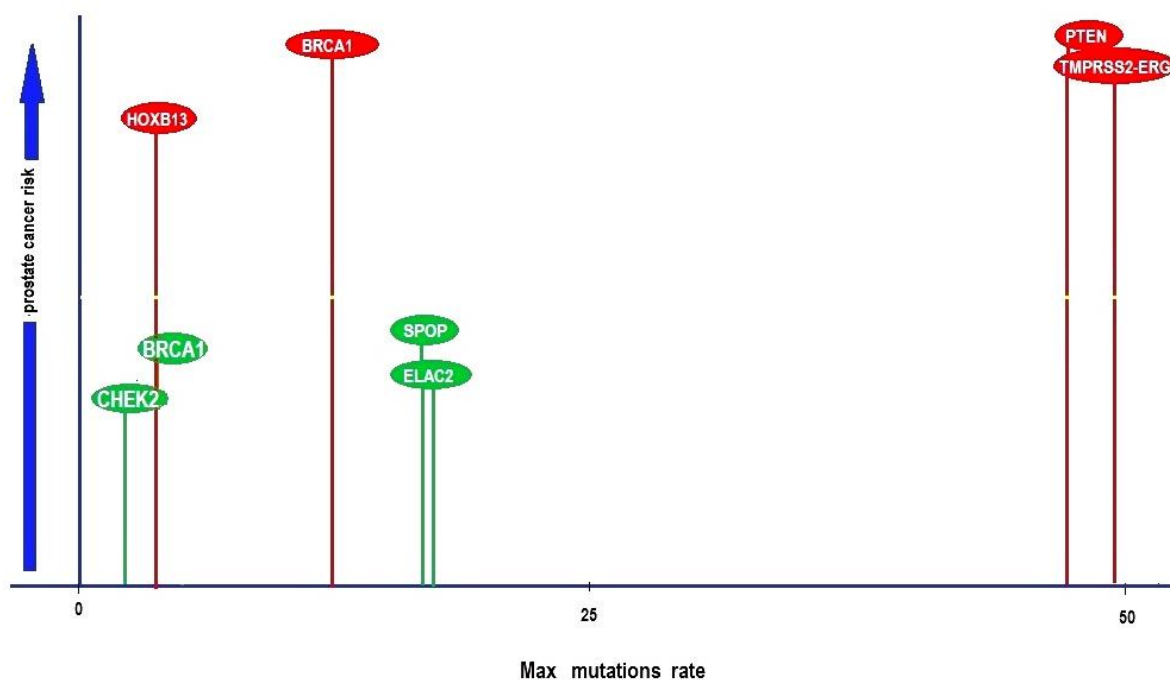


Fig. 1. Relative risk of prostate cancer of eight candidate genes: BRCA, CHEK2, HOXB13, ELAC2, SPOP, PTEN, and TMPRSS2-ERG fusion, versus maximum mutations rate according to the researches listed in this review

successfully as diagnostic tools for prostate cancer [37]. The specific complication of chromosomal rearrangement related to TMPRSS2/ERG needs more enlightenment, as well as how this fusion interferes with prostate tumors initiation.

The relative risk of prostate cancer of eight candidate genes: BRCA1, BRCA2, CHEK2, HOXB13, ELAC2, SPOP, PTEN, and TMPRSS2-ERG FUSION, versus maximum mutations rate, is given in Fig. 1 based on the risk criteria genes reviewed in this study.

9. MORE OTHER CANDIDATE GENES ASSOCIATED WITH HEREDITARY PROSTATE CANCER

SPINK1 serine peptidase inhibitor, Kazal type 1 (5q32), the protein encoded by this gene is a trypsin inhibitor, this pancreatic origin protein, which found in pancreatic juice secreted from acinar cells. The known function is inhibiting trypsin-catalyzed premature activation of zymogens in the pancreas. At the same time, SPINK1 is responsible for a small protein (56 amino acids) secreted in the prostate gland whose function is to inhibit serine proteases. Some reports suggested a role of SPINK1 in ETS rearrangement may represent a link to the

risk of prostate cancer progression, but not an aggressive disease [32]. p300 transcriptional co-activator protein alterations correlate individually with aggressive features in prostate cancer by inducing quantifiable nuclear alterations [38]. Other data suggested that the genetic variation in gene encodes a member of the Eph receptor family of receptor tyrosine kinase transmembrane glycoproteins; might increase the risk of sporadic PCa among African-Americans [39]. And downregulation of EZH2 (enhancer of zeste homolog 2), might affect prostate tumor cell growth [40]. Mutational analyses of macrophage scavenger receptor 1 MSR1, revealed P275A, INDEL7, P346P, 3'UTR 70006, P346P G allele (AG 1 GG), R293X and D174Y of MSR1 variants; are associated with an increased risk of sporadic prostate cancer, particularly in African-Americans, China, Asia and other populations worldwide [41,42]. The signal transducer and activator of transcription 3 (STAT3) significantly impaired the ability of prostate cancer cells to initiate the development of the prostate tumor [43]. Besides, Glycine N-methyltransferase GNMT, considered as a tumor susceptibility gene for prostate cancer, especially the rs10948059 variant. In addition to STRP1 variants are associated with prostate cancer risk in men of European descent [44,45]. Ribonuclease L (RNASEL) mutations, and some

variants like Arg462Gln and Asp541Glu; are associated with the risk of presenting prostate cancer have been reported elsewhere [46]. Two independent variants in HNF1 homeobox B (HNF1B), considered also as susceptibility loci for prostate cancer risk [47]. Since genetic variation within the Ldl receptor-related protein 2 megalin gene may serve as a means for the malignant cell to increase androgen uptake; it's found to be associated with prostate cancer [48]. Genetic variant Leu1074Phe in the DNA repair gene Werner syndrome RecQ like helicase (WRN) in Chinese subjects [49], and germline 3381del allele of ATBF1 (16q22) coding for cell cycle active protein were linked to risk of prostate tumors [50]. Choi et al. study revealed a relation between steroid 5 alpha-reductase 2 SRD5A2 SNPs and prostate cancer in the Korean population [51], in contrast, another study from Turkey, concluded that there was no evidence of an association between SRD5A2 polymorphism and PCa risk in the Turkish population [52]. In addition, other data suggested that transforming growth factor-beta receptor 1 TGFBR1*6A, does not contribute to the

development of prostate cancer [53], as well as Suarez et al., who revealed that there is no compelling evidence for an association of the variant in exon 1 of the TGFBR1 gene *6A variant with prostate cancer [54]. The overexpression of mediator complex subunit 12 (MED12), found to be a frequent event in castration-resistant prostate cancer (CRPC), in comparison with androgen-sensitive PCa and is directly implicated in TGFb signaling [55]. While Nibrin (NBN) gene overexpression associated with prostate cancer risk, maybe PCa predictive biomarker [56]. A suspected relation of prostate cancer initiation and development with each of: KAL1/CD82, Kruppel like factor 6 (KLF6) splice variants expression, overexpression of insulin-like growth factor 2 (IGF2), PlexinB1, interactor 1 dimerization protein MX11, micro semino protein beta (MSMB), mitotic arrest deficient like 1 (MAD1L1) mutations; were discussed elsewhere [57-63]. A summary of genes variants detected, frequency of alleles, population studied, and association with PCa collected from various sources in the literature; are given in Table 1.

Table 1. Summary of genes variants detected, frequency of alleles, population studied, and association with PCa

Gene	Variant	Population	Variant Frequency	Association with PCa	Reference
HOXB13	G84E	D	0.7%	1	[64]
		D	0.5%	1	[65]
		D	0.99%	1	[66]
		European	1.4%	1	[67]
		British	1.5%	1	[68]
		D	5.0%	1	[69]
MSR1	999C>T (R293X) c.877C4T (R293X) Asp174Tyr 14,742 A > G 14,742 A > G R293X, P275A, -14743A>G	D	0.027%	2	[70]
		German	1.9%	2	[71]
		A.A	6.8%	1	[72]
		A.A	0.253%	1	[73]
		E.A	0.105%	1	[73]
		Finnish	1.1%	2	[74]
ELAC2	Thr541 Thr541 Leu217 650 C > T 650 C > T Ala541Thr Leu217 Thr541	British	*	2	[75]
		D	2.9%	1	[76]
			31.6%,		
		A.A	0.211%	1	[73]
		E.A	0.301%	1	[73]
		D	6.3%	2	[77]
		D	32.3%	1	[23]
D	5.4%	1	[23]		
RNASEL	Arg462Gln and Asp541Glu E265X G282A, G1385A and	Chilean	Multiple	1	[46]
		German	1.4%	2	[78]
		Japanese	*	1	[79]

Gene	Variant	Population	Variant Frequency	Association with PCa	Reference
	T1623G				
	1385 G > A	A.A	0.159%	1	[73]
	1385 G > A	E.A	0.370%	1	[73]
	E265X	Swedish	1.9%	2	[80]
BRCA	Clinical Pathological Features	Ashkenazi Jews	*	1	[81]
	BRCA1: 185delAG , 5382insC	Ashkenazi Jews	5.2%	1	[6]
	BRCA2: 6174delT				
	Deleterious Mutations	British	0.45%	1	[82]
CHEK2	1100delC	Polish	1.6%	1	[17]
	Multiple	D	4.8%	1	[18]
GNMT	(STRP1), SNP: rs10948059	European	*	1	[45]
	4-bp insertion/deletion (INS/DEL)			2	
	Multiple	Taiwanese	Multiple	1	[44]
HNF1B SNPs	rs4430796, rs4430769, rs11649743	European	*	2	[47]
SPOP	Multiple Missense Mutations	D	8.1%	1	[29]
FGFR4	rs351855	Caucasian ,A.A	Multiple	2	[83]
Megalin SNPs	Multiple	Caucasian	Multiple	2	[48]
TGFBR1	(*9A) exon 1	D	0.086%	2	[53]
WRN	Leu1074Phe (rs1801195)	Chinese	41.5%	1	[49]

D: Deferent Ethnic Group, *Not estimated, 1 Associated, 2 Not Associated, A.A: African American, A.E: American European, PCa: Prostate Cancer

10. CONCLUSION

Men with particular variations in particular genes have a risk of developing prostate cancer. But a wide difference of variant frequencies was obtained among many populations. Consequently, these differences lead to differences in relative risk associated with hereditary prostate cancer or the importance of such variants as a biomarker for the early development of prostate cancer. There are hundreds of mutations in BRCA1 gene have been estimated, to be associated with an increased risk of prostate cancer, this gene is widely studied among different populations, with hundreds of variants, major of them are deleterious, and many mutations estimated in BRCA2 gene related to prostate cancer risk. The majority of results confirmed that BRCA1, BRCA2, PTEN are a high-risk prostate cancer susceptibility genes. Genetic variations of CHEK2 are associated with inherited susceptibility to prostate cancers, as well as missense variants (Ser217Leu and Ala541Thr) in

the ELAC2 gene. The HOXB13 G84E missense mutation represents a unique variant increases the risk of prostate cancer in European-American men. Whilst the SPOP is mutated in patients with prostate cancer across different ethnic and demographic backgrounds. TMPRSS2-ERG gene fusion has been suggested as a biomarker for prostate cancer, but there are confusing conclusions about use SPINK1 as biomarkers for prognostication of early-stage prostate cancer. Other variants have been detected as genetic risk factors of prostate cancer by different degrees of risk.

The molecular biology of prostate cancer is very complex, this complexity originates from multi genetic factors interfere with prostate tumorigenesis, or may due to the complexity of prostate gland function originally, and slow, long time initiation of prostate tumors. For decades, hundreds of variants were screened and evaluated to determine the risk degree of such variants on prostate cancer. Along with studies progression, researches range increased

significantly. Today; we have big knowledge about genes functions that affect prostate cancer tumors, but some areas still not demonstrated clearly. Such as detailed mechanisms, genes interactions involved in the tumorigenesis process. Furthermore, there is some mistiness about what genes leads strongly this vital process, and the value of other genes as prospective therapy targets, or diagnosis biomarkers. Besides, more studies are needed to estimate more major high-risk candidate genes of hereditary and sporadic prostate cancer or establish special local databases related to these genetic variations among different regions and populations. The purpose of this review was not to discuss the detailed mechanisms but to highlights the generally accepted about the role of major candidate genes instead of prostate cancer. For the reason that the mutations mentioned in this review, have been estimated in wide range of human tumors and through many ethnic and demographic sites, it's the time to go forward to explore the certain mechanisms and the other genes complicated with, in order to pave the way for serious steps toward drug designs, or other specialized gene therapy processes.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard, ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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