Protective effect of an endothelial lipase gene variant on coronary artery disease in a Chinese population

Na-Ping Tang,1,* Lian-Sheng Wang,1,† Li Yang,1,§ Bo Zhou,1,* Hai-Juan Gu,* Qing-Min Sun,* Ri-Hong Cong,* Huai-Jun Zhu,* and Bin Wang2,*

Key Laboratory of Reproductive Medicine,* Department of Pharmacology, Nanjing Medical University, Nanjing, China; and Departments of Cardiology† and General Surgery,§ First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Abstract The aim of the present study was to assess the influence of the endothelial lipase (EL) gene 584C/T variant, which results in a change at codon 111 of the EL gene from threonine to isoleucine, on the risk of coronary artery disease (CAD) in a Chinese population. The study population consisted of 265 CAD patients and 265 age- and sex-matched control subjects. The T allele frequency was significantly lower among CAD patients than among control subjects (18.3% vs. 29.8%; P < 0.001). In both the CAD and control groups, the T allele carriers had higher high density lipoprotein cholesterol (HDL-C) levels than homozygote C allele carriers. In a multiple logistic regression model adjusted for age, sex, body mass index, smoking, hypertension, diabetes, hyperlipidemia, and low density lipoprotein cholesterol, a significantly decreased risk of developing CAD was found in subjects carrying a variant CT or TT genotype (odds ratio = 0.496, 95% confidence interval = 0.341–0.723; P < 0.001), and the significance persisted after further adjustment for HDL-C. In conclusion, our observation that the EL 584T allele was associated with protection from CAD in this Chinese population replicates the findings in a Japanese study, which found a similar association of this allele with acute myocardial infarction, independent of HDL-C levels.—Tang, N-P., L-S. Wang, L. Yang, B. Zhou, H-J. Gu, Q-M. Sun, R-H. Cong, H-J. Zhu, and B. Wang. Protective effect of an endothelial lipase gene variant on coronary artery disease in a Chinese population. J. Lipid Res. 2008, 49: 369–375.

Supplementary key words genetic variant • polymorphism • high density lipoprotein cholesterol

Growing evidence indicates that low plasma high density lipoprotein cholesterol (HDL-C) levels are associated with the risk of coronary artery disease (CAD) and that high HDL-C levels constitute a major risk-reducing factor for CAD (1, 2). For instance, in the Prospective Cardiovascular Munster study, data showed that men with HDL-C levels < 0.90 mmol/l had a 4-fold increased risk of CAD over a 6 year period compared with men with HDL-C ≥ 0.90 mmol/l (3). It has also been shown that an increase of HDL-C of 0.026 mmol/l would decrease the CAD risk by 2% in men (Framingham Heart Study, Coronary Primary Prevention Trial, and Multiple Risk Factor Intervention Trial studies) and 3% in women (Framingham Heart Study) and decrease the CAD death rate by 3.7% in men and 4.7% in women (Lipid Research Clinics Prevalence Mortality Follow-up Study) (4).

Endothelial lipase (EL) is a newly discovered member of the triglyceride (TG) lipase gene family, which is highly homologous to LPL and HL (5, 6). It is expressed in many tissues, such as liver, lung, macrophage, testis, ovary, and placenta (5). However, unlike LPL and HL, EL is synthesized by endothelial cells and has relatively low TG lipase and high phospholipase activities (5–7). Similar to the other members of this gene family, EL is a secreted protein and has an 18 residue hydrophobic secretory signal peptide, which when cleaved predicts a 482 residue, 55 kDa mature EL species (6). It has also been indicated that EL is a heparin binding protein that is displaced from the cell surface by heparin, suggesting that EL is anchored to the luminal endothelial surface via heparin sulfate proteoglycans (8). Recently, Badellino et al. (9) used a newly developed sandwich enzyme-linked immunosorbent assay to measure the plasma EL concentration and confirmed that there was a highly statistically significant negative association between EL levels and HDL-C levels. Studies in mouse have also shown that, like LPL and HL,
EL may play an important regulatory role in lipid metabolism, in particular, HDL-C metabolism (6, 10–14).

To date, several genetic variants have been identified in the EL gene (14–16). One of the most frequently studied variants is 584C/T (rs2000813), which results in a change at codon 111 of the EL gene from threonine to isoleucine (15, 16). Numerous studies have associated this variant with increased levels of HDL-C (14, 16–19), whereas other studies failed to find a significant association (15, 20, 21). In addition, Shimizu et al. (21) reported that the T allele was significantly associated with acute myocardial infarction (AMI), suggesting that this variant might play a potential role in the susceptibility to cardiovascular disease.

Studies of the impact of the 584C/T variant on lipid levels have been mainly carried out in American, Japanese, and Caucasian populations (14–16, 19–21). There is a lack of data regarding the impact of the 584C/T variant on HDL-C levels in the Chinese population. Moreover, no study has been conducted in a Chinese population to evaluate the influence of the 584C/T genotype on CAD. Therefore, in the present work, we performed a case-control study to assess the potential association between the 584C/T variant and the risk of CAD and HDL-C levels in a Chinese population.

MATERIALS AND METHODS

Study population

The study population was composed of 265 CAD patients and 265 control subjects. All enrolled subjects were unrelated ethnic Han Chinese residing in or near Jiangsu province. The CAD patients were consecutively recruited from the inpatients who were admitted to Nanjing Medical University Affiliated Hospital because of angina pectoris or other symptoms or signs of cardiovascular disease. CAD was defined as angiographic evidence of at least one segment of a major coronary artery, including the left anterior descending, left circumflex, or right coronary artery, with ≥50% organic stenosis. The coronary angiograms were reviewed by experienced cardiologists who were unaware that the patients were to be included in this study. Among the 265 CAD patients, 34 had AMI.

The non-CAD control group consisted of 265 patients who were selected during the same period in the same hospital as the CAD patients and matched by age (±5 years) and sex. These patients mainly had cataract, glaucoma, keratitis, or hernia. Considering that it was unethical to perform coronary angiography to rule out the presence of asymptomatic CAD, the following inclusion criteria were used: no history of angina and no history of symptoms or signs of other atherosclerotic vascular diseases.

All subjects (CAD patients and control subjects) included in this study had no family history of CAD and no history of significant concomitant diseases, including cardiomyopathy, bleeding disorders, renal failure, previous thoracic irradiation therapy, and malignant diseases. Informed consent was obtained from each subject. This study was approved by the Nanjing Medical University Affiliated Hospital Ethics Committee. Hypertension, diabetes mellitus, and dyslipidemia were defined as described in our previous studies (22). In brief, subjects were considered to be hypertensive if their systolic blood pressure was >140 mm Hg and/or their diastolic pressure was >90 mm Hg or if they were already being treated with antihypertensive drugs. Diabetes was defined as fasting blood glucose > 7.8 mmol/l or a diagnosis of diabetes needing diet therapy or already on antidiabetic drug therapy. Dyslipidemia was defined as total cholesterol (TC) level of >6.2 mmol/l or already on drugs. One hundred two (38%) CAD patients but none of the control subjects were on lipid-lowering medications. Subjects were defined as smokers if they smoked ≥10 cigarettes per day.

Laboratory measurements

Approximately 5 ml fasting blood samples were obtained by venipuncture in the early morning of the day after admission. The levels of plasma HDL-C, TC, TG, and low-density lipoprotein cholesterol (LDL-C) were measured enzymatically (First Chemical Co.) on a chemistry analyzer (Olympus AU2700) as described previously (22). Glucose levels were measured by a glucose oxidase method (Reagent kit; Diagnostic Chemicals, Ltd., Oxford, CF). The levels of plasma lipids and glucose in AMI patients were measured 3 months after the event.

Genotyping

Genomic DNA was isolated from white blood cells by standard phenol-chloroform extraction. Genotyping of the 584C/T variant was performed by PCR-restriction fragment length polymorphism analysis. The region in exon 3 (254 bp) containing the polymorphic site was amplified by PCR in the T1 Thermocycler (Biometra, Gottingen, Germany) using the following primer pair (14): forward primer, 5'-CAT GAG CTG AGA TTG TTG TCA GTG C-3' and reverse primer, 5'-CAT GAG CTG AGA TTG TTG TCA GTG C-3'. The primer was modified at position 35 by inserting a single base A (nucleotide 586), thus creating a recognition site for the restriction endonuclease NdeI (CATATG) in the presence of a T allele at position 584. PCR was performed in a total volume of 20 μl containing 2 μl of 10X PCR buffer, 0.875 mmol/l MgCl2, 0.15 mmol/l deoxynucleoside triphosphates, 0.25 μmol/l each primer, 100 ng of genomic DNA, and 1.5 units of Taq DNA polymerase (MBI Fermentas, Vilnius, Lithuania). The amplification protocol consisted of the following conditions: initial denaturation at 94°C for 8 min, amplification for 35 cycles at 94°C for 45 s, 57°C for 60 s, and 72°C for 60 s, followed by a final elongation step at 72°C for 7 min. An aliquot of 5 μl of the PCR product was digested with 10 units of NdeI (New England Biolabs, Waltham, MA) in 2 μl of 10X NEB buffer 4 (50 mmol/l potassium acetate, 20 mmol/l Tris-acetate, 10 mmol/l magnesium acetate, and 1 mmol/l dithiothreitol) and 12.5 μl of deionized water at 37°C for 16 h. The 254 bp PCR product was cleaved into two fragments of 217 and 37 bp for the T homozygote, three fragments of 254, 217, and 37 bp for the CT heterozygote, and the C homozygote remained uncleaved showing a 254 bp PCR product. After electrophoresis through a 2% agarose gel, the digestion products were visualized by staining with 0.5 μg/ml ethidium bromide. Approximately 10% of the samples were randomly selected to perform the repeated assays, and the results were 100% concordant. Two researchers, blinded to the clinical data, scored the genotypes independently.

Statistical analysis

Statistical analyses were performed with SPSS version 15.0 (SPSS, Inc., Chicago, IL). Continuous variables were presented as means ± SEM. The Kolmogorov-Smirnov test was used to analyze the normality of the distribution. Differences of continuous variables without skewness between cases and controls were calculated by the Student’s t-test. Differences of continuous variables departing from the normal distribution even after log-
transformation between the two groups were analyzed by Mann-Whitney U-test. Categorical variables were presented using frequency counts and compared by Chi-square test. The Hardy-Weinberg equilibrium was evaluated by Chi-square goodness-of-fit test. General linear measurement multivariate analyses for 584C/T genotype groups (CC and CT+TT) were used for lipid parameters after adjustment for age, sex, and lipid-lowering medications. Univariate analysis and multiple logistic regression analysis were performed to determine the variables that independently contributed to the presence of CAD. Odds ratio (OR) and 95% confidence interval (CI) were calculated. A value of \( P < 0.05 \) was considered statistically significant.

RESULTS

Baseline characteristics

The baseline characteristics of the case and control groups are presented in Table 1. As expected, there was no significant difference between the cases and controls in age (62.8 ± 0.6 vs. 62.2 ± 0.7 years; \( P = 0.504 \)) and sex (male, 73.2% vs. 73.2%; \( P = 1.000 \)), indicating that the subjects were well matched. However, compared with the control subjects, patients with CAD had higher body mass index (BMI), prevalence of hypertension, dyslipidemia, and rate of smoking, and higher levels of TC, TG, and LDL-C but lower HDL-C.

584C/T genotypes and allele frequencies

Table 2 shows the distribution of the 584C/T genotypes and allele frequencies in CAD patients and control subjects. Genotype frequencies did not deviate from the Hardy-Weinberg equilibrium in control subjects (Chi-square = 2.656, \( P = 0.103 \)) and CAD patients (Chi-square = 1.397, \( P = 0.237 \)). The frequencies of the CC, CT, and TT genotypes were 47.2, 46.0, and 6.8%, respectively, in the control group, compared with 65.7, 32.1, and 2.3% in the case group. The frequency of the variant T allele was significantly lower among CAD patients compared with control subjects (18.3% vs. 29.8%; \( P < 0.001 \)).

Table 1. Baseline characteristics of cases and controls

| Characteristics        | Cases (n = 265) | Controls (n = 265) | \( P \) |
|------------------------|----------------|-------------------|-------|
| Sex (male), n (%)      | 194 (73.2)     | 194 (73.2)        | 1.00  |
| Age (years)            | 62.8 ± 0.6     | 62.2 ± 0.7        | 0.504 |
| BMI (kg/m²)            | 25.1 ± 0.2     | 23.8 ± 0.2        | <0.001|
| Diabetes, n (%)        | 60 (22.6)      | 44 (16.6)         | 0.080 |
| Dyslipidemia, n (%)    | 21 (7.9)       | 8 (3.0)           | 0.013 |
| Smoking, n (%)         | 127 (47.9)     | 83 (31.3)         | <0.001|
| TC (mmol/l)            | 4.17 ± 0.07    | 3.99 ± 0.06       | 0.036 |
| TG (mmol/l)            | 1.78 ± 0.09    | 1.32 ± 0.05       | <0.001|
| LDL-C (mmol/l)         | 2.40 ± 0.05    | 2.19 ± 0.04       | 0.005 |
| HDL-C (mmol/l)         | 1.00 ± 0.02    | 1.11 ± 0.02       | <0.001|

BMI, body mass index; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride. BMI (normally distributed) and TG (after log-transformation) were compared by Student’s t-test. Age, TC, HDL-C, and LDL-C (abnormally distributed even after log-transformation) were analyzed by Mann-Whitney U-test. Other data were expressed as frequencies and percentages and evaluated by Chi-square test.

Cholesterol levels before lipid-lowering medications were commenced. Ninety-one (34%) coronary artery disease (CAD) patients were on lipid-lowering medications despite being normolipidemic as defined in the current study.

DISCUSSION

To our best knowledge, this is the first study to assess the potential influence of the 584C/T variant on the risk of CAD in a Chinese population. The data show that the variant T allele is independently and significantly associated with the reduced risk of CAD in this Chinese population, although the T allele is related to higher levels of HDL-C in both CAD patients and control subjects.

Studies in mouse and human have indicated that the EL may play an important role in the regulation of HDL metabolism (6, 10–14). It has been demonstrated in transgenic mice that high expression of EL was significantly associated with reduced HDL-C levels (6, 10, 11). Maugeais et al. (12) also reported dose-dependent effects of EL on HDL metabolism in mice. In addition,
loss-of-function studies (10, 13, 14) confirmed that the low-level expression of EL in mice related to increased levels of HDL-C. Badellino et al. (9) also showed that plasma EL levels were negatively associated with HDL-C levels in humans. Although much progress has been made in identifying the role of EL in HDL-C metabolism, the precise mechanism remains to be defined. Data from Jin et al. (13) and Ma et al. (14) suggested that EL could increase the catabolism of HDL and promote the transfer of cholesterol and phospholipids from HDL to other lipoproteins or tissues. The nuclear magnetic resonance analysis by Ma et al. (14) also revealed that EL knockout mice had increased HDL particle size, indicating that EL phospholipid activity might contribute to the generation of smaller, lipid-depleted HDL and facilitate the catabolism of HDL (12, 14). In addition to the catalytic activity, EL may also have a potential noncatalytic effect on HDL-C metabolism, which is the ability to bridge HDL (23). However, investigations by Broedl et al. (11) have suggested that the role of bridging is less important than the role of catalytic activity in HDL-C metabolism.

To date, numerous studies have linked the 584C/T variant to variations in HDL-C levels (14, 16–19). Ma et al. (14) previously reported that this variant was significantly associated with HDL-C levels in a well-characterized population of 372 individuals from the Lipoprotein and Coronary Atherosclerosis Study. The Quebec Family Study performed by Paradis et al. (16), which involved 281 women and 216 men, showed that plasma HDL3-C levels of TT homozygote women were higher than those of women carrying the wild-type allele. Modest associations of the T allele were also found with HDL-C, HDL3-C, and apolipoprotein A-I levels in 541 adult Japanese Americans (17). In addition, data from a study conducted in 83 healthy sedentary people in Maryland suggested that the T allele might be associated with interindividual variability in HDL-C and its subfractions (18). Moreover, Mank-Seymour et al. (19) compared EL variants in 355 individuals with HDL-C > 60 mg/dl and 239 individuals with HDL-C < 35 mg/dl from the Atorvastatin Comparative Cholesterol Efficacy and Safety Study; they found that the T allele was significantly associated with HDL-C in women. Our observations of significantly higher plasma HDL-C levels among T allele carriers (CT+TT) compared with CC carriers are consistent with these previous findings and suggest that this variant may have functional effects and subsequently contribute to variations in HDL-C levels.

In contrast to previous findings and our results, the study by deLemos et al. (15), involving 176 black controls, 165 white controls, and 123 white subjects with high HDL-C, showed that the T allele was not significantly associated with plasma HDL-C levels. Yamakawa-Kobayashi et al. (20) found no relationship between serum HDL-C levels and the T allele in Japanese school-aged children. Shimizu et al. (21) also found no association between the 584C/T

| Genotype | CC | CT | TT | C Allele | T Allele |
|----------|----|----|----|----------|----------|
| Cases (n = 265) | 174 (65.7) | 85 (32.1) | 6 (2.3) | 433 (81.7) | 97 (18.3) |
| Controls (n = 265) | 125 (47.2) | 122 (46.0) | 18 (6.8) | 372 (70.2) | 158 (29.8) |

Values shown are n (%). Distributions of the 584C/T genotypes in both cases and controls were in Hardy-Weinberg equilibrium (Chi-square = 1.397, \( P = 0.257 \) and Chi-square = 2.656, \( P = 0.103 \), respectively, calculated by Chi-square goodness-of-fit test).

a Chi-square = 29.644, degrees of freedom = 2, \( P < 0.001 \) for genotype.

b Chi-square = 19.215, degrees of freedom = 1, \( P < 0.001 \) for allele.
polymorphism and HDL-C levels in 107 Japanese AMI patients and control subjects.

The different observations of the association between the 584C/T variant and HDL-C levels may be explained, at least in part, by the different 584C/T genotype distributions among different races or ethnic groups. Data from deLemos et al. (15) showed that the T allele frequency in white subjects (31.2%) is significantly higher than in black subjects (10.3%). In addition, the T allele frequency in Caucasians (19) was observed to be >29%; in Canadians (16), it was ~28%; in American populations (14), it was observed to be ~26%; and in Japanese, it was <26% (23, 24). In our control group, the T allele was 29.8%, which is in the range of previous reports (14–16, 19–21) and significantly higher than in our CAD patients. Another possibility that may account for the observed inconsistencies across studies is that the EL 584T variant allele is in linkage disequilibrium with the causative allele and that the extent of linkage disequilibrium across the EL locus varies in different populations (17, 20). Hutter et al. (17) reported that the 584T allele and the ~384C allele were in moderate linkage disequilibrium ($r^2 = 0.3$ in Japanese-American families. However, among school-aged Japanese children, significant linkage disequilibrium (D’ = 0.91) was observed between the two alleles (20). Moreover, another explanation for the diversity of the results is the gene-environment interaction. Paradis et al. (16) have reported an interaction between the 584C/T variant and diet on the modulation of apolipoprotein A-I and HDL-C levels. Shimizu et al. (21) also observed an interaction between the 584C/T genotype and smoking.

 Considering the important role of the 584C/T variant in HDL-C metabolism, we wished to determine whether it influenced the risk of CAD in our population. Shimizu et al. (21) previously reported that the T allele was significantly associated with the risk of AMI in a Japanese population, although no relationship was detected between the T allele and HDL-C levels. In the present study, we noted that, compared with the CC genotype, the T allele carriers had a 53.3% reduced risk of CAD. After adjustment for age, sex, BMI, smoking, hypertension, diabetes, hyperlipidemia, and LDL-C, the difference still existed, confirming that this variant was related to the risk of CAD in this Chinese population.

A substantial body of evidence derived from epidemiological and clinical studies and intervention trials has suggested that low levels of HDL-C are powerful lipid predictors of CAD and that increasing HDL-C levels have a protective effect on CAD (1–4). Thus, as the 584C/T variant in the EL gene is associated with plasma HDL-C levels in our population, it is reasonable to assume that the 584C/T genotype may influence the susceptibility to CAD by influencing plasma HDL-C levels. However, when logistic regression analysis was carried out including only the 584C/T genotype and HDL-C, we noted that the protective effect was reduced, although it remained significant. Furthermore, after further adjustment for age, sex, BMI, smoking, hypertension, diabetes, dyslipidemia, and LDL-C, the association remained significant, suggesting that the T allele (or allele in linkage disequilibrium) might decrease CAD risk through a mechanism(s) other than increasing plasma HDL-C levels.

Recent data have suggested that, apart from its effect on plasma HDL-C, EL may have direct atherogenic actions (9, 25–28). A study carried out in human umbilical vein and coronary artery endothelial cells showed that EL mRNA levels were upregulated by inflammatory cytokines, including tumor necrosis factor-α and interleukin-1β (25). In addition, increased levels of EL mRNA were found in response to both fluid shear stress and cyclic stretch, indicating that the expression of EL at the atherosclerotic lesion site may have direct atherogenic actions (25). Studies conducted in the mouse model also showed that EL mRNA and protein levels were markedly increased in tissues with acute inflammation (26). Adhesion assays in vitro and ex vivo also demonstrated that EL could modulate monocyte adhesion and infiltration into diseased tissues (26, 27), although these findings were not consistently observed in another study (29). Besides studies in cell culture and mouse models, other studies in humans have found that EL was expressed in the infiltrating cells, such as smooth muscle cells and macrophages in the atheromatous plaques (29), and the EL concentrations were significantly associated with coronary artery calcification (9). Therefore, the presence of the T allele, if associated with lower plasma levels of EL or decreased EL activity, could potentially explain, at least in part, the significantly decreased risk of developing CAD in subjects carrying the variant genotypes.

Naturally, currently, it cannot be ruled out that the variant 584T allele is not associated with the alteration of plasma EL concentrations or EL activity, although it occurs in a relatively poorly conserved area of the EL
sequence and outside of the catalytic pocket (24). The 584T allele changes codon 111 of EL to an isoleucine residue (15, 16); thus, in future studies, it will be important to determine the impact of this residue on protein mass and activity.

Several limitations of the current study should be considered. First, a hospital-based control group recruited among patients with a variety of non-CAD diseases was used in this study. This may cause the possibility of selection bias and confound the results. However, the genotype distribution of controls was in Hardy-Weinberg equilibrium, and the T allele frequency was in the range of those in previous reports (14–16, 19–21). In addition, although controls were selected from subjects who had no history of angina pectoris and no symptoms or signs of other atherosclerotic vascular diseases, without performing coronary angiography, asymptomatic CAD in these subjects cannot be completely ruled out. A second limitation is the relatively small sample size of our study. To replicate our findings, power calculations based on the OR of 0.528 and the probability of exposure of 0.495 in controls (21) indicate that we would need to study >385 CAD patients and 385 matched controls. Finally, as for all case-control studies, there is a risk of a false-positive finding linking the 584C/T variant and CAD. However, our results confirm previous work that found an association between this variant and cardiovascular disease (21).

In conclusion, the data of this study show that the 584C/T variant in exon 3 of the EL gene is positively related to plasma HDL-C levels, supporting previous findings that the EL plays an important role in HDL-C metabolism. This study furthermore provides evidence that the 584C-to-T variant is significantly associated with the decreased risk of CAD in this Chinese population and that the association is independent of plasma HDL-C levels. Further studies are needed to explore the underlying mechanisms of our findings.

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