

Association of intercellular adhesion molecule-1 gene polymorphism with coronary heart disease

JUN-YI LUO¹, YI-TONG MA¹, XIANG XIE¹, YI-NING YANG¹, XIAO-MEI LI¹,
XIANG MA¹, ZIXIANG YU¹, BANG-DANG CHEN² and FEN LIU²

¹Department of Cardiology, First Affiliated Hospital of Xinjiang Medical University;

²Xinjiang Key Laboratory of Cardiovascular Disease Research,
Urumqi, Xinjiang 830054, P.R. China

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Abstract. Intercellular adhesion molecule-1 (ICAM-1) is an important adhesion molecule that has a crucial role in lymphocyte migration and atherosclerosis pathogenesis activation. The aim of the present study was to explore the association between the rs5498 polymorphism of the *ICAM-1* gene and coronary heart disease (CHD). The rs5498 polymorphism of the *ICAM-1* gene was detected using polymerase chain reaction-restriction fragment length polymorphism in 674 patients with CHD and 779 control subjects. The results showed that the frequency of the G allele was significantly higher in patients with CHD than that in controls (29.1 vs. 23.3%; $P < 0.001$). The frequency of the AG+GG genotypes was higher in patients with CHD than that in controls (49.7 vs. 40.8%; $P = 0.001$). Multiple logistic regression analysis showed that AG+GG was an independent risk factor for CHD (odds ratio, 1.919; 95% confidence intervals, 1.471-2.503; $P < 0.001$). For males, the frequencies of the G allele and AG+GG genotype were also higher in patients with CHD than those in control subjects (frequency of G allele, 29.9 vs. 22.7%; $P < 0.001$; frequency of AG+GG genotype, 50.6 vs. 40.3%; $P = 0.001$). For females, no significant differences in genotype or allele distribution were observed between the two groups. In conclusion, it was demonstrated in the present study that the rs5498 polymorphism of the *ICAM-1* gene was associated with CHD in males. Males with the G allele (AG and GG genotype) may therefore have a higher risk for CHD than those with the AA genotype.

Introduction

Coronary heart disease (CHD) is one of the primary causes of mortality in humans in developed and developing countries. Previous studies have demonstrated that the plasma levels of intercellular adhesion molecule-1 (ICAM-1) may serve as a molecular marker for atherosclerosis and the development of CHD (1,2). ICAM-1, which belongs to the immunoglobulin superfamily, is typically expressed in endothelial cells and leukocytes where it serves as a receptor for the leukocyte integrins lymphocyte function-associated antigen 1 and Mac-1 (3-5). In the pathogenesis of atherosclerosis, ICAM-1 plays an important role in recruiting mononuclear cells into the basement membrane of the vasculature (6,7). Therefore, ICAM-1 may be an important factor in the development and progression of atherosclerosis. Several polymorphisms for the *ICAM-1* gene have been described. rs5498, a single-base A-G transition polymorphism, is located in exon 6 of the *ICAM-1* gene. The missense mutation results in an amino acid substitution from glutamine (E) to lysine (K), and it has been found to be related to inflammatory diseases and atherosclerosis. Thus, in the present case-control study, the association between the rs5498 polymorphism of the *ICAM-1* gene and CHD was investigated in patients with CHD and control subjects in a Chinese Han population.

Subjects and methods

Ethics statement. This study was conducted according to the Declaration of Helsinki, and was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (Urumqi, China). Written informed consent was obtained from all participants prior to the start of the study.

Subjects. All participants were genetically unrelated Chinese Han individuals from Xinjiang, China. Participants with CHD were recruited from the First Affiliated Hospital of Xinjiang Medical University between 2007 and 2010. All patients with CHD were diagnosed according to their medical history, clinical symptoms, 12-lead electrocardiogram and laboratory examinations, and the diagnosis was confirmed by coronary arteriography (>50% stenosis in at least one coronary artery).

Correspondence to: Professor Yi-Tong Ma, Department of Cardiology, First Affiliated Hospital of Xinjiang Medical University, 1 Liyushan Road, Urumqi, Xinjiang 830054, P.R. China
E-mail: myt-xj@163.com

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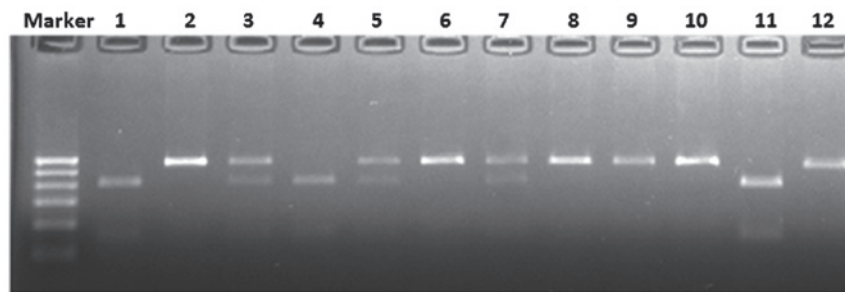


Figure 1. Restriction fragment length polymorphism analysis for genotype determination. The AA genotype shows a single band of 541 bp (lanes 2, 6, 8, 9, 10 and 12). The AG genotype shows three bands of 541, 417 and 124 bp (lanes 3, 5 and 7). The GG genotype shows two bands of 417 and 124 bp (lanes 1, 4 and 11).

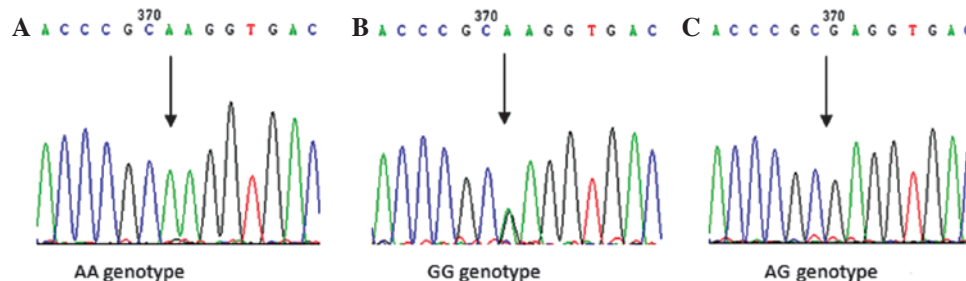


Figure 2. Results of the intercellular adhesion molecule-1 sequencing: (A) AA genotype, (B) GG genotype and (C) AG genotype.

The control participants were selected from the cardiovascular risk survey (CRS) (8). The CRS is a prospective, observational cohort study designed to investigate the prevalence, incidence and risk factors for cardiovascular disease in the Han, Uygur and Kazakh populations in Xinjiang, China. The baseline data for the control participants were collected between June 2007 and March 2010. Inclusion criteria were as follows: No chest pain, normal electrocardiograph, normal blood biochemistry values and normal coronary arteriography.

Lifestyle data collection. Lifestyle data (age, smoking and drinking habits and medical history) were collected using questionnaires, and height, body weight and blood pressure were measured by doctors. Participants who had smoked at least one cigarette per day in the previous 12 months were considered as current smokers. Individuals who had consumed ≥ 50 mg alcohol once a week in the previous 12 months were considered as current alcohol users. Essential hypertension (EH) was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least two separate occasions, or antihypertensive treatment.

Laboratory examination and DNA extraction. A total of 5 ml peripheral venous blood samples were collected in EDTA-containing tubes from all participants following fasting for 12 h. Serum and plasma collected for measurement were immediately frozen at -80°C for further analysis. The concentrations of triglyceride (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) were measured using standard methods in the Central Laboratory of the First Affiliated Hospital of Xinjiang Medical University. DNA was extracted from peripheral vein blood leukocytes using a whole

blood genome extraction kit (BioTeke Corporation, Beijing, China).

Genotyping of *ICAM-1*. The primers were designed by Primer Premier 5.0 software (Premier Biosoft International, Vancouver, BC, Canada). The primers were as follows: forward, 5'-GGCCAGCTTATACACAAGAACC-3' and reverse, 5'-TGTCATCATACTGTGGTAGCA-3'. Synthesis was performed by Shanghai Hi-Tech Bioengineering Co., Ltd. (Shanghai, China). The reaction was performed in a 25- μl volume, containing 12.5 μl Power Mix (BioTeke Corporation), 10.5 μl distilled water, 0.5 mM forward and reverse primer, respectively, and 1 μl genomic DNA. The reaction conditions were as follows: Initial denaturation at 95°C for 5 min, 30 cycles of denaturation at 95°C for 30 sec, annealing at 53°C for 30 sec, extension at 72°C for 40 sec and extension at 72°C for 7 min. The reaction products were then stored at 4°C . The polymerase chain reaction (PCR) products (10 μl) were incubated with 3 units Bsh1236I (Fermentas, Burlington, ON, Canada) in a total volume of 20 μl at 37°C overnight. The fragments were separated on a 2% agarose gel with ethidium bromide. Under the ultraviolet ray, three genotypes were observed: The AA genotype produced one 541-base pair (bp) band; the AG genotype produced three bands of 541, 417 and 124 bp; and the GG genotype produced two bands of 417 and 124 bp (Fig. 1). To confirm the results, sequenced genomic DNAs were used as positive controls (Fig. 2). Sequencing reactions were undertaken by Biomed-Beijing (Beijing, China).

Statistical analysis. All analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA). Continuous data are shown as the mean \pm standard deviation and categorical data are shown as percentages (%). The differences between

patients with CHD and control subjects were assessed using an independent-sample t-test. The Hardy-Weinberg equilibrium and differences in categorical data between the two groups were analyzed using a χ^2 test. Differences in the distribution of genotypes and alleles between the two groups were also analyzed using a χ^2 test. Logistic regression analysis was used to assess the contribution of the major risk factors to CHD. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of participants. A total of 1,453 individuals (674 patients with CHD and 779 healthy controls) participated in this study. The clinical characteristics of the individuals are shown in Table I. For the three groups, i.e. total study population, males and females, there were no differences in age between patients with CHD and healthy controls, suggesting that the study was an age-matched case-control study. For the total study population, males and females, there were significantly higher concentrations of TG, TC and LDL-C and a greater percentage of EH in patients with CHD than those in healthy controls. However, the concentration of HDL-C was significantly lower in the CHD group than that in the control group. For the total study population and males, the body mass index (BMI) and percentage of individuals with a smoking habit were significantly different between the two groups; however, for females, no significant differences in BMI or smoking were observed between the two groups.

Allele and genotype distribution of rs5498 (A>G). The distribution of genotypes between patients with CHD and healthy controls in the three groups (total study population, males and females) was consistent with the Hardy-Weinberg equilibrium. Table II shows the distribution of alleles and genotypes of rs5498 for the *ICAM-1* gene. For the total study population and males, the distribution of the three genotypes was significantly different between patients with CHD and control subjects (total study population, AA vs. AG, $P = 0.003$; AA vs. GG, $P = 0.01$; males, AA vs. AG, $P = 0.007$; AA vs. GG, $P = 0.003$). The frequency of the G allele was significantly higher in the CHD group than that in the control group ($P < 0.001$ in the total study population and males). The distributions of the three models of rs5498 were significantly different between the two groups (all $P < 0.05$). There was no significant difference in the distribution between the two groups in the females.

Logistic regression analysis of CHD risk factors. Multifactor logistic regression analysis revealed six independent risk factors for CHD: AG+GG dominant model, smoking, TC, TG, LDL-C and EH. It also showed that HDL-C was a protective factor for CHD. Following adjustments for smoking, TC, TG, LDL-C, HDL-C and EH, the subjects with the G allele in rs5498 of the *ICAM-1* gene had a significantly higher risk of CHD [total study population, odds ratio (OR), 1.919; 95% confidence intervals (CI), 1.471-2.503; $P < 0.001$; males, OR, 2.028; 95% CI, 1.456-2.825; $P < 0.001$; females, OR, 1.661; 95% CI, 1.046-2.637; $P = 0.031$] (Table III).

Table I. Demographic and risk profile of the study population.

	Total			Males			Females		
	Controls	CHD	P-value	Controls	CHD	P-value	Controls	CHD	P-value
Total n	779	674		543	490		236	184	
Age (years) ^b	58.71±14.17	58.47±9.52	0.71	59.39±16.00	58.75±10.43	0.454	57.14±8.43	57.72±6.465	0.445
BMI (kg/m ²) ^b	24.46±3.43	25.83±3.28	<0.001 ^a	24.16±3.27	26.19±3.32	<0.001 ^a	25.18±3.69	24.84±2.96	0.322
TG (mmol/l) ^b	1.49±1.56	7.15±17.47	<0.001 ^a	1.49±1.23	7.05±19.41	<0.001 ^a	1.51±0.98	7.38±10.93	<0.001 ^a
TC (mmol/l) ^b	4.59±0.98	5.56±3.95	<0.001 ^a	4.5±0.93	5.55±4.11	<0.001 ^a	4.79±1.05	5.83±3.5	<0.001 ^a
LDL-C (mmol/l) ^b	2.27±1.45	2.87±0.92	<0.001 ^a	2.3±1.53	2.87±0.92	<0.001 ^a	2.17±1.2	2.84±0.93	<0.001 ^a
HDL-C (mmol/l) ^b	1.26±0.42	0.89±0.4	<0.001 ^a	1.27±0.41	5.55±4.11	<0.001 ^a	1.23±0.43	1.00±0.62	<0.001 ^a
Smokers (%)	28.3	35.8	0.002 ^a	40.0	48.8	0.004 ^a	1.3	1.1	0.859
EH (%)	24.8	55.2	<0.001 ^a	22.8	54.5	<0.001 ^a	29.2	57.1	<0.001 ^a

^a $P < 0.05$ compared with controls. ^bPresented as mean ± standard deviation. BMI, body mass index [weight (kg)/height² (m²)]; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; EH, essential hypertension; CHD, coronary heart disease.

Table II. Genotype and allele distributions in patients with CHD and controls subjects.

	Total			Males			Females					
	Controls, n (%)	CHD, n (%)	OR	P-value	Controls, n (%)	CHD, n (%)	OR	P-value	Controls, n (%)	CHD, n (%)	OR	P-value
Total n	779	674			543	490			236	184		
Genotype												
AA	461 (0.592)	339 (0.503)	1.000	-	324 (0.597)	242 (0.494)	1.000	-	137 (0.581)	97 (0.527)	1.000	-
AG	273 (0.350)	278 (0.412)	1.385	0.003 ^a	191 (0.352)	203 (0.414)	1.423	0.007 ^a	82 (0.347)	75 (0.408)	1.292	0.218
GG	45 (0.058)	57 (0.085)	1.723	0.01 ^a	28 (0.051)	45 (0.092)	2.152	0.003 ^a	17 (0.072)	12 (0.065)	0.997	0.994
Dominant model												
AA	461 (0.592)	339 (0.503)			324 (0.597)	242 (0.494)			137 (0.581)	97 (0.527)		
AG+GG	318 (0.408)	335 (0.497)	1.433	0.001 ^a	219 (0.403)	248 (0.506)	1.516	0.001 ^a	99 (0.419)	87 (0.592)	1.241	0.275
Recessive model												
AG+AA	734 (0.942)	617 (0.915)			515 (0.948)	445 (0.908)			219 (0.928)	172 (0.935)		
GG	45 (0.058)	57 (0.085)	1.507	0.047 ^a	28 (0.052)	45 (0.092)	1.860	0.013 ^a	17 (0.072)	12 (0.065)	1.113	0.785
Additive model												
AA	461 (0.911)	339 (0.856)			324 (0.921)	242 (0.843)			137 (0.890)	97 (0.890)		
GG	45 (0.089)	57 (0.144)	1.723	0.01 ^a	28 (0.079)	45 (0.157)	2.152	0.003 ^a	17 (0.110)	12 (0.110)	1.003	0.994
Allele												
A	1195 (0.767)	956 (0.709)			839 (0.773)	687 (0.701)			356 (0.754)	269 (0.731)		
G	363 (0.233)	392 (0.291)	1.350	<0.001 ^a	247 (0.227)	293 (0.299)	1.449	<0.001 ^a	116 (0.246)	99 (0.269)	1.129	0.444

^aP<0.05 compared with controls. CHD, coronary heart disease; OR, odds ratio.

Table III. Multiple logistic regression analysis for patients with CHD and control subjects.

Risk factors	Total			Males			Females		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
AG+GG vs. AA	1.919	1.471-2.503	<0.001 ^a	2.028	1.456-2.825	<0.001 ^a	1.661	1.046-2.637	0.031 ^a
Smoking	1.231	0.993-1.625	0.141	1.223	1.456-2.825	<0.001 ^a	0.445	0.043-4.734	0.506
TC	2.590	1.586-4.230	<0.001 ^a	4.831	2.227-10.479	<0.001 ^a	1.557	0.801-3.106	0.187
TG	2.001	1.443-2.775	<0.001 ^a	2.085	1.383-3.143	<0.001 ^a	1.933	1.098-3.403	0.022 ^a
LDL-C	2.142	1.223-3.750	0.008 ^a	3.099	1.428-6.725	0.004 ^a	1.307	0.565-3.025	0.531
HDL-C	0.244	0.188-0.316	<0.001 ^a	1.995	1.769-2.249	<0.001 ^a	0.549	0.348-0.865	0.01 ^a
EH	4.251	3.236-5.585	<0.001 ^a	4.473	3.429-5.835	<0.001 ^a	3.114	1.956-4.958	<0.001 ^a

^aP<0.05 compared with controls. CHD, coronary heart disease; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; EH, essential hypertension; OR, odds ratio; CI, confidence intervals.

Discussion

The human *ICAM-1* gene is located on chromosome 19p13.3-p13.2, and it consists of seven exons separated by six introns. The rs5498 polymorphism of the *ICAM-1* gene, which is located in exon 6, is a functional mutation resulting in the substitution of lysine to glutamate (K469E). This mutation may have a possible functional value in the etiology of atherosclerosis (9). Using human peripheral mononuclear cells and Epstein-Barr virus-transformed peripheral mononuclear cells, Iwao *et al* (10) demonstrated that individuals carrying the G-allele may have increased difficulty splicing the ICAM-1 short isoform (ICAM-1-S) compared with individuals carrying the A-allele. Therefore, cells with the GG genotype may have decreased levels of ICAM-1-S mRNA and, thus, higher sensitivity to apoptosis than cells with the AA genotype. Kitagawa *et al* (11) demonstrated that the level of soluble ICAM-1 (sICAM-1) was closely associated with the severity of atherosclerosis and cardiovascular events. It was also suggested that the inhibition of ICAM-1 expression could delay the progression of atherosclerosis in apolipoprotein E-knockout mice.

The effect of rs5498 on plasma ICAM-1 levels has also been investigated. Hulthe *et al* (12) reported that the level of sICAM-1 was associated with subclinical atherosclerosis and inflammatory variables in clinically healthy middle-aged males. Puthothu *et al* (13) found a significant association between rs5498 and the serum levels of sICAM-1 in German children with asthma. It was also found that rs5498 was associated with sICAM-1 levels in Chinese and European Americans (14). Therefore, in this study, it was hypothesized that variability in the rs5498 polymorphism of the *ICAM-1* gene had the potential to affect the risk of CHD. To investigate this, the polymorphism of the *ICAM-1* gene was genotyped in a Chinese population and the association between the *ICAM-1* gene and CHD was determined using case-control analysis.

In the present study it was found that there was a significant difference in the genotype distribution of rs5498 between patients with CHD and control subjects in the total population. When analyzing males and females separately, the G allele frequency was higher in males with CHD than that in male control subjects. This indicates that the risk of CHD was increased in males carrying the G allele. For males, the distribution of the dominant model (AG+GG vs. AA) was significantly higher in patients with CHD than that in control subjects, and this difference remained significant following adjustment for risk factors. This indicates that the risk of CHD may increase in males with the AG or GG genotype of rs5498. In the present analysis, however, no differences in allele frequency or genotype distribution were observed between the two groups in females. The results of the present study were in accordance with the results from Zhou *et al* (15). Using nested PCR, Zhou *et al* demonstrated that the G allele of rs5498 was a genetic risk factor for CHD in the Han population in Hubei, China. Several previous studies have shown that the A allele of rs5498 is associated with CHD in different ethnicities. In the Chinese Han population, Zhang *et al* (16) genotyped 173 patients with CHD and 141 control subjects using PCR-restriction fragment length polymorphism, and they demonstrated that the rs5498 polymorphism was associ-

ated with CHD and that the A allele may serve as a genetic risk factor for CHD. Lu *et al* (17) used nested PCR with allele-specific oligonucleotide primers in 160 patients with CHD and 64 control subjects and found that the A allele frequency and plasma levels of ICAM-1 were higher in patients with CHD than those in control subjects. It was also found that the frequency of the A genotype (AG and GG) was significantly higher in patients with CHD than that in controls in the Egyptian population (18). However, McGlinchey *et al* (19) found that rs5498 was not associated with ischemic heart disease in Irish populations. Another study also demonstrated that there was no strong association between rs5498 polymorphisms and the occurrence of CHD and myocardial infarction in the studied population in Iran (20). In addition, Milutinović and Petrovic (21) found that the rs5498 polymorphism was not associated with myocardial infarction in subjects with type 2 diabetes in the Slovenian population. These contradictory results may be due to differences in the ethnic background, geographical factors and the relatively small sample size in each study.

There were certain limitations in this study. Firstly, in the present study, only one variant, rs5498, was investigated rather than other variants in the *ICAM-1* gene. Although the main aim of the present study was to investigate the role of rs5498, this may underestimate the association between the *ICAM-1* gene and CHD. The rs5498 and rs5491 polymorphisms of the *ICAM-1* gene may also affect the plasma sICAM-1 expression levels (22). Secondly, the sICAM-1 levels were not measured in either patients with CHD or in control subjects. Therefore, the association between the rs5498 polymorphism and sICAM-1 levels was not investigated. There were two advantages in the present study. One was that the sample size in the study was relatively large. The other was that it was the first study, to the best of our knowledge, to demonstrate the different distribution of the rs5498 polymorphism of the *ICAM-1* gene in males and females.

In conclusion, the present study demonstrated that the rs5498 polymorphism of the *ICAM-1* gene was associated with CHD in males in the Chinese Han population. Males with the G allele (AG and GG genotype) may have a higher risk of CHD than those with the AA genotype. However, an age-matched study with a larger sample size is required to investigate the association between the *ICAM-1* gene and CHD in females.

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