Effect of polymorphisms in interleukin-18 gene on the susceptibility to coronary artery disease in a Chinese population

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ABSTRACT. Coronary artery disease (CAD) has a high mortality rate in several countries. Interleukin (IL)-18 has been previously correlated with atherosclerotic plaque rupture. In this case-control study, the relationship between -607A/C and -372C/G promoter polymorphisms in *IL-18* and risk of CAD development was investigated. A total of 326 CAD patients were consecutively recruited from the First Hospital of Yulin between March 2013 and May 2015. The *IL-18* -607A/C and -372C/G polymorphisms were genotyped by polymerase chain reaction-restriction fragment length polymorphism. Patients with CAD had a higher body mass index, a history of hypertension or diabetes (all $P < 0.001$), cigarette smoking habit ($P = 0.002$); as well as higher plasma total cholesterol, triglyceride, and low-density lipoprotein cholesterol

levels (all P < 0.001) and lower high-density lipoprotein cholesterol (P < 0.001) levels compared to the control subjects. Unconditional logistic regression analysis revealed significant correlation between the CC genotype of *IL-18* -607A/C and CAD development, compared to the AA genotype [adjusted odds ratio (OR) = 2.42; 95% confidence interval (CI) = 1.52-3.89; P < 0.001]. The recessive model showed a significant association between the CC genotype of *IL-18* -607A/C and an increased risk of CAD, compared to the AA+AC genotype (OR = 2.51, 95%CI = 1.65-3.85). However, *IL-18* -372C/G did not contribute to the risk of glioma development in the co-dominant, dominant, and recessive models. Therefore, the *IL-18* -607C/A polymorphism was significantly correlated with the risk of CAD development.

Key words: IL-18; -607A/C; -372C/G; Polymorphism; Coronary artery disease

INTRODUCTION

Coronary artery disease (CAD) is commonly associated with a high mortality rate in most countries; more than 80% of the CAD cases have been reported in low- to median-income countries (He et al., 2005). CAD develops as a result of vascular tract stenosis or occlusion caused by coronary atherosclerotic lesions and several environmental and lifestyle factors (Campbell et al., 1998; Erbel and Görge, 2014; Bullock-Palmer, 2015). Previous experimental studies at the molecular level have indicated that many genetic factors, including the genes encoding angiotensinogen and angiotensin-converting enzyme, hepatic lipase, insulin receptor substrate-1, kinesin family member 6, cholesteryl ester transfer protein, ATP-binding cassette subfamily A member 1, and apoptotic extrinsic death receptor, have an important role in the risk of CAD development (Bonfim-Silva et al., 2016; Cyrus et al., 2016; Kishore Kumar et al., 2016; Mohammadzadeh et al., 2016; Vatte et al., 2016; Zhang et al., 2016).

The inflammatory response could promote the formation and stability of plaques (Libby et al., 2002). Previous studies have indicated that several inflammatory factors contribute to the development of CAD, such as C-reactive protein, tumor necrosis factor, interleukin-6 (IL-6), IL-17A, and transforming growth factor (Zernecke et al., 2008; Yang et al., 2015; Zheng et al., 2016). An association has also been reported between IL-18 and atherosclerotic plaque rupture (de Nooijer et al., 2004), which, in turn, is believed to influence the occurrence of CAD (Opstad et al., 2011). Polymorphisms in *IL-18* are also believed to influence gene transcription, alter IL-18 expression, and promote development of cardiovascular diseases (Liu et al., 2013; Lu et al., 2013; Opstad et al., 2013; Hazzaa et al., 2014). Here, we performed a case-control study to investigate the relationship between the -607A/C and -372C/G polymorphisms in the promoter region of *IL-18* and risk of CAD development.

MATERIAL AND METHODS

Patients

A total of 326 patients with CAD were consecutively recruited from the First Hospital

of Yulin between March 2013 and May 2015. CAD was newly diagnosed and confirmed by coronary angiography in all patients. CAD was characterized by a stenosis diameter of 50% in any of the major coronary arteries, such as the left main, left anterior descending, left circumflex, and right coronary arteries.

Control subjects were randomly selected from among individuals who visited the outpatient clinic of our hospital for a regular health check-up during the same time period. The controls were age- (± 5 years) and gender-matched with the CAD patients. All control subjects were confirmed to be free of CAD or other cardiovascular diseases, chronic or acute infectious diseases, or malignant tumors.

The demographic, environmental, and clinical characteristics of the recruited patients and controls were obtained from medical records. The demographic and environmental factors included the gender, age, body mass index (BMI), history of hypertension and diabetes, habit of cigarette smoking and alcohol consumption levels, and so on. The clinical variables included the total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels. Signed informed consent forms were obtained from all participants. This study was approved by the Ethics Committee of the First Hospital of Yulin.

Genotyping

Blood samples were collected from the cases and controls in EDTA-coated tubes. Total genomic DNA was extracted from these samples, using the Tiangen® DNA Blood Min kit (Tiangen Biotech Co., Ltd., Beijing, China). The *IL-18* -607A/C and -372C/G polymorphic sites were genotyped by polymerase chain reaction (PCR)-restriction fragment length polymorphism. The forward and reverse primers for *IL-18* -607A/C and -372C/G were 5'-GTTGCAGAAAGTGAAAAATTATTAC-3' and 5'-GTTGCAGAAAGTGTAAAAATTATTAA-3' and 5'-CCCCAACTTTTACGGAAGAAAAG-3' and 5'-CCCCAACTTTTACGGAAGAAAAC-3', respectively. The *IL-18* -607A/C and -372C/G polymorphic sites were digested with *Mse*I and *Bfu*CI, respectively. The PCR conditions were set as follows: initial denaturation at 94°C for 5 min, 30 cycles of denaturation at 94°C for 45 s, annealing at variable temperatures for 30 s, and extension at 72°C for 45 s. The amplification was verified on a 1.5% agarose gel.

Statistical analysis

Statistical variations between the demographic and clinical variables of the two study groups were determined using the chi-square (χ^2) test for categorical data and the Student *t*-test for continuous variables. Probable deviations of the *IL-18* -607A/C and -372C/G polymorphisms from the Hardy-Weinberg equilibrium (HWE) were determined using the chi-square test, where the observed values were compared with the expected values. The correlation between *IL-18* -607A/C and -372C/G polymorphisms and risk of CAD was analyzed by multivariate logistic regression analysis, and the results are reported as odds ratios (ORs) with their corresponding 95% confidence intervals (CI). Interactions between the *IL-18* -607A/C and -372C/G polymorphisms and the potential risk factors of CAD were analyzed by the Spearman correlation analysis. Data analysis was performed using SPSS v.17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

As expected, the CAD patients and controls are comparable in terms of age (χ^2 = 0.09, P = 0.75) and gender (χ^2 < 0.001, P = 1.00) (Table 1). The chi-square and Student *t*-tests showed no significant differences in the alcohol consumption levels (χ^2 = 1.16, P = 0.28) between the CAD patients and control subjects. The patients with CAD had higher BMI (χ^2 = 19.83, P < 0.001), higher probability of a history of hypertension (χ^2 = 52.49, P < 0.001) or diabetes (χ^2 = 8.65, P = 0.003), cigarette smoking habit (χ^2 = 9.29, P = 0.002), as well as higher plasma TC (*t* = 4.61, P < 0.001), TG (*t* = 4.70, P < 0.001), and LDL-C (*t* = 9.01, P < 0.001) levels, and lower HDL-C (*t* = 12.31, P < 0.001) levels compared to the control subjects.

Table 1. Demographic, lifestyle, and clinical characteristics of patients with coronary artery disease (CAD) and control subjects included in this study.

Variables	Patients (N = 326)	%	Controls (N = 326)	%	χ^2 or *t*-value	P value
Age (years)						
<60	148	45.40	152	46.63		
≥60	178	54.60	174	53.37	0.09	0.75
Gender						
Male	214	65.64	214	65.64		
Female	112	34.36	112	34.36	<0.001	1.00
BMI (kg/m^2)						
<24	187	57.36	241	73.93		
≥24	139	42.64	85	26.07	19.83	<0.001
Hypertension						
No	180	55.21	266	81.60		
Yes	146	44.79	60	18.40	52.49	<0.001
Diabetes						
No	246	75.46	276	84.66		
Yes	80	24.54	50	15.34	8.65	0.003
Alcohol consumption						
Never	210	64.42	223	68.40		
Yes	116	35.58	103	31.60	1.16	0.28
Cigarette smoking						
Never	179	54.91	217	66.56		
Yes	147	45.09	109	33.44	9.29	0.002
TC (mM/dL)		195.52 ± 41.67		181.34 ± 36.75	4.61	<0.001
TG (mM/dL)		135.34 ± 39.52		121.53 ± 35.40	4.70	<0.001
LDL-C (mM/dL)		121.50 ± 34.20		98.64 ± 30.55	9.01	<0.001
HDL-C (mM/dL)		36.72 ± 8.63		45.60 ± 9.76	12.31	<0.001

BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

The AA, AC, and CC genotypes of *IL-18* -607A/C were observed in 33.13% (108), 39.26% (128), and 27.61% (90) of all patients, and 38.34% (125), 48.47% (158), and 13.19% (43) of the control subjects, respectively. Alternately, the GG, GC, and CC genotypes of the *IL-18* -372G/C polymorphism were observed in 69.02% (225), 27.61% (90), and 3.37% (11) of all patients, and 73.01% (238), 24.54% (80), and 2.45% (8) controls, respectively (Table 2). The chi-square test revealed significant differences between genotype distributions of *IL-18* -607A/C (χ^2 = 21.00, P < 0.001) and no significant differences between the genotype distributions of *IL-18* -372C/G (χ^2 = 1.43, P = 0.49). The genotype frequencies of *IL-18* -607A/C (χ^2 = 0.40, P = 0.53) and -372C/G (χ^2 = 0.17, P = 0.68) in the control subjects were in line with the HWE.

Table 2. Genotype distributions of the interleukin 18 (*IL-18*) -607A/C and -372C/G polymorphisms in the patients and controls.

IL-18	Patients (N = 326)	%	Controls (N = 326)	%	χ^2	P value	HWE in controls	
							Chi-square	P value
-607A/C								
AA	108	33.13	125	38.34				
AC	128	39.26	158	48.47				
CC	90	27.61	43	13.19	21.00	<0.001	0.40	0.53
-372G/C								
GG	225	69.02	238	73.01				
GC	90	27.61	80	24.54				
CC	11	3.37	8	2.45	1.43	0.49	0.17	0.68

HWE, Hardy-Weinberg equilibrium.

Unconditional logistic regression analysis revealed a significant correlation between the CC genotype of *IL-18* -607A/C and CAD development, compared to the AA genotype (adjusted OR = 2.42; 95%CI = 1.52-3.89; P < 0.001) (Table 3). Alternately, the recessive model showed a significant correlation between the CC genotype of *IL-18* -607A/C and an increased risk of CAD, compared to the AA+AC genotype (OR = 2.51, 95%CI = 1.65-3.85). However, the *IL-18* -372C/G did not contribute to the risk of glioma development.

Table 3. Relationship between *IL-18* -607A/C and -372C/G polymorphisms and risk of coronary artery disease (CAD).

IL-18	Patients (N = 326)	%	Controls (N = 326)	%	Multivariate logistic regression analysis	
					Adjusted OR (95%CI)[1]	P value
-607A/C						
Co-dominant model						
AA	108	33.13	125	38.34	1.0 (Ref.)	-
AC	128	39.26	158	48.47	0.94 (0.65-1.35)	0.72
CC	90	27.61	43	13.19	2.42 (1.52-3.89)	<0.001
Dominant model						
AA	108	33.13	125	38.34	1.0 (Ref.)	-
AC+CC	218	66.87	201	61.66	1.26 (0.90-1.75)	0.16
Recessive model						
AA+AC	236	72.39	283	86.81	1.0 (Ref.)	-
CC	90	27.61	43	13.19	2.51 (1.65-3.85)	<0.001
-372G/C						
Co-dominant model						
GG	225	69.02	238	73.01	1.0 (Ref.)	-
GC	90	27.61	80	24.54	1.19 (0.82-1.72)	0.33
CC	11	3.37	8	2.45	1.45 (0.52-4.24)	0.43
Dominant model						
GG	225	69.02	238	73.01	1.0 (Ref.)	-
GC+CC	101	30.98	88	26.99	1.21 (0.85-1.73)	0.26
Recessive model						
GG+GC	315	96.63	318	97.55	1.0 (Ref.)	-
CC	11	3.37	8	2.45	1.39 (0.50-4.03)	0.48

[1]Adjusted for body mass index, hypertension, diabetes, cigarette smoking, total cholesterol, triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. OR, odds ratio; CI, confidence interval.

Spearman correlation analysis revealed no significant correlation between the *IL-18* -607A/C and -372C/G polymorphisms and BMI, hypertension, diabetes, and cigarette smoking habit, and the TC, TG, LDL-C, and HDL-C levels in CAD risk (P values for all correlations >0.05).

DISCUSSION

The *IL-18* -607C/A and -137G/C polymorphisms are located at the junction of the response elements of nuclear factor cAMP binding protein. Previous studies have indicated that the *IL-18* -607C/A and -137G/C polymorphisms influence the expression of IL-18 and IFN-γ; moreover, the expression of *IL-18* -607CC and -137GG genotypes were significantly higher those of other genotypes (Giedraitis et al., 2001). IL-18 expression is also positively correlated with the expression of *IL-18* mRNA (Giedraitis et al., 2001). Additionally, the A and C alleles of *IL-18* -607C/A and -137G/C are believed to induce low IL-18 activity (Giedraitis et al., 2001; Liang et al., 2005; Arimitsu et al., 2006). Some studies have also indicated that patients with cardiovascular and cerebrovascular diseases have significantly higher levels of IL-18 in the plasma compared to the healthy controls, which was associated with disease development (Chen et al., 2007; Gao et al., 2010; Liu et al., 2013; Li et al., 2014). Here, we attempted to elucidate the association between the *IL-18* -607C/A and -137G/C polymorphisms and risk of CAD; we determined that the CC genotype of *IL-18* -607A/C could elevate the risk of CAD, compared to the wild-type genotype.

Previous studies have indicated a close association between functional *IL-18* polymorphisms and the risk of developing cardiovascular and cerebrovascular diseases (Thompson et al., 2007; Liu et al., 2009; Pei et al., 2009; Hernesniemi et al., 2010a,b; Zhang et al., 2010; Lu et al., 2013). Liu et al. (2009), in a study conducted in 241 Chinese patients with CAD and 145 control subjects, reported that the *IL-18* -137G/C polymorphism influenced IL-18 expression and the occurrence of CAD. Pei et al. (2009) and Lu et al. (2013) reported that the *IL-18* -607C/A polymorphism influenced the risk of acute myocardial infarction or ischemic stroke in a northern Chinese Han population. However, other studies did not find any significant association between *IL-18* polymorphisms and coronary heart disease and atherosclerosis (Thompson et al., 2007; Hernesniemi et al., 2010a,b). The discrepancies among these studies could be attributed to differences in the diseases investigated, study populations, study design, and sample size.

Three major limitations should be paid attention. Firstly, patients and controls were selected from only one hospital, which could induce selection bias in our study. Secondly, polymorphisms in genes other than *IL-18* (-607C/A and -137G/C) may influence the development of this disease, and interact with *IL-18*.

In summary, we observed a statistically significant relationship between the *IL-18* -607C/A polymorphism and risk of developing coronary artery disease; however, the *IL-18* -137G/C polymorphism was not correlated with this disease. Our results should be confirmed by further studies.

Conflicts of interest

The authors declare no conflict of interest.

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