Polymorphism analysis of APOE and SLCO1B1 genes in Meizhou area of southern China

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Abstract

Background APOE and SLCO1B1 genetic polymorphisms are relevant in statin pharmacokinetics.Objective Aim of this study was to investigate the polymorphisms of APOE and SLCO1B1 gene in Meizhou area.Methods Genotying of APOE and SLCO1B1 genetic polymorphisms were conducted in 4761 individuals.Results Among two variants of SLCO1B1 in Meizhou, the frequencies of 388A>G and 521T>C allele were 74.89% and 11.54% separately. The frequency of SLCO1B1 gene hplotype *1b/*1b was 40.37% followed by *1a/*1b (31.93%) and *1b/*15(14.14%). There were no significant differences between men and women in this study except SLCO1B1 521T>C (SLCO1B1 521TT, P =0.019; SLCO1B1 521TC, P =0.028) and haplotypes *1a/*15 of SLCO1B1 (*1a/*15, P=0.02). Moreover, the frequencies of APOE ε3/ε3 was 69.94%, followed by 15.77% in ε3/ε4, 11.30% in ε2/ε3, 1.56% in ε2/ε4, 1.02% in ε4/ε4 and 0.54% in ε2/ε2, with considerably higher rate of allele ε3 (83.48%).Conclusions The population of Meizhou has different distribution feature. This study provides a reference to optimize the individualization of drug use in this area.

Background

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are currently the most common and effective lipid-lowering drugs through the reduction of low-density lipoprotein cholesterol (LDL-c), widely used to reduce the risk of myocardial infarction, stroke, and other cardiovascular events(Baigent *et al.*, 2005). In general, the currently used of statins are well-tolerated, however, there are still 25-50 % of patients with coronary artery disease nonadherence after one year's medication mostly for adverse drug reactions (ADRs)(Ho *et al.*, 2008) mainly manifest as statin-induced myopathy and rhabdomyolysis. According to previous researches, the development of statin-induced ADRs and lipid-lowering effect are usually connected with the action of hepatic organic anion-transporting polypeptide (OATP) encoded by *SLCO1B1* gene(Link *et al.*, 2008).

The non-coding *SLCO1B1* 388A>G (rs2306283) and 521T>C (rs4149056) single nucleotide polymorphism have been shown to be significantly related gene to statin-induced ADRs(Jiang *et al.*, 2017; Jiang *et al.*, 2016). Patients carried 521C allele (located in exon 4) had reduced hepatic uptake and increases the concentration of statins in blood, which might increase the ADRs risk and the A388G allele may be associated with reduced statin bioavailability(Nies *et al.*, 2013). Four distinct haplotypes develop though combining these two functional SNPs: *SLCO1B1**1B (388G-521T), *1A (388A-521T), *15 (388G-521C) and *5 (388A-521C)(Kameyama *et al.*, 2005; Nozawa *et al.*, 2005; Tirona *et al.*, 2003). It is known that patients carrying at least one C-allele in SLCO1B1*5 (T521C) are more likely to increase risk of myopathy during treatment with statins, however, the circumstance is the most prominent for simvastatin, but is not so important for other statins(Carr *et al.*, 2013; Voora *et al.*, 2009). Moreover, haplotype analysis further suggested that SLCO1B1*15 haplotype (388G-521C) is associated with low activity of the transporter.

APOE is genetically polymorphic and regulated by 3 alleles (ε2, ε3 and ε4) at chromosome 19q13.2 (*APOE* gene; OMIM 107741), giving rise to 6 genotypes: ε3/ε3, ε2/ε3, ε2/ε2, ε4/ε4, ε2/ε4, and ε3/ε4. Apo E

serves as the ligand for LDLR and LDL-related protein (LRP)(Bennet *et al*., 2007; Mahley & Rall, 2000; Wanmasae *et al*., 2017). Compared with □3 homozygotes, patients with □2 allele manifest lower circulating total cholesterol (TC) levels and higher triglyceride levels, whereas those who carry □4 allele appear to have higher plasma levels of TC and low-density lipoprotein cholesterol (LDLC) that makes them more likely to develop coronary artery disease(Zintzaras *et al*., 2009).

The polymorphisms of the *SLCO1B1* and *APOE* genes are important for guiding the individualization of statins, thus, it is necessary to explore the genotype distribution of different ethnic and different regions. With a total area of 15,876 km^2 and a population of 5.44 million, Meizhou area is situated in the northeast of Guangdong Province, bordering Fujian Province to northeast and Jiangxi Province to northeast. Hakka population is known as an intriguing Han Chinese population accounted for the vast majority in Meizhou residents. The Hakkas living in a mixed environmentally and small inhabited lifestyle makes many genetic distribution of frequency in this region comparatively distinctive(Li, 2014). However, Meizhou area lacks sufficient data on *SLCO1B1* and *APOE* gene polymorphisms to guide the use of statins.

Methods

Population Samples

In this study, a total of 4,761 individuals were collected, including 2949(61.94%) men and 1812(38.06%) women who were admitted to Meizhou *People's Hospital (also named Huangtang Hospital), Meizhou Academy of Medical Sciences, Meizhou* Hospital Affiliated to Sun Yat-sen University from September 2016 to December 2018, aged between 20 and 99 years old. We conducted a retrospective analysis for the relevant results of all subjects. This study was approved by Human Ethics Committees of Meizhou *People's Hospital (Huangtang Hospital), Meizhou Academy of Medical Sciences, Meizhou* Hospital Affiliated to Sun Yat-sen University, Guangdong province, China. The informed consent was signed by the patients or their guardians.

Plasma lipid measurements

A blood sample of about 3 ml was taken from the subject for examination of blood lipid levels. Plasma is supposed to isolate and store at -80℃ for further analysis. After laboratory assays, we obtained the results of total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), apolipoprotein B (Apo-B) and apolipoprotein A1 (Apo-A1).

DNA extraction and genotyping assay

Genomic DNA was extracted from whole blood in EDTA by QIAamp DNA Blood Mini Kit (Qiagen, Germany) according to the protocol provided. DNA concentration was quantified using Nanodrop 2000^{TM} Spectrophotometer (ThermoFisher Scientific, Waltham, MA). Polymerase chain reaction (PCR) was used to amplify the sequences of interest (step 1: 37°Cfor 10 min; step 2: 95°Cfor 5 min; step 3 for 40 cycles: 95°C for 15 sec and 60°Cfor 1min). 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).

Statistical analysis

All analysis was conducted using SPSS statistical software version 21.0. The study sample alleles and genotype frequencies were estimated with a gene counting method and descriptive statistics were expressed as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. Comparing the genotype and allele frequencies with Chi-square and Independent-Samples T-Test. $P < 0.05$ is considered statistically significant.

Results

Population characteristics

Genetic polymorphisms of *SLCO1B1* and *APOE* were studied in 4761 subjects in total, including 2949 males and 1812 females. The vast majority of these individuals are native to Meizhou area. As shown in Table 1，the average age of the subjects was 65.70±11.86 years, with 65.06±11.82 years for males and 66.76±11.84 years for females. Comparing the lipid levels of males and females, the P values were all less than 0.01, and the difference was statistically significant.

Genotype and haplotype frequencies

The observed allelic frequencies of 388A>G and 521T>C in Meizhou area of southern China (N=4761) were 74.89% and 11.54% respectively. In the *SLCO1B1* gene 521T>C, the frequencies of genotype TT and TC between males and females were statistically different (*SLCO1B1* 521TT, c^2=5.510, P=0.019; *SLCO1B1* 521TC, c^2=4.809, P=0.028) (Table 2).

Four haplotypes from the two SNPs of *SLCO1B1* were analyzed. Wild haplotype having both normal alleles AT (*1A) showed a frequency of 25.11% while GT (*1B) haplotype (63.32%) presented the highest frequency. However, the GC (*15) and AC (*5) haplotypes occurred at lower frequencies of 11.51% and

0.05% respectively. The differences between man and woman in haplotypes of GT (*1B) and GC (*15) were significantly statistical (Table 3).

As can be seen from Table 4, ε3 is the most common allele of *APOE* gene, accounting for 83.48% in all subjects, in which ε3 is the allele with greatest frequency, followed by ε4 (9.59%) and ε2 (6.93%). The frequencies of *APOE* ε3/ε3, ε3/ε4, ε2/ε3, ε2/ε4, ε4/ε4, ε2/ε2 were 69.94%, 15.77%, 11.30%, 1.34%, 1.03% and 0.61%, respectively.

Distribution of SLCO1B1 allele frequencies among major study populations

We compared the estimated *SLCO1B1* allele frequency here with previous reports published in other ethnic populations (Table 5). Geek, German, Indian (North) and Macedonian manifest the relatively lower rate of G allele in G388A, less than 50%, whereas Thailand and Chinese population show higher than former, generally above 70%. By contrast, the allele frequency exhibits little difference in *SLCO1B1* gene 521T>C.

Discussion

Statins, as a class of lipid-lowering drugs that competitively inhibit HMG-CoA reductase, have become the most common drug to treat the dyslipidemia and to promote primary and secondary prevention against cardiovascular events(Miller & Kung, 2018). Nonetheless, despite of the undoubted clinical benefits, the efficacy and adverse effect of statins present individual difference(Feng *et al.*, 2012; Hamilton-Craig, 2001). To a certain extent, genetic polymorphisms of *SLCO1B1* and *APOE* genes could be responsible for the lipid-lowering effects and the adverse drug reactions (ADRs) of statin treatment(Rocha *et al.*, 2018; Zhong *et al.*, 2018).

The polymorphisms of *SLCO1B1* gene are significant difference in different population. According to the studies, investigations of parts area about *SLCO1B1* are showed clearly: Geek, German, Indian (North) and Macedonian manifest the relatively lower rate of G allele in G388A, less than 50%, whereas Thailand and Chinese population show higher than former, generally above 70%. By contrast, the allele frequency exhibits little difference in *SLCO1B1* gene 521T>C polymorphism(Dendramis, 2011; Giannakopoulou *et al.*, 2014; Hubacek *et al.*, 2015; Kaewboonlert *et al.*, 2018; Melo *et al.*, 2015; Meyer zu Schwabedissen *et al.*, 2015; Mladenovska *et al.*, 2017; Ramakumari *et al.*, 2018; Treenert *et al.*, 2018; Wu *et al.*, 2018). In this study, the mutation allele frequency of *SLCO1B1* gene 388A>G and 521T>C were 74.89% (74.64% in male and 75.30% in female) and 11.54% (12.14% in male and 10.57% in female) respectively. The frequencies of hplotypes GT (*1B) showed the predominance accounting for 63.32%, others are as follow: AT (*1A) 25.11%, GC (*15) 11.51% and AC (*5) 0.05% separately. These results complied with previous researches(Griffin *et al.*, 2018; Hubacek *et al.*, 2015; Melo *et al.*, 2015; Mladenovska *et al.*, 2017; Wu *et al.*, 2018).

The *APOE* genetic polymorphism studied in this investigation illustrated that ε3 was the most common allele of *APOE* gene, accounting for 83.33%, which was consistent with most studies(Griffin *et al.*; Marais, 2019). This indicates that the *APOE* allele frequencies in Meizhou area were similar to that of the Chinese-Northeast(Zhou *et al.*, 2005), Chinese-Jinangsu Han(Liang *et al.*, 2009) and Chinese-Kunming Han(Tang *et al.*, 2005), while the ε4 allele frequency in Meizhou area is lower than that in Chinese-Shanghai(Yang *et al.*, 2003).

As living and eating conditions get better and better, more and more people have a tendency to develop hyperlipermia so much as increase the risk of cardiovascular disease. Statins have lipid-lowering effect, with different efficacy and side effects in different person. A large part of the cause is related to genetic polymorphism, including *SLCO1B1* gene and *APOE* gene. This study obtained more credible results by analyzing the polymorphisms of *APOE* and *SLCO1B1* genes in the large population of Meizhou area to guide the clinical implementation of precision medicine.

Conclusions

The polymorphisms of *APOE* and *SLCO1B1* genes in Meizhou area were analyzed. This study provides a reference for personalized meditation in this region.

Declarations

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Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Authors' contributions

Zhixiong Zhong and Heming Wu designed the study. Hailing Wu performed the experiments. Qiuyan Zhu and Hailing Wu collected clinical data. Qunji Zhang, Zhikang Yu and Qingyan Huang helped to analyze

the data. Heming Wu and Qiuyan Zhu prepared the manuscript. All authors were responsible for critical revisions, and all authors read and approved the final version of this work.

Ethics approval and consent to participate

This study was approved by Human Ethics Committees of Meizhou *People's Hospital (Huangtang Hospital), Meizhou Academy of Medical Sciences, Meizhou* Hospital Affiliated to Sun Yat-sen University, Guangdong province, China.

Patient consent for publication

Prior to sample collection, written informed consent was obtained from the patients or their guardians, and patient/study subject privacy was carefully protected.

Declaration of interest

None.

References

Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R (2005) Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 366: 1267-1278.

Bennet AM, Di Angelantonio E, Ye Z, Wensley F, Dahlin A, Ahlbom A, Keavney B, Collins R, Wiman B, de Faire U and Danesh J (2007) Association of apolipoprotein E genotypes with lipid levels and coronary risk. Jama 298: 1300-1311.

Carr DF, O'Meara H, Jorgensen AL, Campbell J, Hobbs M, McCann G, van Staa T and Pirmohamed M (2013) SLCO1B1 genetic variant associated with statin-induced myopathy: a proof-of-concept study using the clinical practice research datalink. Clin Pharmacol Ther 94: 695-701.

Dendramis G (2011) Interindividual differences in the response to statin therapy and gene polymorphisms related to myopathy during statin therapy. G Ital Cardiol (Rome) 12: 182-185.

Feng Q, Wilke RA and Baye TM (2012) Individualized risk for statin-induced myopathy: current knowledge, emerging challenges and potential solutions. Pharmacogenomics 13: 579-594.

Giannakopoulou E, Ragia G, Kolovou V, Tavridou A, Tselepis AD, Elisaf M, Kolovou G and Manolopoulos VG (2014) No impact of SLCO1B1 521T>C, 388A>G and 411G>A polymorphisms on response to statin therapy in the Greek population. Mol Biol Rep 41: 4631-4638.

Griffin BA, Walker CG, Jebb SA, Moore C, Frost GS, Goff L, Sanders TAB, Lewis F, Griffin M, Gitau R, Lovegrove JA (2018) APOE4 Genotype Exerts Greater Benefit in Lowering Plasma Cholesterol and

Apolipoprotein B than Wild Type (E3/E3), after Replacement of Dietary Saturated Fats with Low Glycaemic Index Carbohydrates. Nutrients 10.

Hamilton-Craig I (2001) Statin-associated myopathy. Medical Journal of Australia 175: 486-489.

Ho PM, Magid DJ, Shetterly SM, Olson KL, Maddox TM, Peterson PN, Masoudi FA, Rumsfeld JS (2008) Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. Am Heart J 155: 772-779.

Hubáček JA, Dlouhá D, Adámková V, Zlatohlavek L, Viklický O, Hrubá P, Češka R, Vrablík M (2015) SLCO1B1 polymorphism is not associated with risk of statin-induced myalgia/myopathy in a Czech population. Med Sci Monit 21: 1454-1459.

Jiang F, Choi JY, Lee JH, Ryu S, Park ZW, Lee JG, Na HS, Lee SY, Oh WY, Chung MW, Choi SE (2017) The influences of SLCO1B1 and ABCB1 genotypes on the pharmacokinetics of simvastatin, in relation to CYP3A4 inhibition. Pharmacogenomics 18: 459-469.

Jiang J, Tang Q, Feng J, Dai R, Wang Y, Yang Y, Tang X, Deng C, Zeng H, Zhao Y, Zhang F (2016) Association between SLCO1B1 -521T>C and -388A>G polymorphisms and risk of statin-induced adverse drug reactions: A meta-analysis. Springerplus 5: 1368.

Kaewboonlert N, Thitisopee W, Sirintronsopon W, Porntadavity S and Jeenduang N (2018) Lack of association between SLCO1B1 polymorphisms and lipid-lowering response to simvastatin therapy in Thai hypercholesterolaemic patients. J Clin Pharm Ther 43: 647-655.

Kameyama Y, Yamashita K, Kobayashi K, Hosokawa M and Chiba K (2005) Functional characterization of SLCO1B1 (OATP-C) variants, SLCO1B1*5, SLCO1B1*15 and SLCO1B1*15+C1007G, by using transient expression systems of HeLa and HEK293 cells. Pharmacogenet Genomics 15: 513-522.

Li, SM (2014) Population migration regional economic growth and income determination: a comparative study of Dongguan and Meizhou China. Urban Studies 34: 999-1026.

Liang S, Pan M, Geng HH, Chen H, Gu LQ, Qin XT, Qian JJ, Zhu JH, Liu CF 2009 Apolipoprotein E polymorphism in normal Han Chinese population: frequency and effect on lipid parameters. Mol Biol Rep 36: 1251-1256.

SEARCH Collaborative Group, Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, Lathrop M and Collins R (2008) SLCO1B1 variants and statin-induced myopathy–a genomewide study. N Engl J Med 359: 789-799.

Mahley RW and Rall SC Jr (2000) Apolipoprotein E: far more than a lipid transport protein. Annu Rev Genomics Hum Genet 1: 507-537.

Marais AD (2019) Apolipoprotein E in lipoprotein metabolism, health and cardiovascular disease. Pathology 51: 165-176.

Melo MS, Balanco L, Branco CC and Mota-Vieira L (2015) Genetic variation in key genes associated with statin therapy in the Azores Islands (Portugal) healthy population. Ann Hum Biol 42: 283-289.

Meyer zu Schwabedissen HE, Albers M, Baumeister SE, Rimmbach C, Nauck M, Wallaschofski H, Siegmund W, Völzke H, Kroemer HK (2015) Function-impairing polymorphisms of the hepatic uptake transporter SLCO1B1 modify the therapeutic efficacy of statins in a population-based cohort. Pharmacogenet Genomics 25: 8-18.

Miller BR and Kung Y (2018) Structural Features and Domain Movements Controlling Substrate Binding and Cofactor Specificity in Class II HMG-CoA Reductase. Biochemistry 57: 654-662.

Mladenovska K, Grapci AD, Vavlukis M, Kapedanovska A, Eftimov A, Geshkovska NM, Nebija D, Dimovski AJ (2017) Influence of SLCO1B1 polymorphisms on atorvastatin efficacy and safety in Macedonian subjects. Pharmazie 72: 288-295.

Nies AT, Niemi M, Burk O, Winter S, Zanger UM, Stieger B, Schwab M, Schaeffeler E (2013) Genetics is a major determinant of expression of the human hepatic uptake transporter OATP1B1, but not of OATP1B3 and OATP2B1. Genome Med 5: 1.

Nozawa T, Minami H, Sugiura S, Tsuji A and Tamai I (2005) Role of organic anion transporter OATP1B1 (OATP-C) in hepatic uptake of irinotecan and its active metabolite, 7-ethyl-10-hydroxycamptothecin: in vitro evidence and effect of single nucleotide polymorphisms. Drug Metab Dispos 33: 434-439.

Ramakumari N, Indumathi B, Katkam SK and Kutala VK (2018) Impact of pharmacogenetics on statin-induced myopathy in South-Indian subjects. Indian Heart J 70 Suppl 3: S120-s125.

Rocha KCE, Pereira BMV and Rodrigues AC (2018) An update on efflux and uptake transporters as determinants of statin response. Expert Opin Drug Metab Toxicol 14: 613-624.

Tang H, Yan X, Hua Y, Wei M, Zhang L, Gao J, Dong H (2005) Distribution of apoE polymorphism in Chinese Yunnan Dehong Dai ethnic group. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 22: 224-226.

Tirona RG, Leake BF, Wolkoff AW and Kim RB (2003) Human organic anion transporting polypeptide-C (SLC21A6) is a major determinant of rifampin-mediated pregnane X receptor activation. J Pharmacol Exp Ther 304: 223-228.

Treenert A, Areepium N and Tanasanvimon S (2018) Effects of ABCC2 and SLCO1B1 Polymorphisms on Treatment Responses in Thai Metastatic Colorectal Cancer Patients Treated with Irinotecan-Based Chemotherapy. Asian Pac J Cancer Prev 19: 2757-2764.

Voora D, Shah SH, Spasojevic I, Ali S, Reed CR, Salisbury BA, Ginsburg GS (2009) The SLCO1B1*5 genetic variant is associated with statin-induced side effects. J Am Coll Cardiol 54: 1609-1616.

Wanmasae S, Sirintronsopon W, Porntadavity S and Jeenduang N (2017) The effect of APOE, CETP, and PCSK9 polymorphisms on simvastatin response in Thai hypercholesterolemic patients. Cardiovasc Ther 35.

Wu X, Gong C, Weinstock J, Cheng J, Hu S, Venners SA, Hsu YH, Wu S, Zha X, Jiang S, Li Y, Pan F, Xu X (2018) Associations of the SLCO1B1 Polymorphisms With Hepatic Function, Baseline Lipid Levels, and Lipid-lowering Response to Simvastatin in Patients With Hyperlipidemia. Clin Appl Thromb Hemost, 1076029618805863.

Yang JD, Feng GY, Zhang J, Cheung J, St Clair D, He L, Ichimura K (2003) Apolipoprotein E -491 promoter polymorphism is an independent risk factor for Alzheimer's disease in the Chinese population. Neurosci Lett 350: 25-28.

Zhong Z, Wu H, Li B, Li C, Liu Z, Yang M, Zhang Q, Zhong W, Zhao P (2018) Analysis of SLCO1B1 and APOE genetic polymorphisms in a large ethnic Hakka population in southern China. J Clin Lab Anal.

Zhou J, Xue YL, Guan YX, Yang YD, Fu SB, Zhang JC (2005) Association study of apolipoprotein e gene polymorphism and cerebral infarction in type 2 diabetic patients. Yi Chuan 27: 35-38.

Zintzaras E, Kitsios GD, Triposkiadis F, Lau J and Raman G (2009) APOE gene polymorphisms and response to statin therapy. Pharmacogenomics J 9: 248-257.

Tables

Table 1 Clinical characteristics of males and females in subjects

	Male	Female	*P* values
No. of subjects	2949	1812	
Age, y	65.06±11.82	66.76±11.84	<0.001
TG, mmol/L	1.835±1.765	1.976±1.740	0.007
TC, mmol/L	4.909±1.318	5.269±1.342	<0.001
HDL, mmol/L	1.225±0.347	1.360±0.374	<0.001
LDL, mmol/L	2.828±0.932	2.947±0.962	<0.001
Apo-A1, g/L	1.101±0.291	1.235±0.335	<0.001
Apo-B, g/L	0.884±0.284	0.922±0.290	<0.001
Apo-A1/ Apo-B	1.364±0.568	1.456±0.581	<0.001

Values for age expressed as mean±SD.

TG, triglycerides;

TC, total cholesterol;

HDL, high density lipoprotein;

LDL, low density lipoprotein;

Apo-A1, apolipoprotein A1;

Apo-B, apolipoprotein B.

Table 2 Genotype and allele frequencies of *SLCO1B1* gene 388A>G and 521T>C in Meizhou area

Genotypes and alleles	Total (n=4761,alleles=9522)		Male (n =2949, alleles=5898)		Female (n =1812, alleles=3624)		*P* values
	No. of individuals	Relative frequency(%)	No. of individuals	Relative frequency(%)	No. of individuals	Relative frequency(%)	
SLCO1B1 388A>G							
AA	293	6.15%	179	6.07%	114	6.29%	0.757
AG	1805	37.91%	1138	38.59%	667	36.81%	0.219
GG	2663	55.93%	1632	55.34%	1031	56.90%	0.293
A (AF)	2391	25.11%	1496	25.36%	895	24.70%	
G (AF)	7131	74.89%	4402	74.64%	2729	75.30%	
SLCO1B1 521T>C							
TT	3730	78.34%	2278	77.25%	1452	80.13%	0.019
TC	963	20.23%	626	21.23%	337	18.60%	0.028
CC	68	1.43%	45	1.53%	23	1.27%	0.469
T (AF)	8423	88.46%	5182	87.86%	3241	89.43%	
C (AF)	1099	11.54%	716	12.14%	383	10.57%	

AF: allele frequency.

Table 3 Hplotypes frequencies of *SLCO1B1* gene in Meizhou area

Haplotypes Frequencies(%)	GT (*1b) (n, %)	AT (*1a) (n, %)	AC (*15) (n, %)	AC (*5) (n, %)
Total	6017 63.32%	2386 25.11%	1094 11.51%	5 0.05%
Male	3690 62.56%	1492 25.30%	712 12.07%	4 0.07%
Female	2347 64.76%	894 24.67%	382 10.54%	1 0.03%
Males vs females P values	0.031	0.492	0.023	0.405

Table 4 Genotypes and alleles of *APOE* gene in Meizhou area

Genotypes	***APOE* gene polymorphisms**					
	ε3/ε3	**ε3/ε4**	**ε2/ε3**	**ε2/ε4**	**ε4/ε4**	**ε2/ε2**
Males	2058 (69.79%)	467 (15.84%)	332 (11.26%)	46 (1.56%)	30 (1.02%)	16 (0.54%)
Females	1272 (70.20%)	284 (15.67%)	206 (11.37%)	18 (0.99%)	19 (1.05%)	13 (0.72%)
Total	3330 (69.94%)	751 (15.77%)	538 (11.30%)	64 (1.34%)	49 (1.03%)	29 (0.61%)
Males vs females *P* values	0.099	0.881	0.907	0.277	0.917	0.451
Alleles	**ε3**	**ε4**	**ε2**			
Males	4915 (83.33%)	573 (9.72%)	410 (6.95%)			
Females	3034 (83.72%)	340 (9.38%)	250 (6.90%)			
Total	7949 (83.48%)	913 (9.59%)	660 (6.93%)			
Males vs females *P* values	0.823	0.638	0.921			

Numbers in parentheses are percentages.

Table 5 Distribution of *SLCO1B1* gene frequencies among major study populations.

Population	total	G388A(percentage)				T521C(percentage)				References
		AA	AG	GG	G(MAF)	TT	TC	CC	C(MAF)	
Geek	403	32.0	49.4	18.6	43.3	69.5	28.5	2.0	16.3	22
Thailand	49	10.2	22.5	67.4	78.6	-	-	-	-	23
Thai (hyperlipidemic patients)	391	7.8	34.8	57.5	75.0	78.5	19.4	2.1	11.8	24
German	214	32.7	55.1	12.2	39.7	69.2	29.4	1.4	16.1	25
Indian	202	-	-	-	-	93.6	6.4	0	3.2	26
Indian(North)	270	31.9	46.7	21.4	45.0	-	-		-	27
Macedonian	156	34.6	51.3	14.1	39.7	74.4	23.1	2.6	14.1	28
Czechs	111	9	35.1	55.9	73.4	73.8	24.3	1.8	14.0	29
Portuguese	100	5.0	21.0	64.0	79.5	75.0	24.0	1.0	13.0	30
Beijing/Anhui	542	8.67	31.99	52.21	71.77	78.41	20.85	0.74	11.16	31
Meizhou	4761	6.2	37.9	55.9	74.9	78.3	20.2	1.5	11.5	Current study

MAF: minor allele frequency

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ChecklistforsubmissionGENG.docx