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RESEARCH PAPER

Association between *LAPTM4B* gene polymorphism and prostate cancer susceptibility in an Iranian population

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ABSTRACT

Lysosome associated protein transmembrane 4 β (LAPTM4B) is an oncogene associated with many human cancers. In the present study we aimed to examine the possible association between *LAPTM4B* polymorphism and risk of prostate cancer (PCa) in an Iranian population. This case control study was performed on 168 patients with PCa and 176 controls with benign prostatic hyperplasia (BPH). Genomic DNA was extracted from whole blood and *LAPTM4B* genotypes were identified by polymerase chain reaction. The distributions of *LAPTM4B* genotypes were significantly different between PCa patients (60.7% for *1/1, 32.8% for *1/2, and 6.5% for *2/2) and controls (44.9% for *1/1, 49.4% for *1/2, and 5.7% for *2/2). Both the *1/2 and *1/2+*2/2 genotypes significantly decreased the risk of PCa compared with the *1/1 genotype (OR = 49, 95% CI = 0.31–0.77, p = 0.002 and OR = 0.53, 95% CI = 0.34–0.81, p = 0.004, respectively). The minor allele (LAPTM4B*2) was associated with a decreased risk of PCa compared with the *LAPTM4B**1 allele (OR = 0.68, 95% CI = 0.48–0.96, p = 0.031). Moreover, *LAPTM4B* polymorphism was not associated with clinicopathological characteristics of PCa patients. The results of this study showed that *LAPTM4B**2 was associated with a decreased risk of PCa but the clinicopathological characteristics of PCa were not linked to *LAPTM4B* polymorphism. Further studies with larger sample sizes and different ethnicities are needed to confirm our findings.

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Introduction

Prostate cancer (PCa) is the most common cancer and the second most common cause of cancer-related deaths in men.[1] PCa occurs mostly in older men. The incidence of PCa in Iran varies from 3.2 to 16.0 per 100,000 according to geographical setting[2,3] and is comparable to that in the Asia-Pacific region (9.9 per 100,000), but considerably lower than the rate in Western countries and the worldwide rate (32.8 per 100,000).[4] It has been proposed that genetic factors play an important role in the development of prostate cancer.[5-7]

Lysosome-associated protein transmembrane-4 β (LAPTM4B) is an oncoprotein that has been efficiently cloned in human hepatocellular carcinoma (HCC).[8] The *LAPTM4B* gene maps to chromosome 8q22 and contains 7 exons[9,10] that encode 2 protein isoforms, LAPTM4B-35 and LAPTM4B-24. LAPTM4B is a tetratransmembrane protein that is localized mainly to the late endosome and lysosome.[11] It has been shown that inappropriate expression of LAPTM4B promotes normal cell transformation and tumorigenesis[12] (Li et al., 2011a; Yang et al., 2010). LAPTM4B is involved in cancer cell proliferation by upregulating the PI3K/ATK signaling pathway.[13] Studies have shown that LAPTM4B-35 is overexpressed in several human cancers.[14-23] *LAPTM4B* exists as 2 allelic genes, termed *LAPTM4B**1 and *LAPTM4B**2 (GenBank accession No. AY219176 and AY219177, respectively). These alleles have similar sequences except for a 19-bp fragment in the 5′ untranslated region (UTR) of the first exon: allele *1 has a single copy of a 19-bp sequence in the 5UTR (TGCTTGGAGCTCCAGCAGC), but this sequence is duplicated as tandem repeats in allele *2 (TGCTTGGAGCTCCAGCAGCTGCTTGGAGCTCCAGCAGC).

Previous studies have investigated the possible association between *LAPTM4B* polymorphism and susceptibility to numerous cancers, but the findings were inconsistent.[14,24-31] To the best of our knowledge, there is no report on the impact of *LAPTM4B* genotype on PCa. Therefore, in the present study we aimed to evaluate the possible association between *LAPTM4B* gene polymorphism and the risk of PCa in a sample of the Iranian population.

Materials and methods

Patients

This case-control study was performed on 168 patients with histopathologically confirmed PCa (aged 61.37 ± 6.61 years) and 176 men with benign prostatic hyperplasia (BPH) (aged 62.39 ± 7.64 years). There was no significant different in age between the groups (p = 0.188). The cases and controls were

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selected from individuals referred to the Department of Urology, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The enrollment process and study design are described elsewhere.[5] Ethical approval for recruitment was obtained from the local Ethics Committee of Zahedan University of Medical Sciences, and written informed consent was obtained from all participants. Genomic DNA was extracted from blood samples using the salting out method as described previously.[32] The clinicopathological characterization of the patient group is summarized in Table 1.

Genotyping of LAPTM4B

Genotyping of *LAPTM4B* polymorphism was performed by a polymerase chain reaction (PCR) method as described previously.[30] Briefly, the primer set used was 5′-GAGTTACACGAACGGCCAGA-3′ and 5′-ATGTGACCCGAGTCCGTGA-3′. Each 0.20-ml PCR reaction tube contained 1 μl of genomic DNA (~100 ng/ml), 1 μl of each primer (10 μM), 10 μl of 2× Prime Taq Premix (Genet Bio, Korea), and 7 μl ddH_2O. PCR cycling conditions were initial denaturation at 95°C for 5 min, 30 cycles of denaturation at 95°C for 30 s, annealing at 62°C for 30 s, extension at 72°C for 30 s, and final extension at 72°C for 5 min. PCR products were verified by electrophoresis on a 2.5% agarose gel containing ethidium bromide and observed under UV light. The *LAPTM4B**1 allele produces a 162-bp product whereas the *LAPTM4B**2 allele produces a 181-bp product.

Statistical analysis

Statistical analysis of the data was performed using statistical package SPSS 22 software (SPSS Inc., Chicago, IL, USA). Data were analyzed by independent sample t-test and $\chi 2$ test. The association between genotype and PCa was calculated by computing the odds ratio (OR) and 95% confidence intervals (95% CI) from logistic regression analyses. A p-value less than 0.05 was considered statistically significant.

Table 1. Clinicopathological characteristics of prostate cancer patients.

Characteristic	
Age (years), mean (range)	61.37 (42–79)
PSA at diagnosis mean ± SD (ng/ml)	14.1 ± 13.3
Gleason score	
≤6	57 (34.7)
7	69 (42.1)
>7	38 (23.2)
Stage	
pT1	8 (4.9)
pT2a	27 (16.5)
pT2b	12 (7.3)
pT2c	72 (43.9)
pT3a	13 (7.9)
pT3b	32 (19.5)
Perineural invasion	105 (64.0)
Impotency	25 (15.2)
Loss of libido	25 (15.2)
Post-void residual, mean ± SD (ml)	26.7 ± 25.0
Addiction	7 (4.3)
Hypertension	20 (12.2)
Diabetes mellitus	20 (12.2)
Any history of smoking	25 (15.2)
Alcohol drinking	6 (1.8)

Table 2. Genotype and allelic frequencies of *LAPTM4B* gene polymorphism among prostate cancer patients and controls.

LAPTM4B genotype	Cases n (%)	Controls n (%)	OR (95%CI)	p-value
Co-dominant				
LAPTM4B *1/1*	102 (60.7)	79 (44.9)	1.00	—
LAPTM4B *1/2*	55 (32.8)	87 (49.4)	0.49 (0.31–0.77)	0.002
LAPTM4B *2/2*	11 (6.5)	10 (5.7)	0.85 (0.34–2.11)	0.817
Dominant				
LAPTM4B *1/1*	102 (60.7)	79 (44.9)	1.00	—
LAPTM4B *1/2+*2/2*	66 (39.3)	97 (55.1)	0.53 (0.34–0.81)	0.004
Recessive				
LAPTM4B *1/1+*1/2*	157 (93.5)	166 (94.3)	1.0	—
LAPTM4B *2/2*	11 (6.5)	10 (5.7)	1.16 (0.48–2.82)	0.823
Allele				
LAPTM4B *1*	259 (77.1)	245 (69.6)	1.00	—
LAPTM4B *2*	77 (22.9)	107 (30.4)	0.68 (0.48–0.96)	0.031

Results

The genotype and allele frequencies of *LAPTM4B* gene polymorphism are shown in Table 2. The frequency distributions of *LAPTM4B* genotypes were significantly different between PCa patients (60.7% for *1/1, 32.8% for *1/2, and 6.5% for *2/2) and controls (44.9% for *1/1, 49.4% for *1/2, and 5.7% for *2/2) ($X^2 = 10.0$, $p = 0.008$). The LAPTM4B genotype was associated with decreased risk of PCa in co-dominant (OR = 49, 95% CI = 0.31–0.77, p = 0.002, *1/2 *versus* *1/1) and dominant (OR = 0.53, 95% CI = 0.34–0.81, p = 0.004, *1/2+*2/2 *versus* *1/1) inheritance models tested.

The minor allele frequency (MAF) in cases and controls was 0.229 and 0.304, respectively (Table 2). The *LAPTM4B**2 allele significantly decreased the risk of PCa compared to *LAPTM4B**1* (OR = 0.68, 95% CI = 0.48–0.96, p = 0.031).

As presented in Table 3, the *LAPTM4B* genotype was not associated with clinicopathological characteristics of PCa patients such as age, stage, prostate-specific antigen (PSA), grade (Gleason score), perineural invasion, and surgical margin.

Discussion

In the current study we examined the impact of *LAPTM4B* polymorphism on risk of PCa in a sample of the Iranian population. Our findings revealed that *LAPTM4B**2 significantly decreased the risk of PCa in our study population. To the best of our knowledge this is the first report describing *LAPTM4B* polymorphism and risk/protection of PCa.

Previous studies indicated that *LAPTM4B* polymorphism was associated with susceptibility to liver cancer,[26,33] gall bladder carcinoma[26] cervical carcinoma,[34] gastric cancer,[27] breast cancer,[24,25] colon cancer,[28] endometrial carcinoma,[20] and ovarian cancer.[14] Other studies showed no statistical differences between alleles for nasopharyngeal carcinoma,[29] lung cancer,[31] breast cancer,[30] rectal or esophageal cancers,[28] melanoma,[35] and pancreatic cancer.[36] A meta-analysis conducted by Xia et al.[37] showed that *LAPTM4B* polymorphism is associated with an increased risk of cancer in the Chinese Han population.

Table 3. Association of *LAPTM4B* polymorphism with clinicopathologic parameters in prostate cancer patients.

	LAPTM4B			
Factors	*1/1	*1/2	*2/2	p-value
Age at diagnosis (y), n				0.315
≤ 60	55	24	4	
> 60	47	31	7	
Stage				0.642
pT1	7	1	0	
pT2a	16	10	1	
pT2b	4	7	1	
pT2c	42	25	5	
pT3a	9	3	1	
pT3b	21	9	2	
PSA at diagnosis (ng/ml), n				0.826
≤ 4	1	1	0	
4–10	49	25	6	
>10	49	28	3	
Gleason score, n				0.843
≤ 6	35	18	4	
7	40	26	3	
>7	24	11	3	
Perineural invasion, n				0.886
Positive	59	39	7	
Negative	40	16	3	
Surgical margin, n				0.813
Positive	39	20	3	
Negative	60	35	7	

The exact reason for the inconsistent findings among different studies is unknown. Ethnic, genetic, and/or environmental factors may interact in various ways to either increase or decrease the risk of cancer in distinct geographical areas.

Zhang et al.[23] showed that LAPTM4B-35 is overexpressed in PCa and that high LAPTM4B-35 expression correlated with PCa progression and poor prognosis. They concluded that overexpression of LAPTM4B-35 may serve as a new molecular marker to predict the prognosis of PCa patients.

It has been shown that miR-188-5p, which acts as a tumor suppressor, inhibits PCa cell proliferation, invasion, and migration through downregulation of *LAPTM4B* by directly binding to its 3′-UTR[38] and subsequent inhibition of the PI3K/AKT signaling pathway. Decreased expression of miR-188-5p is associated with poor prognosis in patients with PCa, which strongly suggests a potential role of miR-188-5p in suppression of PCa.[38]

In summary, our findings are the first to show an association between *LAPTM4B* polymorphism and risk of PCa in a sample of the Iranian population. Further studies with larger sample sizes and different ethnicities are required to validate our findings.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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