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Polymorphisms of rs2483205 and rs562556 in Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Gene are Associated With Coronary Artery Disease

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Abstract

PCSK9 plays a pivotal role in lipid metabolism. The present study is to explore the potential novel single nucleotide polymorphisms (SNPs) of the PCSK9 gene which is associated with coronary artery disease (CAD) in the Han population who lived in Xinjiang, China. We conducted a case-control study and genotyped four tag SNPs of the PCSK9 gene in 950 CAD and 1082 health subjects in the Han population. This study showed that for rs2483205, the distributions in genotypes had significant differences between the CAD and control groups (p = 0.025), and the subjects with TT genotype had lower total cholesterol (TC) level than CT genotype (p = 0.025). For rs562556, there were significant differences between the CAD and control groups for distributions of genotypes (p = 0.020), and the individuals with a G allele had a lower low-density lipoprotein cholesterol (LDL-C) level than an A allele (p = 0.048). Furthermore, the TT genotype of rs2483205 and GG genotype of rs562556 were independently associated with CAD (odds ratio [OR] = 0.53, 95% confidence interval [CI] = 0.29-0.95, p = 0.032 and OR = 0.57, 95%CI = 0.34-0.95, p = 0.032, respectively). In conclusion, the rs2483205 and rs562556 were significantly associated with CAD.

Introduction

CAD is the main cause of death worldwide. An epidemic study predicts that the prevalence of CAD has been increased rapidly at least until 2030.[1,2] Gene and environment are the main factors to affect the development of CAD, and 40%-60% is attributed to genetic factors.[3] Moreover, genes are involved in lipid metabolism and it usually have a significant effect on CAD.[4]

The human PCSK9 gene, located on chromosome 1p32.3, was mainly expressed as an amino acid glycoprotein. As studies reported, PCSK9 has effects on lipid metabolism mainly through the degradation of the LDL receptors.[5] The specific mechanisms are as follow, in intracellular, the PCSK9 was binding to the LDL receptor to promoted the lysosomal degradation of the receptor,[6,7] meanwhile in extracellular, PCSK9 in circulating is conjoined the EGF-A domain of LDL receptors to prevent the LDL receptors from recycling to the cell surface.[7] Dozens of studies have indicated that the PCSK9 genetic mutations were associated with CAD, and more than 50 functional PCSK9 genetic mutations affected cholesterol levels in plasma.[8,9] The individuals with a loss-of-function (LOF) mutation of PCSK9 probably presented as a life-long low total cholesterol (TC) and LDL-C levels, and notably reduced incidence of CAD risk. On the contrary, the individuals with a gain-of-function (GOF) mutation probably manifested hypercholesterolemia and susceptibility to CAD.[10,11] According to studies, there were 2.6% of nonsense mutations in PCSK9 that are responsible for a 28% decrease of LDL-C level and 88% decrease in the risk of CAD.[11] Some missense mutations of the PCSK9 gene have also a notable effect on plasma LDL-C levels and usually cause mild hypocholesterolemia to protect against CAD.[8]

Polymorphic sites of the PCSK9 gene are various in different regions and races. The polymorphisms of the PCSK9 gene in the Han population living in the northwestern part of China have not ever been reported. Moreover, finding novel lipids related polymorphisms would contribute to finding potential

therapeutic targets for hyperlipemia and CAD. Therefore, this study was to investigate whether the polymorphisms of the PCSK9 gene were associated with CAD in the Han population who lived in Xinjiang, China. Furthermore, we also explored the association between different genotypes of the polymorphisms in the PCSK9 gene and lipids levels in all subjects.

Methods

Ethical approval of the study

All subjects have permitted to proceed with DNA analysis, collect relevant clinical data, and sign informed consent. The Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University has reviewed the operating protocol and approved this study. All procedures were accorded to the requirements of the Declaration of Helsinki.

Subjects

In this study, we included 950 cases and 1082 healthy controls in the Han population who lived in Xinjiang, China. This study has recruited the patients who underwent angiography examination and were diagnosed with CAD at the First Affiliated Hospital of Xinjiang Medical University from 2008 to 2015. The control groups were randomly selected with age-matched participants from the cardiovascular risk survey (CRS) study which has been reported previously.[29,30] In brief, it was a cross-sectional study, which collected blood samples, demographic information, lifestyle data, and cardiovascular-related clinical characteristics from seven representative regions and multiethnic populations to explore the potential cardiovascular-related risk factors in the Xinjiang population of China. Individuals were excluded if they had a history of CAD. All the DNA samples of participants were extracted from the blood samples collected by EDTA contained tubes.

Inclusion criteria: all the patients occurred the symptom of typical chest pain, and they have performed the coronary angiography examination according to guidelines[31]. CAD was defined as the coronary angiography examined results demonstrated that at least one coronary artery stenosis >50%. Exclusion criteria: the patients accompanied with valvular heart disease, non-ischemic cardiomyopathy, heart failure, or congenital heart disease.

Definition of cardiovascular risk factors

The diagnosis standard of hypertension was that, according to the medical history and examination, individuals have been diagnosed with hypertension before, or at least 2 separate times examine results were showed the systolic blood pressure (SBP) ≥ 140mmHg, or diastolic blood pressure (DBP) ≥ 90mmHg at sedentary state[32]. The diagnosis standard for diabetes was that the subjects with a diabetes history, or a glucose value >11.1mmol/L (200mg/dl) at any one time, or glucose level >7.0mmol/L (126mg/dl) in fasting plasma on 2 separate occasions. Smoking is defined as the subjects declared regular tobacco use in 6 months

Routine blood test

Using fresh collected fasting peripheral blood samples, we processed routine biochemical variables testing. Lipids parameters, including high-density lipoprotein (HDL), TC, triglyceride (TG), and LDL-C, were tested by the Dimension AR/AVL Clinical Chemistry System (DADE Bchring, Newark, NJ) in the Clinical Laboratory.

Polymorphism Selection and Genotyping

We selected four tag SNPs by screening from the International HapMap Project website database (https://www.hapmap.org) and Haploview 4.2 software. At last, rs11583680, rs2483205, rs2495477, and rs562556 were picked for the Chinese Han population. The cutoff of minor allele frequency (MAF) was set as >0.05, and linkage disequilibrium (LD) patterns with r^2 were set as >0.8. The rs11583680, rs2483205, rs2495477, and rs562556 belonged to upstream transcript variant, intron variant, intron variant, and coding variant, respectively. The SNPs were using an improved multiplex ligation detection reaction (iMLDR) technique (Genesky Biotechnologies Inc., Shanghai, China) to genotype. A blinded fashion was applied in genotyping, which in the absence of information on the patients' clinical data. About 10% of the samples were genotyped twice to test the quality of genotyping results.

Statistical analysis

According to data categories, we arranged different present forms and analysis methods. Continuous variables with normal distribution were presented as mean ± standard deviation (SD), and as the median in case of non-normal distribution. The difference between two groups was examined by the independent Student *t*-test in variables with normal distribution and was analyzed by the Mann–Whitney U test when variables distributed as non-normally. The Chi-square test was applied to explore the differences in categorical variables. The independent association between polymorphisms and CAD was assessed by multiple logistic regression analysis. The Hardy–Weinberg equilibrium (HWE) was analyzed by the Chi-square test by separately calculated the frequencies of genotype in CAD and control subjects. Haplotype construction and LD test were conducted by the SHEsis software platform[33]. The p-value <0.05 represents statistical significance (2-tailed). SPSS version 22.0 software (SPSS, Inc., Chicago, IL) was used to perform all statistical analyses.

Results

Clinical characteristics of participants

There were 950 CAD subjects (mean age of 58.68±7.30 and 47.14% of men) and 1082 controls (mean age of 58.68±7.29 and 46.43% of men) that were involved in the analysis. As Table 1 shown, comparing the control groups, the clinical characteristics of CAD patients at baseline showed lower HDL, and higher body mass index (BMI), glucose, blood pressure, uric acid, TG, and prevalence of smoking, hypertension,

alcohol intake, and diabetes (all $p<0.05$). However, the parameters of age, gender, LDL-C, and TC have not shown any differences between the groups.

Distribution of genotypes in the polymorphisms of the PCSK9 gene between the CAD and control groups.

Four SNPs of PCSK9 (rs11583680 C>T, rs2483205 C>T, rs2495477 A>G and rs562556 G>A) were genotyped in both CAD and control groups. As Table 2 exhibited, the distribution of each genotype, genetic models, and alleles of the four SNPs was separately examined in CAD patients and controls. Except for the rs2495477 in the CAD group, all the genotype frequencies in both groups were in HWE ($p > 0.05$). For the rs2483205, the distributions in CC, CT, and TT genotypes, and in its recessive model（TT vs. CC+CT）were different between the two groups ($p = 0.025$, and $p = 0.008$, respectively). For the rs562556 , the distributions in AA, AG, and GG genotype, A and G alleles, and its dominant model （AA vs. GG+AG） were also significantly different between the two groups ($p = 0.020$, $p = 0.005$ and $p = 0.006$, respectively). However, comparing the control group, the distributions of genotypes, models, or alleles of rs11583680 and rs2495477 have not shown any significant differences in the CAD and control groups ($p = 0.294$, and $p = 0.342$, respectively).

Independent risk factors for CAD

To determine whether the polymorphisms of the PCSK9 gene were the independent risk factors for CAD, we adjusted confounding risk factors, including BMI, TG, TC, HDL-C, and LDL-C, the prevalence of hypertension, diabetes, smoking, and drinking. We found that the recessive model (CC vs. TT+CT) of rs2483205 and the dominant model (AA vs. GG+AG) of rs562556 were still showed a significant association with CAD. The TT genotype of rs2483205 was indicated the protective effects on CAD (OR = 0.53, 95%CI = 0.29-0.95, $p = 0.032$) (Table 3), and the GG genotype of rs562556 was also exhibited a benefit effect (OR = 0.57, 95%CI = 0.34-0.95, $p = 0.032$) (Table 4).

LD analysis

Table 5 is displayed the patterns of LD analysis in the PCSK9 gene. We have identified that these four SNPs are located in the same haplotype block. Except for rs2483205 (SNP2) and rs2495477 (SNP3), all the r^2 values of SNPs were below 0.5, which means that we could not construct haplotypes by SNP2 and SNP3 simultaneously. In addition, because the minor allele frequency (MAF) of SNP2 is larger than SNP3, we just used SNP1, SNP2, and SNP4 to construct the haplotypes. In further, because the |D'| for rs11583680 (SNP1)-SNP2, SNP1–SNP3, and SNP1–(rs562556) SNP4 were <0.5. So we do not use the SNP1 to construct haplotypes. At last, the SNP2 and SNP4 were used to construct haplotypes.

Relationship between the haplotypes of the PCSK9 gene and CAD

As Table 6 is shown, we established the haplotypes by combining the SNP2 and SNP4. Then, the distribution of the SNP2–SNP4 constructed haplotypes between the two groups was analyzed. The haplotype distributions of C–G (H2) and T-G (H4) were significantly different between the two groups

(p<0.05). The frequencies of H2 haplotype were significantly higher in the CAD group than in the control group (OR = 1.97, 95%CI: 1.013-3.842, p = 0.042). However, compared with the healthy control subjects, the frequencies of H4 haplotype were significantly lower in patients with CAD (OR = 0.495, 95%CI: 0.351-0.699, p < 0.001).

The relationship between PSCK9 genotypes and lipids levels

The relationship between the genotypes of polymorphisms and lipids levels was analyzed. Individuals with TT genotype in rs2483205 had significantly lower mean TC level than CT genotype (4.62±2.62mmol/L vs. 3.91±1.20 mmol/L, p = 0.025), Figure 1a. And there is lower mean LDL-C level in G allele than A allele in the rs562556 (2.71±0.99mmol/L vs. 2.41±0.97mmol/L, p = 0.048), Figure 1b. Nevertheless, neither HDL-C nor TG showed any significant difference among different genotypes of rs562556 or rs2483205 (p > 0.05).

Discussion

In this study, we found that polymorphisms of rs562556 and rs2483205 in the PCSK9 gene associated with CAD, it was the first time reported in the Han population who lived in Xinjiang, China. The TT genotype of rs2483205 polymorphism and GG genotype of rs562556 had protective effects in patients with CAD. Furthermore, we found that the mutations of rs2483205 and rs562556 polymorphisms exhibited reduced TC and LDL-C levels, respectively. Moreover, we revealed the individuals with H4 haplotype presented as a protective effect on CAD.

High LDL-C or TC concentrations have the causal association with increased cardiovascular risk. Multiple randomized controlled trials and meta-analyses indicated that reduced LDL-C levels were usually connected with a consistent and graded reduction in cardiovascular risk[12-16]. As a cornerstone and routine medicine for hyperlipidemia therapy, statins could effectively lower LDL-C most of the time, and are generally well tolerated. However, due to potential side effects, some individuals' poor response, and misinformation of statins therapy, many patients are reluctant in taking statins or adhere to treatment[17,18]. In recent years, PCSK9 has been regarded as a promising therapeutic target to regulate cholesterol metabolism. On lipid and metabolite profiles, metabolic effects of PCSK9 gene inhibitors are comparable with statin therapy[18]. In addition, studies indicated that combining PCSK9 inhibitors and statin can reduce LDL-C by 50-60%, which is higher than statin therapy alone. Besides, in patients with atherosclerotic cardiovascular disease (ASCVD), PCSK9 inhibitors may reduce overall mortality and adverse cardiovascular events by combination with high-dose statins. Moreover, according to the 2019 guidelines for the management of dyslipidemias, PCSK9 inhibitors have been included in therapy for very high-risk ASCVD patients who would reach treatment targets on the maximum dose of ezetimibe and statin [19,20]. However, whether there are novel genetic targeted inhibitors of PCSK9 that could be applied to therapy ASCVD patients with fewer side effects and higher efficiency required further exploration.

Population-based studies suggested that PCSK9 variants are associated with cholesterol levels and CAD in homozygous or compound heterozygous carriers [8]. Missense and nonsense mutations of PCSK9 probably result in hypocholesterolemia and have a protective effect on CAD. Previously, most studies about the PCSK9 gene were focused on several polymorphisms, such as E670G or R46L, which suggested that the PCSK9 gene was significantly associated with LDL-C levels and CAD[21-23]. Few studies explored the relationship between the rs562556 polymorphism and CAD. Two published studies have evaluated the associations between the rs562556 polymorphism and high levels of lipids in patients with hypercholesterolemia and polycystic ovary syndrome, respectively[24,25]. Currently, a meta-analysis study proceeded with a pooled analysis and concluded that the G carriers of rs562556 polymorphism had lower TC, LDL-C levels, and relative risk than the non-carriers[26]. These findings are in agreement with our results. In the present study, we also found that the G carriers of rs562556 polymorphism were associated with lower LDL-C levels. Furthermore, several studies also explored the relationship between rs562556 polymorphism and different diseases. A published study showed that the rs562556 polymorphism had no association with myocardial infarction[27]. A clinical study indicated the mutations of the rs562556 polymorphism were related to incidence of the carotid arterial plaques and elevated PCSK9 level [28]. Here, the present study for the first time uncovered that the GG genotype of 562556 polymorphism plays a protective role in CAD in the Han population. Meanwhile, few studies about rs2483205 polymorphism were reported. The protective effects of the TT genotype in rs2483205 polymorphism for CAD might be attributed to its lower TC level which proved in the present study. However, as a nonsense mutation, the specific mechanisms of how the rs2483205 polymorphism affects the TC level and the effects of rs2483205 on prognosis in patients with CAD were not clear.

The present studies have several limitations. First of all, this is a case-control study, which provides less information about the relationship between PCSK9 polymorphisms and long-term prognosis or adverse cardiovascular events. Second, the sample size is still small in this study. A large sample size prospective cohort study is required to further determine the relationship between PCSK9 polymorphisms and CAD disease and its prognosis. Third, the specific mechanisms of how rs562556 or rs2483205 influencing cholesterol metabolism and lowering the risk of CAD is still needing further research.

In conclusion, we for the first time proved that the polymorphisms of rs562556 and rs2483205 were associated with CAD in the Han population who lived in Xinjiang, China. The TT genotype of rs2483205, GG genotype of rs562556, and H4 haplotype had protective effects on CAD. In addition, mutations of rs2483205 and rs562556 polymorphisms were associated with lower levels of TC and LDL-C, respectively. The polymorphisms of rs562556 and rs2483205 in the PCSK9 gene would be a potential therapeutic target for the treatment of CAD by reducing lipid levels.

Declarations

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Author contributions

Y.T.M. and B.D.C. conceived the present study; M.T.G. and D.A. designed the experiments and wrote the draft of the manuscript; Y.N.Y., G.X.M., Y.T.M. and B.D.C. gave the suggestion for this manuscript; X.C.C., X.M. and Z.Y.F. collected data; F.L., Y.N.Y. and X.X. performed statistical analyses; M.T.G., D.A., C.X.C., X.X. and X.M. collected samples and undertook laboratory experiments; Y.T.M. and B.D.C. supervised this study. All authors reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Tables

Table 1. **Baseline characteristics of control subjects and patients with coronary heart disease**

Characteristics	control（n=1082）	CAD（n=950）	*p* value
Age	56.67±8.73	58.68±7.29	0.981
Male gender, n (%)	514(46.43）	436(47.14)	0.746
Smoking, n (%)	327(30.31)	453(47.62)	<0.001*
Alcohol intake, n (%)	182(16.80)	479(50.45)	<0.001*
BMI, kg/m2	25.56±4.02	26.37±3.46	<0.001*
SBP, mmHg	134.99±22.61	150.50±31.83	<0.001*
DBP, mmHg	85.42±16.63	92.10±20.46	<0.001*
Hypertension, n (%)	485(45.07)	516(54.3)	<0.001*
Uric Acid, mmol/L	270.74±85.22	310.77±112.61	<0.001*
Glucose, mmol/L	5.30±1.90	6.23±2.62	<0.001*
Diabetes, n (%)	88(8.13)	233(24.53)	<0.001*
TG, mmol/L	1.56±1.07	2.03±1.33	<0.001*
TC, mmol/L	4.27±0.93	4.38±1.63	0.058
HDL-C, mmol/L	1.25±0.47	0.98±0.40	<0.001*
LDL-C, mmol/L	2.66±0.69	2.68±0.98	0.591

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol. * compared with control group, *p*-values <0.001.

Table 2. Genotype and allele distributions in control subjects and patients with CAD

Variants	Control, n (%) (n=1082)	CAD, n (%) (n=950)	CAD *p*-Value*(H-W)	Control *p*-Value*(H-W)	P-Value∮
rs11583680(SNP1)					
Genotyping					
CC	882(81.52)	750(78.95)			
CT	187(17.28)	184(19.37)			
TT	13(1.20)	16(1.68)			0.294
Dominant model					
CC	882(81.52)	750(78.95)			
TT+CT	200(18.48)	200(21.05)	0.231	0.389	0.146
Recessive model					
TT	13(1.20)	16(1.68)			
CC+CT	1069(98.80)	934(98.32)			0.360
Allele					
C allele	1951(90.16)	1684(88.63)			
T allele	213(9.84)	216(11.37)			0.114
rs2483205(SNP2)					
Genotyping					
CC	523(48.34)	488(51.37)			
CT	456(42.14)	402(42.32)			
TT	103(9.25)	60(6.32)			0.025∮
Dominant model					
CC	523(48.34)	488(51.37)			
TT+CT	559(51.66)	462(48.63)	0.057	0.803	0.173
Recessive model					
TT	103(9.52)	60(6.32)			
CC+CT	979(90.48)	890(93.68)			0.008∮
Allele					
C allele	1502(69.41)	1298(71.32)			

T allele	662(30.69)	522(28.78)			0.189
rs2495477(SNP3)					
Genotyping					
AA	502(46.40)	463(48.74)			
AG	486(44.92)	419(44.11)			
GG	94(8.69)	68(7.16)			0.342
Dominant model					
AA	502(46.40)	463(48.74)			
GG+AG	580(53.60)	487(51.26)	0.041*	0.120	0.292
Recessive model					
GG	94(8.69)	68(7.16)			
AA+AG	988(91.31)	882(92.84)			0.204
Allele					
A allele	1490(68.9)	1345(70.79)			
G allele	674(31.1)	555(29.21)			0.180
rs562556(SNP4)					
Genotyping					
AA	962(88.91)	879(92.53)			
AG	118(10.91)	70(7.37)			
GG	2(0.18)	1(0.11)			0.020ϕ
Dominant model					
AA	962(88.91)	879(92.53)			
GG+AG	120(11.09)	71(7.47)	0.746	0.411	0.005ϕ
Recessive model					
GG	2(0.18)	1(0.11)			
AA+AG	1080(99.82)	949(99.89)			0.641
Allele					
A allele	2042(94.36)	1828(96.21)			
G allele	122(5.54)	72(3.79)			0.006ϕ

Abbreviations: CAD, coronary artery disease.

***** *p* values <0.05 for Hardy–Weinberg equilibrium in CAD patients and controls.

$\oint$ *p* values <0.05 for distribution frequency for genotypes and alleles of the 4 SNPs in PCSK9 gene.

Table 3. Multiple logistic regression analysis for CAD patients and control subjects

Risk factors	OR	95%CI	wals	*p*
rs2483205(TT vs. CC+CT)	0.53	(0.29-0.95)	4.60	0.032*****
smoking	1.43	(0.97-2.03)	3.23	0.072
BMI, kg/m2	1.04	(0.99-1.08)	2.89	0.069
Hypertension, n (%)	0.86	(0.62-1.20)	0.78	0.377
Diabetes, n (%)	2.46	(1.29-4.68)	7.46	0.006*****
TG, mmol/L	1.61	(1.36-1.92)	29.21	<0.001*****
HDL-C, mmol/L	0.94	(0.89-1.00)	3.74	0.053
TC, mmol/L	0.81	(0.62-1.07)	2.14	0.144
LDL, mmol/L	1.40	(0.99-1.97)	3.75	0.053

Adjust: RS205RM, smoking, alcohol intake, hypertension, diabetes, TG, TC, HDL-C, LDL-C, and BMI.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, Diastolic Blood Pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol. ***:** *p*-values <0.05.

Table 4. Multiple Logistic Regression Analysis for CAD Patients and Control Subjects

Risk factors	OR	95%CI	wals	*p*
rs562556GG+AG vs. AA	0.57	(0.34-0.95)	4.58	0.032*
smoking	1.40	(0.97-2.02)	3.21	0.073
BMI, kg/m2	1.04	(0.99-1.09)	3.27	0.071
Hypertension, n (%)	0.86	(0.62-1.20)	0.77	0.380
Diabetes, n (%)	2.46	(1.29-4.69)	7.43	0.006*
TG, mmol/L	1.60	(1.35-1.90)	28.75	<0.001*
HDL-C, mmol/L	0.95	(0.89-1.01)	3.26	0.071
TC, mmol/L	0.81	(0.61-1.07)	2.21	0.137
LDL, mmol/L	1.40	(0.99-1.96)	3.67	0.055

Adjust: rs562556DM, smoking, alcohol intake, hypertension, Diabetes, TG, TC, HDL-C, LDL-C, and BMI.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, Diastolic Blood Pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol. *: *p*-values <0.05.

Table 5. Pairwise linkage disequilibrium for the four SNPs.

		D'values			
		SNP1	SNP2	SNP3	SNP4
r2 values	SNP1		0.44	0.41	0.08
	SNP2	0.06		0.82	0.72
	SNP3	0.05	0.63		0.78
	SNP4	0.00	0.06	0.07	

|D'| above the diagonal and r^2 below the diagonal. The shadowed portion indicates |D'|<0.5 and r^2>0.5
SNP1-4 = rs11583680, rs2483205, rs2495477, rs562556.

Table 6. Haplotype analysis in patients with CAD and control subjects.

Haplotype	SNP2	SNP4	Control, n (%) (n=1082)	CAD, n (%) (n=950)	OR[95%CI]	*P* value
H1	C	A	1488.21(0.69)	1354.26(0.71)	1.13 [0.99-1.29]	0.082
H2	C	G	13.79(0.01)	23.74(0.01)	1.97 [1.01-3.84]	0.042*
H3	T	A	553.79(0.26)	473.74(0.25)	0.97 [0.84-1.11]	0.630
H4	T	G	108.21(0.05)	48.26(0.03)	0.49 [0.35-0.70]	<0.001*

SNP2: rs2483205; SNP4: rs562556. *: p <0.05.

Figures

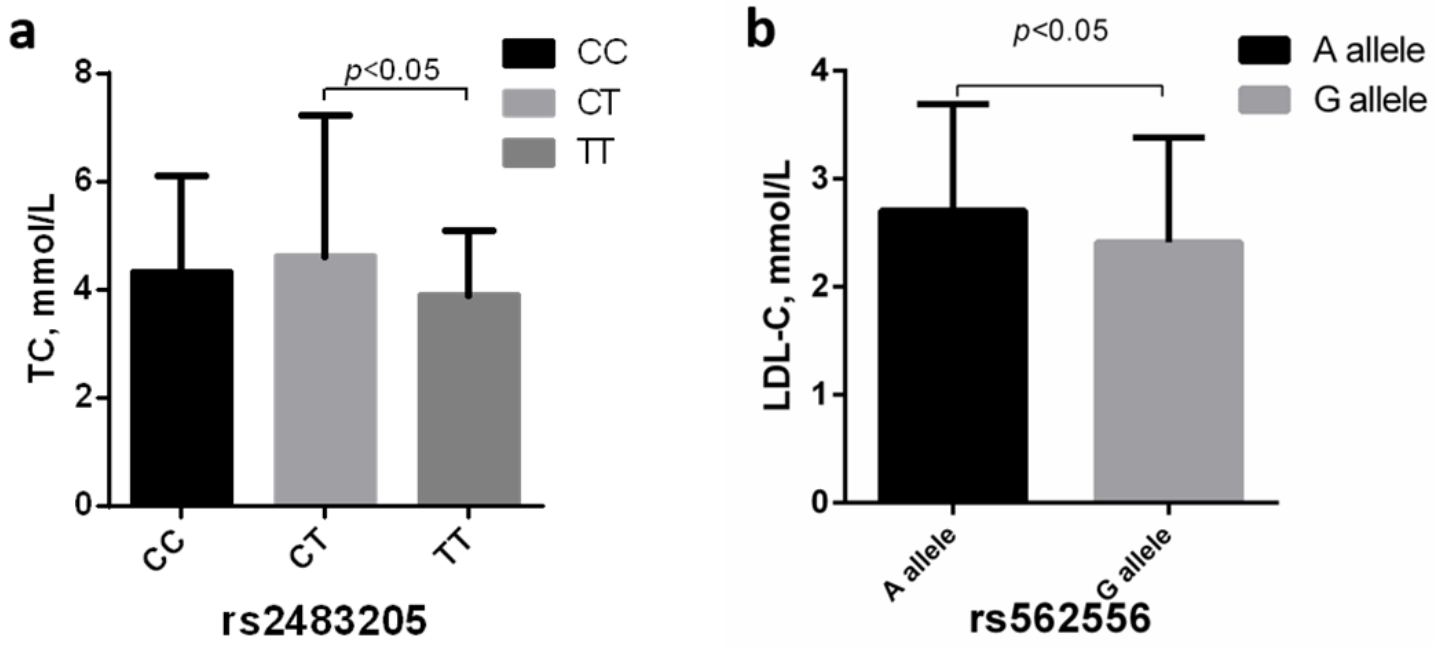

Figure 1

TC and LDL-C levels for different genotypes of rs2483205 and rs562556, respectively. a, TC levels for different genotypes of rs2483205. Individuals with TT genotype in rs2483205 polymorphism has significantly lower TC level than CT genotype (4.62±2.62mmol/L vs. 3.91±1.20 mmol/L, p = 0.025). b, LDL-C levels for different alleles of rs562556. There is lower LDL-C level in G allele than A allele in the rs562556 (2.71 ±0.99mmol/L vs. 2.41±0.97mmol/L, p = 0.048).