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*Taq*IB polymorphism in the *CETP* gene modulates the impact of HC/LF diet on the HDL profile in healthy Chinese young adults☆

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Abstract

The aim of this study was to investigate the interactions of genetic variants in the genes of cholesterol ester transfer protein (*CETP*) and low-density lipoprotein receptor (*LDLR*) with high carbohydrate and low fat (HC/LF) diet on lipid profiles in a young and healthy Chinese Han population. Fifty-six healthy subjects (22.89±1.80 years) were given washout diets of 31% fat and 54% carbohydrate for 7 days, followed by HC/LF diets of 15% fat and 70% carbohydrate for 6 days, with no total energy restriction. Serum lipid profiles at baseline, after washout and following HC/LF diets, as well as *CETP* and *LDLR* polymorphisms were analyzed. Carriers of B2 allele of *CETP Taq*IB polymorphism had significantly higher levels of high density lipoprotein cholesterol (HDL-C) and apo A-I in the whole study population after the diet intervention. Notably, males with *CETP Taq*IB B1B1 experienced significantly increased HDL-C and apo A-I *after* HC/LF diet. Regarding the *LDLR Pvu* II polymorphism, both P1P1 subjects and P2 carriers experienced decreased total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels after HC/LF diet with no statistically significant differences between the genotypes. Our results demonstrate that the elevated HDL-C levels after HC/LF diet in healthy Chinese Han youth are associated with *CETP Taq*I B2 allele while males with B1B1 genotype are more susceptible to the influence of HC/LF diet on their HDL-C levels. The decreased TC and LDL-C levels after HC/LF diet are not associated with *LDLR Pvu* II polymorphism.

Keywords: Cholesterol ester transfer protein; Low-density lipoprotein receptor; Polymorphisms; Serum lipids; High-carbohydrate/low-fat diet

1. Introduction

Hypertriacylglycerolemia, characterized by elevated serum levels of triacylglycerol (TG) and lowered concentrations of high density lipoprotein cholesterol (HDL-C), is a well-recognized independent risk factor for coronary artery disease (CAD) [1–3]. Understanding of the mechanism of hypertriacylglycerolemia is crucial for effective prevention and treatment of this disorder and subsequent CAD. Carbohydrate-induced hypertriacylglycerolemia can be an excellent model in investigating hypertriacylglycerolemia in different populations [1,4]. As coronary artery disease is diagnosed mostly after 45 years of age [5], almost all of the previous studies on carbohydrate-induced hypertriacylglycerolemia have been focused on middle-aged or senior subjects. Although the risk of CAD in younger populations has been steadily increasing over the past few decades [6], much less effort has been made in understanding the biochemical mechanisms and gene–environmental interaction in lipid homeostasis in younger populations, especially in young Chinese population.

A lower incidence of CAD in the Chinese population has been well documented [7,8]. This low incidence has been attributed to their more favorable lipid profile, including lower total cholesterol (TC) and higher HDL-C and apolipoprotein A-I/apolipoprotein B-100 (apoA-I/B-100) ratio [9,10], which is most likely a reflection of both genetic and environmental characteristics in the Chinese population. It has been reported that the Chinese population has a diet containing lower fat and higher carbohydrate [11,12]. Therefore, studies on the carbohydrate-induced hypertriacylglycerolemia in young Chinese populations may provide new insight into the development of hypertriacylglycerolemia in a quarter of the world's population.

One of the key proteins involved in lipoprotein remodeling and metabolism is cholesterol ester transfer protein (CETP). This protein enables the transfer of cholesteryl esters in plasma from HDL towards triglyceride-rich lipoproteins in exchange for triglycerides. Several common restriction fragment length polymorphisms (RFLPs) have

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been reported in the CETP gene (*CETP*) locus [13–16]. The most widely studied variant is *Taq*IB, a silent base change affecting the 277th nucleotide in the first intron of *CETP* [13]. It has been well documented that the *Taq*IB polymorphism has been associated with higher HDL-C levels and lower risk of coronary heart disease end points in men with HDL deficiency [13,17,18]. Another key protein involved in the metabolism of lipoproteins containing apolipoproteins (apo) B and E is the low density lipoprotein receptor (LDLR), which transports cholesterol-carrying lipoprotein particles into the cells through endocytosis. The primary ligand for this receptor is low density lipoprotein cholesterol (LDL-C), which contains a single copy of apoB-100, apo E and approximately 65–70% of plasma cholesterol.

A RFLP in the *LDLR* gene detectable with the restriction enzyme *Pvu* II is associated with variations in not only LDL-C [20,21] but also TG , TC, HDL-C and very low density lipoprotein cholesterol (VLDL-C) [19–23]. The *Pvu* II cutting site (CAGCTG) is created by the transition of a CpG to a TpG, within the sequence CAGCCG, at a position 600 bp upstream of the splice acceptor site of exon 16. People who are homozygous for the absence of the *LDLR Pvu* II restriction site (the P1P1 genotype) have a significantly higher total cholesterol level than heterozygotes [20,22,23]. However, the effect of these gene polymorphisms on the plasma lipid profiles in healthy young populations remains to be elucidated.

In this study, we investigated the interactions of genetic variants in the *CETP* and *LDLR* with high carbohydrate and low fat diet on lipid profiles in a young and healthy Chinese Han population. It was found that interactions between *CETP Taq*IB polymorphisms and gender contribute to the heterogeneity in HDL responsiveness to HC/LF diet in healthy Chinese Han youth.

2. Methods and materials

2.1. Subjects

Volunteers were recruited via advertisement seeking healthy young students in West China Medical Center, Sichuan University. Recruitment criteria included no history of metabolic disease, understanding of the procedures involved, and providing written consent. Volunteers with diabetes or cardiovascular, renal, or endocrinological diseases were excluded. Volunteers who took lipid-lowering drugs, hormones, consumed alcohol, smoked, or whose physical activity or sleeping time varied widely were also excluded. A total of 209 university students were recruited and 60 of these who met the above criteria finally entered the study. They were all apparently healthy, as indicated by the medical questionnaire and physical examination. All of them were Chinese Han people. Fifty-six subjects (27 males and 29 females) completed the study with good compliance. Their baseline characteristics are shown in Table 1. All volunteers were asked to maintain sleeping and physical activity in a constant manner during the study.

2.2. Study design

This is a study of dietary intervention. Previous studies have shown that after 5-7 days of HC/LF diet, serum triacylglycerol reaches a new steady state and remains constant throughout the period of the diet [24,25]. Therefore, a regime of a 7-day washout diet followed by a 6-day intervention was adopted for this study. The study protocol was approved by the Human Research Ethics Committee of Sichuan University.

Table 1
Demographic and biochemical characteristics of the study subjects

Variables	All (n=56)	Males (n=27)	Females (n=29)
Age, y	22.9±1.8	23.0±2.0	22.8±1.7
TG, mg/dl	76.5±43.4	89.1±55.7	65.2±24.3 *
TC, mg/dl	145.9±38.6	135.5±45.5	155.6±28.3
HDL-C, mg/dl	63.6±16.0	55.5±15.6	71.2±12.5 *
LDL-C, mg/dl	68.9±37.7	64.3±44.1	73.2±30.8
ApoA-I, mg/dl	204.6±23.4	193.6±26.4	213.8±15.9 *
ApoB-100, mg/dl	67.8±20.3	65.9±22.7	69.3±18.4

Values are expressed as mean±SD.
* P<.05 compared with that of the males (ANOVA).

2.3. Diets

The meals were composed of breakfast (received at 7:00–8:00 a.m.), lunch (received at 11:30 a.m.–12:30 p.m.) and dinner (received at 5:00–6:00 p.m.). The foods of each meal were changed every day. However, each meal had constant ratios of carbohydrate, protein, and fat. The washout diet contained 54% carbohydrate, 15% protein, and 31% fat. The HC/LF diet contained 70% carbohydrate, 15% protein, and 15% fat. All the meals were prepared from foods consumed by local people daily and were provided by the Department of Nutrition, West China Hospital, Sichuan University. No restriction of total energy intake was imposed for each meal. All the subjects ate to their satiation as usual in their daily life, though subjects were instructed not to take any other food or drink, except water. A daily dietary log was used to assess the compliance of each subject to the study design.

2.4. Blood collection

On the mornings of the first day of the study, the day starting the HC/LF diet, and the day after the HC/LF diet was completed; 12 hour-fasting venous blood samples were collected between 7:00 and 8:00 a.m., and the subject's weight and height were recorded.

2.5. Laboratory analysis

Serum was prepared by centrifugation of blood samples at 3000*g* for 15 min at 4°C. Multiple aliquots of each sample were stored in cryovials at −20°C until the end of the study when all samples were analyzed. Serum TG, TC, and glucose were measured enzymatically using a semi-automated biochemistry analyzer (BT-224). HDL-C was determined enzymatically after precipitation of apo B-containing lipoproteins with phosphotungstic-Mg^{2+}. LDL-C was quantified by the polyvinyl sulfate precipitation method using a semi-automated biochemistry analyzer (BT-224). apoB-100 and apoA-I were measured by an immunoturbidimetry assay with a Hitachi 7070 Analyzer and insulin concentration was determined by electrochemical luminescence with a Roche E170 Analyzer. The inter- and intra-assays coefficients of variation were less than 6%. Each analyte of a given sample was measured three times, and the average value of three measurements was used for statistical analysis.

2.6. DNA extraction and genotyping

Variations of *CETP Taq*IB and *LDLR Pvu* II were analyzed by polymerase chain reaction (PCR) and RFLP analysis [18]. Genomic DNA was isolated from white blood cells using a DNAout kit (Tiandz, Mianyang, China). *CETP Taq*IB genotype was determined by amplifying a 535 bp fragment of intron 1 of the gene by PCR followed by *Taq*IB digestion. The resulting DNA fragments are 174 and 361 bp in length for the B1 allele and an intact 535-bp fragment for the B2 allele. For *LDLR Pvu* II genotyping, amplification of an 1148-bp fragment of the 15th intron of this gene was carried out using PCR, followed by digestion with *Pvu* II. The P2 allele has two fragments of 951 and 197 bp, respectively, while the P1 allele is characterized by one band of 1148 bp.

2.7. Statistical analysis

The results are expressed as mean±S.D. unless otherwise stated. Normality in each group was tested using Shapiro-Wilk test. For positively skewed distribution (e.g. TGs), a log power transformation was applied. The means of variables were compared among subjects with different genotype before or after HC/LF diet by one-way analysis of variance (ANOVA). Two-tailed paired t tests were performed to analyze the statistical significance of the changes of the variables before and after HC/LF diet in the whole study population and in each genotype subgroups. Statistical significance was defined as P<.05.

3. Results

3.1. Biochemical and molecular characterization of the study population

In this study, isoenergetic design was not adopted because it does not reflect the real energy intake of people as the amount of energy intake is governed by the individual's satiation and cannot always be kept isoenergetic in real life. In addition, the variation of energy intake is also an important factor that determines the lipids response to HC/LF diet.

The demographic and biochemical characteristics of the study subjects are summarized in Table 1. Among the 60 volunteers admitted, 56 completed the study. Of these 56, two subjects missed a lunch in the third day of washout diet and ate their own meal. These two participants followed all the other dietary intervention and their data were not excluded.

Table 2
Molecular characterization of the study population

	Total (n=56) n (%)	Males (n=27) n (%)	Females (n=29) n (%)
CETP *Taq*IB			
B1B1	21 (37.5%)	10 (37%)	11 (37.9%)
B1B2	29 (51.8%)	14 (51.9%)	15 (51.7%)
B2B2	6 (10.7%)	3 (11.1%)	3 (10.3%)
LDLR *Pvu* II			
P1P1	45 (80.4%)	22 (81.5%)	23 (79.3%)
P1P2	10 (17.9%)	4 (14.8%)	6 (20.7%)
P2P2	1 (1.8%)	1 (3.7%)	0
Allele frequency			
B1	0.634	0.630	0.638
B2	0.366	0.370	0.362
P1	0.893	0.889	0.897
P2	0.107	0.111	0.103

Genotype and allele frequencies of *CETP Taq*IB and *LDLR Pvu* II polymorphisms in the study population are shown in Table 2. For *CETP Taq*IB polymorphism, the B1 allele represents the presence of *Taq*I restriction site, while the B2 allele denotes the absence of the *Taq*I restriction site. In the case of *LDLR Pvu* II polymorphism, the P1 allele refers to the absence of *Pvu* II restriction site, while the P2 allele symbolizes the presence of the *Pvu* II restriction site. As shown in Table 2, no deviation from the Hardy-Weinberg equilibrium was found in the distribution of genotypes (*CETP*: P=.386; *LDLR*: P=.618). No statistically significant gender difference for genotype frequencies of *CETP Taq*IB (P=.927) or *LDLR Pvu* II (P=.896) was observed in this study population.

3.2. Effects of CETP TaqIB polymorphism on changes of lipid profiles induced by HC/LF diet

Table 3 shows lipid profiles at baseline, after washout diet and after HC/LF diet in the subjects with different *CETP Taq*IB genotypes. Due to the small number of homozygotes for the rare alleles, heterozygotes and homozygotes lacking the *Taq*I cutting site in the *CETP* were combined and referred to as B2 carriers for statistical analysis. No statistically significant differences in the biochemical parameters were found at baseline between the subjects with genotype of B1B1 and B2 carriers for *CETP Taq*IB in either the whole study sample or in males and females separately. After the washout diet, male carriers of B2 had statistically significantly higher HDL-C (53.98±11.20 vs. 45.04±7.31 mg/dl, P<.05), and apoA-I (176.29±24.96 vs. 152.50±24.43 mg/dl, P<.05) than males with B1B1. Following the HC/LF diet intervention, no statistically significant differences of the variables were found between the subjects with B1B1 and B2 carriers in the whole study population, in males or females. However, in the whole study population, an increased level of TG and decreased levels of TC and LDL-C levels were observed in both genotypes when compared with those after the washout diet. Notably, a statistically significantly elevated HDL-C level was observed in B2 carriers but not in B1B1 homozygotes after the HC/LF diet. When gender was taken into account, statistically significantly increased HDL-C (from 45.04±7.31 to 49.81±10.46 mg/dl, P<.05), together with increased apoA-I (from 152.50±24.43 to 158.10±25.72 mg/dl, P<.05) was found in males with B1B1 after the HC/LF diet intervention. A statistically significantly decreased LDL-C in both the males and females with B1B1 was observed after the HC/LF diet (male: from 72.23±25.04 to 55.19±12.25 mg/dl, P<.05; female: from 74.70±14.23 to 64.98±12.99 mg/dl, P<.05).

3.3. Effects of LDLR Pvu II polymorphism on changes of lipid profiles induced by HC/LF diet

In this study, heterozygotes and homozygotes having the *Pvu* II cutting site in the *LDLR* were combined and referred to as P2 carriers due to the small sample sizes in the genotype subgroups. As shown in Table 4, no statistically significant changes in the variables between

Table 3
Serum lipid profile of subjects with different *CETP Taq*IB genotypes at baseline, before and after HC/LF diet

Variables	Males		Females		All	
	B1B1	B2 carriers	B1B1	B2 carriers	B1B1	B2 carriers
n (%)	10 (37%)	17 (63%)	11 (37.9%)	18 (62.1%)	21 (37.5%)	35 (62.5%)
Age, y	23.30±1.95	22.76±1.99	23.27±2.10	22.56±1.34	23.29±1.98	22.66±1.66
TG, mg/dl						
Baseline	96.88±56.46	84.28±56.48	58.45±17.57	69.36±27.25	76.75±44.44	76.38±43.47
After washout diet	84.79±40.06	79.58±37.07	62.76±17.87	67.40±15.04	73.25±31.76	73.32±28.25
After HC/LF diet	95.99±53.13	82.71±28.64	77.20±19.65***	80.47±25.67**	86.15±39.44**	81.56±26.77**
TC, mg/dl						
Baseline	154.48±32.46	124.29±49.08	159.29±23.54	153.28±31.34	157.00±27.52	139.20±42.91
After washout diet	155.63±31.85	142.65±16.06	163.40±17.23	157.88±31.59	159.70±24.92	150.48±26.08
After HC/LF diet	116.71±21.20***	117.28±18.77***	134.64±12.58***	130.59±24.30***	126.10±19.12***	124.12±22.51***
HDL-C, mg/dl						
Baseline	56.13±10.43	55.12±18.30	73.36±14.13	69.89±11.56	65.15±15.05	62.72±16.75
After washout diet	45.04±7.31	53.98±11.20*	63.59±9.21	58.17±10.08	54.76±12.52	56.14±10.69
After HC/LF diet	49.81±10.46**	57.14±9.39	62.57±5.49	62.25±11.37	56.50±10.34	59.77±10.62**
LDL-C, mg/dl						
Baseline	77.31±40.43	56.68±45.51	80.84±23.62	68.53±34.28	79.16±31.91	62.78±39.98
After washout diet	72.23±25.04	62.20±20.91	74.70±14.23	68.07±24.13	73.53±19.63	65.22±22.49
After HC/LF diet	55.19±12.25**	54.55±10.16	64.98±12.99**	62.63±13.72	60.32±13.30**	58.70±12.63**
ApoA-I, mg/dl						
Baseline	190.78±30.42	195.33±24.68	216.73±18.06	211.94±14.67	205.05±27.14	204.39±21.24
After washout diet	152.50±24.43	176.29±24.96*	193.45±21.24	191.67±23.61	173.95±30.55	184.20±25.15
After HC/LF diet	158.10±25.72**	177.76±23.21	196.27±22.65	196.33±22.06	178.10±30.59	187.31±24.20
ApoB-100,mg/dl						
Baseline	77.00±27.91	59.20±16.62	71.45±16.50	68.06±19.79	73.95±21.89	64.03±18.68
After washout diet	65.10±21.27	53.82±18.65	59.10±14.22	59.17±18.07	61.95±17.72	56.57±18.29
After HC/LF diet	62.80±20.12	53.76±21.66	60.73±13.45	58.33±18.66	61.71±16.54	56.11±20.01

Data are mean±S.D.

* P<.05 compared with that of the males with B1B1 after washout diet (ANOVA).

** P<.05 compared with that after washout diet (Paired t-tests).

*** P<.001 compared with that after washout diet (Paired t-tests).

Table 4
Serum lipid profile of subjects with different LDLR *Pvu* II genotypes at baseline before and after HC/LF diet

Variables	Males		Females		All	
	P1P1	P2 carriers	P1P1	P2 carriers	P1P1	P2 carriers
n (%)	22 (81.5%)	5 (18.5%)	23 (79.3%)	6 (20.7%)	45 (80.4%)	11(19.6%)
Age, y	22.95±1.96	23.00±2.12	22.78±1.83	23.00±0.89	22.87±1.88	23.00±1.48
TG, mg/dl						
Baseline	92.11±60.91	76.56±24.14	62.98±23.54	73.83±27.48	76.88±47.18	75.07±24.75
After washout diet	86.07±38.89	61.47±24.31	63.82±15.14	72.59±18.85	74.70±31.03	67.53±21.16
After HC/LF diet	94.22±40.07	58.64±13.78	77.54±23.71***	85.73±22.14**	85.69±33.44***	73.42±22.83
TC, mg/dl						
Baseline	135.16±48.60	136.82±32.16	152.54±27.38	167.14±31.57	144.04±39.74	153.36±34.10
After washout diet	152.13±20.68	126.88±26.17*	158.75±26.16	164.69±31.34	155.51±23.61	147.50±33.98
After HC/LF diet	120.04±16.67***	103.99±26.43**	129.68±17.19***	141.49±30.24	124.97±17.44***	124.44±33.47***
HDL-C, mg/dl						
Baseline	55.06±16.69	57.39±10.90	71.20±12.47	71.22±13.64	63.31±16.65	64.94±13.88
After washout diet	51.57±11.44	46.74±6.13	59.51±8.75	62.99±14.38	55.63±10.81	55.60±13.80
After HC/LF diet	55.20±10.69	51.04±8.09	62.87±9.66	60.47±9.13	59.12±10.79**	56.18±9.60
LDL-C, mg/dl						
Baseline	61.45±46.78	76.96±30.03	69.54±30.00	87.26±32.55	65.58±38.87	82.58±30.32
After washout diet	68.50±22.59	54.54±20.98	68.37±21.79	79.08±15.69	68.44±21.93	67.92±21.53
After HC/LF diet	55.94±10.45**	49.70±11.75	64.27±12.88	60.62±15.55**	60.20±12.36**	55.66±14.44**
ApoA-I, mg/dl						
Baseline	195.16±25.43	187.80±32.37	213.87±16.21	213.33±16.10	205.40±22.67	201.73±26.95
After washout diet	169.73±28.13	157.60±20.55	190.61±23.33	199.00±18.46	180.40±27.59	180.18±28.40
After HC/LF diet	171.82±25.83	164.60±26.37	193.78±20.90	206.00±24.84	183.04±25.69	187.18±32.47**
ApoB-100, mg/dl						
Baseline	67.79±23.43	58.60±20.40	68.65±18.59	72.00±19.02	68.26±20.65	65.90±19.91
After washout diet	60.14±20.64	48.60±15.45	57.78±16.06	64.33±18.42	58.93±18.26	57.18±18.24
After HC/LF diet	59.50±21.65	46.60±16.91	58.26±15.00	63.00±23.28	58.87±18.35	55.55±21.42

Data are mean±S.D.
* $P<.05$ compared with that of the males with P1P1 after washout diet (ANOVA).
** $P<.05$ compared with that after washout diet (paired *t* tests).
*** $P<.001$ compared with that after washout diet (paired *t* tests).

the subjects with genotype of P1P1 and P2 carriers for *LDLR Pvu* II in either the whole study sample or in males and females separately were observed at the baseline. After the washout diet, male carriers of P2 had lower serum TC than males of P1P1 genotype. No differences in other serum lipid profiles were observed in both the whole study subjects or in males and females separately.

Although after the HC/LF diet, no statistically significant difference of the variables were detected between subjects with P1P1 and P2 carriers in the whole study population, both P1P1 homozygotes and P2 carriers experienced significant decreases in TC and LDL-C levels when compared with those after the washout diet. In other words, the changes of TC and LDL-C levels after the HC/LF diet were independent of the genotype of P1P1 or P2. In contrast, an increased TG level was only observed in subjects with P1P1 genotype after HC/LF diet while an elevated apoA-I level was only shown in P2 carriers. Thus, it seems that the *LDLR Pvu II* polymorphism did not modify the TC and LDL-C levels after the HC/LF diet in the whole study population.

4. Discussion

Most of the available data on the effect of substitution of fatty acids with carbohydrate as the main dietary energy intake on serum lipids were obtained from the studies of middle-aged subjects, senior populations or the population with CAD or dyslipidemia [1,2,26–29]. Much less effort, however, has been made in studying the effect of diet intervention on lipid profiles in young and healthy adults. Here, we investigated the effects of HC/LF diet on serum lipid profile in young subjects with different genotypes of *CETP Taq*IB and *LDLR Pvu* II polymorphisms in a Chinese population well characterized with a lower incidence of CAD and *a diet containing low fat and higher carbohydrate*. Conceivably, other genetic and environmental factors affecting lipoprotein metabolisms [30,31] would remain constant for each individual, especially in such a short time of 6 days of HC/LF diet. Therefore, the differences in changes of lipid biochemistry profile upon HC/LF diet intervention were most likely attributed to specific genetic background of individuals.

A number of studies of the effects of HC/LF diet on lipid profiles reported a decreased HDL-C level after the diet intervention [1,4,32]. For example, a study on healthy males in Dunedin, New Zealand, with an average age of 37 years indicated that HDL-C decreased significantly after the high carbohydrate diet intervention [33]. Another study on healthy postmenopausal women in California, USA found a steady decreased HDL-C with the reduction of fat-intake in diet [34]. Here, we provide evidence of statistically significantly increased HDL-C level after the HC/LF diet in B2 carriers in healthy young Chinese adults (Table 3). This finding indicates that the *CETP Taq*IB B2 allele could counteract the decrease of HDL-C induced by the high carbohydrate diet in healthy Chinese adults in their early 20s. Since *CETP Taq*IB polymorphism affects the first intron of the CETP gene, it is very unlikely that these are functional mutations [35]. One possibility is that these polymorphisms are in linkage disequilibrium with some otherwise unknown functional mutations. For example, one study showed that *CETP Taq*IB polymorphism was in linkage disequilibrium with *CETP*-629C>A polymorphism which might influence the expression of CETP [36]. In addition, the elevated HDL-C level after the HC/LF diet might also be due to the adaptation to long-term effects of high carbohydrate diets in this population. It is well known that people in China generally have high dietary carbohydrate intake [1,37], but they enjoy more favorable lipid profiles, including a higher HDL-C level [9,10]. Long-term high carbohydrate diets may reset the metabolism of this population to a new equilibrium that results in the high level of HDL-C at baseline and the swiftly increased HDL-C level after the HC/LF diet. Taken together, young adult Chinese with *CETP Taq*IB B2 allele might be more adaptable to the increase of dietary carbohydrate than those with

B1B1 genotype and may be less susceptible to develop dyslipidemia as a result of high dietary carbohydrate intake.

When gender is taken into account, the interaction of *CETP Taq*IB polymorphism with gender on HDL-C seems to be race-dependent. A meta-analysis of a Caucasian population with an average age of 58 showed that the association between *Taq*IB genotype and HDL-C levels was stronger in women [38], while others found that the association was stronger in healthy male subjects aged 40-69 years living in a rural community in Japan [39]. In contrast, there was no significant association between *CETP Taq*IB polymorphism and HDL-C after the intervention of fat-intake in either African-American or Caucasian adults [40]. These studies suggest that not only dietary components but also ethnicity should be taken into account when the effects of gender on the association of *CETP Taq*IB polymorphism with HDL-C are studied. In the present study, significantly increased HDL-C and apoA-I after the HC/LF diet were observed only in males with B1B1 (Table 3). This indicates that in Chinese healthy young population, males with *CETP Taq*IB B1B1 genotype might be more susceptible to the effect of the HC/LF diet on HDL-C than males with B2 allele and females. This hypothesis is echoed by a recent report showing that, in an American population, the B1B1 men had the greatest response to the triglyceride-lowering drug gemfibrozil despite that fact they had the least favorable plasma lipid profile at baseline [41].

Although *LDLR Pvu* II polymorphism is located in an intron, it might interact with *apoE* gene, which could influence the cholesterol levels [19]. However, the reported associations of LDLR *Pvu* II polymorphism with TC and LDL-C levels varied with the study populations and were sometimes contradictory [19–23], partly due to the interaction among genes or between gene and environment [42]. In our study, both P1P1 subjects and P2 carriers experienced decreased levels of TC and LDL-C after HC/LF diet with no statistically significant between different genotype. These results suggested that the effects of HC/LF diet on the TC and LDL-C levels were not associated with *Pvu* II polymorphism in healthy young Chinese adults. When considering the gender, statistically significantly lower TC levels in P2 carriers than subjects with P1P1 after the washout diet were observed only in males but not in females (Table 4). However, due to the small size of P2 carriers in male and female subgroups in our cohort, more studies are needed to elucidate the interactions of *Pvu* II polymorphism with gender on cholesterol levels induced by HC/LF diet in young Chinese population.

In summary, the lipid and lipoprotein response to HC/LF diet is likely to be under multifactorial control. Our results suggest that *CETP Taq*IB polymorphism contributes to the heterogeneity in HDL-C responsiveness induced by the HC/LF diet while the TC and LDL-C levels after the HC/LF diet are not modified by LDLR *Pvu* II polymorphism in healthy young Chinese adults. Although the analyses were based on a small sample size and thus suggestive, the findings justify the need for future studies with much larger sample sizes. Once confirmed, it will provide new insight into the mechanisms involved in lipid metabolism. As preventative measures of cardiovascular diseases would be most effective and lasting if they are implemented early in life, future studies will pave the way to personalized dietary intervention to reduce risks of cardiovascular diseases in young adults, especially in a country with a quarter of the world's population.

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