Association between genetic polymorphisms of long non-coding RNA PRNCR1 and prostate cancer risk in a sample of the Iranian population

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Abstract. The aim of the present study was to determine whether there is an association between the long non-coding RNA (lncRNA) prostate cancer-associated non-coding RNA 1 (*PRNCR1*) polymorphisms and prostate cancer (PCa) risk in a sample of the Iranian population. This case-control study was performed on 178 patients with PCa and 180 subjects with benign prostatic hyperplasia (BPH). Genotyping assay was performed by polymerase chain reaction-restriction fragment length polymorphism. The findings indicated that the GG genotype of the rs13252298 A>G variant significantly increased the risk of PCa (odds ratio=3.49, 95% confidence interval: 1.79-6.81, P=0.0001) compared with AA+AG. As regards the rs1456315 G>A polymorphism, the AG genotype and G allele significantly increased the risk of PCa. As regards the rs7841060 T>G variant, the findings demonstrated that this TG genotype and the G allele significantly increased the risk of PCa. The rs7007694 T>C variant was not found to be associated with the risk of PCa. Haplotype analysis indicated that GTGA and GTGG significantly increased the risk of PCa compared with rs1456315A/rs7007694T/rs7841060T/rs13252298G (ATTG). The *PRNCR1* variants were not found to be significantly associated with the clinicopathological characteristics of PCa patients. In conclusion, our findings support an association between *PRNCR1* variants and the risk of PCa in a sample of the Iranian population.

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Introduction

Prostate cancer (PCa) is one of the most frequently diagnosed cancers in men and the sixth leading cause of cancer-related mortality among men worldwide (1). The prevalence of PCa differs significantly among populations, indicating that the host's genetic background may play an important role in susceptibility to PCa (2). Single-nucleotide polymorphisms (SNPs) are the most common type of genetic variations in human genome, and they have been found to be associated with the risk of PCa (3-6). Genome tiling arrays have indicated that 1% of the human genome is composed of protein-coding sequences and ~4-9% of the sequences of the human genome are transcribed to non-coding RNAs (ncRNAs) (7).

NcRNAs are documented to be the main regulators of a number of biological processes, such as transcription, splicing, translation, epigenetic gene expression, cell cycle (8-12), stem cell pluripotency and reprogramming (12,13), embryogenesis (14), and regulation of the immune response (15). They are divided into small ncRNAs (<200 nt) and long ncRNAs (lncRNAs; >200 nt) (16,17). LncRNAs are classified according to the correlation between their location and the location of the corresponding protein-coding gene, such as sense, antisense, intergenic, intronic and bidirectional lncRNAs (18,19). Aberrant expression of lncRNAs may contribute to the development and progression of various cancers (20-25).

The lncRNA prostate cancer-associated non-coding RNA 1 (*PRNCR1*), also referred to as PCAT8 and CARLo3, is mapped to 8q24.21 (26). It has been stated that *PRNCR1* is upregulated in PCa and is involved in PCa development by modulating androgen receptor (AR) activity (27). Binding of *PRNCR1* to the acetylated AR and its association with DOT1L recruit a second lncRNA, PCGEM1, to the DOT1L-mediated methylated N-terminus of the AR (27). The interactions of these overexpressed lncRNAs may serve as important regulators in PCa.

To date, certain studies have investigated the impact of *PRNCR1* polymorphisms on the risk of various cancers, including prostate (26,28-30), gastric (31,32) and colorectal cancer (33).

PRNCR1 variants that were identified as potential risk factors for cancer were selected (26,28-30,34,35). Genetic risk factors for cancer may vary among diverse populations. Consequently, repeating previously reported genetic associations in other populations is necessary to determine the genetic risk in each population. To the best of our knowledge, there has yet been no study investigating the effect of *PRNCR1* variants on cancer risk in the Iranian population. Therefore, the aim of the present study was to determine whether there is an association between the *PRNCR1* rs13252298, rs1456315, rs7841060 and rs7007694 polymorphisms and the risk of PCa in a sample of the Iranian population.

Patients and methods

Patients. In total, 358 subjects participated in this hospital-based case-control study, including 178 unrelated men with histopathologically confirmed prostate cancer and 180 age-matched unrelated men with benign prostatic hyperplasia (BPH), with no history of any type of cancer, as the control group (36-39). All cases and controls were selected from a university-affiliated referral center (Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran). The local Ethics Committee of Zahedan University of Medical Sciences approved the project (IR.ZAUMS.REc.1395.102), and written informed consent was obtained from all the participants. Genomic DNA was extracted by the salting out method and stored at -20˚C until use. Peripheral blood samples were collected in tubes containing EDTA and genomic DNA was extracted by the salting out method.

Genotyping. The polymerase chain reaction (PCR)-restriction fragment length polymorphism assay was used for genotyping of the *PRNCR1* rs13252298, rs1456315, rs7841060, and rs7007694 polymorphisms. The primer sequences, restriction enzymes and the length of the PCR products are listed in Table I. PCR was performed with the commercially available prime Taq Premix (Genet Bio, Daejeon, Korea) according to the manufacturer's recommended protocol. Into each 0.20-ml PCR reaction tube, 1 μl of genomic DNA (100 ng/ml), 1 μl of each primer (10 μM), 7 μl of 2X master mix and 6 μl of ddH_2O were added. Amplification was performed with an initial denaturation at 95˚C for 30 sec, followed by 30 cycles of 30 sec at 95˚C, 30 sec at 62˚C for rs13252298, 60˚C for rs1456315, 56˚C for rs7841060, and 64˚C for rs7007694, 72˚C for 30 sec, with a final extension step at 72˚C for 10 min. Subsequently, 10 μl of the PCR products were digested with the appropriate restriction enzymes (Table I). The digested products were separated by agarose gel electrophoresis, visualized by a UV transilluminator and photographed (Fig. 1).

Statistical analysis. All data were analyzed using the statistical package SPSS 22.0 software (IBM Corp., Armonk, NY, USA). The continuous and categorical data were analyzed by the independent samples t-test and χ^2 test, respectively. The association among polymorphisms and PCa was calculated by computing the odds ratio (OR) and 95% confidence interval (95% CI) from unconditional logistic regression analyses. Haplotype analysis was performed using SNPStats software (40). The level of statistical significance was set at $P<0.05$.

Results

Genotypes and allele frequencies of PRNCR1 polymorphisms. The present study included 178 PCa patients with a mean age ± standard deviation of 61.53±6.91 years, and 180 patients with BPH with a mean age of 62.40±7.64 years. No significant difference was found between the groups in terms of age (P=0.258). The genotypes and allele frequencies of *PRNCR1* polymorphisms in cases and controls are presented in Table II. As regards the rs13252298 A>G variant, our findings demonstrated that this variant significantly increased the risk of PCa in the recessive (OR=3.49, 95% CI: 1.79-6.81, P=0.0001, GG vs. AA+AG) inheritance model. As regards the rs1456315 A>G polymorphism, the AG genotype as well as the G allele significantly increased the risk of PCa (OR=5.16, 95% CI: 3.16-8.41, P<0.0001 and OR=2.20, 95% CI: 1.60-3.03, P<0.0001, respectively). The TG genotype as well as the G allele of the rs7841060 variant significantly increased the risk of PCa (OR=5.14, 95% CI: 3.15-8.37, P<0.0001 and OR=2.37, 95% CI: 1.71-3.26, P<0.0001, respectively). Our findings demonstrated that the rs7007694 T>C polymorphism was not significantly associated with the risk of PCa. A haplotype analysis was performed, and the findings indicated that GTGA and GTGG significantly increased the risk of PCa compared with rs1456315A/rs7007694T/rs7841060T/rs13252298G (ATTG) (Table III).

Association between clinicopathological characteristics and PRNCR1 polymorphisms. The associations between clinicopathological characteristics, including age, stage, prostate-specific antigen (PSA) levels, Gleason score, perineural invasion and surgical margin, and *PRNCR1* polymorphisms are shown in Table IV. The findings did not support an association between *PRNCR1* polymorphisms and the clinicopathological characteristics of PCa patients.

The Hardy-Weinberg equilibrium (HWE) was calculated and the findings revealed that the genotype distribution in controls was not in HWE.

Discussion

LncRNAs are involved in tumorigenesis through their function as proto-oncogenes (41) or tumor-suppressor genes (42). Androgen receptor, a member of the nuclear receptor family, is a ligand-activated transcription factor (43). It has been suggested that lncRNA *PRNCR1* promotes prostate carcinogenesis via activating AR (26). SNPs, a class of genetic variations, are commonly used in the prediction of cancer risk (38,44,45), prognosis (46) and clinical outcome (47). Cumulative evidence indicates that non-coding genes may be involved in gene expression complexity in humans (48,49). Abnormal expression of lncRNAs has been found to be associated with the development of numerous cancers (50-52). Genome-wide association studies suggested significant and consistent associations of multiple genetic polymorphisms on chromosome 8q24 with PCa susceptibility (53-58). To

Table I. Primer sequences for detection of *PRNCR1* by PCR-RFLP.

PRNCR1 SNPs	PCR primers (5'→3')	Restriction enzyme	Fragment length (bp)
rs13252298 A>G	F: CAGCACTTGCTGTCTTCTCAGATACgAT R: TACTCCCCAATCTCTGGTCTTACCT	*Eco*RV	AA:196+28 AG:224+196+28 GG:224
rs1456315 G>A	F: TTGCATTACCTCAACTAAGCCAAG R: GGATGAAGAACTGAGGTTGCTAATAAGTC	*Acc*I	GG:213+30 GA:243+213+30 AA:243
rs7841060 T>G	F: CACCAATCCCAGAGCCATTTTGT R: CATTTCTCAGGTAGACCATGAACCTCGTA	*Rsa*I	TT:225 TG:225+197+28 GG:197+28
rs7007694 T>C	F: GCGAATGCCATTTGTTTGGACG R: CCTCCAAAGAGAAGAACGGCT	*Bst*uI	TT:222 TC:222+200+22 CC:200+22

PRNCR1, prostate cancer-associated non-coding RNA 1; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; SNP, single-nucleotide polymorphism; F, forward; R, reverse.

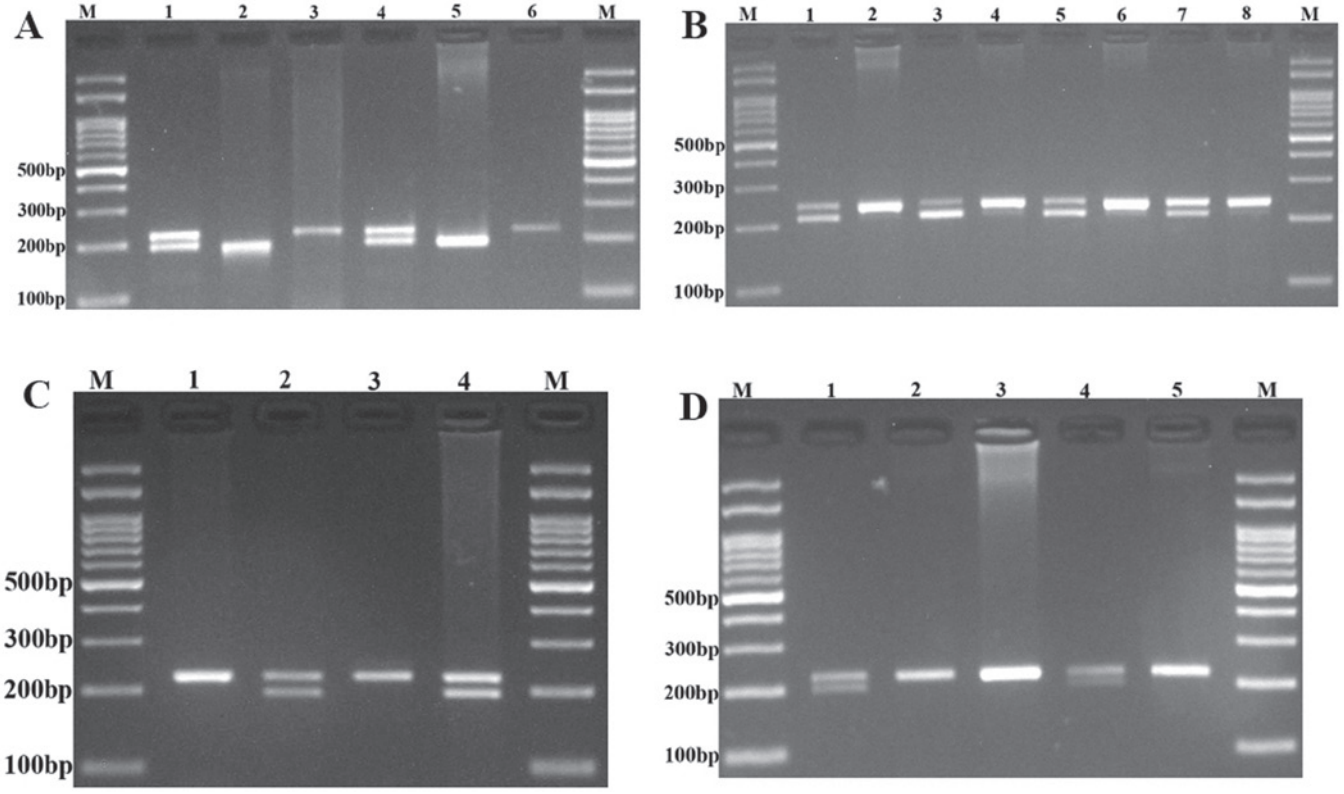

Figure 1. Electrophoresis pattern of the mismatch polymerase chain reaction-restriction fragment length polymorphism method for the detection of *PRNCR1* polymorphisms (A) rs13252298 A>G and (B) rs1456315 G>A, (C) rs7841060 T>G and (D) rs7007694 T>C. (A) For rs13252298 A>G, M: DNA marker; lanes 1 and 4: AG; lanes 2 and 5: AA; lanes 3 and 6: GG. (B) For rs1456315 G>A, M: DNA marker; lanes 1, 3, 5, and 7: GA; lanes 2, 4, 6, and 8: AA. (C) For rs7841060 T>G, M: DNA marker; lanes 1, and 3: TT; lanes 2, and 4: TG. (D) For rs7007694 T>C, M: DNA marker; lanes 1, and 4: TC; lanes 2, 3, and 5: TC. *PRNCR1*, prostate cancer-associated non-coding RNA 1.

date, several studies investigated the effect of *PRNCR1* polymorphisms on the risk of PCa (26,28-30). However, to the best of our knowledge, no study investigating the impact of *PRNCR1* variants on cancer risk in an Iranian population has been conducted to date. The present study aimed to evaluate the possible association between rs13252298, rs1456315, rs7841060 and rs7007694 polymorphisms of *PRNCR1* and the risk of PCa in a sample of Iranian population.

Our findings suggested that the *PRNCR1* rs13252298, rs1456315 and rs7841060 polymorphisms are significantly associated with increased risk of PCa in our population.

Table II. The genotype and allele frequencies of *PRNCR1* polymorphisms in PCa patients and controls with benign prostatic hyperplasia.

Polymorphisms	PCa, n (%)	Controls, n (%)	OR (95% CI)	P-value
rs13252298 A>G				
Codominant				
AA	33 (18.6)	25 (14.0)	1.00	-
AG	107 (60.1)	141 (78.8)	0.57 (0.32-1.04)	0.078
GG	38 (21.3)	13 (7.2)	2.21 (0.98-5.01)	0.070
Dominant				
AA	33 (18.5)	25 (14.0)	1.00	-
AG+GG	145 (81.4)	154 (86.0)	0.71 (0.40-1.26)	0.254
Recessive				
AA+AG	140 (78.7)	167 (92.8)	1.00	-
GG	38 (21.3)	13 (7.2)	3.49 (1.79-6.81)	0.0001
Allele				
A	173 (48.6)	191 (53.4)	1.00	-
G	183 (51.4)	167 (46.6)	1.21 (0.90-1.62)	0.231
rs1456315 A>G				
AA	30 (16.9)	92 (51.1)	1.00	-
AG	148 (83.1)	88 (48.9)	5.16 (3.16-8.41)	<0.0001
GG	0 (0.0)	0 (0.0)	-	-
A	208 (58.4)	272 (75.6)	1.00	-
G	148 (41.6)	88 (24.4)	2.20 (1.60-3.03)	<0.0001
rs7841060 T>G				
TT	29 (16.3)	96 (53.3)	1.00	-
TG	149 (83.7)	84 (46.7)	5.14 (3.15-8.37)	<0.0001
GG	0 (0.0)	0 (0.0)	-	-
T	207 (58.1)	276 (76.6)	1.00	-
G	149 (41.9)	84 (23.4)	2.37 (1.71-3.26)	<0.0001
rs7007694 T>C				
TT	150 (84.3)	139 (77.2)	1.00	-
TC	28 (15.7)	41 (22.8)	0.63 (0.37-1.08)	0.108
CC	0 (0.0)	0 (0.0)	-	-
T	328 (92.1)	319 (88.6)	1.00	-
C	28 (7.9)	41 (11.4)	0.66 (0.40-1.10)	0.128

PCa, prostate cancer; *PRNCR1*, prostate cancer-associated non-coding RNA 1; OR, odds ratio; CI, confidence interval.

In a meta-analysis performed by Chu *et al* (34), the rs1016343 and rs16901946 variants of *PRNCR1* were found to significantly increase the risk of cancer; however, their findings did not support a significant association of the rs13252298, rs7007694 and rs1456315 polymorphisms with cancer risk. Another meta-analysis conducted by Lv *et al* (35) also revealed that two polymorphisms (rs1016343 and rs16901946) of *PRNCR1* were associated with increased cancer risk.

LncRNAs, a new class of functional ncRNAs, are composed of >200 nucleotides and lack protein-coding ability (19). LncRNAs potentially interact with DNA, RNA, as well as protein molecules, to perform diverse regulatory functions, including chromatin remodelling (59), RNA splicing and editing (60), translational inhibition (61), mRNA destruction (62) and epigenetic regulation of gene expression (63-65). The most important function of lncRNAs is involvement in the transcriptional or post-transcriptional regulation of gene expression (66). Abnormal expression of lncRNAs may facilitate tumor cell proliferation, invasion and metastasis (67-70).

There were certain limitations to the present study, including the number of SNPs that were investigated for the *PRNCR1* gene, as well as lack of the information regarding survival outcomes and the patients' response to treatment. The reason for the deviation from HWE in our population was not clear; it may be attributed to genetic drift.

In conclusion, our findings indicated that the *PRNCR1* rs13252298, rs1456315 and rs7841060 polymorphisms may be a biomarker for PCa development in a sample of the Iranian population. However, further studies should be performed on PCa and other cancers in different ethnicities with larger

Table III. Haplotype association of *PRNCR1* polymorphisms with PCa risk.

rs1456315	rs7007694	rs7841060	rs13252298	Controls (frequency)	PCa (frequency)	OR (95% CI)	P-value
A	T	T	G	0.3828	0.3367	1.00	-
A	T	T	A	0.227	0.1987	1.29 (0.60-2.79)	0.52
G	T	G	A	0.146	0.2293	5.09 (2.45-10.59)	<0.0001
G	T	G	G	0.0303	0.1473	18.85 (4.93-72.00)	<0.0001
A	C	T	G	0.0492	0.0293	0.82 (0.16-4.17)	0.81
A	C	T	A	0.0496	0.011	0.85 (0.21-3.37)	0.81
G	T	T	A	0.053	0.0031	0.21 (0.02-1.74)	0.15
A	T	G	A	0.047	0.0062	0.61 (0.15-2.52)	0.49

PRNCR1, prostate cancer-associated non-coding RNA 1; PCa, prostate cancer; OR, odds ratio; CI, confidence interval.

Table IV. Association of *PRNCR1* polymorphisms with clinicopathological characteristics of PCa patients.

	rs13252298				rs1456315			rs7841060			rs7007694		
Characteristics	AA	AG	GG	P-value	AA	AG	P-value	TT	TG	P-value	TT	TC	P-value
Age at diagnosis (years), n				0.276			0.275			0.373			0.935
≤65	27	72	27		24	102		23	103		106	20	
>65	6	35	11		6	46		6	46		44	8	
Stage				0.770			0.107			0.144			0.361
pT1	2	3	3		3	5		3	5		8	0	
pT2a	7	17	3		6	21		6	21		23	4	
pT2b	1	7	3		0	11		0	11		10	1	
pT2c	16	48	19		13	70		14	69		65	18	
pT3a	3	9	2		0	14		0	14		12	2	
pT3b	4	23	8		8	27		6	29		32	3	
PSA at diagnosis (ng/ml), n				0.279			0.571			0.797			0.769
≤4	1	0	1		0	2		0	2		2	0	
4-10	17	49	22		13	75		14	74		73	15	
>10	15	57	15		17	70		15	72		74	13	
Gleason score, n				0.462			0.150			0.483			0.806
≤7	26	79	32		20	117		21	116		116	21	
>7	7	26	6		10	30		8	32		33	7	
Perineural invasion, n				0.576			0.838			0.680			0.836
Positive	22	67	21		18	92		17	93		92	18	
Negative	11	39	17		12	55		12	55		57	10	
Surgical margin, n				0.690			0.839			0.679			0.292
Positive	12	44	13		11	58		10	59		61	8	
Negative	21	62	25		19	89		19	89		88	20	

PRNCR1, prostate cancer-associated non-coding RNA 1; PCa, prostate cancer; PSA, prostate-specific antigen.

sample sizes to fully elucidate the association between *PRNCR1* polymorphisms and cancer risk. In addition, the impact of genetic variants on the expression profile of *PRNCR1* should be considered in future studies.

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