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Critical Reviews in Clinical Laboratory Sciences

ISSN: 1040-8363 (Print) 1549-781X (Online) Journal homepage: https://www.tandfonline.com/loi/ilab20

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To cite this article: Majid Ghayour-Mobarhan, Gordon A. Ferns & Meysam Moghbeli (2019): Genetic and molecular determinants of prostate cancer among Iranian patients: An update, Critical Reviews in Clinical Laboratory Sciences, DOI: 10.1080/10408363.2019.1657061

To link to this article: https://doi.org/10.1080/10408363.2019.1657061

CRITICAL REVIEWS IN CLINICAL LABORATORY SCIENCES
https://doi.org/10.1080/10408363.2019.1657061

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REVIEW ARTICLE

Genetic and molecular determinants of prostate cancer among Iranian patients: An update

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ABSTRACT

Prostate cancer (PCa) is one of the most common age-related cancers among men. Various environmental and genetic factors are involved in the development and progression of PCa. In most cases, the primary symptoms of disease are not severe. Therefore, it is common for patients to be referred with severe clinical manifestations at advanced stages of disease. Since this malignancy is age related and Iran will face a significant increase in the number of seniors, it is expected that the prevalence of PCa among Iranian men will rise. PCa progression has been observed to be associated with genetic and ethnic factors. It may therefore be clinically useful to determine a panel of genetic markers, in addition to routine diagnostic methods, to detect tumors in the early stages. In the present review, we have summarized the reported genetic markers in PCa Iranian patients to pave the way for the determination of an ethnic specific genetic marker panel for the early detection of PCa. To understand the genetic and molecular biology of PCa among Iranians, we have categorized these genetic markers based on their cellular functions.

Abbreviations: ABCC1: ATP binding cassette subfamily C member 1; AR: androgen receptor; BACH1: BTB domain and CNC homolog 1; BAX: BCL-2 associated X; BCL-2: B-cell lymphoma 2; BPH: benign prostatic hyperplasia; CTA: cancer-testis antigen; CCNA2: cyclin A2; CDC34: cell division cycle 34; CDK8: cyclin-dependent kinase 8; CTAs: cancer-testis antigens; CXCR4: C-X-C chemokine receptor type 4; DAB2IP: disabled homolog 2 interacting protein; ECM: extracellular matrix; EMT: epithelial mesenchymal transition; ERs: estrogen receptors; FGF: fibroblast growth factor; FOXP3: forkhead box P3; GNB3: G protein subunit beta 3; GPCR: G protein coupled receptor; GSTs: glutathione S-transferases; HGPIN: high grade prostatic intraepithelial neoplasia; HMGA2: high mobility group AT-hook 2; HOTAIR: HOX transcript antisense RNA; IDC-P: intra-ductal carcinoma of the prostate; LAPTM4B: lysosome-associated protein transmembrane-4b; LEMD1: LEM domain-containing 1; MAGI2: membrane associated guanylate kinase; MAPK/ERK: mitogen-activated protein kinase/extracellular-signal-regulated kinase; MARE: Maf recognition element; MDM2: mouse double minute 2 homolog; MIF: migration inhibitory factor; MMP: matrix metalloproteinase; MTHFR: methylenetetrahydrofolate reductase; ncRNA: noncoding RNA; NKX3.1: androgen related and homeodomain-containing prostate-specific transcription factor; NO: nitric oxide; PCa: prostate cancer; PSA: prostate-specific antigen; PSCA: prostate stem cell antigen; PSGR: prostate-specific G-protein coupled receptor; PTEN: phosphatase and tensin homolog; RAMP1: receptor activity-modifying protein 1; RARB: retinoic acid receptor beta; RARE: retinoic acid response elements; ROS: reactive oxygen species; RTK: receptor tyrosine kinases; SAM: S-adenosylmethionine; SETD8: set domain-containing protein 8; SNP: single nucleotide polymorphism; SPATA19: spermatogenesis-associated protein 19; SPRY2: sprouty homolog 2; TGF-β: transforming growth factor-β; UGT: UDP-glucuronosyl transferase; VEGF: vascular endothelial growth factor

ARTICLE HISTORY
Received 24 April 2019
Revised 16 July 2019
Accepted 14 August 2019
Published online 6 September 2019

KEYWORDS
Prostate cancer; early diagnosis; genetic panel marker; Iran

Introduction

Prostate cancer (PCa) is a heterogeneous age-related disorder that is a leading cause of cancer related deaths among men [1]; it is the second most common cancer among men worldwide [2], and the most common cancer among American and European males [3]. Approximately 1.1 million cases of PCa were reported in 2012, of which 70% were in developing countries [4]. The prevalence of PCa, which varies among ethnic groups, may be related to genetic and environmental factors. PCa, the third most common cancer in men in Iran, is less common than in Western countries [4,5]

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and other Asian countries such as Turkey and Lebanon; Iran has a low incidence of PCa (9.11 per 100,000). Such differences of PCa incidence in different countries may be associated with such factors as lifestyle and socioeconomic conditions. In Iran the prevalence also varies regionally, and the highest age-standardized rate was observed among immigrants to British Columbia, Canada (25.2 per 100,000), while Kerman province in Iran had the lowest rate (3.2 per 100,000) [6]. Age is the main risk factor for PCa and the majority of cases are observed in those over 60 years [7,8]. There is a hereditability of up to 10% in the general population and about 40% in men younger than 55 years [9,10]. Ethnicity is an important risk factor of PCa, and Asians and African/Americans have the lowest and highest incidences in the world, respectively [11]. Black men have a noticeably higher risk of PCa and mortality than white men [11]. A relationship between ethnicity and genetic factors has been observed in the risk of PCa; for example, black patients have a lower number of CAG repeats in the androgen receptor (*AR*) gene [12], higher polymorphic variation of *VDR* [13], and type 25-alpha reductase [14]. Physical exercise, dietary pattern, hormone deficiency, and metabolic syndrome are also involved in PCa risk [15–17]. There is also a relationship between diet and PCa in which high consumption of fat and red meat is associated with an increased risk of PCa [18]. Furthermore, various infectious agents such as cytomegalovirus, human herpesvirus-8, herpes simplex virus 1, hepatitis, and human papillomavirus-16 are also associated with PCa through inflammatory processes [19]. The primary clinical manifestation of PCa are urinary problems, followed by bone pain, renal impairment and hematuria, and weight loss in advanced stages of PCa. PCa biomarkers have been identified in serum, urine, and tissues, and include prostate-specific antigen (PSA), miRNAs, sarcosine, and epigenetic markers [20–23]. Although serum PSA levels and digital rectal examination are common methods of PCa diagnosis, other factors such as ejaculation, trauma, and infection can also increase the levels of serum PSA. Because most patients are referred for treatment after the occurrence of severe clinical symptoms at advanced stages, a panel of genetic markers, in addition to routine diagnostic methods, may be useful to detect PCa in the primary stages. In the present review, we have summarized the reported genetic markers used in studies of Iranian PCa patients (Table 1). We have categorized the reported markers based on their involvement in cellular processes among Iranian patients (Figure 1).

Intracellular defense systems and drug resistance

Drug resistance in tumor cells can be related to genetic differences among people. The glutathione S-transferases (GSTs) family of enzymes are a group of multifunctional proteins involved in detoxification of carcinogens through glutathione conjugation [24]. A correlation between *GSTM1* and *GSTT1* null genotypes and PCa susceptibility was reported in a subpopulation of Iranian patients. The Ile/Val or Val/Val genotype of *GSTP1* was also associated with PCa [25]. Moreover, there were significant correlations between GST genotypes, Gleason scores, and cancer stages [25]. In addition to extracellular stresses like anti-cancer drugs, reactive oxygen species (ROS) are another group of intracellular stresses that are the results of oxidative metabolism in mitochondria. ROS at low levels can induce proliferation or survival, and at high levels can oxidize DNA and proteins [26]. Therefore, cells must regulate the levels of ROS via different signaling pathways. BTB domain and CNC homolog 1 (*BACH1*) is a MAF-related basic leucine zipper transcription factor associated with oxidative stress [27] and tumor metastasis through matrix metalloproteinase (*MMP*)-1 and C-X-C chemokine receptor type 4 (*CXCR4*) [28]. *BACH1* heterodimer with MafK suppresses the Maf recognition element (MARE) that is present in the regulatory region of various oxidative stress-responsive genes [29]. Significantly higher levels of *BACH1* expression were observed in PCa tissues compared with normal tissues in a subpopulation of Iranian subjects [30]. *BACH1* upregulation in DU145 cells was associated with higher cell motility, and *BACH1* acted as an inducer for several metastatic genes such as *CXCR4*, *MMP1*, *MMP9* and *MMP13* in a PCa cell line. The authors concluded that *BACH1* over-expression induced PCa invasion and aggressiveness [30].

Signaling pathways and transcription factors

The G protein coupled receptor (GPCR) family are cell surface receptors involved in a variety of cellular processes. G proteins are mediators that transfer the signals from the cell surface receptor to intracellular signaling pathways involved in cell growth and transcription [31]. Prostate-specific G-protein coupled receptor (PSGR) is expressed mainly in human prostate epithelium, which is upregulated in PCa [32]. PSGR upregulation is synergistically associated with phosphatase and tensin homolog (*PTEN*) loss during PCa progression and metastasis [33]. LGR4, a member of the GPCRs, is involved in epithelial mesenchymal transition (EMT) and metastasis of PCa cells through the PI3K/Akt signaling

Table 1. Genetic factors associated with PCa susceptibility in the Iranian population.

	Year	Gene	Purpose	Population	Results
Intracellular defense systems and drug resistance					
Safarinejad [25]	2011	GSTM1 and GSTT1	Diagnosis	336 controls 168 patients	Polymorphism was correlated with PCa risk
Shajari [30]	2018	BACH1	Diagnosis	26 N/Ta	Over expression
Signaling pathways and transcription factors					
Safarinejad [38]	2012	GNB3	Diagnosis	344 controls 172 patients	Polymorphism was correlated with PCa risk
Samadaian [45]	2018	DAB2IP and SPRY2	Prognosis	50 N/T	DAB2IP and SPRY2 under expressions
Zahir [46]	2014	HER-2/neu	Diagnosis	40 patients	Expression was correlated with PSA level
Hashemi [53]	2016	LAPTM4B	Diagnosis	176 controls 168 patients	Polymorphism was correlated with PCa risk
Ameri [55]	2011	RARB and CDKN2a	Prognosis	63 patients	RARB and CDKN2a promoter methylation
Torabi-Nezhad [61]	2016	PTEN and P63	Diagnosis	250 patients	PTEN and P63 expression
Nodouzi [70]	2015	NKX3.1 and PTEN	Diagnosis	81 patients	Under expressions
Amini [76]	2014	NANOG	Diagnosis and prognosis	20 patients	NANOG expression
Inflammatory factors					
Chatrabnous [84]	2019	FOXP3 and IL-35	Diagnosis	150 controls 150 patients	Higher levels of serum IL-35 FOXP3 polymorphism was correlated with PCa risk
Hashemi [90]	2018	IL1A	Diagnosis	155 controls 150 patients	Polymorphism was correlated with PCa risk
Razzaghi [93]	2018	MIF	Diagnosis	135 controls 128 patients	Polymorphism was correlated with PCa risk
Taheri [95]	2018	IL-6	Diagnosis	200 controls 130 patients	Polymorphism was correlated with PCa risk
Dargahi Abbasabad [97]	2018	IL-6	Diagnosis	250 controls 112 patients	Polymorphism was correlated with PCa risk
Apoptosis					
Karimian [100]	2018	Survivin	Diagnosis	145 controls 157 patients	Polymorphism was correlated with PCa risk
Eslami [101]	2016	Survivin	Diagnosis	94 controls 94 patients	Over expression
Behfarjam [102]	2015	p53 and ABCC1	Diagnosis	45 controls 45 patients	Polymorphism was correlated with PCa risk
Babaei [103]	2014	TP53	Diagnosis	120 patients	Polymorphism was correlated with PCa risk
Hashemi [104]	2017	MDM2	Diagnosis	245 patients	Polymorphism was correlated with PCa risk
Safarinejad [109]	2013	eNOS	Diagnosis	340 controls 170 patients	Polymorphism was correlated with PCa risk
Steroid metabolism					
Habibi [115]	2017	UGT2B	Diagnosis	360 patients	Polymorphism was correlated with PCa risk
Amirghofran [116]	2004	AR	Diagnosis	50 patients	AR expression was correlated with BCL-2/BAX
Karimpur-Zahmatkesh [119]	2013	CYP17	Diagnosis	128 controls 74 patients	A2 allele was significantly correlated with PCa
Safarinejad [122]	2012	ER-a	Diagnosis	324 controls 162 patients	Polymorphism was correlated with PCa risk
Taeb [125]	2014	PSCA	Diagnosis	185 patients	Correlation with Gleason score
Noncoding RNAs and post transcriptional regulation					
Taheri [134]	2017	HOTAIR	Diagnosis	250 controls 271 patients	Polymorphism was correlated with PCa risk
Bayat [137]	2018	PRCAT17.3 and PRCAT38	Diagnosis	98 patients	Over expressions
Taheri [138]	2017	ANRIL	Diagnosis	220 controls 250 patients	Polymorphism was correlated with PCa risk
Sattarifard [140]	2017	PRNCR1	Diagnosis	358 patients	Polymorphism was correlated with PCa risk
Saffari [144]	2018	miR-let7b and miR-548	Diagnosis	40 controls 53 patients	miR-let7b under expression and miR-548 over expression
Narouie [151]	2017	SETD8	Diagnosis	351 patients	Polymorphism was correlated with PCa risk
Ghorbanmehr [154]	2019	miR-21-5p, miR-141-3p, and miR-205-5p	Diagnosis	20 controls 45 patients	Over expression

(*continued*)

Table 1. Continued.

	Year	Gene	Purpose	Population	Results
Aghaee-Bakhtiari [157]	2015	miR-23a and b	Diagnosis	26 patients	Under expression
Hashemi [162]	2016	miR-499	Diagnosis	351 patients	Polymorphism was correlated with PCa risk
Hashemi [164]	2017	miR-3131	Diagnosis	340 patients	Polymorphism was correlated with PCa risk
DNA repair and cell cycle					
Ebrahimi [167]	2017	MTR	Diagnosis	100 controls 100 patients	Polymorphism was correlated with PCa risk
Safarinejad [170]	2010	MTHFR	Diagnosis	348 controls 174 patients	Polymorphism was correlated with PCa risk
Jafary [172]	2012	MSH3	Diagnosis	60 controls 18 patients	Polymorphism was correlated with PCa risk
Pourmand [176]	2007	PTEN	Diagnosis and prognosis	51 patients	Mutation
Cancer testis antigens					
Ghafouri-Fard [180]	2010	LEMD1 and SPATA19	Diagnosis	55 patients	Over expressions
Ousati Ashtiani [183]	2009	TGIFLX/Y	Diagnosis	75 patients	Correlation with Gleason score
Cell adhesion and extracellular matrix					
Foroozan [188]	2017	CD34 and CD117	Diagnosis	90 patients	Correlation with Gleason score
Dehghani [193]	2014	CXCL12	Diagnosis and prognosis	33 controls 79 patients	Correlation with Gleason score
Kalantari [196]	2017	CD44 and CD133	Diagnosis	148 patients	Inverse correlation between CD44 expression and Gleason score
Mostafavi-Pour [199]	2015	Integrin α4 and E-cadherin	Diagnosis	70 patients	Methylation
Mahdian [203]	2014	MAGI2	Diagnosis	81 patients	Under expression
Mohsenzadegan [204]	2015	NGEP	Prognosis	183 patients	High level of expression was correlated with good prognosis
Mohsenzadegan [205]	2013	NGEP	Prognosis	186 patients	Expression was correlated with grade

[a]Tumor tissues and normal margins.

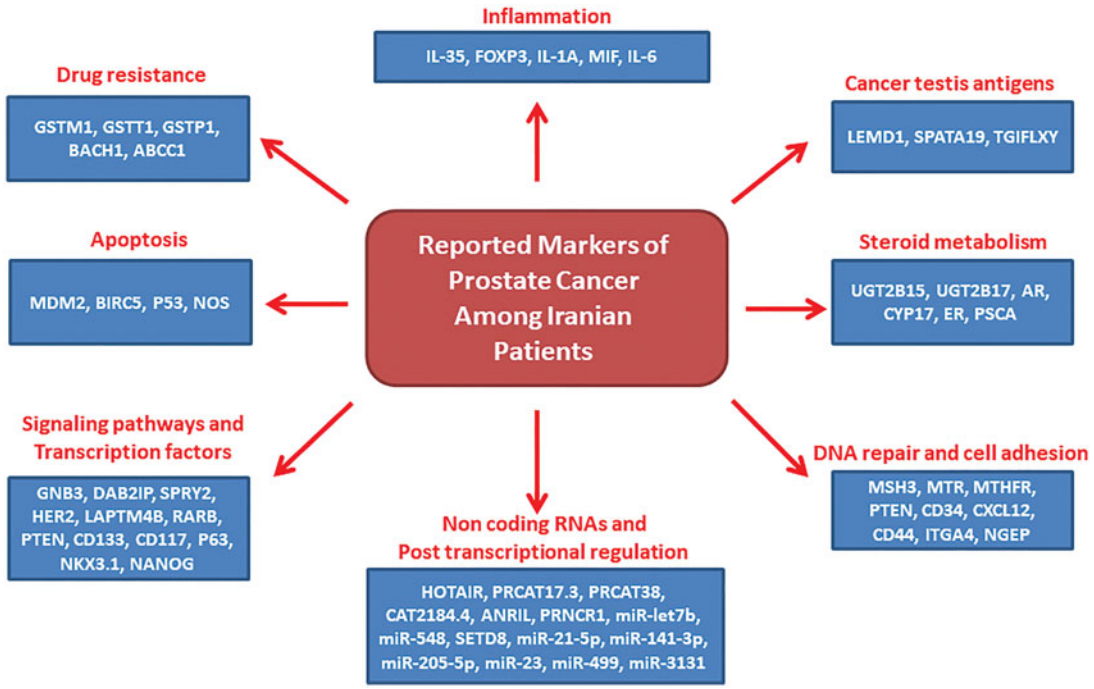

Figure 1. Cell and molecular processes which are involved in prostate cancer progression among Iranian patients.

pathway [34,35]. Moreover, *GPR160* is associated with apoptosis and cell cycle arrest; *GPR160* silencing significantly increased the levels of CASP1 in PCa cells [36]. Initial GPCR signal transduction is triggered by activation of heterotrimeric G proteins, which activate messenger systems, small GTPases, and kinase cascades.

These proteins are composed of several subunits (α, β, and γ). The G protein subunit beta 3 (*GNB3*) encodes the β3 subunit of G proteins [37]. When the role of rs5443 single nucleotide polymorphisms (SNP) in PCa progression was evaluated in a subpopulation of Iranian patients, a significant correlation between PCa and T allele of the *GNB3* C825T SNP was observed. Moreover, the presence of the *GNB3* 825 T allele was significantly related to tumor grade and stage [38].

The mitogen-activated protein kinase/extracellular-signal-regulated kinase (MAPK/ERK) pathway is a cascade of signaling from cell surface into the nucleus. The ERK pathway integrates the external signals of mitogens into signaling pathways and leads to cell growth and proliferation. This process of activation of receptor tyrosine kinases (RTK) and subsequently Ras [39] finally results in the phosphorylation and activation of ERK, which is involved in the regulation of various cell cycle mediators such as *CDK4* and *CDK6* [40]. *EPHB4,* a member of the RTKs, has been show to regulate *ITGB8* expression, a finding that highlights the role of RTK in PCa cell migration and metastasis [41]. Moreover, RTK may also be associated with drug resistance in PCa [42]. Deregulation of the MAPK/ERK pathway may be associated with an androgen-independent condition in PCa. Therefore, aberrations of disabled homolog 2 interacting protein (*DAB2IP*) and sprouty homolog 2 (*SPRY2*), as regulators of the RTK signaling pathway, may also be involved in PCa progression. *DAB2IP* is a tumor suppressor that regulates cell proliferation and apoptosis through Ras and other signaling pathways [43]. *SPRY2* is one of the regulators of the RTK pathway and a negative regulator of such growth factors as fibroblast growth factor (FGF), vascular endothelial growth factor (*VEGF*) receptors, and *BRAF* [44]. When the expression of *DAB2IP* and *SPRY2* transcript variants were assessed in Iranian PCa patients, there was significant *DAB2IP* and *SPRY2* under expression of variant 1 and 2, respectively, in PCa in comparison with normal tissue [45]. The *HER-2/neu* proto-oncogene is an RTK associated with cell proliferation, migration, and apoptosis. *HER-2/neu* protein upregulation has been reported in 27.5% of a group of Iranian PCa patients. Moreover, an inverse correlation was observed between age and *HER-2/neu* expression [46]. *EGFR* and *HER2* support the survival and growth of prostate tumor initiating and circulating cells that metastasize to bone [47]. *HER-2/neu* is involved in activation of AR and hormone-independent growth of PCa. *HER-2/neu* induces PCa cell growth in the absence of androgen through AKT activation [48]. Lysosomal degradation is a critical process in the termination of EGFR signaling. Lysosome-associated protein transmembrane-4b (*LAPTM4B*) prolongs EGFR signaling through inhibition of lysosomal degradation [49]. *LAPTM4B* is a tetratransmembrane protein involved in neoplastic transformation and cell proliferation through the PI3K/AKT pathway [50–52]. A relationship has been observed between the *LAPTM4B* polymorphism and PCa susceptibility in a sub-population of Iranian patients [53]. There is also a correlation between *LAPTM4B* and the PI3K/AKT signaling pathway in which the *miR-188-5p* inhibits PI3K/AKT signaling through *LAPTM4B* suppression [54].

In addition to cell surface receptors, nuclear receptors participate in cellular transduction systems. Retinoic acid receptor beta (*RARB*) is a nuclear thyroid-steroid hormone receptor associated with cell growth and differentiation through binding with retinoic acid and retinoic acid response elements (RARE). Assessment of *RARB* and *CDKN2a* promoter methylation status in a subpopulation of Iranian subjects showed the prognostic value of *RARB* and *p16* promoter hypermethylation in PCa compared with benign prostatic hyperplasia (BPH) cases. Hypermethylation of *RARB* and *p16* was more frequent among patients with a poor prognosis compared with those with a good prognosis [55]. RARB methylation in benign prostate samples was significantly correlated with increased risk of subsequent PCa among black men [56].

PTEN is a phosphatase antagonist of PI3K signaling that participates in cell cycle regulation and DNA damage checkpoints [57,58]. *PTEN,* a tumor suppressor, targets proteins in signaling pathways that are involved in cell growth and survival [59]. Loss of *PTEN* could function in coordination with the TMPRSS2-ERG fusion protein to induce PCa progression. Fallahabadi et al. observed TMPRSS2-ERG fusion in 64% of 42 Iranian PCa tissues while none was observed in normal samples [60]. Therefore, TMPRSS2-ERG fusion was PCa specific and could be considered as a marker to discern PCa from normal tissue. Moreover, the PCa cases had decreased *PTEN* expression compared with controls, and they concluded that simultaneous TMPRSS2-ERG fusion and *PTEN* deletion could be a reliable diagnostic method to detect PCa in Iranian men [60]. Another study reported *PTEN* loss in 89% of Iranian cases with intra-ductal carcinoma of the prostate (IDC-P) [61]. Regarding the presence of *PTEN* in high grade prostatic intraepithelial neoplasia (HGPIN) cases, the authors recommended *PTEN* as an efficient marker for differentiation between IDC-P and HGPIN. Moreover, based on the expression of P63 in IDC-P cases and the lack of P63 expression in adenocarcinoma, they suggested that *P63* may be used as a marker to differentiate between IDC-

P and adenocarcinoma. The sensitivity and specificity of *P63* to distinguish HGPIN from IDC-P was 100% and 0% respectively, while *PTEN* had a specificity and sensitivity of 100% and 88.9%, respectively [61]. Activation of *CXCL12* signaling in PCa is driven through *PTEN* loss and subsequent AKT activation [62]. *PTEN* loss upregulates cell cycle genes such as *CDC6* and *CCNE2* that induce distant metastasis in PCa [63]. *PTEN* is also associated with drug resistance in PCa; *PTEN* promotes drug-induced apoptosis by *caspase-8* activation and *BID* suppression via a Fas-associated protein with death domain (FADD)-dependent signaling pathway [64]. Another study showed that the *PTEN* loss could promote PCa progression through unopposed activity of AR, which is associated with resistance toward androgen ablation therapy [65]. *PTEN* is also associated with the inhibitory effects of transforming growth factor-β (*TGF-β)* on cell proliferation, which in its absence increases the effects of *TGF-β* on the PI3-kinase pathway activation and cell migration in PCa [66].

NKX3.1, an androgen related and homeodomain-containing prostate-specific transcription factor, is regulated by other transcription factors such as *ETS1* and *SP1* [67,68]. Moreover, the WNT signaling pathway regulates *NKX3.1* expression during epithelial differentiation [69]. A significant correlation has been shown between *NKX3.1* and *PTEN* under expressions and the risk of PCa in a subpopulation of Iranian patients [70]. The receptor activity-modifying protein 1 (RAMP1), as a coreceptor for GPCRs, is a direct *NKX3.1* target gene that is upregulated in PCa [71]. *TWIST1* is one of the main regulators of EMT-mediated tumor invasion and metastasis. *NKX3-1* downregulates *TWIST1* expression during PCa progression and metastasis [72]. *NKX3.1* also regulates cell cycle progression and DNA damage response in PCa cells [73]. As well, *NKX3.1* is involved in lymphangiogenesis in advanced stages of PCa through the regulation of *VEGF-C* expression [74]. Cancer stem cells are a subpopulation of tumor cells with self-renewal ability and resistance toward chemotherapy. Various pluripotent transcription factors such as *SOX2*, *OCT4*, and *NANOG* are responsible for the maintenance of self-renewal ability in normal and cancer stem cells [75]. Expression of *NANOG*, nucleostemin, *SOX2*, *ZFX*, *TCL1*, *TBX3*, *ESRRb*, and *DPPA4* self-renewal and stem cell markers have been reported in Iranian PCa patients. *NANOG* expression was observed in 80% of Iranian PCa tissues [76]. NANOG-expressing tumor cells have stem cell properties that promote aggressive castration-resistant features in PCa cells. *NANOG* regulates AR/FOXA1 signaling in PCa cells, which results in upregulation of genes associated with the cell cycle, self-renewal, cell migration, and castration resistance [77].

Inflammatory factors

Deregulation of the immune system plays an important role in tumor progression [78]. Chronic inflammation, which is associated with inflammatory cytokines such as interleukins, has an important role in neoplastic transformation of PCa [79]. Regulatory T cells have a key function in the termination of T cell response, immunologic tolerance, and inhibition of autoimmune responses [80,81]. Regulatory T cells exert their functions through anti-inflammatory cytokines including transforming growth factor (*TGF-β*) and *IL-35* [82,83]. *IL-35* is produced mainly by forkhead box P3 (*FOXP3*) positive regulatory T cells. Significant higher levels of serum *IL-35* in PCa were observed compared with healthy cases in a sub-population of Iranian subjects [84]. An association between SNP rs3761548 of *FOXP3* and PCa, in which the AA genotype and A allele had significantly higher levels of serum *IL-35* compared with cases with CC genotype and C allele, was seen. There was a rising trend in serum *IL-35* concentrations with more advanced stages of disease. Also Gleason score and *IL-35* were correlated: PCa tissues with Gleason scores of 7–10 had higher levels of serum *IL-35* compared with cases with scores of 1–6 [84]. *IL-1A,* a cytokine produced by cells such as monocytes, macrophages, and smooth muscle cells [85,86], is involved in tumor progression through *IL-6*, *TNF-a*, *VEGF*, *MMPs*, and *TGF-β* [87–89]. A group assessed the correlation between the *IL-1A* rs3783553 (-/TTCA) polymorphism and the risk of PCa in a subpopulation of Iranian patients [90]. The authors observed a significant correlation between the *IL-1A* 4-bp ins/del polymorphism and the risk of PCa and the stage. Moreover, miR-125a-3p has a more stable interaction with *IL-1A* in the del compared with the ins type [90]. Macrophage migration inhibitory factor (*MIF*) is a multifunctional cytokine that belongs to the *TGF-β* family and acts as an inducer of *TNF-α* and *IL-1* [91,92]. *MIF* is involved in inflammatory and immune responses and is ubiquitously expressed in various organs. A correlation between the *MIF* -173 G/C polymorphism and PCa was observed, and *MIF* has been proposed as a marker of aggressive PCa among Iranian patients [93]. Cytokine *IL-6* functions as a protective agent in tumor cells against therapy-induced DNA damage, apoptosis, and oxidative stress, is associated with EMT and bone metastasis in aggressive PCa [94], and is involved in cell proliferation and apoptosis inhibition through various pathways including the JAK-STAT, MAPK, and PI3-K

pathways [94]. A significant higher frequency of the *IL-6* rs1800795 C variant was seen among a group of Iranian PCa patients in comparison with healthy cases [95]. Inflammatory factors that are produced by immune and tumor cells are associated with cell proliferation. *IL-6* is an inflammatory cytokine that is involved in metastasis as well as cell proliferation [96]. Significant differences between the *IL-6* –174G>C (rs1800795) GG variant and G allele frequencies were seen between Iranian PCa patients and controls. Moreover, the authors reported that the *IL-6* (-174 C) allele was more frequent among PCa patients who had bone metastasis [97].

Apoptosis

Programmed cell death is a fundamental process that eliminates damaged or unwanted cells during organogenesis, immune response, cellular aging, and innate tumor-suppression. Apoptosis is related to the activation of caspase enzymes. Therefore, apoptosis deregulation can induce tumorigenesis and drug resistance. Neoplastic transformation of PCa is associated with the inability of cells to undergo apoptosis. Survivin belongs to the inhibitor of apoptosis family that represses the apoptosis process through inhibition of caspase 9, 3, and 7 [98]. This factor is highly expressed in tumor cells and is related to poor prognosis and patient survival. Survivin is also involved in the cell cycle, chromosome movement, drug resistance, and stress responses [99]. Significant correlations between 31G>C, 454G>A, and 148T>C polymorphisms and the risk of PCa in a subpopulation of Iranian patients were observed [100]. Moreover, a significant role of age and smoking was seen in the relationship to 31G>C and PCa risk, and similarly there was a correlation between the role of smoking between 571T>C and PCa susceptibility [100]. Another group that assessed protein expression of survivin among Iranian PCa patients observed negative expression in normal tissues, whereas there was a direct correlation between high survivin expression and advanced Gleason scores. The PCa tissues had higher levels of survivin expression compared with BPH tissue [101]. TP53 tumor suppressor plays key roles in DNA repair, cell cycle regulation, angiogenesis, genomic stability, and apoptosis. Moreover, *P53* regulates the expression of ATP binding cassette subfamily C member 1 (*ABCC1*), a member of the ATP-binding cassette superfamily involving in antioxidative defense system and drug resistance. Significant direct correlations were seen between the codon 72 polymorphism of p53 (Pro/Pro) and the *ABCC1* G-1666A polymorphism and increased risk of PCa among a group of Iranian cases [102]. Another group also reported a correlation between the *TP53* codon 72 polymorphism and PCa susceptibility among Iranian patients, in which Pro/Pro carriers had a higher risk of PCa in comparison with the cases with the Arg/Arg phenotype. Moreover, the *TP53* variant was correlated with age >65 years in PCa patients [103]. Mouse double minute 2 homolog (*MDM2*) is a p53-specific E3 ubiquitin ligase that ubiquitinates p53 for degradation by nuclear and cytoplasmic proteasomes. A significant correlation was seen between the 40-bp I/D polymorphism in the *MDM2* promoter sequence and PCa risk in a subpopulation of Iranian patients; the I/D variant raised the PCa risk in comparison with the I/I genotype [104]. High levels of nitric oxide (NO) is also associated with cyclooxygenase-2, *HIF-1α*, *MAPK*, *EGFR*, and *RAS*. Moreover, deregulation of NO has an important role in angiogenesis induction and MMP regulation during tumor progression [105]. NO is produced by nitric oxide synthase (*NOS*) and is involved in angiogenesis and cell adhesion [106]. NO can also exert some oncogenic effects including DNA strand breaks [107] and *P53* deregulation [108]. Significant correlations were seen between T-786C and intron 4 VNTR *eNOS* polymorphisms and the risk of PCa in a subpopulation of Iranian cases. Moreover, the T786C variant was associated with high grade and advanced PCa [109].

Steroid metabolism

Steroid hormones are critical for the normal function of the prostate gland. The prolonged presence of androgens may be associated with PCa progression that could be mediated through the regulation of growth factors and growth factor receptors [110]. Deregulated steroid hormones are critical for prostate growth and function [111]. The UDP-glucuronosyl transferase (UGT) gene family participates in steroid metabolism through glucuronidation [112]. An inverse correlation was reported between *UGT2B* activity and the risk of PCa [113,114]. A significant relationship was found between the *UGT2B15* D85Y and null *UGT2B17* variants and the risk of BPH in a subpopulation of Iranian PCa cases [115]. *AR,* a nuclear receptor for androgenic hormones, functions as a transcription factor in the regulation of target genes associated with cell proliferation, migration, and differentiation. Another study evaluated the correlation between AR and B-cell lymphoma 2 (*BCL-2*), BCL-2 associated X (*BAX*), Ki-67 and *P53,* factors that are involved in cellular processes such as apoptosis and cell cycle regulation, in a subpopulation of Iranian PCa patients [116]. All the PCa cases had positive nuclear

expression of AR. Moreover, there were correlations between *AR*, *BCL-2*, and Ki-67, and *P53* expression [116].

CYP17, which belongs to the *CYP450* family, has 17a-hydroxylase and 17, 20-lyase activity in testosterone metabolism [117]. *CYP17A1* is also involved in the synthesis of progestins, glucocorticoids, and other androgens. The A2 allele of *CYP17* is a T/C transition in -34 5UTR, which creates an additional SP1 promoter site that may cause increased *CYP17* expression [118]. The A2 allele has been shown to be significantly correlated with PCa in a subpopulation of Iranian patients [119]. PCa is an age dependent malignancy in which the PCa risk increases with age because of hormonal imbalance. Although aging reduces the androgen levels, the levels of estrogen have an unchanging or rising trend at older ages [120]. Estrogen receptors (ERs) are comprised of the ER-α and ER-β members of the nuclear receptor family [121]. The ER-α PvuII C, ER-α XbaI G, and ER-β AluI G alleles were significantly correlated with PCa susceptibility in a sample of Iranian cases. Moreover, the *ER-β* PvuII CC and *ER-β* RsaI AG homozygotes and heterozygotes carriers were associated with high grade and stage tumor [122].

Prostate stem cell antigen (PSCA) may be a diagnostic marker and also a target for therapy in PCa [123,124]. *PSCA* is a small cell surface glycoprotein belonging to the Thy-1/Ly-6 family that may be associated with the regulation of cell proliferation. *PSCA* expression is stimulated by androgens through the androgen responsive element, which is located upstream of *PSCA*. Moreover, *hTERT* also functions as an inhibitor for *PSCA* expression [124]. When the expression pattern of *PSCA* was investigated in a subpopulation of Iranian PCa cases, *PSCA* was observed in the cytoplasm of 47% of PCa samples, while it was expressed mainly in the cell membrane of benign samples. *PSCA* expression had a rising trend during neoplastic transformation from normal to malignant prostate samples. Moreover, there was a significant association between *PSCA* expression and Gleason score among PCa cases [125].

Noncoding RNAs and post transcriptional regulation

In addition to coding sequences in genome, non-coding regions may also be associated with tumor progression [126]. Small and long noncoding RNAs (ncRNAs) are involved in tumor progression through regulation of protein-coding regions [127]. NcRNAs are regulators of various biological processes including cell cycle [128,129], self-renewal [130], embryogenesis [131], and immune response [132]. HOX transcript antisense RNA (HOTAIR) is a long ncRNA which is transcribed from *HOXC* locus and has been reported in several tumor types [133]. *HOTAIR* plays vital roles in the regulation of gene expression and chromatin dynamics through interaction with histone methyltransferases and demethylases such as polycomb repressive complex 2 and lysine-specific histone demethylase 1, which resulted in H3K27 methylation and H3K4 demethylation. There was a significant correlation between the rs12826786 T allele and TT genotype of *HOTAIR* and PCa susceptibility in a subpopulation of Iranian cases. Moreover, the PCa cases had significantly higher presentation of the rs1899663 T allele and TT variant in comparison with BPH subjects. rs1899663 and rs12826786 were shown to be involved in the regulation of various transcription factors such as *SOX*, hepatocyte nuclear factor 4, and retinoid X receptor alpha [134]. Long ncRNAs, with a length of more than 200 nucleotides, are involved in regulation of differentiation and tissue development [135,136]. *PRCAT17.3* and *PRCAT38* overexpression has been observed in PCa in comparison with BPH tissues in a group of Iranian patients. They showed that the sensitivity and specificity of *PRCAT17.3* in urine samples were 78% and 69%, respectively. Moreover, the PCa tissues had *CAT2184.4* under expression compared with BPH tissues. *PRCAT17.3* and *PRCAT38* may be the inducers of *TMPRSS2* expression [137]. *ANRIL* is a long ncRNA involving in regulation of *CDKN2A/B* tumor suppressors and *PRC1*. There was a correlation between rs10757278, G/G genotype of *ANRIL* and the risk of PCa that could be related to its role in the modification of the *STAT1* and *PAX5* binding sites. It was concluded that the rs4977574 G variant decreased the PCa risk in a subpopulation of Iranian patients [138]. *PRNCR1* is a long ncRNA that is associated with PCa progression through *AR* regulation [139]. There was significant correlation between *PRNCR1* rs13252298, rs1456315, and rs7841060 polymorphisms and high risk of PCa in a sample of Iranian population [140].

MicroRNAs are ∼22 nucleotide ncRNAs that function as posttranscriptional gene regulators through 3′UTR of target mRNAs [141]. *Let-7* microRNA is a regulator for oncogenes such as *RAS* genes and high mobility group AT-hook 2 (*HMGA2*). Moreover, various cell cycle regulators, such as cyclin A2 (*CCNA2*), cell division cycle 34 (*CDC34*), and cyclin-dependent kinase 8 (*CDK8*), are associated with *Let-7* [142,143]. *miR-let7b* was under expressed and *miR-548* was over expressed in PCa tissues in comparison with the normal margins in a subpopulation of Iranian patients [144]. Set domain-containing protein 8 (*SETD8*), one of the targets of *miR-502,* encodes

a histone methyltransferase that participates in preservation of genome integrity [145], cell-cycle regulation [146], and DNA repair [147]. Moreover, it is associated with factors such as *P53*, *TWIST*, *ERα*, and *AR* [148–150]. The *SETD8* rs16917496 SNP (*miR-502* binding site in *SETD8* 3UTR) was correlated with PCa risk in a subpopulation of Iranian patients [151]. *MiR-21* mediates tumor cell invasion through targeting *PTEN* which results in FAK/AKT phosphorylation [152]. Moreover, *miR-21-5p* is involved in EMT through signaling pathways such as *TGFβ* and Hedgehog [153]. The levels of *miR-21-5p*, *miR-141-3p*, and *miR-205-5p* expression were significantly increased in urine samples of a subpopulation of Iranian patients with PCa, with specificities of 0.88, 0.86, and 0.69, and sensitivities of 0.81, 0.81, and 0.82, respectively [154]. MAPK and JAK/STAT play critical roles in cell proliferation and differentiation [155,156]. *MiR-23a* and *miR-23b* may be involved in regulation of these signaling pathways through *IL-6R*. Significant under expression of these miRNAs was observed in PCa tissues of a group of Iranian patients [157]. *MiR-499* regulates H_2O_2-induced apoptosis through *PDCD4* [158], which is also associated with inflammatory response [159] and differentiation [160]. Moreover, *miR-499* directly targets *TGFβR1,* which stimulates cell proliferation [161]. The *miR-499* rs3746444 variant significantly elevated the PCa risk among Iranian patients [162]. Death domain containing 1, XIAP associated factor 1, and caspase 7 have been demonstrated to be targets of *miR-3131* that are involved in apoptosis [163]. The correlation between a 3-bp indel polymorphism (rs57408770) in pre-miR-3131 and the risk of PCa was assessed in a subpopulation of Iranian patients, and the ins/ins genotype was significantly associated with a high risk of PCa [164].

DNA repair and cell cycle

Methionine, an essential amino acid and precursor of cysteine, has been found to be a regulator of the innate immune system, lipid metabolism, antioxidant enzymes, and DNA repair [165]. Methionine synthase (MTR), an important factor in DNA repair, plays a critical role in tumor progression [166]. Since MTR has a key role in DNA repair and methylation, the *MTR*-A2756G polymorphism was assessed in a subpopulation of Iranian PCa patients, and the G allele and GG genotype were observed to be associated with PCa progression [167]. *MTHFR* is a key factor in folate metabolism and the production of 5-methyltetrahydrofolate, which is involved in remethylation of homocysteine to methionine [168]. Finally, S-adenosylmethionine is generated as the methyl donor for DNA repair [169]. There was a significant correlation between 1298AC and 677TT genotypes of *MTHFR* and low PCa risk in a subpopulation of Iranian patients [170]. The mismatch repair system is an essential repair mechanism to detect and repair DNA synthesis errors such as insertion, deletion, and mismatched bases. Therefore, deregulation of the mismatch repair system could result in genomic instability and aberrant cell proliferation [171]. A significant correlation between *MSH3* polymorphisms and PCa risk was observed in a subpopulation of Iranian subjects [172]. *PTEN* is a tumor suppressor phosphatase associated with dephosphorylation of the PI3-kinase pathway. Moreover, *PTEN* functions as a negative regulator of cell cycle progression through G1 arrest and apoptosis induction [173–175]. A mutational analysis in a subpopulation of Iranian PCa patients showed *PTEN* mutations in high grade PCa tissues and highlighted *PTEN* as a major prognostic factor in PCa [176].

Cancer testis antigens

Cancer-testis antigens (CTAs) are a family of proteins expressed in normal testis and tumor cells. Because such specific expression patterns are seen only in normal testis and tumor cells, targeted therapy (cancer vaccines) that are based on such markers should have the least side effects because they will not affect normal tissue [177]. Spermatogenesis-associated protein 19 (*SPATA19*) is a CTA involved in the preservation of the normal mitochondrial membrane. Among epithelial tumors, PCa is considered to be one of the best diseases for targeted immunotherapy because the immune system can exert a significant response toward PCa cells and this immune response against PCa cells can also be stimulated by various immunotherapeutic methods [178]. High glucose uptake and upregulation of glycolysis are strategies for tumor cells to solve the problem of hypoxia and ROS production through the Warburg effect. Therefore, the mitochondria can be used as a target for apoptosis induction in cancer cells [179]. It was observed that 23% and 40% of 30 PCa samples expressed LEM domain-containing 1 (*LEMD1*) and *SPATA19*, respectively, while there was no expressions of such genes in BPH samples. Therefore, these CTAs were considered to be promising targets for immune therapy in Iranian PCa patients [180]. *TGIFLX/Y* belong to the TALE family of transcription factors that are expressed in adult testis [181]. *NIR1* and *NIR2* as the main targets of *TGIF2LX* are involved in cell morphogenesis, cytokinesis, and metastasis [182]. A significant association was observed between Gleason score of C6

and *TGIFLX/Y* expressions in a sample of Iranian PCa patients [183].

Cell adhesion and extracellular matrix

The biology and function of cells relate to their surrounding environment. The extracellular matrix (ECM) and cell adhesion are the main regulators of tissue homeostasis, cell growth, migration, and differentiation. Therefore, deregulation of the ECM and cell adhesion can be associated with tumor progression through facilitation of cell migration and invasion. Indeed, the ability of tumor cells to migrate is associated not only with the extra cellular environment but also with intracellular processes such as cytoskeletal remodeling, which is involved in preparing cytoskeletal flexibility during cell migration. *CD34,* a transmembrane phosphoglycoprotein involved in cell-cell adhesion and angiogenesis, is a marker of hematopoietic cancer stem cells [184,185]. *CD117* is a receptor tyrosine kinase protein that is associated with cell proliferation and differentiation through the stem cell factor [186,187]. The patterns of *CD34* and *CD117* expression in PCa were compared with benign tissues in a subpopulation of Iranian cases. *CD34* over expression was observed in PCa in comparison with the benign samples. Moreover, there were direct correlations between *CD34* expression and Gleason score and serum PSA level. In the case of *CD117*, there was also a correlation with advanced Gleason score. Generally, a significant correlation was seen between the *CD34* high/CD117 high phenotype and advanced Gleason score. It was concluded that *CD34* and *CD117* had a synergistic role during PCa progression [188]. Metastasis, the ability of tumor cells to detach from the primary bulk tumor and generate secondary lesions in the other organs, is associated with cell-cell and cell-ECM adhesion and release [189]. Integrins are cell-surface receptors that regulate the cytoskeleton and signaling pathways through ECM attachment. Chemokines also affect tumor cell metastasis through cytoskeletal rearrangement and cell adhesion [190]. *CXCL12* is associated with metastasis via regulation of migration, proliferation, and angiogenesis [191,192]. There was a significantly high level of *CXCL12* in a group of Iranian PCa patients. Moreover, the Gleason scores were significantly associated with plasma *CXCL12* level. *CXCL12* may affect prostate tumor cell adhesion and metastasis through regulation of integrins [193]. *CD44* is a cell surface glycoprotein associated with cell adhesion and migration [194]. *CD133,* a transmembrane glycoprotein expressed on adult stem cells to maintain stem cell properties, is also involved in cell proliferation, apoptosis [195] and the regulation of the MAPK and AKT signaling pathways. The over expression of *CD44* and *CD133* was observed in almost half of the PCa cases in a group of Iranian patients. Moreover, a significant association was seen between *CD44* expression and Gleason score in which the tumors with lower Gleason scores had higher levels of *CD44* expression [196]. Cadherins and integrins, the main ECM adhesion proteins to hold cells together, have key function in tumor aggressiveness [197,198]. Aberrant DNA methylation of integrin α4 has been observed in 66.6% of a sample of Iranian PCa patients, while E-cadherin methylation was observed in only 6.6% of PCa cases [199]. Membrane associated guanylate kinase (*MAGI2*), a scaffold molecule belonging to the guanylate kinases family, is involved in anchoring proteins, including glutamate receptors, b-catenin and *PTEN* [200]. PTEN-MAGI2 interaction increases *PTEN* stability through reduction of its degradation [200–202]. A study reported that there was significant *MAGI2* under expression, which increases AKT activation, in Iranian PCa tissues. *MAGI2* had a sensitivity and specificity of 0.88 and 0.83, respectively [203]. *NGEP* belongs to the anoctamin/TMEM16 family and is involved in cell-cell interactions and transportation of compounds such as sugars, bile salts, and metal ions. There were inverse correlations between *NGEP* expression, Gleason score, and stage in a subpopulation of Iranian PCa cases. *NGEP* had low expression in poorly differentiated tumors and tumors with metastatic lymph nodes. *NGEP* was introduced as a diagnostic marker for the low risk patients [204]. Another study reported that Iranian benign prostate tissues had higher levels of *NGEP* expression in comparison with malignant tumor tissues. There was an inverse correlation between the level of *NGEP* expression and grade of tumor. The tumor samples with metastatic lymph nodes were also *NGEP* positive [205].

Conclusion

In the present review, we have summarized, for the first time, all of the significant genes that have been reported to date among Iranian PCa patients. We have categorized them based on their involvement in cellular processes to provide an overview of cellular processes during the progression of PCa among Iranian cases. Regarding the recent studies, post transcriptional regulation via ncRNAs can be considered to be the main aberrant molecular process during PCa progression among Iranians. This review may help to pave the way to the determination of a unique panel of genetic prognostic and diagnostic markers for PCa in our country.

However, since the majority of studies were pilot studies, more studies will be required to develop an efficient clinical diagnostic genetic panel marker.

Disclosure statement

No potential conflict of interest was reported by the authors.

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