Screening for 392 polymorphisms in 141 pharmacogenes

JASON YONGHA KIM[1*], HYUN SUB CHEONG[2*], TAE-JOON PARK[1], HEE JUNG SHIN[3], DOO WON SEO[3], HAN SUNG NA[3], MYEON WOO CHUNG[3] 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]Division of Clinical Reaserch, Department of Toxicological Evaluation and Research, National Institute of Food and Drug Safety Evaluation, Osong Health Technology Administration Complex, Osong, Chungcheongbuk 363-700, Republic of Korea

Received February 17, 2014; Accepted March 28, 2014

DOI: 10.3892/br.2014.272

Abstract. Pharmacogenomics is the study of the association between inter-individual genetic differences and drug responses. Researches in pharmacogenomics have been performed in compliance with the use of several genotyping technologies. In this study, a total of 392 single-nucleotide polymorphisms (SNPs) located in 141 pharmacogenes, including 21 phase I, 13 phase II, 18 transporter and 5 modifier genes, were selected and genotyped in 150 subjects using the GoldenGate assay or the SNaPshot technique. These variants were in Hardy-Weinberg equilibrium (HWE) (P>0.05), except for 22 SNPs. Genotyping of the 392 SNPs revealed that the minor allele frequencies of 47 SNPs were <0.05, 105 SNPs were monomorphic and 22 variants were not in HWE. Also, based on previous studies, we predicted the association between the polymorphisms of certain pharmacogenes, such as cytochrome P450 2D6, cytochrome P450 2C9, vitamin K epoxide reductase complex, subunit 1, cytochrome P450 2C19, human leukocyte antigen, class I, B and thiopurine S-methyltransferase, and drug efficacy. In conclusion, our study demonstrated the allele distribution of SNPs in 141 pharmacogenes as determined by high-throughput screening. Our results may be helpful in developing personalized medicines by using pharmacogene polymorphisms.

Introduction

Inter-individual variation in drug response among patients is a major obstacle in medicine application, due to the different response of each patient to the same medication (1). Several cases of adverse drug reactions occurring in certain patients, such as renal/hepatic disorders, congestive heart failure and anemia, were previously reported (1,2). The variations in drug responses may result from disease determinants, genetics, environmental factors and idiosyncratic response, which collectively affect drug metabolism (3). The knowledge of variations in efficacy and toxicity caused by the same doses of medications may enhance the effectiveness of drug therapy (3).

The initial human genome sequencing identified ~1.42 million single-nucleotide polymorphisms (SNPs), including >60,000 SNPs in the exonic region of genes (4). Some of these SNPs have been suggested to be associated with considerable changes in drug disposition and metabolism or the effects of medication (5-7), whereas others are used for the diagnosis of clinical response (8). The interaction of several gene products is known to affect the pharmacokinetics and pharmacodynamics of medications. For example, inherited variations in drug targets, drug disposition and polygenic factors of drug effects are determinants of the majority of drug effects and have become increasingly important in pharmacogenomics (9).

Pharmacogenomics is the study of how genetic differences among individuals affect the variability in their response to medications (6,10). Pharmacogenomic research includes clinical and basic science regarding genetic variation and drug response. The field of pharmacogenomics has attracted significant attention along with the completion of the Human Genome Project (11). Consequently, there has been an increase in the number of pharmacogenomic studies published (11). Furthermore, the continuous development of genotyping technologies may allow pharmacogenomic applications to move into the mainstream of medicine and pharmacy practice (12,13).

Over the last few years, the available technologies for genomic analyses have increased significantly (14). For example, the TaqMan and the SNPlex assays from Applied Biosystems (Foster City, CA, USA), the GeneChip assay from Affymetrix (Santa Clara, CA, USA) and the Infinium and GoldenGate assays developed by Illumina (San Diego, CA, USA) are the most frequently used techniques in genome research (15). In addition, the SNaPshot technique has been tested on a small scale of multiplex for analysis of gene polymorphisms (16). In this study, we used the GoldenGate assay and the SNaPshot technique for genotyping to investigate the

Correspondence to: Professor Hyoung Doo Shin, Department of Life Science, Sogang University, 1 Shinsu-dong, Mapo-gu, Seoul 121-742, Republic of Korea
E-mail: hdshin@sogang.ac.kr

*Contributed equally

Key words: gene screening, pharmacogene, single-nucleotide polymorphism

allele distribution of 392 SNPs from 141 pharmacogenes in 150 Korean subjects.

Materials and methods

Study subjects. DNA samples from a total of 150 Korean subjects was used for this study. The 150 unrelated Korean samples were provided by the Center for Genome Science, Korea Centers for Disease Control and Prevention. The protocol and consent forms of this study were reviewed and approved by the Institutional Review Board of Sogang University (no. 2010_690).

SNP selection and genotyping. We selected a total of 378 SNPs of 141 well-known pharmacogenes, based on the score assigned by the Illumina GoldenGate assay design tool (ADT; Illumina). The SNPs were genotyped using the GoldenGate assay with the VeraCode microbead (Illumina) (17,18), followed by a scan using the BeadExpress® system (Illumina). Normalized bead intensity data obtained for each sample were loaded into the GenomeStudio® software (Illumina), which converted fluorescent intensities into SNP genotypes. SNP clusters for genotype calling were examined for all SNPs using the GenomeStudio® software. The cluster plots were then visually assessed and SNPs with poor cluster quality were removed. The overall call rate for all SNPs was 99.99%. For quality control, SNPs that met the following criteria were retained: call rate ≥0.98% and no triplicate error after three repetition tests. Fourteen additional SNPs which did not pass ADT scoring were genotyped using the SNaPshot technique (Invitrogen Life Technologies, Carlsbad, CA, USA). The SNaPshot technique is single- extension-based method, which enables the simultaneous analysis of multiple SNPs (19). The information of SNaPshot primers used for the 14 SNPs are shown in Table I. The GoldenGate and SNaPshot assays were conducted three times in order to increase the accuracy of the test.

Statistical analysis. The Chi-square test was used to determine whether individual variants were in Hardy-Weinberg equilibrium (HWE) at each locus in a Korean population. Haplotypes of SNPs representing the star-alleles of each pharmacogene investigated in this study were defined using PHASE software (Stephen Laboratory, University of Chicago, Chicago, IL, USA).

Results and Discussion

A total of 392 SNPs located in 141 pharmacogenes (including 21 phase I, 13 phase II, 18 transporter and 5 modifier genes) were successfully genotyped in 150 Korean subjects and their minor allele frequencies (MAFs) were calculated (Table II). These variants were in HWE (P>0.05), except for 22 SNPs. Among the SNPs, 47 variants exhibited a MAF<0.05, while 105 variants exhibited a monomorphic allele distribution in the Korean population (Table III). In addition, there were 22 SNPs with HWE<0.05, 9 of which exhibited significantly lower HWE compared to others [*rs2230037*, *rs2472393*, *rs743544* [all in the glucose-6-phosphate dehydrogenase (*G6PD*) gene], *rs2227291* [copper-transporting ATPase 1 (*ATP7A*) gene], *rs1414334*, *rs518147*, *rs3813928*, *rs6318* and *rs3813929* [all in the 5-hydroxytryptamine receptor 2C (*HTR2C*) gene]. The 3 genes were all located in the X chromosome, although located far away from each other (*G6PD* at Xq28, *ATP7A* at Xq21.1 and *HTR2C* at Xq24). The classifications and SNP numbers of each pharmacogene investigated in this study are listed in Table IV. Among these, cytochrome P450 2D6 (*CYP2D6*), cytochrome P450 2C19 (*CYP2C19*), thiopurine S-methyltransferase (*TPMT*), cytochrome P450 2C9 (*CYP2C9*), vitamin K epoxide reductase complex, subunit 1 (*VKORC1*) and human leukocyte antigen, class I, B *(HLA-B)* are of great significance, due to their association with well-known drugs. Therefore, we investigated the respective genes and their effects on enzyme activity or associated drugs below.

First, 14 *CYP2D6* SNPs (*rs1065852*, *rs16947*, *rs1135822*, *rs35742686*, *rs3892097*, *rs5030655*, *rs79738337*, *rs1058164*, *rs1135840*, *rs28371525*, *CYP2D6_2*, *rs5030867*, *rs5030865* and *rs5030656*) were used for the investigation of 17 star-alleles (**1*, **2*, **3*, **4*, **5*, **6*, **7*, **8*, **9*, **10*, **14A*, **14B*, **34*, **36*, **41*, **49* and **60*). *CYP2D6* is one of the most important pharmacogenes involved in the metabolism of foreign substances in the body. Overall, the genotypes associated with decreased activity or a non-functional enzyme were ~20% of all the investigated genotypes (Table V). Specifically, screening of polymorphisms such as *rs3892097*, *rs1065852*, *rs16947* and *rs1135840* may be useful for detecting the enzyme activity level of CYP2D6. *CYP2C19* is clinically important for the metabolism of drugs including clopidogrel (20), which is an inhibitor of adenosine diphosphate-induced platelet aggregation (21-23). To investigate the association between *CYP2C19* and clopidogrel response, 15 *CYP2C19* SNPs were used for the investigation of seven alleles (**1*, **2*, **3*, **4*, **5A*, **8* and **17*) (Table V). In general, over half of the subjects were found to have genotypes that reduced the efficacy of clopidogrel, while 11.5% of the subjects carried genotypes which enhanced the efficacy of clopidogrel. This information may be used to adjust the dose of clopidogrel depending on the patient genotypes of the investigated polymorphisms.

TPMT encodes an enzyme involved in the detoxification of azathioprine, mercaptopurine and thioguanine, which are immunosuppressive drugs used in organ transplantation (24-27). Five SNPs (*rs75543815*, *rs1142345*, *rs1800460*, *rs1800462 and rs1800584*) were used to investigate the frequency of five alleles (**2*, **3B*, **3C*, **4* and **6*) in this study (Table V). The results suggested that the majority of Korean subjects have *TPMT* genotypes, which render them more prone to the toxicity of the aforementioned drugs. The dihydropyrimidine dehydrogenase gene (*DPYD*) encodes an enzyme catabolizing 5-fluorouracil (5-FU), which is commonly used for the treatment of solid carcinomas (28,29). A decrease in enzyme activity involved in 5-FU catabolism due to the mutational variants in *DPYD* may lead to an increase in the half-life of 5-FU and an increased risk of dose-dependent toxicity (28,30,31). In our study, all the Korean subjects were found to carry the *DPYD* genotypes associated with normal enzyme activity (**1/*5*, **5/*5*, **1/*9A*, or *c.496A>G*; Table V). A polymorphism of interleukin 28B (*IL28B*), *rs8099917* has been reported to be associated with the virologic response to peginterferon-α (PEG-IFNα) and ribavirin (RBV) combination therapy in hepatitis C virus-infected patients (32-34), whereas the GT and GG genotypes of *rs8099917* have been suggested to be less responsive to treatment compared to

Table I. SNaPshot primer sequences for 14 single-nucleotide polymorphisms (SNPs).

Gene	SNP	Primer	Sequence
CYP2D6		Forward	GTTATCCCAGAAGGCTTTGCAGGCTTCA
		Reverse	GCCGACTGAGCCCTGGGAGGTAGGTA
	rs1065852[a]	SNaPshot	AACGCTGGGCTGCACGCTAC
	rs16947[a]	SNaPshot	TCAGAGAACAGGTACCACCACTATGC
	rs1135822[a]	SNaPshot	T(11)CGGGCCCATAGCGCGCCAGGA
	rs35742686[a]	SNaPshot	T(10)CCAGCTGGATGAGCTGCTAACTGAGCAC
	rs3892097[a]	SNaPshot	T(20)CCTTACCCGCATCTCCCACCCCCA
	rs5030655[a]	SNaPshot	T(24)GCCTGGGCAAGAAGTCGCTGGAGCAG
	rs79738337[a]	SNaPshot	T(31)GGCAAGGAGAGAGGGTGGAGGCTGG
	rs1058164[a]	SNaPshot	T(41)CGAGCAGAGGCGCTTCTCCGT
DPYD	*rs72981743*	Forward	CGAAAACAGGCAGACTAGGG
		Reverse	AGAGCGGGTGCTCTACTCC
		SNaPshot	TCTGCTTGCAGGCTGGGGCGC
CYP2A6	*rs56256500*	Forward	AGTTGGCAGGTTGTGGTAGG
		Reverse	CTCCAATGTCATCAGCTCCA
		SNaPshot	GAACTGGAAGATTCCTAGCATCATGC
NR1I2	*rs1464603*	Forward	CACCAGCCCACACTCTGAAC
		Reverse	CAAATCTGCCGTGTATGTGG
		SNaPshot	CTGGGGGACAGGTCAAGCTGAGGCCCTGAGA
CYP2A6	*rs1809810*	Forward	TCCAGCCCCTGTGTACTTTC
		Reverse	AAACTGCCCCTTCTCATTCA
		SNaPshot	T(7)CAACTTCCTCCTCCCTACCAGGGCACCGAAGTGT
ABCB1	*rs2032582*	Forward	TTGAAATGAAAATGTTGTCTGGA
		Reverse	AAAAGATTGCTTTGAGGAATGG
		SNaPshot	T(13)CAAGCACTGAAAGATAAGAAAGAACTAGAAGGT
CYP2C19	*rs3758580*	Forward	TTCATGTACCCCTGAATTGCT
		Reverse	CATCTGTGTAGGGCATGTGG
		SNaPshot	T(24)GCATGCAGGGGCTCCGGTTTCTGCCAAC

[a]The *CYP2D6* SNPs share the same forward and reverse primers.

TT (32). In this study, subjects carrying the TT genotype were the most common (86.7%), whereas the GT and GG genotypes were significantly less frequent (12.7 and 0.7%, respectively) in the Korean population (Table V). These results may be used to identify patients with reduced responsiveness to PEG-IFNα/RBV combined therapy and adjust the amount accordingly.

Warfarin is an anticoagulant used for the prevention of thromboembolic events and stroke (35). *CYP2C9*2* variants, **3* variants (36-40) and *VKORC1* polymorphism *rs8050894* (41) were reported to be significantly associated with warfarin dose in European or African populations. In this study, we evaluated the variability of warfarin dose according to the *CYP2C9* and *VKORC1* genotypes using *CYP2C9*2*, **3* and *rs8050894*, based on previous reports (Table VI). Combinations of the CG or CC genotype of *rs8050894* and *CYP2C9* wild-type (**1/*1*) yielded the highest warfarin dose requirement (5-7 mg/day), whereas a combination of the GG genotype of *rs8050894* and *CYP2C9*1/*1*, demanding 3-4 mg/day of warfarin, was the most frequent (76.0%) in the Korean population. Furthermore, the warfarin dose requirement in *CYP2C9* wild-type (**1/*1*) was higher compared to that in **2* or **3* variant allele-containing genotypes (**1/*2*, **1/*3*, **2/*2*, **2/*3* and **3/*3*), which was also observed in European and African-American populations (42). As regards *rs8050894* in *VKORC1*, an overall higher warfarin dose requirement in CG (heterozygote) or CC (minor homozygote) compared to that in GG (major homozygote) was observed. However, in European and African-American populations, GG exhibited a higher warfarin dose requirement compared to the CG or CC genotype (42). Further investigations may be required to verify the different genetic effect on warfarin response in various ethnic groups.

HLA-B encodes for a protein which is an important part of the human immune system and its polymorphisms have been associated with various drug reactions (43-45). Carbamazepine, which is often used for treatment of chronic pain, bipolar disorder, seizure disorder and trigeminal neuralgia, is one of the most common causes of drug hypersensitivity reactions (46). The star-allele *HLA-B*1502* is associated with various toxic events resulting from carbamazepine, such as cutaneous

Table II. Minor allele frequency of 287 polymorphic single-nucleotide polymorphisms (SNPs) from 141 pharmacogenes in a Korean population (n=150).

Gene	SNP	Alternative name	Alleles	MAF	HWE	Gene	SNP	Alternative name	Alleles	MAF	HWE
CYP2D6	*rs1065852*	*10, *36, *49, 100C>T	C>T	0.163	0.551	*G6PD*	*rs2230037*	1311C>T	C>T	0.080	4.69×10^{-19}
	rs16947	*2, 2850C>T	C>T	0.140	0.472		*rs2472393*	IVS1+2955A/G	C>T	0.130	8.31×10^{-12}
	rs3892097	*4, 1846G>A	G>A	0.073	0.152		*rs743544*	IVS1-773C/T	C>T	0.407	7.44×10^{-10}
	rs79738337	*60, 2303C>T	C>T	0.007	0.934	*HLA-B*1502*	*rs3909184*	HLA-B*1502	C>G	0.053	0.354
	rs1058164	*2, *4, *8, *10, 1661G>C	G>C	0.217	0.645		*rs2844682*	HLA-B*1502	C>T	0.157	0.674
	rs1135840	*2A, 4180G>C	C>G	0.400	0.496	*NAT1*	*rs4986988*	*11, c.-344C>T	C>T	0.007	0.934
	rs28371525	*41, 2988G>A	G>A	0.003	0.967		*rs4986989*	*11, c.-40A>T	A>T	0.007	0.934
	rs5030865	*8, 1758G>T	G>T	0.003	0.967		*rs4986783*	*11, c.640T>G, p.S214A	T>G	0.007	0.934
CYP2C9	*rs1057910*	*3, 42614A>C	A>C	0.043	0.579	*NAT2*	*rs1799929*	*11, *5B	C>T	0.033	0.673
	rs9332092	-	T>C	0.043	0.579		*rs1041983*	*13, *5G, *6A	C>T	0.313	0.011
	rs9332096	-	C>T	0.073	0.816		*rs1799930*	*5E, *6A	G>A	0.173	0.153
	rs9332098	-	G>A	0.043	0.579		*rs1799931*	*7, G286E, *6I	G>A	0.140	0.524
	rs4918758	*1C, C1188T	T>C	0.443	0.624		*rs4646241*	-	T>C	0.173	0.779
VKORC1	*rs9934438*	C6484T, 1173C>T	A>G	0.087	0.368		*rs4646242*	-	A>G	0.167	0.203
	rs8050894	*2, 1542G>C, 6853G>C	G>C	0.083	0.964		*rs4646243*	-	T>C	0.360	0.008
	rs2359612	*2, 2255C>T, 7566C>T	A>G	0.083	0.964		*rs4646246*	-	A>G	0.280	0.923
	rs7294	3730G>A	G>A	0.080	0.965	*TPMT*	*rs1800460*	*3B	G>A	0.003	0.967
	rs17708472	*4, 6009C>T, 698C>T	G>A	0.003	0.967		*rs1142345*	*3C, C240Y, 18485A>G	A>G	0.013	0.869
CYP2C19	*rs12248560*	*17, -806C>T	C>T	0.067	0.662		*rs75543815*	*6, 15327A>T	A>T	0.023	0.770
	rs4244285	*2, G681A	G>A	0.313	0.011		*rs12201199*	-	A>T	0.013	0.869
	rs4986893	*3, G636A	G>A	0.077	0.891	*UGT1A1*	*rs4124874*	*60, -3263T>G	A>C	0.300	0.560
	rs28399504	*4, A1G	A>G	0.003	0.967		*rs887829*	*28	G>A	0.127	0.764
	rs17885098	*2, *4, 99C>T	C>T	0.037	0.641		*rs4148323*	*6, Gly71Arg	G>A	0.173	0.153
	rs3758580	*2, 80160C>T	C>T	0.240	0.872		*rs34993780*	*7	T>G	0.007	0.934
	rs11568732	-888T/G	T>G	0.133	0.814		*rs10929302*	*93, -3156G>A	G>A	0.127	0.764
	rs4986894	-97T/C	T>C	0.313	0.011		*rs3755319*	-	A>C	0.137	0.579
	rs17886522	G417G	A>C	0.077	0.891		*rs2003569*	-	G>A	0.127	0.764
	rs17878649	IVS1-47G/A	G>A	0.077	0.891	*CYP2E1*	*rs2031920*	*5, -1053C>T	C>T	0.127	0.299
	rs4417205	IVS5-51C/G	C>G	0.313	0.011		*rs6413432*	*6, 7632T>A	T>A	0.070	0.357
	rs4917623	IVS7-106T/C	C>T	0.460	0.567		*rs3813867*	*5A, *5B	G>C	0.207	0.484
	rs11188072	*17, -3402C>T	C>T	0.013	0.869		*rs2070673*	*7, -333T>A	T>A	0.420	0.410
DPYD	*rs1801159*	*5, I543V, A1627G	A>G	0.277	0.311		*rs2070875*	-	G>T	0.290	0.879
	rs1801265	*9A, C29R, T85C	T>C	0.053	0.490		*rs2515641*	-	C>T	0.173	0.779
	rs2297595	496A>G, Met166Val	T>C	0.010	0.902	*CYP3A4*	*rs28371759*	*18, L293P (T>C)	T>C	0.030	0.015
	rs72981743	-243G/A	G>A	0.017	0.836	*CYP3A5*	*rs776746*	*3, 6986A>G	G>A	0.223	0.475
	rs1042482	3651G/A	G>A	0.090	0.434		*rs55965422*	*5, 12952T>C	A>G	0.007	0.934
	rs291593	3858T/C	T>C	0.353	0.417	*CYP4B1*	*rs4646487*	Arg173Trp	C>T	0.143	0.472
	rs56279424	-	G>T	0.173	0.779	*CYP4F2*	*rs2108622*	V433M	C>T	0.323	0.387

Table II. Continued.

Gene	SNP	Alternative name	Alleles	MAF	HWE	Gene	SNP	Alternative name	Alleles	MAF	HWE
CYP19A1	*rs4646*	-	C>A	0.320	0.893		*rs4148356*	Arg723Gln	G>A	0.067	0.382
	rs6493497	-	G>A	0.180	0.938		*rs119774*	-	G>A	0.003	0.967
CYP1A2	*rs762551*	*1F, -163C>A	A>C	0.363	0.259	*ABCC2*	*rs717620*	-24C>T	G>A	0.243	0.696
	rs2069526	*K, *1E, -739T>G	T>G	0.027	0.737		*rs3740066*	3972C>T	G>A	0.273	0.620
	rs2470890	*1B, 5347T>C	C>T	0.153	0.740		*rs2273697*	V417I	G>A	0.087	0.896
	rs2069522	-	T>C	0.027	0.737		*rs12762549*	-	G>C	0.360	0.876
	rs3743484	-	G>C	0.147	0.614	*ABCC4*	*rs1751034*	3463 A>G	T>C	0.177	0.132
	rs2472304	-	G>A	0.153	0.740		*rs9561778*	c.3366+1243G>T	G>T	0.243	0.068
	rs4646427	-	T>C	0.023	0.770	*ABCC6*	*rs2238472*	Arg1268Gln	G>A	0.173	0.779
	rs2069521	-	G>A	0.057	0.462	*ABCG2*	*rs13120400*	-	T>C	0.007	0.934
CYP1B1	*rs1056836*	*3, 4326C>G, L432V	C>G	0.123	0.832		*rs17731538*	-	G>A	0.057	0.020
CYP2A6	*rs28399433*	*13, *15, -48T>G	T>G	0.173	0.391		*rs2622604*	-	C>T	0.143	0.957
CYP2B6	*rs1042389*	-	T>C	0.270	0.041		*rs2231142*	Q141K	C>A	0.257	0.632
	rs8192709	*2, 64C>T	C>T	0.020	0.803	*ABO*	*rs8176746*	-	C>A	0.160	0.481
CYP2C8	*rs11572177*	-	A>G	0.053	0.490		*rs495828*	-	G>T	0.310	0.589
	rs1113129	-	G>C	0.453	0.547	*ACE*	*rs4341*	-	C>G	0.410	0.201
	rs1341164	-	T>C	0.047	0.549	*ADM*	*rs11042725*	-1923C>A	C>A	0.273	0.187
CYP2C18	*rs12777823*	-	G>A	0.313	0.011	*ADRB2*	*rs1042713*	Arg16Gly	A>G	0.437	0.259
ABCB1	*rs1045642*	3435C>T	C>T	0.360	0.610	*ADRB3*	*rs4994*	Trp64Arg	T>C	0.157	0.299
	rs1128503	Gly412Gly	T>C	0.407	0.342	*AGTR1*	*rs5182*	573C>T	T>C	0.210	0.198
	rs10280101	-	A>C	0.037	0.641	*AKT1*	*rs2494732*	-	C>T	0.313	0.388
	rs7787082	-	G>A	0.447	0.094	*ANKK1*	*rs1800497*	-	C>T	0.380	0.565
	rs4148739	-	A>G	0.037	0.641	*APOB*	*rs1367117*	711C>T	G>A	0.107	0.144
	rs11983225	-	T>C	0.037	0.641	*APOC3*	*rs5128*	3238C>G	G>C	0.307	0.967
	rs12720067	-	G>A	0.037	0.641		*rs2854117*	-482C>T	G>A	0.437	0.595
	rs3213619	-129T>C	T>C	0.067	0.382	*ARG1*	*rs2781659*	-	A>G	0.320	0.376
	rs2235015	287-25G>T	G>T	0.037	0.641	*ATM*	*rs4585*	-	G>T	0.450	0.266
	rs10276036	IVS9-44a>G	C>T	0.407	0.342	*ATP7A*	*rs2227291*	Val767Leu	G>C	0.210	2.10×10^{-8}
	rs28364274	V1251I	G>A	0.003	0.967	*ATXN1*	*rs179997*	A-241G	A>G	0.133	0.814
	rs2032582	-	G>T	0.153	0.112	*BAT3*	*rs750332*	-	A>G	0.113	0.383
	rs3789243	-	C>T	0.373	0.703	*BDKRB1*	*rs12050217*	-	A>G	0.400	0.089
ABCC1	*rs3784862*	-	G>A	0.320	0.102	*BDKRB2*	*rs1799722*	C-58T	T>C	0.433	0.542
	rs246240	-	A>G	0.377	0.428	*C6orf10*	*rs3129900*	-	T>G	0.020	0.803
	rs2238476	-	C>T	0.033	0.673	*CACNG2*	*rs2284017*	-	C>T	0.467	0.229
	rs35592	16081823T>C	T>C	0.480	0.610		*rs2284018*	-	C>T	0.300	0.174
	rs35605	1684C>T	C>T	0.240	0.463		rs5750285	-	C>G	0.477	0.496
	rs2230671	4002G>A	G>A	0.163	0.551	*CAT*	*rs10836235*	c.66+78C>T	C>T	0.210	0.096
	rs212090	5462T>A	T>A	0.227	0.891	*CBR1*	*rs9024*	1096G>A	G>A	0.220	0.549

Table II. Continued.

Gene	SNP	Alternative name	Alleles	MAF	HWE	Gene	SNP	Alternative name	Alleles	MAF	HWE
KCNH2	*rs3807375*	-	A>G	0.193	0.172		*rs2661319*	-	A>G	0.473	0.006
KCNJ11	*rs5219*	Lys23Glu, E23K	C>T	0.350	0.346		*rs2842030*	-	T>G	0.450	0.127
KNG1	*rs4686799*	-	C>T	0.397	0.892	*SCN5A*	*rs12053903*	-	C>T	0.457	0.453
	rs5030062	-	A>C	0.283	0.431		*rs1805124*	H558R	A>G	0.100	0.174
	rs698078	-	T>C	0.287	0.286	*SLC10A1*	*rs2296651*	800C>T	G>A	0.023	0.770
LDLR	*rs688*	16730C>T	C>T	0.140	0.968	*SLC10A2*	*rs2301159*	c.*755C>T	C>T	0.293	0.667
LEMD2	*rs2395402*	-	T>C	0.177	0.858	*SLC19A1*	*rs1051266*	Arg27His, c.*746C>T	A>G	0.497	0.022
LRP2	*rs2075252*	-	A>G	0.480	0.402	*SLC1A1*	*rs2228622*	-	G>A	0.240	0.775
LTC4S	*rs730012*	-444C	A>C	0.167	0.096		*rs3780413*	-	C>G	0.263	0.152
METTL21A	*rs7569963*	-	G>A	0.083	0.964		*rs3780412*	-	A>G	0.243	0.404
	rs4675690	-	T>C	0.343	0.543	*SLC22A16*	*rs714368*	146A>G, His49Arg	A>G	0.443	0.405
MICA	*rs2848716*	-	C>G	0.293	0.223	*SLC22A2*	*rs316019*	*4, A270S	G>T	0.113	0.451
MLH1	*rs1800734*	-93	A>G	0.433	0.782	*SLC28A2*	*rs2413775*	16334845T>A	A>T	0.153	0.354
MTHFR	*rs1801131*	1298A>C	A>C	0.163	0.232	*SLCO1B1*	*rs2306283*	*1B, N130D	C>T	0.237	0.470
	rs1801133	Ala222Val	C>T	0.423	0.768		*rs4149056*	*5, c.521T>C	T>C	0.160	0.264
NEFM	*rs1379357*	-	G>C	0.333	0.391		*rs4149081*	Intronic A/G	G>A	0.453	0.296
NOS1AP	*rs10918594*	-	G>C	0.487	0.877		*rs11045879*	Intronic C/T	T>C	0.453	0.296
	rs10494366	-	G>T	0.317	0.251	*SLCO1B3*	*rs11045585*	-	A>G	0.170	0.440
NOS3	*rs2070744*	-786T>C	T>C	0.130	0.699	*SLCO2B1*	*rs12422149*	Arg312Gln	G>A	0.390	0.334
NPPA	*rs5065*	T2238C	A>G	0.010	0.902	*SULT1C4*	*rs1402467*	p.Asp5Glu	C>G	0.080	0.965
NQO1	*rs1800566*	*2, c.558C>T	C>T	0.437	0.426	*TCF7L2*	*rs12255372*	-	G>T	0.007	0.934
NR1I2	*rs1464603*	g.252A>G	T>C	0.440	0.181	*TNF*	*rs1800629*	-308G>A	G>A	0.053	0.354
NTRK1	*rs2768759*	-	A>C	0.083	0.964	*TP53*	*rs1042522*	Arg72Pro	G>C	0.363	0.138
OPRM1	*rs1799971*	A118G	A>G	0.383	0.719	*UGT1A7*	*rs7586110*	-57T>G	T>G	0.220	0.282
P2RY1	*rs701265*	-	A>G	0.363	0.672	*UGT1A8*	*rs1042597*	*2, c.518C>G, Ala173Gly	G>C	0.447	0.723
	rs1065776	893C>T	C>T	0.097	0.576	*UGT2B15*	*rs1902023*	*2, Y85D	T>G	0.487	0.630
P2RY12	*rs2046934*	T744C	T>C	0.233	0.027	*UGT2B17*	*rs6552182*	*2, CNV	C/T	0.163	0.999
PTGS1	*rs3842787*	P17L	C>T	0.090	0.226	*ULK3*	*rs2290573*	-	C>T	0.150	0.689
PTGS2	*rs20417*	-765G>C	G>C	0.027	0.005	*VDR*	*rs1544410*	*Bsm*I	G>A	0.040	0.106
RGS4	*rs951439*	-	C>T	0.413	0.256						

MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium.

Table II. Continued.

Gene	SNP	Alternative name	Alleles	MAF	HWE	Gene	SNP	Alternative name	Alleles	MAF	HWE
CBR1	*rs20572*	627C>T, A209A	C>T	0.220	0.549	*GGH*	*rs11545078*	452C>T	C>T	0.077	0.309
CBR3	*rs1056892*	Val244Met	G>A	0.380	0.642		*rs3780126*	c.109+1307G>C	C>T	0.313	0.783
CCND1	*rs17852153*	870G>A	A>G	0.460	0.567		*rs11545077*	Ala31Thr	G>A	0.177	0.345
CDA	*rs2072671*	Lys27Gln, K27Q	A>C	0.180	0.303	*GNB3*	*rs5443*	Ser275Ser	C>T	0.457	0.082
	rs60369023	c.208G>A, Ala70Thr	G>A	0.007	0.934	*GRIK4*	*rs1954787*	-	C>T	0.123	0.333
	rs532545	-451C>T	G>A	0.173	0.153	*GSK3B*	*rs334558*	-50T>C	G>A	0.350	0.622
CETP	*rs708272*	Taq1B	C>T	0.340	0.224		*rs13321783*	IVS7+9227A>G	G>A	0.420	0.246
CHST3	*rs4148943*	c.*1278C>T	C>T	0.103	0.596		*rs2319398*	IVS7+11660G>T	T>G	0.430	0.362
	rs4148945	c.*1361C>T	C>T	0.073	0.816		*rs6808874*	IVS11+4251T>A	A>T	0.493	0.252
	rs4148950	c.*3477G>A	G>A	0.073	0.816	*GSTP1*	*rs1138272*	C341T, A114V	C>T	0.080	0.965
	rs1871450	c.*3785G>A	G>A	0.073	0.816		*rs1695*	*B, Ile105Val	A>G	0.193	0.400
	rs730720	c.*4533C>T	G>A	0.103	0.596	*HLA-E*	*rs1059510*	Asn98Asn	G>A	0.293	0.252
	rs12418	c.*4785G>A	G>A	0.073	0.816	*HMGCR*	*rs12654264*	-	T>A	0.450	0.902
CNTF	*rs1800169*	FS63TER	G>A	0.143	0.957		*rs3846662*	-	C>T	0.450	0.902
COMT	*rs737865*	-	T>C	0.277	0.844	*HSPA1L*	*rs2227956*	-	T>C	0.067	0.662
	rs165599	-	A>G	0.443	0.864		*rs2075800*	E602K	G>A	0.367	0.682
	rs4680	Val158Met	G>A	0.313	0.214	*HTR1A*	*rs6295*	-	C>G	0.267	0.781
CRHR2	*rs2267715*	-	G>A	0.383	0.719		*rs10042486*	-	T>C	0.213	0.568
	rs2284220	-	A>G	0.440	0.499		*rs1364043*	-	G>T	0.370	0.608
	rs7793837	-	A>T	0.183	0.107	*HTR2A*	*rs9316233*	-	C>G	0.323	0.623
CYTSA	*rs5760410*	g.4205975G>A	A>G	0.353	0.060		*rs7997012*	Intron 5, 2 variant	G>A	0.203	0.919
DRD2	*rs4436578*	-	T>C	0.487	0.863		*rs6311*	-1438G>A	C>T	0.470	0.541
	rs1799978	A-241G	A>G	0.183	0.982		*rs6313*	102C>T	C>T	0.467	0.662
	rs6277	C957T	C>T	0.050	0.519	*HTR2C*	*rs1414334*	-	G>C	0.013	1.53×10^{-9}
	rs1076560	-	C>A	0.403	0.135		*rs518147*	-697G/C	C>G	0.140	6.36×10^{-14}
DRD3	*rs167771*	-	A>G	0.147	0.882		*rs3813928*	c.-995G>A	G>A	0.123	5.77×10^{-16}
	rs6280	Ser9Gly	T>C	0.300	0.560		*rs6318*	Cys23Ser	G>C	0.013	1.53×10^{-9}
EGFR	*rs2227983*	R497K	G>A	0.233	0.704		*rs3813929*	-759C>T	C>T	0.123	5.77×10^{-16}
EPHX1	*rs1051740*	Y113H, 337T>C	T>C	0.447	0.760	*HTR3B*	*rs2276307*	-	A>G	0.223	0.486
	rs2234922	H139R, 416A>G	A>G	0.143	0.957	*HTR7*	*rs1935349*	-	G>A	0.277	0.067
ERBB2	*rs1136201*	Ile655Val	A>G	0.133	0.099	*IL1B*	*rs16944*	-511C/T	G>A	0.463	0.793
ERCC1	*rs3212986*	8092C>A	G>T	0.277	0.833	*IL28B*	*rs8099917*	-	T>G	0.070	0.740
	rs11615	19007T>C, Asn118Asn	C>T	0.230	0.341		*rs12980275*	-	A>G	0.077	0.891
ERCC2	*rs13181*	2251A>C, Lys751Gln	T>G	0.043	0.579		*rs8105790*	-	T>C	0.070	0.740
FDPS	*rs2297480*	-	C>A	0.187	0.677		*rs11881222*	-	A>G	0.070	0.740
FKBP5	*rs1360780*	-	C>T	0.250	0.057		*rs7248668*	-	G>A	0.067	0.662
	rs3800373	-	T>G	0.223	0.101	*ITPA*	*rs1127354*	P32T	C>A	0.147	0.882
GGCX	*rs699664*	8016G>A	G>A	0.367	0.682	*KCNH2*	*rs3815459*	-	A>G	0.187	0.903

Table III. List of 105 monomorphic single-nucleotide polymorphisms (SNPs).

Gene	SNP	Alternative name	Alleles	Gene	SNP	Alternative name	Alleles
CYP2D6	*rs1135822*	*49, 1611T>A	T>A	*G6PD*	*rs1050828*	202G>A	C>T
	rs35742686	*3, 2549delA	Ins>del		*rs1050829*	376A>G	A>G
	rs5030655	*6, 1707delT	Ins>del		*rs34193178*	H350D	G>C
	CYP2D6_2	*60, 1887insTA	Del>ins	*HLA-B*1502*	*rs3130690*	HLA-B*1502	C>A
	rs5030867	*7, 2935A>C	A>C	*HLA-B*5701*	*rs2395029*	HLA-B*5701	T>G
	rs5030656	*9, 2615_2617delAAG	Ins>del	*NAT1*	*rs4986990*	*11, c.459G>A, p.T153T	G>A
CYP2C9	*rs28371685*	*11, R335W	C>T		*rs5030839*	*15, c.559C>T, p.R187X	C>T
	rs9332239	*12, 50338C>T	C>T		*rs56379106*	*17, c.190C>T, p.R64W	C>T
	rs72558187	*13, 3276T>C	T>C		*rs56318881*	*19, c.97C>T, p.R33X	C>T
	rs72558190	*15, 9100C>A	C>A		*rs56172717*	*22, c.752A>T, p.D251V	A>T
	rs72558193	*18, 47391A>C	A>C		*rs55793712*	*5, c.884A>G	A>G
	rs1799853	*2, Arg144Cys	C>T		*rs72554612*	*5, c.976delA	A>G
	rs72558188	*25, 353_362delAGAAATGGAA	Ins>del	*NAT2*	*rs1805158*	*19, 190C>T, R64W	C>T
	rs9332131	*6, 818delA	Ins>del		*rs4986996*	*12D	G>A
VKORC1	*rs7200749*	*3F, 3462C>T, 8773C>T	G>A	*TPMT*	*rs1800462*	*2, 238G>C, A80P	G>C
CYP2C19	*rs41291556*	*8, 12711T>C, W120R	T>C		*rs1800584*	*4	G>A
	rs56337013	*5A, 1297C>T, R433W	C>T	*UGT1A1*	*rs28934877*	*38	A>G
DPYD	*rs3918290*	*2A, IVS14+1G>A	G>A		*rs55750087*	*29, R367G	C>G
	rs1801268	*10, 2983G>T, V995F	G>T	*CYP3A4*	*rs4987161*	*17, F189S, 670T>C	T>C
	rs72549309	*7, 295delTCAT	A>T		*rs2740574*	*1B, -392A>G	A>G
	rs1801266	*8, R235W	C>T	*CYP3A5*	*rs10264272*	*6, 14690G>A	C>T
	rs1801267	*9B, 2657G>A, R886H	G>A		*rs41303343*	*7, 27131_27132insT	A>T
	DPYD_2	-268C/A	C>A		*rs28383479*	*9, 19386G>A	G>A
	DPYD_1	N151D	A>G		*rs41279854*	*10, 29753T>C	A>G
	DPYD_3	S811S	C>T	*CYP1A2*	*rs72547513*	*11, F186L, 558C>A	C>A
	DPYD_4	T735A	A>G		*rs72547511*	*15, P42R, 125C>G	C>G

Table III. Continued.

Gene	SNP	Alternative name	Alleles	Gene	SNP	Alternative name	Alleles
CYP1A2	*rs72547515*	*16, R377Q, 2473G>A	C>T	*BCHE*	*rs1799807*	Asp70Gly	A>G
	rs55889066	*5, C406Y, 3497G>A	G>A		*rs28933390*	Gly390Val	G>T
	rs28399424	*6, R431W, 5090C>T	C>T		*rs28933389*	Thr243Met	C>T
	rs72547517	*8, R456H, 5166G>A	G>A	*CBR3*	*rs2835285*	Val93Ile	G>A
CYP2A6	*rs28399468*	*10, 6600G>T	G>T	*COMT*	*rs9332377*	-	C>T
	rs1809810	*18, 5668A>T	A>T	*EGFR*	*rs121434568*	L858R	T>G
	rs56256500	*23, R203C, 607C>T	C>T	*F2*	*rs1799963*	-	G>A
	rs28399444	*20, 2141_2142delAA	A>C	*GRIK2*	*rs2518224*	-	A>C
	rs12721655	*8, 415A>G, K192E	A>G	*GSTM3*	*rs1799735*	Intron 6, 3-bp deletion	G>T
	rs34223104	*22, -82C>T	T>C	*HTR2A*	*rs6314*	C1354T	C>T
	rs36079186	*27, 593T>C, M198T	T>C	*ITGB3*	*rs5918*	Leu33Pro	T>C
	rs34097093	*28, 1132C>T, R378X	C>T	*KCNH2*	*rs12720441*	R784W	C>T
	rs3211371	*1C, *5, *7, 1459C>T, Arg487Cys	T>C	*SCN5A*	*rs7626962*	S1103Y	G>T
	rs28399499	*18, 983T>C, I328T	T>C	*SLC22A1*	*rs34059508*	1393G>A, G465R	G>A
	rs58425034	c.646-159G>C	G>C		*rs12208357*	148C>T, R61C	C>T
	rs12721646	c.646-17C>T	C>T	*SLC22A2*	*rs8177517*	K432Q	A>C
CYP2C8	*rs11572103*	*2, I269F, A805T	A>T		*rs8177507*	M165I	C>T
	rs10509681	*5, 2189delA	Ins>del		*rs8177516*	*7, R400C	C>T
ABCB1	*rs35810889*	M89T	T>C	*SLC28A3*	*rs11568388*	1099G>A	G>A
	rs35023033	R669C	C>T	*SLCO1B1*	*rs56199088*	*10, D655G	A>G
	rs35730308	W1108R	T>C		*rs56101265*	*2, F73L	T>C
	rs35529209	Ala989Thr	G>A		*rs72559745*	*3, E156G	A>G
	rs45511401	Gly671Val	G>T		*rs56061388*	*3, V82A	T>C
ABCC2	*rs8187710*	Cys1515Tyr	G>A		*rs59502379*	*9, G488A	G>C
	rs17222723	Val1188Glu	T>A	*ST6GAL1*	*rs10937275*	-	G>A
ADRB2	*rs1800888*	Thr164Ile	C>T	*UGT2B10*	*rs7657958*	Asp67Tyr tagging	G>A
AOX1	*rs55754655*	Asn1135Ser	A>G				

Table IV. Summary of 141 pharmacogenes investigated in a Korean population (n=150).

Class	Gene (no. of SNPs)	Class	Gene (no. of SNPs)	Class	Gene (no. of SNPs)	Class	Gene (no. of SNPs)
Phase I	*CYP2D6* (14)		*ABCC2* (6)		*ATM* (1)		*HTR7* (1)
	CYP2C9 (13)		*ABCC4* (2)		*ATXN1* (1)		*IL1B* (1)
	CYP2C19 (15)		*ABCC6* (1)		*BAT3* (1)		*IL28B* (5)
	DPYD (16)		*ABCG2* (4)		*BCHE* (3)		*ITGB3* (1)
	CYP2E1 (6)		*SLC10A1* (1)		*BDKRB1* (1)		*ITPA* (1)
	CYP3A4 (3)		*SLC10A2* (1)		*BDKRB2* (1)		*KCNH2* (3)
	CYP3A5 (6)		*SLC19A1* (1)		*C6orf10* (1)		*KNG1* (3)
	CYP4B1 (1)		*SLC1A1* (3)		*CACNG2* (3)		*LDLR* (1)
	CYP4F2 (1)		*SLC22A1* (2)		*CCND1* (1)		*LEMD2* (1)
	CYP19A1 (2)		*SLC22A16* (1)		*CETP* (1)		*LRP2* (1)
	CYP1A2 (14)		*SLC22A2* (4)		*CNTF* (1)		*LTC4S* (1)
	CYP1B1 (1)		*SLC28A2* (1)		*COMT* (4)		*METTL21A* (2)
	CYP2A6 (5)		*SLC28A3* (1)		*CRHR2* (3)		*MICA* (1)
	CYP2B6 (10)		*SLCO1B1* (9)		*CYTSA* (1)		*MLH1* (1)
	CYP2C8 (5)		*SLCO1B3* (1)		*DRD2* (4)		*MTHFR* (2)
	CYP2C18 (1)		*SLCO2B1* (1)		*DRD3* (2)		*NEFM* (1)
	AOX1 (1)		*ATP7A* (1)		*EGFR* (2)		*NOS1AP* (2)
	CBR1 (2)		*CAT* (1)		*ERBB2* (1)		*NPPA* (1)
	CBR3 (2)	Modifier	*CDA* (3)		*ERCC1* (2)		*NQO1* (1)
	EPHX1 (2)		*KCNJ11* (1)		*ERCC2* (1)		*NTRK1* (1)
	NOS3 (1)		*NR1I2* (1)		*F2* (1)		*OPRM1* (1)
Phase II	*NAT1* (10)		*VKORC1* (6)		*FDPS* (1)		*P2RY1* (2)
	NAT2 (10)		*G6PD* (6)		*FKBP5* (2)		*P2RY12* (1)
	TPMT (6)	Others	*HLA-B*1502* (3)		*GGCX* (1)		*PTGS1* (1)
	UGT1A1 (9)		*HLA-B*5701* (1)		*GGH* (3)		*PTGS2* (1)
	CHST3 (6)		*ABO* (2)		*GNB3* (1)		*RGS4* (3)
	GSTM3 (1)		*ACE* (1)		*GRIK2* (1)		*SCN5A* (3)
	GSTP1 (2)		*ADM* (1)		*GRIK4* (1)		*ST6GAL1* (1)
	SULT1C4 (1)		*ADRB2* (2)		*GSK3B* (4)	Others	*TCF7L2* (1)
	UGT1A7 (1)		*ADRB3* (1)		*HLA-E* (1)		*TNF* (1)
	UGT1A8 (1)		*AGTR1* (1)	Others	*HMGCR* (2)		*TP53* (1)
	UGT2B10 (1)		*AKT1* (1)		*HSPA1L* (2)		*ULK3* (1)
	UGT2B15 (1)	Others	*ANKK1* (1)		*HTR1A* (3)		*VDR* (1)
	UGT2B17 (1)		*APOB* (1)		*HTR2A* (5)		
Transporter	*ABCB1* (16)		*APOC3* (2)		*HTR2C* (5)		
	ABCC1 (11)		*ARG1* (1)		*HTR3B* (1)		

Table V. Frequencies and effects of *CYPD6*, *CYP2C19*, *TPMT*, *DPYD* and *IL28B* genotypes on enzyme activity and drug toxicity.

Gene	Star-allele genotype	Star-allele-defining SNPs (genotype of each SNP)	No.	Freq. (%)	Enzyme activity[a]	Clopidogrel efficacy[b]	Adverse reactions of azathioprine, mercaptopurine and thioguanine[c]	5-FU toxicity[d]	Treatment outcome for hepatitis C[e]
CYP2D6	**1/*1*	Wild-type	95	63.3	Normal	N/A	N/A	N/A	N/A
	**1/*2*	*rs16947* (CT), *rs1135840* (GG)	6	4	Normal	N/A	N/A	N/A	N/A
	**2/*2*	*rs16947* (TT), *rs1135840* (GG)	2	1.3	Normal	N/A	N/A	N/A	N/A
	**1/*4*	*rs3892097* (AG)	18	12	Decreased	N/A	N/A	N/A	N/A
	**4/*4*	*rs3892097* (AA)	2	1.3	None	N/A	N/A	N/A	N/A
	**1/*10*	*rs1065852* (CT or TT), *rs1135840* (GG or CG)	7	4.7	Normal	N/A	N/A	N/A	N/A
	**1/*14A*	*rs1065852* (CT or TT), *rs16947* (CT or TT), *rs1135840* (GG or CG)	12	8	Decreased	N/A	N/A	N/A	N/A
	**1/*34*	*rs16947* (CT)	34	22.7	Normal	N/A	N/A	N/A	N/A
	**34/*34*	*rs16947* (TT)	4	2.7	Normal	N/A	N/A	N/A	N/A
	**1/*36*	*rs1065852* (CT or TT), *rs1135840* (GG or CG)	7	4.7	Normal	N/A	N/A	N/A	N/A
	**1/*60*	*CYP2D6_2*[f] (ins/del or del/del), *rs79738337* (TT or CT)	2	1.3	Normal	N/A	N/A	N/A	N/A
CYP2C19	**1/*1*	Wild-type	45	25.9	Normal	Typical	N/A	N/A	N/A
	**1/*2*	*rs4244285* (AG)	78	44.8	Decreased	Reduced	N/A	N/A	N/A
	**2/*2*	*rs4244285* (AA)	8	4.6	Decreased	Greatly reduced	N/A	N/A	N/A
	**1/*3*	*rs4986893* (AG)	21	12.1	Decreased	Reduced	N/A	N/A	N/A
	**3/*3*	*rs4986893* (AA)	1	0.6	Decreased	Greatly reduced	N/A	N/A	N/A
	**1/*4*	*rs28399504* (AG)	1	0.6	Decreased	Reduced	N/A	N/A	N/A
	**1/*17*	*rs11188072* (CC or CT), *rs12248560* (CC or CT)	20	11.5	Increased	Enhanced	N/A	N/A	N/A
TPMT	**1/*3B*	*rs1800460* (AG)	1	0.7	Decreased	N/A	Increased drug toxicity	N/A	N/A
	**1/*3C*	*rs1142345* (AG)	4	2.7	Decreased	N/A	Increased drug toxicity	N/A	N/A
	**1/*6*	*rs75543815* (AA)	139	92.7	Decreased	N/A	Increased drug toxicity	N/A	N/A
	**6/*6*	*rs75543815* (AT)	7	4.7	Decreased	N/A	Increased drug toxicity	N/A	N/A
DPYD	**1/*1*	*rs3918290* (GG)	150	100	-	N/A	N/A	Low risk	N/A
	**1/*5*	*rs1801159* (AG)	65	43.3	Normal	N/A	N/A	-	N/A
	**5/*5*	*rs1801159* (GG)	9	6	Normal	N/A	N/A	-	N/A
	**1/*9A*	*rs1801265* (CT)	16	10.7	Normal	N/A	N/A	-	N/A
	c.496A>G	*rs2297595* (AG)	3	2	Normal	N/A	N/A	-	N/A
IL28B	-	*rs8099917* (TT)	130	86.7	N/A	N/A	N/A	N/A	Normal
	-	*rs8099917* (GT)	19	12.7	N/A	N/A N/A	N/A N/A	N/A	1.64 times less likely to respond
	-	*rs8099917* (GG)	1	0.7	N/A	N/A N/A	N/A N/A	N/A	2.39 times less likely to respond

[a]Enzyme activity based on previous studies [*CYP2D6* (21,76-80), *CYP2C19* (81), *TPMT* (82,83), *DPYD* (84)]. [b]The efficacy of clopidogrel was estimated based on a previous study (81). [c]The adverse reactions to azathioprine, mercaptopurine and thioguanine were estimated based on previous studies (8). [d]5-Fluorouracil (5-FU) toxicity estimation was based on a previous study (84). [e]Odds of responding to peginterferon-α and ribavirin (PEG-IFNα/RBV) treatment for hepatitis C. The outcome estimation was based on previous studies (74,85). [f]TA insertion at position 1887. N/A, not applicable.

Table VI. Frequencies and effect of combined *CYP2C9* and *VKORC1* genotypes on the response to warfarin.

CYP2C9			*VKORC1* (*rs8050894*)								
			CC			CG			GG		
Star-allele genotype	Star-allele-defining SNPs	Genotype in each SNP	n	Freq. (%)	Warfarin dose (mg/day)[a]	n	Freq. (%)	Warfarin dose (mg/day)[a]	n	Freq. (%)	Warfarin dose (mg/day)[a]
**1/*1*	*rs1799853* CC *rs1057910* AA		1	0.7	5-7	22	14.7	5-7	114	76.0	3-4
**1/*2*	*rs1799853* CT *rs1057910* AA		0	0	5-7	0	0	3-4	0	0	3-4
**1/*3*	*rs1799853* CC *rs1057910* AC		0	0	3-4	1	0.7	3-4	12	8.0	0.5-2
**2/*2*	*rs1799853* TT *rs1057910* AA		0	0	3-4	0	0	3-4	0	0	0.5-2
**2/*3*	*rs1799853* CT or TT *rs1057910* AC or CC		0	0	3-4	0	0	0.5-2	0	0	0.5-2
**3/*3*	*rs1799853* CC *rs1057910* CC		0	0	0.5-2	0	0	0.5-2	0	0	0.5-2

[a]Warfarin dose estimation was based on previous studies (52,86,87).

Table VII. Frequencies and combined effects of *rs2844682* and *rs3909184* (tagging *HLA-B*1502*) on adverse reactions to carbamazepine.

SNP/Genotype					
rs2844682	*rs3909184*	n	Freq. (%)	*HLA-B*1502 type*	Adverse reactions to carbamazepine[a]
CC	CC	95	63.3	None	Low risk
CC	CG	10	6.7	None	Low risk
CC	GG	1	0.7	None	Low risk
CT	CC	37	24.7	None	Low risk
CT	CG	4	2.7	Unable to be determined	-
CT	GG	0	0	**1502* (one copy)	High risk
TT	CC	3	2.0	None	Low risk
TT	CG	0	0	**1502* (one copy)	High risk
TT	GG	0	0	**1502* (two copies)	High risk

[a]Reaction estimation based on a previous study (88).

Table VIII. Frequency and effects of *HCP5/HLA-B*5701* and *TPMT/COMT* polymorphisms on adverse drug reaction.

SNP ID/Genotype				
rs2395029 (HCP5)	*HLA-B*5701*	n	Freq. (%)	Abacavir hypersensitivity[a]
TT	None	150	100	Low risk
TG	**5701 (one copy)	0	0	High risk
GG	**5701 (two copies)	0	0	High risk
rs1142345 (TPMT)	*rs9332377 (COMT)*	n	Freq. (%)	Adverse reactions to cisplatin[b]
AA	CC	146	93.7	Low risk
AG	CC	4	2.7	High risk
GG	CC	0	0	High risk

[a]Estimated based on a previous study (89). [b]Risk estimation of adverse reactions to cisplatin was based on a previous study (39).

adverse drug reactions or Stevens-Johnson syndrome in Asian populations (47-51). In this study, two tagging SNPs of *HLA-B**1502*, *rs3909184* and *rs2844682*, were used for the evaluation of the *HLA-B**1502* frequency in the Korean population (Table VII). No subject was identified as carrying one or two copies of *HLA-B**1502*, which is associated with increased risk of adverse reactions to carbamazepine. Thus, the Korean population may have a relatively low risk of adverse reactions to carbamazepine.

*HLA-B**5701*, which is in linkage disequilibrium with *rs2395029* in *HCP5*, was reported to be a predictive marker of abacavir hypersensitivity (52). Abacavir is an inhibitor of nucleoside reverse-transcriptase and is used as an anti-retroviral agent for human immunodeficiency virus treatment (53). All 150 Korean subjects were found to carry the combination of the TT genotype of *rs2395029* and *HLA-B**5701*-negative type, which is associated with a low risk of hypersensitivity to abacavir (Table VIII). The genotype frequencies of *TPMT* and catechol O-methyltransferase (*COMT*) polymorphisms, which are associated with the risk of hearing loss due to cisplatin toxicity (54), were also estimated in the Korean population (Table VIII) and the combination of the AA genotype of *rs1142345* (*TPMT*) and the CC genotype of *rs9332377* (*COMT*), which are associated with a lower risk of cisplatin ototoxicity (54), exhibited the highest frequency (93.7%) in the Korean population.

In conclusion, we conducted extensive analyses of the distribution of various pharmacogene polymorphisms in 150 Korean subjects and identified the genotype frequencies of important pharmacogene polymorphisms, such as *CYP2D6*, *CYP2C9*, *VKORC1*, *CYP2C19*, *HLA-B* and *TPMT* among others, which may affect the efficacy and side effects of various drugs, including warfarin, clopidogrel, carbamazepine, azathioprine and others. To the best of our knowledge, our study was the first to simultaneously investigate a large number of pharmacogene polymorphisms in multiple samples in a Korean population. The findings from the present study may be helpful in developing personalized medicines for Korean patients. Moreover, the methods used in the present study may also be applied in other populations in order to study their unique pharmacogenomics.

Acknowledgements

This study was supported by a grant from the Ministry of Food and Drug Safety, Republic of Korea, in 2011 (no. 10182MFDS572).

References

1. Lazarou J, Pomeranz BH and Corey PN: Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 279: 1200-1205, 1998.
2. Dormann H, Neubert A, Criegee-Rieck M, *et al*: Readmissions and adverse drug reactions in internal medicine: the economic impact. J Intern Med 255: 653-663, 2004.
3. Shastry BS: Pharmacogenetics and the concept of individualized medicine. Pharmacogenomics J 6: 16-21, 2006.
4. Sachidanandam R, Weissman D, Schmidt SC, *et al*; International SNP Map Working Group: A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. Nature 409: 928-933, 2001.
5. Evans WE and Relling MV: Pharmacogenomics: translating functional genomics into rational therapeutics. Science 286: 487-491, 1999.
6. Evans WE and Johnson JA: Pharmacogenomics: the inherited basis for interindividual differences in drug response. Annu Rev Genomics Hum Genet 2: 9-39, 2001.
7. McLeod HL and Evans WE: Pharmacogenomics: unlocking the human genome for better drug therapy. Annu Rev Pharmacol Toxicol 41: 101-121, 2001.
8. Yates CR, Krynetski EY, Loennechen T, *et al*: Molecular diagnosis of thiopurine S-methyltransferase deficiency: genetic basis for azathioprine and mercaptopurine intolerance. Ann Intern Med 126: 608-614, 1997.
9. Evans WE and McLeod HL: Pharmacogenomics - drug disposition, drug targets, and side effects. N Engl J Med 348: 538-549, 2003.
10. Johnson JA: Pharmacogenetics: potential for individualized drug therapy through genetics. Trends Genet 19: 660-666, 2003.
11. Guttmacher AE and Collins FS: Welcome to the genomic era. N Engl J Med 349: 996-998, 2003.
12. Zineh I, Gerhard T, Aquilante CL, Beitelshees AL, Beasley BN and Hartzema AG: Availability of pharmacogenomics-based prescribing information in drug package inserts for currently approved drugs. Pharmacogenomics J 4: 354-358, 2004.
13. Schmitz G, Aslanidis C and Lackner KJ: Pharmacogenomics: implications for laboratory medicine. Clin Chim Acta 308: 43-53, 2001.
14. Collins FS, Green ED, Guttmacher AE, Guyer MS, *et al*: A vision for the future of genomics research. Nature 422: 835-847, 2003.
15. Ragoussis J: Genotyping technologies for genetic research. Annu Rev Genomics Hum Genet 10: 117-133, 2009.
16. Kapoor G, Maitra A and Brahmachari V: Application of SNaPshot for analysis of thiopurine methyltransferase gene polymorphism. Indian J Med Res 129: 500-505, 2009.
17. Fan JB, Gunderson KL, Bibikova M, *et al*: Illumina universal bead arrays. Methods Enzymol 410: 57-73, 2006.
18. Lin CH, Yeakley JM, McDaniel TK and Shen R: Medium- to high-throughput SNP genotyping using VeraCode microbeads. Methods Mol Biol 496: 129-142, 2009.
19. Sanchez JJ, Borsting C, Hallenberg C, Buchard A, Hernandez A and Morling N: Multiplex PCR and minisequencing of SNPs - a model with 35 Y chromosome SNPs. Forensic Sci Int 137: 74-84, 2003.
20. Hulot JS, Bura A, Villard E, *et al*: Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood 108: 2244-2247, 2006.
21. Savi P, Herbert JM, Pflieger AM, *et al*: Importance of hepatic metabolism in the antiaggregating activity of the thienopyridine clopidogrel. Biochem Pharmacol 44: 527-532, 1992.
22. Savi P, Combalbert J, Gaich C, *et al*: The antiaggregating activity of clopidogrel is due to a metabolic activation by the hepatic cytochrome P450-1A. Thromb Haemost 72: 313-317, 1994.
23. Hollopeter G, Jantzen HM, Vincent D, *et al*: Identification of the platelet ADP receptor targeted by antithrombotic drugs. Nature 409: 202-207, 2001.
24. Derijks LJ, Gilissen LP, Engels LG, *et al*: Pharmacokinetics of 6-thioguanine in patients with inflammatory bowel disease. Ther Drug Monit 28: 45-50, 2006.
25. Heneghan MA, Allan ML, Bornstein JD, Muir AJ and Tendler DA: Utility of thiopurine methyltransferase genotyping and phenotyping, and measurement of azathioprine metabolites in the management of patients with autoimmune hepatitis. J Hepatol 45: 584-591, 2006.
26. Roman M, Cabaleiro T, Ochoa D, *et al*: Validation of a genotyping method for analysis of TPMT polymorphisms. Clin Ther 34: 878-884, 2012.
27. Hakooz N, Arafat T, Payne D, *et al*: Genetic analysis of thiopurine methyltransferase polymorphism in the Jordanian population. Eur J Clin Pharmacol 66: 999-1003, 2010.
28. Amstutz U, Froehlich TK and Largiader CR: Dihydropyrimidine dehydrogenase gene as a major predictor of severe 5-fluorouracil toxicity. Pharmacogenomics 12: 1321-1336, 2011.
29. Meyerhardt JA and Mayer RJ: Systemic therapy for colorectal cancer. N Engl J Med 352: 476-487, 2005.
30. Ezzeldin H and Diasio R: Dihydropyrimidine dehydrogenase deficiency, a pharmacogenetic syndrome associated with potentially life-threatening toxicity following 5-fluorouracil administration. Clin Colorectal Cancer 4: 181-189, 2004.
31. van Kuilenburg AB, Maring JG, Schalhorn A, *et al*: Pharmacokinetics of 5-fluorouracil in patients heterozygous for the IVS14+1G>A mutation in the dihydropyrimidine dehydrogenase gene. Nucleosides Nucleotides Nucleic Acids 27: 692-698, 2008.

32. Suppiah V, Moldovan M, Ahlenstiel G, *et al*: IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat Genet 41: 1100-1104, 2009.
33. Tanaka Y, Nishida N, Sugiyama M, *et al*: Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 41: 1105-1109, 2009.
34. Rauch A, Kutalik Z, Descombes P, *et al*: Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. Gastroenterology 138: 1338-1345, 2010.
35. Glurich I, Burmester JK and Caldwell MD: Understanding the pharmacogenetic approach to warfarin dosing. Heart Fail Rev 15: 239-248, 2010.
36. Schalekamp T, Brasse BP, Roijers JF, *et al*: VKORC1 and CYP2C9 genotypes and phenprocoumon anticoagulation status: interaction between both genotypes affects dose requirement. Clin Pharmacol Ther 81: 185-193, 2007.
37. Wadelius M, Chen LY, Eriksson N, *et al*: Association of warfarin dose with genes involved in its action and metabolism. Hum Genet 121: 23-34, 2007.
38. Sconce EA, Khan TI, Wynne HA, *et al*: The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood 106: 2329-2333, 2005.
39. D'Andrea G, D'Ambrosio RL, Di Perna P, *et al*: A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin. Blood 105: 645-649, 2005.
40. Schalekamp T, Brasse BP, Roijers JF, *et al*: VKORC1 and CYP2C9 genotypes and acenocoumarol anticoagulation status: interaction between both genotypes affects overanticoagulation. Clin Pharmacol Ther 80: 13-22, 2006.
41. Wang D, Chen H, Momary KM, Cavallari LH, Johnson JA and Sadee W: Regulatory polymorphism in vitamin K epoxide reductase complex subunit 1 (VKORC1) affects gene expression and warfarin dose requirement. Blood 112: 1013-1021, 2008.
42. Limdi NA, Arnett DK, Goldstein JA, *et al*: Influence of CYP2C9 and VKORC1 on warfarin dose, anticoagulation attainment and maintenance among European-Americans and African-Americans. Pharmacogenomics 9: 511-526, 2008.
43. Fuerst D, Parmar S, Schumann C, *et al*: HLA polymorphisms influence the development of skin rash arising from treatment with EGF receptor inhibitors. Pharmacogenomics 13: 1469-1476, 2012.
44. Melis R, Lewis T, Millson A, *et al*: Copy number variation and incomplete linkage disequilibrium interfere with the HCP5 genotyping assay for abacavir hypersensitivity. Genet Test Mol Biomarkers 16: 1111-1114, 2012.
45. Maekawa K, Nishikawa J, Kaniwa N, *et al*: Development of a rapid and inexpensive assay for detecting a surrogate genetic polymorphism of HLA-B*58:01: a partially predictive but useful biomarker for allopurinol-related Stevens-Johnson syndrome/toxic epidermal necrolysis in Japanese. Drug Metab Pharmacokinet 27: 447-450, 2012.
46. Leeder JS: Mechanisms of idiosyncratic hypersensitivity reactions to antiepileptic drugs. Epilepsia 39 (Suppl 7): S8-S16, 1998.
47. Wu XT, Hu FY, An DM, *et al*: Association between carbamazepine-induced cutaneous adverse drug reactions and the HLA-B*1502 allele among patients in central China. Epilepsy Behav 19: 405-408, 2010.
48. Hung SI, Chung WH, Liu ZS, *et al*: Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. Pharmacogenomics 11: 349-356, 2010.
49. Chen P, Lin JJ, Lu CS, *et al*: Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med 364: 1126-1133, 2011.
50. Zhang Y, Wang J, Zhao LM, *et al*: Strong association between HLA-B*1502 and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in mainland Han Chinese patients. Eur J Clin Pharmacol 67: 885-887, 2011.
51. Wang Q, Zhou JQ, Zhou LM, *et al*: Association between HLA-B*1502 allele and carbamazepine-induced severe cutaneous adverse reactions in Han people of southern China mainland. Seizure 20: 446-448, 2011.
52. Colombo S, Rauch A, Rotger M, *et al*: The HCP5 single-nucleotide polymorphism: a simple screening tool for prediction of hypersensitivity reaction to abacavir. J Infect Dis 198: 864-867, 2008.
53. Sanchez-Giron F, Villegas-Torres B, Jaramillo-Villafuerte K, *et al*: Association of the genetic marker for abacavir hypersensitivity HLA-B*5701 with HCP5 rs2395029 in Mexican Mestizos. Pharmacogenomics 12: 809-814, 2011.
54. Ross CJ, Katzov-Eckert H, Dube MP, *et al*: Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. Nat Genet 41: 1345-1349, 2009.