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PHARMACOGENETICS

SLCO1B1 521T > C polymorphism associated with rosuvastatin-induced myotoxicity in Chinese coronary artery disease patients: a nested case–control study

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Abstract
Purpose This nested case–control study aimed to evaluate the association of candidate genetic variants with statin-induced myotoxicity in Chinese patients with coronary artery disease (CAD).
Methods One hundred forty-eight Chinese patients experiencing statin-induced myotoxicity were included in our study, and 255 patients without muscular side effects served as controls. Five SNPs in CYP3A5, SLCO1B1, and APOE were genotyped. The effect of genetic variants on statin-induced myotoxicity was assessed.
Results Patients who carried at least one SLCO1B1 521C allele had a higher risk for myotoxicity (OR = 1.69, 95%CI = 1.07–2.67, $P = 0.024$). Significant association was found between SLCO1B1 521C mutant allele mutation and risk of myotoxicity in individuals that received rosuvastatin (OR = 3.67, 95%CI = 1.42–9.47, $P = 0.007$). However, non-significant association was observed between 521C mutant allele and risk of myotoxicity ($P > 0.5$) in patients that received atorvastatin and simvastatin. The other four single nucleotide polymorphisms (SNPs), namely rs776746, rs2306283, rs7412, and rs429358, showed no significant association with any statin induced myotoxicity ($P > 0.5$).
Conclusions SLCO1B1 (rs4149056, 521T > C) is associated with statin-induced myotoxicity in Chinese patients with coronary artery disease. In addition, SLCO1B1 521C mutant allele increased the risk of rosuvastatin-associated myotoxicity.

Keywords SLCO1B1 · Genetic variant · Statin-induced myotoxicity

Introduction

Statins are commonly prescribed medications that are well tolerated and effective at reducing cardiovascular end points. However, statins frequently lead to muscle-related adverse

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effects, ranging from myalgia, which occurs in 10% [1] of statins users, to life-threatening rhabdomyolysis, which occurs at a rate of ~0.4 per 10,000 patient years [2]. Their adverse muscular effects, which result in poor patient compliance or even drug discontinuation, limit application of statins. The variability of myotoxicity is caused not only by traditional clinical factors, such as female sex and diabetes, but also by genetic variations [3, 4].

A significant barrier to statin therapy is skeletal muscle toxicity associated with elevated systemic drug exposure [5]. Any factor that increases the serum concentration of statins may increase the risk of myopathy [6]. Therefore, factors that affect the pharmacokinetics of statins and consequently increase the concentrations of the drugs in blood or tissue may result in predisposition to myotoxicity.

Genetic variation influences myotoxicity risk, and various candidate genes have been implicated, including genes that encode organic anion-transporting polypeptides such as influx and efflux transporters (e.g., SLCO1B1, ABCB1) and genes that encode the cytochrome P450 (CYP) enzymes involved in statin metabolism (e.g., CYP3A5).

A non-synonymous variant of the drug transporter gene SLCO1B1 (rs4149056, 521T > C), which decreases statin clearance [7–9] and has been associated with statin-related muscle injury, significantly contributes to simvastatin-related muscle injury in Caucasians alone [5, 10, 11] or Caucasians and African-Americans [12]. Some studies reported that the SLCO1B1 521T > C polymorphism was associated with statins (including rosuvastatin without statin-stratification analysis) that induced muscle symptoms in westerns [13, 14]. However, some other studies reported that SLCO1B1 521C allele was not an increased risk of myalgia among users of rosuvastatin in Europe and America [15–17]. Nevertheless, there were no study that reported the effect of SLCO1B1 521T > C polymorphism on statin-induced myotoxicity in Chinese. The CYP3A5 6986A > G mutation might elevate the plasma levels of simvastatin acid, and simvastatin is associated with systemic exposure of simvastatin [18].

All of previous studies were conducted in the white subjects, and the results of it may not be generalized to Chinese populations for two reasons. Firstly, different racial groups significantly differ in pharmacokinetic response to statins. Previous studies have reported increase in levels of parent drugs and their metabolites, such as atorvastatin, simvastatin acid, and rosuvastatin, in Asians compared with whites [19, 20]. Secondly, although the frequencies of the SLCO1B1 521C mutant allele in Chinese populations are similar to those in white populations (roughly 15%), the variant frequency indicates a remarkable difference in CYP3A5 6986A > G among different racial groups (http://www.ncbi.nlm.nih.gov/snp/). The frequency of the CYP3A5 6986G allele is approximately 94.3% among whites, 18% among Africans/-Americans, and 71% among Han Chinese. The CYP3A5 6986G allele increases simvastatin concentration in African-Americans but is not significantly associated with simvastatin concentration in whites [21]. Most of the previous studies investigated the effects of gene polymorphism on statin-induced myotoxicity in whites, but few studied Chinese subjects.

Therefore, the present study aimed to assess the relationship of candidate genetic variations with inter-patient variability of statin-induced myotoxicity (SIM) in Han Chinese patients with coronary artery disease (CAD).

Methods

Study design and patients

Between January 2010 and December 2013, 2200 Han Chinese participants from China, who had CAD undergoing percutaneous transluminal coronary intervention (PCI), were assigned in the prospective study (Chinese Clinical Trial Registry No.: ChiCTROCH-11001198). All of the participants gave written informed consent, and approval was obtained from the Human Research Ethics Committee (HREC) for Guangdong General Hospital. At each follow-up assessment (every 6 months), participants were questioned about new, inexplicable muscle symptoms (pain, soreness, weakness, cramps, spasms, or twitches). By December 2014, muscle-related adverse symptoms (muscle symptoms with muscle pain, soreness, weakness, or twitches) with defined anatomical site had developed in 146 of the 1728 participants who had received statin. An additional two participants were diagnosed with rhabdomyolysis (severe muscle symptoms, with creatine kinase levels that were more than 10 times the upper limit of the normal range, plasma aminotransferase, and myoglobin increasing) by clinician. This study was restricted to the 148 participants in whom myotoxicity (muscle-related adverse symptoms in 146 and rhabdomyolysis in 2) developed while they were taking statin. Among the remaining participants who received statin, 255 controls were selected who were matched with the case subjects with respect to sex and age. Cases and controls were not related in this study.

Genotyping

Genomic DNA was extracted using TIANamp Genomic DNA Kit (Tiangen Biotech Co., Ltd., Beijing, China). The quality and quantity of DNA were assessed using a NanoDrop 2000 Spectrophotometer (Thermo Scientific, USA). All subjects (cases and controls) were genotyped for five SNPs: rs776746 (CYP3A5, 6986A > G), rs2306283 (SLCO1B1, 388A > G), rs4149056 (SLCO1B1, 521T > C), rs7412 (APOE, 526C > T), and rs429358 (APOE, 388T > C) alleles by allelic discrimination with a TaqMan SNP assay using the

ABI Vii7 Real-Time PCR system (Applied Biosystems, USA). The following thermal profile was used for PCR: initial denaturation at 95 °C for 10 min, followed by 40 cycles of denaturation at 95 °C for 15 s, and extension at 60 °C for 1 min.

Statistical analysis

All SNPs were tested for deviations from Hardy–Weinberg disequilibrium by using a chi-square test. Demographic and clinical characteristics were summarized using counts (percentages) for categorical variables and the mean (standard deviation, SD) for continuous variables. The normality of distribution of continuous variables was checked by the Shapiro–Wilk test.

Logistic regression analyses were applied to evaluate the effect of genotypes on the risk of statin-induced myotoxicity with or without adjustment for patient characteristics. Variables with $P < 0.10$ were entered into the multivariate model. Statistical significance was considered at $P < 0.05$ when controlling the FDR at 0.05. Data analyses were performed in SAS9.1 (SAS Institute, Cary, NC).

Results

Subject demographic characteristics

Two thousand two hundred patients finished at least one follow-up assessment for statin-induced myopathy. At the time of the reported event, 56.9% were receiving atorvastatin at the time of recruitment, 26.8% were on rosuvastatin, 14.4% were on simvastatin, and 1.9% received fluvastatin and pravastatin in the CAD cohort (Fig. 1a). Of these patients, 159 (9.2%) were documented to have experienced "myalgia," 54 (3.1%) "muscle weakness," 31(1.8%) "muscle cramp," 34 (2.0%) undefined pain, and 2 (0.1%) rhabdomyolysis (Fig. 1b).

One hundred forty-eight participants were selected to be cases, while 255 others were controls. The baseline characteristics of the patients are summarized in Table 1. Univariate binary logistic regression analyses showed statistically significant differences between the cases and controls in terms of BMI ($P = 0.025$) and HDLc ($P = 0.006$). No significant difference in baseline CK values and use of β-blockers, ACE inhibitors, calcium channel blockers, and proton pump inhibitors was observed between the cases and controls ($P > 0.05$).

Effect of polymorphisms on statin-induced myotoxicity

All SNPs conformed to Hardy–Weinberg equilibrium ($P > 0.05$). The SLCO1B1 521T > C polymorphism was associated with risk of myotoxicity regardless of prescribed statins, even after adjustment for confounding factors, including age, BMI, and HDLC. Patients who carried at least one C allele had a higher risk for myotoxicity [odds ratio (OR) per allele 1.69, 95% confidence interval (CI) 1.07–2.67, $P = 0.024$] (Table 2). In individuals who received rosuvastatin ($n = 90$), significant association was found between SLCO1B1 521C mutant allele and risk of myotoxicity (OR = 3.67, 95%CI = 1.42–9.47, $P = 0.007$). However, in patients receiving atorvastatin or simvastatin, no significant association was detected between SLCO1B1 521T > C and risk of myotoxicity ($P > 0.05$). The four other SNPs (rs776746, rs2306283, rs7412, rs429358) showed no significant association with all SIM or specific statin SIM ($P > 0.5$) (Tables 2, 3, 4, and 5).

Discussion

To our knowledge, the results of the present study are the first to report the association between the SLCO1B1 521T > C polymorphism and statin-induced myotoxicity in Chinese and the first to reveal that the SLCO1B1 521C mutant allele

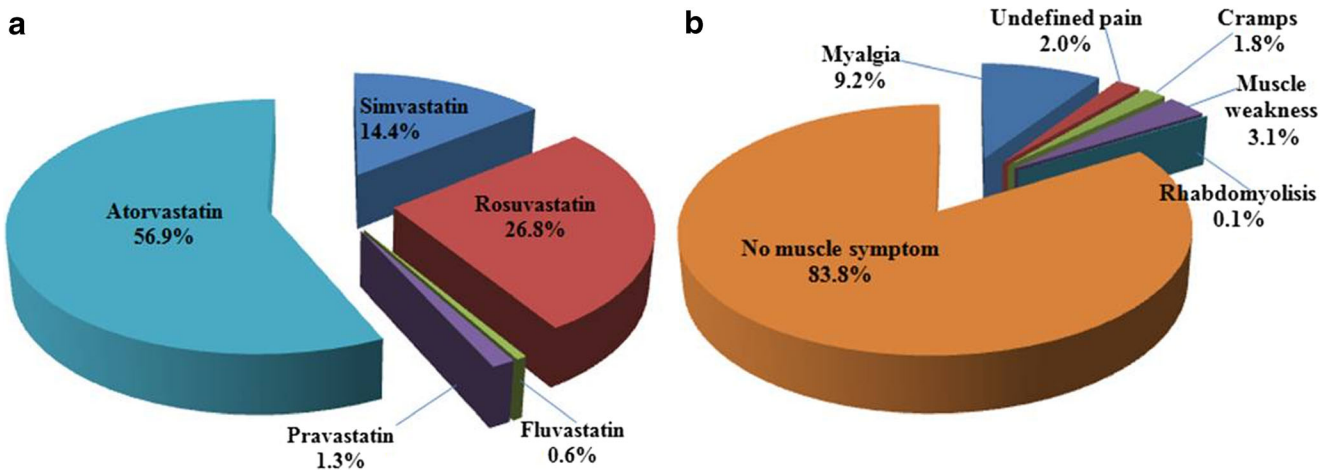

Fig. 1 Distribution of five statins and incidents of muscle symptoms in our cohort

Table 1 Baseline demographic and clinical characteristics of cases and controls

Variable	Control	Case	*P* value	OR (95%CI)
Demographic data				
Total no. of patients	255	148		
Male	211 (82.7)	122 (82.4)	0.936	0.98 (0.57–1.67)
Age	63.25 (10.72)	60.56 (10.81)	0.168	0.98 (0.96–1.00)
BMI	24.05 (3.21)	24.85 (3.03)	0.025	1.08 (1.01–1.16)
Medical history				
ACS	189 (74.1)	105 (70.9)	0.558	0.87 (0.55–1.37)
Arrhythmia	26 (10.2)	10 (6.8)	0.254	0.64 (0.30–1.37)
DM	72 (28.2)	47 (31.8)	0.429	1.19 (0.77–1.86)
Hypertension	154 (60.4)	90 (60.8)	0.869	1.04(0.68–1.57)
HF	27 (10.6)	14 (9.5)	0.734	0.89 (0.45–1.76)
Hyperlipidemia	19 (7.5)	16 (10.8)	0.242	1.52 (0.76–3.05)
Biochemical measurements				
APOA	1.04 (0.34)	1.03 (0.30)	0.899	0.96(0.47–1.95)
CHOL	4.41 (1.26)	4.42 (1.23)	0.929	1.01 (0.85–1.19)
CK, U/L	155.47 (353.83)	162.09 (247.25)	0.855	1.00 (0.99–1.00)
CK-MB, U/L	8.36 (21.66)	9.22 (12.25)	0.691	1.00 (0.99–1.01)
CREA, μmol/L	96.83 (87.85)	83.47 (25.95)	0.020	0.99 (0.98–1.00)
GLUC	6.92 (3.23)	7.08 (3.16)	0.636	1.02 (0.95–1.08)
HDLc, mmol/L	0.91 (0.25)	0.99 (0.29)	0.006	3.02 (1.37–6.66)
LDLc, mmol/L	2.64 (0.97)	2.66 (1.01)	0.916	1.01 (0.82–1.25)
LPa	332.72 (335.22)	288.41 (278.62)	0.238	1.00 (0.99–1.00)
Triglycerides, mmol/L	1.54 (1.00)	1.61 (1.67)	0.583	1.04 (0.89–1.22)
Medication				
β-blockers	237 (92.9)	139 (93.9)	0.527	1.32 (0.56–3.11)
ACE inhibitors	183 (71.8)	108 (73.0)	0.713	1.09 (0.69–1.72)
Calcium channel blockers	84 (32.9)	45 (30.4)	0.630	0.90 (0.58–1.39)
Proton pump inhibitors	128 (50.2)	78 (52.7)	0.580	1.12 (0.75–1.68)

Demographic and clinical characteristics were summarized using counts (percentages) for categorical variables and the mean (standard deviation, SD) for continuous variables

BMI Body Mass Index, *ACS* acute coronary syndrome, *DM* diabetes mellitus, *HF* heart failure, *APOA* apolipoprotein A, *CHOL* cholesterol, *CK* creatine kinase, *CK-MB* creatine kinase-MB, *CREA* creatinine, *GLUC* glucose, *HDLc* high-density lipoprotein cholesterol, *LDLc* low-density lipoprotein cholesterol, *LPa* lysophosphatidic acid, *ACE* angiotensin-converting enzyme

Table 2 Logistic regression analysis of five genetic variants on statin-induced myopathy of all statins

SNPs	Genotype	Control	Case	OR(95%CI)	*P* value
rs776746	AA	26 (10.2)	8 (5.4)	1.12 (0.82–1.54)	0.484
(CYP3A5, 6986A > G)	GA	96 (37.6)	63 (42.6)		
	GG	133 (52.2)	77 (52.0)		
rs2306283	AA	16 (6.3)	10 (6.8)	0.74 (0.53–1.04)	0.082
(SLCO1B1, 388A > G)	GA	110 (43.1)	46 (31.1)		
	GG	129 (50.6)	92 (62.2)		
rs4149056	TT	200 (78.4)	101 (68.2)	1.69 (1.07–2.67)	0.024
(SLCO1B1, 521T > C)	TC or CC	55 (21.6)	47 (31.8)		
rs7412	CC	212 (83.5)	129 (87.2)	0.74 (0.41–1.33)	0.320
(APOE, 526C > T)	CC or TC	42 (16.5)	19 (12.8)		
rs429358	TT	45 (17.6)	24 (16.2)	1.11 (0.64–1.91)	0.713
(APOE, 388T > C)	TC or CC	210 (82.4)	124 (83.8)		

Table 3 Logistic regression analysis of five genetic variants on statin-induced myopathy of atorvastatin

SNPs	Genotype	Control	Case	OR(95%CI)	*P* value
rs776746 (CYP3A5, 6986A > G)	AA	12 (8.6)	3 (3.1)	1.31 (0.85–2.02)	0.216
	GA	58 (41.7)	42 (42.9)		
	GG	69 (49.6)	53 (54.1)		
rs2306283 (SLCO1B1, 388A > G)	GG	73 (52.5)	64 (65.3)	0.75 (0.50–1.12)	0.157
	GA	54 (38.8)	25 (25.5)		
	AA	12 (8.6)	9 (9.2)		
rs4149056 (SLCO1B1, 521T > C)	TT	109 (78.4)	71 (72.4)	1.38 (0.76–2.52)	0.291
	TC or CC	30 (21.6)	27 (27.6)		
rs7412 (APOE, 526C > T)	CC	110 (79.7)	85 (86.7)	0.77 (0.37–1.61)	0.163
	CC or TC	28 (20.3)	13 (13.3)		
rs429358 (APOE, 388T > C)	TT	28 (20.1)	16 (16.3)	1.29 (0.66–2.55)	0.457
	TC or CC	111 (79.9)	82 (83.7)		

increases the risk of rosuvastatin-associated myotoxicity by using case–control study in Chinese population. SLCO1B1 521T > C polymorphism was identified as being associated with statin-induced myotoxicity in many previous studies in whites. However, no study reports the effect of SLCO1B1 521T > C polymorphism on statin-induced myotoxicity in Chinese population.

Our study focused on the effect of genetic factors on statin-induced myotoxicity and found that SLCO1B1 (rs4149056, 521T > C) is associated with statin-induced myotoxicity in Chinese patients with coronary artery disease. In addition, SLCO1B1 521C mutant allele increased the risk of rosuvastatin-associated myotoxicity.

In the present study, we found that the SLCO1B1 521T > C polymorphism was significantly associated with statin-related myotoxicity. The variant C allele increased the risk of developing statin-related myotoxicity. Nonetheless, when stratified by statin type, the association was significant in patients receiving rosuvastatin, but not in patients receiving other statins (atorvastatin and simvastatin), suggesting that the association depends on statin type.

Previous study suggests that the SLCO1B1 521T > C polymorphism is associated with an increased risk of statin-related myopathy, especially in individuals receiving simvastatin [5, 22]. SLCO1B1 521C variant was not increased risk of myalgia among users of rosuvastatin in Europe and Americ [15–17], while there were studies reported that the 521T > C polymorphism was associated with statins (including rosuvastatin without statin-stratification analysis) that induced muscle symptoms in westerns [13, 14]. The results of our study do not appear to be consistent with previous studies. The results of previous studies on white may not be generalized to Chinese populations. Ethnic differences likely result indifferent pharmacokinetic responses to statins and statin-induced myotoxicity. Plasma exposure of rosuvastatin and its metabolites is known to be significantly higher in Asian populations compared with white subjects in the same environment [23, 24]. In addition, SLCO1B1 521T > C polymorphism was associated with increased exposure to rosuvastatin [7, 19, 20, 25]. Thus, the exposure of rosuvastatin of Chinese may be more susceptible to SLCO1B1 521T > C variant. The 521T > C polymorphism decreasing function in OATP1B1

Table 4 Logistic regression analysis of five genetic variants on statin-induced myopathy of simvastatin

SNPs	Genotype	Control	Case	OR(95%CI)	*P* value
rs776746 (CYP3A5, 6986A > G)	AA	5 (10.6)	2 (10.5)	0.68 (0.32–1.46)	0.321
	GA	11 (23.4)	8 (42.1)		
	GG	31 (66.0)	9 (47.4)		
rs2306283 (SLCO1B1, 388A > G)	GG	24 (51.1)	9 (47.4)	1.15 (0.46–2.85)	0.767
	GA	21 (44.7)	9 (47.4)		
	AA	2 (4.3)	1 (5.3)		
rs4149056 (SLCO1B1, 521T > C)	TT	38 (80.8)	15 (79.0)	1.13 (0.30–4.22)	0.860
	TC or CC	9 (19.2)	4 (21.0)		
rs7412 (APOE, 526C > T)	CC	40 (85.1)	17 (89.5)	0.67 (0.13–3.57)	0.642
	CC or TC	7 (14.9)	2 (10.5)		
rs429358 (APOE, 388T > C)	TT	7 (14.9)	2 (10.5)	1.49 (0.28–7.91)	0.642
	TC or CC	40 (85.1)	17 (89.5)		

Table 5 Logistic regression analysis of five genetic variants on statin-induced myopathy of rosuvastatin

SNPs	Genotype	Control	Case	OR(95%CI)	*P* value
rs776746	AA	8 (12.7)	2 (7.4)	1.15 (0.59–2.26)	0.685
(CYP3A5, 6986A > G)	GA	23 (36.5)	11 (40.7)		
	GG	32 (50.8)	14 (51.9)		
rs2306283	GG	29 (46.0)	18 (66.7)	0.42 (0.17–1.04)	0.060
(SLCO1B1, 388A > G)	GA	32 (50.8)	9 (33.3)		
	AA	2 (3.2)			
rs4149056	TT	47 (74.6)	12 (44.4)	3.67 (1.42–9.47)	0.007
(SLCO1B1, 521T > C)	TC or CC	16 (25.4)	15 (55.6)		
rs7412	CC	56 (88.9)	24 (88.9)	1.00 (0.24–4.20)	1.000
(APOE, 526C > T)	CC or TC	7 (11.1)	3 (11.1)		
rs429358	TT	10 (15.9)	6 (22.2)	0.66 (0.21–2.05)	0.472
(APOE, 388T > C)	TC or CC	53 (84.1)	21 (77.8)		

that is responsible for statin uptake has been found to explain the majority of statin-associated muscle symptoms. Our results revealed that the SLCO1B1 521C mutant allele increases the risk of rosuvastatin-associated myotoxicity in Chinese population and suggests that SLCO1B1 521C carrier is more susceptible to muscle adverse reactions when patient using rosuvastatin in Chinese. These results must call our attention for muscle myotoxicity when the patient who carries 521C mutant allele is using rosuvastation, especially in Chinese.

In our present study, no significant relationship was found between the SLCO1B1 388A > G polymorphism and statin-induced myotoxicity. Previous studies showed that patients carrying SLCO1B1 388 A > G SNPs were associated with decreased risk of statin-induced intolerance [13, 26]. The G allele in the 388A > G polymorphism increases the efficiency of the OATP1B1 transporter and results in the decreased bioavailability of atorvastatin [25, 27], while some other studies reported that SLCO1B1 388 A > G would not influence exposure to rosuvastatin, atorvastatin, simvastatin, or simvastatin acid [19]. The recent meta-analysis showed that there are no significant association between 388 A > G polymorphism and statin-induced adverse reactions [28].

Recently, Ajay Gupta et al. [29] found that there were no significant differences between atorvastatin users and non-users in the rates of myotoxicity in blinded randomized study, while in the non-blinded non-randomized study myotoxicity was at a significantly higher rate in participants taking atorvastatins than in those who were not. Their research shows that atorvastatin-induced myotoxicity was interfered by nocebo effect. Many high-quality articles revealed that the musculoskeletal problem is the most common intolerance symptoms of using statin [2, 30]. Statin-induced myotoxicity includes asymptomatic elevations of creatine kinase (CK), muscle symptoms with and without raised CK levels. Thus, not all people who have myotoxicity have circulating biomarkers and statin-induced myotoxicity mainly reported by patients. To the current knowledge, routine monitoring of CK measurements is not recommended for statin therapy patients [31]. Our study focused on the effect of genetic factors on statin-induced myotoxicity and found that SLCO1B1 (rs4149056, 521T > C) is associated with rosuvastatin-induced myotoxicity in Chinese patients with coronary artery disease. According to their results, the muscle adverse symptoms reported by patients would be excessively estimated in our study. However, our study focused on the effect of genetic factors on statin-induced myotoxicity. Actually, randomized double-blind placebo-controlled trial could provide powerful and valuable evidences to clinical practice. We hope that our results could be verified by more studies in the future.

In conclusion, this nested case–control study showed that rs4149056 (SLCO1B1, 521T > C) was associated with rosuvastatin-induced myotoxicity in Chinese patient, and that 521C mutant allele increased the risk of rosuvastatin-associated myotoxicity.

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Authors' contributions In this project, SLZ and WHL contributed for the design and management; JEL, XYL, SC, BR, and SLZ contributed to performing experiment and data analysis; JEL, LYC, and SC contributed to the patient recruitment; JEL and YZ contributed to writing of the manuscript; MY and BR contributed to revised the manuscript. All authors approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest None.

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