Intercellular Adhesion Molecule-1 E469K Gene Polymorphism and Coronary Artery Disease in the Chinese Population: A Meta-Analysis Involving 3065 Subjects

Li Yanyan, PhD

Department of Geriatrics, First Affiliated Hospital of Nanjing Medical University, Nanjing, China

ABSTRACT

Background: The intercellular adhesion molecule-1 (*ICAM-1*) E469K gene polymorphism has been implicated in increased coronary artery disease (CAD) susceptibility, but the individual study results are still controversial.

Hypothesis: The *ICAM-1* E469K gene polymorphism may be associated with CAD risk.

Methods: The current meta-analysis involving 3065 subjects and 11 separate studies was conducted to explore the relationship between the *ICAM-1* E469K gene polymorphism and CAD in the Chinese population. The pooled odds ratio (ORs) for the distribution of K allele frequency of *ICAM-1* E469K gene and its corresponding 95% confidence interval (CI) was assessed by random effect model.

Results: The distribution of the K allele frequency was 0.67 for the CAD group and 0.60 for the control group. The pooled OR for the distribution of the K allele frequency of the *ICAM-1* E469K gene was 1.32 (95% CI, 1.02–1.72; $P_{\text{heterogeneity}} < 0.00001$; inconsistency index $I^2 = 81.8\%$). The association between the *ICAM-1* E469K gene polymorphism and CAD in the Chinese population was significant ($P = 0.04$).

Conclusions: In the Chinese population, the distribution of the K allele frequency of the *ICAM-1* E469K gene was indicated to be associated with CAD risk. The K allele of the *ICAM-1* E469K gene might predispose to the CAD susceptibility.

Introduction

The role of inflammation in the pathogenesis of coronary artery disease (CAD) has received more and more attention over the past few years. Atherosclerosis has been considered a chronic inflammation process.¹ Inflammation cells adhered to endothelial cells and traversed the endothelium in the early stage of CAD onset. As 1 member of the immunoglobulin (Ig) superfamily, intercellular adhesion molecule-1 (*ICAM-1*), a 95-kD cell surface glycoprotein, fulfills a pivotal function in mediating leukocytes to adhere to vascular endothelial cells and to access the vascular wall. This suggested that *ICAM-1* exerted an important role in the development of the inflammation reaction, atherosclerosis, and thrombosis.²

The *ICAM-1* gene, located in 19p13.3–p13.2, spans 15.5 kb and contains 7 exons and 6 introns.³ The E469K gene polymorphism is located in the *ICAM-1* gene coding region. The mutation of thymine (T base) substituting for cytosine (C base) in the 1548th base of the 6th exon of the *ICAM-1* gene results in the glutamate (E) being supplanted by lysine (K) in the 469th of the corresponding amino acid

sequence Ig domain 5 of *ICAM-1*. This gene polymorphism might influence the serum level and activity of *ICAM-1*.⁴ Research has shown that the E469K gene polymorphism is correlated with ulcerative colitis, Crohn's disease, primary sclerosing cholangitis, multiple sclerosis, ischemic stroke, and Alzheimer's disease.^{5–9}

In 2002, Jiang et al reported that the KK and EK genotypes of the *ICAM-1* E469K polymorphism were possibly associated with the susceptibility for coronary heart disease (CHD) and myocardial infarction (MI) in Germans.¹⁰ Similar results were demonstrated by several studies in the Chinese population.^{11–17} However, Zhou et al¹⁸ and Mo et al¹⁹ both found that E allele of *ICAM-1* E469K might be a genetic risk factor for CHD.^{12–19}

Although the studies of the *ICAM-1* E469K gene polymorphism and CAD were conducted extensively, the results were still controversial. Therefore, the present meta-analysis, which included 3065 participants, was performed to obtain a reliable conclusion on the relationship between the *ICAM-1* E469K gene polymorphism and CAD in the Chinese population.

Methods

Publication Search and Inclusion Criteria

The studies chosen were acquired by a search of the following electronic databases: PubMed, Embase, Web of Science,

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China Biological Medicine Database (CBMD), and China National Knowledge Infrastructure (CNKI), using the following Medical Subject headings (MeSH) terms: “coronary artery disease” or “coronary heart disease,” “polymorphism,” “intercellular adhesion molecule-1,” “gene,” and “Chinese,” published from 2004 to 2010 (last research updated on June 15, 2011).

The selected studies had to be fitted with the major included criteria as follows: (1) evaluation of the *ICAM-1* E469K gene polymorphism and CAD in Chinese population; and (2) the diagnosis of CAD was in the light of the examination results of coronary arteriography, and clinical symptoms combined with electrocardiogram, echocardiography, treadmill exercise test, and myocardial perfusion imaging in emission computed tomography (ECT).

Data Extraction

The data were independently drawn in duplicate by 2 researchers on the basis of a standard protocol. If there was disagreement between them, the inconsistency was resolved by discussion. In the current meta-analysis, excluded literature consisted of repeated publications, poor-quality research papers, and studies violating the inclusion criteria or providing little information. If the same results came out from different research studies, only 1 study result was adopted. The extracted data contained the following: the first author's name, publication year, region, number of genotypes, genotyping, study design, matching criteria, gender distribution, and total number of cases and controls.

Statistical Analysis

The distribution frequency of the K allele of *ICAM-1* E469K between CAD and control groups was compared by using the odds ratio (OR) corresponding to the 95% confidence interval (CI). The presence of between-study heterogeneity and significance was calculated by chi-square-based Q-test (significance was set at $P < 0.10$ level).²⁰ The inconsistency index I^2 was calculated to assess the variation caused by heterogeneity. If there was heterogeneity among the researches, the random-effects model was adopted to estimate the pooled OR (the DerSimonian and Laird method).²¹ Otherwise, the fixed-effects model was adopted (the Mantel-Haenszel method).²² The Z test was used to determine the pooled OR and significance was set at $P < 0.05$. The postulated heterogeneity sources was examined by the random effects meta-regression of the logarithm of the OR. The between-study variance was estimated by the restricted maximum likelihood approach.²³ Publication year, ethnicity, control quantity total sample size, and the ratio of the number of CAD patients and controls (RR) were assigned as independent variables. The Han ethnicity was set as 1 and the other was set as 2.

The Fisher's exact test was used to assess the Hardy-Weinberg equilibrium (HWE) with significance set as $P < 0.05$. The potential publication bias was estimated by funnel plot. The Egger's linear regression test was applied to assess the funnel plot asymmetry on the natural logarithm scale of the OR (significance was set at $P < 0.05$).²⁴ STATA 10.0 software (StataCorp, College Station, TX) was used for statistical analysis.

Results

Studies and Populations

Through the literature search, 26 papers were achieved, of which 11 papers were in accordance with the research inclusion criteria. Of the 15 excluded studies, 3 papers were literature published repeatedly, 6 papers were reviews, and 6 studies were unconcerned with the *ICAM-1* E469K gene polymorphism. No study was excluded for deviation from HWE. The total data were gathered from 1507 CAD patients and 1558 controls from 2 ethnicities, Han and Uygur (Table 1).^{11–19,25,26} The 7 investigated regions comprised the provinces Hubei, Hebei, Guangdong, Zhejiang, Guangxi, Xinjiang, and Shandong.

Pooled Analyses

The distribution of the K allele frequency was 0.67 for the CAD group and 0.60 for the control group. The pooled OR for the distribution of the K allele frequency of the *ICAM-1* E469K gene was 1.32 (95% CI, 1.02–1.72; $P_{\text{heterogeneity}} < 0.00001$; $I^2 = 81.8\%$). The association between the *ICAM-1* E469K gene polymorphism and CAD in the Chinese population was significant ($P = 0.04$) (Figure 1).

In consideration of the significant heterogeneity, the meta-regression was performed with the logarithm of OR as the dependent variable. In the meta-regression, the heterogeneity was significantly explained by the ratio of CAD group sample size to control group sample size (RR) ($P = 0.026$), CAD group sample size ($P = 0.055$), and total sample size ($P = 0.078$). By contrast, publication year, ethnicity, control group sample size, and gender distribution were not associated with the heterogeneity ($P > 0.10$). (Table 2)

The subgroup analysis was performed and stratified by RR. All of the 11 studies were divided into 3 subgroups. The 6 studies for $RR > 1.0$ were referred to as subgroup 1, the 3 studies for $0.8 < RR < 1.0$ were defined as subgroup 2, and the others for $RR < 0.6$ were defined as subgroup 3. The estimated pooled OR for the distribution frequency of the K allele was 1.36 (95% CI, 0.90–2.05; $I^2 = 85.1\%$) in subgroup 1. Among the 3 studies of subgroup 2, the estimated pooled OR was 1.39 (95% CI, 1.15–1.69; $I^2 = 0$). In subgroup 3, the estimated pooled OR was 1.15 (95% CI, 0.41–3.18; $I^2 = 93.2\%$) (Figure 2).

Bias Diagnostics

The publication bias of the research was assessed by funnel plot and Egger's test. There was no visual publication bias in the funnel plot (Figure 3). There was no statistically difference in the Egger's test, which indicated that the publication bias was low in the current meta-analysis ($P > 0.05$).

Discussion

Recent research advances have manifested that inflammation was closely correlated with atherosclerosis. Systematic and local inflammation participated in the whole process of atheroma occurrence, progress, and erosion.²⁷ *ICAM-1* consisted of the extracellular domain, transmembrane domain, and intracellular domain. There were 5 immunoglobulin functional domains in the extracellular domain of *ICAM-1*.

Table 1. Characteristics of the Investigated Studies of the Association Between *ICAM-1* E469K Gene Polymorphism and CAD

References	Year	Region	Ethnicity	CAD Group				Control Group				Matching Criteria	Study Design	Gender Distribution			Weight (%)
				KK	KE	EE	KE	KK	KE	EE	KE			Sample Size (CAD/Control)	CAD (M/F)	Control (M/F)	
Yin ¹¹	2008	Hubei	Han	98	49	42	89	44	67			Age, sex, ethnicity	Case-control	189/200	122/67	140/60	9.96
Rao et al ¹²	2005	Hubei	Han	84	41	20	59	19	66			Age, sex, ethnicity	Case-control	145/144	96/49	88/56	9.47
Shang et al ¹³	2005	Shandong	Han	48	50	24	29	33	35			Age, sex, ethnicity, BMI, smoker, BP	Case-control	122/97	74/48	59/38	9.14
Wang et al ¹⁴	2005	Hubei	Han	96	61	8	91	90	18			Age, sex, ethnicity, BMI	Case-control	165/199	136/29	151/48	9.59
Wei et al ¹⁵	2006	Guangxi	Han	124	84	17	101	103	26			sex	Case-control	225/230	167/58	165/65	9.99
Zhang et al ¹⁶	2006	Zhejiang	Han	111	52	10	69	59	13			Age, ethnicity	Case-control	173/141	136/37	84/57	9.30
Zhou et al ¹⁸	2006	Hubei	Han	38	45	20	102	62	33			Age, sex, ethnicity, BMI	Case-control	103/197	57/46	114/83	9.44
Wen et al ¹⁷	2008	Shandong	Han	28	30	13	40	65	59			Age, sex, ethnicity, BMI	Case-control	71/164	43/28	94/70	8.95
Abdiryim et al ²⁵	2009	Xinjiang	Uygur	55	54	15	21	26	3			Sex, ethnicity	Case-control	124/50	63/61	25/25	8.05
Mo et al ¹⁹	2009	Guangdong	Han	15	35	47	12	12	11			Age, sex, ethnicity, BMI, smoker, BP	Case-control	97/35	58/39	18/17	7.50
Li et al ²⁶	2010	Hebei	Han	47	39	7	52	36	13			NA	Case-control	93/101	72/21	51/50	8.61

Abbreviations: BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CAD group, frequency of the 3 genotypes in the CAD group; CAD (M/F), the number of male and female subjects in the CAD group; Control group, frequency of the 3 genotypes in the group; Control (M/F), the number of male and female subjects in the control group; *ICAM-1*, intercellular adhesion molecule-1; NA, not applicable; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; Weight (%), the percentage of weight.

Figure 1. Forest plot of CAD associated with ICAM-1 E469K polymorphism (distribution frequency of K allelic of E469K gene). Abbreviations: CAD, coronary artery disease; ICAM-1, Intercellular adhesion molecule-1.

Table 2. The Meta-Regression Results Among 11 Studies

Item	Coefficient	Standard Error	T Value	P Value	95% CI
CAD sample size	0.0089685	0.00390503	2.30	0.055 ^a	−0.0002662 to 0.0182031
Total sample size	−0.0046656	0.0022647	−2.06	0.078 ^a	−0.0100207 to 0.0006896
RR (CAD/control)	−0.458788	0.1634367	−2.81	0.026 ^a	−0.8452544 to −0.0723215
Summation	0.7408388	0.349982	2.12	0.07 ^a	−0.0867371 to 1.568415

Abbreviations: CAD, coronary artery disease; CAD sample size, CAD group sample size; CI, confidence interval; RR, the ratio of CAD group sample size to control group sample size; Total sample size, the sum of CAD group and control group sample size. ^aP < 0.10.

The soluble ICAM-1 (sICAM-1) in the serum was generated either by protease splitting of the extracellular fragment or by the different montages of *ICAM-1* messenger RNA (mRNA).

As an inflammation cytokine, ICAM-1 could mediate monocytes, macrophagocytes, T lymphocytes, and platelets to assemble and adhere to the vascular wall, which plays a key role in the pathogenesis of atherosclerosis. Not only did the expression level of ICAM-1 increase in the atheroma plaque, but also the circulating ICAM-1 level increased the CAD risk. The *ICAM-1* knock-out mouse experiments, conversely, demonstrated that *ICAM-1* could impair the vascular endothelium.^{28,29} The K allele of the *ICAM-1* E469K gene polymorphism could alter the structure and function of the ICAM-1 D5 function region, which was implicated in the ICAM-1 molecular dimerization and adhesion function and changed the combination of ICAM-1 and ligands such as the lymphocyte function-associated antigen-1 (LFA-1) and the complement receptor 3 (CR3). The combination alterations contributed to leukocytes adhering to vascular endothelial cells more strongly and passing through the vascular wall more easily, which caused the atherosclerosis.³⁰

As yet, there is no final conclusion on the association of the *ICAM-1* E469K polymorphism and CAD. In 2004, McGlinchey et al. explored the possible role of the *ICAM-1* E469K gene polymorphism in the susceptibility to ischemic heart disease (IHD) and found no association between

the *ICAM-1* E469K polymorphism and IHD in the Irish population.³¹ In contrast, in 2010, Mohamed et al found that the *ICAM-1* gene polymorphism in codon 469 is associated with a risk for CHD development in Egyptian subjects.³² In 2004, Liu et al found that KK homozygotes of *ICAM-1* E469K might have a higher risk of restenosis after coronary stenting, especially in obesity or hyperlipemia patients.³³ In 2010, author Pi³⁴ also reached a similar conclusion as Liu et al.³³

In the current meta-analysis, the distribution of the K allele frequency was 0.67 for the CAD group, 0.60 for the control group. The pooled OR for the distribution of K allele frequency of the *ICAM-1* E469K gene was 1.32 (95% CI, 1.02–1.72; $P_{\text{heterogeneity}} < 0.00001$; $I^2 = 81.8\%$). The association between the *ICAM-1* E469K gene polymorphism and CAD in the Chinese population was significant ($P < 0.05$). Hence, in the Chinese population, the distribution of the K allele frequency of the *ICAM-1* E469K gene was indicated to be associated with the increased CAD risk. The K allele of *ICAM-1* E469K gene might predispose to the CAD susceptibility.

In the subsequent meta-regression for the heterogeneity source, the heterogeneity was significantly explained by RR ($P = 0.026$), CAD group sample size ($P = 0.055$), and total sample size ($P = 0.078$). The subgroup analysis was stratified by RR. Among the 3 studies of subgroup 2 for $0.8 < \text{RR} < 1.0$, the estimated pooled OR for the distribution frequency of the K allele was 1.39 (95% CI, 1.15–1.69;

Review: intercellular adhesion molecule-1 gene K469E polymorphism and coronary artery disease in Chinese population (Version 02)
 Comparison: 01 CAD group versus control group
 Outcome: 01 Distribution of K allelic frequency of ICAM-1 E469K gene polymorphism

Figure 2. Forest plot of CAD associated with ICAM-1 E469K polymorphism (distribution frequency of K allelic of ICAM-1 E469K gene) stratified by RR. Abbreviations: CAD, coronary artery disease; ICAM-1, intercellular adhesion molecule-1; RR, ratio of CAD group sample size to control group sample size.

Figure 3. Funnel plot for studies of the association of CAD and ICAM-1 E469K polymorphism (distribution frequency of K allelic of ICAM-1 E469K gene). The horizontal and vertical axis correspond to the OR and confidence limits. Abbreviations: CAD, coronary artery disease; ICAM-1, intercellular adhesion molecule-1; OR, odds ratio; SE, standard error.

$I^2 = 0$). This suggested that RR was the main source of heterogeneity between the individual studies. It implied that the sample size should be better to be matched between cases and controls to decrease the heterogeneity in future research.

The present research result was in accordance with the previous study by Zhang et al.³⁵ In 2007, Zhang et al.³⁵ performed a meta-analysis on the correlation between the

ICAM-1 gene E469K polymorphism and CAD. They found that the ICAM-1 E469K polymorphism was associated with CAD in the Chinese population and people who carried the K allele (KK and KE genotypes) had a higher risk to be subject to CAD. In Zhang et al's work,³⁵ the recessive model adopted to analyze the 6 separate studies results was not quite suitable to combining the studies under heterogeneity. By contrast, in the current meta-analysis, the log-additive model of analysis following the recommendation by Pereira et al was used, which was the most plausible genetic model of action.³⁶ Moreover, the heterogeneity source was determined and the subsequent subgroup analysis was additionally performed in the present research. Besides, the quantity of literature in Zhang et al's work³⁵ was relatively small, and more research has been added in the present research, which suggested that the current result was more objective and reasonable.

Some limitations still exist in the present research. There was inadequate large-scale research on the arteriosclerosis and E469K. The studies in the Chinese population might need to be conducted with a larger sample size in the future.

Conclusion

In conclusion, the present meta-analysis suggests that the distribution frequency of the K allele of the ICAM-1 E469K gene might predispose to CAD susceptibility in the Chinese

population. This deduction was potentially crucial to guide the CAD individual treatment. In consideration of the above limitations, further survey studies are needed to verify these points in the future.

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