Association of interleukin gene polymorphisms with the risk of coronary artery disease

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ABSTRACT. We conducted a case-control study to investigate the genetic variants *Interleukin-1β* (*IL-1β*) +3953 C/T (rs1143634), *IL-6* -174G/C (rs1800795), *IL-8* -251T/A (rs4073), and *IL-10* -1082A/G (rs1800896) and -819C/T (rs1800871) in the development of coronary artery disease (CAD). A total of 410 individuals with CAD were enrolled between January 2012 and December 2014. Genotyping of the five gene polymorphisms was performed using the polymerase chain reaction combined with restriction fragment length polymorphism methodology. By multivariate logistic regression analysis, we found that the frequencies of the CC genotype and the C allele of *IL-6* -174G/C were significantly correlated with a higher risk of CAD; the adjusted ORs (95%CIs) were 2.37 (1.37-4.14) and 1.49 (1.19-1.86), respectively. In addition, the AG and GG genotypes and the G allele of *IL-10* -1082A/G were also significantly associated with a higher risk of CAD, and the ORs (95%CIs) were 1.42 (1.04-1.95), 2.16 (1.42-3.30), and 1.56 (1.27-1.93), respectively. However, *IL-1β* +3953 C/T, *IL-8* -251T/A, and *IL-10* -819C/T did not significantly correlate with CAD risk.

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Our study suggests that the *IL-6* -174G/C (rs1800795) and *IL-10* -1082A/G (rs1800896) polymorphisms might be involved in the pathogenesis of CAD, and likely contribute to the genetic susceptibility for CAD.

Key words: Interleukin gene; Polymorphism; Coronary artery disease

INTRODUCTION

Cardiovascular disease is a complex-trait disease and is the leading cause of morbidity and mortality worldwide, including in China (Go et al., 2014; He et al., 2005). Coronary artery disease (CAD) is the most common heart disease associated with atherosclerosis, the development of which involves a complex, multistep, and multifactorial process, including both genetic and environmental factors (Guo et al., 2010; Go et al., 2014). It has been reported that hypertension, hypercholesterolemia, diabetes, obesity, and tobacco smoking as well as alcohol drinking play critical roles in the development of CAD (Marenberg et al., 1994). However, environmental factors are not the best predictors of CAD risk, suggesting that genetic variants might influence the development of CAD. Previous studies have reported that a number of genetic polymorphisms might play an important role in the development of CAD including cytochrome P450 17A1 (*CYP17A1*), toll-like receptors, metallothionein 2A, and retinol binding protein 4, as well as matrix metalloproteinase 1 (Qintao et al., 2014; Wan et al., 2014; Yang et al., 2014; Dai et al., 2015; Guven et al., 2015).

It has been reported that inflammatory processes influence the progression of atherogenesis, and that cytokines are involved in the migration of neutrophils, lymphocytes, and antigen-presenting cells including dendritic cells and cells of a monocyte/macrophage lineage (Kaur et al., 2013). Polymorphisms in cytokine genes could alter the function of protein expression and thus influence their roles in the process of cardiovascular disease. Specifically, previous studies have indicated that genetic variants of interleukin genes, such as interleukin-1β (*IL-1β*), *IL-1α*, *IL-6*, *IL-10*, *IL-16*, *IL-18*, and *IL-23A* could affect the development of CAD (Romani et al., 2014; Armingohar et al., 2015; Chi et al., 2015; Jia et al., 2015; Tripathi et al., 2015; Yue et al., 2015).

Identification of such genetic variants could help evaluate the risk of CAD; for example, by identifying high-risk individuals. In this study, we conducted a case-control study to investigate the role of the genetic variants *IL-1β* +3953C/T (rs1143634), *IL-6* −174G/C (rs1800795), *IL-8* −251T/A (rs4073), and *IL-10* −1082A/G (rs1800896) and −819C/T (rs1800871) in the development of CAD.

MATERIAL AND METHODS

Subjects

In the present case-control study, a total of 410 individuals with CAD and 410 unaffected individuals were enrolled from Henan Provincial People's Hospital between January 2012 and December 2014. The patients with CAD were diagnosed by angiography, and CAD was defined as the presence of at least one significant coronary artery stenosis of ≥50% luminal diameter, as identified by coronary angiography. The patient exclusion criteria were myocardial spasms or a myocardial bridge, congenital heart disease, childhood hypertension, severe kidney or liver disease, or malignant tumors. A total of 410 subjects were randomly selected from the physical examination center in our hospital. The control subjects were diagnosed as having no history of atherosclerotic lesions or CAD.

Clinical and demographic details of all included patients and controls were recorded from a self-designed questionnaire or medical records. A written informed consent was obtained from each subject before entering the study group. The collection of blood samples for this study was previously approved by the Ethics Committee of Henan Provincial People's Hospital.

Genetic analysis

All patients and control subjects were asked to provide a 5 mL peripheral venous blood sample after enrolling into this study. The collected blood samples were stored at -20°C until use. Genomic DNA was extracted from peripheral blood using the TIANamp Blood DNA kit (Tiangen Biotech Co., Ltd., Beijing, China). Genotyping of *IL-1β* +3953 C/T (rs1143634), *IL-6* -174G/C (rs1800795), *IL-8* -251T/A (rs4073), and *IL-10* -1082A/G (rs1800896) and -819C/T (rs1800871) polymorphisms was performed using polymerase chain reaction combined with restriction fragment length polymorphism (PCR-RFLP) analysis. The primers and probes for the five gene polymorphisms were shown as follows. For *IL-1β* +3953 C/T (rs1143634), the primers were 5' - CTC AGG TGT CCT CGA AGA AAT CAA A - 3' and 5' - GCT TTT TTG CTG TGA GTC CCG - 3', and the restriction enzyme used for RFLP was *Taq*I. For *IL-6* −174G/C (rs1800795), the primers were 5' - TTA CTC TTT GTC AAG ACA TGCC A - 3' and 5' - ATG AGC CTC AGA CAT CTC CAG - 3', and the restriction enzyme was *Sfa*NI. For *IL-8* −251T/A (rs4073), the primers were 5' - CAT GAA GCA TCT GTA ATT AAC TG - 3' and 5' - CTC ATT TTT CAT TAT GTC AGA G - 3', and the restriction enzyme was *Mun*I. For −1082A/G (rs1800896), the primers were 5' - CCA AGA TTA CAC TAC TAA GGC TTC TTG AGG A - 3' and 5' - AGG TAG TGC TCA CTA TTA CC - 3', and the restriction enzyme was *B*seRI. For *IL-10* −819C/T (rs1800871), the primers were 5' - ATC CAA GAC AAC ACT ACT AA - 3' and 5' - TAA ATA TCC TCA AAG TTC C - 3', and the restriction enzyme was *Mae*III. PCR was performed using the following reaction conditions: an initial denaturation step of 95°C for 5 min, then 30 cycles of annealing with denaturation at 94°C for 30 s, touchdown annealing at 60°C for 30 s, and final annealing at 72°C for 1 min, with a final extension at 72°C for 10 min.

Statistical analysis

Continuous variables were represented as means ± SD, and categorical variables were expressed as frequencies and percentages. The differences between continuous and categorical variables were evaluated by the two tailed Student's *t*-test and the chi-square test, respectively. The genotype distributions between patients and controls were compared using a chi-square test, and association between genetic polymorphisms and CAD risk was assessed by conditional logistic regression analysis; OR and 95%CI was taken to evaluate their association. Homozygotes of the most frequent genotype were taken as the reference group. All statistical analyses were performed using SPSS software, version 16.0 (SPSS, Chicago, IL, USA). A P value less than 0.05 was taken as a statistically significant.

RESULTS

The demographic characteristics and clinical variables of included patients and control subjects are compared in Table 1. In our study, the demographic risk factors that were found to be significantly more prevalent among patients compared with healthy controls included gender, hypertension, type 2 diabetes mellitus, obesity, and tobacco smoking (P < 0.001). However, drinking

status was not significantly different between patients and controls (P = 0.19). Furthermore, the mean values of total cholesterol, low- and high density lipoprotein-cholesterol, and triglycerides were significantly different between patients and controls (P < 0.001).

Genotype frequencies of *IL-1β* +3953 C/T (rs1143634), *IL-6* -174G/C (rs1800795), *IL-8* -251T/A (rs4073), and *IL-10* -1082A/G (rs1800896) and -819C/T (rs1800871) are shown in Table 2. Genotype frequencies of *IL-6* -174G/C, and *IL-10* -1082A/G and -819C/T in the controls were in line with Hardy-Weinberg equilibrium, but the genotypes of *IL-1β* +3953 C/T and *IL-8* -251T/A were not. We found that the frequencies of the CC genotype and the C allele of *IL-6* -174G/C were significantly correlated with a higher risk of CAD; the adjusted ORs (95%CIs) were 2.37 (1.37-4.14) and 1.49 (1.19-1.86), respectively. The AG and GG genotypes and the G allele of *IL-10* -1082A/G were also significantly associated with a higher risk of CAD; the ORs (95%CIs) were 1.42 (1.04-1.95), 2.16 (1.42-3.30), and 1.56 (1.27-1.93), respectively. However, *IL-1β* +3953 C/T, *IL-8* −251T/A, and *IL-10* -819C/T did not significantly correlate with CAD risk.

By interaction analysis, we found that patients carrying the C allele of *IL-6* -174G/C (rs1800795) and the G allele of *IL-10* -1082A/G (rs1800896) were correlated with an elevated risk of CAD in individuals with hypertension, type 2 diabetes mellitus, obesity, and tobacco smoking. However, the *IL-6* -174G/C and *IL-10* -1082A/G gene polymorphisms had no significant interactions with hypertension, type 2 diabetes mellitus, obesity, or tobacco smoking. Furthermore, *IL-6* -174G/C (rs1800795) and *IL-10* -1082A/G (rs1800896) gene polymorphisms showed no significant association with total cholesterol, low- or high density lipoprotein-cholesterol, or triglycerides in the risk of CAD.

Table 1. Demographic and clinical characteristics of included patients and control subjects.

Characteristics	Patients with CAD (N = 410)	%	Controls (N = 410)	%	χ^2 or t-test	P value
Age						
<60	219	53.41	222	54.15		
≥60	191	46.59	188	45.85	0.04	0.83
Gender						
Female	173	42.20	233	56.83		
Male	237	57.80	177	43.17	17.56	<0.001
Hypertension						
No	151	36.83	71	17.32		
Yes	259	63.17	339	82.68	39.53	<0.001
Type 2 diabetes mellitus						
No	337	82.20	379	92.44		
Yes	73	17.80	31	7.56	19.43	<0.001
Obesity (BMI ≥ 30)						
No	281	68.54	350	85.37		
Yes	129	31.46	60	14.63	32.74	<0.001
Tobacco smoking						
Never	92	22.44	222	54.15		
Current or former	318	77.56	188	45.85	87.22	<0.001
Alcohol drinking						
Never	155	37.80	137	33.41		
Current or former	255	62.20	273	66.59	1.72	0.19
TC (mg/dL)	196.2 ± 36.7		172.4 ± 32.2		9.87	<0.001
LDL-c (mg/dL)	108.1 ± 28.5		95.4 ± 10.2		8.5	<0.001
HDL-c (mg/dL)	37.1 ± 8.2		42.3 ± 6.5		10.06	<0.001
TG (mg/dL)	132.6 ± 43.2		117.2 ± 30.5		5.9	<0.001

The disease status of hypertension and diabetes mellitus, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and triglycerides (TG) were measured according to standard guidelines and the values were collected from medical records. CAD = coronary artery disease; BMI = body mass index.

Table 2. Genotype distributions of gene polymorphisms in patients with CAD and controls and their association with CAD risk.

Gene polymorphisms		Patients with CAD	%	Controls	%	Hardy-Weinberg equilibrium	OR (95%CI)[1]	P value
IL-1β +3953 C/T (rs1143634)	CC	266	64.88	285	69.51		1.0 (Ref.)	-
	CT	91	22.20	83	20.24		1.17 (0.82-1.68)	0.35
	TT	54	12.93	42	10.24	<0.05	1.38 (0.87-2.19)	0.15
Allele	C	623	75.98	653	79.63		1.0 (Ref.)	-
	T	199	24.02	167	20.37		1.25 (0.98-1.59)	0.06
IL-6 -174G/C (rs1800795)	GG	198	48.29	239	58.29		1.0 (Ref.)	-
	GC	163	39.76	146	35.61		1.35 (0.99-1.82)	0.05
	CC	49	11.95	25	6.10	0.67	2.37 (1.37-4.14)	0.03
Allele	G	559	68.17	624	76.10		1.0 (Ref.)	-
	C	261	31.83	196	23.90		1.49 (1.19-1.86)	0.001
IL-8 -251T/A (rs4073)	TT	118	28.78	134	32.68		1.0 (Ref.)	-
	TA	178	43.41	171	41.71		1.18 (0.84-1.66)	0.31
	AA	114	27.80	105	25.61	<0.05	1.23 (0.84-1.80)	0.26
Allele	T	414	50.49	439	53.54		1.0 (Ref.)	-
	A	406	49.51	381	46.46		1.13 (0.93-1.38)	0.22
IL-10 -1082A/G (rs1800896)	AA	166	40.49	215	52.44		1.0 (Ref.)	-
	AG	158	38.54	144	35.12		1.42 (1.04-1.95)	0.02
	GG	85	20.98	51	12.44	0.07	2.16 (1.42-3.30)	0.04
Allele	A	490	59.76	574	70.00		1.0 (Ref.)	-
	G	328	40.24	246	30.00		1.56 (1.27-1.93)	<0.001
IL-10 -819C/T (rs1800871)	CC	153	37.32	166	40.49		1.0 (Ref.)	-
	CT	177	43.17	173	42.20		1.11 (0.81-1.52)	0.5
	TT	80	19.51	71	17.32	0.28	1.22 (0.81-1.84)	0.31
Allele	C	483	58.90	505	61.59		1.0 (Ref.)	-
	T	337	41.10	315	38.41		1.12 (0.91-1.37)	0.27

[1]Adjusted for sex, age, hypertension, type 2 diabetes mellitus, obesity, tobacco smoking, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglyceride levels. CAD = coronary artery disease.

DISCUSSION

Cytokines are involved in modifying immune responses and play a role in maintaining the balance between proinflammatory and anti-inflammatory stimuli in the process of cardiovascular disease. Genetic variants impacting cytokine function might also alter the expression of cytokine genes, and thus influence the pathology of vascular lesions (Weng et al., 2010; Khankhanian et al., 2013). Previous studies have indicated that genetic variants of interleukin genes such as interleukin-1β (*IL-1β*), *IL-1α*, *IL-6*, *IL-10*, *IL-16*, *IL-18*, and *IL-23A* could affect the development of CAD (Romani et al., 2014; Armingohar et al., 2015; Chi et al., 2015; Jia et al., 2015; Tripathi et al., 2015; Yue et al., 2015), but the results have been inconsistent. In our study, we reported that the *IL-6* -174G/C and *IL-10* -1082A/G polymorphisms are correlated with an elevated risk of CAD in a multivariate analysis.

The *IL-16* gene is located at chromosome 15q26.3, and is translated into a 631 amino acid precursor protein (Kim, 1999). The *IL-6* gene generates two functional proteins, including a secreted C-terminal peptide with cytokine function and an N-terminal product that functions in cell cycle control. Manginas et al. (2008) conducted a study in small sample size population, and found that the *IL-6* -174G/C polymorphism had a critical role in the development of CAD (Manginas et al., 2008). However, Bhanushali and Das (2013) reported no association *IL-6* -174G/C variants with CAD risk. In this study, our results supported the findings of the former study, suggesting that the *IL-6* -174G/C gene polymorphism was correlated with CAD pathogenesis. Therefore, further large sample studies are greatly needed to confirm our results.

The human *IL-10* gene maps to chromosome 1q31-32, and contains three important gene locus mutations upstream of the transcription start site including *IL-10* -1082G/A, -819C/T, and -592C/A (Kim et al., 1992; Turner et al., 1997). Previous studies have demonstrated that the *IL-10* gene is affected by these upstream polymorphisms (Turner et al., 1997; Eskdale et al., 1998; Koch et al., 2001; Lio et al., 2004); however, the results have been inconsistent. Turner et al. (1997) reported that the three single base pair substitutions in the *IL-10* gene promoter were correlated with IL-10 protein production *in vitro*. In another study, Eskdale et al. (1998) suggested that a haplotype of *IL-10* was associated with the highest overall IL-10 secretion, and that the levels of secreted IL-10 could vary in humans according to the genetic composition of the *IL-10* locus. However, more recent reports have demonstrated elevated levels of *IL-10* associated with promoter polymorphisms (Heiskanen et al., 2010; Assis et al., 2014).

Several previous studies have reported the association between *IL-10* gene polymorphisms and CAD risk, but these results have also been controversial (Yu et al., 2012; Jin et al., 2013; Elsaid et al., 2014; He et al., 2014). Elsaid et al. (2014) conducted a case-control study in an Indian population, and reported that the C allele of *IL-6* -174G/C (rs1800795) and the G allele of *IL-10* -1082A/G (rs1800896) were associated with an increased risk of CAD. Another study in a Chinese population reported that the *IL-10* -592C/A polymorphism was also associated with the risk of CAD (Jin et al., 2013). Yu et al. (2012) conducted a study in a Korean population, and reported that the *IL-10* -592C/A and -819C/T gene polymorphisms might be associated with ischemic heart disease. However, in one study in a Chinese population, it was reported that *IL-10* gene polymorphism was not correlated with the risk of CAD (He et al., 2014). In contrast, in a recent meta-analysis of 14 case-control studies with a total of 5006 patients and 3968 controls, it was reported that the *IL-10* -1082 gene polymorphism might be associated with an increased overall risk of CAD, especially in Caucasians (Wang et al., 2012). Our results also suggested that the *IL-10* -1082A/G (rs1800896) polymorphism was associated with an increased risk of CAD. The discrepancy between these studies might be caused by differences in populations, study design, and sample size.

Limitations of our study include that patients were selected from a single hospital, which might not be representative of the general population. Second, other genetic polymorphisms might influence the development of CAD in addition to the 5 examined in this study. Therefore, further multicenter studies with a larger sample populations including different ethnicities are needed to investigate the role of IL-1β +3953 C/T (rs1143634), *IL-6* -174G/C (rs1800795), *IL-8* -251T/A (rs4073), and *IL-10* -1082A/G (rs1800896) and -819C/T (rs1800871) gene polymorphisms on the prognosis of CAD.

In conclusion, our study suggests that the *IL-6* -174G/C (rs1800795) and *IL-10* -1082A/G (rs1800896) polymorphisms might be involved in the pathogenesis of CAD, and might contribute to the genetic susceptibility for CAD. Further well designed and large sample size studies are greatly needed to confirm our results.

Conflicts of interest

The authors declare no conflict of interest.

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