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Original Article

The association between *LEP/LEPR* polymorphisms and coronary artery disease: a case-control study in an eastern Chinese Han population

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Abstract: Obesity and being overweight are considered risk factors for coronary artery disease (CAD), but the underlying pathogenesis remains unclear. To investigate whether genetic polymorphisms in leptin (*LEP*) and the leptin receptor (*LEPR*) contribute to the development of CAD, we conducted a case-control study of the *LEP* rs2167270 G>A, rs7799039 A>G and *LEPR* rs1137100 G>A, rs1137101 G>A polymorphisms in the eastern Chinese Han population. In total, 505 CAD patients and 1,109 healthy controls were enrolled. The *LEP/LEPR* polymorphisms were genotyped using the SNPscan™ genotyping method. The results indicate that the *LEP* rs2167270 G>A polymorphism may be a protective factor against CAD (GA vs. GG: adjusted odds ratio [OR], 0.77; 95% confidence interval [CI], 0.61-0.98; P = 0.034), whereas *LEPR* rs1137100 G>A increased the risk of CAD (AA vs. GG: adjusted OR, 1.98; 95% CI, 1.01-3.92; P = 0.048 and AA vs. GG/GA: adjusted OR, 2.02; 95% CI, 1.03-3.97; P = 0.042). In addition, we found that the *LEPR* rs1137100 G>A polymorphism might be associated with an increased susceptibility to CAD among the subgroup of patients without a history of myocardial infarction (AA vs. GG: adjusted OR, 2.23; 95% CI, 1.07-4.62; P = 0.032 and AA vs. GG/GA: adjusted OR, 2.31; 95% CI, 1.11-4.78; P = 0.024). In conclusion, our results suggest that the *LEP* rs2167270 G>A polymorphism may be considered a protective factor against CAD in the eastern Chinese Han population, while the *LEPR* rs1137100 G>A polymorphism is likely a risk factor for CAD. Future studies considering detailed lifestyle and environmental factors are needed to confirm our findings.

Keywords: Polymorphism, *LEP*, *LEPR*, coronary artery disease, risk

Introduction

Coronary artery disease (CAD) is the leading cause of mortality in developed countries, and its prevalence continues to increase in China. The etiology of CAD is complex, but previous studies have shown that obesity and being overweight play important roles in the pathogenesis of CAD [1, 2]. It is well-established that adipose tissue secretes a number of adipokines, and a shift to the production of proinflammatory cytokines by these cells in obesity and overweight individuals likely results in a low-level systematic inflammation that may contribute to some chronic pathologies related to metabolic syndrome such as atherosclerosis [3].

LEP is a hormone mainly secreted by adipose cells that acts to control metabolism and energy homeostasis. In humans, the *LEP* gene is located on chromosome 7, and the encoded 16-kDa *LEP* protein consists of 167 amino acid residues. Several studies have indicated that leptin (LEP) and the *LEP* receptor (*LEPR*) are involved in the development of becoming overweight, as well as obesity [4-6]. *LEP* is known to respond specifically to adipose-derived inflammatory cytokines [7]. Moreover, research indicates that *LEP* may play an important role in the regulation of the immune and inflammatory response [8-10]. Specifically, Taleb et al. reported that *LEP/LEPR* influences the immune response to atherosclerosis, for which obesity is likely a predisposing factor [11]. Together,

these findings suggest that altered *LEP/LEPR* signaling may influence the development of CAD.

Variants located on the *LEP/LEPR* genes likely affect the function of *LEP/LEPR* signaling. Yang et al. reported that the *LEPR* rs1137101 G>A variant is associated with obesity in the Chinese population [12]. Wang et al. suggested that the *LEP* rs7799039 GG homozygous variant is associated with an increased risk of extreme obesity in the Taiwanese aborigine population [13]. Recently, several case-control studies focused on the correlation between *LEPR* variants and the risk of CAD [14-16]. An et al. reported that the *LEPR* rs1137101 G>A polymorphism confers a significant susceptibility to coronary atherosclerosis [17]. With the aim of defining the association between *LEP/LEPR* variants and the risk to CAD, we conducted a case-control study to determine the correlations between the *LEP* rs2167270 G>A, and rs7799039 A>G and *LEPR* rs1137100 G>A, rs1137101 G>A single nucleotide polymorphisms (SNPs) and CAD.

Materials and methods

Study population and sample collection

Five hundred five patients diagnosed with CAD were recruited at the Department of Cardiology and Cardiac Surgery of Fujian Medical University Union Hospital, Fuzhou, China between October 2014 and May 2016. The criterion for the diagnosis of CAD was coronary stenosis ≥ 50% on a coronary angiography [18]. The main inclusion criteria for the CAD cases were: (a) CAD confirmed by coronary angiography, and (b) chest pain associated with specific ischemic electrocardiograph changes. The main exclusion criteria for the CAD cases were: (a) cardiomyopathy, (b) coagulopathy, and (c) acute intoxication (e.g., carbon monoxide or amphetamine). The control group consisted of 1109 healthy age- and sex-matched individuals recruited from the physical examination center of the hospital at the same time. The main inclusion criteria for controls were: (a) no history and symptoms of CAD, and (b) no evidence of myocardial ischemia on electrocardiography examination [18]. Accordingly, participants with a history or symptoms of CAD or who showed specific ischemic electrocardiography changes were excluded.

Each study participant provided written informed consent and completed a questionnaire. We collected the demographic data and data regarding related risk factors through interviews. Sex, age, tobacco use, alcohol consumption, height, weight, body mass index (BMI), history of type 2 diabetes mellitus (T2DM), history of hypertension, and the levels of high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), total cholesterol (TC), fasting blood glucose, and low-density lipoprotein cholesterol (LDL-C) were collected or measured. The criteria for smoking and drinking are described in our previous report [19]. T2DM was diagnosed based on the World Health Organization (WHO) 1999 criteria. Hypertension was defined by a systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg [20]. BMI ≥ 24 kg/m^2 was the criterion for overweight or obese status [21]. According to the Chinese Medical Association 2016 criteria, hyperlipidemia is defined as LDL ≥ 3.37 mmol/L, TG ≥ 1.7 mmol/L, TC ≥ 5.18 mmol/L, or HDL < 1.04 mmol/L. This case-control study was approved by the Ethics Committee of Fujian Medical University.

Isolation of DNA and genotyping

Genomic DNA was isolated from peripheral venous blood samples using the Promega DNA Kit (Madison, WI, USA). The *LEP/LEPR* polymorphisms were genotyped using the SNPscan™ genotyping method (Genesky Biotechologies Inc., Shanghai, China). Genotyping was performed by two technicians blinded to the group assignment. To ensure the accuracy of genotyping, a randomized controlled assay was performed to check the genotyping of 65 samples with consistent results. The genotyping success rate for these SNPs was greater than 99.00%.

Statistical analysis

Continuous variables (e.g., TG, TC, LDL-C, HDL-C, and fasting blood glucose levels as well as height, weight, BMI, and age) are presented as the mean ± standard deviation (SD). We used Student's t-test to assess differences in these variables between the CAD cases and the controls. Differences in categorical variables (e.g., smoking status, drinking status, BMI, age, sex, hypertension, history of T2DM, history of hyperlipidemia, and genotypes of *LEP* rs2167270 G>A, rs7799039 A>G and *LEPR* rs1137100 G>A, rs1137101 G>A polymorphisms) were determined using the x^2 test or Fisher's exact test. The relationships between the *LEP* rs2167270 G>A rs7799039 A>G and *LEPR*

Table 1. Distributions of selected demographic variables and risk factors in CAD cases and controls

Variable	Cases (n = 505)		Controls (n = 1,109)		P[a]
	n	%	n	%	
Age (years)	64.57 ± 9.91		64.75 ± 10.20		0.729
Age (years)					0.942
< 65	249	49.31	549	49.50	
≥ 65	256	50.69	560	50.50	
Sex					0.704
Female	110	21.78	251	22.63	
Male	395	78.22	858	77.37	
Tobacco use					**< 0.001**
Ever	250	49.50	336	30.30	
Never	255	50.50	773	69.70	
Alcohol use					**< 0.001**
Ever	122	21.46	135	12.17	
Never	383	78.54	974	87.83	
Height (cm)	165.00 ±7.52		166.60 ± 6.92		**< 0.001**
Weight (kg)	66.58 ± 10.74		66.08 ± 9.63		0.352
BMI (kg/m^2)	24.41 ± 3.27		23.77 ± 2.91		**< 0.001**
BMI (kg/m^2)					**< 0.003**
< 24	231	45.74	596	53.74	
≥ 24	274	54.26	513	46.26	
Hypertension					**< 0.001**
Yes	352	69.70	660	59.51	
No	153	30.30	449	40.49	
T2 DMD					
Yes	157	31.09	171	15.42	**< 0.001**
No	348	68.91	938	84.58	
Fasting glucose (mmol/L)	6.17 ± 2.04		5.78 ± 1.67		**< 0.001**
Total cholesterol (mmol/L)	4.26 ± 1.22		4.84 ± 1.05		**< 0.001**
Triglyceride (mmol/L)	1.71 ± 1.17		1.61 ± 1.01		0.081
HDL-C (mmol/L)	1.03 ± 0.30		1.23 ± 0.36		**< 0.001**
LDL-C (mmol/L)	2.72 ± 1.09		3.08 ± 0.86		**< 0.001**
Hyperlipidemia					
Yes	374	74.06	754	67.99	**< 0.014**
No	131	25.94	355	32.01	
Type of CAD					
MI	147	29.11			
Non-MI	358	70.89			

[a]Two-sided χ^2 test and Student t test; Bold values are statistically significant (P < 0.05). BMI: body mass index; T2DM: Type 2 diabetes mellitus; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CAD: coronary artery disease; MI: myocardial infarction.

rs1137100 G>A, rs1137101 G>A genotypes and CAD risk were evaluated based on crude/adjusted odds ratios (ORs) and their 95% confidence intervals (CIs). We performed x^2 tests using an online software package (online at http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) [22-25] to assess the Hardy-Weinberg equilibrium (HWE) in controls. All other data analyses were performed with SAS 9.4 software (SAS Institute, Cary, NC, USA).

Results

Characteristics of the study population

The mean age of the patients in the CAD group was 64.57 ± 9.91 years (range, 30-89 years),

Table 2. Basic characteristics of *LEP* rs2167270 G>A rs7799039 A>G and *LEPR* rs1137100 G>A, rs1137101 G>A polymorphisms

SNPs	Chromosome	Chr Pos (NCBI Build 37)	Region of SNP	MAF[a] for Chinese in database	MAF in our controls (n = 1,109)	*P* value for HWE[b] test in our controls	Genotyping method	Genotyping value (%)
LEP rs7799039 A/G	7	127878783	Promoter	0.201	0.274	0.572	SNPscan	99.50
LEP rs2167270 G/A	7	127881349	5'UTR	0.175	0.230	0.282	SNPscan	99.44
LEPR rs1137100 G/A	1	66036441	Exon 4	0.169	0.158	0.139	SNPscan	99.50
LEPR rs1137101 G/A	1	66058513	Exon 6	0.111	0.127	0.119	SNPscan	99.38

[a]MAF: minor allele frequency; [b]HWE: Hardy-Weinberg equilibrium.

and the mean age of patients in the healthy control group was 64.75 ± 10.20 years (range, 33-89 years). The two groups were matched for age and gender (P = 0.942 and P = 0.704, respectively). The frequencies of smoking, drinking, BMI ≥ 24 kg/m^2, T2DM, hyperlipidemia and hypertension were significantly higher in the CAD group than in the healthy control group [49.50% vs. 30.30%, P < 0.001; 21.46% vs. 12.17%, P < 0.001, 54.26% vs. 46.26%, P = 0.003, 30.09% vs. 15.42%, P < 0.001, 74.06% vs. 67.99%, P < 0.001 and 69.70% vs. 59.51%, P < 0.001, respectively (**Table 1**)]. Among the enrolled CAD patients, 147 had a history of myocardial infarction (MI), and 358 did not.

Characteristics of LEP rs2167270 G>A, rs7799039 A>G and LEPR rs1137100 G>A, rs1137101 G>A SNPs

The basis characteristics of the *LEP* rs2167270 G>A, rs7799039 A>G and *LEPR* rs1137100 G>A, rs1137101 G>A polymorphisms are listed in **Table 2**. *LEPR* rs1137100 G>A and rs1137101 G>A are coding variants. *LEP* rs7799039 A>G is located in the promoter. *LEP* rs2167270 G>A is a 5'untranslated region (UTR) SNP. In the controls, the genotype distributions of the *LEP* rs2167270 G>A, rs7799039 A>G and *LEPR* rs1137100 G>A, rs1137101 G>A variants were in HWE (**Table 2**).

Associations between LEP rs2167270 G>A, rs7799039 A>G and LEPR rs1137100 G>A, rs1137101 G>A SNPs and CAD risk

The genotype frequencies of *LEP* rs2167270 G>A, rs7799039 A>G and *LEPR* rs1137100 G>A, rs1137101 G>A polymorphisms in CAD patients and controls are summarized in **Table 3**. We found no association between the *LEP* rs7799039 A>G and *LEPR* rs1137101 G>A polymorphisms and the risk of CAD (**Table 4**).

The frequencies of the *LEP* rs2167270 GG, GA and AA genotypes were 63.73%, 31.46% and 4.81% in CAD patients and 58.77%, 36.53%, and 4.70% in controls, respectively. When the frequency of the *LEP* rs2167270 GG genotype was applied as a reference, the frequency of the *LEP* rs2167270 GA genotype differed significantly between the CAD group and the control group (crude OR = 0.78, 95% CI: 0.62-0.98, P = 0.035). This difference was still observed after adjustment for age, sex, hypertension, T2DM, smoking, drinking, hyperlipidemia and BMI, (GA vs. GG: adjusted OR, 0.77; 95% CI, 0.61-0.98; P = 0.034; **Table 4**).

The frequencies of the *LEPR* rs1137100 GG, GA and AA genotypes were 68.00%, 28.20% and 3.80% in CAD patients and 70.34%, 27.76%, and 1.90% in controls, respectively. When the frequency of the *LEPR* rs1137100 GG genotype was applied as a reference, the frequency of the *LEPR* rs1137100 AA genotype differed significantly between the CAD patients and controls (crude OR = 2.05, 95% CI: 1.09-3.86, P = 0.027). When the frequency of *LEPR* rs1137100 GG/GA genotype was applied as the reference, the frequency of the *LEPR* rs1137100 AA genotype differed significantly between the CAD patients and controls (crude OR = 2.04, 95% CI: 1.09-3.83, P = 0.026). These differences were still observed after adjustments for age, sex, hypertension, T2DM, smoking, drinking, hyperlipidemia and BMI (AA vs. GG: adjusted OR, 1.98; 95% CI, 1.01-3.92; P = 0.048 and AA vs. GG/GA: adjusted OR, 2.02; 95% CI, 1.03-3.97; P = 0.042; **Table 4**).

Association of LEP rs2167270 G>A, rs7799039 A>G and LEPR rs1137100 G>A, rs1137101 G>A polymorphisms with risk of different CAD types

The genotype frequencies of the *LEP* rs21672-70 G>A, rs7799039 A>G and *LEPR* rs1137100 G>A, rs1137101 G>A polymorphisms in different subgroups are listed in **Table 3**. We carried out a stratified analysis to assess whe-

Table 3. Logistic regression analyses of association between *LEP* rs2167270 G>A rs7799039 A>G and *LEPR* rs1137100 G>A, rs1137101 G>A polymorphisms and risk of CAD

Genotype	CAD cases (n = 505)		Non-MI cases (n = 358)		MI cases (n = 147)		Controls (n = 1,109)	
	n	%	n	%	n	%	n	%
LEP rs7799039 A>G								
AA	273	54.60	190	53.82	83	56.46	580	52.44
AG	189	37.80	136	38.53	53	36.05	447	40.42
GG	38	7.60	27	7.65	11	7.48	79	7.14
AG+GG	227	45.40	163	46.18	64	43.54	526	47.56
AA+AG	462	92.40	326	92.35	136	92.52	1,027	92.86
GG	38	7.60	27	7.65	11	7.48	79	7.14
G allele	265	26.50	190	26.91	75	25.51	605	27.35
LEP rs2167270 G>A								
GG	318	63.73	222	63.07	96	65.31	650	58.77
GA	157	31.46	113	32.10	44	29.93	404	36.53
AA	24	4.81	17	4.83	7	4.76	52	4.70
GA+AA	181	36.27	130	36.93	51	34.70	456	41.23
GG+GA	475	95.19	335	95.17	140	95.24	1,054	95.30
AA	24	4.81	17	4.83	7	4.76	52	4.70
A allele	205	20.54	147	20.88	58	19.73	508	22.97
LEPR rs1137100 G>A								
GG	340	68.00	242	68.56	98	66.67	778	70.34
GA	141	28.20	96	27.20	45	30.61	307	27.76
AA	19	3.80	15	4.25	4	2.72	21	1.90
GA+AA	160	32.00	111	31.44	49	33.33	328	29.66
GG+GA	481	96.20	338	95.75	143	97.28	1,085	98.10
AA	19	3.80	15	4.25	4	2.72	21	1.90
A allele	179	17.90	126	17.85	54	18.37	349	15.78
LEPR rs1137101 G>A								
GG	385	77.15	268	76.14	117	79.59	837	75.75
GA	104	20.84	76	21.59	28	19.05	256	23.17
AA	10	2.00	8	2.27	2	1.36	12	1.09
GA+AA	114	22.85	84	23.86	30	20.41	268	24.25
GG+GA	489	98.00	344	97.73	145	98.64	1,093	98.91
AA	10	2.00	8	2.27	2	1.36	12	1.09
A allele	124	12.42	92	13.07	32	10.88	280	12.67

CAD: coronary artery disease; MI: myocardial infarction.

ther the role of the *LEP* rs2167270 G>A, rs7799039 A>G and *LEPR* rs1137100 G>A, rs1137101 G>A variants differed according to the type of CAD. The associations between the *LEPR* rs1137100 G>A polymorphisms and the increased risk of CAD were also found in the non-MI subgroup (AA vs. GG: adjusted OR, 2.23; 95% CI, 1.07-4.62; P = 0.032 and AA vs. GG/GA: adjusted OR, 2.31; 95% CI, 1.11-4.78; P = 0.024; **Table 4**).

Discussion

A number of case-control studies have focused on the relationship between *LEP/LEPR* variants and the risk of T2DM. However, the potential associations of *LEP/LEPR* SNPs with the development of CAD remained unclear. In the present study, the *LEP* rs2167270 G>A polymorphism was found to be a protective factor against CAD, but the *LEPR* rs1137100 G>A increased the risk of CAD in our study population. In addition, we found that the *LEPR* rs1137100 G>A polymorphism was associated with an increased risk of CAD among patients without a history of MI.

The *LEP* rs2167270 G>A (+19 A>G) polymorphism is located on the 5'-UTR of the gene, and it may alter the expression of *LEP* gene. It also

Table 4. Overall and stratified analyses of *LEP* rs2167270 G>A, rs7799039 A>G and *LEPR* rs1137100 G>A, rs1137101 G>A polymorphisms with CAD

Genotype	Overall CAD cases (n = 505) vs. Controls (n = 1,109)				Non-MI cases (n = 358) vs. Controls (n = 1,109)				MI cases (n = 147) vs. Controls (n = 1,109)			
	Crude OR (95% CI)	*P*	Adjusted OR[a] (95% CI)	*P*	Crude OR (95% CI)	*P*	Adjusted OR[a] (95% CI)	*P*	Crude OR (95% CI)	*P*	Adjusted OR[a] (95% CI)	*P*
LEP rs7799039 A>G												
Additive model	0.89 (0.71-1.11)	0.289	0.86 (0.68-1.09)	0.211	0.91 (0.71-1.17)	0.460	0.88 (0.68-1.15)	0.346	0.83 (0.58-1.20)	0.327	0.78 (0.53-1.15)	0.207
Homozygote model	1.01 (0.67-1.52)	0.967	0.97 (0.63-1.50)	0.896	1.02 (0.64-1.63)	0.928	1.00 (0.61-1.63)	0.994	0.98 (0.50-1.91)	0.948	1.00 (0.50-1.99)	0.991
Dominant model	0.92 (0.74-1.13)	0.422	0.89 (0.72-1.12)	0.324	0.95 (0.74-1.20)	0.650	0.92 (0.72-1.19)	0.532	0.85 (0.60-1.20)	0.359	0.81 (0.56-1.16)	0.249
Recessive model	1.07 (0.72-1.60)	0.744	1.04 (0.68-1.59)	0.842	1.08 (0.68-1.70)	0.750	1.07 (0.66-1.72)	0.786	1.05 (0.55-2.03)	0.881	1.10 (0.56-2.16)	0.787
LEP rs2167270 G>A												
Additive model	0.78 (0.62-0.98)	0.035	0.77 (0.61-0.98)	0.034	0.80 (0.62-1.04)	0.091	0.78 (0.59-1.02)	0.065	0.74 (0.51-1.08)	0.120	0.72 (0.49-1.07)	0.103
Homozygote model	0.93 (0.56-1.54)	0.777	0.89 (0.52-1.50)	0.653	0.94 (0.53-1.65)	0.820	0.92 (0.51-1.66)	0.777	0.92 (0.40-2.07)	0.833	0.91 (0.39-2.12)	0.830
Dominant model	0.81 (0.65-1.01)	0.061	0.80 (0.64-1.00)	0.054	0.84 (0.65-1.07)	0.152	0.81 (0.63-1.05)	0.115	0.76 (0.53-1.09)	0.130	0.74 (0.51-1.07)	0.113
Recessive model	1.02 (0.62-1.68)	0.925	0.98 (0.58-1.65)	0.946	1.03 (0.59-1.80)	0.921	1.02 (0.57-1.84)	0.941	1.01 (0.45-2.28)	0.974	1.02 (0.44-2.35)	0.970
LEPR rs1137100 G>A												
Additive model	1.04 (0.82-1.32)	0.747	0.98 (0.76-1.25)	0.854	0.99 (0.76-1.30)	0.935	0.93 (0.70-1.23)	0.613	1.17 (0.80-1.70)	0.419	1.15 (0.78-1.70)	0.488
Homozygote model	2.05 (1.09-3.86)	**0.027**	1.98 (1.01-3.92)	**0.048**	2.26 (1.15-4.45)	**0.019**	2.23 (1.07-4.62)	**0.032**	1.52 (0.51-4.52)	0.452	1.30 (0.39-4.27)	0.669
Dominant model	1.12 (0.89-1.40)	0.345	1.05 (0.83-1.34)	0.678	1.09 (0.84-1.41)	0.524	1.03 (0.78-1.35)	0.845	1.19 (0.82-1.71)	0.362	1.15 (0.79-1.69)	0.464
Recessive model	2.04 (1.09-3.83)	**0.026**	2.02 (1.03-3.97)	**0.042**	2.29 (1.17-4.50)	**0.016**	2.31 (1.11-4.78)	**0.024**	1.45 (0.49-4.27)	0.504	1.24 (0.38-4.05)	0.723
LEPR rs1137101 G>A												
Additive model	0.87 (0.68-1.13)	0.305	0.82 (0.62-1.07)	0.145	0.91 (0.68-1.22)	0.530	0.85 (0.62-1.15)	0.278	0.79 (0.51-1.22)	0.279	0.74 (0.47-1.17)	0.200
Homozygote model	1.79 (0.77-4.19)	0.177	1.59 (0.64-3.94)	0.317	2.05 (0.83-5.06)	0.120	1.78 (0.68-4.66)	0.240	1.20 (0.27-5.42)	0.814	1.10 (0.22-5.56)	0.913
Dominant model	0.93 (0.72-1.19)	0.540	0.86 (0.66-1.12)	0.275	0.98 (0.74-1.30)	0.882	0.91 (0.67-1.22)	0.513	0.80 (0.52-1.22)	0.305	0.76 (0.49-1.17)	0.213
Recessive model	1.86 (0.80-4.34)	0.150	1.68 (0.68-4.18)	0.261	2.12 (0.86-5.23)	0.103	1.88 (0.72-4.94)	0.197	1.26 (0.28-5.67)	0.767	1.16 (0.23-5.88)	0.854

[a]Adjusted for smoking, drinking, BMI, age, sex, hypertension, T2DM and hyperlipidemia; Bold values are statistically significant (P < 0.05). CAD: coronary artery disease; MI: myocardial infarction.

has been suggested that the *LEP* rs2167270 G>A SNP is in linkage disequilibrium with promoter region variation, which might influence gene transcription [26]. Hager et al. reported that the presence of the *LEP* rs2167270 A allele decreased BMI among obese females, suggesting that *LEP* rs2167270 A allele carriers are more sensitive to satiety signals via the *LEP* protein [27]. Additionally, a recent study reported that the *LEP* rs2167270 A allele may decrease the circulating *LEP* level, body weight and BMI, and consequently, may be a protective factor against obesity in females [26]. Obesity and being overweight are considered risk factors in the pathogenesis of CAD [2]. Here, we found that the *LEP* rs2167270 G>A polymorphism was associated with a reduced CAD risk. This findings might be interpreted to mean that the *LEP* rs2167270 G→A variant reduces the risk of CAD by decreasing the BMI. In the future, more epidemiologic studies considering detailed lifestyle and environmental factors are required to confirm these findings.

The *LEPR* rs1137100 G>A polymorphism, a missense SNP, is located on the translation region of the gene, and this common functional polymorphism (Arg109Lys; rs1137100) in the *LEPR* gene is a G→A missense substitution that results in an Arg to Lys substitution in the exon. The A allele of *LEPR* rs1137100 may be associated with the increased risk of T2DM [28] and higher BMI [29]. In the present study, the association between the *LEPR* rs1137100 G>A polymorphism and an increased risk of CAD was found. Thus, the *LEPR* rs1137100 G→A variant may increase the BMI and consequently raise the risk of CAD. More epidemiologic studies in a larger cohort with functional analysis are needed to reinforce our findings and elucidate the biological role of the *LEPR* rs1137100 G>A polymorphism in CAD.

Notably, our case-control study has some limitations. First, patients and controls were enrolled from a local hospital; thus, bias might have occurred. Secondly, the *LEP/LEPR* SNPs studied were selected from related publications. In the future, a fine-mapping study should be carried out to obtain an extensive view of these genes. Thirdly, it would be interesting to define the relationships of *LEP/LEPR* SNPs with the serum protein levels. However, because these proteins were not assessed in this study, we could not conduct such a correlation analysis as part of this investigation. Finally, due to a lack of detailed information on cardiovascular events, we could not determine the roles of the *LEP* rs2167270 G>A, rs7799039 A>G and *LEPR* rs1137100 G>A, rs1137101 G>A variants in CAD progression and prognosis.

In summary, the results of the present study indicate that the *LEP* rs2167270 G>A polymorphism may be considered a protective factor against CAD among the eastern Chinese Han population, whereas *LEPR* rs1137100 G>A may be associated with an increased risk of CAD in this population. Future studies that take into account detailed lifestyle and environmental factors are needed to confirm our findings.

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Disclosure of conflict of interest

None.

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