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Association study between rs1571801 and rs16260 with prostate adenocarcinoma predisposition in Iranian population

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Abstract

Background Prostatic adenocarcinoma is the most frequent malignancy among elderly men after lung cancer, which has the second incidence and the fourth mortality rate in the Iranian population. The primary objective of this study was to investigate how single-nucleotide polymorphisms of the CDH1 gene (rs16260) and DAB2IP (rs1571801) are associated with the risk of prostate cancer through a multi-stage approach.

Results In the first stage of the study (58 men), we compared the genotype frequency of polymorphisms rs16260 and rs1571801 in the case group to the control group to determine significant polymorphisms (P value < 0.4). No statistically significant difference was shown between the genotype frequency of rs1571801 in the case and control groups. Thus, rs1571801 polymorphism was eliminated at this stage, and only rs16260 polymorphism evaluated in the next stage. In the second stage, statistical analysis showed a significant difference between genotype frequency of rs16260 (P value = 0.037) in all participants. The effect of rs16260 on prostate cancer was not modified by age or PSA levels. Only the Gleason Score = 7 reveals a significant difference between the risk allele (A) and the allele (C) (rs16260).

Conclusions According to the results of this study, rs16260 is associated with prostate cancer predisposition and might be used as a potential biomarker in prostate cancer. It should be noted that these results need to be confirmed in a larger population.

Keywords E-cadherin, DAB2IP, Tetra-primer ARMS-PCR, Multi-stage approach

Background

Prostate cancer primarily occurs in older-aged men. This non-cutaneous neoplasm is the most common type of cancer among men after lung cancer in developing countries [1].Recent reports from GLOBOCAN in 2020 indicate that the Age-Standardized Incidence Rate (ASIR) and Age-Standardized Mortality Rate (ASMR) of prostate cancer were 21.3 and 10.0 per 100,000 populations in Iran. Thus, it has the second incidence rate and the fourth mortality rate [2]. There are numerous diagnostic strategies for clinical examination, such as the digital rectal examination (DRE), PSA measurement, and imaging in the form of transrectal ultrasound-guided

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scan (TRUS) with a minimum of 10 prostate biopsies and multiparametric magnetic resonance imaging scan (mpMRI) [3]. One of the most common diagnostic methods is prostate-specific antigen-based screening which is recommended alongside DRE. Normal level of PSA is between 0 ng/ml and 4 ng/ml but benign prostatic hyperplasia (BPH), prostatitis, ejaculation, and exercise can increase the PSA level [4, 5]. The PSA is expressed in tissues such as the small intestine, normal prostate epithelium, kidney, and salivary organs, although, there is 100-to-1000fold overexpression in Prostate Cancer patients [6]. Epithelium cells of prostatic acini and ducts play a fundamental role in the secretion of PSA which is an organ-specific enzyme [7].

SNPs are among genetic risk factors that occur with a frequency of 1%, which is associated with the susceptibility to prostatic tumorigenesis [8]. One of the most prevalent types of genetic variation for studying genetic differences is SNPs. SNPs are considered as the most useful biomarker for the diagnostic or prognostic of the disease due to their common frequency, low cost genotyping, ease of analysis, and the ability to conduct association studies using statistical and bioinformatics tools [9]. A multi-stage approach is one method for efficient genomic investigations. A smaller number of individuals can be utilized in this method to detect the genotypes of participants. A complete set of SNPs is investigated in a few individuals in the first stage (Participants were chosen from two extremes according to the normal distribution to make the maximum difference) at a liberal *P* value. SNPs selected in the first phase of investigations are examined in a larger population with a more rigorous *P* value. Ultimately, only a small number of SNP candidates from the first phase are found to be associated with the relevant feature [10].

E-cadherin, which is composed of 16 coding exons, located on chromosome 16q22.1, is a tumor suppressor gene that encodes an adhesion glycoprotein [11–15]. CDH1 plays a key role in cell polarity, tissue architecture, intercellular adhesion, cell signaling, maintenance of normal tissue morphology, and cellular differentiation [12]. The −160C/A polymorphism (rs16260) has been identified in the promoter region (the −160 location) which is linked to the transcriptional start site of E-cadherin. According to studies, the C allele compared with the A allele may increase the level of transcriptional activity between 10 and 68%. Extensive research has proved the mutant allele's affinity for the transcriptional factor is much lower than the wild-type C allele [11]. The results showed that the mutant allele raises the chance of prostate cancer development [16].

DAB2IP gene which is located on chromosome 9q33.1-q33.3, involves in a variety of biological processes such as autophagy, cancer stem cell, epithelial-to-mesenchymal transition (EMT), proliferation and apoptosis [17]. Furthermore, DAB2IP is also implicated in the regulation of Ras-MAPK, ASK-JNK, PI3K-Akt, and nuclear factor-kB (NF-kB) pathways [18]. Decreased DAB2IP expression in prostate epithelial cells is associated with prostate cancer [19]. Rs1571801 has been identified in intron1; 14 kb upstream of exon 2 in the DAB2IP gene is substantially related to an elevated risk of aggressive prostate adenocarcinoma in African American and European populations. Furthermore, numerous researches have revealed the biological role of the DAB2IP gene in aggressive prostate cancer [20]. Epigenetic regulation leads to downregulation of DAB2IP in prostate cancer, which is inversely related to tumor grade and prostate cancer progression [18]. Based on epigenetic or genetic instability observation, the rs1571801 polymorphism may make the DAB2IP gene more susceptible to genetic change or epigenetic regulation in prostate cancer [20].

The current study aimed to evaluate the association between these polymorphisms (rs16260, rs1571801) and prostate cancer susceptibility in the Iranian population using multi-stage approach. The summary of present study has been shown in Fig. 1.

Methods

Study population

For this study, we recruited 127 men with prostate cancer as case and 99 men with BPH as control from the same geographical region. Both groups were referred to Tehran's Hasheminejad Hospital. All the participants in this study have signed a consent form. Each of these two groups was diagnosed with the aid of a specialist doctor and based on PSA levels, digital rectal tests, and prostate biopsies. Patients' clinical information such as age, PSA level, prostate volume, and disease stage was recorded in the checklist. The study was also reviewed by Kharazmi University's ethics committee, and based on the given document, it was approved by the ethics committee with the ID IR.KHU.REC.1400.031. This study was performed in the Laboratory of Molecular Biology and Genetics at Tehran University of Medical Sciences.

Extraction of genomic DNA

EDTA-anticoagulated peripheral blood (3 ml) was collected and stored at −20 °C. DNA was extracted from blood lymphocytes according to the instruction of the FAVORGENE-Taiwan extraction kit. The quality and quantity of DNA samples were measured after extraction. To determine the quality and quantity of extracted DNA, electrophoresis with 1.5% agarose gel and NanoDrop device were used, respectively. The ratio of 260 to 280 was 1.8. SNP genotyping was done using the

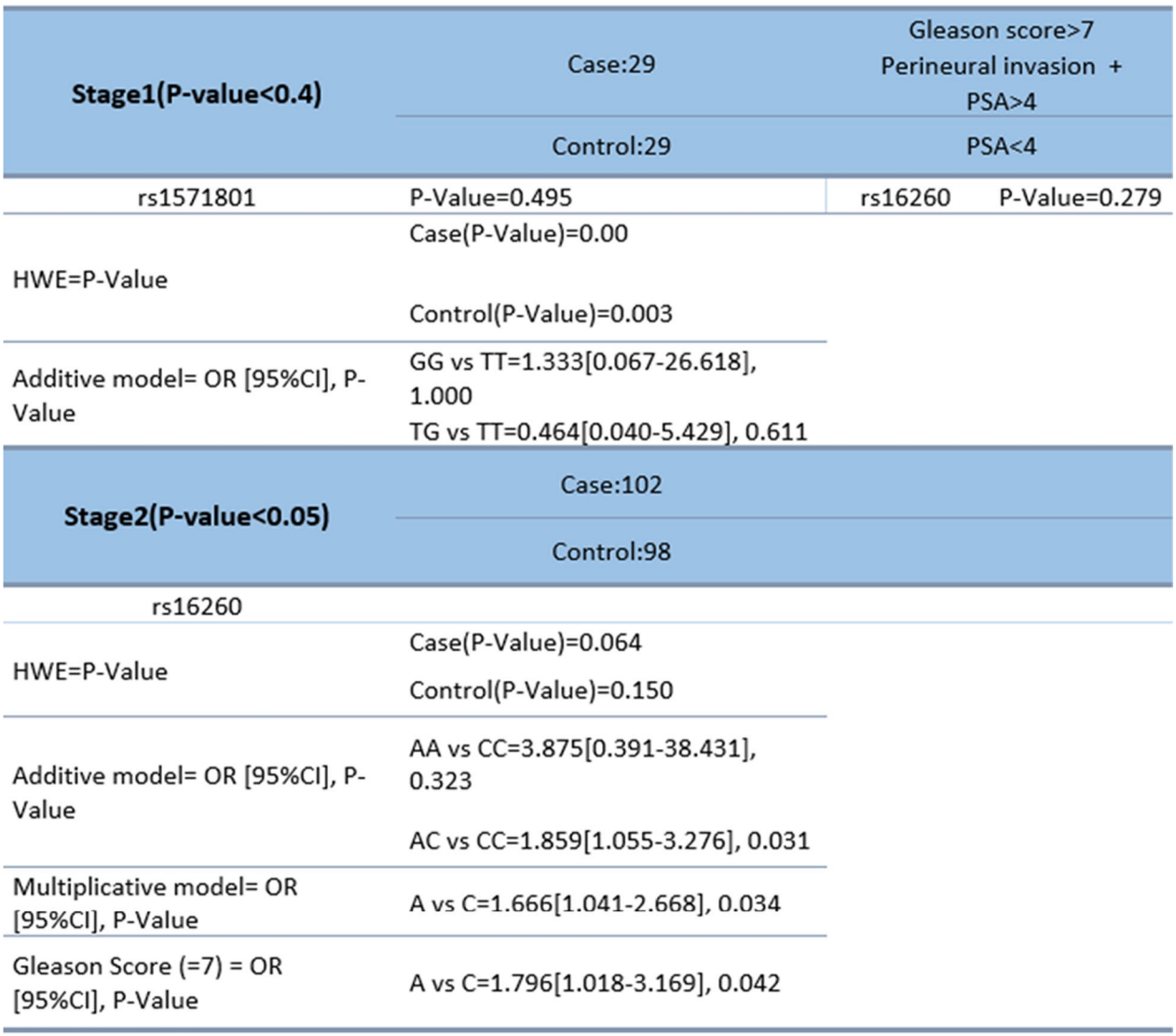

Fig. 1 Flow diagram for the present study

Tetra-primer ARMS-PCR technique. Primer1 and the Primer-BLAST-NCBI database were used to design the primers and confirm their correctness, respectively. In this approach, two non-specific external primers and two internal specific primers were used in a reaction to establish the genotype. Allele-specific inner primers differ in the nucleotide sequence at the 3'-end (bold and underlined letters). One is used to identify wild allele, and the other is used to identify mutant allele. Positive control consists of two non-specific external primers (Table 1).

Statistical analysis

Genotype frequency, allele frequency, Hardy–Weinberg equilibrium (HWE), multiplicative, and additive genetic models were evaluated using Chi-squared and Fisher's exact tests with P value < 0.4 in the first stage and P value < 0.05 in the second stage. Odds Ratio (OR) with 95% confidence interval (95%CI) was determined by logistic regression and chi-square test to study the SNPs associated with prostate cancer and Gleason score in the multiplicative and additive models and effect modification. SPSS v.25.0 was used for statistical analysis.

Results

Stage I

Patients characteristics

At this stage, the participants are divided into two groups: the control group, which includes 29 patients

Table 1 Primer sequences and their products

	rs16260	rs157180
Forward inner	CCAAGCAACTCCAGGCTAGAGGGTTA**C**	ACAGAAAGGTAAAGAAAGTTTCAAAGT**G**
Reverse inner	CCACCCAGCCTCGCATAGACGTG**T**	GTGAGTACATACTGGCTTTTCCATAC**A**
Forward outer	TGTCCGCCCCGACTTGTCTCTCTAC	AGTCTGAGTCAACTGTTCTAGAGGCTAA
Reverse outer	GGTGCTTTGCAGTTCCGACGCCACT	TTCTAATTATAGCACTCCAGAGGGAAC
Primer products	A (mutant) = 397 bp C (wild) = 212 bp A/C = 397/212 bp C + = 559 bp	G (mutant) = 449 bp T (wild) = 181 bp G/T = 449/181 bp C + = 576 bp

with BPH who are the most healthy people, and the case group, which includes 29 prostate adenocarcinoma who are the most unhealthy people. The unhealthiest participants are selected based on Gleason score > 7, positive results of perineural invasion, while the control group (the healthiest) is selected based on PSA < 4. The case group's age range was 55–86 years old, with a mean age of 65.78 ± 9.2, whereas the control group's age range was 47–80 years old, with a mean age of 68.48 ± 9.1.

Statistical analysis

Both polymorphisms with a *P* value (< 0.4) were analyzed in the first stage. The genotype frequencies of polymorphisms between prostate cancer and the control group are represented in Table 2.

No statistically significant difference was shown between the genotype distribution of rs1571801 in the case and control groups. As estimated by the Chi-square test, case group ($P = 0.003$) and control group ($P = 0.00$) for rs1571801 were not in HWE. Thus, the additive genetic model was used to evaluate the association between rs1571801 and prostate cancer. rs1571801 polymorphism was not associated with prostate cancer in the additive genetic model via Fisher's exact test and logistic regression so it was eliminated at this stage (Table 2). Only rs16260 polymorphism is evaluated in the next stage.

Stage II

Patients characteristics

Only the rs16260 polymorphism is evaluated in the second stage. All study participants, including 102 prostate adenocarcinoma and 98 BPH, were evaluated at this stage. The case group's age range was 48–86 years old, with a mean age of 66.26 ± 8.3, the control group's age range was 47–81 years old, with a mean age of 65.32 ± 7.7. The clinical and demographic information of the participants was mentioned in Table 3.

Statistical analysis

At this stage, the statistical analysis was performed for all participants. Significant difference was shown between the genotype frequency of rs16260 in the case and control groups ($P = 0.037$). Observed and expected frequencies in both case and control groups were examined using Pearson's chi-squared test to evaluate HWE. Case (*P*

Table 2 Genotype frequency of polymorphisms in both case and control groups (stage I)

dbSNP	Case (*n* = 29) (%)	Control (*n* = 29) (%)	*P* Value	Additive model			
rs1571801							
GG	1 (3.4)	0 (0.0)			GG vs TT	TG vs TT	TT
TG	26 (89.7)	28 (96.6)	0.495	OR	1.333	0.464	1 (Reference)
GG	2 (6.9)	1 (3.4)		95%CI	0.067–26.618	0.040–5.429	
				P Value	1.000	0.611	
rs16260							
AA	0(0.0)	0 (0.0)					
AC	13(44.8)	9 (31.0)	0.279				
CC	16(55.2)	20(69.0)					

Table 3 The clinical and demographic information of the participants

	Prostate cancer *n* (%)	BPH *n* (%)
Age		
< 65	49 (53.3)	43 (46.7)
65–74	36 (48.6)	38 (51.4)
≥ 75	17 (50.0)	17 (50.0)
PSA (ng/ml)		
> 10	49 (65.3)	26 (34.7)
4.1–10	43 (43.9)	55 (56.1)
4	10 (37.0)	17 (63.0)
Gleason score		
≥ 8	33 (100.0)	–
= 7	48 (100.0)	–
< 7	21 (100.0)	–
Perineural invasion		
+	71 (100.0)	–
–	31 (100.0)	–

value = 0.064) and control (*P* value = 0.150) groups were in HWE. Therefore, multiplicative and additive genetic models were used to study the association of rs16260 with prostate cancer. Our investigation revealed an association of this polymorphism with prostate adenocarcinoma in the multiplicative genetic model. Furthermore, AC (rs16260) showed an association with prostate cancer in the additive genetic model using CC as a reference genotype, whereas AA (rs16260) did not show an association in this genetic model using CC as a reference genotype (Table 4).

This study investigated the genotype and allele frequency of rs16260, as well as the OR [95%CI] (logistic regression), and *P* value (Fisher's exact test) of the risk allele in comparison with the wild allele in three categories of Gleason score. The final results show that there is only a significant difference between the frequency of risk allele (A) and allele (C) in Gleason Score = 7. Besides, no statistically significant difference was revealed between the genotype distribution of rs16260 with the perineural invasion (Table 5).

Effect modification

PSA and age are considered to effect modifications at three levels, there were no differences between the rs16260 polymorphism and prostate cancer at any level (df = 2). Thus, PSA and age were not regarded as effect

Table 4 Genotype frequency of polymorphisms, multiplicative and additive genetic models

dbSNP		Case *n* (%)	Control *n* (%)	*P* Value	Multiplicative model		Additive model		
rs16260	Genotype					A vs C	AA vs CC	AC vs CC	CC
	AA	2 (2.0)	0 (0.0)	0.037	OR	1.666	3.875	1.859	1 (Reference)
	AC	53 (52.0)	37 (37.8)		95%CI	1.041–2.668	0.391–38.431	1.055–3.276	
	CC	47 (46.1)	61 (62.2)		*P* Value	0.034	0.323	0.031	

Table 5 Genotype and allelic frequency, the OR [95%CI], and *P* value of risk allele compared to wild allele at three categories of Gleason score, PSA and Perineural invasion

rs16260			AA *n* (%)	AC *n* (%)	CC *n* (%)	A	C	OR (95%CI)	*P* Value
Control			0 (0.0)	37 (37.8)	61 (62.2)	37 (18.9)	159 (81.1)	1 (reference)	_
Gleason score	≥ 8		0 (0.0)	16 (48.5)	17 (51.5)	16 (24.2)	50 (75.8)	1.375 (0.706–2.679)	0.377
	= 7		1 (2.1)	27 (56.3)	20 (41.7)	28 (29.5)	67 (70.5)	1.796(1.018–3.169)	0.042
	7 >		1 (4.8)	10 (47.6)	10 (47.6)	11 (26.8)	30 (73.2)	1.576 (0.724–3.430)	0.249
PSA	≤ 4	Case	0 (0.0%)	7 (70.0)	3 (30.0)	7 (35.0)	13 (65.0)	2.513 (0.703–8.979	0.194
		Control	0 (0.0%)	6 (35.3)	11 (64.7)	6 (17.6)	28 (82.4)		
	4.1–10	Case	0 (0.0%)	20 (46.5)	23 (53.5)	20 (23.3)	66 (76.7)	1.212 (0.611–2.403)	0.581
		Control	0 (0.0%)	22 (40.0)	33 (60.0)	22 (20.0)	88 (80.0)		
	> 10	Case	2 (4.1%)	26 (53.1)	21 (42.9)	30 (30.6)	68 (69.4)	2.108 (0.913–4.868)	0.077
		Control	0 (0.0%)	9 (34.6)	17 (65.4)	9 (17.3)	43 (82.7)		
Perineural invasion	+		0 (0.0)	37 (52.1)	34 (47.9)				0.093
	–		2 (6.5)	16 (51.6)	13 (41.9)				

modifications (Table 6). As a result, the exposure impact (rs16260) is homogeneous across all categories of age and serum PSA level.

Discussion

The most commonly non-cutaneous cancer in men is prostate cancer. After lung cancer in developing countries, this diagnosed non-cutaneous neoplasm is the most prevalent type among men [1]. Recent reports from GLOBOCAN in 2020 indicate that the ASIR and ASMR of prostate cancer were 21.3 and 10.0 per 100,000 populations in Iran [2]. E-cadherin is a tumor suppressor that encodes an adhesion glycoprotein [12, 15]. There is a link between rs16260 in E-cadherin's promoter region (the −160 position) and the transcriptional start site [11, 13, 15]. Furthermore, multiple investigations have shown that the DAB2IP gene has a biological role in aggressive prostate cancer [20]. Decreased DAB2IP expression in prostate epithelial cells is associated with prostate cancer [19]. In prostate cancer, epigenetic regulation leads to DAB2IP downregulation, which is inversely associated with tumor grade and progression [18]. Rs1571801 has been found in intron 1, 14 kb upstream of exon 2 in the DAB2IP gene is linked to an increased risk of aggressive adenocarcinoma of the prostate in both African American and European populations [20].

In the first stage (59 person) rs1571801 was eliminated since there was no evidence for an association between this polymorphism and prostate cancer in multiplicative and additive genetic models. At this stage, there was a statistically significant difference in the genotype distribution of rs16260 ($P=0.279$) in the case and control groups. Consequently, this polymorphism was selected as a candidate SNP for investigations in the second phase. In the second stage, all participants were evaluated to determine the association between rs16260 polymorphism with prostate cancer in both multiplicative and additive genetic models. There is an association between rs16260 in multiplicative genetic model (A vs C) and the additive genetic model with prostate cancer. In Gleason Score = 7, there is a significant difference in the frequency of risk allele (A) and allele (C).

In 2004, the CDH1 (−160C/A) SNP was shown to be associated with prostate cancer in Swedish men. They identified an association between hereditary prostate cancer and rs16260. As compared to CC genotypes, CA and AA genotypes had a 70% and 150% increased risk of hereditary prostate cancer, respectively. Furthermore, they also discovered evidence that the risk allele did not give an increased risk of sporadic prostate cancer [21].

In 2002, Verhage et al. reported that allele A was associated with a 3.6-fold increased risk of PCa than allele C. Compared to CC genotype, CA genotype of the CDH1 (-160C/A) SNP exhibited an approximately fourfold increased risk of PCa. On the other side, AA genotype was associated with a 1.7-fold increased risk of prostate cancer, which was not statistically significant [22].

Tsukino et al. reported that no statistically significant difference was shown between rs16260 (AA vs CC) (*P* Value = 0.34) (OR [95%CI] = 1.66 [0.58–4.78]), (CA vs CC) (OR [95%CI] = 1.29 [0.86–1.93]) and prostate cancer, and there is not an association between rs16260 (C vs A) (*P* Value = 0.17) and prostate cancer [23].

Bo yang et al. reported that The −160C/A polymorphism has been associated with increased risk of prostate cancer (OR [95%CI] = 1.84 [1.31–2.60] *P* Value = 0.001 for AA vs CC; OR [95%CI] = 1.18 [1.01–1.38] *P* Value = 0.04, for CA vs CC; OR [95%CI] = 1.25 [1.07–1.45] *P* Value = 0.005, in the dominant model AA + CA vs CC; OR [95%CI] = 1.77 [1.27–2.48] *P* Value = 0.001, and in the recessive model AA vs CC + CA; OR [95% CI] = 1.23 [1.04–1.46] *P* Value = 0.02 for A vs C) [24].

Pookot et al. investigated the rs16260 in two groups of black men and white men to observe any racial differences and association with prostate cancer. They reported that allele A was associated with a higher relative risk of prostate cancer than allele C in white men (OR [95%CI] = 1.99 [1.29–3.08]). There was no significant association between the allelic frequency of rs16260 and prostate cancer risk in black men (OR [95%CI] = 0.42 [0.22–0.81]). In white men, genotypes AA and CC in comparison with the CC genotype were significantly associated with an increased risk of prostate cancer (OR [95% CI] = 3.04 [1.26–7.32]). In comparison with the CC genotype, the CA and AA genotypes were not associated with an increased risk of prostate cancer in black men (OR [95%CI] = 0.28 [0.12–0.66] for CA vs CC; OR [95%CI] = 0.40 [0.08–2.00] for AA vs CC)) [25].

In 2007, Goto et al. were shown the association of rs16260 and prostate cancer in the Japanese Population.

Table 6 Effect modification

dbSNP rs16260	OR	X^2
Age		
< 65	1.84	
65–74	1.35	0.41
≤ 75	1.94	
Total	1.6	
PSA		
≤ 4	2.51	
4.1–10	1.21	1.50
> 10	2.1	
Total	1.6	

According to their studies, A allele carriers were at higher relative risk for prostate cancer than C only carriers (OR [95%CI] = 1.88 [1.25–2.84] *P* Value = 0.0023), and in comparison with the CC genotype, the CA and AA genotypes were associated with significantly increased risk of prostate cancer (OR [95%CI] = 9.033 [1.50–172.36] *P* Value = 0.0434 for AA vs CC; OR [95%CI] = 4.44 [2.82–7.11] *P* Value < 0.0001 for CA vs CC) [26].

According to research conducted in Bangladesh on CDH1 genetic polymorphisms, there is an association between rs16260 (CA vs CC) (OR [95%CI] = 2.1 [1.1657–3.7830] *P* Value = 0.0135) and prostate cancer and an association was reported between rs16260 (CA + AA vs CC) (OR [95%CI] = 2.0811 [1.1820–3.6641] *P* Value = 0.0111) and prostate cancer. No statistically significant difference was shown between rs16260 (AA vs CC) (OR [95%CI] = 1.96 [0.5846–6.5711] *P* Value = 0.2756) and prostate cancer. In addition, results suggest that there is an association between rs16260 (A vs C) (OR [95%CI] = 1.6901 [1.0740–2.6597] *P* Value = 0.0233) and prostate cancer [27]. The results of the rs16260 in the present study are consistent with the results of other studies.

Duggan et al. investigated the risk of aggressive prostate cancer in four different groups of people. In comparison with the CC genotype at rs1571801, the CA and AA genotypes exhibited a statistically significant increased risk of aggressive prostate cancer in each of the research groups (OR [95%CI] = 1.50 [1.17–1.93] *P* Value = 0.0015 in CAPS; OR [95%CI] = 1.29 [1.06–1.57] *P* Value = 0.0096 in CGEMS; OR [95%CI] = 1.32 [1.07–1.63] *P* Value = 0.083 in JHH-EA; OR [95%CI] = 1.50 [1.02–2.21] *P* Value = 0.039 in JHH-AA). In CGEMS samples, they found that the risk allele for rs1571801 was more common in non-aggressive instances than in aggressive ones [19].

Lange et al. found evidence of an association between rs1571801 and the initiation of prostate cancer, but no statistically significant differences between this polymorphism and aggressive adenocarcinoma of the prostate (28). In the present study, rs1571801 does not have an association with prostate cancer that can be because of genetic heterogeneity.

Conclusions

Based on the evidence in this study, we reported that rs16260 is significantly associated with the prostate cancer predisposition, but no statistically significant differences between rs1571801 and adenocarcinoma of the prostate. No association was found between rs16260 and clinical features, although the results indicate that the frequency of the risk allele (A) and allele (C) is significantly different in Gleason Score = 7 (medium-grade-prostate cancer). rs16260 might be used as a potential biomarker in prostate cancer. However, further study in larger populations and in other ethnic groups is required to confirm this study.

Abbreviations

ASIR	Age-Standardized Incidence Rate
ASMR	Age-Standardized Mortality Rate
SCNAs	Somatic copy number alterations
SNPs	Single nucleotide polymorphisms
BPH	Benign prostatic hyperplasia
DRE	Digital rectal examination
TRUS	Transrectal ultrasound-guided scan
mpMRI	Multiparametric magnetic resonance imaging scan
EMT	Epithelial-to-mesenchymal transition
NF-Kb	Nuclear factor-kB

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Author contributions

RA made contribution to conception, DNA extraction, SNP genotyping, scoring, analysis and interpretation of data. ASA and KG made contribution to conception, scoring, analysis and interpretation of data. BB made contribution to conception, analysis and interpretation of data. RR and NB contributed to sampling and medical diagnosis. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All participants were subjected to written consent. The study was approved by Kharazmi University's ethics committee (ID IR.KHU.REC.1400.03).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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