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Lack of association between a common polymorphism of the endothelial lipase gene and early-onset coronary artery disease in a Chinese Han population

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ABSTRACT. A growing body of evidence suggests that the 584C/T polymorphism in the endothelial lipase (EL) gene contributes to the process of coronary artery disease (CAD). The present study aimed to reveal the potential relationship between the EL 584C/T gene polymorphism and early-onset CAD, CAD severity, and lipid levels in a Chinese Han population. Participants comprised 135 early-onset CAD patients and 166 controls. EL 584C/T genotypic and allelic frequencies were detected by PCR. The frequencies of the CC, CT, and TT genotypes were 58.4, 38.6, and 3.0%, respectively, within the control group, and 62.2, 33.3, and 4.5%, respectively, in the early-onset CAD group. There was no significant difference in the frequency of CC genotype and T allele carriers between early-onset CAD patients and controls. The frequency of the T allele was 22.3% in the control

group and 21.1% in the early-onset CAD group. The T allele frequency of the variant was not significantly different between the two groups (P = 0.766), even after adjustments for age, gender, smoking status, hypertension, DM, and lipids were made. There was also no significant association between the genotype and the severity of CAD (P = 0.596). Furthermore, there was no correlation between the genotype and lipid levels or their ratios in both groups. The EL 584C/T gene polymorphism, therefore, was not associated with early-onset CAD or the severity of CAD in this Chinese Han population, suggesting that this variant is not always involved in the pathogenesis of early-onset CAD.

Key words: Endothelial lipase; Coronary artery disease; Gene; Polymorphism

INTRODUCTION

Coronary artery diseases (CADs), including stable angina, unstable angina, and acute myocardial infarction (AMI), greatly threaten the lives of people in developing countries. As a complex and multifactorial polygenetic disorder, the development of CAD is dependent on multiple-risk factors, such as age, gender, smoking, hypertension, diabetes mellitus (DM), hypercholesterolemia, low serum high-density lipoprotein cholesterol (HDL-C) level (Maron, 2000), and single nucleotide polymorphisms (SNPs) (Saedi et al., 2012; Zhou et al., 2012).

Endothelial lipase (EL), an enzyme discovered by two independent research groups in 1999 (Hirata et al., 1999; Jaye et al., 1999), is secreted mainly by vascular endothelial cells. EL is a new member of the triglyceride (TG) lipase family, which also includes lipoprotein lipase (LPL) and hepatic lipase (HL). The EL protein has 44 and 41% identity with LPL and HL, respectively. Compared with LPL and HL, EL has greater phospholipase activity and less TG lipase activity. A number of studies have shown that EL plays a key role in HDL-C metabolism, by mediating the selective uptake of HDL-C and HDL-C binding on the cell surface (Strauss et al., 2002). Evidence suggests, however, that EL may influence the regression of atherosclerosis (AS) directly (Ishida et al., 2004; Yasuda et al., 2007; Shiu et al., 2008). Ishida et al. (2004) identified potential direct pro-atherosclerotic actions of EL, namely monocyte recruitment and cholesterol uptake, while Yasuda et al. (2007) found that EL was upgraded by inflammation and induced macrophages to take up native LDL-C. Additional studies also revealed that EL may play an important role in the pathogenesis of cardiovascular disease (CVD) (Badellino et al., 2006; Fang et al., 2007).

The EL 584C/T gene variant was first described in 2002 by Delemos et al. as the common variant that resulted in amino acid substitution. The frequency of the mutation is different in white and black populations (31.2 *vs* 10.3%, respectively), and varies greatly among different countries (Paradis et al., 2003; Mank-Seymour et al., 2004). Recent evidence implies that the presence of the EL 584C/T gene polymorphism (rs2000813) is correlated to the plasma HDL-C level (Hutter et al., 2006). Edmondson et al. (2009) found that the level of HDL-C increases in the loss-of-function variants of EL, and concluded that inhibition of EL may, therefore, raise the HDL-C level. In 2003, Ma et al. reported that patients with the TT genotype have higher HDL-C levels than those with the CC genotype. Indeed, a growing body of

evidence indicates that this common variant likely plays an important role in the development of CVD (Shimizu et al., 2007; Tang et al., 2008). In a case-control study of 107 AMI patients and 107 control subjects, the T allele was determined to be an independent risk factor for the development of AMI.

Some researchs, however, have reported the opposite conclusion (Yamakawa-Kobayashi et al., 2003; Jensen et al., 2009; Vergeer et al., 2010). Yamakawa-Kobayashi et al. (2003) found that the EL 584C/T gene polymorphism is not associated with lipid levels in 340 unrelated school-aged Japanese children, while Jensen et al. (2009) reported that no association exists between the T111I variant and HDL-C or the risk of CVD development among healthy Caucasians of three independent populations.

Currently, the association of this variant with CAD or lipid levels is thus debatable. Moreover, to date, no study has evaluated the association between the EL 584C/T gene polymorphism and the development of early-onset CAD as well as CAD severity in a Chinese Han population. The aim of the present study, therefore, was to determine the relationship between the EL 584C/T gene polymorphism and early-onset CAD, CAD severity, and lipid levels in a Chinese Han population.

MATERIAL AND METHODS

Study participants

The study population comprised of 135 patients with early-onset CAD (72 males and 63 females, mean age of 51.81 ± 7.76 years) and 166 control subjects (52 males and 114 females, mean age of 52.33 ± 8.40 years), all of whom were part of a Chinese Han population living in the south of the Jiangsu Province. All patients admitted to the hospital from July 2008 to February 2011 were recruited for this study. Fasting blood was collected from all subjects. The methods to measure plasma lipid and fasting glucose levels were performed as previously described (Cai et al., 2012), with results obtained from a Olympus AU5400 automatic biochemical analyzer.

Methods

A diagnosis of CAD was defined as luminal diameter stenosis of more than 50% in at least one of the three major epicardial coronary arteries, determined by coronary angiography. Early-onset CAD was defined as the presence of CAD by the age of 55 years in males or 65 years in females. All the subjects were examined by coronary angiography, which was performed using the standard Seldinger's technique. Angiograms were analyzed by two trained cardiologists who were blinded to the study groups. The severity of early-onset CAD was characterized by the number of diseased vessels. Cases were subdivided into either the single-vessel disease group or the multi-vessel disease group according to the results of coronary angiograms. Controls were defined as having <30% organic stenosis in major coronary vessels, and Prinzmetal's variant angina pectoris was excluded.

Hypertension and DM was defined according to features described in our previously report (Cai et al., 2012). Briefly, hypertension was characterized by blood pressure ≥140/90 mmHg and/or treatment with antihypertensive drugs, whereas DM was defined by fasting

blood glucose ≥7.0 mM and/or treatment with antidiabetic drugs. Patients with rheumatic disease, malignant disease, infection, or renal or hepatic disease were excluded. The present study was approved by the Jiangsu University Affiliated Wujin Hospital Ethics Committee and all participants gave written informed consent.

Total genomic DNA was obtained from peripheral blood with standard phenol-chloroform extraction. Genotyping of the EL 584C/T gene variant was performed by polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) analysis. PCR was performed in a final volume of 50 μL that contained of 0.25 μL TaKaRa Ex Taq, 4 μL dNTP mixture, 5 μL 10X PCR Ex Taq buffer (Mg^{2+}), 1 μL genomic DNA, 1 μL of each primer (forward: 5'-CAT GAG CTG AGA TTG TTG TCA GTG C-3'; reverse: 5'-CAG TCA ACC ACA ACT ACA TTG GCG TCT TTC TCT CAT-3', synthesized by Takara Biotechnology, Dalian, China), and double-distilled water up to the final volume. Initial denaturation was performed at 94°C for 5 min, followed by 35 cycles of 94°C for 30 s, 56°C for 30 s and 72°C for 30 s, ending with a final extension step at 72°C for 10 min. The resultant PCR products were digested with the restriction enzyme *Nde*I (Takara Biotechnology) at 37°C overnight. Digested products were subsequently separated by electrophoresis through 3% agarose gels stained with Gelred (Takara Biotechnology), and then observed by UV transillumination. Approximately 10% of the samples were performed in duplicate, and no differences were found between results. Partial PCR products were sent for sequencing (Shangon, Shanghai, China) to confirm our results.

Statistical analysis

All statistical evaluations were carried out with Statistical Package for the Social Sciences (SPSS), version 17.0. Continuous variables are reported as means ± standard deviation and compared using independent-sample *t*-tests. The frequencies of genotypes and alleles were counted directly. Qualitative variables are reported as frequencies and percentages, and compared with chi-square tests. The chi-square test was also used to determine the genotype distributions for the Hardy-Weinberg equilibrium. Binary logistic regression analysis was performed in evaluating the association between early-onset CAD and genotypes as well as environment factors. Results with a P value <0.05 (2-tailed) were considered to be statistically significant.

RESULTS

Baseline characteristics

The clinical characteristics and lipid levels of the control and early-onset CAD groups are shown in Table 1. The age of participants was not significantly different between the early-onset CAD group and controls. The number of males, current smoker status, and DM were significantly higher in patients with early-onset CAD than in control subjects. While the levels of HDL-C and Apo A-I were significantly lower in patients with early-onset CAD than in controls, the levels of Apo B, TC/HDL-C, LDL-C/HDL-C, and Apo B/Apo A-I were significantly higher in patients with early-onset CAD than in controls. There were no differences in the levels of TC, TG, LDL-C, TG/HDL-C, and LP(a) between the two groups.

Table 1. Clinical characteristics between the early-onset CAD group and controls.

Characteristic	Controls (N = 166)	Early-onset CAD group (N = 135)	t (χ^2)	P
Age (years)	52.33 ± 8.40	51.81 ± 7.76	0.550	0.583
Male (%)	52 (31.33)	72 (53.33)	14.886	0.000
Current smoker (%)	26 (15.66)	39 (28.89)	7.692	0.007
Hypertension (%)	76 (45.78)	75 (55.56)	2.844	0.105
Diabetes mellitus (%)	15 (9.04)	27 (20.00)	7.454	0.007
TC (mM)	4.62 ± 0.88	4.65 ± 1.05	0.262	0.793
TG (mM)	1.83 ± 1.31	2.04 ± 1.42	1.337	0.182
HDL-C (mM)	1.21 ± 0.30	1.12 ± 0.26	2.716	0.007
LDL-C (mM)	2.67 ± 0.63	2.77 ± 0.80	1.186	0.237
Apo A-I (g/L)	1.15 ± 0.23	1.10 ± 0.20	2.051	0.041
Apo B (g/L)	0.87 ± 0.33	0.96 ± 0.33	2.145	0.033
LP(a) (g/L)	0.21 ± 0.27	0.22 ± 0.29	0.451	0.652
TC/HDL-C	4.00 ± 1.03	4.30 ± 1.07	2.398	0.017
TG/HDL-C	1.68 ± 1.33	2.00 ± 1.63	1.859	0.064
LDL/HDL-C	2.34 ± 0.74	2.57 ± 0.83	2.581	0.010
Apo B/Apo A-I	0.77 ± 0.24	0.88 ± 0.27	3.733	0.000

Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; LP(a) = lipoprotein(a).

EL 584C/T genotypic and allelic frequencies in controls and the early-onset CAD group

The genotypic distribution of the EL 584C/T gene polymorphism did not deviate from the Hardy-Weinberg equilibrium in both groups. For analysis of the T allele, the 254-bp PCR product was digested into 217- and 37-bp products with *Nde*I. The genotypic and allelic frequencies of the EL 584C/T gene are shown in Table 2. The frequencies of the CC, CT, and TT genotypes were 58.4, 38.6, and 3.0%, respectively, in the control group, and 62.2, 33.3, and 4.5%, respectively, in the early-onset CAD group. Since the number of rare allele homozygotes was small, we combined the CT and TT genotype groups for statistical analysis as T allele carriers. There was no significant difference between the early-onset CAD and control groups in the frequency of CC genotype and T allele carriers (P = 0.555). The frequencies of C and T alleles were 77.7 and 22.3%, respectively, in the control group, and 78.9 and 21.1%, respectively, in the early-onset CAD group. The T allelic frequency of the variant was not significantly different between the early-onset CAD and control groups (P = 0.766). After adjustments for the age, gender, smoking status, hypertension, DM, and lipid levels, no significant association between genotype and early-onset CAD remained. Likewise, there was no significant association between genotype and the severity of CAD (Table 3).

Table 2. Genotype and allele frequencies of the EL 584C/T gene polymorphism between the early-onset CAD group and controls.

	Grouped genotype [N (%)]		Allele [N (%)]	
	CC	CT+TT	C	T
Controls (N = 166)	97 (58.4)	64+5 (41.6)	258 (77.7)	74 (22.3)
Early-onset CAD group (N = 135)	84 (62.2)	45+6 (37.8)	213 (78.9)	57 (21.1)
χ^2	0.446		0.121	
P	0.555		0.766	

Table 3. Genotype and allele frequencies of the EL 584C/T gene polymorphism in different number of diseased vessels.

	Grouped genotype [N (%)]		Allele [N (%)]	
	CC	CT+TT	C	T
Controls (N = 166)	97 (58.4)	64+5 (41.6)	258 (77.7)	74 (22.3)
SVD (N = 94)	56 (59.6)	35+3 (40.4)	147 (78.2)	41 (21.8)
MVD (N = 41)	28 (68.3)	10+3 (31.7)	67 (81.7)	15 (18.3)
χ^2	1.034		0.628	
P	0.596		0.731	

SVD = single-vessel disease; MVD = multi-vessel disease.

Genotypes and lipid levels

As shown in Table 4, there were no differences between genotypes and lipid levels or their ratios in all subjects, or when participants were analyzed as control and early-onset CAD groups or further by gender, divided into two subgroups of males and females.

Table 4. Clinical characteristics in different EL 584C/T genotypes.

Characteristic	CC (N = 181)	CT+TT (N = 120)	t (χ^2)	P
Age (years)	52.29 ± 7.87	51.80 ± 8.49	0.510	0.611
Male (%)	77 (42.54)	47 (39.17)	0.339	0.633
Current smoker (%)	40 (22.10)	25 (20.83)	0.068	0.886
Hypertension (%)	91 (50.28)	60 (50.00)	0.002	1.000
Diabetes mellitus (%)	25 (13.81)	17 (14.17)	0.008	1.000
TC (mM)	4.64 ± 0.98	4.62 ± 0.93	0.162	0.872
TG (mM)	1.92 ± 1.44	1.93 ± 1.25	0.064	0.949
HDL-C (mM)	1.15 ± 0.26	1.19 ± 0.32	1.298	0.195
LDL-C (mM)	2.72 ± 0.72	2.68 ± 0.70	0.671	0.503
Apo A-I (g/L)	1.12 ± 0.23	1.14 ± 0.20	0.900	0.369
Apo B (g/L)	0.90 ± 0.34	0.92 ± 0.32	0.515	0.607
LP(a) (g/L)	0.21 ± 0.27	0.22 ± 0.29	0.440	0.660
TC/HDL-C	4.17 ± 1.02	4.08 ± 1.10	0.732	0.465
TG/HDL-C	1.82 ± 1.54	1.82 ± 1.39	0.009	0.993
LDL/HDL-C	2.48 ± 0.78	2.39 ± 0.80	0.891	0.373
Apo B/Apo A-I	0.81 ± 0.26	0.82 ± 0.27	0.358	0.721

For abbreviations, see legend to Table 1.

DISCUSSION

To the best of our knowledge, the present study is the first to explore the relationship between the EL 584C/T gene polymorphism and early-onset CAD and CAD severity in a Chinese Han population. We found that the variant was not associated with susceptibility to the development of early-onset CAD or CAD severity in the Chinese Han population. Furthermore, we also showed that the variant was not associated with lipid levels and their ratios in early-onset CAD patients.

Findings of a number of studies indicate that an elevated HDL-C level protects against the development and progression of AS, both *in vivo* and *in vitro* (Gordon et al., 1977). Goswami et al. (2008) revealed that Apo B/Apo A-I was a better predictor of the risk of CVD development than traditional lipid ratios. Our observations of significantly higher plasma

HDL-C and Apo A-I levels among controls compared with early-onset CAD subjects are consistent with these previous findings. Moreover, the levels of Apo B, TC/HDL-C, LDL-C /HDL-C, and Apo B/Apo A-I were significantly higher in patients with early-onset CAD than in controls in our study. There were no differences in the levels of TC, TG, LDL-C, TG/ HDL-C, and LP(a) between the two groups.

The mature EL, which is composed of three conserved catalytic regions and binding sites, consists of 482 amino acids and has a molecular mass of about 55 kDa. Compared with LPL and HL, EL has more phospholipase activity and less triglyceridase activity, which mainly hydrolyze HDL-C (McCoy et al., 2002) and increase its clearance from peripheral circulation. In addition to its catalytic phospholipase activity, EL also has non-catalytic legend-bridging functions. EL hydrolyzes HDL-C to generate free fatty acids, lysolecithin, and low-lipid Apo A-I by creating a link between HDL-C and heparan sulfate proteoglycan. A growing body of evidence suggests that EL plays a crucial role in HDL-C metabolism (Ishida et al., 2003; Ma et al., 2003; Tanaka et al., 2009). The EL concentration is negatively correlated with the level of HDL-C, and some studies have determined that EL may influence the regression of AS directly (Ishida et al., 2004; Yasuda et al., 2007; Shiu et al., 2008). Ishida et al. (2004) revealed that EL may have direct pro-atherosclerotic functions by recruiting monocytes and facilitating the uptake of cholesterol, while other studies showed that EL may play an important role in the progress of CVD (Badellino et al., 2006; Fang et al., 2007). The hypothesis, therefore, exists that reduced EL levels delay the progression of AS. Although currently, the exact mechanisms behind the relationship between EL and the progression of AS are not clear.

The EL 584C/T gene variant is a missense polymorphism in exon 3 (Delemos et al., 2002). To date, although several studies have been carried out to explore the relationship between the variant and lipids and CAD (Table 5) (Ma et al., 2003; Yamakawa-Kobayashi et al., 2003; Paradis et al., 2003; Halverstadt et al., 2003; Hutter et al., 2006; Shimizu et al., 2007; Tang et al., 2008; Jensen et al., 2009; Vergeer et al., 2010; Liu et al., 2010; Durlach et al., 2011), the results are not consistent. Liu et al. (2010) found that the EL 584T allele elevates the plasma HDL-C, TC, and Apo B levels in Bai Ku Yao and Han Chinese persons. A prospective case-control study in EPIC-Norfolk (Vergeer et al., 2010) suggested that the minor allele of EL 584C/T is associated with HDL-C and Apo A-I levels, as well as the HDL-C particle number and HDL-C size, while Paradis et al. (2003) found an association between the variant and the HDL_3-C subfraction in 281 women. Ma et al. (2003) not only found a relationship between genotype and lipid levels, but also a relationship between genotype and lipid ratios. Hutter et al. (2006) demonstrated that the SNP is associated with the presence of HDL-C-related risk factors in 541 adult Japanese-Americans. Recently, Durlach et al. (2011) revealed that 396 DM patients with the minor allele have higher HDL-C levels and lower LDL-C levels compared with controls. In 530 age- and gender-matched Chinese subjects, Tang et al. (2008) investigated the relationship between the common variant and CAD. They found that the T allele significantly reduces the risk for CAD development, even in multiple logistic regression. Furthermore, they also found that the serum HDL-C level is significantly higher in T allele carriers than in wide-type CC carriers after adjusting for age, gender, and the use of lipid-lowering medications. In a case-control study of 107 AMI patients and 107 control subjects, Shimizu et al. (2007) showed that the T allele is an independent risk factor for AMI development.

Table 5. Genotype and allele frequencies of the EL 584C/T polymorphism in several ethnic populations and the relationship with disease.

Ethnic group	CC [N (%)]	CT [N (%)]	TT [N (%)]	T allele frequence (%)	Relationship between T allele and disease
Chinese Han (this study)	181 (60.1)	109 (36.2)	11 (3.7)	21.8	No association with lipids and early-onset CAD
American (Ma et al., 2003)	180 (48.4)	167 (44.9)	25 (6.7)	29.2	A major determinant of HDL-C concentration
Japanese school-aged children (Yamakawa-Kobayashi et al., 2003)	198 (58.2)	120 (35.3)	22 (6.5)	24.1	No association with lipids
American (Halverstadt et al., 2003)	44 (53.0)	35 (42.2)	4 (4.8)	26.0	Associated with HDL-C
Japanese-American (Hutter et al., 2006)	311 (57.5)	202 (37.3)	28 (5.2)	23.8	Associated with HDL-C
Japanese (Shimizu et al., 2007)	124 (57.9)	86 (40.2)	4 (1.9)	22.0	Associated with AMI
Chinese Han (Tang et al., 2008)	299 (56.4)	207 (39.1)	24 (4.5)	24.1	Protection from CAD
Caucasian (Jensen et al., 2009)	2054 (49.6)	1759 (42.5)	327 (7.9)	29.1	No association with lipids or risk of CAD
Bai Ku Yao (Liu et al., 2010)	325 (50.4)	298 (46.2)	22 (3.4)	26.5	Associated with lipids
Chinese Han (Liu et al., 2010)	264 (41.4)	339 (53.1)	35 (5.5)	32.1	Associated with lipids
French (Durlach et al., 2011)	176 (44.4)	178 (44.9)	42 (10.7)	33.1	Associated with lipid metabolism and microvascular complications in DM

In contrast, Yamakawa-Kobayashi et al. (2003) failed to find a significant association between the EL 584C/T gene polymorphism and lipid levels in school-aged Japanese children. A similar result was obtained by Shimizu et al. (2007) in Japanese AMI subjects and by Jensen et al. (2009). Moreover, Vergeer et al. (2010) found no relationship between the common polymorphism and CAD. In the present study, a significant association between the variant and lipid levels and their ratios was also not identified. The reasons for the observed differences in study results may be attributed to the ethnic differences among study groups and the complexity of the gene-environment interaction.

To date, the association between the EL 584C/T gene polymorphism and early-onset CAD or the severity of CAD in the Chinese population has not been reported. In this study, we found that the T allelic frequency of the EL 584C/T gene was 21.8% in all subjects (22.3% in controls and 21.1% in early-onset CAD). The T allelic frequency of the variant was not significantly different between the early-onset CAD and control groups ($P = 0.766$). After adjustments were made for the presence of traditional risk factors of CAD, the genotype remained not significantly associated with early-onset CAD. We also found that there was no significant relationship between the genotype and severity of CAD in this study population.

There were several limitations of the present study. Specifically, we have no experimental evidence to examine the influence of the EL 584C/T gene polymorphism on the expression of EL or other inflammatory cytokines. To explore the relationship between the variant and EL and pro-inflammatory factors, our future research will detect serum levels of EL and several pro-inflammatory factors. Furthermore, the sample size of the present study population was relatively small, and all participants lived within the limited area of the Jiangsu Province. Indeed, the gene-environment interaction will affect study conclusions. Environmental factors such as habits and customs, therefore, may have influenced our results.

CONCLUSIONS

We found that the EL 584C/T gene polymorphism is not associated with the development of early-onset CAD or the severity of early-onset CAD in the Chinese Han population. We also found that the variant was not associated with lipids and their ratios in early-onset CAD patients.

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