


RESEARCH ARTICLE

The association between *IL-17A* and *IL-23R* polymorphisms and coronary artery disease risk in a Middle Eastern Chinese population

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Background: Polymorphisms in *IL-17A* and *IL-23R* may affect the expression of these genes and could contribute to a patient's susceptibility to coronary artery disease (CAD). Although this association was investigated by previous studies, the relationship remains unclear.

Method: We conducted this hospital-based case-control study to determine whether polymorphisms in these two genes could be associated with a risk of CAD. A total of 191 patients and 131 controls, as determined by SXscore, were enrolled in this study. The genotyping was performed with the Sequenom MassARRAY platform.

Results: The results showed that the FPG and HbA1C levels were higher in patients with CAD than in the controls. In addition, the HDL and ApoA1 levels were significantly higher in the controls than in the cases. In contrast, the Lp(a) level was significantly lower in the controls than in the patients. The *IL-17A* rs2275913 and *IL-23R* rs6682925 polymorphisms were associated with an increased risk of CAD (rs2275913: AA vs GG: crude OR = 2.16, 95% CI = 1.08-4.30; AG/AA vs GG: crude OR = 1.81, 95% CI = 1.04-3.15; rs6682925 CC vs TT: crude OR = 1.91, 95% CI = 1.00-3.63). The subgroup analysis by SXscore revealed that the *IL-23R* rs6682925 polymorphism (CT/CC vs TT: crude OR = 3.72, 95% CI = 1.19-11.66) was associated with an increased risk of CAD in patients with a high SXscore.

Conclusion: This study suggested that T2DM, Lp(a), HDL-c, and ApoA1 were risk factors of CAD and that the *IL-17A* rs2275913 and *IL-23R* rs6682925 polymorphisms may contribute to susceptibility to CAD.

KEYWORDS

CAD, *IL-17A*, *IL-23R*, polymorphism, susceptibility

1 | INTRODUCTION

Cardiovascular disease remains the leading cause of disability and death and causes a tremendous social and financial burden

worldwide.¹ Coronary artery disease (CAD) is the most common type of cardiovascular disease and accounts for more than half of all cardiovascular events in patients over 75 years old.^{2,3} CAD turns to be the second leading cause of death in China.⁴

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Although the precise mechanisms remain unclear, epidemiology studies have suggested that CAD is the result of an interaction between environmental and genetic factors. Several risk factors, such as chronic diseases (hypertension, hypercholesterolemia, diabetes mellitus, etc), smoking, age, and gender are responsible for the occurrence of CAD. In contrast, genome-wide analysis (GWAS) studies that were based on large sample sizes also deduced that genetic factors contributed to approximately 40%-50% of the risk of CAD and were also supported by family- or twin-based epidemiological studies.^{5,6}

Previous studies have reported that inflammation is involved in the pathogenesis of CAD by producing oxidative damage,⁷ promoting cellular proliferation, and effecting plaque evolution and destabilization⁸; thus, the presence of proinflammatory cytokines is considered to be a risk factor for CAD.

The proinflammatory cytokine IL-17 has six isoforms (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F),⁹ and IL-17A and IL-17F have been found to play role in the formation of plaque lesions during atherogenesis.^{10,11} IL-17A and IL-17F contribute to the T cell-mediated immune response by forming a heterodimer that binds to a receptor to stimulate downstream signaling pathways.¹² In addition, genetic variations in *IL-17* have been suggested to be risk factors of CAD; however, this conclusion is not always consistent,¹³ and this inconsistency may be attributed to differences in sample size, the characteristics of the enrolled participants, and ethnicities. The proinflammatory cytokine IL-23 has been implicated in atherogenesis.^{14,15} Additionally, IL-23 receptor (IL-23R) is composed of the IL-23R subunit and the IL-12R β 1 subunit, which together form the IL-23 receptor complex, and both IL-23 and IL-23R are required for IL-23 signaling, which is essential for the Th17 cell-mediated immune response. Moreover, the IL-23/IL-17 axis has been identified as an important inflammation pathway that plays a vital role in inflammatory and autoimmune diseases. Molecular epidemiological studies have reported that genetic variations in *IL-23R* contribute to the susceptibility of CAD.¹⁶ However, whether genetic variations in the genes of the IL-23/IL-17 axis are associated with an increased risk of CAD is largely unknown, especially in the Chinese Han population. To evaluate the contribution of genetic variations in IL-17A, IL-17F, and IL-23 to the risk of CAD, we conducted this hospital-based case-control study.

2 | MATERIALS AND METHODS

2.1 | Study subjects

The subjects who received their first coronary angiography were recruited from October 2016 to December 2017 from the Department of Cardiology of Tengzhou Central People's Hospital. Patients who were enrolled in this study had to meet the inclusion criterion of having a definitive coronary artery condition that was associated with significant, single, or multiple vessel stenoses, as assessed by an angiographic examination. To lessen the potential effect of related diseases on the real results of this study, we also enrolled the patients

meeting the following exclusion criteria: (a) any malignant disease; (b) liver or renal illness; (c) infection; (d) hematologic and immune disorders; (e) type I diabetes; or (f) history of rheumatic heart disease and cardiomyopathy.

All of the enrolled patients were classified into patients and controls based on their SXscores. Controls were those who had an SXscore of 0, and patients were those with CAD and an SXscore greater than 0; moreover, the patients were divided into two subgroups of low SXscore (≤ 22) and high SXscore (> 22).

The additional patient characteristics of age, gender, smoking status, alcohol consumption, hypertension, and type 2 diabetes mellitus (T2DM) were collected at admission. The body mass index (BMI) of each subject was calculated as weight in kilograms divided by the square of height in meters. The serum lipid profile and fasting blood glucose (FPG) and hemoglobin A1c (HbA1c) levels were measured before the clinical treatment. The protocol of this study was approved by the Ethics Committee of Tengzhou Central People's Hospital, and all subjects provided their written informed consent.

2.2 | Coronary angiography and SXscore

A coronary angiography was performed according to the method of Judkins, and CAD was defined as the presence of a luminal diameter stenosis of $\geq 50\%$ in the left main coronary artery, left anterior descending artery or its first diagonal branch, left circumflex artery or its first obtuse marginal branch, and right coronary artery. The control subjects were those who showed $< 30\%$ stenosis in all major vessels. Two experienced cardiologists performed the coronary angiography on every participant and analyzed the images separately. According to baseline diagnostic angiogram, each coronary lesion that created a stenosis obstructing $\geq 50\%$ of the diameter in vessels ≥ 1.5 mm was scored separately, and these scores were added to produce the overall SXscore, which was calculated using the SXscore algorithm. This algorithm is available on the SYNTAX website. The patients' SXscores were independently assessed by two experienced interventional cardiologists who were blinded to the carotid-US data. These cardiologists had previously calculated SXscore.

2.3 | Laboratory measurements

Blood samples of all subjects were obtained in the morning after a 10-hour overnight fast. The serum levers of FPG, serum creatinine (Scr), serum uric acid (sUA), cysteine (Cys), blood urea and nitrogen (BUN), and the lipid profiles, which included the triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), lipoprotein(a) (Lp(a)), apolipoprotein A1 (ApoA1), and apolipoprotein B (ApoB) levels, were quantified by enzymatic colorimetry methods on a Cobas 8000 autoanalyzer (Roche, Mannheim, Germany). HbA1c was detected by high-performance liquid chromatography (Tosoh Automated Glycohemoglobin Analyzer, TOSOH, Japan).

2.4 | Genotyping of polymorphisms

To identify the gene polymorphisms that are involved in the IL-23/IL-17 axis, we retrieved the information of potential related polymorphisms from the National Center for Biotechnology Information dbSNP database (<http://www.ncbi.nlm.nih.gov/projects/SNP>) and screened the published studies to obtain the potential risk polymorphism; then, the potential polymorphisms that met the following criteria were enrolled: (a) published results reported to be associated with an increased risk of CAD or a related disease; (b) the minor allele frequency (MAF) is not <5% in the Han Chinese population; and (c) located in the exons, promoter region, 5' untranslated regions (UTR) or 3' UTR.

The whole blood of all participants was collected in a vacutainer containing EDTA for the genotyping procedure. The genomic DNA was isolated based on a GoldMag-Mini Whole Blood Genomic DNA Purification kit (GoldMag Co. Ltd., Xian, China). The genotyping was performed on the Sequenom MassARRAY® system (iPLEX GOLD; Sequenom, San Diego, CA) according to the manufacturer's recommendations. Briefly, the DNA purity was measured by spectrometry (DU530UV/VIS spectrophotometer; Beckman Instruments, Fullerton, CA), and then, the PCR was performed with extension primers. The reaction products were dispensed onto a SpectroCHIP bioarray (Sequenom, San Diego, CA) and assayed on the MassARRAY platform. Mass differences were detected with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). The MassARRAY Workstation v.3.3 software was used to process and analyze the iPLEX SpectroCHIP bioarray, while the

Typer Analyzer v.3.4 software was used to analyze all of the genotypes that were obtained from the assays.

2.5 | Statistical analysis

The ANCOVA test was used to compare the differences in biochemical parameters among groups. For the case-control study, the statistical analysis for genotype distribution was performed by the chi-square test with SPSS 13.0 for Windows (SPSS, Chicago, IL). The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a logistic regression model that was adjusted for covariates, including age, sex, BMI, smoking and alcohol consumption, history of hypertension and T2DM, and HDL-C, LDL-C, TG, and TC levels. A *P* value < 0.05 was considered to represent a statistically significant difference.

3 | RESULTS

3.1 | General characteristics

A total of 322 patients were enrolled in this study, and 131 patients with an SXscore of 0 were identified as controls. A total of 191 patients were divided into the Low SXscore (≤ 22) (*n* = 151) and High SXscore (> 22) (*n* = 40) subgroups. There was no significant difference among the cases and controls for BMI, age, and prevalence of hypertension and alcohol consumption ($P_{all} > 0.05$). However, there was a significant difference between groups for gender (*P* = 0.023), prevalence of smokers (*P* = 0.001), and patients with T2DM (*P* < 0.001), as shown in Table 1.

TABLE 1 Characteristics of enrolled subjects

Characteristics	Control	CAD	<i>P</i> -value
Gender, male/female, %	48.85/51.15	61.78/38.22	0.023
Age, y	59.30 ± 7.76	60.82 ± 8.96	0.116
Body mass index, kg/m ²	25.66 ± 3.55	25.58 ± 3.48	0.840
Current or former smoker, %	28.24	47.12	0.001
Alcohol consumption	24.43	25.65	0.682
Hypertension, %	38.17	49.74	0.052
Type 2 diabetes mellitus, %	18.32	41.88	0.000
Fasting plasma glucose, mmol/L	5.84 ± 1.96	6.54 ± 2.37	0.006
Blood hemoglobin A1c, %	5.96 ± 1.06	6.67 ± 1.46	0.000
TG	1.60 ± 1.21	1.58 ± 0.94	0.882
Serum triglycerides, mmol/L	4.39 ± 0.95	4.33 ± 1.18	0.600
Serum HDL cholesterol, mmol/L	1.31 ± 0.36	1.15 ± 0.34	0.000
Serum LDL cholesterol, mmol/L	2.91 ± 0.87	2.74 ± 0.96	0.127
Lp(a)	42.51 ± 71.35	60.34 ± 66.93	0.023
ApoA1	1.27 ± 0.20	1.20 ± 0.26	0.017
ApoB	0.94 ± 0.24	0.97 ± 0.36	0.343
Blood urea nitrogen (BUN)	5.13 ± 1.49	5.35 ± 1.81	0.237
Serum creatinine (Scr), μmol/L	68.80 ± 16.97	72.87 ± 28.48	0.144
Serum uric acid, μmol/L	282.77 ± 76.53	295.23 ± 80.56	0.165
Cys	11.49 ± 4.85	12.77 ± 7.00	0.070

TABLE 2 Associations between polymorphisms and CAD risk

Gene	SNP	Genotype	Cases, n (%)	Controls, n (%)	OR (95% CI)	OR (95% CI) ^a
<i>IL17A</i>	rs8193036	CC	107 (56.02)	75 (57.25)	Reference	Reference
		CT	73 (38.22)	73 (32.82)	1.19 (0.74,1.92)	1.22 (0.72,2.05)
		TT	11 (5.46)	13 (9.92)	0.59 (0.25,1.40)	0.63 (0.25,1.62)
		CT/TT	84 (43.98)	56 (42.75)	1.05 (0.67,1.65)	1.11 (0.69, 1.81)
	rs2275913	GG	30 (15.71)	33 (25.19)	Reference	Reference
		AG	112 (58.64)	73 (55.73)	1.69 (0.95, 3.00)	1.45 (0.78, 2.67)
		AA	49 (25.65)	25 (19.08)	2.16 (1.08, 4.30)*	2.21 (0.95, 5.19)
		AG/ AA	161 (84.29)	98 (74.81)	1.81 (1.04, 3.15) [#]	1.62 (0.89, 2.93)
	rs3748067	CC	141 (73.82)	94 (71.76)	Reference	Reference
		CT	48 (25.13)	33 (25.19)	0.97 (0.58, 1.62)	1.03 (0.59, 1.78)
		TT	2 (1.05)	4 (3.05)	0.33 (0.06, 1.86)	0.36 (0.06, 2.16)
		CT/TT	50 (26.18)	37 (28.24)	0.90 (0.55, 1.48)	0.95 (0.55, 1.62)
<i>IL17F</i>	rs763780	TT	155 (81.15)	109 (83.21)	Reference	Reference
		GT	34 (17.80)	20 (15.27)	1.20 (0.65, 2.19)	1.17 (0.61, 2.25)
		GG	2 (1.05)	2 (1.53)	0.70 (0.10, 5.07)	0.39 (0.04, 3.54)
		GT/GG	36 (18.85)	22 (16.79)	1.15 (0.64, 2.06)	1.09 (0.57, 2.06)
<i>IL23R</i>	rs6682925	TT	52 (27.32)	42 (32.06)	Reference	Reference
		CT	87 (45.55)	67 (51.15)	1.05 (0.63, 1.76)	1.05 (0.60, 1.85)
		CC	52 (27.23)	22 (16.79)	1.91 (1.00, 3.63) [§]	1.94 (0.95, 3.93)
		CT/CC	139 (72.77)	89 (67.94)	1.26 (0.78, 2.05)	1.25 (0.74, 2.12)
	rs1884444	TT	69 (36.13)	47 (35.88)	Reference	Reference
		GT	92 (48.17)	67 (51.15)	0.94 (0.58, 1.52)	1.11 (0.65, 1.89)
		GG	30 (15.71)	17 (12.98)	1.20 (0.60, 2.42)	1.37 (0.63, 2.97)
		GT/GG	122 (63.87)	84 (64.12)	0.99 (0.62, 1.57)	1.13 (0.68, 1.87)
	rs10889677	GG	93 (48.69)	70 (53.44)	Reference	Reference
		GA	85 (44.50)	50 (38.17)	1.28 (0.80, 2.04)	1.38 (0.83, 2.28)
		AA	13 (6.81)	11 (8.40)	0.89 (0.38, 2.10)	0.75 (0.28, 2.00)
		GA/AA	98 (51.31)	61 (46.56)	1.21 (0.78, 1.89)	1.24 (0.77, 2.01)

OR, odds ratio.

^aAdjusted for age, gender, smoking, drinking, hypertension, and type 2 diabetes mellitus.**P* = 0.028,[#]*P* = 0.035,[§]*P* = 0.048

3.2 | Clinical characteristics

For the serum indexes, no significant differences were found for the levels of BUN, Scr, sUA, or Cys ($P_{\text{all}} > 0.05$) between the groups. However, the levels of FPG (CAD: 6.54 ± 2.37 vs controls: 5.84 ± 1.96 , $P = 0.006$) and HbA1C (CAD: 6.67 ± 1.46 vs controls: 5.96 ± 1.06 , $P = 0.006$) were higher in patients with CAD than in controls, as shown in Table 1. For the lipid profile, the levels of HDL (1.31 ± 0.36 vs 1.15 ± 0.34 , $P < 0.001$) and ApoA1 (1.27 ± 0.20 vs 1.20 ± 0.26 , $P = 0.017$) were significantly higher in the controls than those in cases, as shown in Table 1. In contrast, the level of Lp(a) in the cases was significantly higher than that of controls (42.51 ± 71.35 vs 60.34 ± 66.93), as shown in Table 1. In

addition, there were no significant differences among groups for the TG, TC, LDL, and ApoB levels, as shown in Table 1.

3.3 | Association between polymorphisms and CAD risk

The genotype frequencies of the selected polymorphisms in the controls did not deviate from HWE (shown in Table S1). Seven polymorphisms in *IL-17A/F* and *IL-23R* were observed in this study, and the logistic regression analysis revealed that *IL-17A* rs2275913 was associated with an increased risk of CAD (AA vs GG: crude OR = 2.16, 95% CI = 1.08–4.30; AG/AA vs GG: crude OR = 1.81, 95% CI = 1.04–3.15). Similarly, the *IL-23R* rs6682925 polymorphism

TABLE 3 Subgroup analysis of the associations between polymorphisms and CAD risk

Gene	SNP	Genotype	Low SXscore (≤ 22)		High SXscore (> 22)	
			Cases/Controls	OR (95% CI) ^a	Cases/Controls	OR (95% CI) ^a
<i>IL17A</i>	rs8193036	CC	87/75	Reference	20/75	Reference
		CT/TT	64/56	1.05 (0.63, 1.75)	20/56	1.36 (0.62, 2.98)
	rs2275913	GG	26/33	Reference	4/33	Reference
		AG/ AA	125/98	1.42 (0.77, 2.64)	36/98	2.77 (0.83, 9.19)
	rs3748067	CC	112/94	Reference	29/94	Reference
		CT/TT	39/37	0.97 (0.55, 1.70)	11/37	0.87 (0.36, 2.14)
<i>IL17F</i>	rs763780	TT	120/109	Reference	35/109	Reference
		GT/GG	31/22	1.27 (0.66, 2.46)	5/22	0.45 (0.14, 1.47)
<i>IL23R</i>	rs6682925	TT	47/42	Reference	5/42	Reference
		CT/CC	104/89	1.03 (0.60, 1.74)	35/89	3.72 (1.19, 11.66)*
	rs1884444	TT	59/47	Reference	10/47	Reference
		GT/GG	92/84	0.98 (0.58, 1.65)	30/84	2.23 (0.87, 5.71)
	rs10889677	AA	80/70	Reference	13/70	Reference
		CA/CC	71/61	1.07 (0.65, 1.77)	27/61	2.38 (1.03, 5.50) [#]

OR, odds ratio.

^aAdjusted for age, gender, smoking, drinking, and hypertension, and type 2 diabetes mellitus.

* $P = 0.015$,

[#] $P = 0.02$.

was observed to be associated with an increased risk of CAD (CC vs TT: crude OR = 1.91, 95% CI = 1.00-3.63). However, all of these significant associations were not maintained in the adjusted model, as shown in Table 2.

In addition, the logistic regression analysis showed that *IL-17A* rs8193036 and rs3748067, *IL-17F* rs763780, and *IL23R* rs1884444 and rs10889677 were not associated with CAD risk.

3.4 | Subgroup analysis of polymorphisms and CAD risk

The subgroup analysis was conducted based on the SXscore (low SXscore ≤ 22 and high SXscore > 22). The logistic regression analysis revealed that *IL-23R* rs6682925 (CT/CC vs TT: crude OR = 3.72, 95% CI = 1.19-11.66) and rs10889677 (CA/CC vs AA: crude OR = 2.38, 95% CI = 1.03- 5.50) were associated with an increased risk in patients with a high SXscore, as shown in Table 3.

4 | DISCUSSION

It is well-known that T2DM is a risk of CAD, and the published data show that CAD affects approximately 32.2% of all people with T2DM globally,¹⁷ which is consistent with our results showing that the prevalence of T2DM in patients was higher than that in controls and that the levels of FPG and HbA1C were higher in patients than in controls. Lp(a) has been identified as a risk factor for CAD, and

elevated Lp(a) levels were suggested to be independently associated with the presence and severity of CAD in patients with T2DM.¹⁸ In this study, we observed that the level of Lp(a) in patients was higher than that in controls. In contrast, the levels of the protective factors HDL-c and ApoA1 were higher in the controls than in the patients.

The *IL-17A* rs2275913 polymorphism is a substitution of the G by an A nucleotide base in the promoter region, and it has been suggested to be associated with several diseases, including CAD^{19,20}; however, this association may be inconsistent, as a published meta-analysis showed that rs2275913 was not associated with risk of CAD.¹³ In this study, we observed the rs2275913 AA and AG/AA genotype to be associated with an increased risk of CAD, which was consistent with the results of previous studies.²⁰ In contrast, the significant association could not be maintained after the analysis was adjusted for the demographic characteristics of participants, indicating that the association between rs2275913 and CAD risk could be modified by patient characteristics. A functional study found that the rs2275913 A allele is associated with a higher promoter activity of *IL-17A*, suggesting that the rs2275913 AA genotype appears to contribute to greater levels of inflammation, which can lead to several diseases, including CAD; this finding was consistent with the previous results showing that IL-17 may contribute to the severity of CAD.²¹

For the *IL-23R* polymorphisms, we observed a borderline significant association between *IL-23R* rs6682925 and the risk of CAD that was consistent with the results of the previous study.²² A functional study revealed that the rs6682925 C allele may increase

the promoter activity of *IL-23R*.^{22,23} In addition, *IL-23/IL-23R* polymorphisms are involved in pathogenesis of CAD by regulating the immune system.²⁴ A previous study showed that the *IL-23/IL-17* inflammatory signal could adjust the balance of Th17/Treg cells,²⁵ a process which was related to the progression of CAD.²⁶ Moreover, the *IL-23* level was suggested to be a marker of patients with CAD.²⁴

This study attempted to investigate the contributions of the *IL-17A* and *IL-23R* polymorphisms to CAD susceptibility. Although polymorphisms in *IL-17A* or *IL-23R* were shown by several previous studies to be associated with the risk of CAD, to our knowledge, this is the first study that attempted to investigate the polymorphisms in the genes that are involved in the *IL-23/IL-17* axis in an attempt to illustrate the systemic genetic risk of CAD. To confirm the lack of CAD in the individuals of the control group, we enrolled patients who had an SXscore of 0 as controls, which was in accordance with the purpose of this study. In addition, we reported all of the results of this study, which may be discussed in further studies. However, there were some limitations, which will be described. First, the sample size of this study was relatively small, and this may limit the statistical power, especially for the subgroup analysis. Second, CAD is a chronic disease; several environmental factors are involved in the pathology of disease progression, so the results of this study may be affected by limited characteristics of the enrolled subjects. Third, we failed to investigate the association between genotypes and gene expression.

In short, this study suggested that T2DM, Lp(a), HDL-c, and ApoA1 were risk factors of CAD, and the *IL-17A* rs2275913 and *IL-23R* rs6682925 polymorphisms may contribute to the susceptibility of CAD, which should be confirmed by further studies with large sample sizes.

CONFLICT OF INTERESTS

The authors have declared that no competing interest exists.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.