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Screening of Genetic Polymorphisms of *CYP3A4* and *CYP3A5* Genes

Jin Sol Lee[1], Hyun Sub Cheong[2], Lyoung Hyo Kim[2], Ji On Kim[2], Doo Won Seo[3], Young Hoon Kim[3], Myeon Woo Chung[3], Soon Young Han[4], and Hyoung Doo Shin[1,2]

[1]Department of Life Science, Sogang University, [2]Department of Genetic Epidemiology, SNP Genetics, Inc., Seoul 121-742, [3]Clinical Research Division, Toxicological Evaluation and Research Department, National Institute of Food and Drug Safety Evaluation, Osong Health Technology Administration Complex, [4]Toxicological Evaluation and Research Department, National Institute of Food and Drug Safety Evaluation, Osong Health Technology Administration Complex, Osong 363-700, Korea

Given the *CYP3A4* and *CYP3A5*'s impact on the efficacy of drugs, the genetic backgrounds of individuals and populations are regarded as an important factor to be considered in the prescription of personalized medicine. However, genetic studies with Korean population are relatively scarce compared to those with other populations. In this study, we aimed to identify *CYP3A4*/5 polymorphisms and compare the genotype distributions among five ethnicities. To identify *CYP3A4*/5 SNPs, we first performed direct sequencing with 288 DNA samples which consisted of 96 Koreans, 48 European-Americans, 48 African-Americans, 48 Han Chinese, and 48 Japanese. The direct sequencing identified 15 novel SNPs, as well as 42 known polymorphisms. We defined the genotype distributions, and compared the allele frequencies among five ethnicities. The results showed that minor allele frequencies of Korean population were similar with those of the Japanese and Han Chinese populations, whereas there were distinct differences from European-Americans or African-Americans. Among the pharmacogenetic markers, frequencies of *CYP3A4*1B* (*rs2740574*) and *CYP3A5*3C* (*rs776742*) in Asian groups were different from those in other populations. In addition, minor allele frequency of *CYP3A4*18* (*rs28371759*) was the highest in Korean population. Additional *in silico* analysis predicted that two novel non-synonymous SNPs in *CYP3A5* (+*27256C*>*T*, P389S and +*31546T*>*G*, I488S) could alter protein structure. The frequency distributions of the identified polymorphisms in the present study may contribute to the expansion of pharmacogenetic knowledge.

Key Words: *CYP3A*4, *CYP3A*5, Cytochrome P450, Pharmacogenetics, SNP

INTRODUCTION

Given that genetic differences between individuals or populations can impact the efficacy of drugs, defining pharmacogenetic differences is regarded as an important factor to consider in the treatment of diseases and conditions with personalized medicine. Therefore, to enhance the prediction of efficacy and toxicity of drugs in individuals, recent pharmacogenetic studies have focused on phase I and phase II drug-metabolism related genes such as the *N-acetyltransferase* (*NAT*) family, the *Cytochrome P450* (*CYP*) family, and the *Uridine diphosphate glucuronosyl transferase* (*UGT*) family [1-3].

The *CYP3A* family is a well-known phase I metabolism-related gene family and consists of four genes, *CYP3A4*, *CYP3A5*, *CYP3A*7, and *CYP3A4*3, all of which are located in the 231-kb region of chromosome 7q21.1 [4]. It has been demonstrated that the *CYP* enzymes account for approximately 75% of metabolic reactions [5]. The *CYP3A4* and *CYP3A5* genes are known to perform a mono-oxygenase reaction, which is involved in several drug-related reactions such as bio-activation of medicines, excretion of drug compounds, and deactivation of drug compounds [6]. According to previous reports, approximately 30% of CYP enzymes showed a high expression level in the liver and intestine, and activities of CYP3A4 and CYP3A5 constituted approximately 36% of all CYP3A activity [7-9]. It was also reported that *CYP3A4* and *CYP3A5* polymorphisms affected the treatment of various diseases by changing the balance of drug metabolism [10-12]. In addition, it was demonstrated that the CYP enzymes showed genetic variation across individuals, with deficiencies occurring in 1 to 30% of populations, depending on ethnicity [13]. Therefore, a large number of studies were conducted to validate the effect of single-nucleotide polymorphisms (SNPs) of *CYP3A4*

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Corresponding to: Hyoung Doo Shin, Department of Life Science, Sogang University, 1 Shinsu-dong, Mapo-gu, Seoul 121-742, Korea. (Tel) 82-2-3273-1671, (Fax) 82-2-3273-1680, (E-mail) hdshin@sogang.ac.kr

ABBREVIATIONS: NAT, N-acetyltransferase; CYP, cytochrome P450; UGT, uridine diphosphate glucuronosyl transferase; SNP, single-nucleotide polymorphism; HWE, Hardy-Weinberg equilibrium; LD, linkage disequilibrium.

and *CYP3A5* on these polymorphic expressions and the risk of various diseases [14-16].

Previously, 22 and 11 types of pharmacogenetic markers were identified in *CYP3A4* and *CYP3A5*, respectively (reviewed in [17]). Also, it is well-known that frequency differences of the genetic polymorphisms are responsible for diverse gene expressions which are related with various drug responses. For example, the high frequency of *CYP3A5**3 allele in Caucasian led to a high area under curve value for cyclosporine metabolism [18]. Moreover, it was also demonstrated that the *CYP3A5**6 and *7 alleles, which were responsible for loss of the protein synthesis, showed frequencies of 10 to 20% in African but were not found in other ethnicities [19].

A number of previous studies showed that the frequencies of the *CYP3A4* and *CYP3A5* polymorphisms were different based on ethnicities. However, genetic studies of the two genes with Korean population are insufficient. Therefore, we performed direct sequencing of *CYP3A4* and *CYP3A5* to define the genotype frequencies for known genetic polymorphisms and identify novel polymorphisms in a Korean population. Following this, we compared allele distributions in five different ethnic groups comprising 96 Koreans, 48 Japanese, 48 Han Chinese, 48 African-Americans, and 48 European-Americans.

METHODS

Study subjects

DNA samples were obtained from a total of 288 subjects consisting of 96 Koreans, 48 African-Americans, 48 European-Americans, 48 Japanese, and 48 Han Chinese. DNA samples from 96 unrelated Korean individuals were provided by the Center for Genome Science, Korea Centers for Disease Control and Prevention. DNA samples from other ethnic groups were obtained from a large panel of anonymous, unrelated DNA samples from the Human Variation Panels available at the Coriell Institute (Camden, NJ, USA).

Sequencing analysis of CYP3A4/5 genes

The promoter, all exons, and exon-intron boundaries (±50 bp) were PCR-amplified and directly sequenced using the ABI PRISM 3730 genetic analyzer (Applied Biosystems, Foster City, CA, USA). Primers for the amplification and sequencing analysis were designed using Primer3 software [20] based on the GenBank sequence of respective genes (Ref. genome seq.: NG_008421.1 and NG_007938.1 for *CYP3A4* and *CYP3A5*, respectively). The sequences of primers are displayed in Supplementary Table 1. Sequence variants were verified by chromatograms using SeqMan software (Supplementary Fig. 1).

Statistical analysis

The χ^2 tests were used to determine whether individual variants were in Hardy-Weinberg equilibrium (HWE) at each locus in each population. HaploView software was used for obtaining linkage disequilibrium (LD) blocks of each gene [21,22]. The Helical Wheel project, web-based software (http://cti.itc.virginia.edu/~cmg/Demo/wheel/wheelApp.html), was used to predict the functional role of novel SNPs.

Table 1. Results from direct sequencing of *CYP3A4* and *CYP3A5* with five different ethnic groups

Gene	Polymorphism	Star nomenclature	Allele change	Position	Amino acid change	Minor allele frequency				
						Korean (n=92)	Han Chinese (n=48)	Japanese (n=48)	African-American (n=48)	European-American (n=48)
CYP3A4	*rs36231117*	.	C>T	Promoter	.	-	-	-	0.010	-
	−1887T>C†	.	T>C	Promoter	.	0.005	-	-	-	-
	rs28907269	.	C>T	Promoter	.	-	-	-	0.021	-
	−1258A>C†	.	A>C	Promoter	.	-	-	-	-	0.011
	rs12114000	.	C>T	Promoter	.	-	-	-	0.281	-
	rs1851426	.	C>T	Promoter	.	-	-	-	0.229	0.043
	rs11773597	.	C>G	Promoter	.	-	-	-	-	0.062
	rs28988569	.	A>G	Promoter	.	-	0.010	-	-	-
	rs2740574	*1B	A>G	Promoter	.	-	-	-	0.271	0.042
	rs4986908	.	C>T	Exon6	D174N	-	0.010	-	-	-
	rs12721623	.	T>G	Intron6	.	-	-	-	-	0.021
	rs12721624	.	C>T	Intron8	.	-	-	-	0.01	-
	rs56153749	.	A>-	Intron9	.	0.021	0.021	-	0.01	-
	rs28371759	*18	T>C	Exon10	L293P	0.026	-	0.010	-	-
	+20157A>G†	.	A>G	Exon10	V318V	-	0.010	-	-	-
	rs2242480	.	G>A	Intron10	.	0.219	0.271	0.260	0.219	0.083
	rs4986911	.	G>C	Intron10	.	-	-	-	0.042	-
	rs4986909	*13	G>A	Exon11	P416L	-	0.011	-	-	-
	rs4986910	*3	A>G	Exon12	M445T	-	-	-	-	0.021
	rs4986913	*19	G>A	Exon12	P467S	-	0.011	-	-	-
	rs28988604	.	C>T	3'-UTR	.	-	-	-	0.052	0.021

Table 1. Continued

Gene	Polymorphism	Star nomenclature	Allele change	Position	Amino acid change	Minor allele frequency				
						Korean (n=92)	Han Chinese (n=48)	Japanese (n=48)	African-American (n=48)	European-American (n=48)
CYP3A5	*rs115450823*	.	T>A	Promoter	.	-	-	-	0.094	-
	−1308C>T†	.	C>T	Promoter	.	-	-	-	0.094	-
	rs36231118	.	A>C	Promoter	.	-	-	-	0.115	0.010
	rs3823812	.	T>A	Promoter	.	0.237	0.312	0.229	0.052	0.010
	rs28365073	.	T>C	Promoter	.	-	-	-	0.021	-
	rs28365079	.	C>A	Promoter	.	-	-	-	0.117	0.010
	−352A>G†	.	A>G	Promoter	.	-	0.010	-	-	-
	−344A>G†	.	A>G	Promoter	.	-	0.010	-	-	-
	rs28365095	*1B	G>A	5'UTR	.	-	-	-	-	0.031
	rs28371764	*1C	C>T	5'UTR	.	-	0.010	-	0.01	0.062
	+3626T>A†	.	T>A	Intron1	.	0.010	-	-	-	-
	rs28365067	.	C>T	Intron2	.	0.021	0.021	0.032	-	0.062
	rs41301652	.	G>A	Intron2	.	-	-	-	0.01	-
	rs28969392	.	T>A	Intron3	.	-	-	-	0.011	-
	rs776746	*3C	T>C	Intron3	.	0.255	0.344	0.260	0.198	0.085
	+7070T>A†	.	T>A	Intron3	.	-	0.011	-	-	0.010
	+7074G>A†	.	G>A	Intron3	.	-	-	0.022	-	-
	+7078T>A†	.	T>A	Intron3	.	-	-	-	0.01	-
	+7080G>A†	.	G>A	Intron3	.	-	0.032	-	-	-
	rs28365078	.	C>A	Intron3	.	-	-	0.011	-	-
	rs8175345	.	C>T	Intron3	.	-	-	-	0.042	0.010
	+7355T>C†	.	T>C	Intron4	.	-	-	-	0.010	-
	+12801T>C†	.	T>C	Intron4	.	-	-	-	-	0.010
	rs55965422	.	T>C	Intron5	.	0.016	0.011	-	-	-
	rs10264272	*6	C>T	Exon7	K208K	-	0.010	-	0.188	-
	rs28383472	.	A>G	Exon7	P218P	-	-	-	0.073	-
	rs41303322	.	A>G	Intron7	.	-	-	-	0.100	-
	rs28383478	.	C>T	Intron9	.	-	-	-	-	0.010
	rs4646453	.	G>T	Intron9	.	0.234	0.302	0.240	0.042	0.010
	rs28383479	*9	G>A	Exon10	A337T	-	-	-	-	0.010
	rs28365094	.	A>G	Intron10	.	-	-	0.010	0.011	0.083
	rs41303343	*7	A>-	Exon11	.	-	-	-	0.146	-
	+27256C>T†	.	C>T	Exon11	P389S	0.005	-	-	-	-
	rs28365069	.	T>C	Intron12	.	-	-	-	0.031	-
	+31546T>G†	.	T>G	Exon13	I488S	0.005	0.021	-	-	-
	rs15524	.	T>C	3'UTR	.	0.247	0.323	0.281	0.365	0.031

Variants which are monomorphic in all ethnicities are not shown in the Table. A hyphen (-) indicates that the variant was monomorphic in the particular ethnicity. Data not applicable are marked with a dot (.).
†These polymorphisms were newly identified in this study.

RESULTS

In the present study, we identified the *CYP3A4/5* polymorphisms in five ethnicities using direct sequencing, and compared the genotype distributions among ethnicities. The direct sequencing of *CYP3A4/5* was performed in a total of 288 healthy subjects consisting of 96 Koreans, 48 European-Americans, 48 African-Americans, 48 Han Chinese, and 48 Japanese.

From the direct sequencing, we obtained a total of 15 novel polymorphisms which consist of 3 *CYP3A4* SNPs (*−1887T>C*, *−1258A>C*, and *+20157A>G* (V318V) and 12 *CYP3A5* variants (*−1308C>T*, *−352A>G*, *−344A>G*, *+3626T>A*, *+7070T>A*, *+7074G>A*, *+7078T>A*, *+7080G>A*, *+7355T>C*, *+12801T>C*, *+27256C>T* (P389S), and *+31546T>G* (I488S) (Table 1). Also, we observed 18 and 24 previously reported SNPs in *CYP3A4*/5 genes, respectively (Table 1). Locations of the polymorphisms are shown in each physical gene map along with their minor allele frequencies (MAFs) (Fig. 1).

Most of the *CYP3A4* and *CYP3A5* polymorphisms showed low frequencies or monomorphic genotypes. In general, the MAFs of *CYP3A4* polymorphisms were similar across the Asian populations, whereas MAFs of African-American and European-American populations differed from those of Asians. Among the pharmacogenetic markers, MAFs of *CYP3A4***1B* (*rs2740574*) were detected in European-Americans (0.042) and African-Americans (0.271), whereas the polymorphism was not detected in any Asian populations. On the other hand, *rs2242480* was identified with

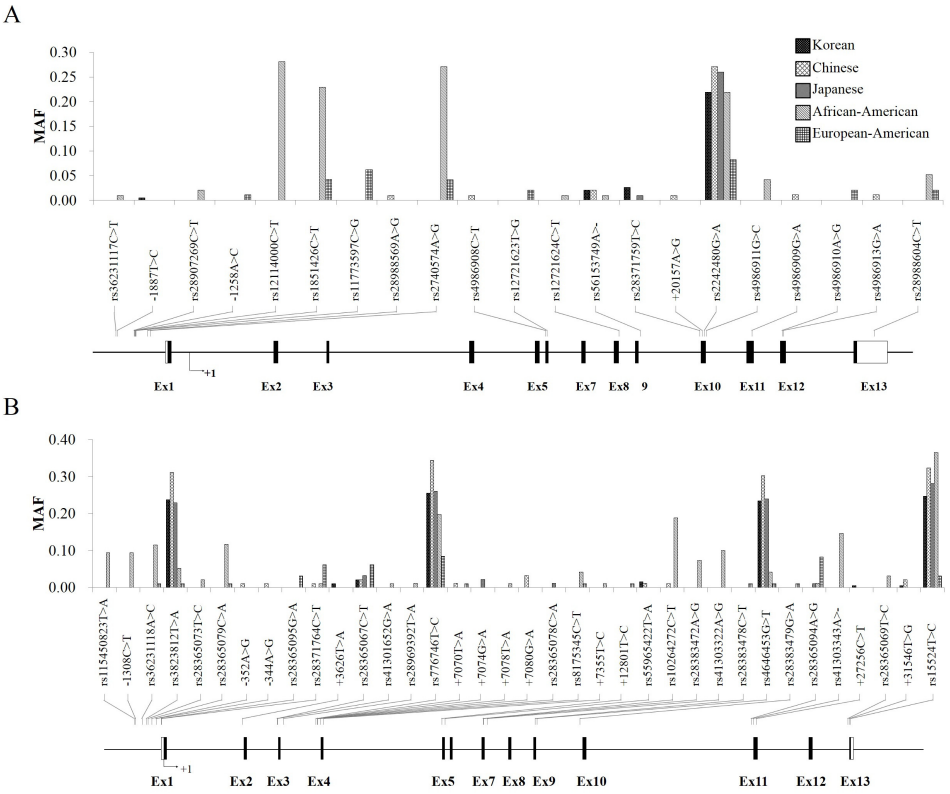

Fig. 1. (A) A physical map of *CYP3A4* with minor allele frequencies using results from Korean, African-American, European-American, Han Chinese, and Japanese populations. Novel SNPs are labeled with their locations and allele changes. (B) A physical map of *CYP3A5* with minor allele frequencies using results from Korean, African-American, European-American, Han Chinese, and Japanese populations. Novel SNPs are labeled with their locations and allele changes.

a low frequency in the European-American population (0.083) compared to other ethnicities (>0.200), and three SNPs (*rs12114000*, *rs1851426*, and *rs2740574*) were identified as having high frequencies among African-Americans (0.281, 0.229, and 0.271, respectively), but was almost monomorphic in other populations. Detailed information regarding SNPs in *CYP3A4* is displayed in Table 1.

In *CYP3A5*, *CYP3A5*3C* (*rs776746*) showed higher MAFs in Asian populations (0.255, Korean; 0.344, Han Chinese; 0.260, Japanese) than in other ethnic groups (0.198, African-American; 0.085, European-American). Other two polymorphisms (*rs3823812* and *rs4646453*) were also detected that had higher MAFs among Asians (>0.200) compared to other populations (<0.060). On the other hand, the MAF of *rs15524* was lowest in European-Americans (0.031), while the frequencies in other populations were higher than 0.200. *CYP3A5*6* (*rs10264272*) and *CYP3A5*7* (*rs41303343*) were detected with high as having MAFs in African-Americans (0.188 and 0.146, respectively), but was almost monomorphic in other populations. Detailed information regarding SNPs in *CYP3A5* is displayed in Table 1.

p-values for Hardy-Weinberg equilibrium of each polymorphism were calculated for the five ethnic groups (Supplementary Table 2). All of *CYP3A4* alleles were in Hardy-Weinberg equilibrium. However, in *CYP3A5*, p-values of *rs28365067* in Japanese and *+7080G>A* in Han Chinese were not in Hardy-Weinberg equilibrium.

LD structures of *CYP3A4* and *CYP4A5* in five ethnicities were calculated by using SNPs which were identified in more than two ethnicities, and the results were displayed in Supplementary Fig. 2. However, LD structures were not clearly constructed due to the SNPs with low or monomorphic frequencies.

DISCUSSION

CYP3A4 and CYP3A5 enzymes are regarded as important markers in the development of the personalized medicine due to the enzymes' impact on efficacy of drugs based on genetic background of individuals or populations. Therefore, we conducted the present study to compare genetic differences in the *CYP3A4* and *CYP3A5* genes among five ethnicities. The sequencing results showed that many pharmacogenetic markers in *CYP3A4* and *CYP3A5* were either monomorphic or had low frequencies. This trend was consistent with previous observations in which a large number of *CYP3A* polymorphisms exhibited low frequencies (reviewed in [23]). This indicates that a larger sample size may be needed to detect the polymorphisms.

Among the pharmacogenetic markers in *CYP3A4*, *CYP3A4* 1B* (*rs2740574*) is known to be the polymorphism that increases expression by changing the transcription factor binding affinity [24]. Recently, it was demonstrated that *CYP3A4*1B* carriers showed higher drug clearance for anti-cancer agents, such as docetaxel and cyclophosphamide, than wild type subjects [25-27]. However, although *CYP3A4* 1B* plays an important role in the enzyme activity, the marker has not been detected in Asian populations in previous studies [28-30]. Our results also showed that *CYP3A4*1B* was not detected in Asians, including a Korean population. These observations suggest that the alteration of metabolism of docetaxel and cyclophosphamide by *CYP3A4*1B* might be difficult to find in Asian populations.

The other pharmacogenetic marker, *CYP3A4*18* (*rs28371759*)

has been reported as the polymorphism that accounts for bidirectional enzyme activity. Previous studies showed that the polymorphism increased the turnover rate of testosterone and chlorpyrifos, but decreased the metabolic turnover rate of midazolam and nifedipine [31-35]. In addition, previous studies reported that *CYP3A4*18* was frequently identified in Asian populations such as Chinese (frequency, 0.008～0.01), Japanese (frequency, 0.013), Koreans (frequency, 0.012～0.017) and Malaysians (frequency, 0.021) [33,36-40]. The result of the present study also showed that the polymorphism was detected in two Asian populations (Korean, 0.021 and Japanese, 0.010), while other populations showed monomorphic genotypes. Therefore, Asian populations may have more genetic protection against toxicity of chlorpyrifos than other populations. Moreover, Asian populations tend to experience an effective dose with lower amounts of midazolam and nifedipine for treatment of seizure and cardiac/circulatory disorders.

A recent study reported that the *CYP3A4*22* (*rs35599367*) allele played an important role in the hepatic *CYP3A4* expression and CYP3A4 activity, as well as alteration of statin, tacrolimus and cyclosporine metabolism [17]. This SNP was not found in our subjects. According to the NCBI database, the polymorphism had a frequency of around 0.025 in only Caucasian population. Therefore, no detection of the polymorphisms in the present study may occur due to the low frequency of the allele.

In *CYP3A5*, *CYP3A5*3C* (*rs776746*) is well known as the polymorphism that causes severe decrease of enzyme activity by a splicing defect [41]. It has been reported that individuals with *CYP3A5*3C* show a lower clearance rate of drugs such as carbamazepine, vincristine, and ifosfamide, which are used for treatment using anticonvulsants, mood-stabilizers, and anti-cancer agents [42-45]. In the present study, we observed that the frequency of the *CYP3A5*3C* polymorphism was relatively higher in Asian populations than in other populations (Korean, 0.255; Han Chinese, 0.344; Japanese, 0.260 vs. African-American, 0.198; European-American, 0.085). Therefore, identifying the *CYP3A5*3C* genotype could be important for application of carbamazepine, vincristine, and ifosfamide in treating Asian epilepsy, bipolar disorder, trigeminal neuralgia, and cancer patients.

Due to the important roles of non-synonymous SNPs in protein functions, we selected exonic variants that cause amino acid change (*+27256C>T*, P389S and *+31546T>G*, I488S in *CYP3A5*) so as to predict the functional role of the SNPs using web-based software. Results from the analysis showed that the amino acid substitutions by the polymorphisms could change the charge of residues from nonpolar to polar. These alterations of amino acid properties can cause a change in protein structure [46]. Therefore, the two polymorphisms may affect enzyme activity through the modification of protein structure, although further functional studies would be required to confirm the result.

Conclusively, we performed direct sequencing of the *CYP3A4*/5 in five ethnicities to identify SNPs, and compared the frequency differences of the polymorphisms among ethnicities. From the analysis, we obtained a total of 57 SNPs composed of 15 novel polymorphisms and 42 known variants. Our results indicated that genotype frequencies of Asian populations were different from those of other ethnic groups. Additional *in silico* analysis revealed that two novel non-synonymous SNPs could cause alteration of protein folding. Although our LD structures were not accurately calculated due to the low frequencies of the SNPs, there appears to be no linkage between novel polymorphisms and known pharmacogenetic marker. Further studies with large scale sample may be required to obtain reliable results, as well as exact p-values for Hardy-Weinberg equilibrium. The results of the present study may be helpful for further understanding of pharmacogenetics.

SUPPLEMENTARY MATERIALS

Supplementary data including one figure can be found with this article online at http://pdf.medrang.co.kr/paper/pdf/Kjpp/Kjpp017-06-01-s001.pdf.

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