Apolipoprotein C3 genetic polymorphisms are associated with lipids and coronary artery disease in a Chinese population

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Abstract

Background: The disorder of triglyceride (TG) metabolism leading to hypertriglyceridemia is an independent risk factor for coronary artery disease (CAD). Variants in the apolipoprotein C3 (APOC3) gene were found to be associated with elevated TG levels. The purpose of this study was to investigate the effect of two polymorphisms (1100 C/T and 3238 C/G) of APOC3 on plasma lipid and risk of CAD in a Chinese population.

Methods: The study population consisted of 600 patients with CAD and 600 age- and gender-matched controls. The APOC3 gene polymorphism was analyzed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: Patients with CAD had a significantly higher frequency of APOC3 3238 GG genotype (odds ratio (OR) = 1.64, 95% confidence interval (CI) = 1.10, 2.43; P = 0.01) and APOC3 3238 G allele (OR = 1.27, 95% CI = 1.04, 1.55; P = 0.02) than controls. The findings are still emphatic by the Bonferroni correction. When stratifying by hyperlipidemia, CAD patients with hyperlipidemia had a significantly higher frequency of APOC3 3238 GG genotype (OR = 1.73, 95% CI = 1.13, 2.64; P = 0.01) than without hyperlipidemia. The APOC3 3238 G allele was significantly associated with increasing plasma TG levels and very-low-density lipoprotein cholesterol (VLDL-C) levels both in cases and controls (P < 0.001).

Conclusions: The APOC3 3238 G allele might contribute to an increased risk of CAD as a result of its effect on TG and VLDL-C metabolism.

Keywords: Apolipoprotein C3, Gene polymorphism, Lipid, Coronary artery disease

Introduction

Coronary artery disease (CAD), one of the most common cardiovascular diseases, is the leading cause of morbidity and mortality worldwide [1]. It is caused by multiple interacting endogenous and exogenous factors [2]. There are several emerging risk factors for CAD including smoking, obesity, stress, diabetes, lack of exercise, high alcohol consumption, and hyperlipidemia [3]. Genetic risk, estimated to account for 40-60% of susceptibility to CAD, has until recently been unknown [4-7]. Recently, genome-wide association studies (GWAS) identified a series of single-nucleotide polymorphisms (SNPs) associated with CAD [8-10].

Apolipoprotein C3 (APOC3), a component of triglyceride (TG)-rich lipoproteins and high-density lipoprotein (HDL), was mainly synthesized in the liver and to some extent in the intestine [11]. APOC3 gene, mapped to chromosome 11q23, was involved in transport and clearance of chylomicron remnants, and very-low-density lipoprotein (VLDL) and HDL from the bloodstream [12,13]. Two common SNPs have been identified in the APOC3 gene: 1100 C/T and 3238 C/G [14,15]. The APOC3 3238 C/G polymorphisms have been found to be associated with altered plasma TG concentrations [16].

Recently, case–control study has suggested that the APOC3 3238G allele was a risk factor for CAD in Indians
However, no other studies have confirmed this finding, and no similar studies were represented in Chinese. The purpose of this study was to investigate the effect of two polymorphisms (1100 C/T and 3238 C/G) of APOC3 on plasma lipid and risk of CAD in a Chinese population.

Materials and methods

Study population

A hospital-based case–control study was carried out in 600 patients with CAD and 600 age- and gender-matched controls from January 2012 to January 2014 in the Yantai Yuhuangding Hospital and Clinical College of Yanbian University, China. Based on WHO criteria, CAD cases were defined as those having severe angiostenosis (>50%) in at least one major coronary artery determined by angiography. The control group was composed of age- and gender-matched subjects who had undergone a coronary angiography in the same recruitment period as the CAD patients, without angio-graphic evidence of CAD. Controls selected also had at least one conventional predisposing factor of CAD. The controls were required to have no history or ECG signs of angina pectoris, myocardial infarction, or other cardiovascular diseases. In addition, similar to the cases the controls were all required to be born in China to native Chinese Han parents. To confirm the diagnosis, two physicians reviewed the hospital records and validated each case. The Institutional Ethical Committee approved this study, and all participants gave written informed consent according to the Declaration of Helsinki.

DNA extraction and genotyping

The commercially available Qiangen kit (QIAGEN Inc., Valencia, CA, USA) was used to extract DNA from peripheral blood leukocytes. Genomic DNA was isolated from 20 g/L ethylenediaminetetraacetic acid (EDTA) or sodium citrate anticoagulated 3 ml venous blood and stored at 4°C. Polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) assay was applied to assess the APOC3 gene polymorphisms. Based on the GenBank reference sequence, the PCR primers designed for APOC3 1100 C/T and 3238 C/G were 5′-AGA GGC CGA TCC ACC CGA TCT AGG C-3′ (forward) and 5′-GGC GGT CTT GGT GGC GTG CTT CAG G-3′ (reverse); 5′-CAT GGT TGC CTA CAG AGG AGT-3′ (forward) and 5′-TGA CCT TCC GCA CAA AGC TGT-3′ (reverse), respectively. The amplified PCR products were digested with SstI (3238 C/G) and SacI (1100 C/T) (New England BioLabs, Missisauga, ON, Canada). Details of PCR conditions have been described elsewhere [20]. The digested PCR products were resolved on a 3% agarose gel and stained with ethidium bromide for visualization under UV light. For quality control, two independent observers, read all genotypes without knowing about the case or control status. Direct DNA sequencing was performed to confirm the genotyping results.

Statistical analysis

All statistical tests were performed using the program SPSS (SPSS Inc., Chicago, IL). Linkage disequilibrium was calculated by EXCEL and the method of Chakravarti et al. [21]. Hardy–Weinberg equilibrium was assessed by the x^2 goodness-of-fit test. Differences between continuous variables were assessed by Student’s t test, while those between categorical variables were evaluated using Pearson x^2 test. The existence of differences in genotypic frequencies between groups was assessed by means of Pearson x^2 test and calculating the odds ratio (OR) with the 95% confidence intervals (CI). OR adjusted for other covariates (hypertension, diabetes, smoking, age and gender) were determined using logistic regression models. We also use the Bonferroni correction for total number of independent comparisons. A P-value was considered significant at a level of <0.05.

Results

Characteristics of participants

General characteristics of cases and controls were showed in Table 1. No significant differences were found between the CAD cases and controls in age, gender, family history, hypertension, ApoA1 and ApoB (Table 1). Univariate study
was performed to identify that smoking status \((P < 0.001)\),
diabetes \((P < 0.001)\), obesity \((P < 0.001)\), hyperlipidemia
\((P < 0.001)\), TG \((P < 0.001)\), TC \((P < 0.001)\), HDL-C \((P =
0.002)\), LDL-C \((P = 0.001)\) and VLDL-C \((P < 0.001)\) were
risk factors of CAD (Table 1). Hardy–Weinberg proportions
were observed for all the SNPs. The 1100 C/T and
3238 C/G in the APOC3 gene are in complete linkage
disequilibrium in the Chinese population (Table 2).

**APOC3 3238 C/G polymorphisms, lipids and CAD**

Patients with CAD had a significantly higher frequency
of APOC3 3238 GG genotype \((OR = 1.64, 95\% CI = 1.10, 2.43; P = 0.01)\)
and APOC3 3238 G allele \((OR = 1.27, 95\% CI = 1.04, 1.55; P = 0.02)\) than controls (Table 2). The
findings are still emphatic by the Bonferroni correction.
When stratifying by hyperlipidemia, CAD patients with
hyperlipidemia had a significantly higher frequency of
APOC3 3238 GG genotype \((OR = 1.73, 95\% CI = 1.13, 2.64; P = 0.01)\) than without hyperlipidemia (Table 3). The
APOC3 3238 G allele was significantly associated with
increasing plasma TG levels and VLDL-C levels both in
cases and controls \((P < 0.001)\) (Table 4).

**APOC3 1100 C/T polymorphisms, lipids and CAD**

No association was found between APOC3 1100 C/T
polymorphisms and CAD (Table 2). When stratifying by
smoking status, diabetes, obesity and hyperlipidemia, no
significant differences were found in any groups
(Table 3).

**Discussion**

A lot of studies have been conducted to examine the
association of genetic polymorphism and risk of CAD. A
meta-analysis of 9 studies that included 1,700 CAD
patients and 4,081 healthy controls suggested that ALDH2
Glu504Lys polymorphism may be associated with in-
creased risk of CAD and myocardial infarction in East
Asians, especially among Chinese and Korean populations
[22]. A meta-analyses of 26 studies that included 12,776
cases and 6,371 controls found that -1562C>T polymorph-
ism in the promoter region of matrix metalloproteinase-9
may have association with CAD risk in Asian populations
[23]. A meta-analyses of 22 studies including 3,502 CAD
patients and 3,071 controls suggested that the angiotensin
II receptor, type 1 gene A1166C polymorphism might
be a genetic marker for the development of CAD in
Chinese populations, especially in the context of studies
with northern and older subjects [24,25]. A meta-
analyses of 11 studies involving 22,584 subjects showed that
PTGS2 -765G/C was associated with a decreased
risk of CAD [26]. A meta-analyses of ten studies with
4,413 patients found that apolipoprotein M T-778C
polymorphism was associated with serum lipid levels
and the risk of CAD in the Chinese population [27]. A
meta-analyses of 11 studies involving 5,535 CAD pa-
tients and 5,626 controls indicated that the Connexin37
C1019T polymorphism may be a moderate risk factor
for CAD [28]. A meta-analyses of 20 studies comprising
15,591 participants found that apolipoprotein C3 Sst I
and T-455C polymorphisms might be associated with
CAD risk [14]. A meta-analyses of 9 studies that in-
cluded 3,439 cases and 14,182 controls suggested that
Cyclooxygenase-2 (COX-2) rs20417 polymorphism may
contribute to CAD development, especially in Asians
[29]. A prospective case–control study found that the
rsl2221497 polymorphism in liver X receptor alpha gene
was associated with susceptibility of CAD in Han popu-
lation [30]. A meta-analyses of 40 studies including
4,564 CAD cases and 3,985 controls suggested an asso-
ciation between apolipoprotein E (ApoE) epsilon4 allele
and increased risk of CAD in Chinese population [31].

The APOC3 gene polymorphisms were also associated
with many other diseases. The polymorphisms −482 C/T
and −455 T/C in APOC3 were associated with nonalco-
holic fatty liver disease and insulin resistance [32]. A
case–control study suggested that APOC3 1100 C/T was

### Table 2 Genotype and allele frequencies of APOC3 gene polymorphisms among coronary artery disease cases and healthy controls

| Genotypes   | Cases (%) | Controls (%) | OR (95% CI)       | P    |
|-------------|-----------|--------------|--------------------|------|
| 1100 CC     | 224(37.3) | 235(39.2)    | 1.00(Reference)    |      |
| 1100 CT     | 202(33.7) | 215(35.8)    | 0.99(0.76,1.29)    | 0.92 |
| 1100 TT     | 174(29.0) | 150(25.0)    | 1.22(0.92,1.62)    | 0.18 |
| 1100 C allele frequency | 650(54.2) | 685(57.1)    | 1.00(Reference)    |      |
| 1100 T allele frequency | 550(45.8) | 515(42.9)    | 1.13(0.96,1.32)    | 0.15 |
| 3238 CC     | 414(69.0) | 433(72.2)    | 1.00(Reference)    |      |
| 3238 CG     | 114(19.0) | 121(20.2)    | 0.99(0.74,1.32)    | 0.92 |
| 3238 GG     | 72(12.0)  | 46(7.6)      | 1.64(1.10,2.43)    | 0.01 |
| 3238 C allele frequency | 942(78.5) | 987(82.3)    | 1.00(Reference)    |      |
| 3238 G allele frequency | 258(21.5) | 213(17.7)    | 1.27(1.04,1.55)    | 0.02 |
associated with increased risk of diabetes probably through mechanisms other than direct effects on TG [33]. A population-based prospective cohort (n =7,983) APOC3 -482T allele had increased type 2 diabetes risk [34]. APOC3 gene polymorphisms contributed to an unfavorable lipid profile in patients with HIV [13]. A case–control study suggested that the minor alleles of APOC3 -455 T/C polymorphisms were closely associated with acute coronary syndrome [35]. A case–control study suggested that APOC3 -482TT genotype was independently associated with elevated fasting triglyceride concentrations in obese men [36]. A case–control study involving 374 Chinese type 2 diabetic patients with and 392 without diabetic nephropathy found that the hepatic lipase -514C/T polymorphism interaction with polymorphisms in APOC3 -482C>T increased the risk of diabetic nephropathy [37]. A case–control study suggested that APOC3 SstI polymorphism was weakly associated with sporadic Alzheimer’s disease in a Chinese population [38]. A case–control study suggested that APOC3 promoter polymorphisms (−482 C/T and −455 T/C) were associated with the metabolic syndrome [39,40]. Although the exact mechanism by which the APOC3 3238 G allele might contribute to an increased risk of CAD is still unclear, it is widely suspected that as a result of its effect on lipid metabolism. A meta-analyses of 29 Western prospective studies involving 262,525 participants indicated mode rate and highly significant associations between triglyceride values and CAD risk [41]. The Bogalusa Heart Study found that APOC3 3238 C/G polymorphisms were associated with higher serum triglyceride levels [42]. Our study also found that the APOC3 3238 G allele was significantly associated with increasing plasma TG levels and VLDL-C levels. Strength of this study was a relatively large sample size. Several limitations of our study should be addressed. First of all, potential selection bias might have been present, because this is a hospital based case control study and the subjects may not be representative of the general population. Second, this study only considers a Chinese population that may limit the application of these findings to other ethnic populations. Third, CAD is induced by multiple genes and environmental factors, which were not explored in the present study.

| Smoking status | Cases | n (%) | OR (95% CI) | P  | Controls | n (%) | OR (95% CI) | P  |
|----------------|-------|-------|-------------|----|----------|-------|-------------|----|
| Smoking status | CC    | 600   | 414(69.0)   | 1(Reference) | 144(19.0) | 1(Reference) | 72(12.0) | 1(Reference) |
| Smoking status | CG    | 192   | 133(69.3)   | 1.000(78,129) | 35(18.2)  | 0.96(0.64,1.45) | 24(12.5) | 1.04(0.64,1.70) |
| Smoking status | GG    | 408   | 281(68.9)   | 0.99(0.82,1.22) | 79(19.4)  | 1.02(0.75,1.39) | 48(11.7) | 0.98(0.67,1.44) |

Table 3 Stratification analysis of APOC3 3238 C/G polymorphisms in coronary artery disease cases

| Diabetes | Smoking status | Cases | n (%) | OR (95% CI) | P  | Controls | n (%) | OR (95% CI) | P  |
|----------|----------------|-------|-------|-------------|----|----------|-------|-------------|----|
| Diabetes | Ever | 600   | 414(69.0)   | 1(Reference) | 144(19.0) | 1(Reference) | 72(12.0) | 1(Reference) |
| Diabetes | Never | 192   | 133(69.3)   | 1.000(78,129) | 35(18.2)  | 0.96(0.64,1.45) | 24(12.5) | 1.04(0.64,1.70) |
| Diabetes | Ever | 408   | 281(68.9)   | 0.99(0.82,1.22) | 79(19.4)  | 1.02(0.75,1.39) | 48(11.7) | 0.98(0.67,1.44) |
| Diabetes | Never | 114   | 107(93.6)   | 1.000(78,129) | 30(27.2)  | 1.01(0.65,1.57) | 19(12.2) | 1.02(0.69,1.73) |

Table 4 Lipid profiles of coronary artery disease cases and controls according to APOC3 3238 C/G polymorphisms

| CAD | CC    | TG (mg/dL) | 162.3 ± 86.5 | 197.6 ± 90.4 | 253.9 ± 104.7 | <0.001 | 138.7 ± 75.8 | 170.5 ± 80.6 | 224.6 ± 95.7 | <0.001 |
|-----|-------|------------|--------------|--------------|---------------|--------|--------------|--------------|---------------|--------|
| CAD | CG    | TC (mg/dL) | 194.5 ± 58.5 | 215.4 ± 62.7 | 196.3 ± 58.4 | 0.65   | 182.3 ± 47.1 | 213.8 ± 49.8 | 194.4 ± 48.7 | 0.74   |
| CAD | GG    | HDL-C (mg/dL) | 37.5 ± 11.1 | 40.8 ± 10.4 | 31.5 ± 9.8 | 0.56   | 37.4 ± 11.7 | 46.2 ± 14.5 | 41.7 ± 12.4 | 0.52   |
| CAD | CC    | LDL-C (mg/dL) | 127.1 ± 49.8 | 128.8 ± 49.8 | 105.7 ± 42.3 | 0.09   | 115.3 ± 34.9 | 130.6 ± 37.4 | 104.5 ± 32.7 | 0.34   |
| CAD | CG    | VLDL-C (mg/dL) | 34.8 ± 19.8 | 45.8 ± 24.1 | 59.1 ± 27.4 | <0.001 | 29.6 ± 18.7 | 37.0 ± 20.1 | 48.2 ± 21.3 | <0.001 |
| CAD | GG    | ApoA1 (mg/dL) | 126 ± 22.9 | 138.4 ± 25.6 | 125.2 ± 23.4 | 0.78   | 124.5 ± 22.1 | 135.6 ± 24.1 | 124.7 ± 21.8 | 0.68   |
| CAD | GG    | ApoB (mg/dL) | 88.3 ± 28.1 | 99.8 ± 30.1 | 89.1 ± 27.9 | 0.73   | 87.3 ± 24.2 | 97.7 ± 28.7 | 91.4 ± 25.7 | 0.82   |
Conclusion

In conclusion, our study suggested that the APOC3 3238 G allele might contribute to an increased risk of CAD as a result of its effect on TG and VLDL-C metabolism. Additional studies are needed to confirm this finding.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

FHC and CSA carried out the molecular genetic studies and drafted the manuscript. KZL performed the statistical analysis. YFL XXW and CSA conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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