

Association between *SLCO1B1* polymorphism distribution frequency and blood lipid level in Chinese adults

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ABSTRACT

Background: The variation of serum lipid levels can be part-related to certain genes. One such gene, *SLCO1B1*, encodes a transporter that may have a role in lipid metabolism. We hypothesised that differences in certain *SLCO1B1* genotypes are related to levels of serum lipids.

Materials and methods: We recruited 636 subjects who were genotyped for *SLCO1B1* variants *1a, *1b, *5 and *15. Routine liver function tests, renal function tests and routine lipid indices were measured by standard techniques.

Results: The most frequent genotypes were *1b/*1b (29.3%), *1b/*15 (27.5%), *1a/*1b (21.1%), *1a/*15 and *1b/*5 (10.2%) and *1a/*1a (8.5%). There were significant differences in levels of triglycerides and HDL in the four *SLCO1B1* genotypes *1a/*1a, *1b/*1b, *1a/*1b and *1b/*15 (all $p < 0.05$).

Conclusion: The genotypes *1a/*1a and *1a/*1b indicate a high risk of cardiovascular disease, while the *1b/*1b group may have a relatively low risk. *SLCO1B1* may be involved in the metabolism of triglycerides and HDL. We have provided a tool for identifying potentially high-risk groups that could be helpful for early diagnosis and prevention, individualized drug therapy and even gene therapy.

ARTICLE HISTORY

Received 29 March 2020
Accepted 17 June 2020

KEYWORDS

SLCO1B1 genotype; gene polymorphism; genotyping; blood lipid; statins; cardiovascular disease

Introduction



Dyslipidaemia is a major risk factor for cardiovascular disease, serum levels being determined by diet and the genetic-controlled production, and accordingly, serum triglyceride, cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) are commonly used in screening. A well-documented lipid-lowering therapy (statins) reduces the risk of death or cardiovascular events in populations with or without a history of coronary artery disease [1,2].

The organic anion-transporting polypeptide 1B1 (OATP1B1), encoded by solute carrier organic anion transporter family member *SLCO1B1*, is a hepatic uptake transporter predominantly expressed in the basolateral side of hepatocytes [3]. OATP1B1 has a role in the transport of a wide variety of drugs, such as statins. Several pharmacogenetic studies and meta-analyses have focused on the potential contribution of *SLCO1B1* variations in the response to statins or repaglinide, but little attention has been paid to whether *SLCO1B1* is involved in lipoprotein transformation and metabolic process that affects individual lipid levels [4–15]. We therefore hypothesised that common variants of *SLCO1B1* have an impact on levels of serum lipids, and so by extension, a potential role in risk assessment.

Materials and methods

We tested our hypothesis in a cohort of 636 subjects (352 men and 284 women) who visited the Physical Examination Centre in Foshan Hospital of Traditional Chinese Medicine from August 2019 to January 2020. We retrospectively reviewed the results of the subjects through laboratory information system. The study was approved by the local ethical committee at Foshan Hospital of Traditional Chinese Medicine and informed consent was obtained from each participant.

Blood samples were collected in 2 mL vacuum tubes containing EDTA. DNA was obtained by an extraction kit and matching NES-32 Nucleic acid extraction instrument (Aikang, Hangzhou, China) following the manufacturer's instructions. DNA concentration was quantified using Bio Tek Gen5 Spectrophotometer (BioTek Instruments Inc., Vermont, USA). PCR was performed by ABI7500 PCR amplification fluorescence detector (Life Technologies, Waltham, USA) according to the following protocol: 37 °C for 10 minutes, pre-denaturation at 95 °C for 5 minutes, followed by 40 cycles at 95 °C for 15 seconds, and 60 °C for 45 seconds. The fluorescence signals were collected as FAM (*SLCO1B1**1b 388A, *SLCO1B1**5 521 T) and VIC (*SLCO1B1**1b 388 G, *SLCO1B1**5 521 C) and ROX (Internal standard genes) (PCR-fluorescence probe

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method) (Youzhiyou, Wuhan, China). A second sample of 3 mL was drawn in vacuum tubes containing separation gel, and centrifuged to separate the serum. The levels of glucose, total cholesterol, triglycerides, HDL, LDL, urea, alanine transaminase (ALT), aspartic transaminase (AST), gamma-glutamyl transferase (GGT), creatinine and uric acid were measured by ADVIA 2400 Automatic biochemical analyser (Siemens, Munich, Germany) and these showed that no participant had diabetes or abnormal liver or kidney function.

Data are presented as numbers and frequencies for categorical variables and as means and standard deviation (SD) for continuous variables. A 1-way analysis of variance (ANOVA) test was used in case of parametric data and one-way analyses of variance with multiple comparison post-test (LSD) was used to compare the means between *SLCO1B1* genotype groups as indicated. $P < 0.05$ was considered to be significant. A Kruskal–Wallis test was used in case of nonparametric data. Statistical analysis was performed using the SPSS 21.0 software (SPSS; Inc, Armonk, USA).

Results

Demographic and laboratory characteristics of the 636 participants are shown in Table 1. There was no significant difference in age, sex or any of the biochemical markers when analysed by *SLCO1B1* genotypes. A schematic of the various *SLCO1B1* alleles is shown in Figure 1. The most frequent genotypes were *1a/*1a, *1b/*1b, *1a/*1b and *1b/*15. We excluded genotypes *15/*15, *1a/*5 and *5/*5 for further analysis due to their small sample size, and genotypes *1a/*15 and *1b/*5 as for methodological reasons they cannot be separated.

Analysis of the remaining 614 subjects is shown in Table 2. There were significant differences in serum triglycerides and HDL between the four genotypes. Triglycerides were highest in those genotypes *1a/*1a and *1a/*1b and lowest in *1b/*1b (Figure 2). Levels of HDL were lowest in *1a/*1a and highest in genotype *1b/*1b (Figure 3). Thus, genotype *1b/*1b has the preferred profile (lowest triglycerides and

highest HDL) whilst genotype *1a/*1a has an unfavourable profile (highest triglycerides and lowest HDL).

Discussion

Variation in numerous genes coding for drug transport and/or metabolic pathways are linked to levels of serum metabolites, including lipids. One of these genes, *SLCO1B1* is located on chromosome 12, with single nucleotide polymorphisms (SNPs) (388A>G and 521 T > C) [16,17]. We found significant differences in the frequency of haplotypes *SLCO1B1* *1a(388A-521 T), *1b(388 G-521 T), *5(388A-521 C), *15(388 G-521 T): *1b/*1b, *1b/*15, *1a/*1b, *1a/*15 and *1a/*1a are common, together accounting for 96.5% of our cohort. However, these data differ from those of Zhong et al. [18], who found, for example, an *1b/*1b frequency of 40%, whereas in our population the frequency is 29%. The reasons for this are unclear but may reflect difference in recruitment in that their cohort is some five times larger than ours.

Organic anion-transporting polypeptide 1B1 (OATP1B1) is a membrane transport protein of the organic anion-transporting polypeptide (OATP) transporter superfamily, coded for by *SLCO1B1* [19–21]. A form of OATP1B1 coded by a mutant *SLCO1B1* causes a decreased ability to transport proteins, which decreased ability of liver to ingestion drugs, resulting in increased blood concentration of statins, and increased risk of rhabdomyolysis or myopathy [15,22]. Hepatic uptake transporters such as OATP1B1 are well-recognized determinants of drug disposition. Therefore, it is important to gain insights into protein regions important for substrate recognition and transport [23].

Genotypes of *SLCO1B1* influence adverse reactions with statins [18]. *SLCO1B1* *5/*5, *5/*15, *15/*15 are high-risk genotypes with adverse reactions to statins. *1a/*5, *1a/*15, *1b/*15 genotypes are at medium risk. *1a/*1a, *1a/*1b, *1b/*1b genotypes are low risk [24,25]. Accordingly, we calculate that 2.7% of our cohort are at high risk for adverse statins reactions, a finding that promotes the view that those at high-risk need additional prevention and control guidance

Table 1. Demographic and laboratory characteristics of the study participants.

	*1a/*1a	*1b/*1b	*1a/*1b	*1b/*15	*1a/*15 and *1b/*5	*15/*15	*1a/*5	*5/*5
Subjects (n, %)	54(8.5)	186(29.3)	134(21.1)	175(27.5)	65(10.2)	14(2.2)	5(0.8)	3(0.5)
Men (n, %)	33(61.1)	110(59.1)	74(55.2)	84(48.0)	40(61.5)	9(64.3)	2(40)	0(0)
Age (years)	48.6(12.2)	48.8(12.6)	49.4(12.7)	49.0(13.2)	50.7(13.6)	49.2(5.3)	56.0(13.8)	49.0(13.8)
Glucose (mmol/L)	5.6(2.1)	5.3(1.4)	5.7(2.0)	5.6(2.4)	5.5(1.7)	5.4(0.6)	7.0(2.7)	4.7(0.2)
Urea (mmol/L)	4.9(1.0)	5.3(2.8)	4.9(1.3)	4.9(1.7)	5.8(2.9)	5.1(1.1)	5.2(0.9)	4.1(0.3)
ALT (IU/L)	32(18.6)	27(24.3)	31(27.3)	31(45.9)	27(14.0)	51(51.5)	21(3.9)	20(4.9)
AST (IU/L)	26(10.2)	24(19.6)	25(23.6)	29(58.4)	30(46.2)	35(20.4)	19(3.1)	18(1.6)
GGT (IU/L)	50(48.0)	38(105.3)	39(38.2)	37(41.3)	46(63.2)	127(182.8)	29(8.8)	16(5.8)
Creatinine (μmol/L)	70(29.0)	67(16.7)	65(31.2)	67(32.2)	72(28.9)	64(14.9)	63(18.5)	47(3.5)
Uric Acid (μmol/L)	384(105)	356(96)	372(107)	355(110)	358(116)	368(82)	347(119)	362(12)

^aThe SNPs 521 T > C and 388A>G are within *SLCO1B1*. Due to methodological limitations, when the SNPs is 388AG,521 TC, it may be *1a/*15 or *1b/*5.
^bCase (%), Biochemical marker values are mean (SD).

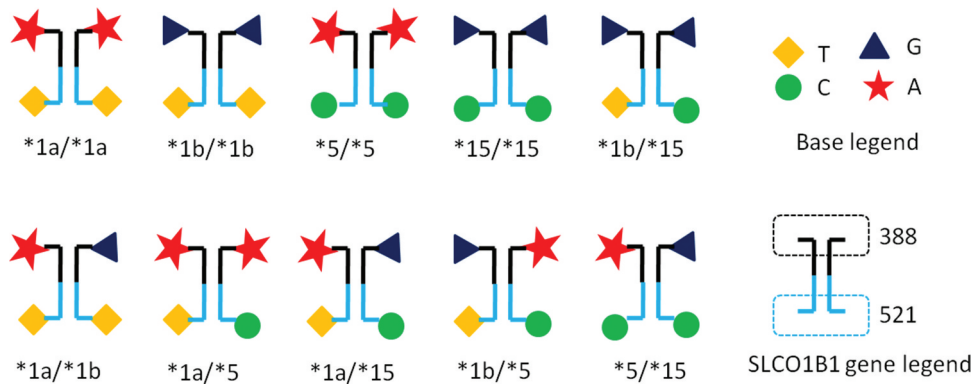


Figure 1. Representation of possible *SLCO1B1* allele/genotype combinations and their particular nucleotide composition.

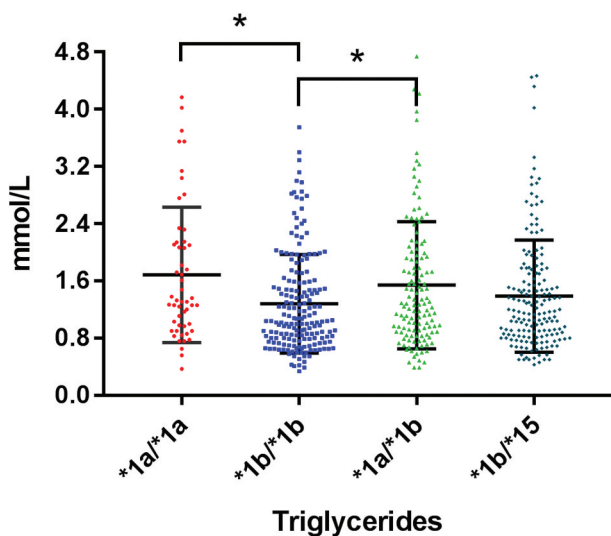


Figure 2. Association of *1a/*1a, *1b/*1b, *1a/*1b and *1b/*15 genotypes and their triglycerides levels. *, $P < 0.05$. ^a $P = 0.012$, compared *1a/*1a with *1b/*1b groups. ^b $P = 0.041$, compared *1b/*1b* with *1a/*1b groups. The long and short black bars, mean and SD.

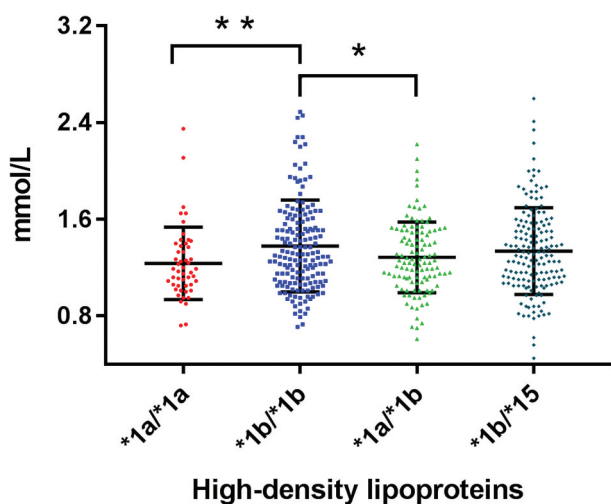


Figure 3. Association of *1a/*1a, *1b/*1b, *1a/*1b and *1b/*15 genotypes and their high-density lipoproteins levels. *, $P < 0.05$. **, $P < 0.01$, ^a $P = 0.007$, compared *1a/*1a with *1b/*1b groups. ^b $P = 0.015$, compared *1b/*1b* with *1a/*1b groups. The long and short black bars, Mean and SD.

Table 2. Association between *SLCO1B1* genotypes and serum lipids.

	Cholesterol (mmol/L)	Triglycerides (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
*1a/*1a	5.1(0.8)	1.3(1.0,2.2) ^a	1.24(0.30) ^c	3.2(0.9)
*1b/*1b	5.0(0.9)	1.1(0.8,1.6) ^{a,b}	1.39(0.42) ^{c,d}	3.2(1.2)
*1a/*1b	5.1(1.0)	1.3(0.9,2.1) ^b	1.28(0.29) ^d	3.1(0.9)
*1b/*15	5.2(1.2)	1.2(0.8,1.8)	1.34(0.36)	3.1(1.0)
<i>P</i> value	0.378	0.004	0.018	0.965

^a $p = 0.012$, ^b $p = 0.041$, ^c $p = 0.007$, ^d $p = 0.015$. Data mean (SD) or median (interquartile range). Overall *p* values by ANOVA except triglycerides – Kruskal-Wallis.

such as diet control and lifestyle improvement, and also regular health care screening, so enabling early diagnosis and targeted treatment.

In addition to raised serum cholesterol, the risk of coronary heart disease is increased in people with mild to moderate elevated serum triglycerides levels [26]. It is now well accepted that triglycerides have independent effects on CHD risk. HDL can transport cholesterol in peripheral tissues to the liver for catabolic metabolism. The reverse transport of cholesterol can reduce the deposition of cholesterol in the vascular wall and play an anti-atherosclerosis role. High triglycerides or low HDL levels were also associated with an increased risk of atherosclerotic cardiovascular disease [27]. The results showed that *1a and *1b were the most common haplotypes in *SLCO1B1*. Those with genotypes *1a/*1a and *1a/*1b were at high risk for cardiovascular disease (CVD) because they had higher triglyceride levels and lower HDL levels. The *1b/*1b group had lower triglycerides levels and higher HDL levels, so the risk of cardiovascular disease might be relatively low.

The important and essential action to prevent cardiometabolic diseases is to promote a healthy lifestyle throughout life. Common recommendations have been developed to guide actions for the primary prevention of cardiometabolic diseases among all populations [26–28]. Should this prove difficult, drugs treatments are required, but these have side effects. *SLCO1B1* genotypes affect the incidence of adverse reactions to statin therapy, and *SLCO1B1* genotyping can be used to identify high-risk groups so that this knowledge may be useful in patients

who are using or considering treatment with statins. We recognise certain limitations: the number of subjects per genotype is not large, and we cannot be certain that some were taking lipid-lowering therapy. Nevertheless, we have identified potentially high-risk *SLCO1B1* genotypes that could be helpful for early diagnosis and prevention, individualized drug therapy, and even gene therapy.

This paper represents an advance in biomedical science because it points to a link between SNPs in *SLCO1B1* and triglycerides and HDL.

Summary table

What is known about this subject?

- Increased serum triglycerides and reduced HDL are risk factors for cardiovascular disease
- Certain *SLCO1B1* genotypes are linked to adverse effects of statins

What this paper adds

- Certain *SLCO1B1* genotypes are linked to increased serum triglycerides and reduced HDL
- Around 2.7% of this population carry *SLCO1B1* genotypes that put them at risk of adverse effects of statins.

Disclosure statement

No potential conflict of interest was reported by the authors.

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