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Original Article

Association between Pri-miR-34b/c rs4938723 polymorphism and bladder cancer risk

Mohammad Hashemi[1,2,✉], Vahed Hasanpour[3], Hiva Danesh[2], Fatemeh Bizhani[2], Behzad Narouie[4]

[1] *Cellular and Molecular Research Center,* [2]*Department of Clinical Biochemistry, School of Medicine,* [3]*Student Research Committee, Zahedan University of Medical Sciences, Zahedan, Sistan and Baluchistan 98167-43181, Iran;*
[4] *Urology and Nephrology Research Center, Department of Urology, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Tehran 198396-3113, Iran.*

Abstract

Several studies examined the impact of miR-34b/c rs4938723 polymorphism and cancer risk, but the findings are inconsistent. However, no study has been conducted to inspect the impact of miR-34b/c polymorphism on bladder cancer. This study aimed to assess possible association between rs4938723 polymorphism and bladder cancer risk. This case-control study was done on 136 pathologically proven bladder cancer patients and 144 controls. Genotyping of Pri-miR-34b/c rs4938723 polymorphism was achieved by using the polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method. Our findings did not show any statistically significant differences in genotype and allele frequencies between bladder cancer and controls. Larger sample sizes with diverse ethnicities are required to validate our findings.

Keywords: Pri-miR-34 b/c, bladder cancer, polymorphism, microRNA

Introduction

Bladder cancer is the ninth most common malignancy in the world, and the fourth most common cancer in the United States[1]. Men are more than four times more likely to get bladder cancer than women. Bladder cancer has a multifactorial etiology. It has been proposed that the development of bladder cancer is a result of environmental factors such as smoking, occupational exposure to carcinogens, obesity, physical inactivity[2–4], genetic variants and the interaction of genes with the external factors[5–8].

MicroRNAs (miRNAs) are a class of small single-stranded noncoding RNA molecules that play key roles in a variety of cellular processes by targeting mRNAs for cleavage or translational repression[9–10]. The data provides strong evidence that dysregulation of miRNAs expression affects the tumorigenesis by acting as oncogenes or tumor suppressors[11–15]. Single-nucleotide polymorphisms (SNPs) in miRNAs can affect cancer susceptibility by disturbing miRNAs biosynthesis and expression, altering mature miRNAs, or by combining with target genes[16–19].

The miR-34 family members comprises miR-34a,

✉Corresponding author: Mohammad Hashemi, PhD, Professor of Clinical Biochemistry, Department of Clinical Biochemistry, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Sistan and Baluchistan 98167-43181, Iran. Tel/Fax: +98-5433295791/+98-5433295796, E-mail: mhd.hashemi@gmail.com/ hashemim@zaums.ac.ir.

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miR-34b, and miR-34c that are encoded by two different primary miRNAs. The miR-34a is encoded by its own transcript, while the miR-34b and miR-34c are encoded by a shared primary transcript (pri-miR-34b/c)[20]. A potentially functional rs4938723 variant (T to C substitution), located in the promoter region of pri-miR-34b/c, may affect miR-34b/c expression via genetic and epigenetic mechanisms and in turn influence the individual susceptibility to cancer[21–23]. Though the association between miR-34b/c rs4938723 polymorphism and the risk of developing several cancers were reported in various case-control studies[20,23–34], but to the best of our knowledge, there is no report concerning the impact of miR-34b/c rs4938723 variant on the risk of bladder cancer. Accordingly, this case-control study was aimed to evaluate the possible association between pri-miR-34b/c rs4938723 polymorphism and susceptibility to bladder cancer in a sample from the Iranian population.

Subjects and methods

Patients

A total of 136 patients with histopathologically confirmed papillary urothelial cancers of the bladder and 144 healthy controls were enrolled in this case-control study. The study design and recruitment procedures were described previously[35]. All participants were from the Department of Urology, 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 and informed us that written consent was obtained from all of the study participants. The genomic DNA was extracted from peripheral blood cells using the salting-out method[36].

Genotyping

Genotyping of the Pri-miR-34b/c rs4938723 polymorphism was done by a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique as explained previously[37]. Briefly, the forward and reverse primers to amplify the Pri-miR-34b/c gene sequences containing the rs4938723 polymorphisms were 5′-CCTCTGGGAACCTTCTTTGACCTGT-3′ and 5′-CCTGGGCCTTCTAGTCAAATAGTGA-3′, respectively. PCR amplification was done using Prime Taq Premix (Genet Bio, Korea) by the following amplification procedure: denaturation at 95 °C for 5 minutes, followed by 30 cycles of 95 °C for 30 seconds, 57 °C for 30 seconds, 72 °C for 30 seconds, with a final extension of 10 minutes at 72 °C. Ten microliters of the PCR products of 212 bp fragments were digested by NmuCI restriction enzyme (Fermentas) and separated by 2.5% agarose gel electrophoresis. The T allele was undigested (212 bp fragment), but the C allele digested and produced two fragments of 186 and 26 bp **(*Fig. 1*).**

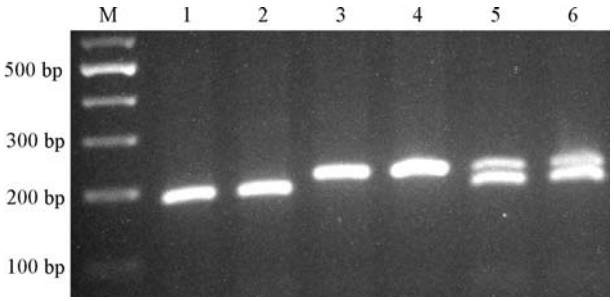

Fig. 1 **Genotypes of pri-miR-34b/c rs4938723.** M: DNA marker; lanes 1, 2: CC genotype; lanes 3, 4: TT genotype. lane 5, 6: TC genotype.

Statistical analysis

Statistical analysis was carried out using statistical package SPSS 22 software. The categorical and continuous data were analyzed using χ^2 and *t*-test, respectively. Odds ratio (OR) and 95% confidence interval (CI) was computed by unconditional logistic regression analysis to determine the association between the variant and the bladder cancer. The statistical level of significance was set as the $P<0.05$ level.

Results

The miR-34b/c rs4938723 $t>$C polymorphism was successfully genotyped for 136 bladder cancer patients (117 males, 19 females) with an average age of (63.8±12.3) years and 144 controls (134 males, 10 females) with mean age of (64.3±10.2) years. No significant difference was found between the groups regarding age (P = 0.701) and sex (P = 0.076). The genotype and allele frequencies of pri-miR-34b/c rs4938723 polymorphism in bladder cancer patients and controls are shown in ***Table 1***. The results indicated that pri-miR-34b/c rs4938723 $t>$C polymorphism was not associated with the risk of bladder cancer in codominant (OR = 1.08, 95% CI = 0.66–1.78, P = 0.800; OR = 2.13. 95%CI = 0.91–5.01, P = 0.094, TC *vs*. TT), dominant (OR = 1.22, 95%CI = 0.76–1.95, P = 0.468, TC + CC *vs.* TT), recessive (OR = 2.04, 95%CI = 0.91–4.60, P = 0.110, CC *vs*. TT + TC), over-dominant (OR = 0.94, 95%CI = 0.59–1.50, P = 0.812, TC *vs.* TT + CC) and allelic (OR = 1.28, 95%CI = 0.90–1.82, P = 0.181, C *vs*. T) inheritance model tested. We also calculated adjusted OR and 95%CI for sex and

Table 1 **Association between pri-miR-34b/c rs4938723 *t*>C polymorphism and risk of bladder cancer**

rs4938723	Case [*n* (%)]	Control [*n* (%)]	OR (95%CI)	*P*	*OR (95%CI)	*P*
Codominant						
TT	54 (39.7)	64 (44.4)	1.00	-	1.00	-
TC	64 (47.1)	70 (48.6)	1.08 (0.66–1.78)	0.800	1.06 (0.64–1.77)	0.813
CC	18 (13.2)	10 (6.9)	2.13 (0.91–5.01)	0.094	2.11 (0.89–4.99)	0.089
Dominant						
TT	54 (39.7)	64 (44.4)	1.00	-	1.00	-
TC + CC	82 (60.3)	80 (55.5)	1.22 (0.76–1.95)	0.468	1.19 (0.74–1.93)	0.474
Recessive						
TT + TC	118 (86.8)	134 (93.1)	1.00	-	1.00	-
CC	18 (13.2)	10 (6.9)	2.04 (0.91–4.60)	0.110	2.04 (0.90–4.63)	0.086
Overdominant						
TT + CC	72 (52.9)	74 (51.4)	1.00	-	1.00	-
TC	64 (47.1)	70 (48.6)	0.94 (0.59–1.50)	0.812	1.09 (0.67–1.75)	0.732
Allele						
T	172 (41.9)	198 (68.8)	1.00	-	-	-
C	100 (58.1)	90 (31.2)	1.28 (0.90–1.82)	0.181	-	-

*adjusted for sex and age

age (***Table 1***). The findings revealed that the variant was not associated with bladder cancer risk.

The association between pri-miR-34b/c rs4938723 polymorphism and clinicopathological characteristics of bladder cancer patients are shown in ***Table 2***. The findings propose a significant association between age and rs4938723 variant so that the TT genotype frequencies was significantly higher in patients with ages > 60 years (48.2%) than that of patients with ages ⩽ 60 years (26.4%).

The genotype rs4938723 polymorphism of pri-miR-34b/c in controls and cases were in HWE ($\chi^2 = 2.483$, $P = 0.115$ and $\chi^2 = 0.019$, $P = 0.88$, respectively).

Table 2 **Association of rs4938723 polymorphism of Pri-miR-34b/c gene with clinicopathological characteristics of bladder cancer patients. (*n*)**

Factors	rs4938723 *t* > C			*P*-value
	TT	TC	CC	
Age at diagnosis (years)				0.039
⩽60	14	30	9	
>60	40	34	9	
Stage				0.770
pT2c	0	1	0	
pT3b	2	1	1	
LpT1	14	22	9	
pT2a	6	6	1	
pT2b	2	4	0	
pT3a	3	2	2	
HpT1	12	8	2	
LpTa	9	14	2	
pT4a	1	4	1	
Surgical margin				0.647
Positive	2	3	0	
Negative	52	61	18	

Discussion

In the present study, for the first time, we inspected whether the pri-miR-34b/c rs4938723 *t* > C polymorphism modifies the risk of bladder cancer in a sample from the Iranian population. The results showed that rs4938723 variant of pri-miR-34b/c was not associated with the risk of bladder cancer. As shown in ***Table 3***, several preceding studies have investigated the association between pri-miR-34b/c rs4938723 polymorphism and cancer risk in some populations and various types of cancer with inconsistent findings. It has been shown that rs4938723 variant was not associated with the risk of breast cancer (BC)[37] and retinoblastoma[38]. The variant has been shown to be associated with increased risk of papillary thyroid carcinoma (PTC)[27] and nasopharyngeal carcinoma[39]. The rs4938723 variant

Table 3 **Genotype distribution of miR-34b/c rs4938723 *t*>C among various studies and association with risk of cancer**

Study	Country	Cancer type	Case/Control	Cases			Controls			Association
				TT	TC	CC	TT	TC	CC	
Chen *et al.*[27]	China	Papillary thyroid carcinoma	787/1,006	271	402	111	456	451	99	Increased risk
Li *et al.*[39]	China	Nasopharyngeal carcinoma	217/360	82	104	31	168	155	37	Increased risk
Liu *et al.*[40]	China	Hepatocellular carcinoma	164/305	63	80	21	152	141	13	Increased risk
Xu *et al.*[23]	China	Hepatocellular carcinoma	501/548	204	236	62	266	229	54	Increased risk
Chen *et al.*[41]	China	Hepatocellular carcinoma	286/572	102	146	38	272	267	33	Increased risk
Son *et al.*[42]	Korea	Hepatocellular carcinoma	157/201	69	75	13	110	74	17	Increased risk
Pan *et al.*[28]	China	Gastric cancer	197/289	102	76	19	121	137	31	Decreased risk
Yang *et al.*[43]	China	Gastric cancer	419/402	193	186	40	156	184	62	Decreased risk
Wu *et al.*[44]	China	Gastric cancer	897/992	405	396	92	476	430	84	No association
Zhang *et al.*[45]	China	Esophageal squamous cell carcinoma	1,109/1,275	489	536	84	569	573	133	Decreased risk
Zhu *et al.*[24]	China	Esophageal squamous cell carcinoma	237/274	113	99	25	122	122	30	No association
Oh *et al.*[46]	Korea	Colorectal cancer	545/428	272	233	40	216	171	41	No association
Gao *et al.*[47]	China	Colorectal cancer	347/488	175	144	28	216	210	62	Decreased risk
Yuan *et al.*[32]	China	Cervical cancer	328/568	117	157	36	242	258	68	Increased risk
Zhang *et al.*[20]	China	Renal cell carcinoma	710/760	302	324	84	352	344	64	Increased risk
Carvalho *et al.*[38]	Brazil	Retinoblastoma	130/105	52	64	14	45	44	16	No association
Sanaei *et al.*[37]	Iran	Breast cancer	263/221	125	115	23	100	106	15	No association
Hashemi *et al.*[48]	Iran	Prostate cancer	151/152	85	56	10	109	38	5	Increased risk
Tong *et al.*[49]	China	Childhood ALL	570/673	245	281	35	301	296	76	Decreases risk
Hashemi *et al.*[50]	Iran	Childhood ALL	110/120	77	31	2	62	52	6	Decreased risk
Current study	Iran	Bladder cancer	136/144	54	64	18	64	70	10	No association

was found to be associated with increased risk of hepatocellular carcinoma (HCC) in the Chinese[23,40–41] and Korean populations[42].

Pan *et al.* and Yang *et al.* have found that pri-miR-34b/c rs4938723 variants significantly decreased the risk of gastric cancer (GC) in Chinese population[28,43]. On the other hand, the findings of Wu *et al.* did not support an association between the variant and risk of GC in Chinese population[44]. Zhang *et al.* findings revealed that rs4938723 variant significantly decreased the risk of esophageal squamous cell carcinoma (ESCC) in the Chinese population[45]. While, Zhu *et al.* has found no significant association between the variant and risk of ESCC in the Chinese population[24].

Oh *et al.* have found no significant association between rs4938723 variant and colorectal cancer (CRC) in Korean population, while Gao *et al.* reported that this variant decrease the risk of CRC in Chinese population[46–47]. The rs4938723 variant have been shown to be associated with increased risk of cervical cancer[32], renal cell carcinoma[20] and prostate cancer[48].

Tong *et al.*[49] and Hashemi *et al.*[50] reported that the rs4938723 variant significantly decreases the risk of childhood acute lymphoblastic leukemia (ALL).

There is no clear reason for the inconsistent findings regarding the association between pri-miR-34b/c rs4938723 variant and cancer risk. Ethnic, genetic, and/or environmental factors as well as gene-diet interaction may interact in various modes to either increase or decrease the risk of various cancers in different regions.

In summary, our findings did not support an association between rs4938723 polymorphism in the promoter region of pri-miR-34b/c and the risk of bladder cancer in a sample from the Iranian population. Further large-scale studies with diverse ethnicities are warranted to reveal the impact of rs4938723 on bladder cancer.

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