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Original Article

Human acetyl-CoA acetyltransferase-2 (ACAT-2) gene was associated with hyperlipidemia in han chinese population: a case-control study

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Abstract: Background: ACAT2 is a ubiquitous class of enzymes involved in biosynthesis pathway of cholesterol. Hyperlipidemia is a strong predictor for coronary artery disease (CAD). Little is known about the association of ACAT2 gene with hyperlipidemia. The aim of the present study was to assess the relationship between the human ACAT2 gene and hyperlipidemia by conducting case-control study. Methods: A total of 233 hyperlipidemia patients and 526 controls were genotyped for the three SNPs used as genetic markers for the human ACAT2 gene (rs3798211, rs15892, and rs3465). Three SNPs were selected from the HapMap website and genotyped by using TaqMan (Applied Biosystems) Genotyping Assays. Data analysis was performed by using SPSS 17.0 and haploview 4.0. Results: The distributions of the genotypes and alleles in three SNPs (rs3798211, rs15892, and rs3465) were significantly different between the hyperlipidemia patients and the control subjects (all P=0.000, respectively). We have found that the frequencies of all three SNPs were significantly higher in hyperlipidmia patients when compared to the controls in a dominant model and the significance remained after adjusting multivariable confounders, such as sex, age, BMI, SBP, DBP, glucose, smoking, drinking, education and physical activity by using multiple logistic regressions (Odds ratio=1.336, 95% CI: 1.188-1.502; Odds ratio=1.410, 95% CI: 1.034-1.924; Odds ratio=2.754, 95% CI: 1.610-4.114; all P=0.000, respectively). Further, the triglycerides, total cholesterol, and low density lipoprotein-cholesterol concentrations were significantly higher in the TT genotype of rs3798211, and GG genotype of rs3465 when compared to other genotypes of the two SNPs after adjusting age, sex, smoking, drinking, education and physical activity in hyperlipidemia patients and control subjects (all P<0.05). Conclusions: The results of this study indicate that TT genotype of rs3798211, AA genotype of rs15892, and GG genotype of rs3465 in human ACAT2 gene might be the possible risk genetic marker for hyperlipidemia in Han Chinese population.

Keywords: Genetic polymorphism, ACAT2 gene, hyperlipidemia, case-control study

Introduction

Hyperlipidemia is an abnormal lipid metabolism and is associated with an increased incidence of atherosclerosis and coronary artery disease (CAD) [1]. High concentrations of total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), or triglyceride (TG) and along with low concentrations of high density lipoprotein cholesterol (HDL-C) in the blood plasma can cause hyperlipidemia [2]. Genetics, age, diet, smoking, physical activity and stress are the possible risk factors for hyperlipidemia [3, 4]. Among these, genetic factors including single nucleotide polymorphisms (SNPs) plays pivotal role by influencing blood lipid levels [5].

Single nucleotide polymorphisms (SNPs) are the most common source of genetic variation in populations and provide important information

about genetic linkages [6]. Recent human genetic studies have demonstrated that genetic variants of proteins/transporters are involved in lipid and cholesterol metabolism [7-9]. Acetyl-CoA acetyltransferase is an enzyme that in humans is encoded by the ACAT2 (acetyl-Coenzyme A acetyltransferase 2) gene, also known as cytosolic acetoacetyl-CoA thiolase. It catalyses the condensation of two molecules of acetyl-CoA to acetoacetyl-CoA, which is the first step of the metabolic pathway (mevalonate pathway, MVA) leading to the synthesis of cholesterol [10, 11].

ACAT2 deficiency has been reported in humans and showed severe mental retardation and hypotonus and other clinical symptoms [12, 13]. Many animal studies have revealed that there exit a correlation between cholesterol and this gene [14, 15]. Simrinder et al have identified several SNPs of ACAT-2 gene and analyzed their proposed role in metabolic processes in Pig [11]. Additionally, researchers have been suggested that ACAT2 maintained enzymes involved in lipogenosis in beef cattle [16]. However, little is known about ACAT2 gene in human population regarding lipid levels, as well as the single nucleotide polymorphisms (SNPs). Hence, the purpose of the current study was to investigate the relationship between polymorphisms of human ACAT2 gene and hyperlipidemia in a case-control study.

Materials and methods

Subjects

A total of 759 (male: 452 and female: 307) Han Chinese subjects all randomly selected from the First Affiliated Hospital of Xinjiang Medical University from July 2010 to May 2014. We have conducted a case-control study including 233 patients and 526 control subjects who had passed the eligibility criteria and had complete data on ACAT2 genotype for the current study. Hyperlipidemia was defined as a total plasma cholesterol >6.22 mmol or low density lipoprotein cholesterol >4.14 mmol/L or plasma triglycerides >2.26 mmol and /or the current use of lipid-lowering drugs with an established diagnosis of hyperlipidemia [1]. Further, all subjects live in Xinjiang Uighur Autonomous Region of China and free from thyroid disease, or any history of taking lipid-lowering drugs. Moreover, subjects with renal failure, valvular disease impaired malignancy, connective tissue disease and chronic inflammatory disease were excluded. Additionally, all subjects have given their written informed consent. This study was conducted by following the standards of the Declaration of Helsinki and was approved by the Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University (Urumqi, China).

Assessment of biochemical variables and CAD

Blood urea nitrogen (BUN), creatinine (Cr), uric acid, glucose, total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), Apolipoprotein AI and Apolipoprotein B were measured by using chemical analysis equipment (Dimension AR/AVL Clinical Chemistry System, Newark, NJ) in Clinical Laboratory Department of the First Affiliated Hospital of Xinjiang Medical University [17, 18]. Height, bodyweight and abdominal Circumference were measured as described previously [19], and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). In addition, CAD was defined as the presence of at least one significant coronary artery stenosis with more than 50% luminal diameter on coronary angiography [20].

Assessment of sociodemographic and lifestyle variables

Education was categorized as elementary school, secondary school, and college or more. Physical activity was assessed based on how many days per week subjects had exercised for 30 min or more over the previous six months. Smoking status and alcohol use were dichotomized as smoker/drinker (current and ex-smoker/drinker) or non-smoker/drinker.

SNP selection and genotyping

The human ACAT2 gene cluster on the long arm of chromosome 6, localized to band q25.3-q26, within in a 19 kbp coding region. It has two transcript variants that encode two different isoforms (isoform 1, and isoform 2). Isoform 2 of the ACAT2 gene has the longest length and consists of 426 amino acids and contains 9 exons which are further separated by 8 introns. We have selected three tagging SNPs of ACAT2 gene (rs3798211, rs15892, and rs3465) according to the International HapMap Pro-

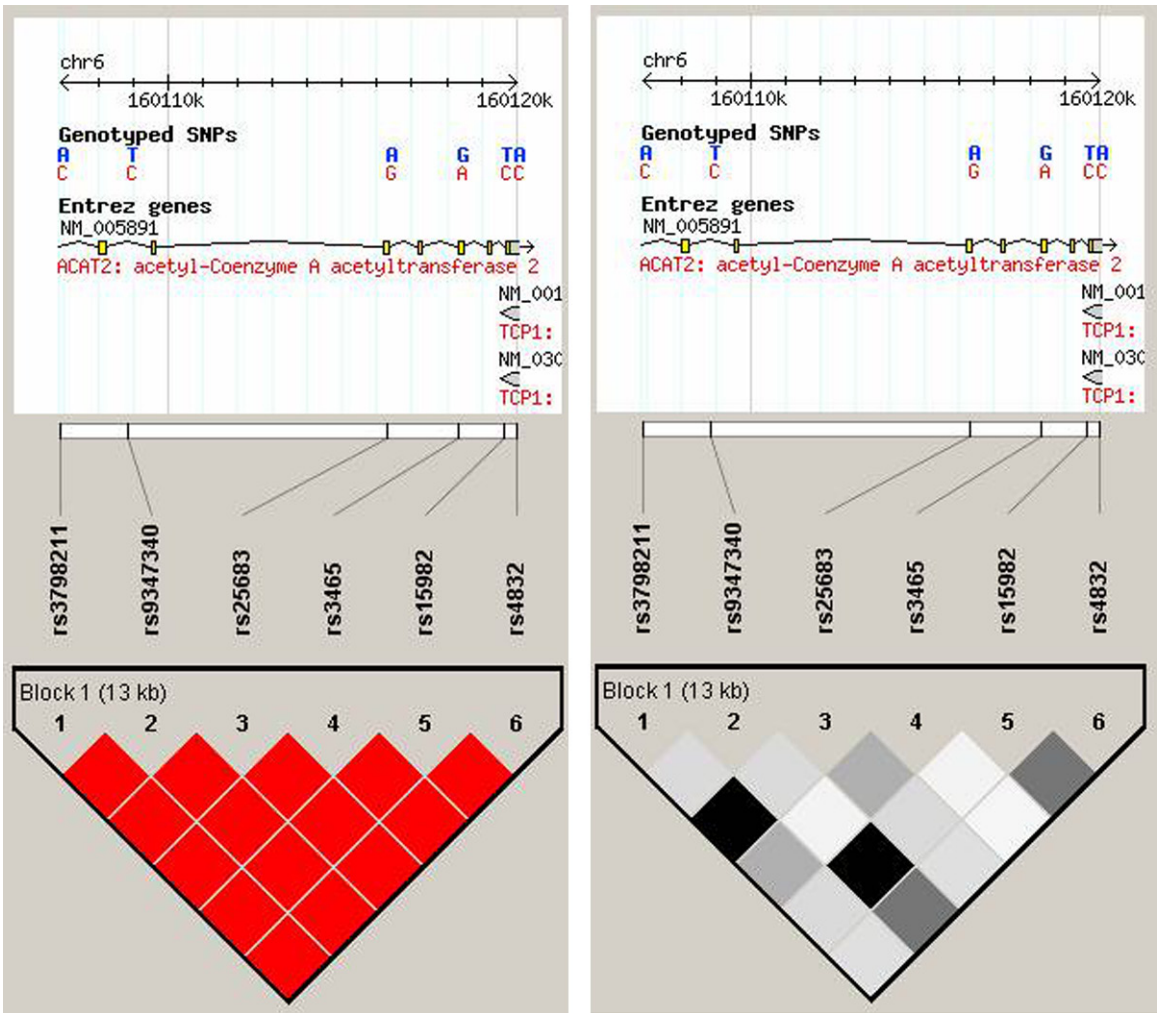

Figure 1. Genetic variation of the human ACAT2 gene. Using Haploview 4.0 software and the HapMap phrase II database, we scanned eight genotyped single-nucleotide polymorphisms (SNPs) in Chinese Han population. Linkage disequilibrium (LD) blocks across this locus in Chinese Han subjects are shown. The LD blocks were identified with the solid spline method in Haploview 4.0. The LD values are displayed as follows: (A) |D'|×100; |D'| color scheme: |D'|=0: white; 0<|D'|<1: shades of pink; and |D'|=1: red; and (B) r^2×100; r^2 color scheme: r^2=0: white; 0<r^2<1: shades of grey; and r^2=1: black.

ject website (http://hapmap.ncbi.nlm.nih.gov/index.html.en) and Haploview 4.0 software and using minor allele frequency (MAF) ≥0.1 and linkage disequilibrium patterns with r^2≥0.8 as a cut-off. In our study, all three SNPs are located in one haplotype block, rs3798211 is located in the 5'UTR of the ACAT2 gene, where as rs15892 is located near the near the exon 9, within a 12 bp region. Moreover, rs3465 is a locus of exon 7, (**Figure 1**) which is defined by a G-to-A nucleotide substitution, but a silent mutation at amino acid position 273 (Glycine-Glycine). Further, blood samples were collected from all subjects, and genomic DNA was extracted from peripheral blood leukocytes by using a DNA extraction kit (Beijing Bioteke Co. Ltd., Beijing, China). Finally, genotyping was undertaken by using TaqMan (Applied Biosystems) Genotyping Assays and whole genome amplified DNAs dried in 384-well plates. We used the ABI Prism 7900HT Sequence Detection System for endpoint fluorescence reading of custom or pre-made TaqMan assays and sequences of primers and probes used for genotyping are available upon request as described previously [21].

Statistical analysis

All statistical analyses were performed via using software for windows, version 17.0 (SPSS).

Table 1. Characteristics of study subjects

Variables	No. (%) or Mean ± SD			
	Case (n=233)	Control (n=526)	T or X^2	*P* Value
Age (yrs)	58.82±9.64	58.12±11.51	0.810	0.418
BMI (kg/m^2)	24.88±4.04	25.27±4.09	-1.142	0.254
Abdominal Circumference	89.77±16.49	92.08±13.82	-1.740	0.082
SBP (mmHg)	138.54±23.94	128.47±17.10	6.579	0.000*
DBP (mmHg)	84.52±11.46	79.21±9.76	6.540	0.000*
Pulse (beats/min)	74.17±9.83	74.47±13.35	-0.313	0.754
BUN (mmol/L)	5.39±1.60	5.25±1.86	0.990	0.322
Creatinine (mmol/L)	73.12±16.13	71.59±16.95	1.160	0.246
Uric acid (umol/L)	349.31±101.98	316.32±89.37	4.473	0.000*
Glucose (mmol/L)	6.20±2.42	5.71±2.55	2.475	0.000*
TG (mmol/L)	3.57±2.29	1.33±0.44	21.560	0.000*
TC (mmol/L)	5.06±1.88	3.99±0.90	10.580	0.000*
LDL-C (mmol/L)	2.86±1.14	2.41±0.73	6.474	0.000*
HDL-C (mmol/L)	1.01±0.46	1.13±0.51	-3.166	0.000*
Apolipoprotein AI (mmol/L)	1.30±0.39	1.24±0.25	2.590	0.010*
Apolipoprotein B (mmol/L)	1.03±0.34	0.79±0.21	11.730	0.000*
CHD n (%)	118 (50.6)	225 (42.8)	4.036	0.048*
Sociodemographic and lifestyle variables				
Sex			0.613	0.470
Male	144 (61.8)	308 (58.8)		
Female	91 (38.2)	216 (41.2)		
Education			8.561	0.029*
Elliterate	14 (6.0)	23 (4.4)		
Elementary	140 (60.1)	277 (52.7)		
Secondary	71 (30.5)	184 (35.0)		
Collge or more	8 (3.4)	42 (8.0)		
Physical activity			25.105	0.001*
Never or Rarely	19 (8.2)	26 (4.9)		
1-2 days/week	94 (40.3)	139 (26.4)		
3-4 days/week	58 (24.9)	160 (30.4)		
>5 days/week	10 (4.3)	61 (11.6)		
Smoking n (%)	158 (67.8)	277 (52.7)	15.148	0.000*
Drinking n (%)	129 (55.4)	225 (42.8)	10.283	0.002*

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; BUN: blood urea nitrogen; TC: total cholesterol; TG: Triglyceride; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein- cholesterol; CHD: coronary artery disease.

Hardy-Weinberg equilibrium was assessed by chi-squared analyses. All continuous variables were expressed as mean plus or minus standard deviation and compared by using an independent sample T-test. Further, differences in categorical variables, genotype distribution and allele frequencies were analyzed via using the Fisher's exact test. In addition, logistic regression analyses were used to assess the contribution of the major risk factors. P<0.05 was considered significant.

Results

1) Characteristics (biochemical variables, sociodemo graphic and lifestyle variables) of the study subjects are shown in **Table 1**.

i. The systolic blood pressure (SBP) and diastolic blood pressure (DBP), uric acid levels, plasma concentration of glucose (Glu), Apolipoprotein AI and Apolipoprotein B were statistically higher in patients with CAD when compared to control subjects. No significant differ-

Table 2. Distributions of ACAT2 genotypes in hyperlipidemia and contorl subjects

SNPs			Case n (%)	Control n (%)	*P* Value	MAF	P_{HWE11}	P_{HWE22}	Analyzing Model	OR (95% CI)	P_{OR}
rs3798211	Genotype	T/T	180 (77.3)	309 (58.7)	0.000*	0.365	0.754	0.485	Dominant	1.336 (1.188-1.502)	0.000*
		C/T	49 (21.0)	192 (36.5)					Additive	0.463 (0.323-0.665)	0.000*
		C/C	4 (1.7)	25 (4.8)					Recessive	0.350 (0.120-1.017)	0.054
	Allele	T	409 (87.8)	810 (77.0)	0.000*				Allele (T vs C)	2.261 (1.516-3.371)	0.000*
		C	57 (12.2)	242 (23.0)							
rs15892	Genotype	A/A	132 (56.7)	253 (48.1)	0.000*	0.238	0.378	0.069	Dominant	1.410 (1.034-1.924)	0.030*
		A/G	90 (38.65)	236 (44.9)					Additive	0.773 (0.565-1.059)	0.110
		G/G	11 (4.7)	37 (7.0)					Recessive	0.655 (0.328-1.308)	0.230
	Allele	A	348 (74.7)	742 (70.5)	0.000*				Allele (A vs G)	2.364 (1.788-3.125)	0.000*
		G	118 (25.3)	310 (20.5)							
rs3465	Genotype	G/G	203 (87.1)	406 (77.2)	0.000*	0.235	0.068	0.428	Dominant	2.754 (1.610-4.114)	0.000*
		A/G	27 (11.6)	110 (20.9)					Additive	0.375 (0.228-0.615)	0.000*
		A/A	3 (1.3)	10 (1.9)					Recesive	0.673 (0.184-2.468)	0.550
	Allele	G	433 (92.9)	922 (87.6)	0.000*				Allele (G vs A)	2.348 (1.329-4.150)	0.003*
		A	33 (7.1)	130 (12.4)							

MAF: minor allele frequency; HEW: Hardy-Weinberg equilibrium; Dominant model: TT vs CT+CC; Additive model: CT vs TT+CC; Recessive model: CC vs TT+CT; *P* value: Difference between the case and control group in genotype distribution. P_{OR}: Difference between case and control in each models and alleles.

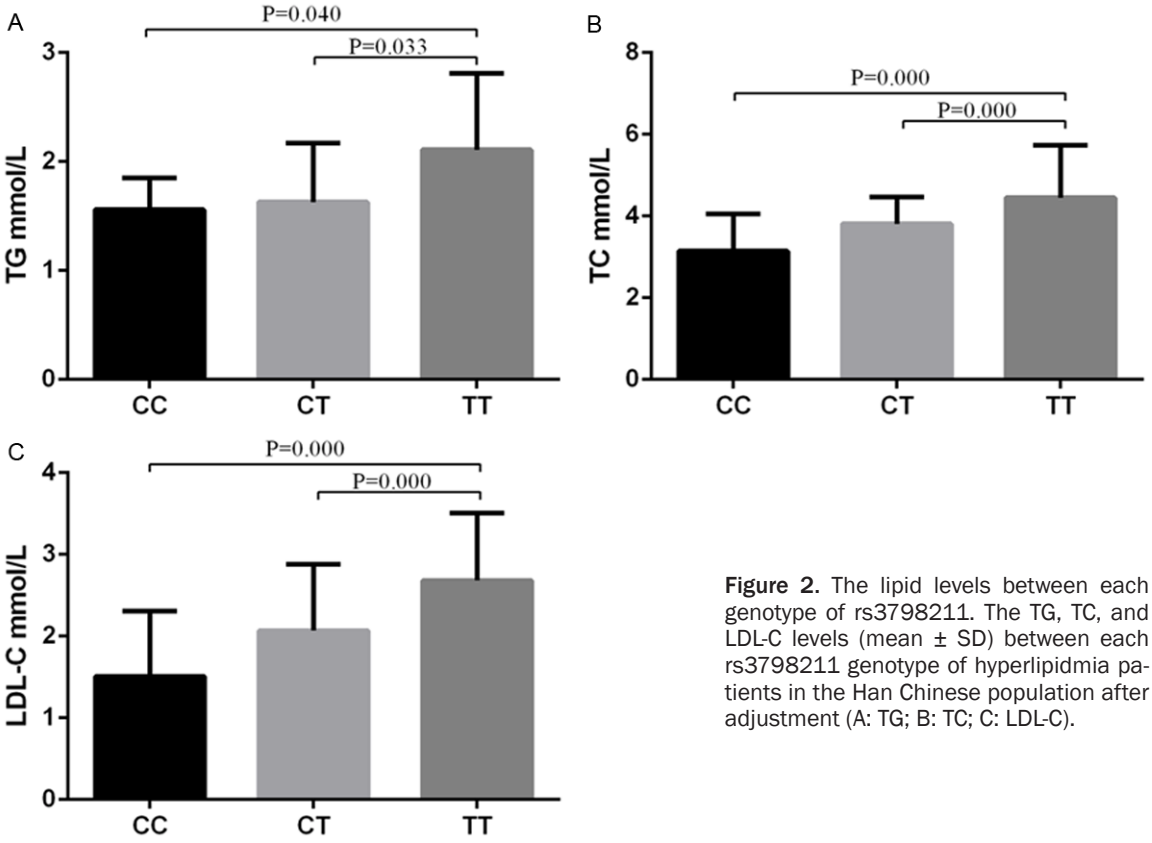

Figure 2. The lipid levels between each genotype of rs3798211. The TG, TC, and LDL-C levels (mean ± SD) between each rs3798211 genotype of hyperlipidmia patients in the Han Chinese population after adjustment (A: TG; B: TC; C: LDL-C).

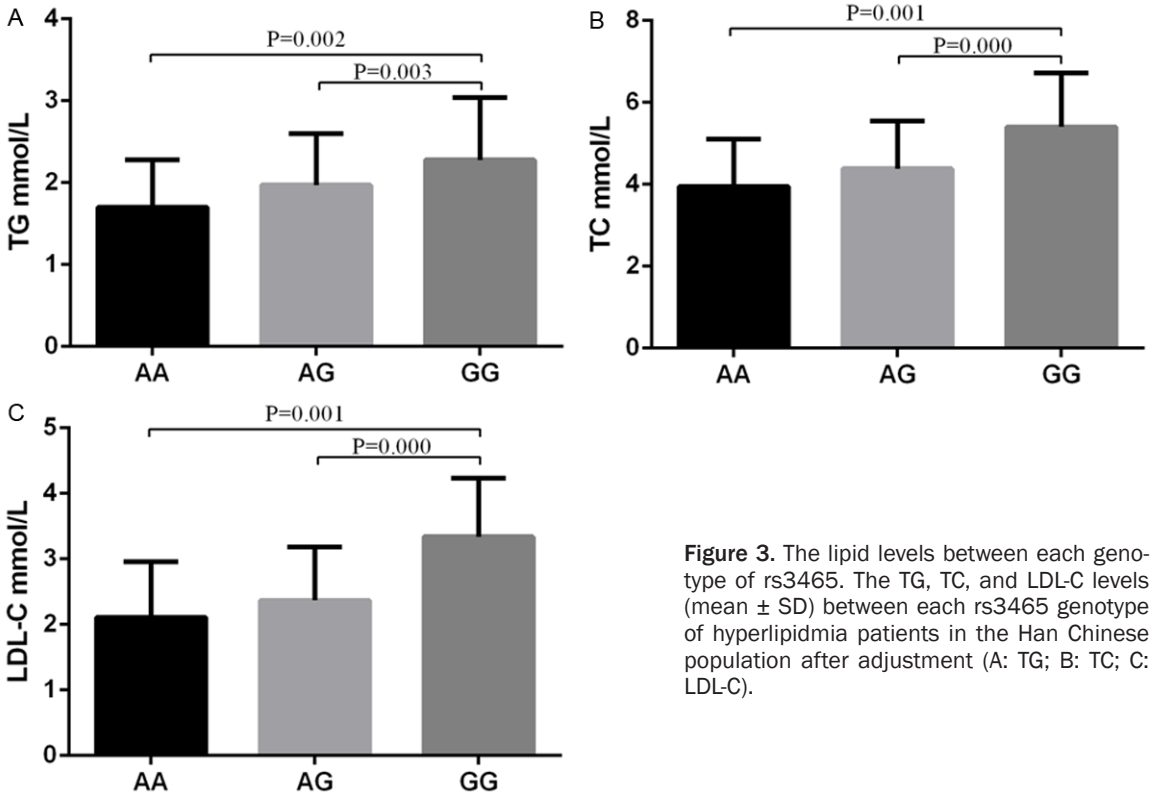

Figure 3. The lipid levels between each genotype of rs3465. The TG, TC, and LDL-C levels (mean ± SD) between each rs3465 genotype of hyperlipidmia patients in the Han Chinese population after adjustment (A: TG; B: TC; C: LDL-C).

ences were observed in body mass index (BMI), pulse, abdominal circumference and creatinine level between the patients and the control subjects (**Table 1**).

ii. The prevalence of coronary artery disease (CAD), smoking and alcohol use were statistically higher in patients with CAD when compared to control subjects. In addition, there was a significant difference between hyperlipidemia patients and control subjects while analyzing the physical activity (P<0.001) (**Table 1**).

2) The distribution of genotypes and alleles of there SNPs of ACAT2 gene analysis and multivariable logistic regression analysis are shown in **Table 2**. In addition, all genotyped SNPs were in Hardy-Weinberg equilibrium (all P>0.05).

i. The rs3798211 TT genotype and T allele, rs15895 AA and A allele, rs3465 GG genotype and G allele were more frequent among the hyperlipidemia patients when compared to the control subjects (rs3798211: 77.3% vs 58.7%, and 87.8% vs 77.0%; rs15895: 56.7% vs 48.1%, and 74.7% vs 70.5%; rs3465: 87.1% vs 77.2%, and 92.9% vs 87.6%; all P=0.000, respectively).

ii. Using a multivariable logistic regression model, the differences remained significant after adjusting confounding factors, such as sex, age, BMI, SBP, DBP, glucose, smoking, drinking, education and physical activity in the dominant models and alleles of all three SNPs of ACAT2 gene (Dominant model: rs3798211: OR=1.336, 95% CI: 1.188-1.502; rs15892: OR=1.410, 95% CI: 1.034-1.924; rs3465: OR=2.754, 95% CI: 1.610-4.114; Alleles: rs3798211: OR=2.261, 95% CI: 1.516-3.371; rs15892: OR=2.364, 95% CI: 1.788-3.125; rs3465: OR=2.348, 95% CI: 1.329-4.150; all P=0.000, respectively).

3) Relationship between ACAT2 genetic polymorphisms and lipid levels in hyperlipidemia patients and control subjects are shown in **Figures 2**, **3**.

We further compared the concentrations of TG, TC, LDL, HDL-C, apolipoprotein AI and apolipoprotein B between each genotype of three SNPs in order to investigate the functional role of ACTA2 polymorphisms.

i. The TG, TC, and LDL-C concentrations were significantly higher in those with the rs3798211 TT genotype than in those with the CT or CC genotype after adjusting age, sex, smoking, alcohol use, education and physical activity (**Figure 2A-C**).

ii. The TG, TC, and LDL-C concentrations were significantly higher in those with the rs3465 GG genotype than in those with the AA or GA genotype after adjusting age, sex, smoking, alcohol use, education and physical activity; **Figure 3A-C**).

iii. For control subjects, the TG, TC, and LDL-C concentrations were also significantly high among the rs3798211 TT genotype, and the rs3465 GG genotype, after adjusting age, sex, smoking, alcohol use, education and physical activity, data not shown (all P<0.05).

iv. There were no significant differences between each genotypes of rs1592 for TG, TC, and LDL-C levels. In addition, the HDL-C, apolipoprotein AI, and apolipoprotein B concentration had showed no significant differences between each genotype of rs3798211 and rs3465 in both groups, data not shown (all P>0.05).

Discussion

This is the first study to investigate the relationship between some polymorphsims in human ACAT2 gene and hyperlipidemia among Han Chinese population and we have found that variation in ACAT2 gene is associated with hyperlipidemia.

Hyperlipdimia is a multifactorial disorder and an elevation of plasma triglycerides, total cholesterol, and low density lipoprotein-cholesterol or a low high-density lipoprotein-cholesterol level that contributes to the development of atherosclerotic cardiovascular disease, such as coronary artery disease. Human studies have been identified genetic variants that confer susceptibility to heperlipidemia and then this approach further involves to analyzing its association with this disease [22, 23].

ACAT2 is a ubiquitous class of enzymes involved in biosynthesis pathway of cholesterol that is expressed at highest levels in liver [24]. There are many evidences confirmed that ACAT2 deficiency is due to congenital disorder of the human genome and causes lots of disease, but poorly characterized [25, 26]. Researchers

have been revealed that ACAT2 gene was associated with the accumulation of abdominal fat while observing its expression in liver [27]. However, few researches have been conducted regarding the relationship between ACAT2 gene and hyperlipdimia and therefore, we assume that ACAT2 gene and hyperlipdimia might be associated.

First of all, we have found that the incidence of smoking, alcohol use and the frequency of the elementary education were higher in the case subjects than the controls and this outcome may suggest that people who had lower level of education may lack of the cognition regarding the diseases. Further, the frequency of never or rarely walk and 1-2 days per week were also higher in the case group than the controls, which indicates that the less psychical activity in daily life, the more people may have a higher risk of suffering hyperlipedima (**Table 1**).

Our study has showed that, T allele frequency of rs3798211, A allele frequency of rs15892, and G allele frequency of rs3465 were significantly higher in the hyperlipedima patients than in the control subjects, and the significance remained after multivariate adjustment, which indicated that T allele of rs3798211, A allele of rs15892, and G allele of rs3465 might be the risk factors for hyperlipidemia. Further, the frequency of TT genotype of rs3798211, AA genotype of rs15892, and GG genotype of rs3465 were also higher in the hyperlipidemia patients than in the control subjects, and the significance also remained after multivariate adjustment, which indicated that the TT genotype of rs3798211 and GG genotype of rs3465 might be risk factors for hyperlipidemia (**Table 2**). In addition, rs3465 is a silent mutation and it is associated with hyperlipdemia as well as the other SNP of ACAT2 gene and recent study have indicated that silent SNP might be related to the protein translation and may contribute to altered gene function. However, further functional study has to be conducted for support such an outcome.

We further observed the relationship between each genotype of three SNPs and lipid profile in hyperlipidemia patients and control subjects. The TT genotype of rs3798211 and GG genotype of rs3465 had higher TG, TC, and LDL-C concentrations when compared to other genotype of the two SNPs and the differences remained significant after adjusting age, sex, smoking, alcohol use, education and physical activity (**Figures 2**, **3**). Such an outcome was presented in the control subjects. These findings suggest that people carrying the TT genotype of rs3798211 and GG genotype of rs3465 have a higher risk of hyperlipedima when compared to other genotypes. In addition, we have not found the significant differences between each genotypes of rs15892 for those lipid levels.

In conclusion, this study is the first to investigate the differences between human ACAT2 gene and hyperlipidemia in the Han Chinese population. The T allele of rs3798211, A allele of rs15892, and G allele of rs3465 could be a susceptible genetic marker, and the TT genotype of rs3798211, AA genotype of rs15892, and GG genotype of rs3465 might be the possible risk for hyperlipidemia and an important and clinically relevant determinant of lipid levels in the Han Chinese population.

Limitations

To our best knowledge, there is evidence to suggest that dietary factors were associated with lipid profile. Because of the absence of dietary information in our database, we could not include this variable to compare between case and control group and in the multivariate analysis and this has become one of the limitations of our research. Further, all subjects were all from the First Affiliate Hospital of Xinjiang Medical University and may have suffering some risk factors of cardiovascular disease. In addition, sample size of the population was small due to the limited time and we should conduct a prospective cohort study in the future.

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Disclosure of conflict of interest

None.

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