Interleukin-6 (IL-6) -174G/C genomic polymorphism contribution to the risk of coronary artery disease in a Chinese population

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ABSTRACT. To investigate the role of *IL-6* polymorphism (-174G/C and -572C/G) in the development of coronary artery disease (CAD), CAD patients (224) and control subjects (260) were recruited between January 2012 and December 2014. Genotyping at *IL-6* -174G/C and -572C/G was conducted via polymerase chain reaction coupled to restriction fragment length polymorphism. Results indicated that several disease risk factors were significantly higher in CAD patients as compared to the control subjects. These factors include hypertension (χ^2 = 20.03, P < 0.001), diabetes mellitus (χ^2 = 33.53, P < 0.001), tobacco smoking (χ^2 = 28.17, P < 0.001), body mass indexes (t = 11.39, P < 0.001), total cholesterol (t = 8.25, P < 0.001), low-density lipoprotein cholesterol (t = 7.24, P < 0.001), high-density lipoprotein cholesterol (t = 3.52, P < 0.001), and triglyceride (t = 6.09, P < 0.001). By unconditional logistic regression analysis, we observed that the CC genotype at *IL-6* -174G/C was had a 2.32 (95%CI = 1.33-4.06) fold risk of developing CAD compared to the GG genotype. Moreover,

IL-6 -174G/C polymorphism was positively associated with the risk of developing CAD in both dominant (OR = 1.63, 95%CI = 1.12-2.38; P = 0.01) and recessive models (OR = 2.18, 95%CI = 1.26-3.77; P = 0.001). However, no statistically significant association was observed between *IL-6* -572C/G polymorphism and risk of CAD. In conclusion, *IL-6* -174G/C polymorphisms are associated with the pathogenesis of CAD.

Key words: Coronary artery disease; Interleukin 6; Polymorphism

INTRODUCTION

Coronary heart disease, also referred to as coronary artery disease (CAD), is the most common cardiovascular disease in both developed and developing regions (He et al., 2005; Go et al., 2014), and is related with high death rate and loss of disability-adjusted life years (Go et al., 2014). CAD is a complex and multifactor disease, and can be attributed to a variety of factors such as hypertension, hypercholesterolemia, lack of physical activities, diabetes, high body mass indexes, tobacco smoking, and intake of high fat and high calorie diet (Wilson et al., 1998), whereas only few of individuals with the risk factors of CAD eventually develop this disease. Therefore, inherited factors appear to be involved in the pathogenesis of CAD (Marenberg et al., 1994). Previous studies have demonstrated that genetic polymorphisms are associated with the risk of CAD, such as methylenetetrahydrofolate reductase (MTHFR) gene, angiotensin type 2 receptor, alcohol dehydrogenase, and acetaldehyde dehyrogenase 2 (Dhar et al., 2010; Tousoulis et al., 2010; Xu et al., 2010; Han et al., 2013).

Research has shown that inflammation is associated with the pathogenesis of CAD through promotion of atherosclerosis (Ross, 1999). Cytokines are the main mediators of the inflammatory response. The *IL-6* gene, located at chromosome 7p21-24, is composed of 4 introns and 5 exons. Since single nucleotide polymorphisms of IL-6 gene promoter may affect the expression and secretion of *IL-6*, and subsequently the altered circulating levels might result in relevant biological responses, and the *IL-6* polymorphism has been regarded as a crucial modulator in pathogenesis of various diseases, including Alzheimer's disease, type 2 diabetes, celiac disease, chronic obstructive pulmonary disease and osteoarthritis (de Albuquerque Maranhão et al., 2015; Fernandes et al., 2015; Xie et al., 2015; Buraczynska et al., 2016; Ramos Dos Santos et al., 2016). Although several studies have shown that *IL-6* polymorphisms could be also involved in the development of CAD, the conclusions were not consistent (Li et al., 2015; Liu et al., 2015; Wang et al., 2015; Yang et al., 2015). Here, we carried out a case-control study to evaluate the association between *IL-6* -174G/C and -572C/G genomic variants and CAD risk in the Chinese population.

MATERIAL AND METHODS

Patients

A hospital-based case-control design was conducted. A total of 224 CAD patients (79 females and 145 males, mean age 62.65 ± 9.72 years) and 260 health subjects (113 females and 147 males, mean age 56.82 ± 9.80 years) were selected from the Department of Cardiology,

Henan Provincial People's Hospital, between February 2012 and January 2015. These patients were confirmed by at least two cardiologists using coronary angiography. CAD was defined as a diameter stenosis of above 70% in any main coronary arteries. Patients who had malignancies, myocardial spasms, myocardial bridges, as well as those suffering from autoimmune diseases, congenital heart diseases, or end-stage kidney or liver diseases were excluded from the study. Healthy control subjects were randomly selected from the physical examination center or the outpatient clinics at the Henan Provincial People's Hospital. These subjects were confirmed to have no history of arteriosclerotic lesions or cardiovascular diseases.

The demographic and lifestyle data of CAD patients and control subjects were selected through face to face interview using structured questionnaires, including information regarding gender, age, body mass index, tobacco smoking, alcohol drinking, diabetes, and hypertension. Clinical data obtained from medical records included information in terms of cholesterol (TC) level, low-density lipoprotein cholesterol (LDL-c) level, and high-density lipoprotein cholesterol (HDL-c) level, as well as triglyceride (TG) level.

The written consent of all participants was obtained by informing them about the details of the study and getting their approval. Study procedures carried out with permission from the Institutional Review Board of the Henan Provincial People's Hospital.

Genetic analysis

Five mL peripheral venous blood sample was obtained from each participant. DNA was extracted from the collected blood samples using the TIANamp Blood DNA Kit (Tiangen, Beijing, China) according to manufacturer recommendation. The genotyping for *IL-6* -174G/C and -572C/G polymorphic sites was determined by polymerase chain reaction (PCR) coupled to restriction fragment length polymorphism (RFLP). DNA samples were amplified using two different primer pairs specific for *IL-6* -174G/C and -572C/G genes. For *IL-6* -572 C/G, primer sequences were 5'-GGA GTC ACA CAC TCC ACC T-3' and 5'-CTG ATT GGA AAC CTT ATT AAG-3', respectively. For IL-6 -572C/G, primer sequences were 5'-GAG ACG CCT TGA AGT AAC TG-3' and 5'-GAG TTT CCT CTG ACT CCA TCG CA-3', respectively. The restriction enzymes for *IL-6* -174G/C and -572C/G were *Hsp*92II and *Mbi*I, respectively. The PCR conditions are as follows: initial melting step of 95°C for 5 min, and followed by 30 cycles of 94°C for 30 s, 60°C for 30 s, and 72°C for 45 s, and final extension was carried out for 7 min at 72°C for the two polymorphic sites. Digestion products were checked by using electrophoresis on ethidium bromide stained agarose gels.

Statistical analysis

The Fisher exact test was carried out to determine whether genotype and allele frequencies of *IL-6* -174G/C and -572C/G were in agreement with the Hardy-Weinberg equilibrium (HWE). An unconditional multivariate logistic model was used to evaluate the association between *IL-6* polymorphisms and the risk of developing CAD. The results are represented by odds ratios (OR) along with their corresponding 95% confidence intervals (CIs). The most frequent genotype (GG for *IL-6* -174G/C and CC for) was used as reference group for *IL-6* -174G/C and -572C/G genes. The SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Results were considered statistically significant when the $P \leq 0.05$.

RESULTS

As compared with the control subjects, some demographic, lifestyle and clinical factors such as hypertension ($\chi^2 = 20.03$, P < 0.001), diabetes mellitus ($\chi^2 = 33.53$, P < 0.001), tobacco smoking ($\chi^2 = 28.17$, P < 0.001), high body mass indexes ($t = 11.39$, P < 0.001), high TC ($t = 8.25$, P < 0.001), high LDL-c ($t = 7.24$, P < 0.001), high HDL-c ($t = 3.52$, P < 0.001), and high TG ($t = 6.09$, P < 0.001) were more prevalent in the CAD patients (Table 1).

Table 1. Demographic, lifestyle and clinical characteristics of the recruited CAD patients and control subjects.

Variables	CAD patients (N = 224)	%	Controls (N = 260)	%	χ^2 test or t test	P value
Mean age, years	62.65 ± 9.72		56.82 ± 9.80			
Gender						
Male	145	64.6	147	56.7		
Female	79	35.4	113	43.3	3.38	0.07
Hypertension						
No	106	47.4	176	67.5		
Yes	118	52.6	85	32.5	20.03	<0.001
Diabetes mellitus						
No	152	67.7	232	89.3		
Yes	72	32.3	28	10.7	33.53	<0.001
Alcohol drinking						
Never	108	48.37	136	52.3		
Current or ever	116	51.63	124	47.7	0.81	0.37
Tobacco smoking						
Never	97	43.1	175	67.4		
Current or ever	127	56.9	85	32.6	28.17	<0.001
Body Mass Index, kg/m^2	24.61 ± 4.16		21.57 ± 3.64		11.39	<0.001
TC, mg/dL	195.25 ± 41.52		167.40 ± 32.65		8.25	<0.001
LDL-c, mg/dL	116.30 ± 25.36		99.43 ± 25.76		7.24	<0.001
HDL-c, mg/dL	39.42 ± 20.44		44.63 ± 11.42		3.52	<0.001
TG, mg/dL	132.56 ± 42.53		113.26 ± 26.30		6.09	<0.001

As confirmed by chi-square tests, CAD patients and control subjects differed significantly in genotype frequencies at *IL-6* -174G/C ($\chi^2 = 10.85$, P = 0.004), whereas no significant difference was observed between *IL-6* -572C/G genetic polymorphism and CAD risk (Table 2). In addition, genotype distributions of *IL-6* -174G/C were not in agreement with HWE in both groups, whereas those of *IL-6* -572C/G were in accordance with the HWE.

The relationship between *IL-6* gene polymorphisms and development of CAD are summarized in Table 3. Using unconditional logistic regression analysis, we observed that the CC genotype at *IL-6* -174G/C was had a 2.32 (95%CI = 1.33-4.06) fold risk of developing CAD compared to the GG genotype. Moreover, *IL-6* -174G/C polymorphism was positively associated with the risk of developing CAD in both dominant (OR = 1.63, 95%CI = 1.12-2.38; P = 0.01) and recessive models (OR = 2.18, 95%CI = 1.26-3.77; P = 0.001). However, no statistically significant association was observed between *IL-6* -572C/G polymorphism and risk of CAD in codominant, dominant, or recessive models.

Table 2. Genotype distributions of *IL-6* -174G/C and -572G/C gene polymorphisms between the two study groups.

IL-6	Patients (N = 224)	%	Controls (N = 360)	%	P value for HWE		χ^2 test	P value
					In cases	In controls		
-174G/C								
GG	142	63.39	267	74.17				
GC	45	20.09	63	17.50				
CC	37	16.52	30	8.33	<0.001	<0.001	10.85	0.004
-572 C/G								
CC	97	43.30	147	40.83				
CG	110	49.11	176	48.89				
GG	17	7.59	37	10.28	0.06	0.14	1.28	0.53

HWE = Hardy-Weinberg equilibrium.

Table 3. Relationship between *IL-6* -174G/C and -572G/C gene polymorphisms and development of CAD.

IL-17	Patients (N = 224)	%	Controls (N = 260)	%	OR (95%CI)[1]	P value
-174G/C						
Co-dominant						
GG	142	63.39	193	74.17	1.0 (Ref.)	-
CG	45	20.09	45	17.5	1.34 (0.85-2.12)	0.18
CC	37	16.52	22	8.33	2.32 (1.33-4.06)	<0.001
Dominant						
GG	142	63.39	193	74.17	1.0 (Ref.)	-
CG+CC	82	36.61	67	25.83	1.63 (1.12-2.38)	0.01
Recessive						
GG+CG	187	83.48	238	91.67	1.0 (Ref.)	-
CC	37	16.52	22	8.33	2.18 (1.26-3.77)	0.001
-572G/C						
Co-dominant						
CC	81	36.3	106	40.83	1.0 (Ref.)	-
GC	110	49.11	127	48.89	1.12 (0.75-1.68)	0.56
GG	33	14.59	27	10.28	1.60 (0.86-2.95)	0.11
Dominant						
CC	81	36.3	106	40.83	1.0 (Ref.)	-
GC+GG	143	63.7	154	59.17	1.21 (0.82-1.77)	0.32
Recessive						
CC+GC	191	85.41	233	89.72	1.0 (Ref.)	-
GG	33	14.59	27	10.28	1.50 (0.85-2.63)	0.13

[1]Adjusted for age, gender, hypertension, diabetes mellitus, tobacco smoking, body mass index, TC, LDL-c, HDL-c, and TG.

DISCUSSION

In recent years, genomic susceptibility to diseases has attracted a growing attention to research the genetic polymorphisms involving in pathogenesis of diseases. The inflammatory status is an important step to keep and promote the pathogenesis of atherosclerosis. It is reported that the gene polymorphisms of inflammatory cytokine could affect cytokine mRNA transcription and thus change the serum levels of inflammatory cytokine (Larcombe et al., 2005). In the recent studies, emphasis often be focused on investigating the role of IL-6 polymorphisms to several kinds of diseases, such as chronic obstructive pulmonary disease, cardiovascular disease, HBV-related liver disease, or osteoporosis (Chang et al., 2015; Xie et al., 2015; Yan et al., 2015; Buraczynska et al., 2016). In our study, we carried out a study to investigate the role of *IL-6* polymorphisms in the risk of CAD, and we revealed that the *IL-6* -174G/C genomic polymorphism was correlated with an elevated risk to CAD in multiple genetic models.

Previous studies have shown that the *IL-6* genomic variants is associated with IL-6 levels to the susceptibility to many diseases (Kiszel et al., 2006; Talar-Wojnarowska et al., 2009; Yeh et al., 2010). Talar-Wojnarowska et al. (2009) done a study with 97 pancreatic cancer or chronic pancreatitis patients and 50 healthy volunteers, and reported that IL-6 -174G/C gene polymorphism was correlated with circulating IL-6 levels and pathogenesis of pancreatic cancer. Yeh et al. (2010) carried out a study in Taiwanese, and revealed that *IL-6* -174G/C genomic variant could affect the expression and serum IL-6 and incidences of colorectal cancer. Therefore, the *IL-6* genomic polymorphism may be associated with plasma level of *IL-6* and thus influence the development of inflammation related diseases.

Although many studies assessed the relationship between *IL-6* gene polymorphisms and pathogenesis of CAD, they reported conflicting results (Nauck et al., 2002; Vakili et al., 2011; Ghazouani et al., 2011; Phulukdaree et al., 2013; Satti et al., 2013; Elsaid et al., 2014; Sun et al., 2014; Wang et al., 2015). Three studies reported that the IL-6 -174 G allele

was associated with higher mRNA expression levels of IL-6 and increased the risk of CAD (Vakili et al., 2011; Satti et al., 2013; Elsaid et al., 2014), whereas Phulukdaree et al. (2013) demonstrated that IL-6 -174 C allele could influence levels of IL-6 and increased the risk of CAD. Two studies carried out studies in Chinese population, and reported that IL-6 -174G/C genomic polymorphisms could influence the risk of CAD (Sun et al., 2014; Wang et al., 2015). However, Nauck et al. (2002) and Ghazouani et al. (2011) reported that IL-6 -174G/C had not significantly correlation with CAD risk. In our study, we revealed that *IL-6* -174G/C genomic variation was correlated with a higher risk of CAD. The discrepancies between our results and those of studies may be due to differences in study populations, experimental designs, and sample size.

In conclusion, based on our results, we suggest that *IL-6* -174G/C polymorphisms are associated with the pathogenesis of CAD. Further studies are needed to elucidate the impact of *IL-6* genomic polymorphisms in the risk of CAD.

Conflicts of interest

The authors declare no conflicts of interest.

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