Original Article

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PCSK9 rs7552841 is associated with plasma lipids profiles in female Chinese adolescents without posttraumatic stress disorder

Qiwei Guo, Yanjun Si, Mi Su, Mei Fan, Jia Lin, Nazakat H Memon, Dingzhi Fang*

Department of Biochemistry and Molecular Biology, West China School of Basic Medical Sciences & Forensic Medicine, Sichuan University, Chengdu, China.

Summary **To explain the inconsistent relationship between *proprotein convertase subtilisin/kexin type 9* (*PCSK9*) rs7552841 and plasma lipids profiles, we hypothesized that interplays might occur among gender, *PCSK9* rs7552841 and posttraumatic stress disorder (PTSD) on plasma lipids levels. To test this hypothesis, a population of 704 Chinese Han high school students was used, which had been recruited after the 2008 Wenchuan Earthquake. In this population, the plasma levels of glucose, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) had been measured by routine methods. PTSD had been assessed by the PTSD Checklist Civilian Version (PCL-C). *PCSK9* rs7552841 was analyzed by polymerase chain reaction-restriction fragment length polymorphism analyses and verified by DNA sequencing. The T allele carriers had significantly higher levels of TG, TC, LDL-C, and glucose than the CC homozygotes of *PCSK9* rs7552841 after the adjustment for age and BMI in the female students, but not in the male students. When PTSD was taken into consideration, the female T allele carriers had significantly higher TG, TC, LDL-C and glucose than the female CC homozygotes after the adjustment for age and BMI only in the subjects without PTSD, but not in the PTSD patients. No significant differences were observed in the male students regardless of PTSD and the adjustment for age and BMI. These results suggest that *PCSK9* rs7552841 is associated with plasma lipids profiles only in female adolescents, but not in male students. This association can be modified and negated by PTSD.**

Keywords: *PCSK9* rs7552841, genetic variation, gender, PTSD, blood lipids

1. Introduction

Posttraumatic stress disorder (PTSD) is a serious chronic anxiety problem (*1*) that develops in some people after experiencing extremely traumatic events such as serious injury, actual or threatened death, childhood abuse and natural disasters (*2-4*). Numerous studies indicated that individuals with PTSD exhibited higher levels of triglyceride (TG), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) but lower levels of high density lipoprotein cholesterol (HDL-C) than healthy control subjects (*5-7*). However, Jendricko *et al*. (*8*) reported that there were no differences of plasma TG, TC, HDL-C and LDL-C between the male war veterans with PTSD and the control subjects. Jergovic *et al*. (*9*) also reported that plasma lipids did not differ between PTSD patients and controls in individual time points. The mechanism of the discrepancy has not been elucidated yet.

In recent years, proprotein convertase subtilisin/kexin type 9 (PCSK9) has emerged as a new, promising key therapeutic target to reduce the plasma levels of TC, especially LDL-C (*10,11*). PCSK9, also known as neural apoptosis-regulated convertase 1, is a serine protease mostly secreted by liver that plays a critical role in cholesterol metabolism (*12*). In particular, PCSK9 promotes the degradation of cell-surface LDL receptor (LDL-R), resulting in reduced clearance of

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**Address correspondence to:*
Dr. Dingzhi Fang, Department of Biochemistry and Molecular Biology, West China School of Basic Medical Sciences & Forensic Medicine, Sichuan University, Chengdu 610041, China.
E-mail: dzfang@scu.edu.cn

LDL-C from circulation through a post-transcriptional mechanism (*12-14*). Human PCSK9 gene (*PCSK9*) is located on chromosome 1p32, expanding promoter region and 12 exons (*15*). Gain-of-function mutations of *PCSK9* were found to increase the degradation of LDL-R, resulting in autosomal dominant hypercholesterolemia. These findings were confirmed by mice experiments using the wild-type and mutant genes such as S127R and F216L (*15-17*). Conversely, heterozygous patients with loss-of-function mutations had lower plasma LDL-C levels and decreases of 80-90% risk of coronary heart disease (*16,18*). Furthermore, previous studies have demonstrated that PCSK9 is not only take part in the regulation of lipids profiles, but also associated with mental disorders. Kang *et al*. (*19*) reported that plasma levels of PCSK9 were increased in both Alzheimer's disease (AD) and mild cognitive impairment patients. It was also shown recently that AD patients had significantly higher levels of PCSK9 in cerebrospinal fluid than non-AD subjects (*20*). However, there are no existing reports about the relationship between PCSK9 and PTSD.

In addition, over 40 single nucleotide polymorphisms have been found at *PCSK9*. Much more recently, *PCSK9* rs7552841 in the intron region with a thymine (T) to cytosine (C) transition has been reported to be associated with statin response in European individuals (*21*). Significant differences of plasma levels of TG, TC and LDL-C were also observed between the T allele carriers and the CC homozygotes of *PCSK9* rs7552841 in a Chinese Jing population (*22*). Forevermore, the distribution of the T allele carriers and the CC homozygotes were significantly different between hypercholesterolaemic and control subjects or between hypertriglyceridaemic and control subjects. After adjusting age, gender, body mass index (BMI), smoking and alcohol consumption, *PCSK9* rs7552841 was found to be associated with not only hypercholesterolaemia but also hypertriglyceridaemia (*23*). On the other hand, no significant differences of plasma lipid levels were observed between the T allele carriers and the CC homozygotes in a Chinese Han population (*22*), and in 101 Chilean hypercholesterolaemic individuals before or after 10 mg/day of atorvastatin therapy although the T allele carrier showed a trend towards less increases of HDL-C after the treatment (*24*). Obviously, more studies are needed to clarify the above discrepancies of the associations reported before between *PCSK9* rs7552841 and plasma lipids profiles.

To explain the discrepancies of the associations between PTSD and plasma lipids profiles, and between *PCSK9* rs7552841 and plasma lipids profiles reported previously by others, we hypothesized that interplays might occur between *PCSK9* rs7552841 and PTSD to influence plasma lipids profiles. The present study was to test the hypothesis. In fact, we had a population of high school students experiencing the 2008 Wenchuan earthquake, which we had explored the PTSD characteristics in 2008 and 2009, and reported them (*25*). We also had measured the plasma lipids profiles after sampling in 2008 (*26*). In the present study, we genotyped *PCSK9* rs7552841 and analyzed the plasma lipids profiles in the students with different genotypes of *PCSK9* rs7552841 and with or without PTSD. To our knowledge, this is the first study exploring the interaction between PTSD and *PCSK9* rs7552841 on plasma lipids profiles.

2. Materials and Methods

2.1. *Study population*

As reported before (*25*), the population was from a boarding high school after the 2008 Wenchuan earthquake. The devastating earthquake occurred in the afternoon of 12 May 2008, measuring 8.0 on the Richter scale and led to 69,227 deaths, 17,923 missing and 374,643 injured. The earthquake extended about 10 thousand km^2 and covered 254 towns in 21 counties, which destroyed 6.5 million houses. About 5 million people were evacuated and lived in temporary shelters after the earthquake. The school is located only 10 km away from the epicenter of the earthquake and was severely damaged during the earthquake. All the teaching halls and students dormitories were destroyed by the earthquake. The students lived and studied in temporary houses.

Although PTSD characteristics had been measured at 6, 12 and 18 months after the earthquake (*25*), only the data at 6 months were used to test the hypothesis in the present study, which included 746 students from grade 11. Among them, 737 (98.8%) had completed the questionnaires evaluating their demographic characteristics and PTSD status. Recruitment criteria were understanding of the procedures involved, no history of metabolic disease and providing written consents and blood samples. The students with cardiovascular, renal, or endocrinological diseases, or diabetes, and the students who took lipid-lowering drugs or hormones, consumed alcohol and smoked were excluded. In the end, 704 students were included in the present study. They were all Chinese Han adolescents at the age of 15 to 18 years with an average of 16.86 ± 0.59 years. There were 310 male students (44.03%) and 394 female students (55.97%). Written consents had been provided by all the participants of the study and their guardians. This study was approved by the Human Research Ethics Committee of Sichuan University, ratifying our lab to analyze not only the psychological characteristic, genetic variations and plasma lipids profiles, but also the interplays psychological characteristic, genetic variations on plasma lipids profiles (*26*).

2.2. *Measurements*

The measurement instrument was composed of two parts, which was reported previously (*25*). The first part had been used to assess measures including demographic characteristics such as gender, age, body weight and height. Body mass index (BMI) had been calculated. The PTSD Checklist-Civilian Version (PCL-C) (*27*) had been used to assess PTSD in the second part, which corresponds to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria (*2*). The PCL-C includes 17 self-report items. The total score ranges from 17 to 85. A total score of 38 was defined as the cutoff point of PTSD in this study (*28*). The assessments had been finished in 2008 and the existing data were used for the present study.

2.3. *Blood collection and laboratory analyses*

Twelve-hour fasting venous bloods had been sampled. The levels of plasma glucose, TG and TC had been measured using enzymatic methods. The levels of HDL-C had been determined after separated by phosphotungstate-magnesium chloride precipitation method. The levels of LDL-C had been examined using the polyvinyl sulfate precipitation method. All the samples had been measured 3 times and the average values were used for statistical analyses. All the measurements had been finished after sampling in 2008 and the existing data were used for the present study.

2.4. *DNA extraction and genotyping*

Genetic DNA had been isolated after sampling by others in the lab from peripheral blood leucocytes using a DNAout kit (Tiandz, China) and stored at −80℃. In the present study, the stored genetic DNA was used for the genotyping of *PCSK9* rs7552841. The genotypes of *PCSK9* rs7552841 were determined by polymerase chain reaction-restriction fragment length polymorphism method and verified by DNA sequencing. The following PCR primers were used for the amplifications of DNA containing *PCSK9* rs7552841 locus: forward primer, 5′-AGGGAAGGGCACGGTTAG-3′, reverse primer, 5′-TGCCAGTTCCTCCACCAC-3′. The PCR cycling parameters were denaturation at 95℃ for 2 min, 30 subsequent cycles of denaturation at 95℃ for 30 sec, annealing at 60℃ for 30 sec and extension at 72℃ for 30 sec, and a final extension at 72℃ for 2 min. The resulting PCR products were DNA fragments of 496 bp. The identification of the genotypes was performed by the restriction digestion with *Msp*I. The digested products were separated by electrophoresis on 1.5% agarose gel. As a result, the digested PCR products with the CC genotype migrated as one band of 496 bp, the TT genotype as two bands of 320 and 176 bp and the CT genotype as three bands of 496, 320 and 176 bp.

2.5. *Statistical analyses*

The results were expressed as mean ± standard deviation (SD) unless otherwise stated. Log power transformations were applied to the levels of TG because they were in positively skewed distribution. The genotype and allele frequencies were determined by counting. The agreement of the genotype distribution of *PCSK9* rs7552841 with Hardy-Weinberg equilibrium was assessed by chi-squared goodness-of-fit tests. Differences of genotype frequencies as well as allele distribution between the male and female students were estimated using Chi-Square (χ^2) tests. Independent-samples *t* tests were used to compare all the other quantitative variables between the male and female students and between the individuals with different genotypes of *PCSK9* rs7552841. Covariance analyses were used to eliminate the potentially confounding bias of age and BMI on biochemical characteristics. The level of statistical significance was set at 0.05.

3. Results

3.1. *Characteristics of the study population*

The levels of plasma lipids and the related metabolic variables in the study population are shown in Table 1. The male subjects were significantly older than the female subjects in the present study. The levels of BMI, TG, TC, HDL-C and LDL-C were significantly higher, but glucose was significantly lower in the female students when compared with those of the male students.

3.2. *Genotype and allele frequencies of PCSK9 rs7552841*

The genotype and allele frequencies of *PCSK9* rs7552841 in the adolescents are presented in Table 2. No deviation was found from Hardy-Weinberg equilibrium of the distribution of the genotypes of *PCSK9* rs7552841 in the study population (χ^2 = 0.17). There were no statistically significant differences in the genotype and allele frequencies between the male and female subjects. As there were limited subjects with the TT genotype, they were combined with the subjects with the CT genotype and defined as the T allele carriers for further analyses and presented as CT/TT in the tables.

3.3. *Prevalence of PTSD in the subjects with different genotypes of PCSK9 rs7552841*

According to the assessment of PCL-C, the prevalence of PTSD in the students with different genotypes of

Table 1. Characteristics of the study population

Variables	All	Males	Females	*p*-Value[a]
n	704	310	394	--
age	16.86 ± 0.59	16.95 ± 0.61	16.78 ± 0.56	< 0.001
BMI, kg/m^2	20.28 ± 2.31	19.81 ± 2.29	20.66 ± 2.27	< 0.001
TG, mmol/L	1.12 ± 0.44	0.96 ± 0.35	1.24 ± 0.47	< 0.001
TC, mmol/L	3.58 ± 0.57	3.41 ± 0.51	3.72 ± 0.58	< 0.001
HDL-C, mmol/L	1.41 ± 0.28	1.36 ± 0.26	1.45 ± 0.29	< 0.001
LDL-C, mmol/L	1.67 ± 0.49	1.61 ± 0.46	1.71 ± 0.50	0.011
Glucose, mmol/L	5.07 ± 0.44	5.15 ± 0.45	5.01 ± 0.42	< 0.001

[a] comparisons between those of the male subjects and those of the female subjects (independent-samples *t* test).

Table 2. Genotype and allele frequencies of *PCSK9* rs7552841 in the study population

Genotype	Total (*n* = 704) *n* (%)	Hardy-Weinberg *p*	Males (*n* = 310) *n* (%)	Females (*n* = 394) *n* (%)	*p*[a]
Genotype Frequencies					
CC	510 (72.4)		221 (71.3)	289 (73.4)	
CT	180 (25.6)		84 (27.1)	96 (24.4)	0.606
TT	14 (1.99)	0.683	5 (1.60)	9 (2.30)	
Allele Frequencies					
C	1,200 (85.2)		526 (84.8)	674 (85.5)	0.715
T	208 (14.8)		94 (15.2)	114 (14.5)	

Data are presented as *n* (%). [a] Male students *vs*. female students by Chi-Square tests.

Table 3. Prevalence of PTSD in the subjects with different genotypes of *PCSK9* rs7552841

Group	All		Males		Females	
	CC	CT/TT	CC	CT/TT	CC	CT/TT
Control	346 (67.8)	136 (70.1)	166 (75.1)	71 (79.8)	180 (62.3)[a]	65 (61.9)[a]
PTSD	164 (32.2)	58 (29.9)	55 (24.9)	18 (20.2)	109 (37.7)	40 (38.1)

Data are expressed as *n* (%). [a] $p < 0.05$ when compared with that of the male students (Chi-Square test).

PCSK9 rs7552841 is shown in Table 3. No significant difference of prevalence was found between the CC homozygotes and the T allele carriers in all the students, the male or the female subjects. The PTSD prevalence of female subjects was significantly higher than the male subjects in both the CC homozygotes ($p = 0.002$) and the T allele carriers ($p = 0.008$).

3.4. *Plasma lipids profiles and the related metabolic variables of the subjects with different genotypes of PCSK9 rs7552841*

Table 4 shows age, BMI, plasma lipids and plasma glucose of the subjects with different genotypes of *PCSK9* rs7552841. The female T allele carriers had higher levels of TC and LDL-C than the female CC homozygotes. After the adjustment for age and BMI, the female T allele carriers had significantly higher levels of TG, TC, LDL-C and glucose than the female CC homozygotes. However, there were no significant differences between the T allele carriers and the CC homozygotes in the male subjects regardless of the adjustment for age and BMI.

3.5. *Effects of PTSD on the association of PCSK9 rs7552841 polymorphism with plasma lipids profiles and the related metabolic variables*

As shown in Table 5, no significant differences were found between the CC homozygotes and the T allele carriers in the male students regardless of PTSD and the adjustment for age and BMI. However, the T allele carriers had higher levels of BMI, TG, TC, and LDL-C than the CC homozygotes in the female subjects without PTSD, but not in the female students with PTSD. After the adjustment for age and BMI, the female T allele carriers had significantly higher levels of TG, TC, LDL-C, and glucose than the female CC homozygotes in the students without PTSD. Still, no significant differences were observed after the adjustment for

Table 4. Serum Lipids Profiles and the Related Metabolic Variables of the subjects with different genotypes of *PCSK9* rs7552841

Variables	Males				Females			
	CC	CT/TT	*p*-Value[a]	ANCOVA *p*-Value[b]	CC	CT/TT	*p*-Value[a]	ANCOVA *p*-Value[b]
n	221	89	--	--	289	105	--	--
Age, year	16.95 ± 0.61	16.96 ± 0.62	0.950	--	16.79 ± 0.59	16.76 ± 0.49	0.635	--
BMI, kg/m^2	19.83 ± 2.36	19.76 ± 2.11	0.810	--	20.74 ± 2.22	20.44 ± 2.38	0.254	--
TG, mmol/L	0.95 ± 0.34	0.98 ± 0.37	0.545	0.486	1.21 ± 0.46	1.31 ± 0.47	0.055	0.025
TC, mmol/L	3.41 ± 0.52	3.41 ± 0.48	0.950	0.975	3.68 ± 0.56	3.85 ± 0.64	0.008	0.004
HDL-C, mmol/L	1.35 ± 0.25	1.36 ± 0.28	0.819	0.867	1.46 ± 0.29	1.43 ± 0.28	0.316	0.212
LDL-C, mmol/L	1.62 ± 0.48	1.60 ± 0.43	0.686	0.717	1.66 ± 0.48	1.82 ± 0.54	0.004	0.002
Glucose, mmol/L	5.15 ± 0.41	5.14 ± 0.52	0.862	0.873	4.98 ± 0.41	5.08 ± 0.43	0.051	0.047

[a] Comparisons between those of the CC homozygotes and those of the T allele carriers (independent-samples *t* test). [b] Analyses of covariance with the adjustment for age and BMI.

Table 5. Effects of PTSD on the association of *PCSK9* rs7552841 with anthropometric and biochemical characteristics

Variables	Group	Males				Females			
		CC	CT/TT	*p*-Value[a]	ANCOVA *p*-Value[b]	CC	CT/TT	*p*-Value[a]	ANCOVA *p*-Value[b]
n	Control	166	71	--	--	180	65	--	--
	PTSD	55	18	--	--	109	40	--	--
Age, year	Control	16.96 ± 0.62	16.93 ± 0.66	0.752	--	16.78 ± 0.58	16.75 ± 0.50	0.717	--
	PTSD	16.93 ± 0.57	17.06 ± 0.42	0.384	--	16.81 ± 0.60	16.78 ± 0.48	0.760	--
BMI, kg/m^2	Control	19.68 ± 2.06	19.58 ± 1.99	0.727	--	20.69 ± 2.08	19.97 ± 2.31	0.021	--
	PTSD	20.25 ± 3.09	20.44 ± 2.46	0.816	--	20.81 ± 2.44	21.21 ± 2.31	0.371	--
TG, mmol/L	Control	0.94 ± 0.28	0.98 ± 0.35	0.312	0.265	1.20 ± 0.42	1.33 ± 0.46	0.036	0.014
	PTSD	1.00 ± 0.49	0.97 ± 0.42	0.836	0.792	1.23 ± 0.52	1.28 ± 0.49	0.579	0.799
TC, mmol/L	Control	3.37 ± 0.52	3.42 ± 0.49	0.506	0.464	3.67 ± 0.64	3.84 ± 0.62	0.042	0.031
	PTSD	3.53 ± 0.52	3.36 ± 0.41	0.208	0.183	3.68 ± 0.59	3.87 ± 0.67	0.090	0.135
HDL-C, mmol/L	Control	1.35 ± 0.25	1.35 ± 0.28	0.992	0.929	1.47 ± 0.28	1.42 ± 0.28	0.234	0.095
	PTSD	1.37 ± 0.26	1.41 ± 0.29	0.562	0.411	1.44 ± 0.30	1.44 ± 0.28	0.907	0.960
LDL-C, mmol/L	Control	1.59 ± 0.47	1.62 ± 0.43	0.659	0.588	1.66 ± 0.45	1.81 ± 0.54	0.041	0.012
	PTSD	1.71 ± 0.49	1.51 ± 0.46	0.127	0.087	1.67 ± 0.52	1.85 ± 0.57	0.079	0.117
Glucose, mmol/L	Control	5.12 ± 0.41	5.14 ± 0.52	0.804	0.833	4.98 ± 0.37	5.09 ± 0.46	0.057	0.041
	PTSD	5.25 ± 0.40	5.16 ± 0.56	0.479	0.463	5.00 ± 0.47	5.06 ± 0.40	0.431	0.484

[a] Comparisons between those of the CC homozygotes and those of the T allele carriers (independent-samples *t* test). [b] Analyses of covariance with the adjustment for age and BMI.

age and BMI between the T allele carriers and the CC homozygotes in the female students with PTSD.

4. Discussion

In the present study, we used the population that we had reported the PTSD characteristics (*25*) and had measured the lipids profiles (*26*). We genotyped *PCSK9* rs7552841 and analyzed the plasma lipids profiles in the students with different genotypes of *PCSK9* rs7552841 and with or without PTSD. To our best knowledge, these analyses have not been reported before. In fact, PTSD characteristics had been measured in the population at 6, 12 and 18 months after the earthquake (*25*). However, only the data at 6 months were used in the present study because the purpose was to test our hypothesis that interplays might occur between *PCSK9* rs7552841 and PTSD to influence plasma lipids profiles. Although the follow-up might provide more information about the changes of PTSD and lipids profiles, analyzing the interplays of course, PTSD and *PCSK9* rs7552841 was not the purpose of the present study.

It has been reported that PCSK9 can regulate plasma levels of LDL-C, while some of the single nucleotide polymorphisms at PCSK9 are associated with plasma lipids profiles (*12-14,16,29*). Recently, the association of *PCSK9* rs7552841 polymorphism with plasma lipids has been explored in two laboratories in China and Chile (*22-24*). Significant differences were found by the Chinese laboratory of the plasma levels of TG, TC and LDL-C between the T allele carriers and the CC homozygotes of *PCSK9* rs7552841 in a Chinese Jing population, but not in Chinese Han population (*22*). The results reported by the Chilean laboratory showed that there were no significant differences

of plasma lipids between the T allele carriers and the CC homozygotes of *PCSK9* rs7552841 in 101 Chilean hypercholesterolaemic individuals before and after 10 mg/day of atorvastatin therapy (*24*). These discrepancies may be explained by ethnicities, healthy status, medication status and even the sample size because the Chilean investigation was carried out in a smaller population. However, other confounding factors such as age, BMI, gender or psychological factors were not included in all the above analyses, which have been generally accepted to be important factors associated with plasma lipids profiles (*30-34*). In the present study, the female students had significantly higher levels of TG, TC, HDL-C and LDL-C but lower levels of glucose than the male students in the whole study population (Table 1). These results confirm again that gender serves as an important confounding factor and influences the levels of plasma lipids. Therefore, we examined the differences of plasma lipids between the T allele carriers and the CC homozygotes of *PCSK9* rs7552841 in the male and female students separately. To eliminate the influence of confounders such as age and BMI on plasma lipids, the adjustment was made of age and BMI. The results show that the female T allele carriers had significantly higher levels of TG, TC, LDL-C and glucose than the female CC homozygotes after the adjustment for age and BMI. Nevertheless, no significant differences were observed between the T allele carriers and the CC homozygotes in the male subjects regardless of the adjustment for age and BMI (Table 4). These results suggest that *PCSK9* rs7552841 may interplay with gender to influence plasma lipids profiles. And therefore, *PCSK9* rs7552841 is associated with plasma lipids in a gender-dependent manner. This finding may be one of the explanations of the discrepancies reported before of the associations between *PCSK9* rs7552841 and the levels of plasma lipids.

Although a biopsychosocial medical model was proposed by Engel in 1977 (*35*), much less efforts have been made to explore the interplays between biomedical factors and psychological factors on plasma lipids profiles. Therefore, in the present study, PTSD was selected as a psychological factor to study its interplays with gender and *PCSK9* rs7552841 on the levels of plasma lipids in a biological-psychological approach. The results indicate that the female T allele carriers had significantly higher levels of TG, TC, LDL-C and glucose than the female CC homozygotes after the adjustment for age and BMI only in the subjects without PTSD, but not in the PTSD patients (Table 5). No significant differences were observed between the male T allele carriers and the male CC homozygotes regardless of PTSD and the adjustment for age and BMI. These results suggest that *PCSK9* rs7552841 may interplay with not only gender but also PTSD to affect plasma levels of TG, TC, LDL-C and glucose. More specifically, the association between *PCSK9* rs7552841 and plasma lipids profiles in female subjects may be modified or eliminated by PTSD. These findings may be one of the explanations that no associations were found between *PCSK9* rs7552841 and the levels of plasma lipids in the same ethnicity reported before (*22*). Therefore, in the future study, gender and psychological factors should be taken into account when the relationship is tested between *PCSK9* rs7552841 and plasma lipids profiles.

Cunningham *et al*. (36) reported that the mutant with the gain-of-function mutation D374Y could bind LDL receptor more tightly than the wild-type *PCSK9*, resulting in the increment of plasma LDL-C. On the other hand, Suzanne *et al*. (*37*) found that *PCSK9* with the natural mutation F216L could increase the levels of circulating LDL-C through resisting to furin digestion and increasing plasma PCSK9 levels. In addition, some other gain-of-function mutations were also reported to increase the levels of plasma LDL-C (*16,38-40*). As the variation of *PCSK9* rs7552841 is located at the intron region, the molecular mechanism of its effects on plasma lipids profiles cannot be the gain-of-function mutation of PCSK9. The possible mechanism may be that its mRNAs are more stable since higher stabilities of mutant intron-containing RNAs have been found to promote translation, resulting in more protein production (*41,42*). Other mechanisms such as linkage disequilibrium should also be taken into consideration.

There were some limitations in the present study. Firstly, only adolescents were included in the present study. The metabolic characteristics of this population may be different from adults. Secondly, the plasma levels of PCSK9 and the levels of *PCSK9* mRNA in liver tissues were not measured. Thirdly, other psychological factors such as depression were not included, which had been reported to be related to dyslipidemia (*43,44*). These measurements are recommended for future studies in this field.

In conclusion, there may be interactions among gender, PTSD and *PCSK9* rs7552841 on plasma lipids profiles. *PCSK9* rs7552841 is associated with plasma lipids profiles in a gender-dependent manner in Chinese Han adolescents without PTSD, but not in Chinese Han adolescents with PTSD. The T allele of *PCSK9* rs7552841 may be a risk factor to increase the levels of plasma TG, TC, LDL-C and glucose in healthy female subjects. This finding may provide novel insights into the regulation of lipids metabolisms by *PCSK9* in younger populations, and pave the way for the precision prevention to reduce risks of CVD in adolescents, especially in a country with a quarter of the world's population.

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