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Linkage and Association Between Several Variants in the *Apo CIII* Gene Regions and risk of Coronary Artery Disease in Chinese Han Population

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Abbreviations: SNPs: Single Nucleotide Polymorphisms; tagSNPs: Tagging SNPs; MALDI-TOF: Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry; HWE: Hardy-Weinberg Equilibrium; MAF: Minor Allele Frequency; 3'UTR: 3'Untranslated Region; 5'NEAR: 5'-near regions; 3'NEAR: 3'-near regions; AD: coronary artery disease; TG: triglyceride; CHOL: cholesterol; HDL: high-density lipoprotein; VLDL: very-low-Density Lipoprotein; LDL: Low-Density Lipoprotein; ApoA: Apolipoprotein A; ApoAIV: Apolipoprotein A IV; ApoB: Apolipoprotein B; ApoC: Apolipoprotein C; ApoE: Apolipoprotein E; OR: Odds Ratios; CI: Confidence Interval; M: Median; SD: Standard Deviation

ABSTRACT

The studies have demonstrated that several polymorphisms in the apolipoprotein CIII (*ApoCIII*) gene are associated with hypertriglyceridemia, but the link with coronary artery disease (CAD) among different ethnicities is still controversial. The aim of this study was to investigate the association between the polymorphisms of *ApoCIII* with plasma lipid levels, lipoprotein subfractions and risk of CAD in Chinese Han population. Four single nucleotide polymorphisms (SNPs) of *ApoCIII* gene, including rs5128, rs2542051, rs11216153 and rs2849174 were detected by TaqMan Genotyping Assays in 268 subjects with CAD who had angiographically documented coronary atherosclerosis, and 108 controls without CAD. Genotype-specific odds ratios (OR) were estimated by logistic regression. The levels of serum lipid profiles were also detected by biochemical methods. Three polymorphisms (rs2542051, rs11216153 and rs2849174) were first studied. The rs11216153 in 5'-near regions of *ApoCIII* gene showed evidences associated with increased risk of CAD (per minor allele OR, 1.56; 95% CI, 1.08-2.26; P= 0.017). Compared with the most common rs11216153 genotype, variant genotypes (TT) increased an individual's susceptibility to CAD (OR, 3.2; 95%CI, 1.15-7.05; P=0.004). However, carriers of the minor allele of rs2542051 had lower risk of CAD (per minor allele OR, 0.67; 95%CI, 0.46-0.97; P=0.035). We also showed that rs2542051 CC genotypes predicted lower risk of CAD than TT genotypes (OR, 0.344; 95% CI, 0.154-0.767; P=0.009). The other *ApoCIII* gene polymorphisms (rs5128, rs2849174) in this study were not associated with the risk of CAD. In addition, we also found that rs2849174 carriers of the *ApoCIII* T allele had higher ApoA plasma levels compared with C allele carriers (t=-2.445, P =0.020) in this study population. Our data supported a relationship between the two polymorphisms of *ApoCIII* gene (rs11216153, rs2542051) and the risk of CAD. SNP rs2849174 was associated with ApoA plasma levels.

Keywords: Coronary Artery Disease; Polymorphism; Apolipoprotein C III

Introduction

Coronary Artery Disease (CAD) remains a significant health concern worldwide. Dyslipidemia has been identified as one of the principal risk factors for the development of CAD [1]. *ApoCIII* is implicated in the adjustment of the metabolism of triglyceride-rich lipoproteins and it is a principal constituent of chylomicrons and VLDL. *Apo CIII* inhibits the hydrolyzing effect of lipoprotein lipase for TG-rich particles and the hepatic absorption mediated by ApoE [2,3], and also is detrimental to the elimination of ApoB lipoproteins from plasma by interrupting their capacity to bind to hepatic lipoprotein receptors [4]. A high *ApoCIII* levels not only correlates with hypertriglyceridemia but also may directly contribute to the development of atherosclerosis [5]. Immense clinical studies have shown that *ApoCIII* level is a better way to predict the risk for evolution and progression of CAD than the traditional way by measuring TG levels [6-11]. Although the risk burden is mainly constituted by traditional risk factors, the heritable factors are critical for the development of CAD [12].

The human *ApoAI* and *ApoCIII* genes are tightly linked and form a gene complex together with the ApoAIV gene on the long arm of the chromosome11. Within and around the ApoC III gene, some polymorphie sites have been determined. ApoC-III gene polymorphisms correlated with coronary atherosclerosis could be a link of label for an atherogenic gene in the *ApoAI-CIII-AIV* gene complex. Numerous studies show a connection between the appearance of the polyporphie SstI(rs5128) site located in the untranslated region of the *ApoCIII* gene and the raised risk of CAD. In addition, polymorphisms in T-455C (rs2854116), and C-482T (rs2854117) have been found to be associated with CAD risk [13-20]. The T2854G polymorphism located in the intergenic region was reported to be associated with elevated fasting or postprandial TAG concentrations in Caucasians [21]. To find a linkage marker for the putative atherogenic gene in *ApoCIII* gene of Chinese Han population, four qualified tag single nucleotide polymorphisms (tagSNPs) of *ApoCIII* gene were selected from the Genbank dbSNP database and we utilize these to appraise the linkage and association between these polymorphisms with plasma lipid levels, lipoprotein subfractions and risk of CAD in Chinese Han population.

Materials and Methods

Study Population

Approval was obtained from the Hebei Medical University Clinical Research Ethics Committee. After informed consent had been given, samples of venous blood were drawn from each subject after an overnight fast. All subjects in the study were ethnically homogenous Han Chinese derived from the Northern Chinese population. Patients who documented by coronary angiography at least a 70% stenosis in a major epicardial artery were eligible. Subjects with congenital heart disease, cardiomyopathy, valvular disease, and renal or hepatic disease were excluded from the study. Age-matched control subjects were judged to be free of CAD by history, clinical examination, electrocardiography, and Rose questionnaire. A set of questionnaires was completed that included details of medical history, family history of CAD, drug intake, cigarette smoking, and alcohol consumption. Blood pressure, weight, height, and the body mass index were calculated.

TagSNPs Selection

Bioinformatics analysis with Haploview software 4.2(Mark Daly's lab of Broad Institute, Cambridge, MA, Britain) was performed to analyze the haplotype block based on the CHB (Chinese Han Beijing) population data of HapMap (HapMap Data Rel 27 PhaseII +III, Feb09, on NCBI B36 assembly, dbSNP b126 (International HapMap Project). Four tagSNPs were found to cover all the potential functional common SNPs in the ApoCIII gene, including rs5128 in the 3'UTR, rs2542051 and rs2849174 in the 5' near regions, and rs11216153 in the 3' near regions.

Genotyping Analysis

Genomic DNA was isolated from the peripheral blood of the study subjects. MassArray (Seque-nom, San Diego, CA, USA) was used for genotyping all markers using allele-specific MALDI-TOF mass spectrometry [22]. Primers and multiplex reactions were designed using the RealSNP.com Website.

Statistical Analysis

The Hardy-Weinberg Equilibrium (HWE) was tested by a goodness-of-fit chi-square test to compare the expected genotype frequencies with observed genotype frequencies ($p2+2pq+q2=1$) in CAD-free controls. The association between case-control status and each SNP was measured by the Odds Ratio (OR), and its corresponding 95% Confidence Interval (CI) was estimated using an unconditional logistic regression model. Logistic regression modeling was used for the trend test. Homogeneity among stratum variable related ORs was tested. Baseline characteristics were shown as mean ± SD. Due to plasma lipid concentrations had a skewed distribution, the median and interquartile ranges (Q: difference of Q25 and Q75) were presented: M ± Q. The difference of lipid levels in different genotypes in CAD and controls was evaluated by one-way ANOVA after rank transformation when necessary. All calculations were computed with the aid of SPSS statistical software (version 16.0). P value <0.05 was considered statistically significant.

Results

A total of 376 individuals were in the analysis. Among individuals in the study, 268 (191 men and 77 women) with CAD were confirmed. CAD was described exactly as stenosis (>70%) of no less than 1 major epicardial coronary artery proved by angiography. The non-CAD group include 108 subjects (78 men

and 30 women) who were in hospital for cardiac examinations and showed no clinical, electrocardiographic, or angiographic the presence of disease symptom of CAD. The mean age of CAD patients and non-CAD subjects was 59.5±9.8 years and 58.5±9.0 years, respectively (P>0.05), and there was no significant difference in the BMI, diabetes, smoking, blood pressure between the two groups (P> 0.05). We genotyped four SNPs in CAD case-control studies. All polymorphisms were in the Hardy-Weinberg equilibrium in both groups. To estimate the CAD risk related to ApoCIII genotypes, we performed logistic regression analysis. Genotyping results showed that rs2542051 and rs11216153 was significantly associated with CAD in Chinese population (Table 1).

Table 1: Odds Ratios for CAD according to ApoC-III genotypes in the study population.

ApoC-III Genotypes	OR(95% CI)	P valuec
rs11216153		
GG	1	
GT	2.180（0.989-4.804）	0.053
TT	3.200（1.1452-7.051）	0.004
rs2542051		
AA	1	
AC	0.549（0.251-1.201）	0.133
CC	0.344（0.154-0.767）	0.009
rs2849174		
CC	1	
CT	3.167（0.184-54.568）	0.427
TT	2.361（0.146-38.129）	0.545
rs5128		
CC	1	
CG	1.167（0.038-0.729）	0.257
GG	1.163（0.037-0.711）	0.06

Compared with the most common rs11216153 genotype, variant genotypes (TT) increased an individual's susceptibility to CAD (OR, 3.2; 95% CI, 1.15-7.05; P=0.004). The result revealed that homozygotes for rs11216153 T had higher risk of CAD than wild-type individuals. Conversely, the adjusted OR of carrying the rs2542051 CC genotype was 0.344, compared with the AA genotype (P=0.009). The result showed that CC homozygotes had lower risk of CAD than those who carried the AA genotype. The previous reports showed evidences of increased CAD risk associated with ApoCIII gene polymorphisms. However, our result suggested that rs2542051 C variation decreased probability of the disease. No associations were found between rs5128, rs2849174 and CAD. In addition, we also evaluated the association between alleles and CAD risk (Table 2). Carriers of the minor allele of rs11216153 had increased risk of CAD (per minor allele OR, 1.56; 95% CI, 1.08-2.26; P=0.017). Conversely, SNP rs2542051 was associated with decreased risk of CAD (per minor allele OR, 0.67; 95% CI, 0.46-0.97; P=0.035). Patients who carried the C allele tended to have a lower rate of CAD than those who carried the A allele. Thus, minor allele of rs2542051 was associated with reduced risk of CAD in Chinese. Our data also indicated that S2 alleles were common and not associated with coronary atherosclerosis (OR, 0.76; 95% CI, 0.51-1.12; P=0.166). Meanwhile, the C allele of rs2849174 that was first measured in the present study, was not related to CAD (P>0.05).

Table 2: Associations between ApoCIII genotypes and CAD risk.

SNPs ID	Base change	Genomic Position	Position	MAFc	Coronary atherosclerosis (268case/108control) OR(95% CI)	P
rs11216153	G/T	116705100	3' NEAR	0.3636	0.613(0.438-0.857)	0.004
rs2542051	A/C	116697738	5'NEAR	0.3273	1.581(1.137-2.197)	0.006
rs2849174	C/T	116697066	5' NEAR	0.0546	1.187(0.632-2.228)	0.594
rs5128	C/G	116703640	3'UTR	0.2636	1.366(0.962-1.938)	0.08

Note: *The most common allele in controls is given first.

[c]MAF: minor allele frequency in CAD controls.

To estimate whether the abnormal lipid metabolism in subject carriers to the mutation contributed to the risk for CAD concerning the emergence of the *ApoCIII* variant, further analyses were performed. A total of 268 patients were analyzed, and the results were showed in Table 3. Although SNP rs2849174 was not associated with risk of CAD, the carriers of the T allele had higher ApoA plasma levels compared with C allele carriers (t=-2.445, P=0.020). However, we did not find any statistically relevant differences between lipid variables levels and *ApoCIII* genotypes.

Table 3: Plasma levels of lipids, lipoproteins and apoproteins related parameters according to ApoC-III genotypes.

	rs11216153		rs2542051		rs2849174		rs5128	
	G	T	A	C	C	T	C	G
TG(mmol/l)	1.57±0.98	1.49±0.87	1.50±0.92	1.50±0.91	1.78±1.07	1.51±0.96	1.55±0.89	1.59±1.25
CHOL(mmol/l)	4.23±1.55	4.03±1.49	4.32±0.91	4.32±1.67	4.53±0.92	4.23±1.54	4.27±1.59	4.23±1.71
HDL(mmol/l)	0.96±0.34	0.91±0.77	0.96±0.38	0.97±0.36	1.01±0.36	0.96±0.34	0.96±0.34	0.98±0.37
LDL(mmol/l)	2.62±0.87	2.49±1.34	4.32±0.79	4.23±90	4.27±0.76	4.23±0.86	4.27±0.85	4.23±0.88
ApoA(g/l)	1.08±0.20	1.06±0.20	1.08±0.21	1.09±0.20	1.15±0.14	1.07±0.20	1.08±0.19	1.09±0.22
ApoB(g/l)	0.79±0.32	0.78±0.24	0.81±0.24	0.79±0.32	0.79±0.20	0.79±0.31	0.79±0.30	0.80±0.23
ApoC(mg/dl)	9.78±4.56	9.9±4.14	8.76±4.35	8.94±4.38	8.62±4.5	9.07±3.4	8.55±4.48	8.78±4.52

Note: Data was shown as mean ± SD; skewed variables were M ± Q. M: median, Q: inter-quartile range, difference of Q25 and Q75.

Discussion

ApoCIII plays an obligatory role in the determination of the levels of possibly atherogenic VLDL and small dense LDL in the circulation. The results of large-scale clinical studies have demonstrated that it is more preferable to use plasma *ApoCIII* concentrations as a predictor of risk for the development and progression of CAD compared with the traditionally measured TG levels [23]. However, the correlation between *ApoCIII* and CAD was provoking strong disapproval, for some studies indicating a likely association with genetic variability at the locus [24] and others not proving those associations. In present study, we genotyped four SNPs. To estimate the risk of disease related to *ApoCIII* genotypes, logistic regression analysis was performed. One of them is S1/S2 polymorphism (rs5128) in the 3'untranslated region. Although the previous studies demonstrated that there were the associations between S2 allele, lipids, glucose and insulin concentrations and risk of CAD, our results couldn't provide any evidence to support the association between increased CAD risk and the S2 allele. Furthermore, no relationship between the rs5128 and plasma or serum lipid levels was observed.

The other three polymorphisms (rs2542051, rs11216153 and rs2849174) were first evaluated whether these were associated with an increased risk of CAD. We found the minor allele of rs11216153 was associated with an increased risk of CAD. The result revealed that homozygotes for rs11216153 T had higher relative risk of CAD than those observed in wild-type individuals. SNP rs11216153 seems to be unique in being strongly associated with CAD risk. Previous studies concerning *ApoCIII* polymorphisms and CAD risk have brought in debatable results, probably relevant to differences in methodological aspects such as the selection of cases and controls, their ethnical composition, and the sample size of this case study [11,16,25-28]. However, no study has reported *ApoCIII* polymorphisms were associated with reduced risk of CAD. Our result suggested that rs2542051 C variation decreased probability of disease. The minor allele of rs2542051 was associated with a reduced risk of CAD. Although SNP rs2849174 which was first studied was not associated with risk of CAD, we found that carriers of the T allele had higher ApoA plasma levels compared with C allele carriers. In this study, we were confident that we maximized the opportunity of precise results in the analysis of the connection with *ApoCIII* genotypes.

Conclusion

The present study genotyped four SNPs of *ApoCIII*. We found some evidences for association of SNP rs11216153 with increased risk of CAD and SNP rs2542051 with reduced risk of CAD. SNP rs5128 was not major risk factors of CAD in Han Population in China. Only rs2849174 was significantly associated with ApoA plasma levels.

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Author Contributions

The study was conceived and designed by WC. The clinical data of all subjects were obtained by HH and SG. Data analyses were performed by MH and MG. The paper was written by HH and all authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The experimental protocol was approved by the Ethics Committee of the Hebei Medical University (Shijiazhuang, China). Written informed consent was obtained from all patients.

Competing Interest

The authors declare that they have no competing interests.

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