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A Genetic Variant in Pre-miR-146a (rs2910164 C>G) Is Associated with the Decreased Risk of Acute Coronary Syndrome in a Chinese Population

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MicroRNAs (miRNAs) can contribute to the development of cardiovascular diseases, and single nucleotide polymorphisms (SNPs) in miRNA genes may influence disease susceptibility by altering mature miRNA expression levels. However, the effect of SNPs located in miR-146a and miR-196a2 genes on risk of acute coronary syndrome (ACS) has not been reported in the Chinese population. Two miRNA polymorphisms located in miRNA genes (miR-146a rs2910164 C>G and miR-196a2 rs11614913 T>C) were genotyped in 722 ACS patients and 721 control subjects. The CG genotype of rs2910164 was significantly associated with decreased risk of ACS [CG vs. CC, odds ratio (OR) = 0.72, 95% confidence interval (CI): 0.55-0.95, P = 0.020; dominant model, OR = 0.77, 95% CI: 0.60-0.99, P = 0.044]. We did not find any association of rs11614913 with the risk of ACS. Stratification analysis showed that the rs2910164 CG genotype was associated with decreased risk of ACS (dominant model) in males, subjects with body mass index more than 24 kg/m^2, and in hypertensive subjects. Significant combined effects were also observed between rs2910164 and blood lipids or C-reactive protein levels. In summary, this study provides the first evidence that the CG genotype of miR-146a rs2910164 is associated with a significantly decreased risk of ACS in a Chinese population. Moreover, rs2910164 and blood lipids or an inflammatory marker may have a combined effect on the onset of ACS. These findings indicate that miR-146a rs2910164 may act as a novel molecular marker for ACS susceptibility.

Keywords: acute coronary syndrome; microRNA; miR-146a; polymorphism; susceptibility
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Introduction

Acute coronary syndrome (ACS), including unstable angina and acute myocardial infarction (AMI), is the leading cause of morbidity and mortality worldwide (Lopez and Murray 1998). ACS is a clinically cardiovascular event resulting from rupture of the atherosclerotic plaque, which is caused by environmental exposure and genetic factors. Traditional risk factors for ACS have been identified, including age, sex, body mass index, hypertension, diabetes mellitus, smoking, and family history of coronary heart disease (CHD). Genome-wide association studies have uncovered numerous susceptible loci for ACS (Myocardial Infarction Genetics Consortium et al. 2009; Akerblom et al. 2014; Hirokawa et al. 2015), few of which were found to locate in microRNA (miRNA) genes.

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miRNAs, about 20~22 nucleotides in length, are a class of highly conserved single-stranded RNA molecules playing key roles in controlling fundamental biological processes by modulating gene expressions (Ambros 2004). Emerging evidence suggests that miRNAs may contribute to the development of ACS (De Rosa et al. 2011) and related diseases, including atherosclerosis (Rayner et al. 2011; Horie et al. 2012; Andreou et al. 2015). The genetic variants in miRNA genes could affect processing and maturation of miRNAs (Saunders et al. 2007), and the development of diseases (Hu et al. 2008). miRNAs are initially transcribed as primary miRNA (pri-miRNA) and then processed into hairpin-structured precursor miRNAs (pre-miRNAs), which are the direct precursor of mature miRNAs with approximately 70 nucleotides in length (Lee et al. 2003). Two well-studied miRNA polymorphisms located in the pre-miRNA sequences (miR-146a rs2910164 C>G and miR-196a2 rs11614913 T>C) have been found to be associated with various diseases (Xu et al. 2009; Xiong et al. 2014; Huang et al. 2015). Moreover, the rs2910164 C>G was found to be able to reduce the expression of mature miR-146a and thus affect the binding with target mRNA (Jazdzewski et al. 2008; Xu et al. 2008). Likewise, the rs11614913 CC genotype was associated with increased mature miR-196a expression in the cardiac tissue samples of congenital heart disease patients (Xu et al. 2009). Interestingly, these two miRNAs also regulate genes related to thrombosis and inflammation pathways in the circulation system (Luthra et al. 2008; El Gazzar et al. 2011). However, no study regarding the relationship between the two miRNA polymorphisms and risk of ACS has been reported. In this study, we aimed to investigate the association between the two miRNA polymorphisms and ACS risk in a Chinese population.

Materials and Methods

Study population

The case-control study was composed of 722 ACS patients, including AMI and unstable angina, and 721 age and sex matched healthy controls. All subjects were unrelated Chinese people with the ethnic Han origin by self-description. Briefly, patients who were hospitalized at two hospitals (Tongji Hospital and Union Hospital) in Wuhan (Hubei, China) from July 2010 to July 2013 were consecutively recruited. All patients underwent coronary angiography and exhibited stenoses ≥ 50% in at least one major coronary artery. The diagnosis of AMI was based on the following criteria (Alpert et al. 2000): (1) chest pain lasting more than 20 min; (2) development of pathologic Q waves on the electrocardiography or ST segment elevation or depression, and (3) elevation markers of myocardial necrosis (such as troponin). Unstable angina was defined as a new onset of severe angina, accelerated angina or angina at rest (Mintz et al. 2003). Patients with stable angina or other heart diseases were excluded from this study. Healthy subjects without medical history of ACS were selected as controls during the physical health examination at hospital, and they were matched with the patients by age, sex, and area of residence. Smoking refers to current or previous smokers. Fasting blood samples were collected from the patients on the morning of the day after admission, and from controls on the day of physical health examination. All blood samples were stored at −80°C until use.

For all participants, structured questionnaires were used to collect information on demographic characteristics and clinical biochemistry by trained interviewers. The ethics committee of Tongji Medical College approved this study, and written informed consent was also obtained from each participant. All experiments were performed in compliance with the relevant laws and/or institutional guidelines.

Genotyping of miRNA polymorphisms

Genomic DNA was extracted from 200 μl EDTA-Na2 anticoagulated blood sample of each participant using the commercial DNA extraction kit (AXYGEN, CA, USA) following manufacturer's instructions. DNA concentration was measured by NanoDrop® ND-1000 Spectrophotometer from Thermo Fisher Scientific Inc. (Waltham, MA, USA). Genotyping was performed using TaqMan assay (Applied Biosystems, CA, USA) on the 7900HT real time quantitative PCR system (Applied Biosystems, CA, USA). Two blank controls (DNA hydration solution) were included in each 384 well plate. About 10% of the samples were randomly selected for repeat genotyping, and the concordance rate between samples was 100% (data not shown).

Statistical analysis

The normal distribution of data was tested by the One-Sample Kolmogorov-Smirnov test. Differences in clinical characteristics between control and case subjects were examined by the χ^2 test (for categorical variable), Mann-Whitney U test (for skewed parameter), or by Student's t test (for normally distributed data). The Hardy-Weinberg equilibrium of single nucleotide polymorphisms (SNPs) was detected among controls using the χ^2 test with one degree of freedom. The multiple logistic regression analysis was used to evaluate associations between the frequency of miRNA polymorphisms and ACS risk with adjustment for traditional risk factors, including age, sex, smoking, body mass index (BMI), hypertension, diabetes mellitus, and family history of CHD. For stratified analysis, we evaluated the gene-environment interactions by entering the multiplicative interaction term into logistic regression models. All statistical analyses were performed using SPSS 11.0 software (Statistical Package for the Social Sciences, Chicago, USA). The P values < 0.05 were considered statistically significant (two-tailed).

Results

Characteristics of the study populations

The clinical characteristics of the case-control population are presented in Table 1. Overall, the proportion of people with a history of hypertension, diabetes and family history of CHD was higher in ACS patients compared with controls ($P < 0.05$). Moreover, the body mass index, blood lipids [total cholesterol (Tc), triglycerides, and high-density lipoprotein cholesterol (HDL-c)] and C-reactive protein (CRP) levels were all significantly higher in ACS patients ($P < 0.05$). These two populations showed no difference in age, sex, smoking status and low-density lipoprotein cholesterol (LDL-c) levels ($P > 0.05$).

Table 1. General characteristics of the study population.

Variables	Control (n = 721)	ACS (n = 722)	*P* value
Age, year	58 (53-67)	59 (52-67)	0.895*
Male, n (%)	558 (77.4)	559 (77.4)	1.000†
BMI, kg/m^2	23.82 ± 3.19	24.36 ± 3.36	0.003‡
Smoking, n (%)	373 (51.7)	465 (64.4)	0.086†
Hypertension, n (%)	228 (31.6)	443 (61.4)	< 0.001†
DM, n (%)	45 (6.2)	175 (24.2)	< 0.001†
Family history of CHD, n (%)	22 (3.1)	111 (15.4)	< 0.001†
Tc, mmol/L	3.81 (1.69-4.79)	4.40 (3.60-5.10)	< 0.001*
Triglycerides, mmol/L	1.25 (0.90-1.83)	1.37 (0.91-2.04)	0.041*
HDL-c, mmol/L	0.99 (0.81-1.21)	1.11 (0.96-1.32)	< 0.001*
LDL-c, mmol/L	2.62 ± 0.81	2.63 ± 0.93	0.818‡
CRP, mg/L	1.09 (0.72-2.17)	4.06 (1.36-17.67)	< 0.001*

Data are expressed as median (25th, 75th quartiles), mean ± SD, or percentages.
ACS, acute coronary syndrome; BMI, body mass index; DM, diabetes mellitus; CHD, coronary heart disease; Tc, total cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; CRP, C-reactive protein.
*Mann-Whitney U tests for the differences between patients with ACS and control subjects.
†Chi-square test for the difference in the distribution frequency between patients with ACS and control subjects.
‡Student's t test for the difference between patients with ACS and control subjects.

miRNA polymorphisms and risk of ACS

The genotype and allele distributions of the miRNA polymorphisms (rs11614913 and rs2910164) in ACS patients and control subjects are shown in Table 2. Due to the missing value, only 720 control subjects and 718 ACS patients have the completed genotype data of rs11614913, and 717 control subjects or ACS patients have the completed genotype data of rs2910164. The polymorphisms were both compatible with Hardy-Weinberg equilibrium (HWE) in controls (P = 0.905 for rs11614913 and 0.830 for rs2910164, respectively). Logistic regression analysis suggests that subjects carrying CG genotype of rs2910164 had a lower risk of ACS compared with CC genotype (OR = 0.79, 95% CI: 0.63-0.99, P = 0.045). After adjustment for traditional risk factors, the association remained significant (CG vs. CC, OR = 0.72, 95% CI: 0.55-0.95, P = 0.020; dominant model, OR = 0.77, 95% CI: 0.60-0.99, P = 0.044). The G allele of rs2910164 showed no significant association with the risk of ACS. Neither TC genotype nor C allele of rs11614913 showed significant association with ACS (P > 0.05).

Stratification analysis

The association between miRNA polymorphisms and ACS risk were further analyzed in the subpopulations stratified by traditional risk factors. Due to the missing data of the genotyping and the risk factors, the number of enrolled subjects with complete genotyping and clinical variables data varies, as shown in Table 3. We found that the CG genotype of rs2910164 was associated with a lower risk of ACS in male subjects (OR_{dom} = 0.72, 95% CI: 0.54-0.96, P = 0.027), in subjects with BMI more than 24 kg/m^2 (OR_{dom} = 0.66, 95% CI: 0.46-0.95, P = 0.025), and in hypertensive subjects (OR_{dom} = 0.61, 95% CI: 0.41-0.90, P = 0.013). As for rs11614913, it showed significant association with a higher risk of ACS in female subjects (OR_{dom} = 1.99, 95% CI: 1.06-3.73, P = 0.031). However, no interaction effect was found between each of these two SNPs and clinical variables ($P_{interaction}$ > 0.05).

Association of rs2910164 with Tc, triglycerides, or CRP levels

Since HDL-c level was higher in patients than control subjects probably due to medication before the hospital admission of the patients, we ignored HDL-c in this part of study and analyzed the combined effects of rs2910164 with Tc, triglycerides, LDL-c, and CRP levels on ACS risk. Generally, high Tc, triglycerides, LDL-c, or CRP levels increase the prevalence of cardiovascular diseases. We divided subjects into high or low group firstly according to the median level of Tc, triglycerides, LDL-c or CRP of the control subjects (3.81 mmol/L, 1.25 mmol/L, 2.60 mmol/L and 1.09 mg/L, respectively), and analyzed the combined effects. Due to the missing data of the genotyping and the four clinical variables, the number of enrolled subjects with complete genotyping and clinical variables data also varies from each other, as shown in Table 4. Results suggest that compared with the reference group, significant combined effects were observed in the subjects carrying G allele of rs2910164 (CG or GG genotype) and with Tc < 3.81 mmol/L, triglycerides < 1.25 mmol/L or CRP < 1.09 mg/L (Table 4).

Table 2. Genotype and allele frequency of miRNA polymorphisms in ACS patients and control subjects.

Polymorphism	Control (n = 721)	ACS (n = 722)	Crude OR (95% CI)	*P* value	OR* (95% CI)	*P* value
rs11614913 (n)	720	718				
TT	204 (28.3)	190 (26.3)	1.00 (reference)		1.00 (reference)	
TC	360 (49.9)	381 (52.8)	1.14 (0.89-1.45)	0.306	1.08 (0.82-1.44)	0.581
CC	156 (21.6)	147 (20.4)	1.01 (0.75-1.37)	0.939	1.14 (0.81-1.62)	0.456
Additive model (TT vs. TC vs. CC)			1.01 (0.87-1.18)	0.853	1.07 (0.90-1.27)	0.448
Dominant model (TC+CC vs. TT)			1.10 (0.87-1.39)	0.426	1.10 (0.84-1.44)	0.488
Recessive model (CC vs. TT+TC)			0.93 (0.72-1.20)	0.579	1.08 (0.81-1.45)	0.594
T allele	768 (53.3)	761 (52.7)	1.00 (reference)		1.00 (reference)	
C allele	672 (46.6)	675 (46.7)	1.01 (0.88-1.17)	0.855	1.07 (0.90-1.27)	0.455
HWE *P*				0.905		
rs2910164 (n)	717	717				
CC	237 (32.9)	266 (36.8)	1.00 (reference)		1.00 (reference)	
CG	348 (48.3)	308 (42.7)	0.79 (0.63-0.99)	0.045	0.72 (0.55-0.95)	0.020
GG	132 (18.3)	143 (19.8)	0.97 (0.72-1.30)	0.814	0.89 (0.63-1.25)	0.509
Additive model (CC vs. CG vs. GG)			0.95 (0.83-1.10)	0.509	0.91 (0.77-1.08)	0.273
Dominant model (CG+GG vs. CC)			0.84 (0.67-1.04)	0.109	0.77 (0.60-0.99)	0.044
Recessive model (CC+CG vs. GG)			1.10 (0.85-1.44)	0.461	1.07 (0.79-1.45)	0.673
C allele	822 (57.0)	840 (58.2)	1.00 (reference)		1.00 (reference)	
G allele	612 (42.4)	594 (41.1)	0.95 (0.82-1.10)	0.496	0.91 (0.76-1.08)	0.257
HWE *P*				0.830		

ACS, acute coronary syndrome; HWE, Hardy-Weinberg equilibrium.
*OR based on the traditional risk factors, including age, sex, smoking, BMI, hypertension, diabetes mellitus, and family history of CHD.

Discussion

In this study, we evaluated the associations between two miRNA polymorphisms and the risk of ACS in a Chinese population. The gene-environment interaction effect and the combined effect of miRNA polymorphisms with clinical parameters were also evaluated. We found that subjects carrying CG genotype of miR-146a rs2910164 had decreased risk for ACS, especially in males and subjects with BMI more than 24 kg/m^2 or with hypertension in dominant model. Moreover, combined effects were observed between miR-146a rs2910164 and Tc, triglycerides, CRP levels in subjects with G allele of rs2910164 (CG or GG genotype). Collectively, our findings imply that miRNA polymorphisms may contribute to the development of ACS.

Saunders and colleagues (2007) surveyed the publicly available miRNA SNPs data and suggested that SNPs in miRNA sequences are relatively rare and highly conserved, which indicates the functional importance of miRNA variations. miRNA polymorphisms could affect the processing of pre-miRNA into its mature form, alter mature miRNA expression levels and also modify common human disease susceptibility. miR-146a rs2910164 and miR-196a2 rs11614913 are both located in the mature miRNA regions. In this study, we found that rs2910164 was significantly associated with the risk of ACS in a Chinese population. Three studies have previously investigated the association between miRNA polymorphisms and CHD risk. Xiong et al. (2014) demonstrated that compared with the GG homozygote, the GC heterozygote and the CC homozygote of rs2910164 were associated with an increased risk of CHD in Chinese population, while Ramkaran et al. (2014) found no difference in the genotypic frequency of rs2910164 in controls and CHD patients in young South African Indians. Chen et al. (2014) found that the CC genotype of rs2910164 was associated with an increased risk of myocardial infarction in Chinese population, although the association disappeared after adjustment for traditional risk factors. The inconsistency among the studies may be partially due to the different genetic backgrounds among races and/or the small sample size. The homozygous GG genotype exerted no noticeable effect on the susceptibility in this study, which might be due to the limited sample size of subjects with GG genotype (only 18.3% or 19.8% in the populations). The miR-146a C>G polymorphism has also been reported to associate with the risk of ischemic stroke (Jeon et al. 2013; Huang et al. 2015), which indicates that ACS or CHD may share genetic risk factors with ischemic stroke. Although rs11614913 was associated with an increased risk of ACS in the females, we found no association in the whole population. Consistent with our study, Zhi et al. (2012) also failed to observe any association between rs11614913 and the risk of CHD in Southeast China. Stratification analysis

Table 3. Stratification analysis of miRNA polymorphisms.

Variables	rs11614913					rs2910164				
	Control* (n)	ACS* (n)	OR_{dom} (95% CI)	P_{dom}†	$P_{interaction}$	Control* (n)	ACS* (n)	OR_{dom} (95% CI)	P_{dom}†	$P_{interaction}$
Age, year	720	718			0.746	717	717			0.642
≤ 60	113/189/79	105/203/78	1.17 (0.81-1.71)	0.399		138/166/74	150/162/73	0.86 (0.61-1.21)	0.373	
> 60	91/171/77	85/178/69	1.02 (0.69-1.52)	0.911		99/182/58	116/146/70	0.69 (0.47-1.00)	0.051	
Sex	720	718			0.081	717	717			0.344
male	160/285/112	157/283/116	0.97 (0.71-1.31)	0.967		176/283/96	210/248/99	0.72 (0.54-0.96)	0.027	
female	44/75/44	33/98/31	1.99 (1.06-3.73)	0.031		61/65/36	56/60/44	1.03 (0.60-1.77)	0.912	
BMI, kg/m^2	637	694			0.518	634	693			0.200
< 24	100/171/74	92/166/58	0.99 (0.68-1.47)	0.992		125/161/58	118/135/60	0.88 (0.61-1.26)	0.477	
≥ 24	82/148/62	92/199/87	1.21 (0.83-1.77)	0.328		87/145/58	141/160/79	0.66 (0.46-0.95)	0.025	
Smoking	720	718			0.177	717	717			0.928
no	99/168/81	64/146/46	1.41 (0.91-2.19)	0.122		117/168/61	94/101/59	0.77 (0.51-1.16)	0.206	
yes	105/192/75	126/235/101	0.95 (0.67-1.35)	0.780		120/180/71	172/207/84	0.78 (0.56-1.08)	0.128	
Hypertension	720	718			0.564	717	717			0.078
no	138/242/113	65/140/72	1.21 (0.83-1.76)	0.318		173/221/95	100/119/58	0.93 (0.67-1.31)	0.690	
yes	66/118/43	125/241/75	1.01 (0.68-1.50)	0.969		64/127/37	166/189/85	0.61 (0.41-0.90)	0.013	
Diabetes mellitus	720	718			0.437	717	717			0.852
no	187/338/150	142/294/108	1.06 (0.80-1.41)	0.694		225/324/123	206/231/108	0.78 (0.60-1.02)	0.064	
yes	17/22/6	48/87/39	1.58 (0.69-3.62)	0.279		12//24/9	60/77/35	0.64 (0.27-1.51)	0.306	
Family history of CHD	720	718			0.891	717	717			0.603
no	199/347/152	165/316/126	1.09 (0.83-1.44)	0.525		231/338/126	225/258/123	0.78 (0.61-1.02)	0.067	
yes	5/13/4	25/65/21	1.31(0.33-5.20)	0.697		6/10/6	41/50/20	0.56 (0.17-1.84)	0.336	

*Wild-type homozygote/heterozygote/variant homozygote.
†Dominant model (wild-type homozygote vs. heterozygote +variant homozygote).
Data were calculated by unconditional logistic regression, adjusted for age, sex, smoking, BMI, hypertension, diabetes mellitus and family history of CHD.

Table 4. Combined effect of rs2910164 with clinical parameters on ACS risk.

Variables	Control, n*	Case, n*	OR (95% CI)†	
			CC	CG+GG
Tc, mmol/L	692	364		
≥ 3.81	110/235	84/160	1.00 (ref)	0.81 (0.53-1.25)
< 3.81	114/233	49/71	0.68 (0.39-1.17)	0.36 (0.22-0.58)
TG, mmol/L	691	693		
≥ 1.25	109/237	141/243	1.00 (ref)	0.76 (0.52-1.09)
< 1.25	115/230	117/192	0.93 (0.60-1.44)	0.67 (0.46-0.98)
LDL-c, mmol/L	329	647		
≥ 2.60	53/115	102/210	1.00 (ref)	0.82 (0.51-1.31)
< 2.60	54/107	130/205	1.15 (0.66-1.98)	0.88 (0.55-1.41)
CRP, mg/L	306	491		
≥ 1.09	46/108	149/251	1.00 (ref)	0.62 (0.39-1.00)
< 1.09	48/104	31/60	0.21 (0.10-0.42)	0.17 (0.10-0.29)

*CC/CG+GG.
†OR based on the risk factors, including age, sex, BMI, hypertension, diabetes mellitus, smoking and family history of CHD.
We divided subjects into high or low group according to the median level of TC, TG, LDL-c or CRP in control subjects, respectively (Tc: 3.81 mmol/L; TG: 1.25 mmol/L; LDL-c: 2.60 mmol/L; and CRP: 1.09 mg/L).
Tc, total cholesterol; TG, triglycerides; LDL-c, low-density lipoprotein cholesterol; CRP, C-reactive protein.

showed that the males, overweighed or hypertensive subjects were more likely to have a decreased risk for ACS if they carry G allele of rs2910164 (CG or GG genotype, dominant model), which may provide a strategy for characterizing the subpopulations with high risk of ACS; however, the small sample size of the stratification analysis calls for further studies with larger sample size to verify our findings.

miR-146a plays important roles in regulating the innate immunity and inflammatory responses (Rusca and Monticelli 2011; Ichii et al. 2012), and aberrant expression of miR-146a was observed in cancer and inflammatory diseases (Li et al. 2010). Increased expression of miR-146a may promote the occurrence and progression of CAD. Two studies have reported that the expression level of miR-146a in peripheral blood mononuclear cells (PBMCs) was higher in the CHD group than that in the non-CHD group (Ramkaran et al. 2014; Xiong et al. 2014). In addition, Guo et al. (2010) found that miR-146a was up-regulated in PBMCs of ACS patients, and over-expression of miR-146a in PBMCs may have a direct function in the differentiation of Th1 cells, which is implicated in the progression and onset of ACS. Although we found CG genotype of rs2910164 was associated with a decreased risk of ACS, the expression of miR-146a in ACS patients with different genotypes remained unknown and need to be clarified in further studies. The combined effects of miR-146a rs2910164 with Tc, triglycerides, and CRP levels further suggested a synergetic interaction effect between miRNA polymorphism and vascular risk factors on the disease susceptibility. In the context of that, previous studies also suggested that miR-146a was involved in regulation of pro-inflammatory NF-kappa B pathway, MAPK pathway (Cheng et al. 2013), and the expression of TNF-α (El Gazzar et al. 2011). Moreover, Dong et al. (2013) found that miR-146a was a novel regulator of VSMC fate.

Limitations of the present study include that like all the case-control studies, potential selection bias could not be ruled out and might influence the interpretation of the results. Second, the relatively small sample size of this study may limit the statistical power, although we have considered this issue by calculating the statistical power according to the minor allele frequency (MAF) of rs11614913 (rs11614913 MAF: 0.341; rs2910164 MAF: 0.354, respectively). The statistical power of this study reaches 0.96 when the parameters were set to: MAF = 0.341, $\alpha = 0.05$, and OR = 1.5. Nevertheless, further studies with larger sample size are required to confirm the function of these miRNA polymorphisms in acute coronary syndromes.

In conclusion, our study provides the first evidence that the CG genotype of miR-146a rs2910164 is associated with decreased risk of ACS in Chinese Han population, particularly among males, overweighed or hypertensive subjects. Moreover, rs2910164 has combined effects with blood lipids and CRP level on the disease susceptibility. Replications by independent genetic studies with larger sample size as well as the functional tests are required to confirm our findings and to explore the underlying mechanism.

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Conflict of Interest

The authors declare no conflict of interest.

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