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Original Article

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Comprehensive analysis of important pharmacogenes in Koreans using the DMET™ platform

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ABSTRACT

Genetic polymorphisms of enzymes and transporters associated with the absorption, distribution, metabolism, and elimination (ADME) of drugs are one of the major factors that contribute to interindividual variations in drug response. In the present study, we aimed to elucidate the pharmacogenetic profiles of the Korean population using the Affymetrix Drug Metabolizing Enzyme and Transporters (DMET™) platform. A total of 1,012 whole blood samples collected from Korean subjects were genotyped using the DMET™ plus microarray. In total, 1,785 single nucleotide polymorphism (SNP) markers for 231 ADME genes were identified. The genotype and phenotype of 13 clinically important ADME genes implemented in the Clinical Pharmacogenetics Implementation Consortium guidelines were compared among different ethnic groups. Overall, the genotype frequencies of the Korean population were similar to those of the East Asian population. Several genes, notably *CYP2C19* and *VKORC1*, showed marked differences in Koreans compared to Europeans (EURs) or Africans (AFRs). The percentage of CYP2C19 poor metabolizers was 15% in Koreans and less than 3% in EURs or AFRs. The frequencies of causative SNPs of the *VKORC1* gene for the low warfarin dose phenotype were 90%, 60%, and 10% in Koreans, EURs and AFRs, respectively. Our findings can be utilized for optimal pharmacotherapy in Korean patients.

Keywords: Pharmacogenetics; Oligonucleotide Array Sequence Analysis; Polymorphism, Genetic

INTRODUCTION

The pharmacokinetic and pharmacodynamic response to a drug is affected by multiple factors, including age, organ function, concomitant drugs, food intake, and genetic variation. Genetic polymorphisms associated with the absorption, distribution, metabolism, and elimination (ADME) of drugs are one of the important factors that affect drug response [1]. ADME-related genes include the genes of phase I and II drug-metabolizing enzymes (e.g., cytochrome P450 [CYP450] superfamily of enzymes, dehydrogenases, monooxygenases, reductases and transferases), transporters and receptors [2-5]. Many studies have demonstrated that the genetic variations (e.g., single nucleotide polymorphisms [SNPs] or copy number variations [CNVs]) of those ADMEs cause the diversity of drug efficacy and safety among individuals [6,7].

Author Contributions

Conceptualization: Kim B, Oh J; Data curation: Kim B, Oh J; Formal analysis: Kim B, Oh J; Investigation: Kim B, Oh J; Methodology: Kim B, Oh J; Supervision: Yoon DY, Oh J; Validation: Kim B; Visualization: Kim B, Yoon DY; Writing - original draft: Kim B; Writing - review & editing: Yoon DY, Lee S, Jang IJ, Yu KS, Cho JY, Oh J.

The Affymetrix Drug Metabolizing Enzyme and Transporters (DMET™) microarray platform is a useful tool for simultaneous genotyping of a large number of genetic variants for genes that encode drug-metabolizing enzymes and transporters [8]. The DMET™ platform enables individuals to test a total of 1,936 SNPs, CNVs, and insertion and deletion markers over 231 ADME-related genes. The DMET™ platform covers 76 phase I enzymes, 62 phase II enzymes, 51 transporters and 41 other genes that regulate intracellular processes that facilitate ADME [8]. The DMET™ plus platform has been repeatedly reported for its usefulness in studying interethnic differences in drug response [9,10].

Because genetic characteristics are strongly linked to ethnicity, interethnic differences in genetic variations can be an important factor for ethnic differences in drug response [11,12]. The evaluation of interethnic differences in pharmacogenomic markers can provide important information needed for translation of foreign clinical data to a domestic population. While there is evidence that Koreans share similar pharmacogenetic profiles with Japanese and Chinese populations, population-wide analysis of various ADME-related genes has not been reported [13]. Additionally, large-scale comprehensive data on pharmacogenetic variation in the Korean population have not yet been reported.

Therefore, we aimed to investigate the comprehensive genotype profiles of ADME-related genes in a large Korean population using the DMET™ plus microarray platform and to compare important pharmacogenetic markers between Korean and other ethnic populations.

METHODS

Ethics statement

This study was performed using banked blood samples at Seoul National University Hospital, and the study protocol was approved by the Institutional Review Board of the Seoul National University Hospital (study identification number: H-0803-022-237). The collection and use of all human samples and all experimental protocols were in accordance with the Declaration of Helsinki. All participants were provided with information on the procedure, including the collection of human-derived materials and the purpose of the study, and each participant provided a signed informed consent form.

SNP and CNV genotyping using the DMET™ Plus microarray

A total of 1,012 whole blood samples obtained from unrelated Koreans were used for genotyping. The samples were obtained from male or female subjects aged 19 to 50, who were determined as healthy based on the results of clinical laboratory tests, 12-lead electrocardiogram, vital signs, and physical examination. Blood samples were collected from participants and stored at −70°C until analysis. DNA samples were then genotyped using the Affymetrix DMET™ Plus GeneChip (Affymetrix, Santa Clara, CA, USA) at DNA Link. Co. Ltd. (Seoul, Korea) using a standard protocol [14]. Genomic DNA was extracted from blood samples and amplified by PCR, and the amplified DNA samples were then ligated to and cleaved from molecular inversion probes, which were then amplified and analyzed on a DMET™ array. SNPs with a less than 95% call rate within each batch and CNVs were excluded. The final dataset consisted of 1,785 genetic markers in 230 genes.

Comparison of genotype and phenotype data with other ethnic populations

SNP frequency data for European (EUR), East Asian (EAS), African (AFR) and global populations were collected as of August 2020 from 5 sources, including the 1000 Genomes Project, Allele Frequency Aggregator, Genome Aggregation Database, Exome Aggregation Consortium, and International HapMap Project [15-19].

A total of 205 SNPs in 13 ADME-related genes that are well implemented in Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (*CYP2C19*, *CYP2C9*, *CYP2C8*, *SLCO1B1*, *VKORC1*, *CYP4F2*, *CYP2B6*, *DPYD*, *CYP2D6*, *UGT1A1*, *TPMT*, *CYP3A5*, and *G6PD*) were compared among Korean, EUR, EAS, AFR and global populations as of January 2020. Globally monomorphic markers, SNPs with little to no functional impact on their respective enzymes and markers with minimum variability across populations (frequency ≤ 0.01 in all populations) were excluded. Clinically relevant SNP markers in the compared genes were further summarized by their star alleles and expected functional changes. Star alleles of each gene were determined by CPIC guidelines as of January 2020. Expected functionality changes in ADME-related genes were presented alongside 22 drugs expected to have a significant impact on their pharmacokinetic/pharmacodynamic profile with such functional changes [20-29].

Genotype data were further translated to expected phenotypes of each diplotype. Diplotypes of each gene were categorized based on their known clinical impact (e.g., extensive metabolizer, EM; ultrarapid metabolizer, UM; rapid metabolizer, RM; intermediate metabolizer, IM; and poor metabolizer, PM), and percentage data for 65 diplotype combinations in 11 genes were presented. The percentages of wild type were (*1/*1 or Ref/Ref) diplotype deduced only when the entire SNP frequency data were available without any missing or excluded results for the respective gene. Phenotypes of each diplotype were determined largely based on CPIC guidelines, while others were determined based on published data as of January 2020 [7].

Statistical analysis

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Genotype and phenotype frequency data were summarized by descriptive statistics. The reference/alternative status of alleles was determined based on the National Center for Biotechnology Information dbSNP database [30]. The major/minor status of alleles was determined based on Korean allele frequencies.

RESULTS

Affymetrix DMET results in the Korean population

The frequencies of several SNPs of important ADME genes, including CYP2C19 and VKORC1, were markedly different in Koreans compared to EURs or AFRs (**Tables 1** and **2**). The frequencies of the four clinically significant SNPs of the *CYP2C19* gene, namely, rs12248560, rs17878459, rs4986893, and rs4244285, showed marked differences between the Korean versus EUR and AFR populations. The allele frequency of an increased function variation (*17, rs12248560) in the EUR or AFR populations was more than 20 times higher than that in the Korean population, whereas the allele frequencies of loss-of-function variations (*2, rs4244285; *3, rs4986893) were approximately 2 times higher in Koreans than in EUR and AFR populations (**Tables 1** and **2**). The SNP frequencies of the VKORC1 gene associated with warfarin dosing, namely, rs7294 and rs9923231, featured marked differences between the

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Korean versus EUR and AFR populations. The allele frequency of the increased warfarin dose variation rs7294 in the EUR or AFR population was approximately 5–6 times greater than that in the Korean population, whereas the frequency of the decreased warfarin dose variation was more than 2 times higher in the Korean population than in the EUR population and more than 15 times higher in the Korean population than in the AFR population. SNP frequencies in the *UGT1A1* gene were comparable between the Korean and EAS populations. Compared to the EUR and AFR populations, the Korean population showed markedly higher frequencies of decreased function variations (*6, rs4148323 and *27, rs35350960). *CYP2C9* allele frequencies in the Korean population featured much lower decreased function (*2, rs1799853) variation than in the EUR or AFR population. Allele frequencies in the *CYP2D6* gene in the Korean population showed overall lower frequency of no function variation and higher frequency of decreased function variation as compared to the EUR or AFR population. Notably, the decreased function variation (*10, rs1065852) in the Korean population was more than 2 times that of the EUR or AFR population. The Korean population showed lower frequencies of no function variation in the *CYP3A5* gene (*3, rs776746) than the EUR population but frequencies more than 2 times higher than the AFR population. The information on all DMET SNP frequencies is listed in **Supplementary Data 1**, and the allele frequencies of important ADME genes are summarized in **Table 1**. A total of 37 clinically relevant markers in 11 genes included in the CPIC guidelines are presented in **Table 2**.

Table 1. Affymetrix DMET results in Korean, EUR, EAS, and AFR populations

Gene*	rs number	Common name	Sample count	Reference allele	Alternative allele	Alternative allele frequency† (%)				
						Korean	Global	EUR	EAS	AFR
CYP2C19	rs12248560	CYP2C19*17_-806C>T	1,012	C	T	1.04	15.32	22.37	1.49	23.52
	rs28399504	CYP2C19*4_1A>G(M1V)	1,012	A	-	0.00	0.08	0.10	0.10	0.00
	rs55752064	CYP2C19*14_50T>C(L17P)	1,012	T	-	0.00	0.00	0.00	0.00	0.00
	rs17878459	CYP2C19*2B_12460G>C(E92D)	1,009	G	C	0.05	0.90	3.58	0.00	0.38
	rs41291556	CYP2C19*8_12711T>C(W120R)	1,012	T	-	0.00	0.10	0.30	0.00	0.08
	rs72558184	CYP2C19*6_12748G>A(R132Q)	1,012	G	-	0.00	0.04	0.04	0.00	0.00
	rs17884712	CYP2C19*9_12784G>A(R144H)	1,009	G	A	0.05	0.28	0.00	0.00	0.98
	rs4986893	CYP2C19*3_17948G>A(W212X)	1,010	G	A	9.55	1.42	0.00	5.56	0.23
	rs6413438	CYP2C19*10_19153C>T(P227L)	1,011	C	T	0.00	0.06	0.00	0.00	0.15
	rs4244285	CYP2C19*2_19154G>A(P227P)	1,012	G	A	29.05	22.14	14.51	31.25	17.02
	rs72558185	CYP2C19_721insG	1,012	-	-	0.00	-	-	-	-
	rs72558186	CYP2C19*7_19294T>A(SpliceDefect)	1,012	T	-	0.00	0.00	0.00	0.00	0.00
	rs17879685	CYP2C19*13_87290C>T(R410C)	1,012	C	-	0.00	0.56	0.00	0.00	1.97
	rs56337013	CYP2C19*5_90033C>T(R433W)	1,012	C	-	0.00	0.00	0.00	0.00	0.00
	rs5787121	CYP2C19_90052delG	1,012	G	-	0.00	-	-	-	-
	rs55640102	CYP2C19*12_90209A>C(X491C)	1,012	A	-	0.00	0.09	0.10	0.00	0.00
CYP2C9	rs72558187	CYP2C9*13_3276T>C(L90P)	1,008	T	C	0.25	0.06	0.00	0.30	0.00
	rs72558188	CYP2C9*25_3531_3540del10	1,012	AGAAATGGAA	-	0.00	-	-	-	-
	rs72558189	CYP2C9*14_3552G>A(R125H)	1,012	G	-	0.00	0.42	0.00	0.10	0.00
	rs1799853	CYP2C9*2_3608C>T(R144C)	1,012	C	T	0.05	4.79	12.43	0.10	0.83
	rs72558190	CYP2C9*15_9100C>A(S162x)	1,012	C	-	0.00	0.00	0.00	0.00	0.00
	rs2256871	CYP2C9*9_10535A>G(H251R)	1,012	A	-	0.00	2.20	0.10	0.00	8.17
	rs9332130	CYP2C9*10_10598A>G(E272G)	1,012	A	-	0.00	0.00	0.00	0.00	0.00
	rs9332131	CYP2C9*6_10601delA(K273X)	1,012	A	-	0.00	0.22	0.00	0.00	0.83
	rs72558192	CYP2C9*16_33497A>G(T299A)	1,012	A	-	0.00	0.02	0.00	0.10	0.00
	rs28371685	CYP2C9*11_42542C>T(R335W)	1,012	C	-	0.00	0.72	0.20	0.00	2.42
	rs1057909	CYP2C9_42612A>G(Y358C)	1,009	A	G	0.00	0.00	0.00	0.00	0.00
	rs56165452	CYP2C9*4_42615T>C(I359T)	1,009	T	C	0.00	0.00	0.00	0.00	0.00
	rs28371686	CYP2C9*5_42619C>G(D360E)	823	C	G	0.00	0.46	0.00	0.00	1.66
	rs2017319	CYP2C9_55221C>T(A441A)	1,012	C	-	0.00	3.39	0.20	0.00	12.03
	rs1057911	CYP2C9_55323A>T(G475G)	1,011	A	T	4.45	4.89	7.26	10.90	0.45
	rs9332239	CYP2C9*12_50338C>T(P489S)	1,012	C	-	0.00	0.08	0.30	0.00	0.00

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Table 1. (Continued) Affymetrix DMET results in Korean, EUR, EAS, and AFR populations

Gene*	rs number	Common name	Sample count	Reference allele	Alternative allele	Alternative allele frequency† (%)				
						Korean	Global	EUR	EAS	AFR
CYP2C8	rs28399518	CYP2C8_32364C>T(3'UTR)	1,010	C	T	0.00	0.58	0.00	0.00	2.19
	rs3832694	CYP2C8*12_32184_32186delTTG(V461X)	1,012	TTG	-	0.00	0.00	0.00	-	0.00
	rs66501115	CYP2C8_30425C>G(P404A)	1,012	C	-	0.00	-	-	-	-
	rs10509681	CYP2C8*3_30411A>G(K399R)	1,012	A	G	0.05	4.57	11.83	0.10	0.83
	rs72558194	CYP2C8_30384T>C(L390S)	1,012	T	-	0.00	0.01	0.01	0.00	0.00
	rs11572103	CYP2C8*2_11054A>T(I269F)	1,012	A	-	0.00	5.47	0.40	0.00	18.91
	rs1058930	CYP2C8*4_11041C>G(I264M)	1,012	C	G	0.20	1.66	5.77	0.00	0.38
	rs72558195	CYP2C8*7or*8_4517C>T>G(R186XorG)	1,012	C	-	0.00	0.04	0.04	0.00	0.10
	rs72558196	CYP2C8*5_2189delA(T159X)	1,012	A	-	0.25	0.01	0.00	0.19	0.00
	rs11572080	CYP2C8*3_2130G>A(R139K)	1,012	G	A	0.05	4.57	11.83	0.10	0.83
	rs11572066	CYP2C8_-86A>C	1,012	A	-	0.00	0.76	0.00	0.00	2.65
SLCO1B1	rs4149015	SLCO1B1*17_c.-11187G>A(Promoter)	1,011	G	A	14.44	5.47	6.46	13.10	0.68
	rs56101265	SLCO1B1*2_c.217T>C(F73L)	1,012	T	-	0.00	0.00	0.00	0.00	0.00
	rs56061388	SLCO1B1_c.245T>C(V82A)	1,011	T	C	0.00	0.01	0.00	3.00	0.00
	rs2306283	SLCO1B1*1B_c.388A>G(N130D)	1,012	A	G	72.33	62.24	59.74	76.19	18.23
	rs2306282	SLCO1B1*16_c.452A>G(N151S)	1,011	A	G	1.29	0.08	0.00	0.40	0.00
	rs72559745	SLCO1B1*3_c.467A>G(E156G)	1,011	A	-	0.00	1.65	1.63	-	-
	rs4149056	SLCO1B1*5_c.521T>C(V174A)	1,012	T	C	14.67	8.77	16.10	12.30	1.36
	rs4149057	SLCO1B1_c.571T>C(L191L)	1,012	T	C	27.17	36.74	60.74	24.31	14.45
	rs72559746	SLCO1B1*18_c.578T>G(L193R)	1,012	T	-	0.00	8.21	8.14	-	-
	rs2291075	SLCO1B1_c.597C>T(F199F)	1,012	C	T	41.85	41.55	39.66	51.09	55.98
	rs72559747	SLCO1B1_c.1007C>G(P336R)	1,011	C	G	0.15	0.08	0.00	0.40	0.00
	rs55901008	SLCO1B1*6_c.1058T>C(I353T)	1,012	T	-	0.00	0.00	0.00	0.00	0.00
	rs56387224	SLCO1B1*7_c.1294A>G(N432D)	1,012	A	-	0.00	0.00	0.00	-	-
	rs72559748	SLCO1B1*8_c.1385A>G(D462G)	1,012	A	-	0.00	-	-	-	-
	rs59502379	SLCO1B1*9_c.1463G>C(G488A)	1,012	G	-	0.00	1.12	0.00	0.00	4.08
	rs56199088	SLCO1B1*10_c.1964A>G(D655G)	1,012	A	-	0.00	0.00	0.00	-	0.00
	rs55737008	SLCO1B1*11_c.2000A>G(E667G)	1,012	A	-	0.00	0.00	0.00	-	0.00
VKORC1	rs7294	VKORC1_c.*134G>A(3'UTR)	1,012	G	A	7.76	38.54	37.39	9.60	45.87
	rs11540137	VKORC1_c.*131C>A(3'UTR)	1,012	C	-	0.00	0.00	0.00	-	-
	rs104894542	VKORC1_c.383T>G(L128R)	1,012	T	-	0.00	-	-	-	-
	rs7200749	VKORC1_c.358C>T(L120L)	1,012	C	-	0.00	5.97	0.00	0.00	21.94
	rs72547528	VKORC1_c.292C>T(R98W)	1,012	C	-	0.00	0.02	0.01	-	0.00
	rs17884982	VKORC1_c.284-882A>T	1,012	A	-	0.00	0.02	0.00	0.00	0.08
	rs17884850	VKORC1_c.283+231G>A	1,012	G	-	0.00	0.08	0.08	0.00	0.03
	rs17886199	VKORC1_c.283+186T>C	1,012	T	-	0.00	1.50	0.10	0.00	5.52
	rs8050894	VKORC1_c.283+124G>C	1,012	C	G	92.09	41.63	39.96	88.49	25.64
	rs72547529	VKORC1_c.196G>A(V66M)	1,012	G	-	0.00	0.20	0.00	0.00	0.68
	rs9934438	VKORC1_c.174-136C>T	1,010	C	T	92.13	35.58	38.77	88.49	5.45
	rs13336384	VKORC1_c.174-429C>T	1,009	C	T	0.00	1.84	0.00	0.00	6.66
	rs17708472	VKORC1_c.173+525C>T	1,012	C	T	0.15	9.37	23.36	0.30	3.33
	rs13337470	VKORC1_c.173+486C>A	1,012	C	-	0.00	0.60	0.00	0.00	2.27
	rs2884737	VKORC1_c.173+324T>G	1,011	T	C	0.54	9.15	25.55	0.10	0.91
	rs104894541	VKORC1_c.172A>G(R58G)	1,012	A	-	0.00	-	-	-	-
	rs104894540	VKORC1_c.134T>C(V45A)	1,011	T	C	0.00	-	-	-	-
	rs104894539	VKORC1_c.85G>T(V29L)	1,006	G	T	0.00	0.00	0.00	-	-
	rs9923231	VKORC1_c.-1639G>A(Promoter)	1,012	G	A	92.05	35.56	38.77	88.49	5.45
	rs17878544	VKORC1_c.-1877A>G(Promoter)	1,011	A	-	0.00	12.08	1.19	0.00	42.44
	rs17884388	VKORC1_c.-5014T>C(Promoter)	1,012	T	-	0.00	0.08	0.00	0.00	0.30
CYP4F2	rs2108622	CYP4F2*3_18000G>A(V433M)	1,011	G	A	31.85	23.86	29.03	21.43	8.25
	rs2074900	CYP4F2_11602C>T(H343H)	1,011	C	T	22.01	23.30	29.72	22.22	17.25
	rs4605294	CYP4F2_8103C>T(L278F)	1,011	C	T	0.00	0.00	0.00	-	-
	rs3093153	CYP4F2_7207G>T(G185V)	1,011	G	T	0.15	3.00	6.96	0.00	3.78
	rs3093136	CYP4F2_5034C>G(A116A)	1,012	C	-	0.00	0.42	0.00	0.00	1.59
	rs8110714	CYP4F2_2099C>T(N112N)	1,011	C	T	0.00	3.49	0.00	0.30	12.41
	rs8100960	CYP4F2_2042A>C(G93G)	1,009	A	C	0.00	3.49	0.00	0.30	12.41
	rs3093106	CYP4F2_165A>G(P55P)	1,011	A	G	13.16	18.01	17.69	5.85	32.00
	rs2906890	CYP4F2_38C>G(P13R)	1,012	C	-	0.00	-	-	-	-
	rs2906891	CYP4F2_36G>C(W12C)	1,012	G	-	0.00	-	-	-	-

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Table 1. (Continued) Affymetrix DMET results in Korean, EUR, EAS, and AFR populations

Gene*	rs number	Common name	Sample count	Reference allele	Alternative allele	Alternative allele frequency† (%)				
						Korean	Global	EUR	EAS	AFR
CYP2B6	rs34223104	CYP2B6*22_-82T>C	1,011	T	C	0.54	1.64	0.89	0.20	3.63
	rs8192709	CYP2B6*2_64C>T(R22C)	1,009	C	T	2.97	4.75	6.26	4.66	4.16
	rs35303484	CYP2B6*11_136A>G(M46V)	1,012	A	-	0.00	0.12	0.40	0.00	0.08
	rs2279341	CYP2B6_12740G>C(P72P)	1,009	G	C	3.12	5.19	6.06	4.86	5.14
	rs36060847	CYP2B6*12_12820G>A(G99E)	1,012	G	-	0.00	0.02	0.00	0.00	0.00
	rs12721655	CYP2B6*8_13072A>G(K139E)	1,012	A	-	0.00	0.08	0.10	0.00	0.15
	rs35773040	CYP2B6*14_13076G>A(R140Q)	1,012	G	A	0.05	0.10	0.20	0.00	0.00
	rs4803418	CYP2B6_14593C>G	1,006	C	G	47.02	29.13	31.91	43.45	9.53
	rs3826711	CYP2B6*26_15614C>G(P167A)	1,010	C	G	0.69	0.10	0.00	0.50	0.00
	rs36056539	CYP2B6*20_15618C>T(T168I)	822	C	T	0.00	0.02	0.00	0.00	0.00
	rs45482602	CYP2B6*3_18045C>A(S259R)	1,012	C	A/T	0.00	0.08/0.06	0.10/0.00	0.00/0.00	0.08/0.23
	rs2279343	CYP2B6*4_18053A>G(K262R)	1,012	A	G	22.18	22.85	22.47	-	22.90
	rs2279344	CYP2B6_18273G>A	897	G	A	66.22	76.16	62.52	69.44	87.07
	rs28399499	CYP2B6*16_21011T>C(I328T)	1,012	T	-	0.00	2.32	0.00	0.00	8.25
	rs34826503	CYP2B6*19_21034C>T(R336C)	1,012	C	-	0.00	0.10	0.00	0.10	0.30
	rs34097093	CYP2B6*28_21160C>T(R378X)	1,012	C	-	0.00	0.00	0.00	-	0.00
	rs35979566	CYP2B6*15_21388T>A(I391N)	1,012	T	-	0.00	0.18	0.50	0.00	0.08
	rs35010098	CYP2B6*21_21498C>A(P428T)	1,011	C	A	0.00	0.00	0.00	-	0.00
	rs8192719	CYP2B6_21563C>T	1,012	C	T	16.11	31.69	24.16	21.63	37.44
DPYD	rs1801268	DPYD*10_c.2983G>T(V995F)	1,012	G	-	0.00	0.00	0.00	-	0.00
	rs1801267	DPYD*9B_c.2657G>A(R886H)	1,012	G	-	0.00	0.02	0.00	0.00	0.00
	rs3918289	DPYD_c.1905C>T(N635N)	1,012	C	-	0.00	0.02	0.10	0.00	0.00
	rs55886062	DPYD*13_c.1679T>G(I560S)	1,012	T	-	0.00	0.02	0.10	0.00	0.00
	rs1801158	DPYD*4_c.1601G>A(S534N)	1,010	G	A	0.00	0.96	3.08	0.00	0.23
	rs1042479	DPYD_c.1074T>A(R358R)	1,012	T	-	0.00	-	-	-	-
	rs1042478	DPYD_c.1035T>C(F345F)	1,012	T	-	0.00	0.00	0.00	-	0.00
	rs72549306	DPYD*11_c.1003G>T(V335L)	1,012	G	-	0.00	0.00	0.00	-	0.00
	rs6675198	DPYD_c.756T>C(G252G)	1,011	T	C	0.00	0.00	0.00	0.00	0.00
	rs1801266	DPYD*8_c.703C>T(R235W)	1,012	C	-	0.00	0.01	0.01	-	0.00
	rs6670886	DPYD_c.525G>A(S175S)	1,012	G	-	0.00	0.01	0.01	0.00	0.16
	rs2297595	DPYD_c.496A>G(M166V)	1,012	A	G	1.68	5.65	11.93	1.79	3.10
	rs72549309	DPYD*7_c.295delTCAT	1,012	TCAT	-	0.00	0.00	0.00	-	-
	rs1801265	DPYD*9_c.85T>C(C29R)	1,011	T	C	5.69	22.57	21.80	4.60	40.28
	rs72549310	DPYD_c.61C>T(R21X)	1,012	C	-	0.00	0.02	0.00	0.00	0.08
CYP2D6	rs1135840	CYP2D6_4180G>C(S486T)	1,007	C	G	65.79	59.06	58.67	-	65.00
	rs1135836	CYP2D6*18_4125dupGTGCCCACT	1,004	T	-	0.00	0.08	0.00	0.40	0.00
	rs72549346	CYP2D6*42_3259insGT	1,011	-	-	0.00	0.02	0.00	0.00	0.23
	rs72549347	CYP2D6*56_3201C>T(R344X)	1,010	C	-	0.00	0.02	0.00	0.00	0.08
	rs59421388	CYP2D6*29_3183G>A(V338M)	1,011	G	-	0.00	2.88	0.00	0.00	10.74
	rs28371725	CYP2D6*41_2988G>A(SpliceDefect)	1,011	G	A	2.67	6.35	9.34	3.77	1.82
	rs72549349	CYP2D6*44_2950G>C(SpliceDefect)	1,011	G	-	0.00	0.00	0.00	-	-
	rs5030867	CYP2D6*7_2935A>C(H324P)	1,011	A	-	0.00	0.18	0.00	0.00	0.00
	rs16947	CYP2D6_2850C>T(R296C)	1,011	C	T	15.18	36.65	35.67	-	46.90
	rs28371720	CYP2D6*9_2615delAAG	1,010	AGA	-	0.05	-	-	-	-
	rs72549351	CYP2D6*38_2587delGACT	1,006	GACT	-	0.00	-	-	-	-
	rs72549352	CYP2D6*21_2573insC	1,000	-	C	0.00	0.02	0.01	0.00	0.00
	rs35742686	CYP2D6*3_2549delA(R259X)	1,010	A	-	0.00	0.56	1.89	0.00	0.23
	rs72549353	CYP2D6*19_2539delAACT	1,009	AACT	-	0.00	0.02	0.01	-	0.00
	rs72549354	CYP2D6*20_1973insG	1,011	-	-	0.00	-	-	-	-
	rs72549356	CYP2D6*40_1863ins(TTTCGCCCC)2	1,011	-	-	0.00	0.24	0.00	0.00	0.91
	rs3892097	CYP2D6*4_1846G>A(SpliceDefect)	1,008	G	A	0.69	9.31	18.59	0.20	6.05
	rs5030865	CYP2D6*14or*8_1758G>A>T(G169RorX)	1,011	G	A	0.69	0.20	0.00	0.99	0.00
	rs1058164	CYP2D6_1661G>C(V136V)	1,011	C	G	66.12	58.12	57.67	-	64.2
	rs61736512	CYP2D6*29_1659G>A(V136I)	781	G	A	0.00	2.94	0.00	0.00	10.97
	rs28371706	CYP2D6_1023C>T(T107I)	1,011	C	-	0.00	5.91	0.20	0.00	21.79
	rs5030863	CYP2D6*11_883G>C(SpliceDefect)	1,010	G	C	0.00	-	-	-	-
	rs72549357	CYP2D6*15_137insT	1,011	T	-	0.00	-	-	-	-
	rs5030862	CYP2D6*12_124G>A(G42R)	1,011	G	-	0.00	0.00	0.00	-	0.00

(continued to the next page)

Table 1. (Continued) Affymetrix DMET results in Korean, EUR, EAS, and AFR populations

Gene*	rs number	Common name	Sample count	Reference allele	Alternative allele	Alternative allele frequency† (%)				
						Korean	Global	EUR	EAS	AFR
	rs1065852	CYP2D6_100C>T(P34S)	1,010	C	T	51.09	23.80	20.18	57.14	11.27
	rs1080985	CYP2D6_-1584C>G	1,010	C	G	12.48	21.57	22.30	-	-
	N/A	CYP2D6_-1961C>G>A	1,010	C	-	0.00	-	-	-	-
	rs28360521	CYP2D6_-2178G>A	1,007	G	A	50.99	26.94	20.18	57.04	23.07
UGT1A1	rs4124874	UGT1A1*60_c.-3279T>G(Promoter)	1,006	T	G	30.27	58.81	41.55	35.62	89.86
	rs10929302	UGT1A1*93_c.-3156G>A(Promoter)	1,011	G	A	13.35	30.21	27.44	12.70	33.81
	rs111741722	UGT1A1_c.-2950A>G	1,012	A	G	13.39	31.86	31.23	-	-
	rs3755319	UGT1A1*112_c.-1353A>C	1,012	A	C	30.04	55.01	41.45	35.52	76.01
	rs887829	UGT1A1*80_c.-364C>T	1,012	C	T	13.39	35.40	29.82	13.00	49.32
	rs4148323	UGT1A1*6_c.211G>A(G71R)	1,011	G	A	17.90	3.43	0.70	13.79	0.08
	rs72551340	UGT1A1*45_c.222C>A(Y74X)	814	C	A	0.00	0.00	0.00	-	-
	rs56059937	UGT1A1*62_c.247T>C(F83L)	1,012	T	-	0.00	0.00	0.00	-	0.00
	rs72551341	UGT1A1*12_c.524T>A(L175Q)	1,012	T	-	0.00	0.01	0.01	-	0.00
	rs72551342	UGT1A1*15_c.529T>C(C177R)	1,012	T	-	0.00	0.00	0.00	-	0.00
	rs72551343	UGT1A1*8_c.625C>T(R209W)	1,012	C	-	0.00	0.02	0.00	0.00	0.00
	rs35350960	UGT1A1*27_c.686C>A(P229Q)	1,012	C	A	1.43	0.28	0.00	1.39	0.00
	rs72551344	UGT1A1*43_c.698T>G(L233R)	1,012	T	-	0.00	0.00	0.00	-	-
	rs72551345	UGT1A1*14_c.826G>C(G276R)	1,012	G	-	0.00	-	-	-	-
	rs62625011	UGT1A1*11_c.923G>A(G308E)	1,010	G	A	0.00	0.00	0.00	-	0.00
	rs72551348	UGT1A1*9_c.992A>G(Q331R)	1,012	A	-	0.00	0.00	0.00	-	-
	rs72551349	UGT1A1*10_c.1021C>T(R341X)	1,012	C	-	0.00	0.00	0.00	-	-
	rs72551350	UGT1A1*4_c.1069C>T(Q357X)	1,012	C	-	0.00	0.00	0.01	0.00	0.00
	rs72551351	UGT1A1*16_c.1070A>G(Q357R)	1,012	A	-	0.00	0.00	0.00	-	-
	rs55750087	UGT1A1*29_c.1099C>G(R367G)	1,011	C	-	0.00	0.00	0.00	-	-
	rs72551352	UGT1A1*20_c.1102G>A(A368T)	1,011	G	-	0.00	-	-	-	-
	rs72551353	UGT1A1*3_c.1124C>T(S375F)	1,012	C	-	0.00	-	-	-	-
	rs72551354	UGT1A1*17_c.1143C>G(S381R)	1,012	C	-	0.00	0.00	0.00	0.00	0.01
	rs72551355	UGT1A1*18_c.1201G>C(A401P)	1,012	G	-	0.00	-	-	-	-
	rs72551357	UGT1A1*24_c.1309A>T(K437X)	1,012	A	-	0.00	-	-	-	-
	rs72551361	UGT1A1*55_c.1487T>A(L496X)	1,011	T	A	0.00	-	-	-	-
	rs1042709	UGT1A1_c.1531G>C(A511P)	1,012	G	-	0.00	0.00	-	-	0.00
	rs10929303	UGT1A1*76_c.*211C>T(3'UTR)	1,010	T	C	88.17	77.29	78.35	88.80	61.79
	rs1042640	UGT1A1*78_c.*339C>G(3'UTR)	1,012	C	G	88.09	82.11	79.92	86.71	80.41
	rs8330	UGT1A1*79_c.*440C>G(3'UTR)	1,012	C	G	88.09	74.50	76.34	86.90	56.20
TPMT	rs1142345	TPMT*3C_c.719A>G(Y240C)	1,012	A	G	1.68	3.91	2.88	2.18	6.66
	rs56161402	TPMT*8_c.644G>A(R215H)	1,012	G	-	0.00	0.56	0.00	0.00	1.97
	rs1800584	TPMT*4_c.626-1G>A(SpliceDefect)	1,012	G	-	0.00	0.05	0.05	-	0.04
	rs6921269	TPMT*24_c.537G>T(Q179H)	1,010	G	T	0.00	0.74	0.00	0.00	2.65
	rs2842934	TPMT_c.474C>T(I158I)	1,012	C	T	73.62	75.3	77.63	76.19	81.01
	rs72552739	TPMT_c.292G>T(E98X)	1,012	G	-	0.00	0.02	0.02	-	0.00
	rs1800462	TPMT*2_c.238G>C(A80P)	1,012	G	-	0.00	0.22	0.60	0.00	0.08
CYP3A5	rs28365085	CYP3A5*3F_31551T>C(I488T)	1,011	T	C	0.64	0.16	0.00	0.79	0.00
	rs41279854	CYP3A5*3K_29753T>C(F446S)	1,011	T	-	0.00	0.02	0.10	0.00	0.00
	rs28365083	CYP3A5*2_27289C>A(T398N)	1,012	C	-	0.00	0.08	0.40	0.00	0.00
	rs41303343	CYP3A5*7_27131insT	1,012	T	-	0.00	3.15	0.00	0.00	11.80
	rs28383479	CYP3A5*9_19386G>A(A337T)	1,012	G	-	0.00	0.00	0.00	-	0.00
	rs10264272	CYP3A5*6_14690G>A(SpliceDefect)	1,012	G	A	0.05	4.45	0.30	0.00	15.43
	rs56411402	CYP3A5*4_14665A>G(Q200R)	1,010	A	G	0.05	0.08	0.00	0.40	0.00
	rs55965422	CYP3A5*5_12952T>C(SpliceDefect)	1,012	T	C	0.69	0.08	0.00	0.40	0.00
	rs41279857	CYP3A5_7303C>A(S100Y)	1,010	C	A	0.00	0.06	0.20	0.00	0.00
	rs56244447	CYP3A5*3D_7249T>G(L82R)	1,004	T	-	0.00	0.02	0.02	0.00	0.00
	rs776746	CYP3A5*3_6986A>G(SpliceDefect)	1,005	A	G	78.06	88.17	93.02	67.70	30.20
	rs72552791	CYP3A5*3L_3775A>G(Y53C)	1,012	A	-	0.00	0.00	0.00	-	0.00
	rs28383468	CYP3A5*3B_3705C>T(H30Y)	1,012	C	-	0.00	0.17	0.16	0.00	0.05
	rs55817950	CYP3A5*8_3699C>T(R28C)	1,012	C	-	0.00	0.01	0.00	-	0.00
G6PD	rs5030870	G6PD_c.427G>A(D143N)	1,012	G	-	0.00	0.00	0.00	-	-

DMET, Drug Metabolizing Enzyme and Transporter; EUR, European; EAS, East Asian; AFR, African.
*These pharmacogenes are referred to in the 'Clinical Pharmacogenetics Implementation Consortium Dosing Guideline'; †EUR, EAS, AFR data from 1000 Genomes, Allele Frequency Aggregator, Exome Aggregation Consortium, Genome Aggregation Database, and HapMap.

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Table 2. Allele frequencies of clinically relevant DMET markers according to ethnic groups

Gene*	Related drugs	rs number	Allele	Function change	Alternative allele frequency† (%)				
					Korean (n = 1,012)	Global	EUR	EAS	AFR
CYP2C19	Amitriptyline clopidogrel citalopram voriconazole	rs12248560	*17	Increased function	1.04	15.32	22.37	1.49	23.52
		rs17878459	*2B	No function	0.05	0.90	3.58	0.00	0.38
		rs4986893	*3	No function	9.55	1.42	0.00	5.56	0.23
		rs4244285	*2	No function	29.05	22.14	14.51	31.25	17.02
CYP2C9	Celecoxib ibuprofen warfarin phenytoin	rs72558187	*13	Decreased function	0.25	0.06	0.00	0.30	0.00
		rs1799853	*2	Decreased function	0.05	4.79	12.43	0.10	0.83
		rs28371685	*11	Decreased function	0.00	0.72	0.20	0.00	2.42
		rs28371686	*5	Decreased function	0.00	0.46	0.00	0.00	1.66
CYP2C8	Ibuprofen rosiglitazone	rs10509681	*3	Decreased function	0.05	4.57	11.83	0.10	0.83
		rs11572103	*2	Decreased function	0.00	5.47	0.40	0.00	18.91
		rs11572080	*3	Decreased function	0.05	4.57	11.83	0.10	0.83
SLCO1B1	Simvastatin	rs4149015	*17	Decreased function	14.44	5.47	6.46	13.10	0.68
		rs72559745	*3	Possible decreased function	0.00	1.65	1.63	-	-
		rs4149056	*5	Decreased function	14.67	8.77	16.10	12.30	1.36
		rs59502379	*9	Possible decreased function	0.00	1.12	0.00	0.00	4.08
VKORC1	Warfarin	rs7294	c.*134G>A	Increased warfarin dose	7.76	38.54	37.39	9.60	45.87
		rs9934438	c.174-136C>T	Inert, linked with rs9923231	92.13	35.58	38.77	88.49	5.45
		rs9923231	c.-1639G>A	Decreased warfarin dose	92.05	35.56	38.77	88.49	5.45
CYP4F2	Warfarin	rs2108622	*3	Decreased function	31.85	23.86	29.03	21.43	8.25
CYP2B6	Efavirenz	rs34223104	*22	Increased function	0.54	1.64	0.89	0.20	3.63
		rs3826711	*26	Decreased function	0.69	0.10	0.00	0.50	0.00
		rs2279343	*4	Increased function	22.18	22.85	22.47	-	22.90
		rs28399499	*16	Decreased function	0.00	2.32	0.00	0.00	8.25
CYP2D6	Amitriptyline atomoxetine codeine tamoxifene	rs59421388	*29	Decreased function	0.00	2.88	0.00	0.00	10.74
		rs28371725	*41	Decreased function	2.67	6.35	9.34	3.77	1.82
		rs35742686	*3	No function	0.00	0.56	1.89	0.00	0.23
		rs3892097	*4	No function	0.69	9.31	18.59	0.20	6.05
		rs5030865	*14or*8	Decreased function/No function	0.69	0.20	0.00	0.99	0.00
		rs61736512	*29	Decreased function	0.00	2.94	0.00	0.00	10.97
		rs1065852	*10	Decreased function	51.09	23.80	20.18	57.14	11.27
UGT1A1	Atazanavir irinotecan	rs4148323	*6	Decreased function	17.90	3.43	0.70	13.79	0.08
		rs35350960	*27	Decreased function	1.43	0.28	0.00	1.39	0.00
TPMT	Azathioprine mercaptopurine thioguanine	rs1142345	*3C	No function	1.68	3.91	2.88	2.18	6.66
CYP3A5	Tacrolimus cyclosporine	rs28365085	*3F	No function	0.64	0.16	0.00	0.79	0.00
		rs41303343	*7	No function	0.00	3.15	0.00	0.00	11.80
		rs10264272	*6	No function	0.05	4.45	0.30	0.00	15.43
		rs776746	*3	No function	78.06	88.17	93.02	67.7	30.2

DMET, Drug Metabolizing Enzyme and Transporter; EUR, European; EAS, East Asian; AFR, African.
*These pharmacogenes are referred to in the 'Clinical Pharmacogenetics Implementation Consortium Dosing Guideline'; †EUR, EAS, AFR data from 1000 Genomes, Allele Frequency Aggregator, Exome Aggregation Consortium, Genome Aggregation Database, and HapMap.

Phenotypes of clinically relevant DMET markers in the Korean population

The frequencies of the expected phenotype for clinically important ADME genes are summarized and presented in **Fig. 1** and **Table 3**. More than 80% of the Korean population with the *CYP2C19* phenotype was classified as either EM or IM. A small population (≤ 1%) was classified as UM, and approximately 1% was classified as PM. The results for *VKORC1* and *CYP4F2* both showed a high percentage of decreased functional variants in the Korean population. In the Korean population, the frequency of causative SNPs of the *VKORC1* gene for the low warfarin dose phenotype was more than 90%, and the decreased functional variant of the *CYP4F2* gene was more than 50%. The diplotype frequencies of the *CYP2C8*, *SLCO1B1* and *CYP3A5* genes mostly showed minimally decreased functional variants, and less than 5% were classified as low-activity or PM variants. The results for the *CYP2C9* and *CYP2B6* genes had some missing allele frequency data, and accurate calculation of the entire diplotype percentage was not possible.

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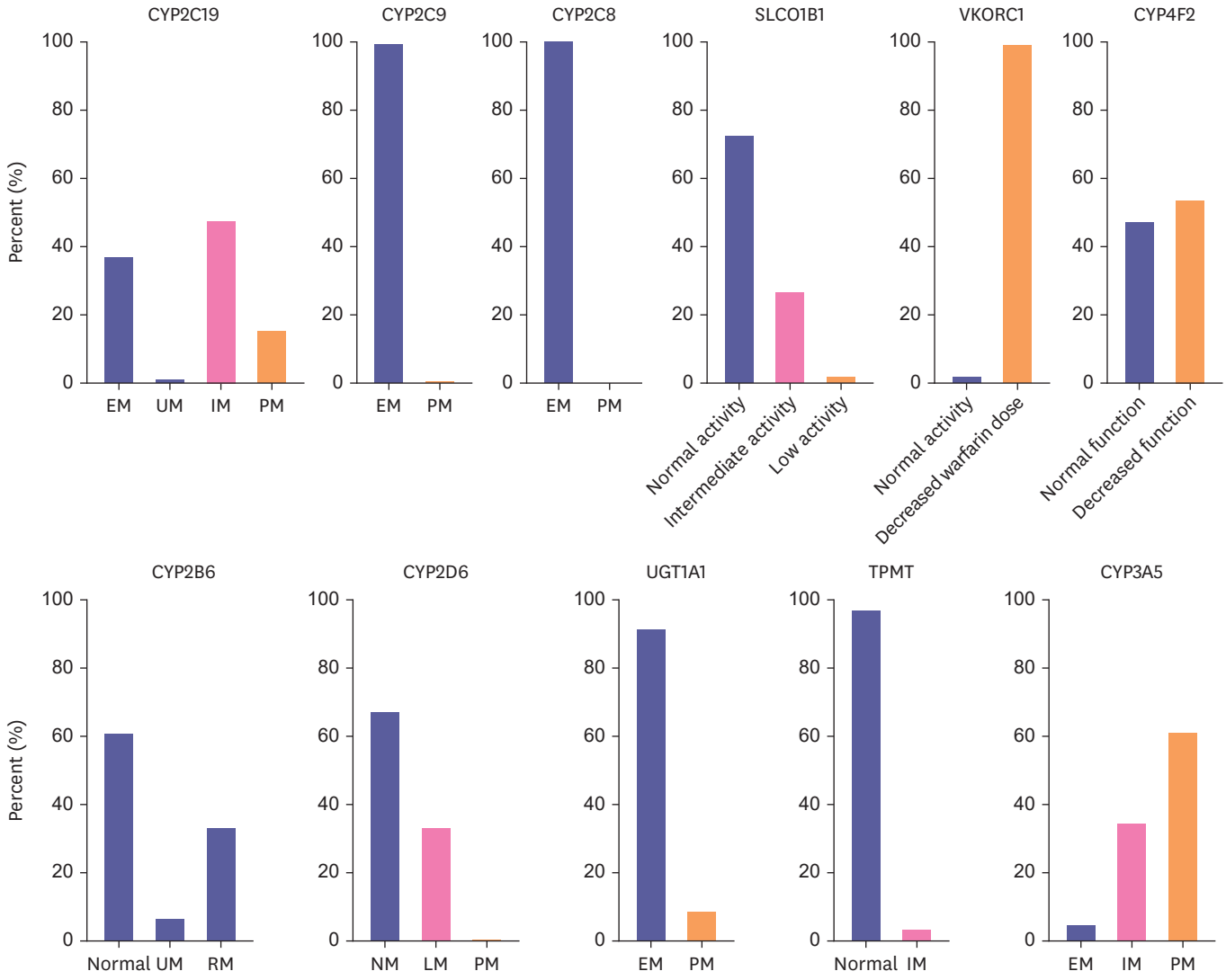

Figure 1. Phenotypes of clinically relevant absorption, distribution, metabolism, and elimination genes.

Table 3. Phenotypes of clinically relevant DMET markers in Korean population (n = 1,012)

Gene*	Related drugs	Diplotype	Phenotype	Sample count (%)
CYP2C19	Amitriptyline, clopidogrel, citalopram, voriconazole	*1/*1	EM	372 (36.76)
		*1/*17	UM	9 (0.89)
		*17/*17	UM	1 (0.10)
		*1/*2A	IM	363 (35.87)
		*1/*2B	IM	0 (0.00)
		*1/*3	IM	106 (10.47)
		*2A/*17	IM	9 (0.89)
		*3/*17	IM	1 (0.10)
		*2A/*2A	PM	76 (7.51)
		*2A/*2B	PM	1 (0.10)
		*2A/*3	PM	62 (6.13)
		*3/*3	PM	12 (1.19)
CYP2C9	Celecoxib, ibuprofen, warfarin, phenytoin	*1/*1	EM	NA (NA)
		*1/*2	PM	1 (0.10)
		*1/*5	PM	0 (0.00)
		*1/*11	PM	0 (0.00)
		*1/*13	PM	5 (0.49)

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Table 3. (Continued) Phenotypes of clinically relevant DMET markers in Korean population (n = 1,012)

Gene*	Related drugs	Diplotype	Phenotype	Sample count (%)
CYP2C8	Ibuprofen, rosiglitazone	*1/*1	EM	1,011 (99.90)
		*1/*2	PM	0 (0.00)
		*1/*3	PM	1 (0.10)
SLCO1B1	Simvastatin	*1/*1	Normal activity	731 (72.23)
		*1/*5	Intermediate activity	265 (26.19)
		*5/*5	Low activity	16 (1.58)
VKORC1	Warfarin	Ref/Ref	Normal activity	14 (1.38)
		Ref/c.-1639G>A	Decreased warfarin dose	133 (13.14)
		c.-1639G>A/c.-1639G>A	Decreased warfarin dose	865 (85.47)
CYP4F2	Warfarin	*1/*1	Normal function	473 (46.74)
		*1/*3	Decreased function	434 (42.89)
		*3/*3	Decreased function	105 (10.38)
CYP2B6	Efavirenz	*1/*1	Normal	NA (NA)
		*4/*4	UM	58 (5.73)
		*22/*22	UM	0 (0.00)
		*4/*22	UM	6 (0.59)
		*1/*4	RM	327 (32.31)
		*1/*22	RM	5 (0.49)
CYP2D6	Amitriptyline, atomoxetine, codeine, tamoxifene	*1 or *2/*1 or *2	NM	NA (NA)
		*1 or *2/*10	NM	416 (41.11)
		*1 or *2/*41	NM	29 (2.87)
		*10/*10	IM	291 (28.75)
		*41/*41	IM	2 (0.20)
		*10/*41	IM	18 (1.78)
		*1 or *2/*8	IM	6 (0.59)
		*4/*10	IM	7 (0.69)
		*8/*10	IM	8 (0.79)
		*8/*41	IM	0 (0.00)
		*4/*4	PM	2 (0.20)
		*4/*8	PM	0 (0.00)
UGT1A1	Atazanavir, irinotecan	*1/*1	EM	NA (NA)
		*1/*6	EM	260 (25.69)
		*1/*80	EM	180 (17.79)
		*27/*27 + *80	EM	11 (1.09)
		*27/*80	EM	6 (0.59)
		*6/*6	PM	27 (2.67)
		*6/*80	PM	38 (3.75)
		*80/*80	PM	11 (1.09)
		*27 + *80/*80	PM	1 (0.10)
		*27/*27 + *80/*80	PM	1 (0.10)
		*6 + *27 + *80	PM	5 (0.49)
		*6 + *27/*27 + *80	PM	5 (0.49)
TPMT	Azathioprine, mercaptopurine, thioguanine	*1/*1	Normal	NA (NA)
		*1/*3C	IM	34 (3.36)
CYP3A5	Tacrolimus, cyclosporine	*1/*3	EM	46 (4.55)
		*3/*3	IM	348 (34.39)
		*3/*6	PM	617 (60.97)
		*3/*6	PM	1 (0.10)

DMET, Drug Metabolizing Enzyme and Transporter; NM, normal metabolizer; EM, extensive metabolizer; UM, ultrarapid metabolizer; RM, rapid metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.
*These pharmacogenes are referred to in the 'Clinical Pharmacogenetics Implementation Consortium Dosing Guideline'.

DISCUSSION

The distribution of genetic markers in the *CYP2C19* gene was significantly different between the Korean population and the EUR and AFR populations (**Table 2**). The *CYP2C19* gene encodes

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CYP450 enzyme 2C19, which is responsible for the metabolism of a variety of drugs, including amitriptyline, clopidogrel, citalopram and voriconazole. Compared to that in the EUR and AFR populations, the allele frequency of an increased function variation (*17, rs12248560) was less frequent in the Korean population, and the allele frequency of a loss-of-function variation (*2, rs4244285; *3, rs4986893) was more frequent in the Korean population. The overall percentage of PM in the Korean population was approximately 15%, whereas the expected percentage in the EUR or AFR population was less than 3% (**Table 3**) [15-19]. Because dose reduction or use of alternative drugs is recommended when prescribing several CYP2C19 enzyme-metabolized drugs to CYP2C19 PM patients, genotype monitoring and subsequent dose modification will be useful for optimal pharmacotherapy of those drugs for Korean patients [31,32].

The distribution of increased VKORC1 function variation (rs7294) and decreased VKORC1 function variation (rs9923231), which are associated with warfarin dose adjustment, were significantly different between the Korean versus the EUR and AFR populations (**Table 2**) [33]. The *VKORC1* gene encodes the catalytic subunit of the vitamin K epoxide reductase complex, which is responsible for the reduction of inactive vitamin K 2,3-epoxide to active vitamin K in the endoplasmic reticulum membrane [34]. Compared to the global population, the Korean DMET results showed a significantly lower allele frequency of rs7294 (increased warfarin dose variation) and higher allele frequency of rs9923231 (decreased function variation). Overall, more than 90% of the Koreans were classified as diplotypes who needed reduced warfarin doses, whereas approximately 60% and 10% of the EURs and AFRs, respectively, were classified as diplotypes who needed reduced warfarin doses (**Table 3**) [15-19].

The Food and Drug Administration-approved warfarin drug label provides a guideline in choosing initial doses of warfarin according to a patient's *VKORC1* and *CYP2C9* genotypes [35]. Reduced dose of warfarin is recommended for patients with decreased *VKORC1* function variation and/or *CYP2C9* allele *2(rs1799853) and *3(rs1057910). *CYP2C9*2* allele was present only at a single sample, and while *3 allele could not be defined for the data set due to quality control, approximately 8.5% of the Korean population is known to possess either CYP2C9*1/*3 or *3/*3 [36]. As dose reduction is recommended for combinations of such genetic variants, genotype monitoring and dose modification need to be considered for optimal pharmacotherapy of warfarin in Korean patients [34].

Our study results showed higher allele frequencies in two clinically significant alleles associated with decreased function of the enzyme (rs4148323 and rs35350960) compared to the global population (**Table 2**). *UGT1A1* encodes UDP-glucuronosyltransferase 1-1, which is also known as UGT1A. The UGT1A PM in Koreans was approximately 8%, whereas the frequency in the EUR or AFR population was less than 1% (**Table 3**) [15-19]. According to the CPIC guidelines, the impact of genetic variation on the metabolism of UGT1A1-mediated drugs, such as atazanavir, may be substantial [26]. This result suggests that different therapeutic options or dose modifications should be considered for optimal pharmacotherapy of *UGT1A1*-related drugs, such as atazanavir and irinotecan, in Korean patients.

In the Korean population, the allele frequencies of decreased function variations of the *SLCO1B1* gene (*17, rs4149015; *5, rs4149056) were comparable with the EUR and EAS populations but were significantly higher than those of the AFR population (**Table 2**). *SLCO1B1* encodes the solute carrier organic anion transporter family member 1B1 protein, and rs4149056 is related to statin-induced myopathy [22]. The overall percentage of *SLCO1B1* low activity individuals (*5/*5) was 1.6% in the Korean population (**Table 3**). Combined

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with the knowledge that statins are generally well tolerated drugs with minimal side effects [37], dosing adjustment or therapeutic drug monitoring of simvastatin from an established regimen may not be needed in Korean patients.

In the Korean population, the overall allele frequencies of no function/decreased function variations of the *CYP2D6* gene (rs59421388, rs28371725, rs35742686, rs3892097, rs5030865, rs61736512, and rs1065852) were lower than those in the EUR or AFR population and were comparable to those in the EAS population (**Table 2**). *CYP2D6* is one of the most extensively studied drug-metabolizing enzymes and encodes CYP450 enzyme 2D6. Approximately 0.2% of the tested samples were classified as PM for *CYP2D6*, which was comparable with previous study results (**Table 3**) [38-40]. With the percentage of *CYP2D6* PM in the Korean population being minimal, monitoring of drugs selectively metabolized by CYP2D6 may not be needed in Korean patients.

The *TPMT* *3C variant (rs1142345) associated with thiopurine methyltransferase deficiency had a lower allele frequency in the Korean population than in global populations (**Table 1**). *TPMT* encodes thiopurine S-methyltransferase, and loss-of-function is related to conditions known as thiopurine methyltransferase deficiency. Dosage adjustment of TPMT-related drugs, such as azathioprine, mercaptopurine and thioguanine, may not be required when prescribing to Korean patients.

CYP3A5 gene alternative allele frequencies in the Korean population were mostly insignificant, except at rs776746, which represents *3 with no function variation. The frequency of *3 loss-of-function variation of *CYP3A5* in the Korean population was ≤ 78% compared to almost 90% in the global population (**Table 2**). According to the CPIC guidelines, dosing adjustment of drugs, such as tacrolimus, is strongly recommended for *CYP3A5* expressers [28]. Because the percentage of *CYP3A5* expressers in the Korean population is significantly higher than that in the global population, routine monitoring of the drug concentration and/or genotyping should be considered when prescribing drugs that are related to the *CYP3A5* genotype to Korean patients.

Our study showed that the frequencies of genes that encode drug-metabolizing enzymes and transporters in the Korean population were largely comparable to those in the EAS population, which agreed with our previous study [13]. Therefore, minimal adjustment is expected to be required when extrapolating clinical data acquired from EAS populations, while caution may be required when applying data from EUR or AFR populations.

One of the limitations of our study is that the results for the *CYP2D6*, *UGT1A1* and *TPMT* genes had some allele frequency data missing, which prevented accurate calculation of the overall diplotype percentage. The missing SNP frequencies in the respective genes (rs5030655 in *CYP2D6*; rs8175347 and rs28900406 in *UGT1A1*; and rs1800460 in *TPMT*) are all known to be monomorphic in the EAS population and are expected to have minimal impact on the calculation of overall diplotype percentage. Based on the assumption that the Korean population is monomorphic for the SNPs stated above, *CYP2D6* and *TPMT* are expected to have a minimal PM phenotype, and the *UGT1A1* gene is expected to have an approximately 10% PM phenotype in the Korean population. There was also an issue of assigning phenotypes to each sample. A limitation of a gene-chip platform such as DMET™ is that, when a star allele has multiple defining SNPs, assigning star allele may not be possible because a gene-chip does not provide information on whether the SNPs are from the same chromosome or not. Consequently, frequencies of star alleles such as CYP2D6*2 was not calculable.

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The aim of this study was to elucidate pharmacogenetic characteristics in a Korean population that contribute to variations in pharmacokinetic and pharmacodynamic responses to drugs. For the comprehensive analysis of pharmacogenetic markers, we used DMET™ microarray platform. The DMET™ platform tests a broad collection of genetic markers in ADME-related genes. One of the advantages of analysis using DMET™ over other genotyping methods is that it allows a time-efficient, large-scale genotyping at an acceptable cost. DNA chips such as DMET™ can be especially useful when testing for specific field of interest.

We analyzed 1,785 ADME related genetic markers from 1,012 Koreans (**Table 1** and **Supplementary Data 1**). Additionally, we compared the genetic markers of Koreans to those of other populations obtained from various previous studies [15-19]. Our study was the first large-scale comprehensive pharmacogenetic investigation in a Korean population. The results from our study will be useful for understanding the diverse genetic properties in Koreans that contribute to interindividual variations in the ADME of drugs. The pharmacogenetic data obtained from this study can be utilized to optimize drug selection, recommend the desirable dosage and prevent adverse events in Korean patients [41].

SUPPLEMENTARY MATERIAL

Supplementary Data 1

Affymetrix DMET SNP frequency results in Korean population.

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REFERENCES

1. Shu WY, Li JL, Wang XD, Huang M. Pharmacogenomics and personalized medicine: a review focused on their application in the Chinese population. Acta Pharmacol Sin 2015;36:535-543.
PUBMED | CROSSREF
2. Davidson AL, Dassa E, Orelle C, Chen J. Structure, function, and evolution of bacterial ATP-binding cassette systems. Microbiol Mol Biol Rev 2008;72:317-364.
PUBMED | CROSSREF
3. Xie HG, Kim RB, Wood AJ, Stein CM. Molecular basis of ethnic differences in drug disposition and response. Annu Rev Pharmacol Toxicol 2001;41:815-850.
PUBMED | CROSSREF
4. Kazui M, Nishiya Y, Ishizuka T, Hagihara K, Farid NA, Okazaki O, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. Drug Metab Dispos 2010;38:92-99.
PUBMED | CROSSREF
5. Jones PM, George AM. The ABC transporter structure and mechanism: perspectives on recent research. Cell Mol Life Sci 2004;61:682-699.
PUBMED | CROSSREF
6. McGraw J, Waller D. Cytochrome P450 variations in different ethnic populations. Expert Opin Drug Metab Toxicol 2012;8:371-382.
PUBMED | CROSSREF
7. Paganotti GM, Gramolelli S, Tabacchi F, Russo G, Modiano D, Coluzzi M, et al. Distribution of human CYP2C8*2 allele in three different African populations. Malar J 2012;11:125.
PUBMED | CROSSREF
8. Arbitrio M, Di Martino MT, Scionti F, Agapito G, Guzzi PH, Cannataro M, et al. DMET™ (Drug Metabolism Enzymes and Transporters): a pharmacogenomic platform for precision medicine. Oncotarget 2016;7:54028-54050.
PUBMED | CROSSREF

9. He YJ, Misher AD, Irvin W Jr, Motsinger-Reif A, McLeod HL, Hoskins JM. Assessing the utility of whole genome amplified DNA as a template for DMET Plus array. Clin Chem Lab Med 2012;50:1329-1334.
PUBMED | CROSSREF
10. Sissung TM, English BC, Venzon D, Figg WD, Deeken JF. Clinical pharmacology and pharmacogenetics in a genomics era: the DMET platform. Pharmacogenomics 2010;11:89-103.
PUBMED | CROSSREF
11. Chen ML. Ethnic or racial differences revisited: impact of dosage regimen and dosage form on pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 2006;45:957-964.
PUBMED | CROSSREF
12. Rosenberg NA, Pritchard JK, Weber JL, Cann HM, Kidd KK, Zhivotovsky LA, et al. Genetic structure of human populations. Science 2002;298:2381-2385.
PUBMED | CROSSREF
13. Yi S, An H, Lee H, Lee S, Ieiri I, Lee Y, et al. Korean, Japanese, and Chinese populations featured similar genes encoding drug-metabolizing enzymes and transporters: a DMET Plus microarray assessment. Pharmacogenet Genomics 2014;24:477-485.
PUBMED | CROSSREF
14. Dumaual C, Miao X, Daly TM, Bruckner C, Njau R, Fu DJ, et al. Comprehensive assessment of metabolic enzyme and transporter genes using the Affymetrix Targeted Genotyping System. Pharmacogenomics 2007;8:293-305.
PUBMED | CROSSREF
15. Clarke L, Fairley S, Zheng-Bradley X, Streeter I, Perry E, Lowy E, et al. The international Genome sample resource (IGSR): a worldwide collection of genome variation incorporating the 1000 Genomes Project data. Nucleic Acids Res 2017;45:D854-D859.
PUBMED | CROSSREF
16. Phan L, Jin Y, Zhang H, Qiang W, Shekhtman E, Shao D, et al. Allele frequency aggregator. Bethesda (MD): National Center for Biotechnology Information; 2020.
17. Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature 2020;581:434-443.
PUBMED | CROSSREF
18. Karczewski KJ, Weisburd B, Thomas B, Solomonson M, Ruderfer DM, Kavanagh D, et al. The ExAC browser: displaying reference data information from over 60 000 exomes. Nucleic Acids Res 2017;45:D840-D845.
PUBMED | CROSSREF
19. International HapMap Consortium. The International HapMap Project. Nature 2003;426:789-796.
PUBMED | CROSSREF
20. Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2C9 and nonsteroidal anti-inflammatory drugs. Clin Pharmacol Ther 2020;108:191-200.
PUBMED | CROSSREF
21. Daily EB, Aquilante CL. Cytochrome P450 2C8 pharmacogenetics: a review of clinical studies. Pharmacogenomics 2009;10:1489-1510.
PUBMED | CROSSREF
22. Wilke RA, Ramsey LB, Johnson SG, Maxwell WD, McLeod HL, Voora D, et al. The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. Clin Pharmacol Ther 2012;92:112-117.
PUBMED | CROSSREF
23. Johnson JA, Caudle KE, Gong L, Whirl-Carrillo M, Stein CM, Scott SA, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. Clin Pharmacol Ther 2017;102:397-404.
PUBMED | CROSSREF
24. Desta Z, Gammal RS, Gong L, Whirl-Carrillo M, Gaur AH, Sukasem C, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2B6 and efavirenz-containing antiretroviral therapy. Clin Pharmacol Ther 2019;106:726-733.
PUBMED | CROSSREF
25. Goetz MP, Sangkuhl K, Guchelaar HJ, Schwab M, Province M, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2D6 and tamoxifen therapy. Clin Pharmacol Ther 2018;103:770-777.
PUBMED | CROSSREF
26. Gammal RS, Court MH, Haidar CE, Iwuchukwu OF, Gaur AH, Alvarellos M, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for UGT1A1 and atazanavir prescribing. Clin Pharmacol Ther 2016;99:363-369.
PUBMED | CROSSREF

27. Relling MV, Gardner EE, Sandborn WJ, Schmiegelow K, Pui CH, Yee SW, et al. Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. Clin Pharmacol Ther 2013;93:324-325.
PUBMED | CROSSREF

28. Birdwell KA, Decker B, Barbarino JM, Peterson JF, Stein CM, Sadee W, et al. Clinical pharmacogenetics implementation consortium (CPIC) guidelines for CYP3A5 genotype and tacrolimus dosing. Clin Pharmacol Ther 2015;98:19-24.
PUBMED | CROSSREF

29. Clinical pharmacogenetics implementation consortium (CPIC) guidelines for CYP2C19 and voriconazole therapy. Clin Pharmacol Ther 2018;103:349.
PUBMED | CROSSREF

30. Sherry ST, Ward M, Sirotkin K. dbSNP-database for single nucleotide polymorphisms and other classes of minor genetic variation. Genome Res 1999;9:677-679.
PUBMED

31. Dean L. Amitriptyline therapy and CYP2D6 and CYP2C19 genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kane MS, Kattman BL, et al. (eds). Medical genetics summaries. Bethesda (MD): National Center for Biotechnology Information; 2012.

32. Dean L. Clopidogrel therapy and CYP2C19 genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kane MS, Kattman BL, et al. (eds). *Medical genetics summaries.* Bethesda (MD): National Center for Biotechnology Information; 2012.

33. Owen RP, Gong L, Sagreiya H, Klein TE, Altman RB. VKORC1 pharmacogenomics summary. Pharmacogenet Genomics 2010;20:642-644.
PUBMED | CROSSREF

34. Dean L. Warfarin therapy and VKORC1 and CYP genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kane MS, Kattman BL, et al. (eds). *Medical genetics summaries.* Bethesda (MD): National Center for Biotechnology Information; 2012.

35. COUMADIN (warfarin sodium tablet). Princeton (NJ): Bristol-Myers Squibb Pharma Company; 2015.

36. Bae JW, Choi CI, Kim MJ, Oh DH, Keum SK, Park JI, et al. Frequency of CYP2C9 alleles in Koreans and their effects on losartan pharmacokinetics. Acta Pharmacol Sin 2011;32:1303-1308.
PUBMED | CROSSREF

37. Voora D, Shah SH, Spasojevic I, Ali S, Reed CR, Salisbury BA, et al. The SLCO1B1*5 genetic variant is associated with statin-induced side effects. J Am Coll Cardiol 2009;54:1609-1616.
PUBMED | CROSSREF

38. Byeon JY, Kim YH, Lee CM, Kim SH, Chae WK, Jung EH, et al. CYP2D6 allele frequencies in Korean population, comparison with East Asian, Caucasian and African populations, and the comparison of metabolic activity of CYP2D6 genotypes. Arch Pharm Res 2018;41:921-930.
PUBMED | CROSSREF

39. Ryu S, Park S, Lee JH, Kim YR, Na HS, Lim HS, et al. A study on CYP2C19 and CYP2D6 polymorphic effects on pharmacokinetics and pharmacodynamics of amitriptyline in healthy Koreans. Clin Transl Sci 2017;10:93-101.
PUBMED | CROSSREF

40. Lee SJ, Lee SS, Jung HJ, Kim HS, Park SJ, Yeo CW, et al. Discovery of novel functional variants and extensive evaluation of CYP2D6 genetic polymorphisms in Koreans. Drug Metab Dispos 2009;37:1464-1470.
PUBMED | CROSSREF

41. Wang L, McLeod HL, Weinshilboum RM. Genomics and drug response. N Engl J Med 2011;364:1144-1153.
PUBMED | CROSSREF