Pharmacogenomics and Personalized Medicine Dovepress

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Associations Between the Polymorphisms in the Coding Sequence of SLCO1B1 and Blood Lipid Levels Before and After Treatment by Atorvastatin in the Chinese Han Adults with Dyslipidemia

Chao Chen[1,*], Yan Tian[2,*], Fengshun Jia[1,*], Mingkun Feng[1], Guoqiang Zhang[2], Qian Li[2], Yanwei Zhang[3], Ningling Sun[4], Songnian Hu[5,6], Zheng Ji[1]

[1]Department of Cardiology, Tangshan Gongren Hospital, Tangshan, Hebei, People's Republic of China; [2]Beijing HuaGengYuan Pharmacogenomics Research Institute Co. Ltd., Beijing, People's Republic of China; [3]Beijing E-Seq Medical Technology Co. Ltd., Beijing, People's Republic of China; [4]Institute of Hypertension, People's Hospital, Peking University, Beijing, People's Republic of China; [5]State Key Laboratory of Microbial Resources, Institute of Microbiology, Chinese Academy of Sciences, Beijing, People's Republic of China; [6]University of Chinese Academy of Sciences, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zheng Ji; Songnian Hu, Email jizheng999@163.com; husn@im.ac.cn

Purpose: Atorvastatin is commonly used to treat dyslipidemia; however, individual responses vary considerably. This study endeavors to evaluate the relationship between polymorphisms in the coding sequence (CDS) of SLCO1B1 gene and blood lipid levels before and after atorvastatin treatment among the Chinese Han adults with dyslipidemia.

Patients and Methods: A total of 165 Chinese Han adults undergoing atorvastatin therapy were enrolled in this study and followed up quarterly. The complete CDS of the SLCO1B1 gene was sequenced to detect polymorphisms. Statistical analysis was utilized to assess the impacts of sex, age, body mass index (BMI), and polymorphisms on blood lipid levels before and after atorvastatin treatment.

Results: Fourteen polymorphisms were identified in the SLCO1B1 CDS. Among them, four polymorphisms had mutant alleles present in over 20 patients. No polymorphism was found to correlate with blood lipid levels before treatment; in contrast, age, sex, and BMI did show correlations ($P<0.05$). Notably, females had higher baseline blood lipid levels than males, indicating that sex had a more significant impact on baseline levels than age and BMI. The polymorphism rs2306283 was significantly correlated with the efficacy of atorvastatin ($P<0.05$), whereas age, sex, and BMI were not. Carriers of the rs2306283 AA allele experienced a substantially greater reduction in total cholesterol (TC) and triglyceride (TG) levels after atorvastatin treatment. The other polymorphisms did not demonstrate any significant impact on atorvastatin's efficacy.

Conclusion: This study delved into the intricate genetic structure of polymorphisms in SLCO1B1 CDS and their roles in lipid metabolism and atorvastatin's efficacy among Chinese Han adults with dyslipidemia. The findings underscore the crucial role of the rs2306283 polymorphism in the response to atorvastatin's efficacy, highlighting the significance of pharmacogenomics in personalized medicine. It is thus advisable to consider genetic testing for SLCO1B1 variants to optimize atorvastatin therapy.

Keywords: pharmacogenomics, SLCO1B1 polymorphisms, atorvastatin, dyslipidemia, Chinese Han

Introduction

Dyslipidemia, characterized by abnormal lipid levels, results from complex interactions between personal characteristics and genetics.[1–7] It is a significant risk factor for atherosclerotic cardiovascular disease, which is the leading cause of death in China, accounting for more than 40% of deaths.[8] Atorvastatin, a commonly prescribed statin, is used to manage dyslipidemia and reduce cardiovascular risk.[9–11] However, patient responses to atorvastatin vary widely, and this variation is partly due to genetic polymorphisms that affect drug metabolism and transport.[12]

Received: 17 August 2024
Accepted: 11 December 2024
Published: 20 December 2024

The SLCO1B1 gene plays a crucial role in this context as it encodes the solute carrier organic anion transporter necessary for the hepatic uptake of atorvastatin.[13] Polymorphisms in SLCO1B1 can significantly impact atorvastatin pharmacokinetics and pharmacodynamics.[14–25] Previous studies on the relationship between SLCO1B1 polymorphisms and atorvastatin response have yielded diverse results across different populations. For instance, A study on Brazil population with hypercholesterolemia reported that subjects carrying SLCO1B1 rs2306283 GG genotype exhibited significantly high LDL-C reduction compared to rs2306283 AA and rs2306283 AG carriers.[26] Research on a cohort of Egyptian patients with hypercholesterolemia showed no statistically significant differences in the percentage change in TC, LDL-C, TG, and HDL-C when compared among the different rs2306283 genotypes.[27] Studies on the Chinese population in Henan Province[28] and the Pomerania population[29] showed that SLCO1B1 rs4149056 and rs2306283 polymorphisms were not associated with the lipid-lowering effects of atorvastatin. Research on the Greek population also reported no impact of SLCO1B1 rs4149056, rs2306283, and rs11045818 (c.411G>A) polymorphisms on atorvastatin therapy response.[30] A study on Chilean hypercholesterolemic subjects showed that rs4149056 and rs2306283 were not associated with reductions in TG, TC, or LDL-C levels, but rs2306283 was associated with higher HDL-C concentrations in response to atorvastatin medication.[31] Research on an Indian population reported that patients with rs2306283 AA genotype showed significantly greater LDL-C reduction in response to atorvastatin therapy.[32] A study on Macedonian subjects found no statistically significant associations of rs4149056, rs2306283, rs2291075 (c.597C>T), rs4149057 (c.571T>C), rs57040246 (c.1086C>T), and rs59502379 (c.1463G>C) polymorphisms with atorvastatin response. However, carriers of the rs4149056 CC genotype exhibited a lower decrease in plasma levels of TG, TC, and LDL-C, and a lower increase in HDL-C compared to carriers of the rs4149056 TT variant.[33] A meta-analysis reported that people with hyperlipidemia carrying the rs4149056 (c.521T>C) C allele had increased lipid-lowering efficacy after atorvastatin treatment compared to those with the T allele, but found no association between rs2306283 (c.388A>G) polymorphism and efficacy.[34] Another study reported that TC and LDL-C levels decreased less after atorvastatin medication in patients with rs4149056 CC genotype.[35]

Despite these previous investigations, they provided mixed findings regarding the associations between specific SLCO1B1 polymorphisms and atorvastatin efficacy and most studies have primarily focused on a few SLCO1B1 polymorphisms, leaving the roles of other polymorphisms in the CDS of SLCO1B1 and their relationships with blood lipid levels before and after atorvastatin treatment unclear. In the context of personalized medicine, understanding the genetic basis of drug response is essential for tailoring treatments to individual patients, thereby improving therapeutic outcomes.

For the Chinese Han population, specifically investigating the associations between polymorphisms in the CDS of the SLCO1B1 gene, along with age, sex, and BMI, with the efficacy of atorvastatin therapy in those with dyslipidemia becomes necessary. This study aims to fill this gap by exploring these associations. By doing so, it is expected to provide insights that could pave the way for more personalized approaches to managing dyslipidemia within this specific population.

Moreover, through SLCO1B1 genotyping, it is possible to complement the monitoring of atorvastatin therapy with other prognostic parameters. By identifying specific genetic polymorphisms within the SLCO1B1 gene, we can predict potential differences in drug metabolism and transport. This, in turn, allows for a more comprehensive understanding of how a patient might respond to atorvastatin therapy. By correlating these genetic findings with other prognostic parameters such as age, sex, and BMI, a more personalized and targeted monitoring of atorvastatin therapy can be achieved, potentially leading to better therapeutic outcomes.

To achieve these goals, this study conducted a comprehensive investigation. Firstly, data collection involved gathering relevant data on Chinese Han adults with dyslipidemia, including their genetic information regarding SLCO1B1 polymorphisms, as well as details about their age, sex, and BMI. Secondly, analysis were carried out to determine if there were any significant associations between the SLCO1B1 polymorphisms, along with age, sex, and BMI, and the efficacy of atorvastatin therapy. Statistical analyses were used to compare lipid level changes before and after treatment among different groups based on their genetic and other characteristics. Thirdly, the results of the analysis were interpreted to understand how the various factors interact and impact the efficacy of atorvastatin therapy. Based on these findings, conclusions were drawn about the importance of SLCO1B1 polymorphisms and other factors in predicting the response to atorvastatin within the Chinese Han population with dyslipidemia. Finally, the findings were applied to inform more personalized approaches to managing dyslipidemia in the Chinese Han population, providing guidance to healthcare providers on how to adjust treatment plans based on a patient's genetic profile and other relevant factors.

Materials and Methods

Study Population

This study enrolled 165 Chinese Han adults with dyslipidemia, admitted to Tangshan Gongren Hospital between September 2021 and September 2023. All participants received a daily 20 mg dose of atorvastatin and were followed up quarterly. Written informed consent confirming voluntary participation was obtained from each patient. This study, along with the previous study,[36] is part of a multi-center research project approved by the Ethics Committee of Xiangya Hospital, Central South University (ethics number K22144).

Data Collection

Baseline demographic characteristics, including sex and age, were collected through interviews using a standardized questionnaire administered by trained researchers. Height and weight measurements were obtained at the nurse's station by experienced nurses, and body mass index (BMI) was calculated by dividing weight (in kilograms) by the square of height (in meters). Blood samples were drawn from the antecubital vein of participants in a fasting state by skilled nurses to measure triglyceride (TG), total cholesterol (TC), LDL-C, and high-density lipoprotein cholesterol (HDL-C) levels. All clinical investigations were conducted in accordance with the principles of the Declaration of Helsinki. At each follow-up, TG, TC, LDL-C, and HDL-C levels were reassessed.

DNA Sequencing

The method for DNA sequencing followed the protocol described in the previous study.[36] From each enrolled patient, 2 mL of peripheral venous blood was collected for genomic DNA extraction using the Magnetic Blood Genomic DNA Kit (DP329, Tiangen Biotech Co., Ltd., Beijing, China). The DNA concentration was quantified with the Qubit® dsDNA HS Assay Kit (Yeasen Biotechnology Co., Ltd, Shanghai, China) according to the manufacturer's protocol. The DNBSEQ-T7 sequencer (MGI Tech Co., Ltd, Shenzhen, China) was used for high-throughput sequencing of the DNA captured from a pharmacogenomics panel with reads of 150 bp in length.

SNP Calling and Genotyping

High-quality sequencing reads were derived by filtering out adapters, unknown bases, and low-quality bases with Trimmomatic (v0.36).[37] The high-quality reads were aligned to the human reference genome hg19 using the Burrows-Wheeler Aligner (BWA, v0.7.15) with the default parameters.[38] The Genome Analysis Toolkit (GATK, v3.8) was used for indel realignment, quality score recalibration, polymorphism calling, and genotyping (using Haplotype Caller).[39]

Statistical Analysis

The RNOmni software package (version 1.0.1.2)[40] was used to normalize the blood lipid levels of TG, TC, HDL-C, and LDL-C at baseline, as well as the differences in these lipids before and after treatment, using a rank-based inverse normal transformation method. A Bayesian linear mixed model regression was conducted using the BLME software package (version 1.0–5)[41] to analyze the impacts of factors such as age, sex, BMI, and polymorphisms on the normalized blood lipid levels at baseline, as well as the differences before and after treatment. A *P*-value threshold of less than 0.05 indicated statistical significance. The EMMEANS software package (version 1.10.1)[42] was used to adjust for confounding factors and evaluate the coefficient of the target factor on the normalized blood lipid levels.

Results

Baseline Characteristics of the Study Cohort

The baseline demographics of the 165 study participants were outlined in Table 1. The cohort predominantly comprised males (approximately 73%). The mean age of participants was 61 years, with a standard deviation of 12 years. The average BMI was 25.83 kg/m², with a standard deviation of 3.71 kg/m².

Table 1 Characteristics of the Patients in This Study

Characteristics	All Patients (n = 165)
Gender	
Male	120 (72.73)
Female	45 (27.27)
Age, years	61±12
BMI, kg/m²	25.83±3.71

Notes: Continuous data were given as mean ± standard deviation. Categorical variables were presented as numbers (percentages).

Identified SLCO1B1 Polymorphisms Within CDS

Fourteen distinct SLCO1B1 polymorphisms within the CDS were identified across the study population, as detailed in Figure 1 and Table 2. The mutant alleles of four polymorphisms (rs2306283, rs2291075, rs4149057, and rs4149056) were identified in more than 20 patients, while the mutant alleles of other ten polymorphisms (rs71581941, rs2306282, rs374859808, rs200467000, rs61760243, rs11045859, rs770420484, rs1376723872, rs140790673, and chr12: g.21370114A>G) were identified in fewer than 3 patients. The rs2306283 mutant allele was common, occurring in heterozygosity in 38.18% and in homozygosity in 45.45% of patients. The rs2306283 is a missense variant where asparagine changes to aspartate and it is located on exon 5. The mutant alleles of rs2291075 and rs4149057 were found in heterozygous form in 44.85% and 36.97% of patients, and in homozygous form in 15.15% and 7.88% of patients, respectively. Both rs2291075 and rs4149057 are synonymous variants located on exon 6. The rs4149056 mutant allele was found in heterozygous form in 15.76% of patients and in homozygous form in 0.61% of patients. The rs4149056 is a missense variant where valine changes to alanine and it is located on exon 6. The mutant alleles of rs71581941, rs2306282, rs374859808, rs200467000, rs61760243, rs11045859, rs770420484, rs1376723872, rs140790673, and chr12: g.21370114A>G were rare, being detected in only one or two individuals.

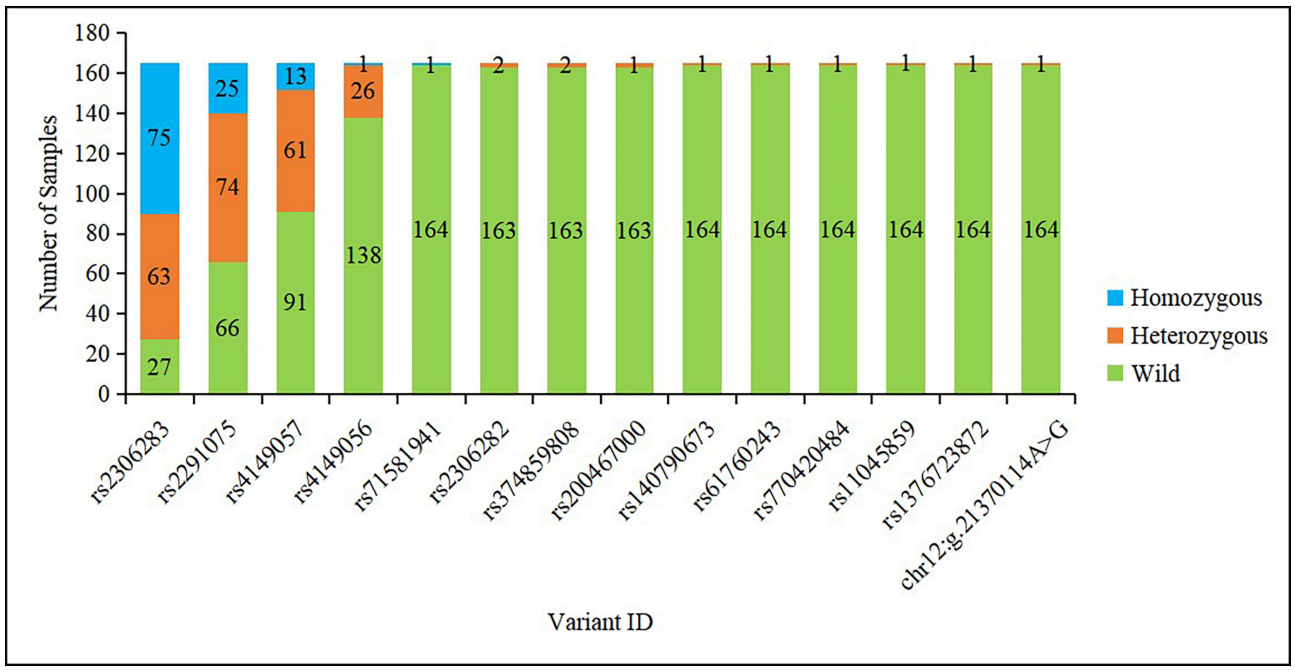

Figure 1 Distribution and frequency of SLCO1B1 polymorphisms identified within CDS in this study.

Table 2 Annotation of SLCO1B1 Polymorphisms Identified Within CDS in This Study

Variant ID	gDNA_coordinate	cDNA_coordinate	protein_coordinate	Variation_type	Exon_No.
rs2306283	chr12:g.21329738A>G	c.388A>G	p.Asn130Asp	Missense	5
rs2291075	chr12:g.21331625C>T	c.597C>T	p.Phe199=	Synonymous	6
rs4149057	chr12:g.21331599T>C	c.571T>C	p.Leu191=	Synonymous	6
rs4149056	chr12:g.21331549T>C	c.521T>C	p.Val174Ala	Missense	6
rs71581941	chr12:g.21375289C>T	c.1738C>T	p.Arg580Ter	Nonsense	13
rs2306282	chr12:g.21329802A>G	c.452A>G	p.Asn151Ser	Missense	5
rs374859808	chr12:g.21358877A>G	c.1407A>G	p.Gln469=	Synonymous	11
rs200467000	chr12:g.21392087C>A	c.2040C>A	p.Val680=	Synonymous	15
rs140790673	chr12:g.21392092C>T	c.2045C>T	p.Ser682Phe	Missense	15
rs61760243	chr12:g.21353505C>T	c.1034C>T	p.Thr345Met	Missense	9
rs770420484	chr12:g.21370226G>A	c.1671G>A	p.Met557Ile	Missense	12
rs11045859	chr12:g.21355537G>T	c.1248G>T	p.Val416=	Synonymous	10
rs1376723872	chr12:g.21391947G>A	c.1900G>A	p.Val634Ile	Missense	15
chr12:g.21370114A>G	chr12:g.21370114A>G	c.1559A>G	p.His520Arg	Missense	12

Comparison of Allele Frequencies of Identified Polymorphisms to Those in Public Databases

The allele frequencies (AFs) of the 14 identified polymorphisms were compared with those reported in public genomic databases, as detailed in Figure 2. The AFs of rs11045859, rs1376723872, and chr12.21370114A>G were not reported in the public databases (August 2015 release of the 1000 Genomes Project (1000g2015aug), Exome Aggregation Consortium (ExAC), and the Genome Aggregation Database (gnomAD)). The AFs of the other 11 identified polymorphisms closely matched those observed in East Asian populations in the public databases. The AFs of four polymorphisms (rs2306283, rs2291075, rs4149057, and rs4149056) were greater than 0.01. The AF for rs2306283 was 0.6455 in this study, slightly lower than the highest recorded AF of 0.7619 in the East Asian population and 0.8177 in the African population in the public databases, but significantly higher than the AFs observed in South Asian (ranging from 0.4795 to 0.5470), American (ranging from 0.4303 to 0.4726), and European (ranging from 0.4026 to 0.4593) populations. The AFs of rs2306283 were greater than 0.4 in all populations studied, indicating that rs2306283 is a common polymorphism across different ethnicities. The AF of rs2291075 was observed to be 0.3758 in this study. In the public databases, the AFs of rs2291075 were reported ranging from 0.5109 to 0.5262 in the East Asian population, from 0.1976 to 0.2014 in

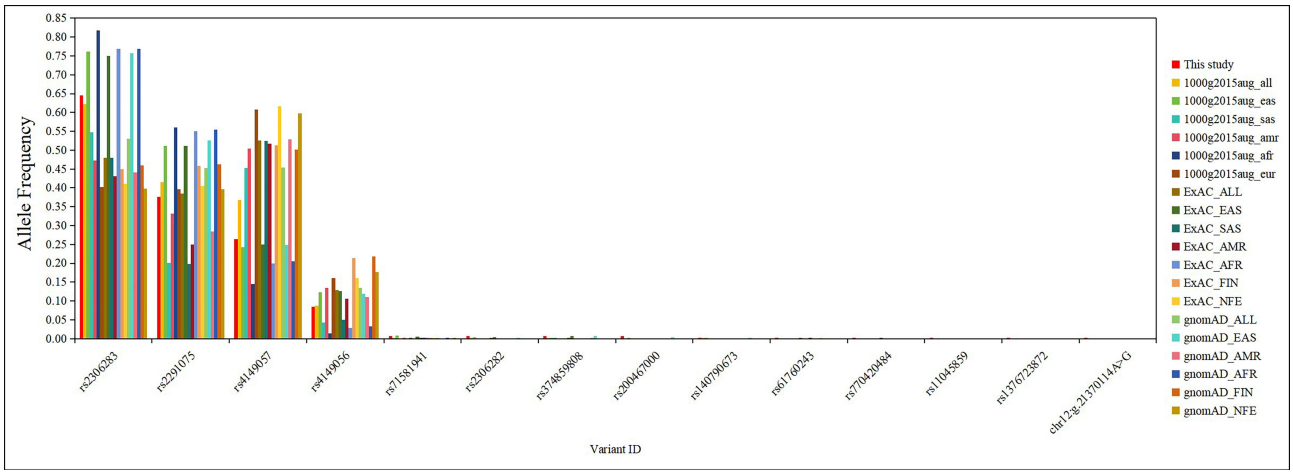

Figure 2 The AFs of the identified polymorphisms in this study and public databases.
Notes: 1000g2015aug: August 2015 release of the 1000 Genomes Project, ExAC: Exome Aggregation Consortium; gnomAD: Genome Aggregation Database. All, EAS, SAS, AMR, AFR, EUR, FIN, and NFE represent ALL, East Asian, South Asian, American, African, European, Finnish, and Non-Finnish European populations, respectively.

the South Asian population, from 0.2493 to 0.3314 in the American population, from 0.5504 to 0.5598 in the African population, and from 0.3966 to 0.463 in the European population. The AFs of rs2291075 ranged from 0.2 to 0.6 in different populations, indicating significant variation and diversity of the rs2291075 polymorphism across different populations. The AF for rs4149057 was 0.2636 in this study, compared to 0.2431 to 0.2497 in the East Asian population, 0.4530 to 0.5240 in the South Asian population, 0.5043 to 0.5287 in the American population, 0.1445 to 0.2051 in the African population, and 0.5014 to 0.6168 in the European population. The AFs of rs4149057 ranged from 0.14 to 0.62 in different populations, indicating high ethnic diversity. The AF of rs4149056 was 0.0848 in this study, compared to 0.1196 to 0.1263 in the East Asian population, 0.0429 to 0.0503 in the South Asian population, 0.1065 to 0.134 in the American population, 0.0136 to 0.0327 in the African population, and 0.1603 to 0.2187 in the European population. The AFs of rs4149056, ranging from 0.01 to 0.22 across different populations, indicate significant ethnic diversity for this polymorphism. The polymorphisms rs71581941, rs2306282, rs374859808, rs200467000, rs140790673, rs61760243, and rs770420484 exhibited low AFs in all populations, each being less than 0.01. This suggests that these are rare polymorphisms.

Impacts of Factors on Blood Lipid Levels at Enrollment

The impact of age, sex, BMI and identified high frequency polymorphisms (rs2306283, rs2291075, rs4149057, and rs4149056) on normalized blood lipid levels at enrollment was assessed, with findings summarized in Table 3. The age, sex, and BMI were correlated with the blood lipid levels before treatment ($P<0.05$), while no polymorphism was correlated with the blood lipid levels before atorvastatin therapy. Although the age and BMI were significantly with normalized blood lipid levels before atorvastatin therapy, their impacts was smaller comparing to sex (Figure 3). Female had higher blood lipid levels at enrollment than male.

Impacts of Factors on Blood Lipid Levels After Atorvastatin Therapy

The relationship between various factors and changes in blood lipid levels after atorvastatin therapy was evaluated, as shown in Table 4. Age, sex, and BMI were not correlated with the therapeutic efficacy of atorvastatin, while the rs2306283 polymorphism of SLCO1B1 was correlated with the therapeutic efficacy of atorvastatin by affecting TC and TG levels ($P<0.05$). The effects of different genotypes of rs2306283 on the normalized differences in TC and TG levels before and after treatment were assessed after adjusting for other factors, with results shown in Figure 4. As shown in Figure 4, the therapeutic effect was worse in individuals with the rs2306283 GG genotype compared to those with the AA genotype in terms of TC and TG reduction.

Table 3 The Correlation Between Factors and Normalized Blood Lipid Levels at Enrollment Assessed by Multivariate Regression Analysis

Factors	*P*			
	nLDL-C	**nHDL-C**	**nTC**	**nTG**
Age	**0.0090**	0.2519	**0.0190**	**0.0066**
Sex	**0.0018**	**0.0000**	**0.0040**	0.4742
BMI	0.9062	**0.0413**	0.6755	**0.0121**
rs2306283	0.7159	0.0888	0.7096	0.5166
rs4149056	0.6906	0.3532	0.3012	0.2443
rs4149057	0.3286	0.3308	0.5861	0.3336
rs2291075	0.9836	0.4918	0.5192	0.9924

Notes: The levels of LDL-C, HDL-C, TC, and TG were normalized using the rank-based inverse normal transformation method (RNOmni software), denoted by the prefix "n" before their respective names. Multivariate regression analysis was conducted using the Bayesian linear mixed model (BLME software). *P* values in bold indicate statistical significance ($P < 0.05$).

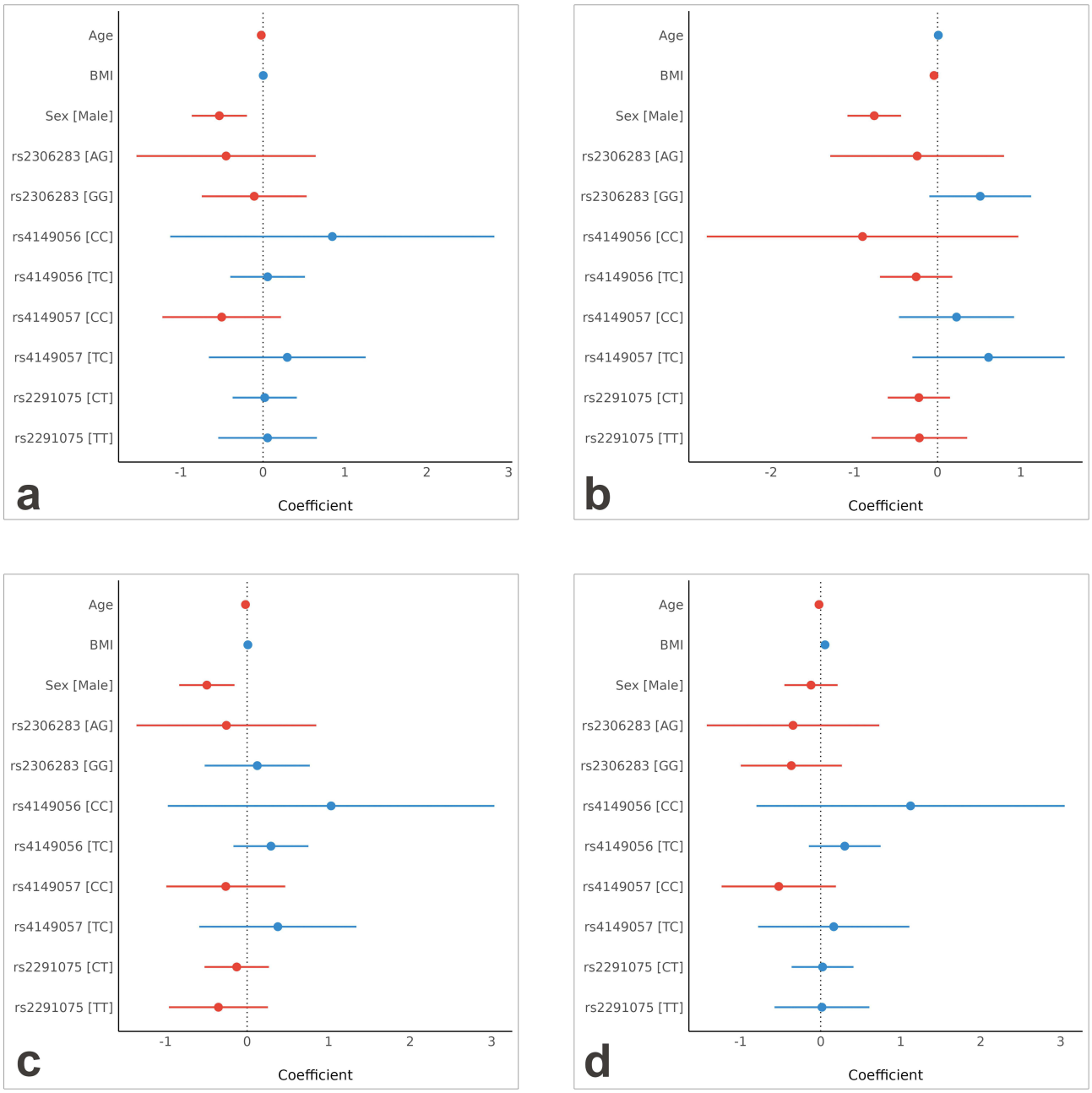

Figure 3 The coefficient of the sex, age, BMI and different genotypes of polymorphism on normalized blood lipid levels before atorvastatin therapy. (**a**) LDL-C, (**b**) HDL-C, (**c**) TC, (**d**) TG.

Discussion

The present study on a cohort of Chinese Han patients with dyslipidemia has yielded several significant findings regarding the impact of SLCO1B1 gene polymorphisms on lipid levels and the efficacy of atorvastatin therapy. Firstly, 14 distinct polymorphisms were identified in the CDS of SLCO1B1, with four polymorphisms (rs2306283, rs2291075, rs4149057, and rs4149056) being more prevalent. Notably, only rs2306283 was significantly associated with the therapeutic efficacy of atorvastatin, where carriers of the AA genotype showed a significantly greater reduction in TC and TG levels after treatment compared to those with the GG genotype. Secondly, demographic factors like age, sex, and BMI influenced baseline lipid levels, with females having higher baseline levels, yet these factors did not significantly affect atorvastatin's efficacy, highlighting the importance of rs2306283.

Table 4 The Correlation Between Factors and Normalized Changes of Blood Lipid Levels After Therapy Assessed by Multivariate Regression Analysis

Factors	*P*			
	ndLDL	ndHDL	ndTC	ndTG
Age	0.1553	0.2743	0.7009	0.6950
Sex	0.8453	0.1614	0.2218	0.8698
BMI	0.7591	0.3409	0.7707	0.5586
rs2306283	0.1068	0.2059	**0.0134**	**0.0337**
rs4149056	0.8740	0.1089	0.3718	0.5482
rs4149057	0.3820	0.4631	0.1722	0.1940
rs2291075	0.0679	0.1907	0.5024	0.0724

Notes: The differences before and after treatment in LDL-C, HDL-C, TC, and TG levels were normalized using the rank-based inverse normal transformation method (RNOmni software), denoted by the prefix "nd" before their respective names. Multivariate regression analysis was conducted using the Bayesian linear mixed model (BLME software). *P* values in bold indicate statistical significance ($P < 0.05$).

The finding of females having higher baseline levels was consistent with a previous research.[43] This may be due to hormonal differences, particularly the effects of menopause on lipid metabolism.[44]

Previous studies on SLCO1B1 polymorphisms and statin response have shown varying results across different populations.[26–35] The study adds to the existing evidence on this topic by focusing on the Chinese Han population and emphasizes the need for further research on other polymorphisms and their interactions.

This study performed a thorough examination of the SLCO1B1 coding region, identifying multiple polymorphisms. Detailed demographic and clinical data allowed for robust statistical analyses, accounting for potential confounders. This study's findings have significant implications for the field of pharmacogenomics and personalized medicine. By

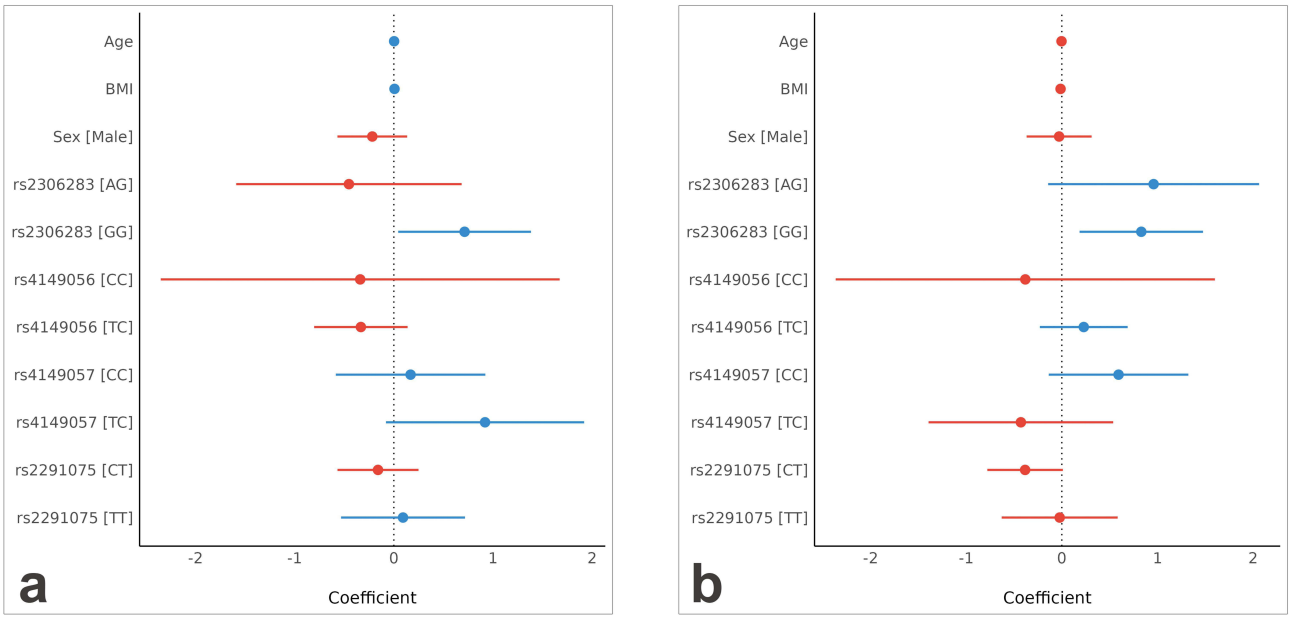

Figure 4 Impacts of different genotypes at rs2306283 locus on normalized changes of TC and TG levels after therapy. (**a**) ndTC; (**b**) ndTG.
Notes: The effects of varying genotypes at the rs230628 locus on changes in TC and TG levels were evaluated by comparing their normalized differences in blood lipid levels before and after treatment using the EMMEANS software. These normalized differences are denoted by the prefix "nd" before the blood lipid name. The analyses are based on marginal means adjusted for sex, rs1045642, rs2032582, and rs2214102. *P* values in bold indicate statistical significance ($P < 0.05$).

incorporating genetic testing for SLCO1B1 polymorphisms, particularly rs2306283, healthcare providers would better predict patient responses to atorvastatin and tailor treatment plans accordingly. This personalized approach would enhance therapeutic efficacy, minimize adverse effects, and improve overall patient outcomes.

While this study provides valuable insights, it also has limitations. The sample size, though sufficient for preliminary findings, limits the generalizability of the results. Additionally, the study is restricted to the Chinese Han population, and the findings may not be directly applicable to other ethnic groups with different genetic backgrounds. Future studies should aim to include larger, more diverse cohorts to validate these findings and explore the impact of SLCO1B1 polymorphisms across different populations.

Conclusions

The identification of SLCO1B1 polymorphisms, especially rs2306283, offers some insights into genetic factors affecting atorvastatin's efficacy in the Chinese Han population. This study indicates the potential of pharmacogenomics in optimizing lipid-lowering treatments, yet the findings need validation on other platforms and with a larger sample size for broader application.

Abbreviations

BMI, Body mass index; CDS, Coding sequence; TG, Triglyceride; TC, Total cholesterol; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol.

Data Sharing Statement

The datasets featured in this article are not openly accessible due to restrictions on the public dissemination of genomic information imposed by the Institutional Ethics Committee. To access the datasets, requests should be made to the corresponding authors.

Ethics Approval and Informed Consent

This study is part of a multicenter study which was approved by the Ethics Committee of Xiangya Hospital Central South University (ethics number K22144), and all participants provided written informed consent.

Consent for Publication

Written informed consent for publication was obtained from all participants.

Acknowledgments

We would like to acknowledge the participants who provided valuable clinical samples for this study. We express sincere appreciation to the State Key Laboratory of Microbial Resources at the Institute of Microbiology, Chinese Academy of Sciences, for their generous provision of the essential facilities and resources required for this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the project named Research on Precision Medication for Chronic Diseases Based on Pharmacogenomics (2019YJY0203).

Disclosure

The authors declare no competing interests.

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