Associations of the SLCO1B1 Polymorphisms With Hepatic Function, Baseline Lipid Levels, and Lipid-lowering Response to Simvastatin in Patients With Hyperlipidemia

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Abstract

Our goal was to examine the associations of the 388A>G and 521T>C polymorphisms in the solute carrier organic anion transporter 1B1 (SLCO1B1) gene with hepatic function, baseline lipid levels, and the lipid-lowering efficiency of simvastatin. We recruited 542 patients with hyperlipidemia. The 388A>G and 521T>C polymorphisms were genotyped. Serum alanine amino-transferase (ALT) and aspartate transaminase (AST), Serum triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels were measured before and after an oral 20-mg dose of simvastatin. Individuals with the 388AA genotype had higher ALT and AST levels than those with the 388AG or 388GG genotypes ($P = .037$ and $P = .002$, respectively). Individuals with both the 388AA and the 521TT genotypes had the highest levels of ALT and AST ($P = .001$ and $P = .001$, respectively). Moreover, we divided all patients into normal and abnormal subgroups based on elevated ALT and AST values (≥ 40 U/L), participants in the abnormal subgroup had a higher frequency of the 388A/521T haplotype and a lower frequency of the 388G/521T haplotype compared to those in the normal subgroup. In addition, compared to 388G allele and 521C allele carriers, individuals with the 388G allele and 521TT genotype carriers had greater TC and LDL-C reduction in response to simvastatin after 4 weeks of treatment. Our conclusion suggests that the interaction between the SLCO1B1 388A>G and 521T>C polymorphisms could be an important genetic determinant of hepatic function and the therapeutic efficiency of simvastatin in Chinese patients with hyperlipidemia.

Keywords

SLCO1B1, polymorphism, hepatic function, hyperlipidemia, simvastatin

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Introduction

Cardiovascular disease (CVD) remains the leading cause of death worldwide. A global burden of disease study in 2013 estimated that CVD caused 17.3 million deaths globally, which accounted for 31.5% of all deaths and 45% of all noncommunicable disease deaths. Hyperlipidemia is a major risk factor for the development of CVD.[1] It is a common metabolic disease characterized by elevated concentrations of total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) with declined levels of high-density lipoprotein cholesterol (HDL-C).[2] Many well-established studies have reported that all types of hyperlipidemia could arise from genetic factors.[3,4]

Organic anion-transporting polypeptide 1B1 (OATP1B1), encoded by the solute carrier organic anion transporter 1B1 gene (SLCO1B1), is an important transporter with 691 amino acids. Organic anion-transporting polypeptide 1B1 is located on the basolateral membrane of hepatocytes and small intestinal enterocytes.[5] It mediates the transport of a wide variety of exogenous and endogenous substrates, such as bile acids, sulfate, and xenobiotic compounds.[6,7] To date, many single-nucleotide polymorphisms (SNPs) have been found within the SLCO1B1 gene.[8] Two common polymorphisms in the SLCO1B1 gene—388A>G (rs2306283) and 521T>C (rs4149056)—are associated with an alteration in the transport activity of OATP1B1 both in vitro and in vivo.[9-13] The SLCO1B1 388A>G polymorphism has been associated with markedly increased activity of OATP1B1.[9] On the other hand, declined activity of the transporter has been related to the SLCO1B1 521T>C polymorphism.[10] Haplotype analysis further suggested that the SLCO1B1*15 haplotype (388G/521C) is associated with low activity of the transporter.[11-13] In addition, several studies have reported the impact of SLCO1B1 gene polymorphisms on the lipid-lowering efficacy of the statins.[14,15]

Alanine aminotransferase (ALT) and aspartate transaminase (AST) are 2 important aminotransferases in vivo. Serum ALT and AST values are independent predictors of fatty liver.[16,17] Recently, several studies have found that hyperlipidemia, especially hypertriglyceridemia, may be a major risk factor for common chronic hepatic diseases such as nonalcoholic fatty liver and fatty infiltration of the liver.[18,19] Although the pathogenesis of nonalcoholic steatohepatitis remains to be determined, lipid peroxidation and oxidative stress are known to be the primary causes.[20,21] To date, however, there have been no studies demonstrating the relationship between SLCO1B1 gene polymorphisms and ALT and AST concentrations in patients with primary hyperlipidemia.

In this article, we conducted a genetic epidemiological study to explore the association of the common SLCO1B1 polymorphisms with baseline plasma lipid levels and hepatic function. Moreover, we also examined the association of the SLCO1B1 388A>G and 521T>C variants with response to lipid-lowering therapy with simvastatin in Chinese patients with hyperlipidemia.

Patients and Methods

Study Population

This is an epidemiological cohort study. All participants were residents of Beijing and Anhui Province, China. The study cohort consisted of 542 patients with hyperlipidemia, including 166 (31%) men and 376 (69%) women. Participants who met the following criteria were considered hyperlipidemic: (1) total cholesterol at least 5.72 mmol/L, TG at least 1.70 mmol/L, or LDL-C at least 3.64 mmol/L; (2) no ischemic heart disease or other vascular disease; and (3) no drug use that could lower plasma lipid levels or otherwise affect the blood lipid profile for at least 1 week prior to the study. Prior to study participation, all patients gave written informed consent, and the study protocol was approved by the ethics committee of the Institute of Biomedicine, Anhui Medical University.

Simvastatin treatment

After a washout period of 7 to 10 days, all participants received a daily fixed oral dosage of 20 mg simvastatin for 8 consecutive weeks. Participants were required to take their simvastatin between 8:00 PM and 10:00 PM. During the study period, participants were required to visit our clinical center weekly for blood lipid measurement and to report any adverse effects. Patients whose laboratory parameters were affected by the treatment were excluded during the study.

Laboratory Analysis

At baseline, 4 weeks, and 8 weeks of treatment, venous blood samples were drawn from all participants at the research center after an overnight fast. Blood samples were stored in EDTA tubes and centrifuged at 2500 r/min for 10 minutes to acquire the serum. Plasma lipid levels (TC, TG, LDL-C, and HDL-C) were determined by enzymatic colorimetric assays (Roche Diagnostics, Mannheim, Germany). Alanine aminotransferase and AST levels were measured by reflective photometry using an automatic biochemistry analyzer. The automatic biochemistry analyzer based on the spectrophotometric principle is one of the necessary instruments for clinical diagnostics in a hospital. The SLCO1B1 388A>G and 521T>C polymorphisms were genotyped by the polymerase chain reaction-restriction fragment length polymorphism technique. The primers were as follows: SLCO1B1 388A>G forward 5'-ATA ATG GTG CAA ATA AAG GGG-3' and reverse 5'-ACT ATC TCA GGT GAT GCT CTA-3', SLCO1B1 521T>C forward 5'-AAA GGA ATC TGG GTC ATA CAT GTG GAT ATA CG-3' and reverse 5'-TTC AAA AGT AGA CAA AGG GAA AGT GAT CAT-3'. The polymerase chain reaction (PCR) conditions for 388A>G were 5 minutes at 94°C for initial denaturation, followed by 36 cycles of denaturation at 94°C for 30 seconds, annealing at 57°C for 30 seconds, and extension at 72°C for 30 seconds, with a final extension at 72°C for 6 minutes. For 521T>C, the

Table 1. Hardy-Weinberg Equilibrium Test for the SLCO1B1 388A>G and 521T>C Polymorphisms.

SLCO1B1		Observed Counts	Expected Counts	χ^2	P Value
388A>G (N = 542)	AA	47	43.19	0.652	0.419
	AG	212	219.62		
	GG	283	279.19		
521T>C (N = 542)	TT	425	427.75	1.422	0.233
	TC	113	107.49		
	CC	4	6.75		

Abbreviations: SLCO1B1, solute carrier organic anion transporter 1B1; TC, total cholesterol.

conditions were 5 minutes at 94°C for initial denaturation, followed by 36 cycles of denaturation at 94°C for 30 seconds, annealing at 57°C for 30 seconds, and extension at 72°C for 30 seconds, with a final extension at 72°C for 6 minutes. After PCR amplification, restriction enzyme digestion was accomplished with Hinf I (at 37°C for 3 hours) for the 388A>G polymorphism (divided into 214∼, 129∼, and 85 base pair [bp]) and Mlu I (at 37°C for 4 hours) for the 521T>C polymorphism (divided into 196∼, 162∼, and 34 bp). The digestion products were then separated on 3% agarose gels and visualized with ethidium bromide staining.

Statistical Analysis

Statistical analysis was performed with SPSS 19.0 (IBM Inc, Armonk, New York). Continuous data were presented as mean (standard deviation), and categorical data were expressed as counts and proportions. Deviation of the genotype distributions for the 2 polymorphisms from the Hardy-Weinberg equilibrium was tested with the χ^2 test. Student *t* test and 1-way analysis of variance were used to compare the mean differences for continuous variables. Multiple linear and logistic regression models were used to estimate the associations between the plasma compounds measuring hepatic function and lipid levels and the SLCO1B1 388A>G and 521T>C polymorphisms. The estimated haplotype frequencies were calculated using PHASE 2.1 software. Value of $P < .05$ were considered to be significant.

Results

Baseline Clinical and Epidemiologic Characteristics

A total of 542 patients with hyperlipidemia were enrolled to participate in our study. As shown in Table 1, the genotype distribution of SLCO1B1 genotype distribution of the SLCO1B1 388A>G and 521T>C polymorphisms did not deviate from Hardy-Weinberg equilibrium ($P = .419$ and $P = .233$, respectively). For all of the study participants, the minor allele frequencies observed for 388A>G and 521T>C were 0.28 and 0.11, respectively. Table 2 showed the clinical and demographic characteristics of the patients with hyperlipidemia.

Table 2. Clinical and Demographic Characteristics of the Study Participants.[a]

Parameter	N = 542
Age, (years)	52.5 (7.9)
BMI, kg/m²	24.2 (3.1)
DBP, mm Hg	77.9 (10.7)
SBP, mm Hg	127.0 (20.2)
TG, mmol/L	1.9 (0.9)
TC, mmol/L	6.5 (0.6)
HDL-C, mmol/L	1.7 (0.5)
LDL-C, mmol/L	3.8 (0.7)
ALT, U/L	28.3 (19.8)
AST, U/L	30.6 (11.1)
CK, U/L	106.1 (47.0)
GLU, mmol/L	5.6 (0.6)
Wc, m	0.9 (0.1)
Men/women, n	166/376
Smoking/no smoking	393/149
Drinking/no drinking	411/131

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CK, creatine kinase; DBP, diastolic blood pressure; GLU, fasting glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides; TC, total cholesterol; Wc, waist circumference.
[a]Values are expressed as mean (standard deviation).

Multiple Regression Analysis for the Association Between the SLCO1B1 388A>G Polymorphism and Plasma Compound Levels

Multiple linear regression analysis results were shown in Table 3. In a dominant model, the average ALT and AST levels were significantly higher in patients with the homozygous 388AA than in those with the 388AG or 388GG genotypes in both the unadjusted and the adjusted models. After adjustment for important covariates, including age, body mass index (BMI), alcohol consumption, and smoking, the average HDL-C level was significantly higher in patients with the 388AA genotype than in those with the 388AG or 388GG genotypes ($P = .049$). However, no significant relationships between the baseline plasma compounds measuring hepatic function and lipid levels and the SLCO1B1 521T>C polymorphism were found in either the unadjusted or the adjusted models (data not shown).

Odds Ratios of the SLCO1B1 G Allele by Dichotomized ALT and AST Level Stratum

As shown in Table 4, we divided all patients into 2 subgroups based on baseline ALT and AST critical values. The average ALT levels in the normal (ALT < 40 U/L) and abnormal (ALT ≥ 40 U/L) subgroups were 22.6 (8.0) and 59.0 (2.8) U/L, respectively; the average AST levels in the normal (AST < 40 U/L) and abnormal (AST ≥ 40 U/L) subgroups were 26.9 (7.1) and 49.3 (9.3) U/L, respectively. Compared to participants in the normal subgroup of baseline ALT levels, the adjusted odds of carrying the 388G allele (388AG or 388GG

Table 3. Multiple Regression Analysis for the Association Between the SLCO1B1 388A>G Polymorphism and Lipid Levels.[a]

Variable	388A>G	N	Mean (SD)	Unadjusted			Adjusted		
				β	SE	P Value	β	SE	P Value
ALT	GG	283	27.4 (22.3)						
	AG	212	28.0 (16.0)	0.675	1.803	.708	0.355	1.767	.841
	AA	47	34.7 (18.9)	3.685	1.72	**.033**	2.988	1.686	.077
	AG+GG	495	27.6 (19.8)						
	AA	47	34.7 (18.9)	7.081	3.051	**.019**	6.137	2.939	**.037**
AST	GG	283	29.8 (10.8)						
	AG	212	30.6 (10.9)	0.798	0.987	.419	0.786	0.977	.422
	AA	47	35.3 (12.8)	2.778	0.877	**.002**	2.703	0.872	**.002**
	AG+GG	495	30.1 (10.9)						
	AA	47	35.3 (12.8)	5.214	1.686	**.002**	5.253	1.667	**.002**
HDL-C	GG	283	1.7 (0.5)						
	AG	212	1.8 (0.5)	0.042	0.046	.364	0.043	0.043	.316
	AA	47	1.9 (0.5)	0.067	0.038	.081	0.08	0.037	**.030**
	AG+GG	495	1.7 (0.5)						
	AA	47	1.9 (0.5)	0.117	0.077	.13	0.143	0.072	**.049**
LDL-C	GG	283	3.8 (0.7)						
	AG	212	3.9 (0.7)	0.042	0.063	.509	0.044	0.062	.482
	AA	47	3.8 (0.7	−0.013	0.053	.812	−0.013	0.052	.805
	AG+GG	495	3.8 (0.7)						
	AA	47	3.8 (0.7)	−0.043	0.106	.684	−0.052	0.104	.616
TG	GG	283	1.9 (0.9)						
	AG	212	1.9 (0.9)	0.035	0.081	.663	0.011	0.077	.886
	AA	47	1.8 (0.9	−0.034	0.069	.622	−0.077	0.064	.226
	AG+GG	495	1.9 (0.9)						
	AA	47	1.8 (0.9)	−0.083	0.135	.542	−0.142	0.129	.27
TC	GG	283	6.4 (0.6)						
	AG	212	6.5 (0.6)	0.058	0.056	.3	0.055	0.055	.325
	AA	47	6.5 (0.6)	0.058	0.049	.24	0.058	0.049	.239
	AG+GG	495	6.5 (0.6)						
	AA	47	6.5 (0.6)	0.091	0.093	.33	0.092	0.093	.323

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; SD, standard deviation; SE, standard error; SLCO1B1, solute carrier organic anion transporter 1B1.
[a]Adjusted for BMI, age, alcohol consumption and smoking.
Bold values denote significant results.

Table 4. Odds Ratios of the SLCO1B1 388 AG+GG Genotype by Dichotomized ALT and AST Level Stratum.[a]

Category	Baseline	Genotype		Unadjusted			Adjusted		
	Mean (SD)	AA	AG+GG	OR	95%CI	P Value	OR	95%CI	P Value
ALT									
Normal	22.6 (8.0)	33	425						
Abnormal	59.0 (32.8)	14	70	0.4	0.2-0.8	.006	0.4	0.2-0.9	.018
AST									
Normal	26.9 (7.1)	34	420						
Abnormal	49.3 (9.3)	13	75	0.5	0.2-0.9	.029	0.5	0.2-1.0	.038

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; OR, odds ratio; SD, standard deviation; SLCO1B1, solute carrier organic anion transporter 1B1
[a]Normal: ALT or AST < 40 U/L, abnormal: ALT or AST≥40 U/L. Adjusted for BMI, age, alcohol consumption, and smoking.

genotype) among the participants in the abnormal subgroup was 0.4 (95% confidence interval [CI], 0.2-0.9). Similarly, compared to the participants in the normal subgroup of baseline AST levels, the adjusted odds of carrying the 388G allele (388AG or 388GG genotype) among the participants in the abnormal subgroup was 0.5 (95% CI, 0.2-1.0). However, no significant associations between the 521T>C polymorphism and baseline ALT and AST levels were

Table 5. Multiple Regression Models Analyzing the Joint Associations of the 2 Polymorphisms in the SLCO1B1 Gene With ALT and AST Levels.[a]

388A>G	521T>C	N	Mean (SD)	Unadjusted			Adjusted		
				β	SE	P Value	β	SE	P Value
ALT									
GG+AG	CC+TC	116	25.9 (12.0)						
GG+AG	TT	379	28.2 (21.7)	2.291	2.104	.277	2.086	2.068	.314
AA	CC+TC	1	-	-	-	-	-	-	-
AA	TT	46	34.9 (19.0)	3.001	0.832	**<.001**	2.628	0.766	**.001**
AST									
GG+AG	CC+TC	116	29.3 (9.1)						
GG+AG	TT	379	30.3 (11.4)	1.015	1.153	.379	0.864	1.144	.451
AA	CC+TC	1	-	-	-	-	-	-	-
AA	TT	46	35.6 (12.9)	2.043	0.599	**.001**	2.03	0.592	**.001**

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; SD, standard deviation; SE, standard error; SLCO1B1, solute carrier organic anion transporter 1B1; TC, total cholesterol.
[a] Adjusted for BMI, age, alcohol consumption and smoking.
Bold values denote significant results.

Table 6. The SLCO1B1 388A>G and 521T>C Haplotype Distributions in Normal and Abnormal Groups.

Haplotype	ALT			AST		
	Normal	Abnormal	P1	Normal	Abnormal	P2
n	458	84		454	88	
388A/521T	244 (0.27)	58 (0.35)	**0.038**	238 (0.26)	64 (0.36)	**0.007**
388A/521C	4 (0.00)	0 (0.00)		4 (0.00)	0 (0.00)	
388G/521T	570 (0.62)	91 (0.54)	**0.04**	566 (0.62)	95 (0.54)	**0.032**
388G/521C	98 (0.11)	19 (0.11)	0.817	100 (0.11)	17 (0.1)	0.583

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; SLCO1B1, solute carrier organic anion transporter 1B1.
Bold values denote significant results.

found in either the unadjusted or adjusted models (data not shown).

Multiple Regression Models Analyzing the Joint Associations of the 2 Polymorphisms in the SLCO1B1 Gene With ALT and AST Levels

Table 5 showed the effects of gene–gene interaction on ALT and AST levels. We found that, compared with the 388G and 521C allele carriers, the patients with the 388AA and 521TT genotypes had significantly higher concentrations of ALT and AST. After adjusting for important covariates, including BMI, age, alcohol consumption, and smoking, the result remained significant.

SLCO1B1 388A>G and 521T>C Haplotype Distributions in the Normal and Abnormal Groups

Linkage disequilibrium was tested for the SLCO1B1 variants. The 388A>G and 521T>C polymorphisms (D' = 0.882) were

in high linkage disequilibrium. As shown in Table 6, when comparing between the dichotomized ALT and AST groups, the results of haplotype analysis indicated that participants in the abnormal subgroup had a higher frequency of the 388A/521 T and a lower frequency of the 388G/521 T in comparison with those in the normal subgroup.

Discussion

This genetic epidemiological study analyzed the relationship of 2 SNPs in the SLCO1B1 gene with hepatic function, baseline lipid levels, and the lipid-lowering efficacy of simvastatin in Chinese patients with hyperlipidemia. Our results suggested that the average HDL-C levels were significantly higher in patients with the 388AA genotype than in those with the 388AG and 388GG genotypes (P = .049). Compared to the normal ALT subgroup, the adjusted odds of having the 388AG or 388GG genotype among the participants in the abnormal subgroup was 0.4 (95% CI, 0.2-0.9). Compared to the participants in the normal AST subgroup, the adjusted odds of having the 388AG or 388GG genotype among the participants in the abnormal subgroup was 0.5 (95% CI, 0.2-1.0). Moreover, when comparing the normal and abnormal groups for either ALT or AST levels, the results of haplotype analysis indicated that the abnormal subgroup had a higher frequency of the 388A/521 T and a lower frequency of the 388G/521 T in comparison to the normal subgroup. These findings need to be replicated and expanded to a larger population of patients with primary hyperlipidemia in order to fully understand the associations of the SLCO1B1 polymorphisms with hepatic function and the therapeutic efficacy of simvastatin.

The exact mechanism associating ALT and AST with genetic variants in the SLCO1B1 gene is poorly understood. The limited evidence available has mainly focused on the relationships among the SLCO1B1 gene, hyperlipidemia, fatty

liver, TG, free fatty acids (FFA), ALT, and AST. The liver plays an important role by removing FFA from the blood. Triglyceride in the liver can be utilized as a metabolic fuel through oxidation, exported out of the hepatocyte as very low density lipoprotein (VLDL), or stored in the liver.[22] The primary sources of TG synthesis in hepatocytes are FFA, which can be derived from food and de novo lipogenesis in the liver.[22,23] In patients with hyperlipidemia, the greater splanchnic consumption of oxygen does not suffice to balance the increased uptake of FFA. This results in a small portion of FFA being oxidized to ketone bodies, CO_2, and water, while two-thirds of FFA escape from oxidation and are stored in the liver.[24] This FFA imbalance between inputs and outputs may lead to steatosis and possibly contributes to inflammation and subsequent downstream effects.[24] In addition, the common symptoms of fatty liver disease are characterized by elevated ALT and AST levels.[19,20,25] Bile acids are substrates of OATP1B1 and play an essential role in lipid absorption, including fatty acids.[26-29] Xiang et al found that individuals with the 388AA-521TT genotypes had significantly higher bile acid levels than those with the 388GG-521TT genotypes.[30] Thus, in our study, it could be inferred that participants with the 388G/521 T haplotype may have lower levels of serum bile acids, which reduces the absorption of fatty acids by the liver, eventually inhibiting the formation of fatty liver and decreasing ALT and AST levels.

In our study, individuals with the 388G allele and 521TT genotype carriers showed significantly greater TC and LDL-C lowering responses to simvastatin treatment after 4 weeks than those with the 388G allele and 521C allele carriers (Supplemental Table 3). Similar to our result, a previous pharmaogenetic study demonstrated a significant attenuated LDL-C lowering in carriers of the 388G/521C haplotype after pravastatin treatment.[31] Sufficient studies have reported that OATP1B1-mediated hepatic uptake of statins can be key in enhancing their therapeutic efficacy.[32] The polymorphisms of 388A>G have been associated with elevated activity of the OATP1B1 and may lower simvastatin acid concentration in plasma.[33,34] The 521C variant allele, especially in the homozygous status, markedly impairs the catabolism of statins, which leads to higher blood levels and reduces their cholesterol-lowering efficacy after an oral dose.[35] Thus, individuals with the 388G allele and 521TT genotype carriers had significantly higher therapeutic response to a single 20 mg dosage of simvastatin.

On the contrary, no significant associations were found between the 521T>C and 388A>G polymorphisms and the lipid-lowering effects of simvastatin treatment after 8 weeks (data not shown). Sortica et al have reported that the SLCO1B1 haplotype showed no statistically significant mean percentage reduction in lipid and lipoprotein levels after simvastatin treatment for 6 months.[36] In addition, Takane et al have also found that the association between the 2 polymorphisms, and the LDL-C lowering effect of pravastatin treatment was lost when the analysis was repeated after 1 year.[37] This may suggest that the interactions between the 2 polymorphisms could be predictive of a slower rather than a prolonged attenuated response to statin therapy.

Few results were found in previous studies investigating the association between the SLCO1B1 polymorphisms and baseline lipid levels. Consistent with our conclusion, Prado et al have found that patients with the AA genotype had higher baseline HDL-C levels than patients with the AG or GG genotype.[35] However, conflicting results from Shabana et al indicated that participants with the GG genotype had higher baseline HDL-C levels than the participants with AA and AG genotypes, although this difference did not reach statistical significance with a small sample size of just 50 participants.[15]

Despite their excellent lipid-lowering efficacy, statins remain underused in clinical practice, partly because of concerns over adverse drug events affecting the musculoskeletal system.[38,39] Thus, our current study also investigated the association between statin-induced elevations in serum creatine kinase (CK) levels and the SLCO1B1 gene polymorphisms. Supplemental Table 7 showed that there was a significant increase in CK levels after both 4 and 8 weeks of treatment. However, no associations between the SLCO1B1 388A>G and 521T>C genotypes and the presence of CK elevations were found (Supplemental Tables 8 and 9). Similar to our results, Santos et al found no significant effects of the SLCO1B1 388A>G and 521T>C polymorphisms or haplotypes on CK elevations after atorvastatin treatment.[40] Nevertheless, Ferrari et al found a contradictory result when participants with either the 388G or the 521C allele had a higher risk of CK elevation.[41] Brunham et al also found that the SLCO1B1 521T>C polymorphism was significantly associated with myopathy in patients who received simvastatin.[39] The genetic structural difference between Eastern and Western populations might be a major reason for these differences. Of course, the statin-induced adverse effects depend on the drug dosage as well. This association needs to be further addressed in larger cohort studies.

Two limitations of our study should be mentioned. First, as is well known, hyperlipidemia is closely associated with fatty liver, but we omitted the effect of fatty liver in the participants. Second, we did not detect the concentrations of bile acids in our participants, meaning we could not determine whether the associations between the polymorphisms of the SLCO1B1 gene and ALT and AST levels were mediated by bile acids levels.

In conclusion, our study revealed that the SLCO1B1 polymorphisms were related with ALT and AST concentrations and could further influence the efficacy of simvastatin treatment. In clinical practice, identifying genetic variants or haplotypes may be helpful to predict the concentrations of ALT and AST and to guide individualized therapy in patients with hyperlipidemia.

Authors' Note

Authors Xiangyu Wu, MS, Chen Gong, MS, and Justin Weinstock, MS contribute to the work equally. The study protocol was approved

by the ethics committee of the Institute of Biomedicine, Anhui Medical University.

Supplemental Material

Supplemental material for this article is available online.

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