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Association of microRNA-423 rs6505162 C>A polymorphism with susceptibility and metastasis of colorectal carcinoma

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Abstract

Studies have evaluated the association between the SNP miRNA-423 rs6505162 C>A and cancer risk in several cancers with contradictory outcomes. It was reported that miRNA-423 rs6505162 C>A polymorphism was associated with the overall survival and the recurrence-free survival of colorectal carcinoma. However, no studies have reported the association between miRNA-423 rs6505162 C>A polymorphism and susceptibility of colorectal carcinoma.

In this study, we investigated the association between miRNA-423 polymorphism with risk and clinicopathological parameters of colorectal carcinoma. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used to genotype 117 colorectal carcinoma patients and 84 healthy controls.

Our data indicated the frequencies of rs6505162 genotypes and alleles were significantly different between colorectal carcinoma patients and controls. Compared with CC homozygote, the AC heterozygote exhibited a significantly decreased risk of colorectal carcinoma; and the combination of AC and AA genotype was associated with decreased risk of colorectal carcinoma. The allele distribution of rs6505162 was significantly different between cases and controls. Furthermore, miR-423 rs6505162 C>A genotype showed a significant association with metastasis in patients ($P = .022$).

Our study suggested that miR-423 rs6505162 C>A polymorphism was associated with the susceptibility and metastasis of colorectal carcinoma, and that miR-423 rs6505162 C>A polymorphism might be a potential biomarker for colorectal carcinoma.

Abbreviations: CEA = carcinoembryonic antigen, CI = confidence interval, CRC = colorectal cancer, miRNAs = microRNAs, OR = odds ratio, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, SNP(s) = single nucleotide polymorphism(s).

Keywords: colorectal carcinoma, microRNA-423, polymorphism, risk

1. Introduction

Colorectal cancer (CRC) is one of the most common solid tumors and the fourth leading cause of cancer-associated mortality worldwide.[1,2] Although CRC remains to be a disease of the developed countries, the incidence rates have been rising in developing countries.[2,3] The incidence rates of CRC are rapidly increasing in several regions historically at low risk, including a number of countries within Eastern Asia and Eastern Europe.[2] The increasing incidence and mortality of CRC have been observed in China.[3,4] The etiology of CRC involved lifestyle and dietary factors, such as smoking, physical inactivity, overweight and obesity, red and processed meat consumption, and excessive alcohol consumption.[5] Previous genetic studies have revealed several single nucleotide polymorphisms (SNPs) are associated with CRC risk, such as those located in *MYC*, *CHIT1*, *TNF*-α, *XRCC1*, and *XRCC6* genes.[6–9] Meanwhile, studies have

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showed that a number of SNPs in microRNAs (miRNAs) are associated with CRC risk and progression.[10–13]

MicroRNAs (miRNAs) are small noncoding RNAs, which play an important role in gene expression.[14,15] Some miRNAs dysregulation are involved in cancer development and progression, functioned as oncogenes and tumor suppressor genes.[16] For instance, microRNA-20a is oncogenic in human uveal melanoma[17] and miR-1 inhibits tumorigenic properties of A549 cells.[18] SNPs in miRNA or pre-miRNA genes may alter their maturation or expression, which may contribute to cancer susceptibility and prognosis.[19,20] Essentially numerous SNPs in miRNA have been reported to be associated with human cancer.[21–26]

The pre-miRNA of miR-423 produces 2 mature transcripts, named miR-423–3p and miR-423–5p. Altered expression of both mature miRNAs has been reported in several types of cancers,[27–29] suggesting a potential role of miR-423 in cancer development. The rs6505162 C>A polymorphism is located in 12 bp from the 3′ end of mature miR-423–3p. Studies have evaluated the association between the SNP rs6505162 and cancer risk in several cancers with contradictory outcomes. Hsa-miR-423 rs6505162 C>A polymorphism was associated with reduced breast cancer risk in Caucasian women[30] and increased the risk of esophageal cancer in Chinese population.[31] Moreover, hsa-miR-423 rs6505162 C>A polymorphism was reported to be associated with both the overall survival and the recurrence-free survival of CRC.[12] The data indicates that SNP rs6505162 plays a potential role in CRC development. However, whether rs6505162 C>A polymorphism affects CRC risk is unclear. In this study, we genotyped the rs6505162 C>A polymorphism in a CRC population to determine the association between miRNA-423 rs6505162 C>A polymorphism and the risk of CRC, as well as clinicopathological parameters of CRC.

2. Materials and methods

2.1. Study population

The study population included 117 colorectal carcinoma (CRC) patients and 84 healthy controls matched by age and gender, from Hunan Tumor Hospital (Changsha, China). The patients were diagnosed by histopathology evidence and received no treatment before the blood drawing. Tumor size, nodal status, and distant metastasis were determined by computed tomography (CT) scan or magnetic resonance imaging (MRI). Clinical stages were assessed with the criteria of Union for International Cancer Control (UICC 2003). There were no restrictions for cases on age, sex, or clinical stage. The selection criteria for controls included no family history of CRC and frequency matched to cases on age and sex. All recruited subjects were unrelated ethnic Chinese adults, resident in Changsha City (Changsha, China) or the surrounding regions. Informed consent was obtained from all participants and the study protocol was approved by the institutional Ethics Committees.

2.2. SNP genotyping

Genomic DNA was isolated using TIANamp Genomic DNA kit (TIANGEN BIOTECH, Beijing, China) according to manufacturer's instruction. SNP genotyping was done using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. Primer sequences used for amplification were—forward primer (5′-CCC CTC AGT CTT GCT TCG TA-3′) and reverse primer (5′-ACT TGA GCT TCT GCC AAG GA-3′). PCR amplification was performed in a total volume of 15 μL reaction mixture, contain 100 ng genomic DNA, 0.3 μL of each primers and 7.5 μL 1 × GoTaq Master Mix (Promega Corporation, Madison, WI). The restriction endonuclease Csp6 I (New England BioLabs, Beverly, MA) was used to digest the PCR products. Then, the cleaved products were separated on polyacrylamide gel electrophoresis and identified by ethidium bromide staining. For the miR-423 rs6505162 C>A polymorphism, fragment sizes of 108 and 19 bp indicated CC homozygote, 127, 108, and 19 bp indicated AC heterozygote, and AA homozygote was designated with 1 band (127 bp) (Fig. 1). The sequences of PCR products were confirmed by DNA sequencing in about 10% of the samples.

2.3. Statistical analysis

Hardy–Weinberg equilibrium was utilized to compare the observed genotype frequencies with the expected ones in the control group. The different distributions of the genotype and allele frequencies were evaluated by chi-square test. The associations between the miRNA-423 rs6505162 C>A genotypes and the risk of CRC were estimated by calculating the odds ratio (OR) and 95% confidence interval (CI), using the multivariate logistic regression analysis adjusted by age and gender. The chi-square test or Fisher's exact test was performed in the association between the genotypes and clinicopathological parameters in patients. Statistical analyses were performed with SPSS 19.0 software and $P < .05$ was considered to indicate statistical significance.

3. Results

3.1. Characteristics of the study population

A total of *117* patients with CRC and *84* healthy controls were recruited in this study. Main characteristics of the study subjects (mean age: 48.1 ± 11.5) were presented in Table 1. There were no statistically significant differences in terms of the distributions of age ($P = .179$) and gender ($P = .978$) between cases and controls.

3.2. Distribution of miRNA-423 genotypes and risk of colorectal carcinoma

The detailed genotyping results of miR-423 rs6505162 C>A were listed in Table 2. The genotype distributions of miR-423 rs6505162 C>A frequencies were in agreement with Hardy–Weinberg equilibrium in the controls ($P = .059$). The genotype frequency distribution of miR-423 rs6505162 C>A was significantly different between patients and controls ($P = .015$, Table 2). Compared with CC homozygote, the AC heterozygote but not AA homozygote exhibited a significantly decreased risk of CRC (OR = 0.421, 95% CI = 0.230–0.772, $P = .005$ for AC heterozygote; and OR = 0.937, 95% CI = 0.157–5.614, $P = .944$ for AA homozygote, respectively, Table 2), and the combination of AC and AA genotype was associated with decreased risk of CRC (OR = 0.450, 95% CI = 0.250–0.812, $P = .008$, Table 2). Interestingly, the allele distribution of miR-423 rs6505162 C>A was also significantly different between cases and controls (OR = 0.582, 95% CI = 0.355–0.952, $P = .030$, Table 2).

3.3. Association between genotypes and clinicopathological parameters

Table 3 summarized the relationship between miR-423 rs6505162 C>A genotype and clinicopathological parameters.

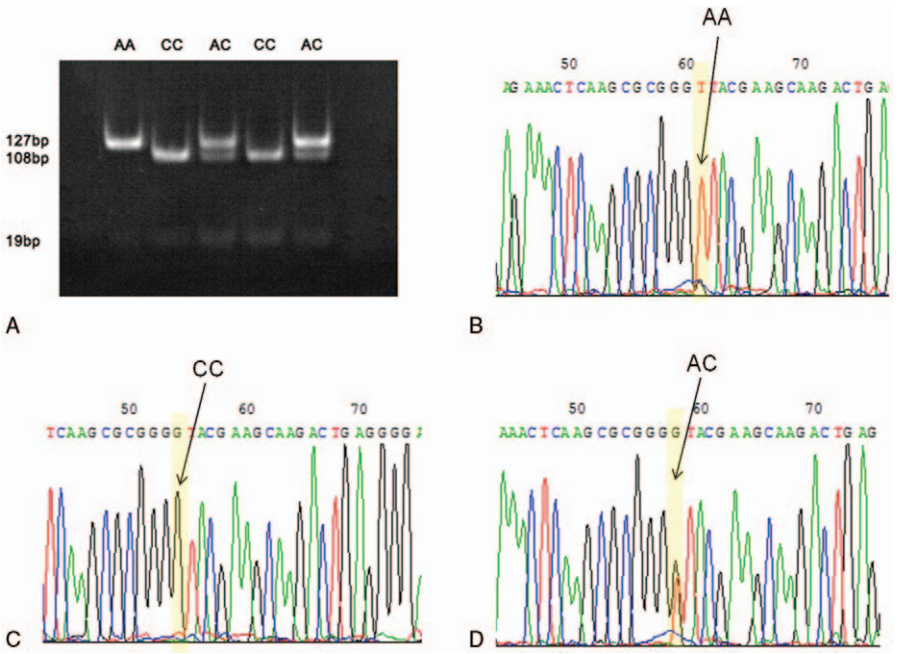

Figure 1. (A) Gel electrophoresis of miRNA-423 rs6505162 C>A genotypes: AA (127 bp), CC (108 bp, 19 bp), AC (127 bp, 108 bp, 19 bp). (B–D) Sequencing validation using reverse primer of (B) Genotype AA. (C) Genotype CC. (D) Genotype AC.

A significant association between rs6505162 C>A genotype and metastasis in patients was found ($P=.022$, Table 3). Compared with CC homozygote, the AA homozygote alone and the combination of AC and AA genotype exhibited a higher rate of metastasis in CRC patients (Table 3). Genotype in miR-423 rs6505162 C>A showed no significant association with parameters including age, gender, serum carcinoembryonic antigen (CEA), primary tumor extension, lymph node status, and clinical stage in patients.

Table 1

Characteristics of colorectal carcinoma patients and controls.

Characteristics*	Patients	Controls	*P* value
Age			
<40	34 (29.1)	32 (38.1)	.179
≥40	83 (70.9)	52 (61.9)	
Gender			
Male	81 (69.2)	58 (69.0)	.978
Female	36 (30.8)	26 (31.0)	
CEA			
<5 μg/L	44	–	
≥5 μg/L	22	–	
Primary tumor extension			
T_1+T_2	9	–	
T_3+T_4	53	–	
Lymph node status			
N_0	22	–	
N_1+ N_2+ N_3	34	–	
Metastasis			
No	53	–	
Yes	10	–	
Clinical stage			
I+II	25	–	
III+IV	38	–	

CEA = carcinoembryonic antigen.
* Data available only in some cases.

4. Discussion

Our study investigated the association between miR-423 rs6505162 C>A polymorphism and CRC risk. The data indicated that the distributions of miR-423 rs6505162 C>A genotypes and alleles were significantly different between the CRC patients and controls. Previous studies reported contradictory results on miR-423 rs6505162 C>A polymorphism and cancer risk. In breast cancer, AA genotype offered a reduced risk in a Jewish population;[32] whereas the CC genotype reduces the risk of sporadic breast cancer development in a Caucasian population.[30] A meta-analysis failed to find any significant association between the risk of breast cancer and miR-423 rs6505162 C>A polymorphism.[33] Contradictory results were also reported in oesophageal cancer, a digestive tract tumors with most studies on rs6505162 C>A polymorphism. In a population consisted of Black and Mixed Ancestry subjects from South Africa, rs6505162 was positively associated with oesophageal cancer risk in the Black population, but no significant association was found in the Mixed Ancestry group.[34] Compared with the

Table 2

Genotype and allele distribution of miRNA-423 rs6505162 C>A in patients and controls.

Polymorphism	Patient	Control	*P* value	OR	95% CI
Genotype					
AA	4 (3.4)	2 (2.4)	.015		
AC	30 (25.7)	38 (45.2)			
CC	83 (70.9)	44 (52.4)			
AC versus CC			.005	0.421*	0.230–0.772
AA versus CC			.944	0.937*	0.157–5.614
AA+AC versus CC			.008	0.450*	0.250–0.812
Allele					
A	38 (16.2)	42 (25.0)	.030	0.582	0.355–0.952
C	196 (83.8)	126 (75.0)			

* Data were calculated by unconditional logistic regression with adjustment for age and gender.

Table 3

Association between the genotype frequencies of miRNA-423 rs6505162 C>A and clinicopathological characteristics of colorectal carcinoma patients.

Parameters*	rs6505162 C>A			*P* value
	AA	AC	CC	
Age				
<40	1 (3.0)	13 (38.2)	20 (58.8)	.136
≥40	3 (3.6)	17 (20.5)	63 (75.9)	
Gender				
Male	4 (5.0)	21 (25.9)	56 (69.1)	.385
Female	0 (0)	9 (25.0)	27 (75.0)	
CEA				
<5 μg/L	3 (6.8)	10 (22.7)	31 (70.5)	.608
≥5 μg/L	1 (4.6)	3 (13.6)	18 (81.8)	
Primary tumor extension				
T1+T2	0 (0)	1 (11.1)	8 (88.9)	.572
T3+T4	3 (5.7)	11 (20.7)	39 (73.6)	
Lymph node status				
N0	0 (0)	3 (13.6)	19 (86.4)	.349
N1+N2+N3	1 (2.9)	9 (26.5)	24 (70.6)	
Metastasis				
No	1 (1.9)	9 (17.0)	43 (81.1)	.022
Yes	2 (20.0)	3 (30.0)	5 (50.0)	
Clinical stage				
I+II	3 (12.0)	7 (28.0)	15 (60.0)	.126
III+IV	1 (2.6)	6 (15.8)	31 (81.6)	

CEA = carcinoembryonic antigen.
* Data available only in some cases.

CC genotype of rs6505162, individuals with CA and AA genotype had a significantly reduced esophageal cancer risk in a Caucasian population.[35] However, no statistical association was found between microRNA-423 rs6505162 polymorphism and esophageal cancer susceptibility in a meta-analysis.[36] Our result indicated that compared with CC homozygote, the AC heterozygote exhibited a significantly decreased risk of CRC. Furthermore, our data indicated that the A allele conferred a significantly reduced CRC risk. It is consistent with the result of a recent meta-analysis.[37] Although the sample size is small, our results suggest that miR-423 rs6505162 C>A polymorphic variants might have an influence on CRC risk.

It was interesting that miR-423 rs6505162 C>A genotype showed significant association with metastasis in CRC patients in our study. Nevertheless, the sample size for this particular analysis is so small that we should not have a certain conclusion on this point. Further studies with larger sample size are needed to confirm this result. These data suggested that miR-423 rs6505162 C>A polymorphism might be a potential prognostic factor in CRC. A previous study has identified rs6505162 to be significantly associated with recurrence-free survival and overall survival of CRC patients. Compared with the homozygous CC genotype, the CA and AA genotypes were associated with unfavorable overall survival and recurrence-free survival.[12] This result is consistent with our data that the AA (or combined with CA) genotype had a higher rate of metastasis.

It seems controversial that the AA (or combined with CA) genotype was associated with a higher metastasis rate while conferred a reduced risk of CRC. It might result from the elusive and inconsistent role of miR-423 in cancers.[37] A tumor promotive function of miR-423 was reported in hepatocellular carcinoma[38] and laryngeal carcinoma.[39] However, enforcing expression of pre-miR-423 with C or A genotype showed a contradictory result. The proliferation ability and migratory capacity was lower in the AA homozygote than that in the CC homozygote in HEC-1b cells.[40] In breast cancer, pre-miR-423-C transfected cells had lower proliferation ability than pre-miR-423-A transfected cells.[41] In colorectal cancer, miR-423-3p was found to enhance cell growth[42] whereas miR-423-5p were decreased in patients with CRC compared with healthy controls.[43] Since both miR-423-3p and miR-423-5p were produced by the pre-miRNA of miR-423, it is possible for the polymorphism of pre-miR-423 to play different roles at various stages of cancer progression.

A limitation of this study was that the gene–environment interaction might contribute to the tumorgenesis of CRC was not examined. Risk factors for CRC include smoking, physical inactivity, overweight and obesity, red and processed meat consumption, and excessive alcohol consumption.[2] Polymorphisms of several genes were reported to be associated with alcohol consumption or red meat consumption of CRC risk.[44,45] Interaction between polymorphism in *miR-423* gene and cooking oil fume exposure on the risk of lung cancer was found in a Chinese population.[46] Association of polymorphism in *miR-423* gene with environmental smoke exposure to risk for oesophageal squamous cell carcinoma was reported.[47] To the best of our knowledge, however, interaction between polymorphism in *miR-423* gene and environmental factors to the risk of CRC was not reported.

In conclusion, our study suggested that the genotype and allele of miR-423 rs6505162 C>A were significantly associated with the risk of CRC, and rs6505162 C>A genotype was significantly associated with metastasis in patients. These data suggested that miR-423 rs6505162 C>A might be a potential biomarker for susceptibility of CRC and metastasis in patients. However, our results were obtained with a limited sample size. Studies with larger sample size and other ethnic populations are needed to confirm current findings.

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