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Background : *Genetic polymorphisms of protein transporters can alter the pharmacokinetics and pharmacodynamics of several substrate drugs including antiretrovirals (ARVs). The polymorphisms of ABCB1 and SLCO1B1 have been investigated in Caucasian and some of Asian populations. However, the information of these single nucleotide polymorphisms (SNPs) in Thai population are limited.*

Objective : *The aim of this study was to determine the frequencies of the variant genotype and allele of ABCB1 and SLCO1B1 in Thai HIV-infected patients and to compare with the frequencies obtained from other populations.*

Methods : *Three SNPs: ABCB1 3435C>T, ABCB1 2677G>T and SLCO1B1 521T>C were identified by Taqman allelic discrimination assays using real time polymerase chain reaction system. Chi-square test was performed to compare the distributions of observed genotypes with expected genotypes according to Hardy-Weinberg equilibrium and to compare the proportions of allele frequencies between our population and other ethnic populations.*

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Results : *A total of 521 patients were included in this study. The homozygous variant genotypes were 22.50%, 29.75%, and 3.84% for ABCB1 3435TT, ABCB1 2677TT and SLCO1B1 521CC, respectively. The allele frequencies of ABCB1 3435C>T, ABCB1 2677G>T and SLCO1B1 521T>C were 47.70%, 51.06%, and 11.90%, respectively. The prevalence of ABCB1 2677G>T was similar to other Asian populations, but the prevalence of ABCB1 3435C>T was different from the Chinese and the Korean populations. In addition, higher variant allele frequencies of ABCB1 3435T, ABCB1 2677T and SLCO1B1 521C were observed in Thais compared to African Americans.*

Conclusion : *We found that gene polymorphisms of ABCB1 and SLCO1B1 were frequent in Thai HIV-infected patients. These results could provide an evidence for future clinical studies regarding the variability in treatment responses and a risk of adverse effects of ARVs which are substrate of these transporters in Thai population.*

Keywords : *ABCB1, SLCO1B1, polymorphisms, Thai HIV-infected patients.*

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เหตุผลของการทำวิจัย : *ภาวะพหุสัณฐานของยีนที่ควบคุมโปรตีนขนส่งยาสามารถส่งผลให้เกิดการเปลี่ยนแปลงทางเภสัชจลนศาสตร์และเภสัชพลศาสตร์ของยาหลายชนิด ซึ่งเป็นซับสเตรทของโปรตีนเหล่านี้ รวมถึงยาต้านไวรัส โดยมีรายงานการกลายพันธุ์ของยีน ABCB1 และ SLCO1B1 ในเชื้อชาติคอเคเซียนและเอเชียบางเชื้อชาติ แต่ข้อมูลการกลายพันธุ์ของยีนดังกล่าวที่เกิดจากการเปลี่ยนแปลงของนิวคลีโอไทด์เพียงตำแหน่งเดียวหรือสนิปส์ยังมีอยู่อย่างจำกัดในประชากรไทย*

วัตถุประสงค์ : *การศึกษานี้มีวัตถุประสงค์เพื่อหาความถี่ของจีโนไทป์และอัลลีลของภาวะพหุสัณฐานของยีน ABCB1 และSLCO1B1 ในผู้ป่วยไทยติดเชื้อเอไอวี และเปรียบเทียบความถี่ของยีนดังกล่าวที่พบในประชากรไทยกับเชื้อชาติอื่น*

วิธีทำการวิจัย : *ตรวจหาภาวะพหุสัณฐานของยีน 3 ชนิด ได้แก่ ABCB1 3435C>T, ABCB1 2677G>T และ SLCO1B1 521T>C ด้วยวิธี Taqman allelic discrimination โดยใช้ real time polymerase chain reaction system แล้ววิเคราะห์ข้อมูลโดยใช้สถิติไคว์สแคว์ เพื่อทดสอบการกระจายตัวของจีโนไทป์ตามกฎของ Hardy–Weinberg Equilibrium และเพื่อเปรียบเทียบความถี่ของอัลลีลของยีนระหว่างประชากรในการศึกษาและเชื้อชาติอื่น*

ผลการศึกษา : *ผู้ป่วยในการศึกษาจำนวน 521 ราย พบความถี่ของจีโนไทป์ที่เกิดการกลายพันธุ์ของยีน ABCB1 3435TT, ABCB1 2677TT และ SLCO1B1 521CC เท่ากับร้อยละ 22.50, 29.75 และ 3.84 ตามลำดับ และพบความถี่ของอัลลีลของยีน ABCB1 3435C>T, ABCB1 2677G>T และ SLCO1B1 521T>C เท่ากับร้อยละ 47.70, 51.06 และ 11.90 ตามลำดับ ประชากรไทยในการศึกษานี้มีความชุกของยีน ABCB1 2677G>T คล้ายคลึงกับประชากรเชื้อชาติเอเชียอื่น ๆ แต่ความชุกของยีน ABCB1 3435C>T มีความแตกต่างจากประชากรเชื้อชาติจีนและเกาหลี นอกจากนี้พบว่าอัลลีลที่เกิดการกลายพันธุ์ของยีน ABCB1 3435T, ABCB1 2677T และ SLCO1B1 521C ในประชากรไทยมีความถี่สูงกว่าเชื้อชาติแอฟริกันอเมริกัน*

สรุป : *ผลการศึกษาพบภาวะพหุสัณฐานของยีน ABCB1 และ SLCO1B1 ในผู้ป่วยไทยติดเชื้อเอไอวี ซึ่งข้อมูลที่ได้สามารถนำไปใช้อ้างอิงเพื่อการศึกษาทางคลินิกในอนาคตเกี่ยวกับความผันแปรในการตอบสนองต่อการรักษาและความเสี่ยงของการเกิดอาการไม่พึงประสงค์จากยาต้านไวรัสที่เป็นซับสเตรทของโปรตีนขนส่งยาเหล่านี้*

คำสำคัญ : *ABCB1, SLCO1B1, ภาวะพหุสัณฐานของยีน, ผู้ป่วยไทยติดเชื้อเอชไอวี.*

Protein transporters play an important role in facilitating drug transfer across the biological membrane. Consequently, the transport pumps are essential in drug depositions including absorption, distribution, metabolism, and excretion.[1] Thus, gene variation of these transporters could affect both intracellular and plasma concentration of substrate drugs.[1 - 3] Drug transporters can be classified into two types: the efflux and influx transporters which are both expressed in many human organs i.e. the small intestine, liver and kidney.[1] The main efflux transporter is adenosine triphosphate (ATP)-binding cassette (ABC) superfamily which includes multidrug resistance protein-1 (ABCB1/MDR1) or P-glycoprotein (P-gp, multidrug resistance-associated proteins (MRP), and breast cancer resistance protein (BCRP). The other type is the influx solute carrier (SLC) superfamily including organic cation transporters (OCTs), organic anion transporter (OATs), and organic anion-transporting peptides (OATPs/SLCO). [1 - 3]

The P-gp efflux transporter encoded by *MDR1*, known as *ABCB1* gene, has broad substrates including antiarrhythmic drugs (digoxin, quinidine), anticancer agents (doxorubicin, paclitaxel), immuno-suppressant agents (cyclosporine, tracolimus), antibiotics (levofloxacin, rifampicin) and antiretroviral (ARV) drugs (indinavir, ritonavir, saquinavir).[1, 2] The *ABCB1* polymorphisms can alter mRNA and protein level, contributing to the change in P-gp functions depending on the substrate.[2] A low expression of P-gp results in enhancing intestinal absorption and intracellular concentration of some medications i.e. digoxin and tacrolimus.[2] Regarding the adverse effects, there was a report of the association between *ABCB1* gene variant and a risk of cyclosporine-induced nephrotoxicity[4] and docetaxel-induced hematological toxicity.[5] Among *ABCB1* polymorphisms, the single nucleotide polymorphisms (SNPs) at position 3435 and 2677 were found to be correlated with efficacy and toxicity of ARVs including non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs).[6, 7] A reduction of mRNA stability was reported for *ABCB1* 3435C>T variant, whereas alteration of amino acid, Ala 893 Ser/Thr, was found for *ABCB1* 2677G>T.[6, 7]

Several drugs are substrate of OATP1B1 uptake transporter encoded by *SCLO1B1* gene including statins (simvastatin, pravastatin), antidiabetic agents (replaglinide), antihypertensive drugs (enalapril, valsartan) and ARV drugs (lopinavir, saquinavir, darunavir).[1, 3] Numerous variant genes in *SLCO1B1* have been identified from *1 (a, b, c) to *14. Among *SLCO1B1* polymorphisms, the SNP at 521T>C in exon 5 (*5 allele) resulting in amino acid substitution (Val174 Ala), showing a decrease in gene expression and transport activity.[8] The *SLCO1B1* 521T>C may also reduce drug metabolism through the decrease of hepatic uptake, leading to higher plasma drug concentration.[3, 8] The clinical significance of this gene polymorphism was described for many substrates i.e. statin, methotrexates, and rifampicin.[3, 8] Patients with *SLCO1B1* 521 variant gene showed a decreased hepatic clearance and an increased AUC of statin, which can cause drug-induced myopathy.[9] The impact of *SLCO1B1* polymorphisms on pharmacokinetics of ARVs was found in patients receiving PIs.[6, 7]

ARVs show a high inter-patient difference in drug concentration which can be explained by the influence of multiple factors including age, gender, body weight, food intake, concomitant medications, medication adherence, underlying diseases, and genetics.[10] There is evidence that the polymorphisms of *ABCB1* and *SLCO1B1* could affect the variability

in pharmacokinetics and pharmacodynamics of ARVs.[2, 3, 6, 7] The varied prevalence of *ABCB1* and *SLCO1B1* have recently been reported across ethnic groups.[11 - 17] Thus, the different allele frequency and genotype distribution of these genetic variants could lead to the difference in efficacy and toxicity of ARVs among different populations. The information regarding the prevalence of these gene polymorphisms in specific population is important for further clinical investigation. However, there are few studies with small sample size describing gene variations of the transporters in Thai HIV population.[11, 12] The purpose of this study was to identify genotype and allele frequencies of drug transporter gene polymorphisms, including *ABCB1* 3435C>T, *ABCB1* 2677G>T and *SLCO1B1* 521T>C in Thai HIV-infected patients. Additionally, the prevalence of each SNP was compared with the values previously reported in other populations.

Patients and Methods

Patients

Five hundred and twenty-one Thai HIV-infected patients were included in the present study. This is a pharmacogenetics sub-study using plasma samples from previous randomized control trial of low dose (200/100 mg) *vs*. standard dose (300/100 mg) of atazanavir/ritonavir with two nucleoside reverse transcriptase inhibitors (NRTIs) in Thai HIV-infected patients with virological suppression (LASA).[18] The LASA study enrolled patients from 14 hospitals in the central, north, northeast and eastern regions of Thailand.[22] All patients provided their written informed consents.The study has been approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (IRB No 403/51).

DNA extraction and genotyping analysis

The buffy coat was collected from blood sample and stored at -20 ^{O}C until analysis. All genomic DNA were extracted using QIAamp® DNA Blood Mini kit for DNA purification (Qiagen, Hilden, Germany. The concentration and purity of DNA were measured by UV/Vis spectrometer (SPECTROsta® Nano, Germany). Three SNPs were identified: *ABCB1* 3435C>T (rs1045642), *ABCB1* 2677G>T (rs2032582) and *SLCO1B1* 521T>C (rs4149056). Genotyping was performed by Taqman allelic discrimination assays with fluorogenic oligonucleotide probes using QuantStudio7 Flex Real-Time PCR System (Applied BiosystemsInc., USA) according to the standard protocol of manufacturer. The allele probes for each SNP are presented in Table 1. The conditions of PCR analysis were set at 95 ^{O}C for 10 min, followed by 50 cycles of 95 ^{O}C for 15 sec and 60 ^{O}C for 1 min.

Statistical analysis

The frequencies and 95% confidence interval (CI) of each genetic polymorphism were calculated. The distribution of observed and expected genotypes was compared according to Hardy-Weinberg equilibrium by Chi-square test. The comparison of allele frequencies of each genotype among Thai HIV-infected patients and other ethnicities including Asians (Chinese, Korean, and Taiwanese), white Americans, African Americans and Hispanics were compared using Chi-square test. The level of significance was set at 5% (a = 0.05). The data were analyzed by the statistical package for social sciences (SPSS version 17, SPSS Co., Ltd., Bangkok Thailand) software.

Table 1. Specific allele probes for the detection of gene polymorphisms.

Variant gene (rs number)	Probe	Sequence of allele probes
ABCB1	1	TGTTGGCCTCCTTTGCTGCCCTCACCATCTCTTCCTGTGACACCACCCGGC
3435C>T	2	TGTTGGCCTCCTTTGCTGCCCTCACTATCTCTTCCTGTGACACCACCCGGC
(rs1045642)		(assay ID: C_7586657_20)
ABCB1	1	TGTTGGCCTCCTTTGCTGCCCTCACGATCTCTTCCTGTGACACCACCCGGC
2677G>T	2	TGTTGGCCTCCTTTGCTGCCCTCACTATCTCTTCCTGTGACACCACCCGGC
(rs2032582)		(assay ID: C_11711720C_30)
SLCO1B1	1	TCTGGGTCATACATGTGGATATATGTGTTCATGGGTAATATGCTTCGTGGA
521T>C	2	TCTGGGTCATACATGTGGATATATGCGTTCATGGGTAATATGCTTCGTGGA
(rs4149056)		(assay ID: C_30633906_10)

rs number: reference single nucleotide polymorphisms number

probe: a fragment of DNA which is used to detect the presence of nucleotide sequences

Results

A total of 521 blood samples from Thai HIV-infected patients were genotyped. Patient demographic data are summarized in Table 2. The homozygous variant genotypes of *ABCB1* 3435TT, *ABCB1* 2677TT and *SLCO1B1* 521CC were 22.50%, 29.75%, and 3.84%, respectively. The observed and expected genotype frequencies of each gene polymorphism are shown in Table 3. Among these three SNPs, the distribution of *ABCB1* 2677G>T and *SLCO1B1* 521T>C were not in Hardy–Weinberg equilibrium (P <0.05).

The comparisons of variant allele frequencies between Thai and other ethnicities are presented in Table 4. The proportion of *ABCB1* 3435T allele found in our study was 47.70% which was similar to the proportions previously reported from other studies in Thai population.[11, 12] When compared with other Asian populations, Thai patients had higher frequency of T allele than the Chinese[13]and the Korean[14], but the frequency was comparable to the Taiwanese.[15] Moreover, the frequency of this variant gene in Thai was significantly higher than the values reported in African Americans (47.70% *vs*. 19%, P <0.001)[16] and the Hispanics (47.70% *vs*. 24%, P = 0.005)[16], but not differ from the white Americans.[16]

The *ABCB1* 2677T allele frequency was 51.06% which was not different from the frequencies previously reported in the Thai [11], Chinese[13], Korean [14] and the Taiwanese[15] patients. On the other hand, the T allele of *ABCB1* 2677 in the Thai population was significantly higher than white Americans (51.06% *vs*. 45%, P = 0.037)[16], African Americans (51.06% *vs*. 10%, P <0.001)[16] and the Hispanics (51.06% *vs*. 32%, P = 0.036). [16]

The variant frequency of *SLCO1B1* 521C allele was found 11.9% in this study, which was consistent with the previous report in Thai population.[11] The frequency reported in this study was similar to the values found in other populations including white Americans (14.8%)[17] and the Hispanics (8.3%)[17], but it was significantly higher than African Americans (11.9% *vs*. 1.4%; P <0.001). [17]

Table 2. Demographic data of Thai HIV infected-patients (n = 521).

Characteristics	Value
Male / Female, n (%)	259 (49.7%) / 262 (50.3%)
Age (years), mean (SD)	41.84 (7.51)
Body weight (kg), mean (SD)	60.59 (11.15)
Antiretroviral regimens	
TDF+3TC+ATV/r	267 (51.2)
AZT+3TC+ATV/r	102 (19.6)
TDF+AZT+ATV/r	84 (16.10
d4T+3TC+ATV/r	17 (3.3)
ddI+AZT+ATV/r	17 (3.3)
TDF+FTC+ATV/r	11 (2.1)
ddI+3TC+ATV/r	9 (1.7)
TDF+AZT+3TC+ATV/r	8 (1.5)
TDF+d4T+3TC+ATV/r	1 (0.2)
TDF+d4T+ATV/r	1 (0.2)
TDF+EFV+ATV/r	1 (0.2)
ABC+3TC+ATV/r	1 (0.2)
TDF+3TC+d4T+ATV/r	1 (0.2)
TDF+AZT+ATV/r+rIL-2	1 (0.2)

TDF = tenofovir, 3TC = lamivudine, ATV/r = atazanavir/ritonavir, AZT = zidovudine, d4T = stavudine, FTC = emtricitabine, EFV = efavirenz, ABC = abacavir, rIL-2 = recombinant interleukin-2

Table 3. Genotype distribution of gene polymorphisms in this study (N = 521).

Polymorphisms	Genotype	n = 521	% Observed frequency [95% CI]	Predicted frequency by Hardy–Weinberg equilibrium (%)	*P* - value*
ABCB1 3435C>T					
	CC	141	27.12 [23.29-31.09]	143 (27)	
	CT	263	50.58 [46.09-54.85]	260 (50)	
	TT	117	22.50 [18.94-26.28]	119 (23)	
					P = 0.756*
ABCB1 2677G>T					
	GG	144	27.64 [23.83-31.69]	125 (24)	
	GT	222	42.61 [38.32-46.98]	260 (50)	
	TT	155	29.75 [25.85-33.87]	136 (26)	
					P = 0.003*

Table 3. (Con) Genotype distribution of gene polymorphisms in this study (N = 521).

Polymorphisms	Genotype	n = 521	% Observed frequency [95% CI]	Predicted frequency by Hardy–Weinberg equilibrium (%)	*P* - value*
SLCO1B1 521 T>C					
	TT	417	80.04 [76.34-83.38]	404 (78)	
	TC	84	16.12 [13.06-19.56]	109 (21)	
	CC	20	3.84 [2.36-5.86]	7(1)	*P* <0.001*

n = number of patients

*Test for Hardy-Weinberg Equilibrium using Chi-square test

Table 4. Comparison of allele frequencies among different HIV-infected populations.

Polymorphisms	Population	n	Allele frequency (%)		*P* - value* [95% CI of difference]	
ABCB1 3435C>T			C	T		
	Thai (present study)	521	52.30	47.70	-	
	Thai [11]	84	55.00	45.00	0.561	[-0.106-0.057]
	Thai [12]	88	57.39	42.61	0.221	[-0.130-0.028]
	Chinese [13]	159	65.41	34.59	<0.001	[-0.191-(-0.071)]
	Korean [14]	129	69.38	30.62	<0.001	[-0.235-(-0.107)]
	Taiwanese [15]	122	46.31	53.69	0.102	[0.001-0.129]
	White American [16]	193	48.00	52.00	0.153	[-0.015-0.102]
	African American [16]	235	81.00	19.00	<0.001	[-0.334-(-0.241)]
	Hispanic [16]	17	76.00	24.00	0.005	[-0.387-(-0.096)]
ABCB1 2677G>T			G	T		
	Thai (present study)	521	48.94	51.06	-	
	Thai [11]	84	55.00	45.00	0.184	[-0.137-0.025]
	Chinese [13]	159	44.65	55.35	0.224	[-0.018-0.107]
	Korean [14]	129	46.12	53.88	0.487	[-0.038-0.098]
	Taiwanese [15]	169	52.07	47.93	0.288	[-0.091-0.032]
	White American [16]	193	55.00	45.00	0.037	[-0.116-0.001]
	African American [16]	235	90.00	10.00	<0.001	[-0.449-(-0.368)]
	Hispanic [16]	17	68.00	32.00	0.036	[-0.345-(-0.025)]

Table 4. (Con) Comparison of allele frequencies among different HIV-infected populations.

Polymorphisms	Population	n	Allele frequency (%)		*P* - value* [95% CI of difference]	
SLCO1B1 521T>C			T	C		
	Thai (present study)	521	88.10	11.90	-	
	Thai [11]	84	88.00	12.00	0.999	[-0.042-0.075]
	White American [17]	140	85.20	14.80	0.222	[-0.018-0.073]
	African American [17]	73	98.60	1.40	<0.001	[-0.133-(-0.0780)]
	Hispanic [17]	55	91.70	8.30	0.276	[-0.092-0.018]

*Chi-square test

Discussion

In this study, the SNPs of *ABCB1* and *SLCO1B1* were identified in a large sample size of Thai HIV-infected patients. The results showed that the observed frequencies of *ABCB1* 3435C>T did not differ from the expected value, whereas the distributions of *ABCB1* 2677G>T and *SLCO1B1* 521T>C were deviated from Hardy-Weinberg equilibrium. This deviation could be due to an ethnic admixture of our population as patients enrolled in the study were from several regions of Thailand. There is evidence of genetic variation in Thai population among the regions of Thailand [19], and consequently this can make the gene distribution inconsistent with Hardy-Weinberg equilibrium.

The results from this study showed that approximately half of the patients carrying the T allele for *ABCB1* 3435 and 2677, which were consistent with the results from previous studies in Thai patients.[11, 12] Even though the allele frequency of *ABCB1* 2677 was similar among Asian populations, the allele frequency of *ABCB1* 3435 was significantly different from the Chinese [13] and the Korean.[14] The allele frequencies of both genes were significantly different between the Thai and African Americans [16] and Hispanics.[16] The influence of *ABCB1* polymorphisms on the efficacy and toxicity of ARVs was studied in various populations, however the results were inconclusive.[2, 20] A minor effect of *ABCB1* 3435C>T variant was observed for PIs such as indinavir[21, 22] and lopinavir[18], whereas the impact of this polymorphism on efavirenz plasma concentrations is controversial.[13, 23 - 25] Furthermore, the variant of *ABCB1* 2677G>T was found to be one of the risk factors for severe atazanavir-associated hyperbilirubinemia.[14]

SCLO1B1 521T>C is a polymorphically expressed influx transporter responsible for hepatic uptake and drug's clearance.[3] The *SCLO1B1* polymorphisms have been shown to be associated with the altered plasma concentrations of PIs.[17, 22, 26, 27] While an increased plasma level of lopinavir was observed [17, 18, 26, 27], a decreased plasma level of amprenavir[17] was shown among patients with this variant gene. The frequency of *SCLO1B1* 521 variant C allele detected in our study (11.90%) was consistent with previous reports in Asian population (10 - 15%)[9], but it was significantly higher than the frequency found

in African Americans.[17] As there is evidence that the impact of *SCLO1B1* 521T>C polymorphisms may depend on the substrate, the effect of this polymorphisms on specific drug substrate should be further examined.

Our study has some limitations. The haplotype of observed SNPs which are in the same chromosome region was not investigated. A strong linkage disequilibrium between *ABCB1* 3435 and 2677 has been described and both SNPs combination was linked to the change in P-gp expression and function.[16, 28, 29] Additionally, as the main objective of this study was to identify genotype and allele frequencies of drug transporter genes, the influence of *ABCB1* and *SLCO1B1* polymorphisms on clinical responses of drugs was not evaluated. Several studies have shown the impact of *ABCB1* and *SLCO1B1* on plasma concentrations of some ARVs.[2, 3, 6, 7] As the effect of these gene mutations on the plasma concentrations or clinical outcomes of drug substrates may be different among populations, further studies are required.

Conclusion

The frequencies of *ABCB1* 3435C>T, *ABCB1* 2677G>T and *SLCO1B1* 521T>C polymorphisms were different between ethnicities. The reported prevalence of the SNPs involving influx and efflux transporters in Thai population could provide an initial information for future research, which could help in explaining the variation in ARV therapy.

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