DMRT2 gene polymorphisms is associated with the coronary artery disease in Han population in Xinjiang, China

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Article

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Abstract

Background

DMRT2 gene plays a significant role in human gonad and skeletal muscle, as well as affecting human immune, inflammatory and metabolic pathways. The main purpose of this study was to explore the relationship between single-nucleotide polymorphisms (SNPs) of DMRT2 gene and coronary artery disease (CAD) in Xinjiang Han population.

Methods

We designed a case–control study including 1092 participants (male: 533; female: 559); Among them, 542 patients with CAD and 550 normal coronary angiographies. We used the improved multiplex ligation detection reaction(iMLDR) method, we genotyped two SNPs (rs12350001 and rs7856817) of DMRT2 gene in all subjects.

Results

We found that the dominant model (A/A vs A/G + G/G) and over-dominant model (G/G + A/A vs A/G) of rs12350001 were significantly different between CAD patients and the controls (P = 0.003, P = 0.002 and P = 0.007, respectively). The dominant model (G/G vs G/A + A/A) of rs7856817 were significantly different between CAD and controls (P = 0.031 and P = 0.029, respectively). The rs12350001 G allele was associated with a significantly elevated CAD risk [AG/GG vs AA: odds ratio (OR) = 1.870, 95% confidence interval (CI) = 1.237–2.824, P = 0.003], and the rs7856817 A allele was associated with a significantly elevated CAD risk [GA/AA vs GG: odds ratio (OR) = 2.062, 95% confidence interval (CI) = 1.353–3.142, P < 0.001]. After adjustment for confounders, the TG and LDL-C levels were significantly higher in rs12350001 AG/GG genotypes than that in AA genotypes (P < 0.05). The TG levels were significantly higher in rs7856817 GA/AA genotypes than that in GG genotypes (P < 0.05).

Conclusions

Rs12350001 and rs7856817 of DMRT2 gene are associated with CAD in Han subjects. Subjects with G allele of rs12350001 or A allele of rs7856817 were associated with an increased risk of CAD.

Introduction

In recent decades, cardiovascular disease (CVD) has developed into the main causes of death in the world, especially in developing countries, such as China[1,2]. According to data from the World Health Organization (WHO) by 2030, the number of deaths in CVD will exceed 23 million. Coronary artery disease (CAD) has become the leading cause of death of cardiovascular diseases. CAD is caused by a variety of

risk factors, including age, smoking, hyperlipidemia, hypertension, diabetes, and other risk factors [3–6]. Large number of studies indicated that the CAD are closely related to genetic factors. In particular, genome-wide association studies have identified several common genetic variants associated with CAD in multiple genes[7,8].

Doublesex and Mab-3-related transcription factor (DMRT) genes are widely distributed in various biological populations, from low invertebrates to higher vertebrates, a large number of DMRT families have been discovered, playing a development important role in gender decisions and neurological[9,10]. Seven DMRT genes (DMRT1 to DMRT7) have been proven to play an important role in mice and humans in the sex regulation, including gender differentiation, sexual difference and sperm[11]. At the same time, the DMRT gene also regulates a variety of developmental processes, including nerve development, muscles and bone development during embryonic development[12,13]. Pei et al. also found that DMRT2 gene was highly expressed in esophageal cancer and could be used as a biomarker of esophageal cancer[14]. Ghosh et al. found that dMRT2 gene is associated with human skeletal muscle phenotype[15]. So far, DMRT2 has rarely been associated with human disease, especially in CAD.

DMRT2 is involved not only in sex determination, but also in muscle tissue development[16]. A recent study found that high expression of the DMRT2 gene was associated with gluteal subcutaneous adipose tissue[17]. Gene polymorphism is not only an independent risk factor in predicting CAD, but also affects the diagnosis, treatment and prognosis of CAD. However, no studies focused on the relationship between DMRT2 gene polymorphism and CAD, our present case–control study aimed to explore the association of DMRT2 gene polymorphisms with CAD in a Han population.

Methods

Subjects

This was a retrospective case-control study. We recruited patients who were hospitalized in the First Affiliated Hospital of Xinjiang Medical University between 2015 and 2018. We included 1092 participants (male: 533; female: 559); Patients were between 30-82 years old, mean ± SD age of 55.23±9.73 years (male 52.48±8.91 years; female 57.83±9.77 years). Among them, 542 patients with CAD were defined as the case group, and 550 normal coronary angiographies were defined as the control group. All the patients were clinically stable and continued to take coronary heart disease drugs during the study period. All patient and control groups provided written informed consent. Exclusion criteria were the presence of tumor disease, recent major surgery, diuretics, accompanying inflammatory diseases, such as infection and autoimmune disease; liver or kidney disease; patients who had undergone coronary artery bypass grafting (CABG); and patients with valvular disease or myocardial or pericardial diseases were also excluded. Blood samples were obtained, including SUA concentration, creatinine, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and fasting blood glucose (FBG). Our study was approved by the Ethics Committee of the First Affiliated

Hospital of Xinjiang Medical University and conducted in accordance with the standards of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Baseline Definitions and Measurements

Hypertension was defined as self-reported use of antihypertensive drugs or in the past two weeks having an average systolic blood pressure ≥140 mmHg, or an average diastolic blood pressure ≥90 mmHg. Diabetes was defined as an FPG level ≥7.0 mmol/l or previous diabetes diagnosis or use of diabetes drugs. Smoking was defined as the patient's current smoking status. Total cholesterol concentration ≥6.22 mmol/L (240 mg/dl) was defined as hypercholesterolemia. Triglyceride concentration ≥2.26 mmol/L (200 mg/dl) was hypertriglyceridemia. Triglyceride concentration ≥2.26 mmol/L (200 mg/dl) was hypertriglyceridemia. Low-density lipoprotein cholesterol concentration ≥ 4.14 mmol/L (160 mg/dl) was defined as high LDL cholesterol. High-density lipoprotein cholesterol concentration ≤ 1.04 mmol/L (40 mg/dl) was defined as low HDL cholesterol. Dyslipidemia is defined as one of the four above-mentioned dyslipidemias or the self-reported use of anti-hyperlipidemia drugs. After 12h of fasting, the patient’s peripheral venous blood was collected for routine laboratory parameter evaluation. SUA, TC, TG, HDL-C, LDL-C, fast glucose, and creatinine concentrations were measured by a clinical laboratory department biochemical analyzer of the First Affiliated Hospital of Xinjiang Medical University (Dimension AR/AVL Clinical Chemistry System, Newark, New Jersey, USA).

Genotyping

We tried to use Haploview 4.2 software and the international HapMap website phase I and Phase II database (https ://www.hapmap.org), we obtained two tag SNPs of DMRT2: SNP1 (rs12350001) and SNP2 (rs7856817) by using minor allele frequency (MAF) ≥ 0.05 and linkage disequilibrium patterns with r^2≥0.8 as a cutoff. Blood samples were taken from all subjects by venipuncture in the catheter lab, and genomic DNA was extracted from peripheral blood leukocytes using DNA extraction kits (Beijing Biotech Co. Ltd., Beijing, China). The SNP genotyping was performed using an improved multiplex ligation detection reaction (iMLDR) technique (Genesky Biotechnologies Inc., Shanghai, China). Genotyping was performed in a blinded fashion without knowledge of the patients’ clinical data, and a total of 10% of the genotyped samples were duplicated to monitor genotyping quality.

Statistical analysis

All statistical analyses were performed using the Social Science Statistical Software Package (SPSS) software (version 25.0; SPSS Inc., Chicago, IL). Continuous variables were expressed as mean±standard deviation (SD), and an independent sample t-test was used for comparison. Categorical variables were expressed as numbers and percentages, and the chi-square test was used for analysis. Logistic regression analysis was used to investigate the relationship between the major risk factors and CAD. The dominant model is defined as homozygote wild vs. (heterozygote+homozygote variant); the recessive mode is defined as (heterozygote+homozygote wild) vs. homozygote variant; the overdominant model is

defined as (homozygote wild+homozygote variant) vs. heterozygote; All statistical tests were two-sided tests, and statistical significance was set at P<0.05.

Result

Characteristics of subjects

The baseline characteristics of the case group and the control group were shown in Table 1. The mean of age, SBP, TC and FBG in case group were higher than those in control group. (P < 0.05) The control group HDL-C were higher than case group. (P < 0.05) The other characteristics like BMI, DBP, TG, LDL-C, Cr, Uric acid in case group were higher than in control group, but there was no statistical significance (P > 0.05).

Table 1
Clinical and metabolic characteristics of subjects

Characteristic	Case (n = 542)	Control (n = 550)	P value
Age (years)	58.20 ± 9.32	52.48 ± 9.29	< 0.001
Male, n(%)	254(46.9)	279(50.7)	0.202
BMI	25.42 ± 3.20	25.11 ± 3.53	0.125
SBP (mmHg)	137.09 ± 27.87	132.72 ± 26.02	0.008
DBP (mmHg)	83.46 ± 16.79	82.74 ± 18.22	0.506
TC	3.92 ± 1.29	3.67 ± 1.38	0.003
TG	2.26 ± 1.65	2.11 ± 1.48	0.119
HDL-C	1.11 ± 0.58	1.17 ± 0.43	0.048
LDL-C	2.54 ± 0.90	2.47 ± 0.71	0.214
Cr (mmol/L)	71.97 ± 60.42	68.30 ± 20.51	0.183
Uric acid (umol/L)	307.79 ± 96.22	302.62 ± 106.14	0.405
FPG (mmol/L)	6.18 ± 2.88	5.39 ± 2.14	< 0.001
Hypertension, n (%)	272(50.2)	203(36.9)	< 0.001
Smoking, n (%)	376(69.4)	216(39.3)	< 0.001
Diabetes, n (%)	144(26.6)	46(8.4)	< 0.001
Abbreviations: BMI, body mass index; SBP, systolic blood pressure;DBP, diastolic blood pressure□TC, total cholesterol; TG, triglyceride□HDL-C, high-density lipoprotein-cholesterol; LDL-C low-density lipoprotein-cholesterol; Cr, creatinine□FPG, fasting plasma glucose□			

Distributions of genotypes and allele in cases and controls.

Table 2 shows the distribution of genotypes and alleles for the two SNPs (rs12350001 and rs7856817) of the DMRT2 gene. The genotype distributions of the two SNPs were in accordance with the Hardy–Weinberg equilibrium in controls (all P > 0.05). For rs12350001, the distribution of the genotypes, the dominant model (A/A vs A/G + G/G), the overdominant model (G/G + A/A vs A/G) showed significant differences

Table 2
Distribution of SNPs of Dmrt2 gene in subjects

Genotype	Model		Case (n, %)	Control (n, %)	P value
rs12350001	Codominant	A/A	441(81.4)	485(88.2)	0.003
(A > G)		A/G	93(17.2)	63(11.5)	
		G/G	8(1.5)	2(0.4)	
	Dominant	A/A	441(81.4)	485(88.2)	0.002
		A/G + G/G	101(18.6)	65(11.8)	
	Recessive	A/A + A/G	534(98.5)	548(99.6)	0.054
		G/G	8(1.5)	2(0.4)	
	Overdominant	G/G + A/A	449(82.8)	487(88.5)	0.007
		A/G	93(17.2)	63(11.5)	
rs7856817					
(G > A)	Codominant	G/G	444(81.9)	447(86.7)	0.031
		G/A	90(16.6)	71(12.9)	
		A/A	8(1.5)	2(0.4)	
	Dominant	G/G	444(81.9)	447(86.7)	0.029
		G/A + A/A	98(18.1)	73(13.3)	
	Recessive	G/G + G/A	534(98.5)	548(99.6)	0.054
		A/A	8(1.5)	2(0.4)	
	Overdominant	G/G + A/A	452(83.4)	479(87.1)	0.085
		G/A	90(16.6)	71(12.9)	

between the case subjects and the controls (P = 0.003, P = 0.002 and P = 0.007 respectively). For rs7856817, the distribution of the genotypes, the dominant model (G/G vs G/A + A/A) showed significant differences between the case subjects and the controls (P = 0.031and P = 0.029 respectively).

Tables 3 and 4 showed the multivariable logistic regression analyses of the major confounding factors for CAD. Following the multivariate adjustments for the confounders, such as Age, Gender, BMI, TG, TC, HDL-C, LDL-C and prevalence of hypertension, Diabetes and smoking, rs12350001 is still an independent risk factor for [CAD (A/A vs A/G + G/G), the odds ratio (OR) = 1.870, 95% confidence interval (CI) = 1.239–2.824, P = 0.003]. And rs7856817 is also an independent risk factor for [CAD (G/G vs G/A + A/A), the odds ratio (OR) = 2.062, 95% confidence interval (CI) = 1.353–3.142, P = 0.001]

Table 3
Results of logistic analysis of risk factors(rs12350001)

Risk factors	OR	95%CI	P value
rs12350001 (A/G + G/G vs. A/A)	1.870	1.239–2.824	0.003
Age	1.063	1.044–1.082	< 0.001
Gender	1.233	0.900–1.690	0.191
Smoking	3.908	2.900-5.267	< 0.001
Diabetes	3.646	2.417–5.501	< 0.001
Hypertension	1.483	1.102–1.997	0.009
BMI	1.041	0.995–1.089	0.079
TC	1.119	0.962–1.302	0.146
TG	1.058	0.950–1.179	0.306
HDL-C	0.887	0.665–1.184	0.416
LDL-C	1.025	0.792–1.327	0.851

BMI, body mass index; TC, total cholesterol; TG, triglyceride;HDL-C, high-density lipoprotein-cholesterol; LDL-C low-density lipoprotein-cholesterol.

Table 4
Results of logistic analysis of risk factors(rs7856817)

Risk factors	OR	95%CI	P value
rs7856817 (G/A + A/A vs. G/G)	2.062	1.353–3.142	0.001
Age	1.062	1.043–1.081	< 0.001
Gender	1.217	0.887–1.670	0.223
Smoking	4.323	3.179–5.877	< 0.001
Diabetes	3.473	2.304–5.237	< 0.001
Hypertension	1.479	1.098–1.993	0.010
BMI	1.036	0.991–1.084	0.121
TC	1.14	0.977–1.331	0.097
TG	1.043	0.935–1.162	0.449
HDL-C	0.863	0.648–1.147	0.31
LDL-C	1.034	0.798–1.341	0.800

BMI, body mass index; TC, total cholesterol; TG, triglyceride;HDL-C, high-density lipoprotein-cholesterol; LDL-C low-density lipoprotein-cholesterol.

Genotypes And Serum Lipid Levels

In Fig. 1, the TG and LDL-C levels were significantly higher in rs12350001 AG/GG genotypes than that in AA genotypes (P < 0.001 and P = 0.001 respectively). In Fig. 2, the TG levels was significantly higher in rs7856817 GA/AA genotypes than that in GG genotypes (P < 0.001). The TC levels was lower in GA/AA genotypes than that in GG genotypes (P = 0.001).

Discussion

In this study, we have investigated the associations between two SNPs (rs12350001 and rs7856817) in the DMRT2 gene and CAD risk in Chinese Han population in Xinjiang. Our findings show that rs12350001 and rs7856817 were significantly associated with CAD. Our study also demonstrated significant associations between two SNPs of DMRT2 gene and serum lipid levels.

The DMRT gene family was first discovered in the late 1990s, mainly because the product of drosophila sex-determining gene DSX was similar to the sequence between the male regulatory gene mab-3[18,19]. Transcriptional factors encoded by sex regulators in some animals share a motif consisting of interlacing

zinc-binding modules followed by an α -helical recognition domain that enforces sequence-specific DNA binding[20]. This DM domain was named after DSX and MAB-3, and the gene family containing this motif was named DMRT genes, meaning " Doublesex and MAB-3 Related Transcription factors"[21]. DMT2, doublesex- and mab-3-related transcription factor 2, locates in 9p24.3, consists of nine exons, and it has expressed in most tissues and organs[22]. Wang et al. found that DMRT2 gene plays an important role in sporadic Parkinson's disease severity, in which the T allele at rs80315856 increased the risk of Parkinson's disease[23]. Sato et al. found that DMRT2 gene plays a significant regulatory role in the formation of human skeletal muscle. In DMRT2 mutants, skeletal muscle was significantly abnormal and muscle production was also affected[24]. Hong et al. found that DMRT2 gene plays an important role in immune and inflammatory pathways in humans[25].

Our study showed that genotyped polymorphisms of rs12350001 and rs7856817 SNPs in the DMRT2 gene and found that two SNPs was associated with CAD and lipid levels. The rs12350001 (AG/GG) genotype and rs7856817(GA/AA) have a higher frequency in CAD patients than that in controls. After adjusting for multiple confounders, we still found that rs12350001(AG/GG) and rs7856817(GA/AA) were risk factors for CAD. Among them, subjects carrying rs12350001 G allele and rs7856817 A allele had a significantly increased risk of coronary heart disease. At the same time, we found that the plasma TG and LDL-C level of subjects carrying rs12350001 G allele was significantly increased, and the plasma TG level of subjects carrying rs7856817 A allele was increased. Lipid levels also demonstrated a significantly increased risk of CAD in subjects with the rs12350001 G and rs7856817 A alleles. We believed that the relationship between polymorphism of rs12350001 and rs7856817 with CAD may be related to the following factors: (1) DMRT2 gene is a transcription factor associated with double sex and monoclonal antibody − 3, which has a great influence on gonad development. Therefore, the change of DMRT2 gene may affect hormone secretion and expression in both male and female, and hormone expression was an independent risk factor in the development of CAD. (2) Dmrt2 gene has an important influence on human inflammatory and immune pathways, and may influence CAD through inflammatory and immune factors. (3) The high expression of DMRT2 gene plays a significant role in hip fat deposition, so the DMRT2 gene could affect CAD from metabolic factors.

There are still some limitations in our study. First, our study subjects all came from the same hospital, so there may be some information and selection bias. Second, this study was an observational study and we were currently unable to verify the causal relationship between multiple risk factors and CAD. Third, our study lacked functional validation, and more tests were needed to verify the molecular mechanism of DMRT2 gene and CAD. Forth, our study was a single-center small sample, and a multi-center large sample may be needed to verify the results.

List Of Abbreviations

Cardiovascular disease (CVD)；Coronary artery disease (CAD)；Doublesex and Mab-3-related transcription factor (DMRT)；coronary artery bypass grafting (CABG)；total cholesterol (TC)；triglycerides (TG)；high-

density lipoprotein cholesterol (HDL-C)；low-density lipoprotein cholesterol (LDL-C)；fasting blood glucose (FBG);

Declarations

Data availability

The data will be provided on reasonable request from corresponding author after another study finished.

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Author contributions

HY.L. and J.T. conceived and designed the experiments, and wrote the draft of the manuscript; HY.L. and J.A. collected data and undertook the statistical analyses; HY.L., J.T. and J.A. performed laboratory experiments; Y.T.M. and Z.Y.F. gave critical comments on the draft and contributed to the manuscript writing; HY.L., J.T., J.A. Y.T.M. and Z.Y.F. reviewed clinical assessments in this study and supervised this study. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Consent for publication

Not applicable.

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Figures

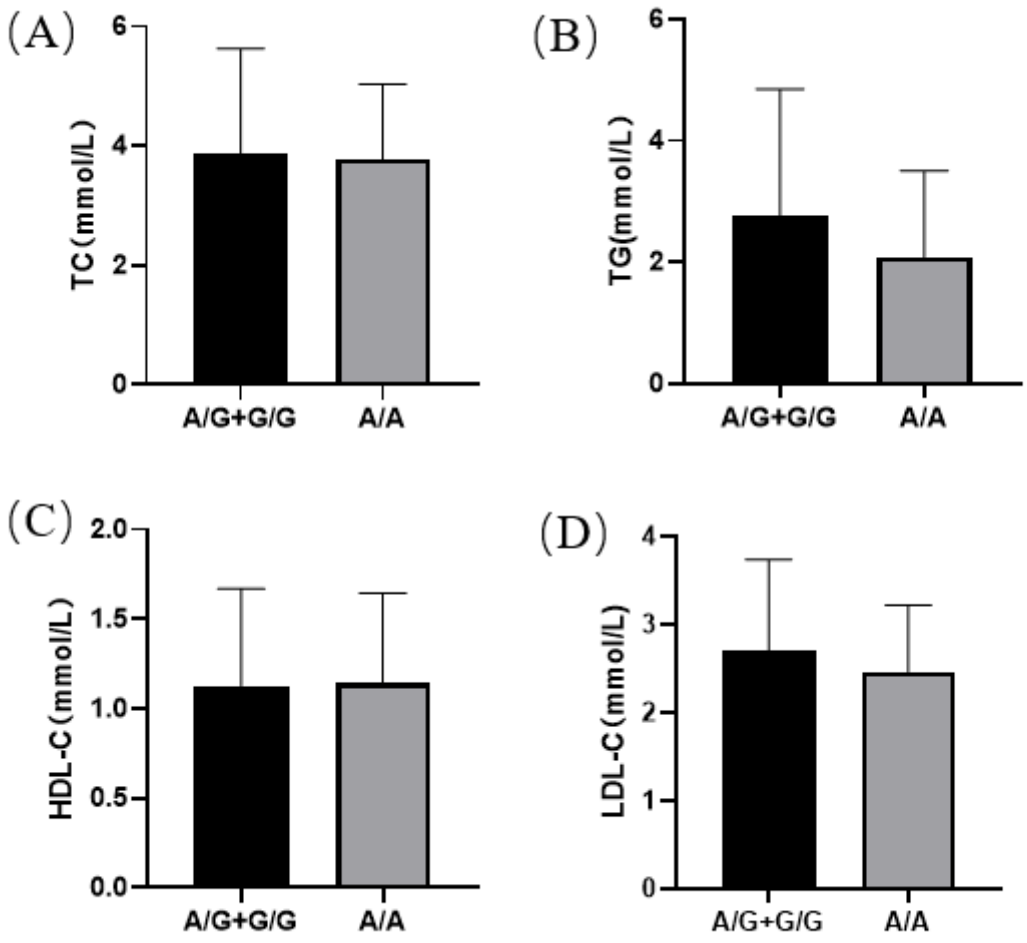

Figure 1

Association between rs12350001 and lipid parameters

(A) There exists no significant difference of TC between rs12350001 A/G+G/G genotypes and A/A genotypes (P>0.05). (B) The TG levels were significantly higher in rs12350001A/G+G/G genotypes than that in TT genotypes (P<0.05). (C) There exists no significant difference of HDL-C between rs12350001

A/G+G/G genotypes and A/A genotypes (P>0.05). (D) The LDL-C levels were significantly higher in rs12350001 A/G+G/G genotypes than that in A/A genotypes (P<0.05).

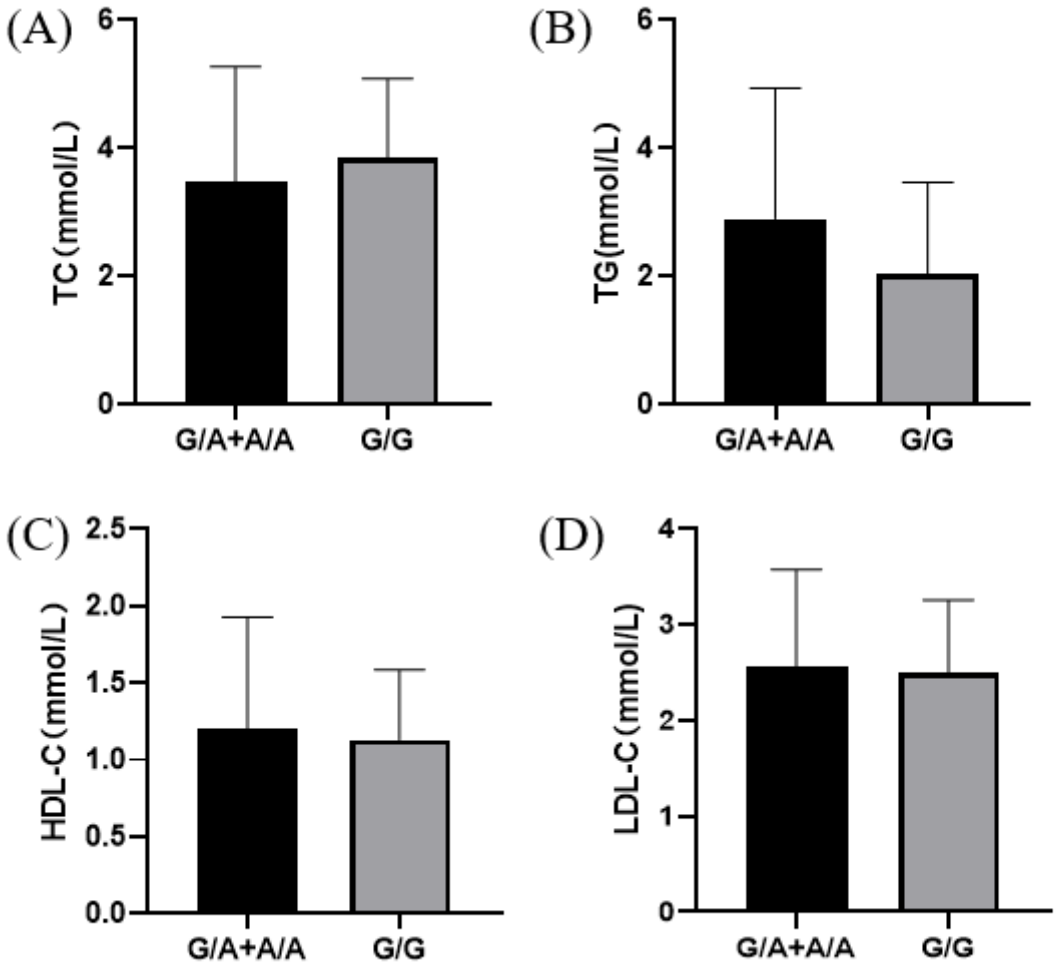

Figure 2

Association between rs7856817 and lipid parameters

(A) The TC levels were significantly higher in rs7856817 G/G genotypes than that in G/A+A/A genotypes (P<0.05). (B) The TG levels were significantly higher in rs7856817 G/A+A/A genotypes than that in G/G genotypes (P<0.05). (C) There exists no significant difference of HDL-C between rs7856817 G/A+A/A genotypes and G/G genotypes (P>0.05). (D) There exists no significant difference of LDL-C between rs7856817 G/A+A/A genotypes and G/G genotypes (P>0.05).