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ORIGINAL RESEARCH

SLCO1B1 and *ABCG2* Gene Polymorphisms in a Thai Population

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Introduction: Genetic polymorphisms of drug transporters influence drug transporter activity and alter pharmacokinetic profiles of the drugs. Organic anion transporting polypeptide 1B1 (OATP1B1) and breast cancer resistance protein (BCRP) are important transporters encoded by solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene and ATP-binding cassette subfamily G member 2 (*ABCG2*) gene, respectively. Polymorphisms in these genes are associated with increased plasma statins concentrations, statin-induced myopathy and poor response to allopurinol treatment.

Purpose: We explored allele and genotype frequencies of S*LCO1B1* and *ABCG2* genes including their predicted phenotypes in 53 Thai participants. Of these, 17 had chronic kidney disease and were on statins.

Materials and Methods: Genotyping analysis for *SLCO1B1* c.521T>C (rs4149056), c.388A>G (rs2306283), g.-11187G>A (rs4149015), and *ABCG2* c.421C>A (rs2231142) was done by using TaqMan® Real time PCR. All were tested for Hardy–Weinberg Equilibrium.

Results: Most of the participants (80%) had normal function haplotypes *SLCO1B1* (**1A* and **1B*) while decreased (**5, *15,* and **17*) and unknown (**21*) function haplotypes were less observed. Four phenotypes of *SLCO1B1* were observed: 69.81% had normal function (**1A/*1A*,**1A/*1B*, and **1B/*1B*), 13.21% had intermediate function (**1A/*17*, **1B/*15* and **1B/*17*), 9.43% had indeterminate function (**1A/*21* and **1B/*21*) and 7.55% had low function (**5/*15, *15/*15,* and **15/*17*). *ABCG2* c.421A allele frequency was 25%. The frequency of *ABCG2* c.421CA and AA phenotypes were 37.7% and 5.7%, respectively. The allele and genotype frequencies observed are consistent with reports in Asians. However, there were differences in major allele distributions between Asians and Caucasians for *SLCO1B1* c.388A>G; *SLCO1B1* c.388G were highly found in Asians, but c.388A were more observed in Caucasians.

Conclusion: This study showed that in the Thai population, there were 4 SNPs of *SLCO1B1* and *ABCG2* genes. This finding may be clinically applied to minimize inter-individual variability of drugs such as statins and allopurinol. Further study with a larger sample size is needed to assess the drug profiles and responses to treatment.

Keywords: pharmacogenetics, pharmacogenomics, drug transporters, *SLCO1B1*, *ABCG2*, OATP1B1, BRCP

Introduction

Drug transporters are mostly localized at the basolateral or apical membranes of organs involved in drug biotransformation such as the liver, intestine, brain, and kidneys, and play an important role in pharmacokinetic process.[1–3] Genetic polymorphisms of drug transporters affect drug transportation across membranes, and contribute to variability in drug disposition and responses.[4]

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Solute-Linked Carrier (SLC) and ATP-binding cassette (ABC) are two major superfamilies of drug transporters. SLC, including *SLCO* (also known as *SLC21), SLC22*, and *SLC47* encode membrane proteins that are mainly responsible for drug uptake. An uptake transporter, organic anion transporting polypeptides (OATPs) including OATP1B1, is encoded by solute carrier organic anion transporter family member 1B1 (*SLCO1B1)* gene. OATP1B1 is a sodium-independent bile acid transporter that generally transports amphipathic molecules through the basolateral membrane of the hepatocytes.[5,6] On the other hand, an efflux transporter, breast cancer resistance protein (BCRP), is encoded by ATP binding cassette subfamily G member 2 (*ABCG2)* gene of the ABC family and is involved in drug resistance.[2–4]

Previous reports have shown the effects of genetic polymorphisms of OATP1B1 hepatic uptake transporter and BCRP efflux transporter on pharmacokinetic properties of statins.[4,5,7–10] The Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline, therefore, recommends genetic testing for these genes prior to starting treatment with statins in order to minimize the risk of developing statins-induced myopathy.[11] Moreover, BCRP transporter polymorphism, rs2231142 c.421C>A, is also associated with urate transporter dysfunction which causes the patients to have a higher risk for developing gout and hyperuricemia by overloading the renal urate and under excreting the products out of the extrarenal system.[12] However, there were reports of differences in allele frequencies of *SLCO1B1* and *ABCG2* genes among different ethnicities. *SLCO1B1* c.521T>C variant is commonly found in Caucasians whereas *ABCG2* c.421C>A variant is highly observed in Asians.[4,7,13–19] However, data in the Thai population in regards to genetic polymorphisms of these drug transporters are limited. It is very important to fully obtain the overall allele and genotype frequencies of both SLC and ABC families of drug transporters and factors associated with clinical data in real-life setting among Thai patients who are treated with statins.

Here, we investigated the allele and genotype frequencies of both *SLCO1B1* gene (rs4149056, rs2306283, rs4149015) and *ABCG2* gene (rs2231142) in a cohort of Thai patients attending an Out-Patients Clinic of the King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

Materials and Methods

This cross-sectional study was a sub-study of a clinical trial entitled, "CYP3A and drug transporters activity changes in Thai elderly with or without chronic kidney disease using a microdose cocktail" (#TCTR20180312002; manuscript in preparation). The study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, and was conducted in compliance with the Declaration of Helsinki and the Principle of Good Clinical Practice. Written informed consents were obtained from all participants prior to the start of the study.

Participants

Fifty-three Thai participants were enrolled into the study. Of these, 36 healthy adults were aged 20–70 years, did not have hypertension or dyslipidemia, had normal physical examination and laboratory results. Seventeen participants had Chronic Kidney Disease (CKD) and were treated with statins (simvastatin or atorvastatin). Comorbidity, history of statin treatment, dose per day, duration of use, and reasons for changing statin were retrospectively extracted from the participants' medical history from 2007 to 2019.

Genotyping Analysis and Predicted Phenotypes

Venous blood sample (3 mL) was collected from each participant into an EDTA tube. Genomic DNA was extracted by PureLink® Genomic DNA kit (ThermoFisher Scientific). *SLCO1B1* c.521T>C (rs4149056), c.388A>G (rs2306283), g.-11187G>A (rs4149015), and *ABCG2* c.421C>A (rs2231142) were detected by TaqMan® Real time Polymerase Chain Reaction (PCR) using TaqMan Drug Metabolism Genotyping Assays (Applied Biosystem, ThermoFisher Scientific). PCR was performed with the quantitative real-time PCR (q-PCR) system (StepOnePlus™ Real-Time PCR System, ThermoFisher Scientific). Predicted functions of the haplotypes were assigned according to PharmGKB.[20] Predicted phenotypes and * allele nomenclature of OATP1B1 were assigned according to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline.[11]

Statistical Analysis

Allele and genotype frequencies were directly calculated and reported using descriptive statistics. Heterogenous and homozygous genotypes were defined as genotypes consisted of one and two copies of variant alleles, respectively. The Hardy-Weinberg equilibrium test was

Table 1 Characteristics of the Participants (n = 53)

Parameters	Mean±Standard Deviation	Reference Range
Age (year)	54±20	
Body mass index (kg/m^2)	23.17±2.95	
Fasting plasma glucose (mg/dL)	94±15	70–105
Serum creatinine (g/dL)	1.29±0.94*	0.73–1.18 (male) 0.55–1.02 (female)
Total protein (g/dL)	7.6±0.4	6.4–8.3
Albumin (g/dL)	4.4±0.2	3.5–5.0
Total bilirubin (mg/dL)	0.69±0.44	0.2–1.2
Direct bilirubin (mg/dL)	0.27±0.11	0.0–0.5
Aspartate aminotransferase (U/L)	21±8	5.0–34.0
Alanine aminotransferase (U/L)	20±12	0.0–55.0
Alkaline phosphatase (U/L)	64±23	40–150
Total cholesterol (mg/dL)	201±43	<200
Triglyceride (mg/dL)	123±75	<150
Low-density lipoprotein cholesterol (mg/dL)	118±34	100–159
High-density lipoprotein cholesterol (mg/dL)	54±14	40–60

Notes: The reference range used was from the HIV-NAT research laboratory for adults (2018). *Chronic kidney disease participants were included in the analysis which increased the level of serum creatinine.

determined by Haploview version 4.2. P-value of <0.05 was considered statistically significant.

Results

The overall characteristics of 53 participants are summarized in Table 1. There were 28 females and 25 males in this cohort. The minor allele frequencies of *SLCO1B1* and *ABCG2* genes in this study and other ethnicities are summarized in Table 2.

The predicted normal function haplotypes of *SLCO1B1* (**1A* and **1B*) were mostly found in the participants while predicted decreased (**5, *15,* and **17*) and unknown (**21*) function haplotypes were also observed in approximately 20% of the participants (Figure 1A).

Four predicted phenotypes were observed (Figure 1B). More than half of the participants had normal function phenotypes of *SLCO1B1* (**1A/*1A*, **1A/*1B,* and **1B/*1B*). Interestingly, 9.43% of the participants had indeterminate function phenotypes of *SLCO1B1* (**1A/*21* and **1B/*21*) while only 7.55% of the participants had low function phenotypes (**5/*15, *15/*15,* and **15/*17*).

Statins treatment for CKD participants are shown in Table 3. Most of the participants received either simvastatin (current dose range 10–40 mg/day) or atorvastatin (current dose range 20–40 mg/day). Fourteen participants had *SLCO1B1* predicted phenotype normal function. One participant (participant number 04) had *SLCO1B1* intermediate function and another one participant (participant number 09) had *SLCO1B1* poor function. Two participants (participant number 08 and participant number 13) were in the indeterminate function group. There was no serious adverse event related to statins-induced myopathy. There were some statin dose reduction/increase or change of statin used but these were due to other factors and were not related to any adverse events.

As *SLCO1B1* c.521T>C and *ABCG2* c.421C>A were associated with the pharmacokinetic process of rosuvastatin, plasma rosuvastatin concentration in 17 CKD participants were estimated (Table 4). Nine out of 17 participants were likely to have increased plasma rosuvastatin concentrations if the standard dose of rosuvastatin were administered. Participant number 09 had *SLCO1B1* c.521T>C and

Table 2 Minor Allele Frequencies of *SLCO1B1* and *ABCG2* Genes

Minor Allele Frequency (%)	*SLCO1B1*			*ABCG2*
	c.521T>C (rs4149056)	c.388A>G (rs2306283)	g.-11187G>A (rs4149015)	c.421C>A (rs2231142)
GMAF[24–27]	8.8	38.8	5.5	11.9
Thai				
Current study (n = 53)	14.2	21.7	12.3	24.5
Medhasi et al2016[21] (n = 119)	12.2	26.9	8.4	30.7
Chamnanphon et al 2020[45] (n = 51)	4.0	n/a	n/a	19.0
Chinese				
Yang et al 2020[13] (n = 140)	11.1	18.9	n/a	n/a
De Jong et al 2004[17] (n = 84)	n/a	n/a	n/a	34.0
Korean				
Choi et al 2008[14] (n = 200)	11.8	28.8	n/a	n/a
Kim et al 2010[18] (n = 250)	n/a	n/a	n/a	28.8
Woo et al 2017[22] (n = 50)	n/a	n/a	17.7	n/a
Japanese				
Nishizato et al 2003[15] (n = 120)	15.8	37.1	n/a	n/a
Yamagishi et al 2010[23] (n = 3923)	n/a	n/a	n/a	31.2
Caucasian				
Pasanen et al 2006[16] (n = 468)	20.2	46.2	9.7	n/a
De Jong et al 2004[17] (n = 172)	n/a	n/a	n/a	11.3
African-American				
Thompson et al2005[46] (n=160)	3.8	25.6	n/a	n/a
De Jong et al 2004[17] (n = 94)	n/a	n/a	n/a	5.3

Abbreviations: *ABCG2*, ATP binding cassette subfamily G member 2; *SLCO1B1*, solute carrier organic anion transporter family member 1B1; SNPs, single nucleotide polymorphisms; GMAF, Global minor allele frequency; n/a indicates data not available.

ABCG2 c.421C>A genes and the genotypes were CC and CA, respectively. This participant is likely to be most affected by these genetic alterations in terms of increased plasma rosuvastatin concentrations.

Discussion

We detected 4 SNPs of *SLCO1B1* and *ABCG2* genes in the Thai population including *SLCO1B1* c.521T>C, *SLCO1B1* c.388A>G, *SLCO1B1* g.-11187G>A and *ABCG2* c.421C>A. We found that the genotype frequencies of *SLCO1B1* and *ABCG2* genes in this cohort were mostly of the wild type except for *SLCO1B1* c.388A>G which was a homozygous variant and was highly observed. Minor allele frequencies of *SLCO1B1* and *ABCG2* genes in this study was comparable to another Thai population study[21] and other Asian populations including Chinese,[13,17] Korean,[14,18,22] and Japanese[15,23] and had slightly higher global minor allele frequency (GMAF)[24–27] (Table 2).

Populations from different regions have distinct genetic variation that can cause variability in the pharmacokinetic of the drug substrates.[16,24] Comparisons of the allele and genotype frequencies of these 4 SNPs among our Thai population and Chinese,[13,17] Korean,[14,18,22] Japanese[15,19] and Caucasian[16,17] are shown in Figures 2 and 3. The allele and genotype frequencies observed in this study were in line with previous reports conducted in Asians (major alleles: c.521T, g.-11187G and wild type genotypes: c.521TT and g.-11187GG, respectively). However, there were differences in major allele distributions between Asians and Caucasians for *SLCO1B1* c.388A>G. *SLCO1B1* c.388G were highly found in Asians but c.388A were more observed in Caucasians (Figure 2B). For *ABCG2* c.421C>A, there were also similar major allele (c.421C) and genotype (c.421CC) among Asians and Caucasians except for Chinese who had slightly different genotype frequencies as shown in Figures 2D and 3D.

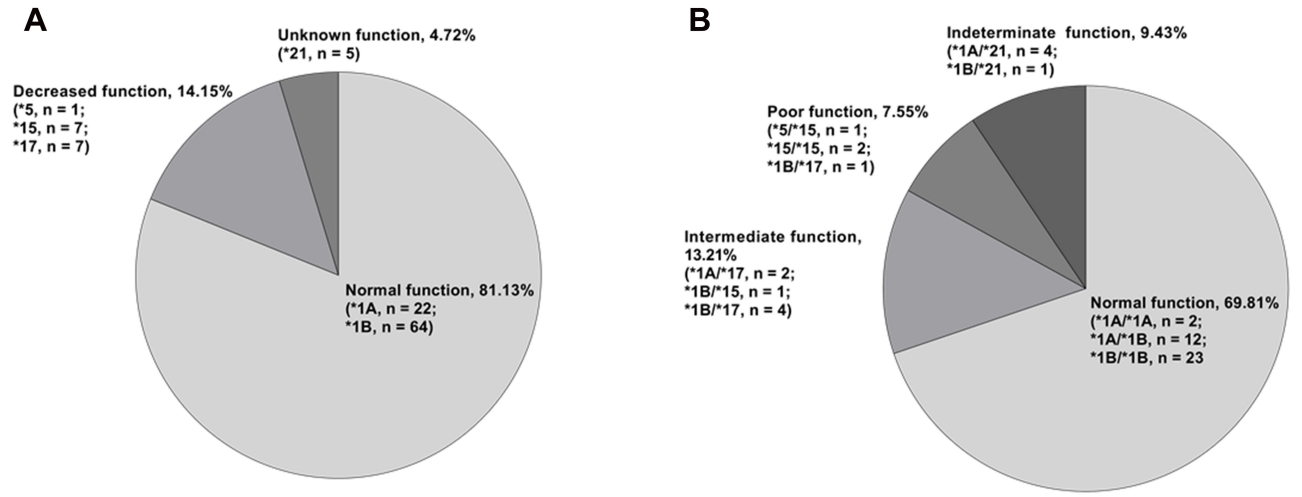

Figure 1 Haplotype, genotype, and predicted phenotype frequencies of *SLOC1B1* gene. (**A**) Haplotype and predicted functions (total n = 106). (**B**) Genotype and predicted phenotypes (total n = 53).
Note: The assigned functions were reported according to PharmGKB[20] and the predicted phenotypes were reported according to the CPIC guideline.[11]

All SNPs measured in this study have been reported to be associated with a decreased OATP1B1 hepatic uptake transporter and BCRP efflux transporter functions. These genetic polymorphisms can result in higher drug exposure and toxicity of statins.[8,14,15,29–31]

Interestingly, our cohort and other Asian populations frequently had *SLCO1B1* c.388GG which corresponded to *SLCO1B1*15* and **17*. The *SLCO1B1*5* (carrying c.521T>C), **15* (carrying c.388A>G and c.521T>C) and **17* (carrying c.388A>G, c.521T>C and g.-11187G>A) were associated with a decreased OATP1B1 activity resulting in a lower clearance of simvastatin acid.[11,29,30,32] In our study, we detected *SLCO1B1*15* and **17* (haplotype frequency 6.6% for both, Figure 3).

The CPIC guideline stated that genotype of *SLCO1B1* may imply *SLCO1B1* phenotype which may implicate that the dose of simvastatin should be adjusted.[11] In this study, we found *SLCO1B1*1A/*17, *1B/*15, *1B/*17* and **5/*15, *15/*15, *15/*17* genotypes which had intermediate and low function phenotypes, respectively, in approximately 20% of the cohort. These phenotypes are associated with myopathy risk. The guideline, therefore, recommends using low dose of simvastatin when initiating statin treatment or the use of alternative statins, for example, pravastatin or rosuvastatin.[11] Unfortunately, the medical history of statins in 17 CKD participants with *SLCO1B1* genotypes and predicted phenotypes were not available so we could not assess the risk of developing myopathy. There was only one participant who had *SLCO1B1* intermediate function and this participant had an improved low-density lipoprotein cholesterol level after lifestyle modification. Another participant had *SLCO1B1* poor function and no medical history of statin use.

Previous studies have reported that *ABCG2* c.421A allele was associated with high plasma rosuvastatin concentration.[10,33] The Annotation of Swissmedic Label for rosuvastatin and *ABCG2, SLCO1B1*[34] also recommended that a lower dose of rosuvastatin (Crestor®) should be administered in patients who have a higher risk of rosuvastatin exposure, especially among Asians or patients with variant *SLCO1B1* c.521T>C and/or *ABCG2* c.421C>A. Tests for genetic polymorphisms should be acquired before starting treatment with statin. For example, participant number 09 had *SLCO1B1* low function phenotype of OATP1B1, and *ABCG2* c.421CA genotype. Hence, if this participant started to use rosuvastatin, the physician should consider reducing the dose of the drug.

The influence of genetic polymorphism on pharmacokinetic of other statins have also been reported. The higher plasma concentrations of pravastatin in patients with *SLCO1B1* c.521C allele is associated with decreased total and non-renal clearance of pravastatin.[15] Area under the plasma concentration-time curve (AUC) of pitavastatin, rosuvastatin and atorvastatin were increased with different magnitude of *SLCO1B1* c.521CC genotype.[8,14,31] *ABCG2* c.421AA genotype was associated with an increased AUC of rosuvastatin, atorvastatin, fluvastatin and simvastatin

Table 3 Genotype and Predicted Phenotype of *SLCO1B1* with Current Types of Statins Used, Doses and Reasons for Changing Type or Dose of the Statins in 17 CKD Participants

SLCO1B1 Predicted Phenotype	Genotype	Participant Number	Previous Type of Statin Used and Dose (mg/day) When Treatment Was Started	Current Type of Statin and Dose Used (mg/day)	Change of Dose	Duration Before Stopping or Changing Type or Dose of Statins	Reason for Changing the Dose of Statins
Normal function	*1B/*1B	01	–	–	–	–	–
	*1A/*1B	02	–	–	–	–	–
	*1B/*1B	03	Simvastatin, 40 mg	None	↓	2 years	Improved LDL by lifestyle modification
	*1B/*1B	05	Simvastatin, 5 mg	Atorvastatin, 40 mg	↓	9 years	Increased serum creatinine
	*1A/*1B	06	Atorvastatin, 40 mg	Simvastatin, 20 mg	–	1 year	No reported data
	*1A/*1B	07	Simvastatin, 40 mg	Simvastatin, 20 mg	↓	3 months	Improved LDL
	*1B/*1B	10	Simvastatin, 10 mg	Atorvastatin, 40 mg	↑	1 year	No reported data
	*1B/*1B	11	Simvastatin, 40 mg	Atorvastatin, 20 mg	–	8 years	Uncontrolled dyslipidemia
	*1B/*1B	12	Simvastatin, 10 mg	Simvastatin, 10 mg	–	–	–
	*1B/*1B	14	Simvastatin, 20 mg	Atorvastatin, 20 mg	↑	2 years	No reported data
	*1A/*1B	15	Simvastatin, 40 mg	Simvastatin, 40 mg	–	–	–
	*1A/*1B	16	Atorvastatin, 40 mg	Atorvastatin, 40 mg	–	–	–
	*1A/*1B	17	Simvastatin, 20 mg	Simvastatin, 20 mg	–	–	–
Intermediate function	*1B/*17	04	Simvastatin, 20 mg	Simvastatin, 10 mg	↓	4 years	Improved LDL by lifestyle modification
Poor function	*15/*17	09	–	–	–	–	–
Indeterminate function	*1B/*21	08	Simvastatin, 20 mg	Atorvastatin, 40 mg	↑	2 years	Ischemic stroke
	*1A/*21	13	Simvastatin, 10 mg	Simvastatin, 10 mg	–	–	–

Notes: The assigned functions were reported according to PharmGKB[20] and the predicted phenotypes were reported according to the CPIC guideline.[11]

Abbreviations: LDL, low-density lipoprotein cholesterol; *SLCO1B1*, solute carrier organic anion transporter family member 1B1; -, no change or no data; ↓, dose of statins was reduced; ↑, dose of statins was increased.

Table 4 *SLOC1B1* c.521T>C Genotype, *ABCG2* c.421C>A Genotype and Estimated Rosuvastatin Plasma Concentrations in 17 CKD Participants

Estimated Plasma Rosuvastatin Concentration When the Participants Were Treated with the Standard Dose of Rosuvastatin	*SLCO1B1* c.521T>C Genotype	*ABCG2* c.421C>A Genotype	Participant Number
Normal rosuvastatin plasma concentration	TT	CC	01
	TT	CC	03
	TT	CC	06
	TT	CC	07
	TT	CC	10
	TT	CC	11
	TT	CC	12
	TT	CC	16
Increased rosuvastatin plasma concentration	TT	CA	02
	TT	CA	05
	TT	CA	08
	TT	CA	14
	TT	CA	15
	TT	CA	17
	TT	AA	13
	TC	CC	04
	CC	CA	09

Abbreviations: *ABCG2*, ATP binding cassette subfamily G member 2; *SLCO1B1*, solute carrier organic anion transporter family 1B1.

lactone as BCRP efflux activity at the small intestine was reduced, resulting in an increased bioavailability of the drugs.[10,35,36]

Furthermore, BCRP is an important transporter for regulating uric acid transport in the kidneys and gastrointestinal tract.[37] *ABCG2* c.421C>A polymorphism

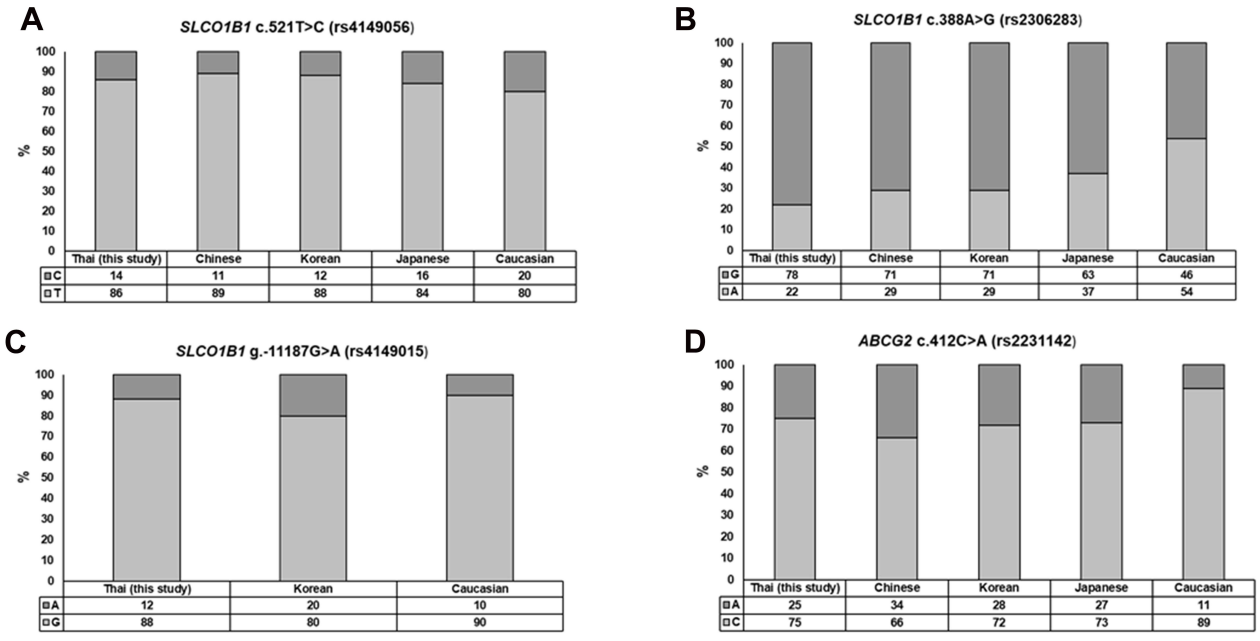

Figure 2 Allele frequencies of SNPs in *SLCO1B1* and *ABCG2* genes in Thai participants compared to other populations.
Notes: (**A**) and (**B**) Chinese,[13] Korean,[14] Japanese,[15] and Caucasians;[16] (**C**) Korean[22] and Caucasians;[16] (**D**) Chinese,[17] Korean,[18] Japanese,[19] and Caucasians.[17]

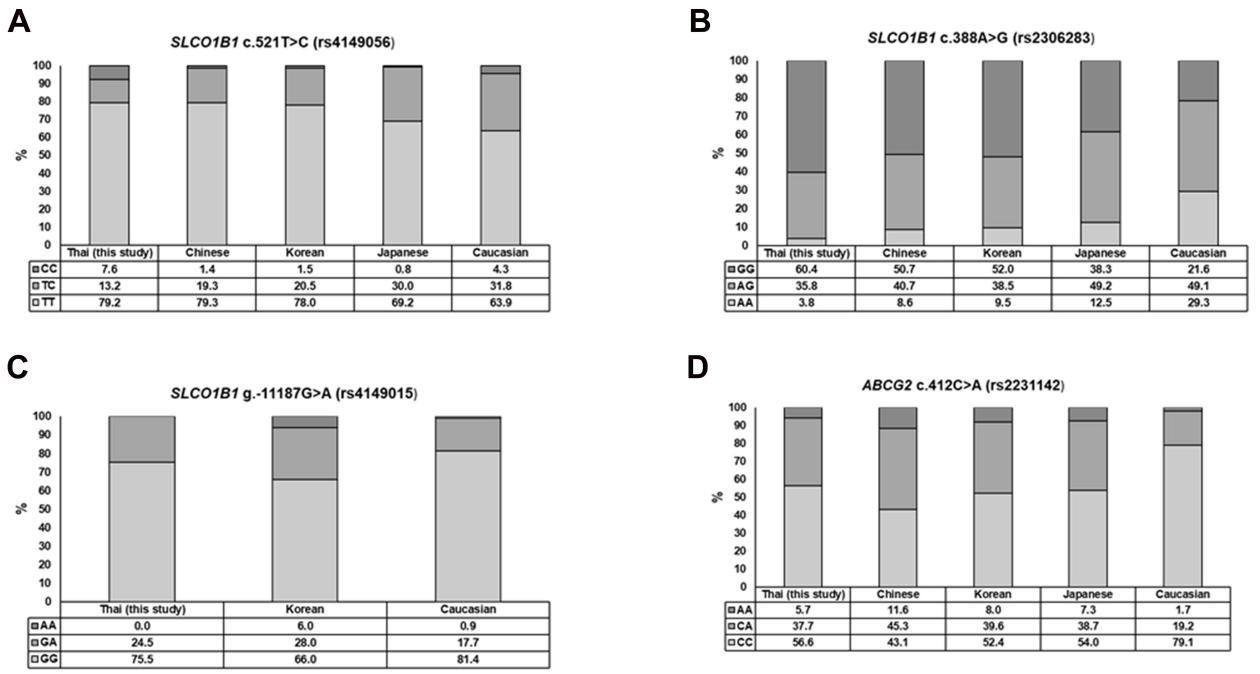

Figure 3 Genotype frequencies of SNPs in *SLCO1B1* and *ABCG2* genes in Thai participants compared to other populations.
Notes: (**A**) and (**B**) Chinese,[13] Korean,[14] Japanese,[15] and Caucasians;[16] (**C**) Korean[22] and Caucasians;[16] (**D**) Chinese,[17] Korean,[18] Japanese,[19] and Caucasians.[17]

reduced 53% of urate transport rate compared to wild type and was found in approximately 10% of the patients with gout in Caucasians.[38] Previous studies have also reported that *ABCG2* c.421C>A polymorphism was associated with significant increase in familial early-onset hyperuricemia and gout in pediatric-onset patients.[39,40] Moreover, it has been reported that *ABCG2* c.421C>A polymorphism reduces the activity of allopurinol, the first-line therapy for lowering serum uric acid.[41,42]

Of note, in our study, 7 CKD participants were on allopurinol. Of these, 3 participants had *ABCG2* c.421CA and 1 participant had *ABCG2*c.421AA (data not shown). Unfortunately, since the data was retrieved retrospectively, we cannot find evidence of allopurinol treatment outcome for these participants. Hyperuricemia/gout is a common comorbidity of CKD. Almost 42% of patients using allopurinol failed to achieve allopurinol treatment goal.[43] The key reasons for allopurinol treatment failure could either be due to the reduced renal function which causes the titration of the allopurinol dose or poor adherence.[41,42] Additionally, the influence of *ABCG2* c.421C>A polymorphism on allopurinol response should also be taken into account as a possible factor for allopurinol treatment failure in CKD patients.

There are some limitations in this study. The sample size was relatively small. We found no deviation from Hardy-Weinberg principle in all detected SNPs except for *SLCO1B1* c.521T>C which may be due to the sample size and linkage disequilibrium.[30,44] There are unknown function haplotypes (approximately 5%) and indeterminate function of predicted phenotypes (approximately 10%) of *SLCO1B1* observed in our cohort which might be of interest to be further explored. However, these limitations do not make our conclusion inaccurate. This study's genetic data are important and beneficial to the patients by providing the physicians the fundamental information on how to manage patients who have these polymorphisms and the need to be on statins.

Conclusion

In summary, this study provided the evidence that Thai patients have 4 SNPs in *SLCO1B1* and *ABCG2* genes. Even though we were not able to find an association of these genetic polymorphisms and the use of statins and allopurinol due to the study's sample size, however, the results indicated that we should be more vigilant in administering drugs to the Thai population because of inter-individual variability of the drug transporter functions. A larger prospective study using genotype-guided therapy and assessing the pharmacokinetic profiles of the drugs are warranted.

Data Sharing Statement

The data are available on reasonable request to the correspondence author.

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Disclosure

The authors report that there are no conflicts of interest in this work.

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