RESEARCH ARTICLE

Analysis of SLCO1B1 and APOE genetic polymorphisms in a large ethnic Hakka population in southern China

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Objective: Statins are the most widely used lipid-lowering drugs, which have a significant effect on the inhibition of cardiovascular disease. The efficacy and side effects of statins are associated with the polymorphisms of *SLCO1B1* and *APOE* genes. The purpose of this study was to analyze the *SLCO1B1* and *APOE* gene polymorphisms in the Hakka population of southern China.

Methods: A total of 3249 subjects including 2019 males and 1230 females participated in this study. Polymerase chain reaction (PCR)-fluorescence probe technique for polymorphisms analysis and analyzed the genotypes frequencies of *SLCO1B1* and *APOE* genes.

Results: The frequencies of *SLCO1B1* 521T>C between men and women were statistically significant (*SLCO1B1* 521TT, $\chi^2 = 8.431$, $P = .004$; *SLCO1B1* 521TC, $\chi^2 = 7.436$, $P = .007$). The frequencies of haplotypes *1b/*1b (40.07%) and *1a/*1b (32.56%) of *SLCO1B1* gene accounted for 72.63%, followed by *1b/*15 (14.40%), *1a/*1a (5.82%), *1a/*15 (5.57%), *15/*15 (1.45%), and *1a/*5 (0.12%). The frequencies of haplotypes *1a/*15 and *1b/*1b of *SLCO1B1* gene between men and women were statistically significant (*1a/*15, $\chi^2 = 6.789$, $P = .009$; *1b/*1b, $\chi^2 = 3.998$, $P = .004$). In this study, genotype $\epsilon 3/\epsilon 3$ accounted for 69.04%, followed by $\epsilon 3/\epsilon 4$ (16.19%), $\epsilon 2/\epsilon 3$ (11.60%), $\epsilon 2/\epsilon 4$ (1.35%), $\epsilon 4/\epsilon 4$ (1.08%), and $\epsilon 2/\epsilon 2$ (0.74%) in all subjects, in which $\epsilon 3$ had the greatest allele frequency (82.93%), followed by $\epsilon 4$ (9.85%) and $\epsilon 2$ (7.22%). We found that 47 subjects carrying the *SLCO1B1* 521 (CC) polymorphism who had not any myopathy caused by statins.

Conclusions: We analyzed the *SLCO1B1* and *APOE* gene polymorphisms in the Hakka population of southern China. This study provides a reference for the individualized medication for Hakka population in this area.

KEYWORDS

APOE, genetic polymorphism, Hakka population, *SLCO1B1*, statin

1 | INTRODUCTION

Statins are the most widely used lipid-lowering drugs in clinic and have a significant effect on inhibiting cardiovascular diseases.¹ Although

statins are generally well tolerated, statin-associated side effects are a common problem in routine clinical practice. Myopathy is a relatively common adverse effect of these drugs, occurring in 1%-5% of cases.²⁻⁴ Some studies show that the level of statin was changed in the blood of patients with genetic mutation of *SLCO1B1*, and so it increases the risk of myopathy and rhabdomyolysis. The risk of myopathy conferred by

Zhong and Wu contributed equally to this work.

SLCO1B1 genetic mutation appears to be statin-specific, that is highest risks with simvastatin and atorvastatin and lowest with pravastatin and rosuvastatin.^{5,6} Apolipoprotein E (ApoE) is an important intrinsic factor affecting blood lipid levels, and ApoE polymorphism is considered to be a susceptible candidate for hyperlipidemia and atherosclerosis, which is related to the efficacy of statins.⁷⁻⁹

Organic anion-transporting polypeptides (OATPs) are membrane influx transporters that regulate the cellular uptake of a number of endogenous compounds and clinically important drugs. *SLCO1B1* gene encodes one of the transporters *SLCO1B1* (solute carrier organic anion transporter family member 1B1, also known as OATP1B1) that mediate the independent uptake of sodium ions by endogenous substances such as bilirubin and leukotriene C₄. OATP1B1 protein is also involved in the metabolism of statins and antituberculosis drugs such as rifampicin.¹⁰⁻¹² *SLCO1B1* gene is located on chromosome 12 (12p12.1), and the 388A>G (rs2306283) and 521T>C (rs4149056) are two common single nucleotide polymorphisms (SNPs) which can form four haplotypes, including *SLCO1B1**1a (388A-521T), *SLCO1B1**1b (388G-521T), *SLCO1B1**5 (388A-521C), and *SLCO1B1**15 (388G-521C). The *SLCO1B1**5 and *SLCO1B1**15 haplotypes (carriers of 521C allele) are associated with reduced activity of OATP1B1 transportation.^{6,12,13}

The human apolipoprotein E (APOE gene; OMIM 107741) is located on chromosome 19 in band 19q13.32.^{14,15} There are two SNPs of APOE, 388T>C (rs429358) and 526C>T (rs7412), which form 3 haplotypes including ϵ 3 (388T-526C), ϵ 2 (388T-526T), and ϵ 4 (388C-526C). By different combinations of these three haplotypes, six genotypes (ϵ 2/ ϵ 2, ϵ 3/ ϵ 3, ϵ 2/ ϵ 3, ϵ 3/ ϵ 4, ϵ 2/ ϵ 4, and ϵ 4/ ϵ 4) are formed.^{16,17} Although the frequency of these alleles/genotypes varies among different populations, APOE ϵ 3/ ϵ 3 is the most common genotype, and ϵ 3 is the most predominant allele in most population.¹⁸⁻²¹ Several studies demonstrated that the APOE polymorphisms have been linked to the cardiovascular disease, lipoprotein glomerulopathy, and Alzheimer's disease II.^{22,23} APOE gene polymorphism is related to the effect of statins on lipid-lowering.^{7,9}

Regarding the high importance of *SLCO1B1* and APOE pharmacogenes in drug dosing of statins, it is important to evaluate the *SLCO1B1* and APOE genotypes in different ethnic populations. Meizhou, located at the junction of Fujian, Guangdong, and Jiangxi provinces in China, covers area of 15 876 km² and possesses a population of 5.44 million. The vast majority people lived in Meizhou are Hakka, which is an intriguing Han Chinese population in northern China.²⁴ In this region, there is no report on the *SLCO1B1* and APOE genetic polymorphisms.

The purpose of this study was to analyze the *SLCO1B1* and APOE genetic polymorphisms in the Hakka population of southern China and provide a theoretical basis for the prevention and treatment of coronary heart disease.

2 | MATERIALS AND METHODS

2.1 | Study subjects

A total of 3249 subjects including 2019 males and 1230 females (1.641:1) participated in this study. Subjects visited Meizhou People's Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun

TABLE 1 Clinical characteristics of male and female subjects

	Male	Female	P values
No. of subjects	2019	1230	
Age, y	64.95 ± 11.73	66.40 ± 11.57	.001
TG, mmol/L	1.844 ± 1.644	2.016 ± 1.777	.005
TC, mmol/L	4.891 ± 1.309	5.240 ± 1.325	<.001
HDL, mmol/L	1.239 ± 0.359	1.362 ± 0.382	<.001
LDL, mmol/L	2.826 ± 0.945	2.936 ± 0.960	.001
Apo-A1, g/L	1.100 ± 0.281	1.215 ± 0.310	<.001
Apo-B, g/L	0.903 ± 0.294	0.937 ± 0.294	.001
Apo-A1/Apo-B	1.337 ± 0.555	1.408 ± 0.542	<.001

TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B. Values for age expressed as mean ± SD.

Yat-sen University, which age from 8 to 96 years enrolled in this study, through September 2016 to October 2017. We reviewed the results of these subjects retrospectively. The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Meizhou People's Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun Yat-sen University.

2.2 | Plasma lipid measurements

About 3 mL of blood samples for the measurement of lipid levels was obtained from subjects, and plasma was separated and stored at -80°C till further analysis. Plasma levels of triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), apolipoprotein A1 (Apo-A1), and apolipoprotein B (Apo-B) were measured.

2.3 | DNA extraction and genotyping

Blood samples were stored in 2-mL vacuum tubes containing ethylenediaminetetraacetic acid (EDTA) from participants. Genomic DNA was extracted from the blood of subjects using QIAamp DNA Blood Mini Kit (Qiagen, Germany) following the manufacturer's instructions, and DNA concentration was quantified using NanoDrop 2000™ Spectrophotometer (ThermoFisher Scientific, Waltham, MA). Polymerase chain reaction was performed according to the following protocol: 37°C for 10 minutes, predenaturation at 95°C for 5 minutes, followed by 40 cycles at 95°C for 15 seconds, and 60°C for 60 seconds. The fluorescence signals were collected as FAM (*SLCO1B1**1b 388A, *SLCO1B1**5 521T, ApoE2 526C, ApoE4 388T) and VIC (*SLCO1B1**1b 388G, *SLCO1B1**5 521C, ApoE2 526T, ApoE4 388C) and ROX (internal standard) (PCR-fluorescence probe method) (Youzhiyou Medical Technology Co., Ltd, Wuhan, Hubei, China).

2.4 | Statistical analysis

SPSS statistical software version 19.0 was used for data analysis. Data were reported as the means ± SD. Chi-square and ANOVA tests

TABLE 2 Genotype and allele frequencies of *SLCO1B1* 388A>G and 521T>C in the Hakka population

Genotypes and alleles	Male (n = 2019, alleles=4038)		Female (n = 1230, alleles=2460)		P values
	No. of individuals	Relative frequency (%)	No. of individuals	Relative frequency (%)	
SLCO1B1 388A>G					
AA	126	6.24	67	5.45	.353
AG	775	38.39	464	37.72	.706
GG	1118	55.37	699	56.83	.418
A (AF)	1027	25.43	598	24.31	
G (AF)	3011	74.57	1862	75.69	
SLCO1B1 521T>C					
TT	1551	76.82	998	81.14	.004
TC	436	21.59	217	17.64	.006
CC	32	1.58	15	1.22	.397
T (AF)	3538	87.62	2,213	89.96	
C (AF)	500	12.38	247	10.04	

AF: allele frequency.

TABLE 3 Haplotypes of *SLCO1B1* gene in the Hakka population

	<i>SLCO1B1</i> gene haplotypes							Total
	*15/*15	*1a/*15	*1a/*1a	*1a/*1b	*1a/*5	*1b/*15	*1b/*1b	
Males	32 (1.58%)	129 (6.39%)	123 (6.09%)	646 (32.0%)	3 (0.15%)	304 (15.06%)	782 (38.73%)	2019
Females	15 (1.22%)	52 (4.23%)	66 (5.37%)	412 (33.50%)	1 (0.08%)	164 (13.33%)	520 (42.28%)	1230
Total	47 (1.45%)	181 (5.57%)	189 (5.82%)	1058 (32.56%)	4 (0.12%)	468 (14.40%)	1302 (40.07%)	3249
Males vs females P values	0.451	0.009	0.397	0.396	0.668	0.181	0.046	

Numbers in parentheses are percentages.

were used to analyze the associations between variant *SLCO1B1* and *APOE* genotypes and clinical characteristics. Statistical significance was set at a $P < .05$.

3 | RESULTS

3.1 | Population characteristics

A total of 3249 subjects, 2019 (62.14%) men and 1230 (37.86%) women, were recruited in the study. The mean age was 65.50 ± 11.69 years, which was 64.95 ± 11.73 years in men and 66.40 ± 11.57 in women. The difference of blood lipid level between men and women was statistically significant as shown in Table 1.

3.2 | Genotype and haplotype frequencies

The frequencies of *SLCO1B1* 521T>C between men and women were statistically significant (*SLCO1B1* 521TT, $\chi^2 = 8.431$, $P = .004$; *SLCO1B1* 521TC, $\chi^2 = 7.436$, $P = .007$). Genotype and allele frequencies of *SLCO1B1* 388A>G and 521T>C in the Hakka population in our research are shown in Table 2.

The frequencies of haplotypes *1b/*1b (40.07%) and *1a/*1b (32.56%) of *SLCO1B1* gene accounted for 72.63%, followed by *1b/*15 (14.40%), *1a/*1a (5.82%), *1a/*15 (5.57%), *15/*15 (1.45%), and *1a/*5 (0.12%). The frequencies of haplotypes *1a/*15 and *1b/*1b of *SLCO1B1* gene between men and women were statistically significant (*1a/*15, $\chi^2 = 6.789$, $P = 0.009$; *1b/*1b, $\chi^2 = 3.998$, $P = .004$) as shown in Table 3.

In this study, genotype $\epsilon 3/\epsilon 3$ accounted for 69.04%, followed by $\epsilon 3/\epsilon 4$ (16.19%), $\epsilon 2/\epsilon 3$ (11.60%), $\epsilon 2/\epsilon 4$ (1.35%), $\epsilon 4/\epsilon 4$ (1.08%), and $\epsilon 2/\epsilon 2$ (0.74%) in all subjects, in which $\epsilon 3$ had the greatest allele frequency (82.93%), followed by $\epsilon 4$ (9.85%) and $\epsilon 2$ (7.22%). Detailed data are listed in Table 4.

3.3 | Effect of *SLCO1B1* 521 (CC) polymorphism on side effects used statins

Presence of *SLCO1B1* 521C variant can lead to increased systemic statin concentrations and is strongly associated with statin-induced myopathy. In this study, we detected 47 subjects carrying the *SLCO1B1* 521 (CC) polymorphism. We checked their medical records and did not find any myopathy caused by statins. The results are shown in Table 5.

TABLE 4 Genotypes and alleles of APOE gene in the Hakka population

Genotypes	APOE gene polymorphisms					
	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4
Males	13 (0.64%)	229 (11.34%)	31 (1.54%)	1396 (69.14%)	329 (16.30%)	21 (1.04%)
Females	11 (0.89%)	148 (12.03%)	13 (1.06%)	847 (68.86%)	197 (16.02%)	14 (1.14%)
Total	24 (0.74%)	377 (11.60%)	44 (1.35%)	2243 (69.04%)	526 (16.19%)	35 (1.08%)
Males vs females <i>P</i> values	0.527	0.572	0.277	0.876	0.844	0.861
Alleles	ε2	ε3	ε4			
Males	286 (7.08%)	3350 (82.96%)	402 (9.96%)			
Females	183 (7.44%)	2039 (82.89%)	238 (9.67%)			
Total	469 (7.22%)	5389 (82.93%)	640 (9.85%)			
Males vs females <i>P</i> values	0.621	0.946	0.731			

Numbers in parentheses are percentages.

4 | DISCUSSION

Since the advent of statins, it has become the most widely used lipid-lowering drugs in clinic. It is 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. HMG-CoA reductase is the rate-limiting enzyme of cholesterol synthesis in vivo during early. Statins achieve lipid-lowering effect by inhibiting the HMG-CoA reductase.^{2,25,26} It has become the first-line prescription for prevention of coronary heart disease. But in clinic, there are great individual differences in the lipid-lowering effect of statins. After taking statins, the level of low-density lipoprotein cholesterol levels in different individuals was significantly different. There are a large part of the patients after treatment were not up to the target and/or appeared lipid-lowering adverse reactions.^{27,28} This is due to the lipid-lowering effect and adverse reaction of statins associated with the genetic polymorphisms of *SLCO1B1* and *APOE*.

The *SLCO1B1* 388A>G SNP has a frequency of 25%-30% in Caucasians,^{29,30} in which 521T>C SNP was 15%-20%.^{29,31-33} The mutation allele frequency of *SLCO1B1* 388A>G was 74.99% (74.57% in male and 75.69% in female), and 521T>C was 11.50% (12.38% in male and 10.04% in female) in the Hakka population in our research. The results were similar to the study results of Liu et al,³⁴ the allele frequency of *SLCO1B1* 388A>G was higher in Chinese Han than in Caucasians, while 521T>C was lower. The frequencies of haplotypes *1b/*1b (40.07%) and *1a/*1b (32.56%) of *SLCO1B1* gene accounted for 72.63%, followed by *1b/*15 (14.40%), *1a/*1a (5.82%), *1a/*15 (5.57%), *15/*15 (1.45%), and *1a/*5 (0.12%). Our

results were consistent with the previous researches in Chinese Han population.³⁵⁻³⁷

In the Chinese population, genotype ε3/ε3 is the commonest one, while allele ε3 is the commonest allele. Our results confirmed previous research conclusions. In this study, genotype ε3/ε3 accounted for 69.04%, followed by ε3/ε4 (16.19%), ε2/ε3 (11.60%), ε2/ε4 (1.35%), ε4/ε4 (1.08%), and ε2/ε2 (0.74%) in all subjects, in which ε3 had the greatest allele frequency (82.93%), followed by ε4 (9.85%) and ε2 (7.22%). It showed that the frequencies of *APOE* allele in the Hakka population were similar to those in the Chinese-Northeast,³⁸ Chinese-Jiangsu Han,³⁹ and Chinese-Kunming Han populations,⁴⁰ in which ε4 allele in the Hakka population was lower than in the Chinese-Shanghai population.⁴¹ Comparison of our results to the geographically neighboring countries showed that the frequency of ε4 allele in the Hakka population was lower than in the Japanese,^{42,43} Mongolian,¹⁶ Vietnamese,⁴⁴ Malay,⁴⁵ Javanese,⁴⁵ and Korean⁴⁶ populations, in which ε4 gene carriers have a higher risk of cardiovascular disease.^{22,47,48}

This is the first study to report the frequencies of the most common *SLCO1B1* and *APOE* gene polymorphisms in this population. Gene polymorphisms related to drug metabolism are one of the important directions in our research group. The association between gene variants and the efficacy and safety of statins is still going on, so as to provide better references for clinical application. Single nucleotide polymorphism (SNP) provides an ideal typing model for complex gene detection. SNP genotyping based on target genes or regional has been applied to the mapping of human genetic maps and disease screening.^{49,50} In practice, PCR-fluorescence probe technique and gene chip technology are carried

TABLE 5 Forty-seven subjects with *SLCO1B1* 521(CC) polymorphism and used drugs and doses of statins

	Drugs and doses of statins					Total
	Atorvastatin (20 mg/d)	Atorvastatin (10 mg/d)	Pravastatin (2 mg/d)	Rosuvastatin (10 mg/d)	Rosuvastatin (5 mg/d)	
Males	10	6	4	12	No	32
Females	3	6	2	3	1	15
Total	13	12	6	15	1	47

out only in a small number of major diseases and some known SNPs. And with the emergence and development of the next-generation sequencing technology (NGS), this situation has been improved. Compared with the classic real-time fluorescence quantitative PCR method and gene chip technology, NGS can detect complex human diseases. The detection sensitivity is high, and the detection depth is wide.⁵¹ The application of NGS to study gene variants with the efficacy and safety of statins is also the focus of our next research direction.

5 | CONCLUSION

We analyzed the *SLCO1B1* and *APOE* gene polymorphisms in the Hakka population of southern China. This study provides a reference for the individualized medication for Hakka population in this area.

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