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Original Article

pri-miR-34b/c rs4938723 polymorphism is associated with hepatocellular carcinoma risk: a case-control study in a Chinese population

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Abstract: Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. miR-34 induces changes of its downstream genes, and plays a key role in altering the apoptotic cycle and pathways of downstream cells, and finally influences the development of cancer. We assessed the relationship of the pri-miR-34b/c rs4938723 polymorphism with hepatocellular carcinoma risk in a Chinese population. During the period of January 2014 and December 2015, a total of 164 HCC patients and 305 healthy controls were recruited from the Inner Mongolia People's Hospital. Genotyping of the *pri-miR-34b/c* rs4938723 was determined using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Using χ^2 test, we observed that HCC patients were likely to have a habit of alcohol consumption (χ^2 = 10.24, P = 0.001) and infect with HBV or HCV (χ^2 = 128.17, P < 0.001). In co-dominant model, the CC genotype of *pri-miR-34b/c* rs4938723 had a significant higher risk of HCC as compared with the TT genotype, and the corresponding adjusted OR (95% CI) was 4.14 (1.91-9.75). In dominant model, we observed that the TC+CC genotype were associated with an increased risk of HCC in comparison to the TT genotype (OR = 1.67, 95% CI = 1.17-2.55). In recessive model, the CC genotype was correlated with an elevated risk of HCC when compared with the TT+TC genotype (OR = 3.46, 95% CI = 1.62-8.54). The *pri-miR-34b/c* rs4938723 polymorphism was associated with a higher risk of HCC in the Chinese population examined. Further large-scale and multi-center studies are required to confirm these results.

Keywords: Pri-miR-34b/c, rs4938723, polymorphism, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers all overall the world, with the seventh highest mortality rate in both males and females [1, 2]. HCC is a common malignancy in Asia and Africa [3]; approximately half the new cases of HCC (every year) have been reported in China [1-5]. Despite the huge advances in epidemiology, the actual etiology of hepatocellular carcinoma remains to be elucidated. The development of HCC involves many environmental and lifestyle factors, such as hepatitis B/C virus (HBV) infection, long-term alcohol drinking, dietary aflatoxin exposure and nutrition deficiency [6-9]. However, not all subjects exposed to the same environmental and lifestyle risk factors display highly individualized susceptibility to HCC [10]. Therefore, genetic factors have been suggested to play an essential role in the pathogenesis of HCC. Previous molecular epidemiologic studies have indicated that many genetic factors may contribute to the development of HCC, such as the genes coding for let-7 family, interleukin-28B, glucose-6-phosphate isomerase, P2X purinoceptor 7, Glutathione S-Transferase Omega, miR-196a2 C > T and miR-499 A > G [11-16].

A number of miRNAs are known to contribute to carcinogenesis by regulating the expression of oncogenes and tumor suppressors [17]. Single-nucleotide polymorphisms (SNPs) in miRNA may influence their expression and properties, thereby affecting their cancer regulatory properties. MicroRNA-34 (*miR-34*) is the direct downstream target gene of P53 [18]. Under the

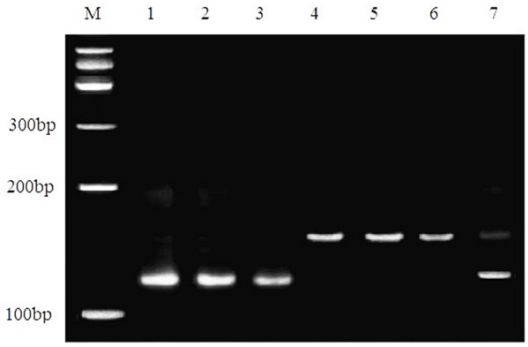

Figure 1. Genotypes of *pri-miR-34b/c* rs4938723. Lane 1-3: CC genotype; lane 4-6: TT genotype; lane: TC genotype.

regulation of P53, miR-34 induces changes of their downstream genes, plays a key role in altering the apoptotic cycle and pathways of downstream cells, and finally influences the development of cancer. Recent studies have reported that methylation of CpG island could inhibit the activity of miR-34 by p53, and p53 cause the cell proliferation through regulation of miR-34b/c, thereby cause the carcinogenesis [19, 20]. Single-nucleotide polymorphisms (SNPs) in *pri-miR-34b/c* may influence its expression, in turn affecting the individualized susceptibility to cancer. In the present study, we performed a case-control study to investigate the association between *pri-miR-34b/c* rs4938723 polymorphism and risk of HCC in a Chinese population.

Material and methods

All the investigated subjects agreed to participate into this study and signed an informed consent form before enrollment. The performance of this study obtained the permission from the ethics committee of the Inner Mongolia People's Hospital.

Subjects

During the period of January 2014 and December 2015, a total of 164 HCC patients were recruited from the Inner Mongolia People's Hospital. Patients with HCC were included in this study when they met the following criteria: histological abnormalities, increase in AFP (≥ 400 ng/mL), and HCC diagnosis by computed tomography and magnetic resonance imaging. Patients who were secondary or metastasis HCC and had a history of other malignant tumors and autoimmune hepatitis were excluded from this study.

During the same period, 305 healthy subjects were selected from the Physical Examination Center of the Inner Mongolia People's Hospital, and all the healthy subjects were confirmed without a history of malignant tumor, liver cirrhosis, and chronic kidney diseases.

The demographic variables of the investigated subjects, including age, gender, tobacco smoking, alcohol consumption and family history of cancer, were collected via a face-to-face interview with questionnaires. The HBV and HCV infection, TNM stage and Child-Pugh score were collected from the patients' medical records. The mean ages of HCC patients and controls were 62.57 ± 8.65 and 61.52 ± 9.01 years, respectively. There were 113 (68.90%) males and 51 (31.10%) females in the HCC patients, and there were 200 (65.57%) males and 105 (34.43%) females in the healthy controls. 92 (56.10%) HCC patients were infected with HBV or HCV, and 26 (8.52%) controls were infected with HBV or HCV.

Genotyping

A five peripheral venous blood was obtained from each investigated subject, and the collected blood samples were kept in tubes containing 0.5 mg/mL ethylenediaminetetraacetic acid as an anticoagulant. The genomic DNA was extracted from peripheral venous blood with a QIAGEN blood DNA kit (QIAGEN, Shanghai, China). Genotyping of the *pri-miR-34b/c* rs4938723 was analyzed by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Primers of the *pri-miR-34b/c* rs4938723 were designed by primer 5.0 software. The forward and reverse primers of the *pri-miR-34b/c* rs4938723 were 5'-CTCACCTCCTCTGGGAACCTT-3' and 5'-AAGGCCATACCATTCAAGACAGTAT-3', respectively. The *TA*SI restriction enzyme was taken to digest the PCR products. PCR was performed in a 25-μL mixture containing 2.5 μL 10× buffer (5 mM $MgCl_2$), 2 μL dNTP mix (25 mM), 1 μL each primer (25 pmol/L), 0.25 μL TaqDNA polymerase (5 U/μL), 1 μL DNA template (20 ng/μL), and 17.25 μL ddH_2O. The PCR cycling started with denaturation at 95°C for 5 min; 35 cycles of denaturation at 95°C for 30 s, annealing at 60°C for 30 s, and extension at 72°C for 2 min; and a final

Table 1. Demographic and clinical variables of investigated subjects

Variables	Patients N = 164	%	Controls N = 305	%	χ^2 test or *t* test	*P* value
Age, years	62.57 ± 8.65		61.52 ± 9.01		1.22	0.11
Gender						
Males	113	68.90	200	65.57		
Females	51	31.10	105	34.43	0.53	0.47
Tobacco smoking						
Never	106	64.63	205	67.21		
Ever	58	35.37	100	32.79	0.32	0.57
Alcohol cdrinking						
Never	72	43.90	181	59.34		
Ever	92	56.10	124	40.66	10.24	0.001
Family history of cancer						
No	155	94.51	296	97.05		
Yes	9	5.49	9	2.95	1.86	0.17
HBV or HCV infection						
No	72	43.90	279	91.48		
HBV infection	78	47.56	21	6.89		
HCV infection	14	8.54	5	1.64	128.37	< 0.001
TNM stage						
I-II	68	41.46				
III-IV	96	58.54				
Child-Pugh score						
A	40	24.39				
B	72	43.90				
C	52	31.71				

HBV: hepatitis B virus; HCV: hepatitis C virus; TNM: Tumor Node Metastasis.

extension at 72°C for 10 min. The PCR products were electrophoresed on a 1% agarose gel and visualized by ethidium bromide (**Figure 1**). A total of 10% of the blood samples were randomly selected to genotype for confirmation, and the results were 100% consistency.

Statistical analysis

Comparison of demographic and clinical variables was performed using the student *t* test or Chi-square (χ^2) test. The TT, TC and CC genotype frequencies of the *pri-miR-34b/c* rs4938723 between the two investigated subjects were compared by χ^2 test. χ^2 test of goodness-of-fit test was taken to determine the Hardy-Weinberg equilibrium (HWE) of genotypes in controls. Multiple logistic regression analysis was taken to assess the relationship between *pri-miR-34b/c* polymorphism and HCC risk. Three genetic models were taken to analyze the association between *pri-miR-34b/c* polymorphism and HCC risk, including co-dominant, dominant and recessive models. A gene-environmental interaction was assessed by Spearman correlation analysis. All the statistical analyses were two-sided test, and *P* value was less than 0.05. The statistical analysis was performed by the SPSS Statistics for Windows, Version 17.0. (Chicago: SPSS Inc. USA).

Results

The demographic and clinical variables of HCC patients and controls are shown in **Table 1**. Using χ^2 test, we observed that HCC patients were likely to have a habit of alcohol consumption (χ^2 = 10.24, P = 0.001), and infected with HBV or HCV (χ^2 = 128.17, P < 0.001).

Of the 164 included HCC patients, we observed that 68 cases presented TNM stage I-II, 96 cases showed TNM stage III-IV, 40 (24.39%) cases showed a Child-Pugh score of A, 72 (43.90%) cases presented a score B, and 52 (31.71%) cases showed a score C.

Table 2. Genotype frequencies of *pri-miR-34b/c* rs4938723 in both two investigated groups

Genotypes	Patients N = 164	%	Controls N = 305	%	χ^2 test	*P* value	HWE in controls	
							χ^2 test	*P* value
TT	58	35.37	142	46.56				
TC	80	48.78	141	46.23				
CC	26	15.85	22	7.21	13.58	0.001	2.69	0.11

Table 3. The association between *pri-miR-34b/c* polymorphism and HCC risk

Genotypes	Patients N = 164	%	Controls N = 305	%	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)[a]	*P* value
Co-dominant								
TT	63	38.41	152	49.84	1.0 (Ref.)	-	1.0 (Ref.)	-
TC	80	48.78	141	46.23	1.37 (0.90-2.09)	0.13	1.42 (0.93-2.17)	0.11
CC	21	12.80	13	3.93	3.90 (1.73-8.98)	< 0.001	4.14 (1.91-9.75)	< 0.001
Dominant								
TT	63	38.41	152	49.84	1.0 (Ref.)	-	1.0 (Ref.)	-
TC+CC	101	61.59	154	50.16	1.58 (1.06-2.38)	0.02	1.67 (1.17-2.55)	0.01
Recessive								
TT+TC	143	87.20	293	96.07	1.0 (Ref.)	-	1.0 (Ref.)	-
CC	21	12.80	13	3.93	3.31 (1.53-7.40)	< 0.001	3.46 (1.62-8.54)	< 0.001

[a]Adjusted for age, gender, alcohol drinking, and HBV or HCV infection.

Table 4. Spearman correlation analysis for the gene-environmental interaction

Variables	Correlation coefficient value	*P* value
Age	0.035	0.25
Gender	0.041	0.21
Alcohol drinking	0.037	0.23
HBV infection	0.052	0.06
HCV infection	0.027	0.55

In the HCC patients, 58 (35.37%), 80 (48.78%), and 26 (15.85%) cases carried TT, TC and CC genotypes, respectively (**Table 2**). In controls, 142 (46.56%), 141 (46.23%) and 22 (7.21%) harbored the TT, TC and CC genotypes, respectively. A significant difference was observed between the HCC patients and controls in the genotype distribution of *pri-miR-34b/c* rs4938723 (χ^2 = 13.58, P = 0.001). The genotype distribution of *pri-miR-34b/c* rs4938723 was in line with the HWE in controls.

Using multiple logistic regression analysis, we observed that the CC genotype of *pri-miR-34b/c* rs4938723 had a higher risk of HCC as compared with the TT genotype in co-dominant model, and the corresponding adjusted OR (95% CI) was 4.14 (1.91-9.75) (**Table 3**). In dominant model, we observed that the TC+CC genotype of *pri-miR-34b/c* rs4938723 was associated with an increased risk of HCC in comparison to the TT genotype, and the adjusted OR (95% CI) was 1.67 (1.17-2.55). In recessive model, the CC genotype of *pri-miR-34b/c* rs4938723 was associated with an elevated risk of HCC when compared with the TT+TC genotype, and the adjusted OR (95% CI) was 3.46 (1.62-8.54).

Spearman correlation analysis revealed no gene-environmental interaction between *pri-miR-34b/c* rs4938723 polymorphism and age (correlation coefficient = 0.035, P = 0.25), gender (correlation coefficient = 0.041, P = 0.21), alcohol drinking (correlation coefficient = 0.037, P = 0.23), and HBV (correlation coefficient = 0.052, P = 0.06) or HCV infection (correlation coefficient = 0.027, P = 0.55) (**Table 4**).

Discussion

Previous studies have reported changes (chiefly down-regulation) in the expression of several miRNAs in several malignant tumors [21]. Changes in miRNA expression are chiefly associated with transcription, mutation, base amplification, and deletion. This SNP induces abnor-

mal expression of miRNA in malignant tumors. SNPs in pri-miRNA have been shown to influence the development of pre-miRNA, consequently interfering in the generation of miRNA [22]. Therefore, SNPs in the pri-miRNA could influence the maturation and target gene identification of miRNA, thereby influencing the development of carcinogenesis [22]. In the present study, our study observed that the pri-miR-34b/c rs4938723 polymorphism was correlated with an increased risk of HCC in co-dominant, dominant and recessive genetic models.

The rs4938723 is located at the CpG island of pri-miR-34b/c, and is also located at its promoter region. It is reported that the rs4938723 can influence its combination with GATA transcription factors, and it also affects the transcription process of matured process and thus impacts on the biological function. GATA transcription factors can combine with many DNA conserved sequence of many gene promoter regions, consequently influencing the tumor differentiation and gene pathway of tumor development [23, 24]. Previous study has reported that the genetic polymorphisms of the core gene promoter region can promote and inhibit the adhesion function of the GATA transcription factor, then influencing the transcriptional activity of the genetic promoter region [25]. The polymorphisms of promoter region in pri-miR-34b/c can influence the apoptotic response of normal and tumor cells, thereby affecting cancer susceptibility [26].

Previous studies have shown that the *pri-miR-34b/c* rs4938723 polymorphism contributes to the pathogenesis of several kinds of malignant tumors, such as cervical cancer, acute lymphoblastic leukemia, esophageal squamous cell carcinoma, renal cell cancer and nasopharyngeal carcinoma [27-31]. However, Sanaei et al. did not find a significant association between pri-miR-34b/c rs4938723 polymorphism and breast cancer risk [32]. Pan et al. reported that miR-34b/c rs4938723 had a protective effect on the risk of gastric risk [33]. Up to now, several previous studies have investigated the relationship between *pri-miR-34b/c* polymorphism and HCC risk with inconsistent results [19, 34, 35]. Xu et al. carried out a case-control study with 501 patients with primary HCC and 548 controls, indicating that rs4938723 in the promoter region of *pri-miR-34b/c* may contribute to the development of HCC [19]. Han et al. performed a huge sample size with 3325 subjects, and they reported that rs4938723 was a risk factor for HCC and was significantly influenced by the HBV mutations [34]. Son et al. found that rs4938723 CC-TP53 Arg/Arg combination elevated the risk of HCC in a Korean population [35]. A recent meta-analysis study with three studies has shown that rs4938723 is not related with the development of HCC. In our study, we showed that rs4938723 was correlated with risk of HCC in co-dominant, dominant and recessive models.

A major strength of our study is that the controls are matched with the patients in our study; moreover, the 1:2 matched case-control study design improves the effectiveness of the statistical test; this study design was not employed by other studies. However, the results of our study are subject to one limitation. The investigated subjects were selected from only one hospital; therefore, the sample population did not represent the overall population. However, the gene distributions of rs4938723 in controls were in line with the HWE, suggesting that the samples could represent the general population.

In conclusion, we suggest that the *pri-miR-34b/c* rs4938723 polymorphism contributes to the development of HCC in co-dominant, dominant and recessive models. Further studies with more samples must be carried out to confirm our findings.

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Disclosure of conflict of interest

None.

Authors' contribution

Chuanjia Liu and Shiqiang Shen designed research; Chuanjia Liu collected material and clinical data from patients and controls, and performed the assays. Chuanjia Liu and Shiqiang Shen analyzed data and wrote the paper. Chun-Jia Liu and Xue-Wei Ma contributed equally to our study.

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