Pharmacogenomics and Personalized Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Genetic Polymorphisms of Very Important Pharmacogene Variants in the Blang Population from Yunnan Province in China

Yuliang Wang[1–3]
Linna Peng[1–3]
Hongyan Lu[1–3]
Zhanhao Zhang[1–3]
Shishi Xing[1–3]
Dandan Li[1–3]
Chunjuan He[1–3]
Tianbo Jin[1–3]
Li Wang[1–3]

[1]Key Laboratory of Molecular Mechanism and Intervention Research for Plateau Diseases of Tibet Autonomous Region, School of Medicine, Xizang Minzu University, Xianyang, 712082, Shaanxi, People's Republic of China; [2]Engineering Research Center of Tibetan Medicine Detection Technology, Ministry of Education, School of Medicine, Xizang Minzu University, Xianyang, Shaanxi, 712082, People's Republic of China; [3]Key Laboratory of High Altitude Hypoxia Environment and Life Health, School of Medicine, Xizang Minzu University, Xianyang, Shaanxi, 712082, People's Republic of China

Background: We aimed to enrich the pharmacogenomic information of a Blang population (BP) from Yunnan Province in China.

Methods: We genotyped 55 very important pharmacogene (VIP) variants from the PharmGKB database and compared their genotype distribution (GD) in a BP with that of 26 populations by the χ^2 test. The minor allele frequency (MAF) distribution of seven significantly different single-nucleotide polymorphisms (SNPs) was conducted to compare the difference between the BP and 26 other populations.

Results: Compared with the GD of 55 loci in the BP, among 26 studied populations, GWD, YRI, GIH, ESN, MSL, TSI, PJL, ACB, FIN and IBS were the top-10 populations, which showed a significantly different GD >35 loci. CHB, JPT, CDX, CHS, and KHV populations had a significantly different GD <20 loci. A GD difference of 27–34 loci was found between the BP and 11 populations (LWK, CEU, ITU, STU, PUR, CLM, GBR, ASW, BEB, MXL and PEL). The GD of five loci (rs750155 (*SULT1A1*), rs4291 (*ACE*), rs1051298 (*SLC19A1*), rs1131596 (*SLC19A1*) and rs1051296 (*SLC19A1*)) were the most significantly different in the BP as compared with that of the other 26 populations. The genotype frequency of rs1800764 (*ACE*) and rs1065852 (*CYP2D6*) was different in all populations except for PEL and LWK, respectively. MAFs of rs1065852 (*CYP2D6*) and rs750155 (*SULT1A1*) showed the largest fluctuation between the BP and SAS, EUR, AFR and AMR populations.

Conclusion: Our data can provide theoretical guidance for safe and efficacious personalized drug use in the Blang population.

Keywords: Blang population, single-nucleotide polymorphism, SNP, very important pharmacogene, genotype distribution, pharmacogenomics, personalized drug use

Introduction

The use of drugs should be different among diverse ethnic groups because of differences in ethnicity, age, sex, environmental factors and genetic factors. If these differences are ignored, then drug sensitivity, metabolic rate, and adverse reactions are affected, which influences the curative effect of drugs and aggravates the illness of patients.

Genetic factors can explain up to 20–95% of the variability in drug response.[1] Variations in genes can affect the pharmacokinetics/pharmacodynamics of drugs, as well as their absorption and metabolism. "Pharmacogenes" are genes that decide the fate of drug pharmacology in a biological system. In general, pharmacogenes correspond to specific gene "superfamilies". Among numerous gene superfamilies,

Correspondence: Li Wang
Tel +86-15706028826
Email wangli_xzmd@163.com

Received: 8 July 2021
Accepted: 10 November 2021
Published: 17 December 2021

the cytochrome P450 superfamily is the most widely researched in pharmacogenomics studies. It has been reported that polymorphisms of cytochrome P450 account for the most frequent variations in the phase-I metabolism of drugs.[2] Variations in most gene superfamilies can affect the metabolism of drugs and disease risk.

The single-nucleotide polymorphism (SNP) is the most common variation of very important pharmacogenes (VIPs). Usually, SNPs are employed to analyze the pharmacogenomic information in different populations.[3,4] "Pharmacogenomics" is an emerging approach to "precision medicine". Pharmacogenomics plays a major part in precision medicine by "tailoring" the selection and dosing to the patient's genetic features.[5] The Pharmacogenomics Knowledge Base (PharmGKB; www.pharmgkb.org/) is one of the most commonly used databases on primary pharmacogenomics. PharmGKB contains information on gene-variant annotations, drug-centered pathways, VIPs and diverse diseases. PharmGKB aims to share genotype, phenotype, or other data on genetic variations among researchers.[6]

It has been demonstrated that pharmacogenomic analysis of a specific population can aid the efficacious, accurate use of drugs in a population.[7,8] For example, Bader et al found that variants of the vitamin K epoxide reductase complex gene (*VKORC*) and cytochrome P450 family 2 subfamily C member 9 gene (*CYP2C9*), which encode enzymes for warfarin metabolism, were the strongest predictors of variability in the warfarin dose among different populations in Middle East and North Africa.[7] In addition, Kim et al demonstrated that adverse drug reactions could be avoided if preemptive genotyping was employed in a South Korean population.[8]

The US Food and Drug Administration (www.fda.gov/) have recognized >250 biomarkers with known pharmacogenomic value, and provided recommendations for therapeutic management.[9] Recently, pharmacogenomics information on increasing numbers of ethnic minorities in China has been explored. For example, Liu et al found that, compared with 11 populations in a dataset from the International HapMap Project (www.genome.gov/), differences in expression between the rs2070676 of the cytochrome P450 family 2 subfamily E member 1 gene (*CYP2E1*) and rs1065852 of cytochrome P450 family 2 subfamily D member 6 gene (*CYP2D6*) in people of Zhuang nationality were the greatest according to genotyping of samples of 105 people of Zhuang nationality.[3] Besides, He et al concluded that expression of rs4291 of the angiotensin I-converting enzyme gene (*ACE*), rs1051296 of the solute carrier family 19 member 1 gene (*SLC19A1*) and rs1065852 of *CYP2D6* differed significantly in a Tibetan population compared with that of 26 other populations after genotyping of 200 samples from a Tibetan population. They also found that the allele frequency in this Tibetan population differed least from that of an East Asian population, and differed most from that of a North American population.[4]

China has 56 ethnic groups. The Blang ethnic group is found in Yunnan Province in China. According to the Sixth National Census in 2010, the total number of people of Blang ethnicity was 119,639. Among them, >30,000 people live in Mount Blang, Xiding, Bada, Daluo, Mengman, Menggang and other towns in Menghai County in Xishuangbanna Dai Autonomous Prefecture.[10] People of Blang ethnicity live in mountainous areas with a mild climate and abundant rainfall, which is very conducive to plant growth. The area in which Blang populations live is one of the main raw material-producing areas of "Pu'er tea" and "Mengku tea". Even though genetic studies on Blang populations have been conducted,[10–12] pharmacogenomics information of the Blang population is lacking. Cheng et al explored the pharmacogenomics information of a Blang population.[13]

Here, we shed light on the pharmacogenomic information of a Blang population by genotyping 55 different loci of 27 VIPs using 200 samples from Yunnan Province. These samples are different from those investigated by Cheng and collaborators. We also compared the distribution of genotype frequency and minor allele frequency (MAF) differences (55 loci of 27 VIPs) with a Blang population and 26 other populations. The genetic variations of the 15 gene superfamilies involved in the present study were related mainly to changes in drug metabolism and disease risk.[2,14–27] We wished to enrich the pharmacogenomics information of a Blang population and provide a theoretical foundation for promoting the development of personalized precise medication for Blang populations in the future.

Materials and Methods

Ethical Approval of the Study Protocol

The study protocol was approved by the Clinical Research Ethics Committee of Xizang Minzu University (Xianyang, China). Written informed consent was obtained from each study participant before a blood sample was given.

Participants

Two-hundred randomly selected healthy, unrelated individuals of Blang ethnicity from Yunnan Province were recruited. Whole-blood samples were collected according to the study protocol. Candidate participants were healthy individuals and had exclusive Blang ancestry for ≥3 previous generations. People suffering from cancer, infectious diseases, drug/alcohol addiction, severe dysfunction of the heart, liver, or kidney or immune disorders were excluded, as were women who were pregnant or lactating. Thus, the recruited individuals were representative of a Blang population.

Variant Selection and Genotyping

PharmGKB was used for selection of genetic variants from published polymorphisms associated with VIP variants. Assays for the loci of 55 genetic variants in 27 VIPs were designed. Loci that could not be designed for an assay were excluded.

We extracted the genomic DNA from the peripheral blood of participants using the GoldMag®-Mini Whole Blood Genomic DNA Purification Kit (GoldMag. Xi'an, China) according to manufacturer protocols. The DNA concentration was measured using the NanoDrop 2000C spectrophotometer (Thermo Scientific, Waltham, MA, USA). MassARRAY Assay Design 3.0 (Sequenom, San Diego, CA, USA) was employed to design multiplexed SNP MassEXTEND assays.[28] SNP genotyping was done using MassARRAY RS1000 (Sequenom) according to manufacturer protocols. Sequenom Typer 4.0 was employed to manage and analyze the data on SNP genotyping.[29] The basic information on the selected 55 loci related to 27 VIPs of the Blang population are listed in Table 1. The polymerase chain reaction (PCR) primers designed for the selected SNPs are shown in Supplemental Table 1. The basic information comprised the gene name, SNP ID, positions, functional consequence, genotype frequencies and MAF in the Blang population. All samples from the Blang population were genotyped with respect to these variants. PharmGKB was also used for the clinical and variant annotations for seven significantly different SNPs in the Blang population compared with 26 other populations.

HapMap Genotype Data

The genotype data of individuals from 26 populations was obtained from the International HapMap Project Internet website (www.genome.gov/10001688/international-hapmap-project/). The 26 populations were as follows: 1) Chinese Dai in Xishuangbanna, China (CDX); 2) Han Chinese in Beijing, China (CHB); 3) Southern Han Chinese, China (CHS); 4) Japanese in Tokyo, Japan (JPT); 5) Kinh in Ho Chi Minh City, Vietnam (KHV); 6) African Caribbeans in Barbados (ACB); 7) African Ancestry in Southwest USA (ASW); 8) Esan in Nigeria (ESN); 9) Gambian in Western Divisions, The Gambia (GWD); 10) Luhya in Webuye, Kenya (LWK); 11) Mende in Sierra Leone (MSL); 12) Yoruba in Ibadan, Nigeria (YRI); 13) Colombian in Medellin, Colombia (CLM); 14) Mexican Ancestry in Los Angeles, Colombia (MXL); 15) Peruvian in Lima, Peru (PEL); 16) Puerto Rican in Puerto Rico (PUR); 17) Utah residents with Northern and Western European ancestry (CEU); 18) Finnish in Finland (FIN); 19) British in England and Scotland (GBR); 20) Iberian populations in Spain (IBS); 21) Toscani in Italy (TSI); 22) Bengali in Bangladesh (BEB); 23) Gujarati Indian in Houston, Texas (GIH); 24) Indian Telugu in the UK (ITU); 25) Punjabi in Lahore, Pakistan (PJL); 26) Sri Lankan Tamil in the UK (STU).

Statistical Analyses

An exact test was used to test the frequency validity of each VIP variant by assessing the departure from the Hardy–Weinberg equilibrium. The comparison of genotype frequencies between the Blang population and 26 other populations was conducted using the χ^2 test. SPSS 17.0 (Armonk, NY, USA) and Excel™ (Microsoft, Redmond, WA, USA) were used to analyze the distribution of genotypes and MAFs. The Bonferroni correction was applied to $p < 0.05$ (two-sided).

Results

Basic Information of VIP Loci

The VIPs corresponding to 55 loci could be classified into 15 gene superfamilies (Table 1): cytochrome P450 superfamily; dihydropyrimidine dehydrogenase; prostaglandin-endoperoxide synthase; calcium voltage-gated channel; ryanodine receptor; alcohol dehydrogenase; potassium voltage-gated ion channel; N-acetyltransferase; angiotensin I-converting enzyme; potassium inwardly rectifying channel; G-protein coupled receptor family; solute carrier organic anion transporter family; nuclear receptor family; sulfotransferase family; solute carrier family. The sequence function of these 55 loci was classified mainly

Table 1 The Basic Information of 55 SNPs

SNP ID	Chromosome	Position	Functional Consequence	Genes	Genotype			MAF
					AA	AB	BB	
rs11572325	1	59896030	Intron_variant	*CYP2J2*	0	19	181	0.048
rs10889160	1	59896449	Intron_variant	*CYP2J2*	2	33	165	0.093
rs890293	1	59926822	Upstream_transcript_variant	*CYP2J2*	0	4	196	0.010
rs1760217	1	97137438	Genic_downstream_transcript_variant,intron_variant	*DPYD*	15	83	99	0.287
rs1801159	1	97515839	Coding_sequence_variant, genic_downstream_transcript_variant,intron_variant, missense_variant	*DPYD*	14	77	109	0.263
rs1801265	1	97883329	Non_coding_transcript_variant,intron_variant, coding_sequence_variant,5_prime_UTR_variant, missense_variant	*DPYD*	2	36	162	0.100
rs5275	1	186673926	3_prime_UTR_variant	*PTGS2*	9	76	115	0.235
rs20417	1	186681189	Upstream_transcript_variant, non_coding_transcript_variant	*PTGS2*	0	1	199	0.003
rs12139527	1	201040054	Missense_variant,coding_sequence_variant, intron_variant	*CACNA1S*	0	44	156	0.110
rs13374149	1	201043356	Missense_variant,coding_sequence_variant, downstream_transcript_variant	*CACNA1S*	0	18	182	0.045
rs3850625	1	201047168	Coding_sequence_variant,missense_variant	*CACNA1S*	0	6	194	0.015
rs2306238	1	237550803	Intron_variant	*RYR2*	9	73	117	0.229
rs2231142	4	88131171	Coding_sequence_variant,missense_variant	*ABCG2*	6	57	136	0.173
rs2231137	4	88139962	Coding_sequence_variant,missense_variant	*ABCG2*	38	98	61	0.442
rs698	4	99339632	Coding_sequence_variant, non_coding_transcript_variant,missense_variant	*ADH1C*	6	37	157	0.123
rs776746	7	99672916	Intron_variant,splice_acceptor_variant, genic_downstream_transcript_variant, downstream_transcript_variant	*CYP3A5*	27	13	160	0.168
rs2242480	7	99763843	Intron_variant	*CYP3A4*	36	104	58	0.444
rs1805123	7	150948446	Missense_variant,coding_sequence_variant, genic_downstream_transcript_variant	*KCNH2*	0	200	0	0.500
rs4646244	8	18390208	Upstream_transcript_variant, genic_upstream_transcript_variant,intron_variant	*NAT2*	12	106	82	0.325
rs4271002	8	18390758	Upstream_transcript_variant, genic_upstream_transcript_variant,intron_variant	*NAT2*	8	90	102	0.265
rs1041983	8	18400285	Coding_sequence_variant,synonymous_variant	*NAT2*	40	103	57	0.458
rs1801280	8	18400344	Missense_variant,coding_sequence_variant	*NAT2*	0	21	179	0.053
rs1799929	8	18400484	Coding_sequence_variant,synonymous_variant	*NAT2*	1	22	177	0.060
rs1799930	8	18400593	Missense_variant,coding_sequence_variant	*NAT2*	18	85	97	0.303

(*Continued*)

Table 1 (Continued).

SNP ID	Chromosome	Position	Functional Consequence	Genes	Genotype			MAF
					AA	AB	BB	
rs1208	8	18400806	Missense_variant,coding_sequence_variant	*NAT2*	1	22	177	0.060
rs1799931	8	18400860	Missense_variant,coding_sequence_variant	*NAT2*	5	53	142	0.158
rs1495741	8	18415371	None	*NAT2*	43	95	59	0.459
rs2115819	10	45405641	Intron_variant	*ALOX5*	11	37	152	0.148
rs12248560	10	94761900	Upstream_transcript_variant	*CYP2C19*	0	12	188	0.030
rs4244285	10	94781859	Coding_sequence_variant,synonymous_variant	*CYP2C19*	8	65	127	0.203
rs1057910	10	94981296	Missense_variant,coding_sequence_variant	*CYP2C9*	1	12	187	0.035
rs11572103	10	95058349	Missense_variant,coding_sequence_variant	*CYP2C8*	0	4	195	0.010
rs7909236	10	95069673	Upstream_transcript_variant	*CYP2C8*	1	20	179	0.055
rs17110453	10	95069772	Upstream_transcript_variant	*CYP2C8*	9	70	119	0.222
rs3813867	10	133526101	Non_coding_transcript_variant, upstream_transcript_variant	*CYP2E1*	2	41	157	0.113
rs2031920	10	133526341	Non_coding_transcript_variant, upstream_transcript_variant	*CYP2E1*	6	30	164	0.105
rs6413432	10	133535040	Intron_variant	*CYP2E1*	0	1	199	0.003
rs2070676	10	133537633	Intron_variant	*CYP2E1*	11	42	147	0.160
rs5219	11	17388025	Missense_variant,stop_gained,5_prime_UTR_variant, intron_variant,coding_sequence_variant	*KCNJ11*	0	32	168	0.080
rs1801028	11	113412762	Missense_variant,coding_sequence_variant	*DRD2*	0	3	197	0.008
rs2306283	12	21176804	Missense_variant,coding_sequence_variant	*SLCO1B1*	5	47	148	0.143
rs4516035	12	47906043	Upstream_transcript_variant	*VDR*	0	7	193	0.018
rs762551	15	74749576	Intron_variant	*CYP1A2*	6	74	119	0.216
rs2472304	15	74751897	Intron_variant	*CYP1A2*	5	53	142	0.158
rs750155	16	28609251	5_prime_UTR_variant,intron_variant, genic_upstream_transcript_variant, upstream_transcript_variant	*SULT1A1*	0	93	107	0.233
rs1800764	17	63473168	None	*ACE*	0	73	127	0.183
rs4291	17	63476833	Upstream_transcript_variant	*ACE*	1	199	0	0.503
rs4267385	17	63506395	None	*ACE*	7	87	106	0.253
rs2108622	19	15879621	Missense_variant,coding_sequence_variant	*CYP4F2*	7	42	151	0.140
rs3093105	19	15897578	Missense_variant,coding_sequence_variant	*CYP4F2*	0	200	0	0.500
rs8192726	19	40848591	Intron_variant	*CYP2A6*	5	63	132	0.183
rs1051298	21	45514912	Intron_variant,3_prime_UTR_variant	*SLC19A1*	0	183	17	0.458
rs1051296	21	45514947	Intron_variant,3_prime_UTR_variant	*SLC19A1*	9	156	35	0.435

(*Continued*)

Table 1 (Continued).

SNP ID	Chromosome	Position	Functional Consequence	Genes	Genotype			MAF
					AA	AB	BB	
rs1131596	21	45538002	Missense_variant,5_prime_UTR_variant, synonymous_variant, genic_upstream_transcript_variant, coding_sequence_variant	*SLC19A1*	14	167	19	0.488
rs1065852	22	42130692	Intron_variant,missense_variant, coding_sequence_variant	*CYP2D6*	0	200	0	0.500

Note: A, reference allele; B, other allele.

Abbreviations: SNP, single-nucleotide polymorphism; MAF, minor allele frequency; *CYP2J2*, cytochrome P450 family 2 subfamily J member 2; *DPYD*, dihydropyrimidine dehydrogenase; *PTGS2*, prostaglandin-endoperoxide synthase 2; *CACNA1S*, calcium voltage-gated channel subunit alpha1 S; *RYR2*, ryanodine receptor 2; *ABCG2*, ATP-binding cassette sub-family G member 2; *ADH1C*, alcohol dehydrogenase 1C (Class I), gamma polypeptide; *CYP3A5*, cytochrome P450 family 3 subfamily A member 5; *CYP3A4*, cytochrome P450 family 3 subfamily A member 4; *KCNH2*, potassium voltage-gated channel subfamily H member 2; *NAT2*, N-acetyltransferase 2; *ALOX5*, arachidonate 5-lipoxygenase; *CYP2C19*, cytochrome P450 family 2 subfamily C member 19; *CYP2C9*, cytochrome P450 family 2 subfamily C member 9; *CYP2C8*, cytochrome P450 family 2 subfamily C member 8; *CYP2E1*, cytochrome P450 family 2 subfamily E member 1; *KCNJ11*, potassium inwardly rectifying channel subfamily J member 11; *DRD2*, dopamine receptor D2; *SLCO1B1*, solute carrier organic anion transporter family member 1B1; *VDR*, vitamin D3 receptor; *CYP1A2*, cytochrome P450 family 1 subfamily A member 2; *SULT1A1*, sulfotransferase family 1A member 1; *ACE*, angiotensin-converting enzyme; *CYP4F2*, cytochrome P450 family 4 subfamily F member 2; *CYP2A6*, cytochrome P450 family 2 subfamily A member 6; *SLC19A1*, solute carrier family 19 member 1; *CYP2D6*, cytochrome P450 family 2 subfamily D member 6.

into eight types: intron variant; upstream transcript variant; downstream transcript variant; coding sequence variant; missense; 3′ untranslated region (UTR) variant; non-coding transcript variant; 5′ UTR variant.

Relationship Between the Blang Population and 26 Other Populations

All selected loci met the Hardy–Weinberg equilibrium (p>0.05) with a call rate >99.9%. Among the 26 populations studied, GWD, YRI, GIH, ESN, MSL, TSI, PJL, ACB, FIN and IBS were the top-10 populations which showed significant differences compared with the Blang population (>35 loci) (Table 2). Conversely, CHB, JPT, CDX, CHS and KHV populations showed the most similarities with the Blang population (genotype distribution <20 loci). The genotype distribution of 27–34 loci in the Blang population showed a significant difference from that of 11 other populations, (LWK, CEU, ITU, STU, PUR, CLM, GBR, ASW, BEB, MXL and PEL). On the one hand, among 26 populations, the GWD population had the greatest number of significantly different loci after Bonferroni correction compared with that in the Blang population, indicating that GWD was the most different population from the Blang population. This significant difference may have resulted from a difference in the genetic background between them. On the other hand, the KHV population showed the least number of different loci after Bonferroni correction. The relatively greater number of similar loci was probably caused by a similar geographic location (East Asian) between them. The distribution of genotypes and allele frequencies of the seven significantly different SNPs are shown in Supplemental Table 2 and Supplemental Figures 1–7.

Genotype Distribution of 55 Loci

Among 55 loci, after Bonferroni correction between the Blang population and 26 other populations, the distribution of genotype frequencies was significantly different in five loci: rs750155 of sulfotransferase family 1A member gene (*SULT1A1*), rs4291 of *ACE*, rs1051298, rs1131596 and rs1051296 of *SLC19A1*. Besides, the genotype distribution of rs1800764 (*ACE*) and rs1065852 (*CYP2D6*) was different in all populations except for PEL and LWK, respectively. Conversely, the genotype distribution of rs1801028 of the dopamine receptor D2 gene (*DRD2*) was significantly different only in the GIH population compared with that in the Blang population. In addition to the eight loci mentioned above, the genotype distribution of the remaining loci in the Blang population also showed a significant difference compared with that in the other 26 populations, but to different degrees.

MAF Distribution of Seven Significantly Different SNPs

The MAF distribution of seven significantly different SNPs is shown in Table 3 and Figure 1. The MAFs of rs1065852 (*CYP2D6*) and rs750155 (*SULT1A1*) showed the greatest similarities among SAS, EUR, AFR and

AMR populations, but also showed the largest fluctuation between the Blang population and SAS, EUR, AFR and AMR populations. The MAFs of rs1800764 (*ACE*) and rs1131596 (*SLC19A1*) among the seven subpopulations of AFR showed distinct differences when compared with those of the Blang population. However, the MAFs of rs4291 (*ACE*), rs1051298 (*SLC19A1*), and rs1051296 (*SLC19A1*) showed relatively less fluctuation between the Blang population and the other 26 populations. Besides, the MAFs of rs1800764 (*ACE*) and rs750155 (*SULT1A1*) in the Blang population were close to those of the PEL population, even though most of other populations showed distinct differences on it. To better observe the phenotypes of these seven significantly different SNPs in the Blang population, their clinical and variant annotations were retrieved from PharmGKB (Supplemental Table 3 and Supplemental Table 4, respectively).

Discussion

We genotyped 55 VIP variants from PharmGKB and compared the genotype distribution and MAF of variants in a Blang population with those of 26 other populations. Among 55 loci, the genotype distribution of five SNPs (rs750155 (*SULT1A1*), rs4291 (*ACE*), rs1051298 (*SLC19A1*), rs1051296 (*SLC19A1*) and rs1131596 (*SLC19A1*)) was significantly different in the Blang population compared with that in the other 26 populations. Two SNPs (rs1800764 (*ACE*) and rs1065852 (*CYP2D6*)) showed a significantly different genotype distribution in the Blang population compared with that in the other 25 populations but, compared with PEL and LWK populations, respectively, a significant difference was not observed. In addition, the MAFs of rs1065852 (*CYP2D6*) and rs750155 (*SULT1A1*) showed the greatest fluctuation between the Blang population and SAS, EUR, AFR and AMR populations.

SULT1A1, encoded by *SULT1A1*, is an isoform of sulfotransferases. The latter are phase-II detoxification enzymes and have a crucial role in the metabolism of several xenobiotics and endogenous compounds (eg, tamoxifen).[30,31] High polymorphism of *SULT1A1* has been reported among Caucasian, Chinese, African–American and Korean populations.[32,33] Moyer et al reported that the genetic variation in *SULT1A1*, including rs750155, which is located in the promoter region (the short arm of chromosome 16) of *SULT1A1*, could explain (at least in part) the interindividual variability in the onset of menopause and symptoms before initiation of hormone therapy, and may represent a step towards individualizing decisions for hormone therapy.[34] Besides, Innocenti et al demonstrated that allele T of rs750155 is not associated with the pharmacokinetic parameters of ABT-751 (novel anticancer agent) in people with neoplasms as compared with allele C.[35] In our study, the genotype frequency distribution of rs750155 (*SULT1A1*) in the Blang population was significantly different from that of the other 26 populations. Also, the MAF distribution of rs750155 (*SULT1A1*) showed the greatest difference between the Blang population and SAS, EUR, AFR and AMR populations. Besides, the allele T frequency of rs750155 was far higher than that of allele C [T (76.7%) vs C (23.3%)], which indicated that the T allele of rs750155 in members of the Blang population with neoplasms could metabolize ABT-751 more readily.

ACE, encoded by *ACE*, is an enzyme that can affect the renin–angiotensin system and regulation of blood pressure.[36,37] ACE inhibitors are first-line treatment for hypertension. They can favorably affect the vascular remodeling of patients with myocardial infarction and heart failure, and reduce its risk and mortality.[38] The functional SNPs rs1800764 (*ACE*) and rs4291 (*ACE*) are located in the promoter region (chromosome 17) of *ACE*.[39] Linkage disequilibrium has been identified between these two SNPs in *ACE* in multiple populations.[40,41] These two SNPs possess the same pharmacokinetic characteristics and are associated with the risk of breast cancer, end-stage renal disease and Alzheimer's disease.[42–44] The SNPs rs1800764 (*ACE*) and rs4291 (*ACE*) show different drug responses in different populations.[45–47] In the present study, the genotype frequency distribution of SNPs rs1800764 (*ACE*) and rs4291 (*ACE*) in the Blang population was different from that of the other populations studied, even though rs1800764 (*ACE*) was not significantly different in the Blang population compared with that in the PEL population. Besides, the MAF of rs1800764 (*ACE*) in the AFR population showed a distinct difference compared with that in the Blang population. However, rs4291 (*ACE*) showed relatively less fluctuation of MAF between the Blang population and the other 26 populations. Although the association between SNPs rs1800764 (*ACE*) and rs4291 (*ACE*) and the risk of breast cancer, end-stage renal disease and Alzheimer's disease have not been elucidated in the Blang population, our pharmacogenomics study of the SNPs rs1800764 (*ACE*) and rs4291 (*ACE*) in the Blang population is important for disease prevention and safe use of drugs.

Table 2 The Genotype Distribution Difference Between Blang and 26 Other Populations After Bonferroni's Multiple Adjustments

SNP ID	Genes	EAS					AFR						
		CDX	CHB	CHS	JPT	KHV	ACB	ASW	ESN	GWD	LWK	MSL	YRI
rs11572325	*CYP2J2*	–	3.55E-01	-	-	-	**3.09E-06**	**1.55E-05**	**6.55E-06**	**1.61E-05**	**6.00E-05**	**2.38E-04**	**1.15E-05**
rs10889160	*CYP2J2*	4.55E-01	3.81E-02	4.33E-02	**1.75E-04**	3.96E-01	**7.04E-20**	**9.00E-11**	**1.21E-22**	**1.60E-16**	**6.80E-17**	**6.87E-20**	**3.92E-22**
rs890293	*CYP2J2*	-	3.91E-02	-	-	-	**5.59E-07**	**4.63E-10**	**8.77E-14**	**5.59E-11**	**4.02E-10**	**1.15E-15**	**1.27E-10**
rs1760217	*DPYD*	2.92E-01	7.58E-01	1.74E-01	3.49E-02	5.72E-01	1.43E-02	3.45E-01	2.16E-01	4.90E-04	1.62E-02	1.27E-01	1.92E-03
rs1801159	*DPYD*	7.64E-01	8.28E-01	3.94E-02	7.46E-01	6.49E-01	2.42E-03	3.35E-02	9.31E-02	3.52E-07	5.19E-01	1.76E-06	5.36E-03
rs1801265	*DPYD*	1.47E-01	3.55E-01	4.06E-01	1.53E-01	5.94E-01	**9.83E-14**	**8.87E-18**	**4.50E-18**	**4.94E-21**	**1.58E-21**	**1.19E-13**	**3.18E-19**
rs5275	*PTGS2*	6.18E-01	6.55E-02	2.65E-01	9.03E-01	7.74E-01	**7.36E-18**	**1.59E-11**	**4.77E-22**	**2.46E-17**	**4.06E-18**	**1.26E-20**	**3.28E-22**
rs20417	*PTGS2*	-	-	-	-	-	**5.38E-29**	**1.81E-26**	**1.16E-37**	**3.26E-27**	**2.82E-24**	**3.93E-36**	**5.95E-33**
rs12139527	*CACNA1S*	2.69E-01	2.51E-02	3.60E-01	1.39E-01	-	**1.30E-23**	**5.47E-20**	**9.80E-32**	**1.53E-34**	**5.79E-27**	**7.64E-31**	**1.14E-30**
rs13374149	*CACNA1S*	-	-	-	-	-	**1.24E-11**	**1.10E-08**	**3.05E-16**	**5.43E-17**	**5.43E-10**	**1.51E-17**	**8.94E-20**
rs3850625	*CACNA1S*	-	-	-	-	-	-	-	-	-	-	-	-
rs2306238	*RYR2*	2.03E-01	4.71E-01	3.91E-01	3.80E-01	3.24E-01	**1.25E-06**	**7.62E-04**	**2.71E-09**	**3.87E-08**	**2.38E-07**	**2.35E-08**	**1.17E-07**
rs2231142	*ABCG2*	3.83E-01	**7.28E-04**	4.98E-02	**1.01E-04**	**2.00E-05**	**6.82E-08**	2.69E-02	**2.34E-09**	**1.24E-08**	**2.34E-09**	**1.78E-06**	**4.56E-10**
rs2231137	*ABCG2*	4.42E-01	2.58E-03	4.35E-02	**3.22E-10**	4.68E-01	**1.08E-20**	**1.73E-17**	**7.65E-21**	**2.84E-24**	**5.61E-14**	**6.23E-15**	**2.16E-21**
rs698	*ADH1C*	1.89E-01	2.21E-02	1.83E-01	1.94E-01	1.82E-01	8.83E-01	8.77E-01	1.89E-01	1.70E-01	1.92E-01	2.72E-01	9.91E-02
rs776746	*CYP3A5*	**3.65E-13**	**1.47E-11**	**1.27E-11**	**3.71E-14**	**1.23E-13**	**4.31E-31**	**2.64E-25**	**4.08E-38**	**2.94E-34**	**1.06E-35**	**7.18E-34**	**6.79E-39**
rs2242480	*CYP3A4*	**1.10E-04**	**4.63E-06**	**2.16E-06**	**1.40E-04**	6.99E-03	**2.26E-14**	**1.87E-08**	**7.16E-26**	**9.51E-19**	**2.91E-26**	**5.51E-23**	**1.17E-20**
rs1805123	*KCNH2*	-	**8.42E-62**	-	-	-	-	-	-	-	-	-	-
rs4646244	*NAT2*	**4.76E-04**	**3.80E-04**	9.25E-02	5.50E-03	3.62E-02	4.31E-02	6.84E-02	2.54E-02	**5.48E-04**	3.84E-02	1.40E-02	**6.42E-04**
rs4271002	*NAT2*	1.60E-02	7.26E-02	4.71E-02	2.33E-02	4.71E-02	**3.71E-06**	**6.54E-04**	**1.92E-12**	**1.61E-12**	**4.58E-07**	**1.19E-05**	**6.13E-08**
rs1041983	*NAT2*	1.48E-01	8.16E-02	8.87E-01	1.40E-02	9.33E-02	4.96E-01	8.62E-01	9.51E-02	1.59E-01	6.87E-01	8.27E-02	4.87E-01
rs1801280	*NAT2*	-	-	-	-	3.41E-01	**1.58E-12**	**1.14E-12**	**1.21E-12**	**3.42E-17**	**7.64E-20**	**1.03E-09**	**5.34E-10**
rs1799929	*NAT2*	7.43E-01	2.56E-01	4.87E-01	7.99E-02	6.50E-01	**1.20E-08**	**1.79E-08**	**2.31E-06**	**1.02E-12**	**1.01E-15**	**1.33E-05**	**1.85E-04**
rs1799930	*NAT2*	1.52E-01	2.12E-02	4.15E-01	2.89E-01	2.79E-01	5.62E-01	5.36E-01	5.15E-01	5.15E-03	6.59E-01	9.95E-02	2.16E-02
rs1208	*NAT2*	7.43E-01	2.56E-01	6.09E-01	7.99E-02	8.57E-01	**1.13E-17**	**2.25E-14**	**4.00E-19**	**2.38E-24**	**2.31E-24**	**4.87E-16**	**3.76E-19**
rs1799931	*NAT2*	3.96E-03	1.54E-01	5.44E-01	5.65E-02	6.41E-01	**1.16E-04**	8.47E-03	**1.04E-06**	**3.81E-07**	**2.94E-07**	1.33E-03	**5.10E-05**
rs1495741	*NAT2*	4.00E-01	3.54E-03	7.00E-01	1.13E-03	4.51E-01	3.38E-01	3.32E-02	8.69E-01	6.81E-01	2.19E-02	6.57E-01	7.58E-01
rs2115819	*ALOX5*	1.34E-03	**6.16E-04**	5.95E-02	1.20E-02	9.48E-02	**2.81E-36**	**1.34E-23**	**7.95E-36**	**8.90E-40**	**1.18E-31**	**1.67E-30**	**1.21E-38**
rs12248560	*CYP2C19*	-	-	-	-	-	**3.08E-17**	**1.17E-09**	**1.83E-14**	**1.92E-14**	**6.70E-09**	**4.56E-15**	**5.78E-14**
rs4244285	*CYP2C19*	2.12E-01	**4.41E-04**	**6.33E-05**	5.24E-03	8.39E-02	2.47E-01	2.93E-01	9.06E-01	7.14E-02	9.15E-01	7.45E-01	3.02E-01
rs1057910	*CYP2C9*	7.73E-01	6.54E-01	7.70E-01	5.56E-01	7.35E-01	1.16E-01	6.06E-01	3.46E-02	2.17E-02	3.46E-02	5.53E-02	2.56E-02
rs11572103	*CYP2C8*	-	-	-	-	-	**1.89E-16**	**6.65E-10**	**8.36E-15**	**1.07E-18**	**3.96E-09**	**5.73E-12**	**1.88E-14**
rs7909236	*CYP2C8*	2.33E-02	9.92E-02	5.29E-01	4.06E-01	7.66E-01	5.84E-01	3.41E-01	3.73E-03	1.73E-03	7.89E-02	8.09E-03	2.28E-03
rs17110453	*CYP2C8*	7.88E-01	7.43E-03	9.72E-04	**1.22E-04**	4.29E-01	**8.63E-11**	**1.13E-07**	**4.23E-11**	**7.52E-14**	**2.06E-12**	**6.08E-11**	**1.15E-12**
rs3813867	*CYP2E1*	2.10E-01	**1.21E-04**	9.66E-03	2.47E-02	2.85E-03	5.71E-02	4.31E-01	3.91E-01	3.31E-01	1.23E-03	1.32E-01	4.68E-01
rs2031920	*CYP2E1*	8.14E-02	**5.81E-04**	6.33E-03	4.16E-03	**2.16E-04**	**5.35E-05**	1.61E-02	**3.99E-05**	**1.02E-05**	**3.99E-05**	**1.58E-04**	**1.66E-05**
rs6413432	*CYP2E1*	**6.35E-26**	**1.06E-22**	**1.12E-21**	**1.81E-22**	**3.82E-26**	-	-	**2.62E-07**	**1.40E-08**	-	**3.64E-05**	**1.64E-08**
rs2070676	*CYP2E1*	**2.05E-04**	1.66E-02	1.76E-01	2.81E-02	4.85E-03	**5.15E-27**	**1.93E-15**	**2.26E-27**	**2.46E-29**	**5.40E-33**	**1.17E-27**	**2.93E-27**
rs5219	*KCNJ11*	**1.47E-06**	**4.47E-16**	**8.46E-20**	**1.57E-13**	**1.13E-14**	-	2.08E-02	-	-	-	-	-
rs1801028	*DRD2*	-	7.96E-03	9.04E-03	-	-	-	-	-	-	-	-	-
rs2306283	*SLCO1B1*	3.04E-01	5.03E-02	1.29E-01	**2.28E-07**	3.97E-02	5.66E-02	1.85E-02	2.80E-01	3.26E-01	4.87E-01	2.84E-01	3.02E-01
rs4516035	*VDR*	-	-	-	-	-	-	**1.96E-05**	-	-	-	-	-
rs762551	*CYP1A2*	3.86E-01	**1.32E-04**	**4.37E-04**	**4.15E-06**	4.03E-01	**4.84E-05**	2.59E-03	**2.04E-10**	**3.06E-07**	**6.14E-13**	**5.59E-07**	**1.95E-09**
rs2472304	*CYP1A2*	6.74E-01	3.04E-01	9.05E-01	2.39E-01	5.01E-01	3.93E-02	4.55E-01	**7.69E-08**	**3.81E-07**	**1.04E-06**	**7.77E-07**	**6.90E-08**
rs750155	*SULT1A1*	**1.53E-13**	**1.10E-21**	**6.16E-13**	**1.52E-24**	**2.79E-16**	**2.51E-19**	**1.42E-21**	**2.46E-28**	**1.38E-33**	**5.49E-24**	**5.54E-25**	**4.44E-27**
rs1800764	*ACE*	**2.58E-08**	**2.67E-06**	**1.89E-06**	**4.61E-13**	**1.81E-08**	**2.40E-45**	**1.17E-35**	**8.71E-53**	**2.63E-58**	**9.85E-48**	**7.85E-56**	**8.85E-58**
rs4291	*ACE*	**2.66E-29**	**1.08E-34**	**4.49E-30**	**2.01E-25**	**4.19E-34**	**1.14E-27**	**2.40E-28**	**2.30E-29**	**6.11E-25**	**4.21E-34**	**6.39E-25**	**2.97E-34**
rs4267385	*ACE*	3.22E-01	2.05E-01	9.11E-01	8.29E-02	3.75E-01	**2.75E-29**	**1.85E-20**	**2.95E-31**	**6.81E-38**	**2.22E-39**	**1.33E-36**	**1.96E-35**
rs2108622	*CYP4F2*	7.51E-02	1.74E-02	4.11E-02	3.01E-02	5.72E-02	6.59E-01	2.74E-01	3.06E-03	2.39E-02	4.39E-01	4.86E-01	9.56E-03
rs3093105	*CYP4F2*	-	-	-	**2.56E-59**	-	**1.15E-37**	**1.86E-30**	**5.69E-33**	**2.44E-41**	**7.01E-38**	**2.46E-36**	**3.69E-35**
rs8192726	*CYP2A6*	5.87E-01	1.07E-01	1.88E-02	4.70E-02	2.40E-02	**2.17E-04**	5.86E-02	1.71E-02	7.30E-05	9.81E-03	1.06E-03	5.91E-03
rs1051298	*SLC19A1*	**8.53E-18**	**5.07E-19**	**1.64E-12**	**1.63E-18**	**1.95E-16**	**9.09E-19**	**3.59E-16**	**5.15E-15**	**2.32E-23**	**1.78E-19**	**2.68E-17**	**4.92E-17**
rs1051296	*SLC19A1*	**5.68E-07**	**1.09E-09**	**5.76E-04**	**4.79E-08**	**2.02E-06**	**9.10E-06**	**2.37E-08**	**3.68E-09**	**2.95E-09**	**1.55E-10**	**1.18E-06**	**8.84E-08**
rs1131596	*SLC19A1*	**3.38E-09**	**1.29E-09**	**2.58E-05**	**9.40E-11**	**4.20E-07**	**3.13E-20**	**2.89E-08**	**3.62E-10**	**7.00E-27**	**4.69E-21**	**1.13E-19**	**2.40E-18**
rs1065852	*CYP2D6*	**4.67E-33**	**4.64E-29**	**3.15E-34**	**2.68E-31**	**2.43E-28**	**2.31E-45**	**1.33E-42**	**7.97E-53**	**1.41E-51**	-	**9.48E-44**	**4.64E-51**

Note: "-" means no data. Bold values means after adjustment $p < 0.05/(55*26)$ the locus has statistical significance.

Abbreviations: EAS, East Asian; SAS, South Asian; EUR, European; AFR, African; AMR, American; CDX, Chinese Dai in Xishuangbanna, China; CHB, Han Chinese in Beijing, China; CHS, Southern Han Chinese, China; JPT, Japanese in Tokyo, Japan; KHV, Kinh in Ho Chi Minh City; Vietnam; BEB, Bengali in Bangladesh; GIH, Gujarati Indian in Houston, Texas; ITU, Indian Telugu in the UK; PJL, Punjabi in Lahore, Pakistan; STU, Sri Lankan Tamil in the UK; CEU, Western European ancestry; FIN, Finnish in Finland; GBR, British in England and Scotland; IBS, Iberian populations in Spain; TSI, Toscani in Italy; ACB, African Caribbeans in Barbados; ASW, African Ancestry in Southwest USA; ESN, Esan in Nigeria; GWD, Gambian in Western Divisions, The Gambia; LWK, Luhya in Webuye, Kenya; MSL, Mende in Sierra Leone; YRI, Yoruba in Ibadan, Nigeria; CLM, Colombian in Medellin, Colombia; MXL, Mexican Ancestry in Los Angeles, Colombia; PEL, Peruvian in Lima, Peru; PUR, Puerto Rican in Puerto Rico.

AMR				EUR					SAS				
CLM	MXL	PEL	PUR	CEU	FIN	GBR	IBS	TSI	BEB	GIH	ITU	PJL	STU
1.21E-02	-	-	**2.65E-05**	2.04E-02	**1.90E-04**	1.08E-01	3.40E-02	2.56E-02	-	-	3.48E-01	-	-
3.38E-01	2.39E-01	1.87E-01	**1.21E-04**	4.49E-01	**1.68E-05**	2.10E-01	2.35E-02	1.40E-01	6.40E-01	2.24E-01	4.11E-01	9.66E-01	7.87E-02
-	-	-	1.68E-03	-	**4.17E-04**	1.96E-02	-	-	-	-	3.37E-03	-	-
4.94E-03	9.26E-01	4.35E-02	**1.27E-04**	4.24E-01	7.04E-04	1.34E-03	3.79E-03	9.42E-03	3.69E-02	2.27E-01	**4.62E-07**	**3.45E-04**	**2.02E-06**
1.05E-01	5.22E-01	**1.17E-05**	2.04E-01	1.17E-02	3.07E-03	5.15E-02	3.91E-01	3.71E-01	**6.95E-05**	**2.89E-05**	**3.85E-09**	**1.46E-05**	**1.55E-07**
4.82E-05	**2.07E-04**	8.95E-02	**2.63E-06**	1.31E-01	**8.44E-09**	1.93E-02	**4.50E-04**	**4.15E-04**	8.23E-03	**2.20E-11**	**1.36E-09**	**2.54E-08**	3.94E-03
2.43E-04	1.10E-02	**3.31E-04**	5.83E-02	**7.08E-04**	2.97E-01	1.72E-01	2.95E-02	1.07E-01	**2.93E-04**	**7.46E-04**	4.78E-03	**2.85E-08**	**1.27E-04**
2.31E-19	**3.44E-19**	**6.57E-17**	**1.57E-18**	**5.14E-15**	**2.82E-09**	**2.64E-12**	**2.26E-13**	**2.04E-16**	**1.85E-15**	**1.81E-15**	**1.45E-14**	**1.54E-19**	**8.50E-18**
-	-	-	1.04E-02	1.17E-01	3.46E-01	5.18E-02	3.79E-01	1.81E-01	-	**2.70E-04**	-	3.54E-02	3.90E-02
2.59E-01	-	-	-	-	2.52E-01	-	-	1.40E-01	-	-	-	-	3.74E-01
1.35E-06	-	**7.60E-06**	-	**1.86E-04**	**1.93E-12**	**7.75E-09**	**8.41E-05**	**5.43E-06**	**2.13E-09**	**3.72E-21**	**1.14E-13**	**2.03E-12**	**4.44E-10**
3.00E-01	5.77E-03	1.01E-03	7.37E-02	4.91E-01	8.12E-01	9.21E-01	8.69E-01	9.45E-01	5.86E-01	6.13E-01	9.64E-03	5.24E-02	2.10E-02
2.06E-01	7.26E-01	7.37E-01	8.76E-02	1.87E-01	2.69E-02	4.91E-01	1.97E-03	**3.84E-04**	3.01E-01	1.82E-03	7.00E-02	6.51E-02	1.89E-02
3.07E-11	**1.47E-05**	9.00E-01	**1.48E-11**	**7.58E-23**	**2.46E-16**	**6.64E-22**	**8.18E-22**	**1.68E-18**	**1.70E-05**	**9.43E-12**	**7.47E-16**	**7.52E-15**	**3.18E-08**
2.15E-03	**6.10E-05**	7.92E-02	**2.88E-11**	**1.86E-18**	**1.08E-18**	**1.12E-13**	**1.17E-06**	**4.24E-07**	5.59E-02	**2.48E-05**	**8.45E-04**	**3.94E-08**	**4.51E-09**
3.35E-07	**2.33E-09**	**1.47E-04**	**4.23E-08**	**6.36E-04**	1.68E-03	**7.13E-04**	**3.69E-04**	**2.60E-04**	**1.58E-14**	**5.94E-13**	**1.05E-13**	**1.75E-12**	**2.07E-13**
9.71E-04	3.29E-01	9.02E-03	7.93E-03	**2.45E-21**	**2.74E-19**	**7.98E-19**	**3.97E-16**	**7.62E-19**	1.13E-01	2.75E-02	7.51E-02	5.52E-01	1.51E-01
9.01E-38	**1.58E-38**	-	**2.64E-37**	**2.71E-32**	**8.05E-41**	**8.46E-37**	**3.53E-36**	**1.52E-33**	**7.44E-30**	**4.15E-39**	**2.84E-33**	**3.31E-36**	**2.65E-35**
1.59E-02	**8.10E-06**	**8.44E-10**	4.94E-03	1.43E-02	1.21E-01	**3.97E-04**	7.38E-03	1.40E-01	1.91E-02	1.39E-01	9.23E-03	1.17E-01	2.23E-02
1.59E-05	1.23E-01	7.97E-03	5.57E-02	**2.57E-08**	**4.56E-05**	7.76E-03	**4.21E-04**	4.40E-03	1.75E-01	**3.57E-04**	**1.00E-05**	**4.48E-04**	**4.01E-04**
2.81E-03	9.50E-04	**3.42E-06**	**4.03E-04**	**2.61E-04**	**6.17E-04**	**3.32E-04**	4.74E-03	**5.44E-04**	1.08E-01	7.79E-01	2.18E-01	4.49E-01	5.39E-01
1.20E-19	**3.04E-17**	**3.71E-13**	**2.07E-20**	**1.67E-23**	**1.31E-25**	**2.01E-25**	**1.96E-28**	**1.39E-24**	**1.80E-17**	**4.68E-17**	**5.09E-18**	**5.22E-23**	**1.73E-13**
3.82E-17	**3.51E-15**	**2.39E-11**	**1.51E-16**	**5.68E-22**	**9.29E-23**	**1.43E-22**	**7.70E-27**	**2.95E-23**	**4.47E-15**	**2.36E-13**	**6.28E-15**	**1.19E-18**	**2.19E-11**
2.06E-01	**6.83E-04**	**1.31E-07**	3.90E-02	2.42E-01	3.02E-01	1.55E-01	7.65E-01	8.14E-01	6.98E-01	9.10E-02	5.47E-01	3.10E-01	1.36E-02
6.68E-19	**5.81E-20**	**5.69E-12**	**4.96E-19**	**1.05E-20**	**2.87E-22**	**1.08E-22**	**3.74E-27**	**7.83E-24**	**1.28E-18**	**8.11E-16**	**6.73E-17**	**2.31E-22**	**3.00E-14**
9.61E-03	4.38E-01	4.63E-02	3.08E-02	**7.69E-08**	**7.48E-05**	**1.18E-05**	**2.32E-05**	**9.66E-07**	1.38E-01	1.12E-03	2.51E-03	2.75E-03	2.27E-02
3.15E-04	3.73E-02	6.55E-01	3.32E-03	**9.05E-05**	**4.08E-06**	**1.81E-06**	**3.86E-09**	**5.79E-05**	**1.41E-04**	**1.40E-07**	**7.46E-06**	**3.73E-10**	**8.61E-09**
1.93E-15	**4.49E-10**	**1.08E-06**	**5.41E-14**	**3.73E-23**	**2.13E-18**	**2.35E-17**	**3.96E-19**	**4.46E-20**	**4.25E-15**	**3.21E-22**	**6.81E-20**	**4.10E-15**	**3.43E-14**
2.31E-05	**7.80E-04**	-	**3.52E-09**	**2.98E-13**	**2.69E-12**	**8.44E-14**	**1.78E-12**	**1.36E-12**	-	**6.49E-06**	**4.16E-06**	**3.07E-06**	**7.37E-06**
1.28E-02	1.41E-01	**1.07E-04**	8.15E-02	9.76E-02	3.79E-01	1.98E-01	7.60E-02	2.40E-03	6.66E-03	1.52E-03	**5.34E-05**	**3.91E-04**	**6.82E-07**
1.15E-01	7.85E-01	3.42E-01	5.35E-01	8.88E-02	2.35E-01	5.32E-02	7.77E-03	3.01E-02	**1.04E-04**	**2.08E-05**	2.44E-03	5.39E-03	1.10E-03
-	-	-	-	-	-	-	-	-	-	-	-	-	-
2.01E-13	**4.96E-12**	**1.43E-17**	**2.60E-05**	**4.80E-12**	**4.84E-11**	**7.46E-08**	**1.66E-06**	**8.49E-06**	**2.97E-06**	**5.61E-10**	**2.88E-08**	**3.10E-06**	1.45E-03
5.08E-04	1.62E-02	**1.88E-06**	3.27E-03	**2.05E-04**	7.93E-01	1.58E-03	6.95E-01	**7.96E-04**	2.62E-02	2.34E-02	1.80E-02	2.56E-01	1.44E-03
8.49E-01	4.02E-01	2.24E-01	1.23E-01	1.15E-01	5.41E-03	2.83E-03	**5.36E-04**	4.01E-02	**2.37E-04**	**3.39E-05**	**3.80E-05**	**7.53E-05**	**1.09E-05**
8.39E-02	5.48E-02	5.67E-02	1.32E-01	1.63E-01	4.00E-02	1.38E-02	3.77E-03	8.79E-02	1.57E-03	**3.24E-04**	**3.55E-04**	**6.19E-04**	**1.10E-04**
7.89E-16	**2.51E-14**	**2.09E-14**	**8.49E-15**	**7.98E-12**	**2.72E-10**	**2.28E-06**	**8.94E-07**	**1.62E-09**	**5.68E-18**	**7.09E-24**	**8.52E-18**	**2.80E-13**	**2.38E-18**
4.86E-02	9.13E-01	5.97E-01	**1.77E-04**	3.06E-02	6.61E-02	1.49E-01	2.85E-01	4.58E-03	1.50E-01	2.79E-01	1.94E-01	1.53E-01	4.12E-01
1.04E-04	**1.72E-16**	**2.61E-12**	**3.68E-10**	**1.21E-18**	**2.33E-23**	**7.54E-09**	**1.51E-17**	**3.22E-10**	**1.18E-17**	**3.00E-19**	**4.27E-19**	**2.69E-19**	**1.72E-11**
-	-	-	-	7.13E-02	-	-	-	-	-	**7.46E-13**	-	-	4.77E-08
1.43E-17	**1.12E-21**	**1.91E-18**	**1.43E-14**	**1.32E-23**	**2.11E-21**	**4.11E-26**	**8.88E-25**	**7.30E-28**	**1.32E-11**	**1.75E-13**	**1.96E-10**	**1.62E-19**	**2.33E-13**
2.59E-20	**1.29E-16**	**1.67E-10**	**6.90E-27**	**3.02E-27**	**5.07E-41**	**8.95E-31**	**5.06E-28**	**4.06E-33**	**3.49E-12**	**8.41E-13**	**5.15E-12**	**2.47E-17**	**1.47E-14**
1.18E-01	9.46E-03	4.26E-02	7.11E-02	1.30E-01	1.15E-02	1.01E-01	**1.87E-04**	**3.26E-05**	**6.78E-07**	**2.63E-10**	**3.58E-09**	**5.35E-09**	**4.15E-12**
1.20E-08	9.89E-03	4.64E-01	**7.02E-15**	**3.98E-27**	**7.17E-20**	**4.64E-26**	**1.52E-23**	**2.03E-17**	7.03E-01	4.30E-01	5.99E-01	2.99E-02	2.52E-01
1.31E-13	**8.50E-13**	**3.16E-05**	**1.52E-20**	**1.43E-18**	**4.47E-14**	**5.33E-18**	**6.25E-20**	**1.09E-20**	**1.75E-32**	**5.10E-25**	**6.27E-31**	**1.42E-27**	**1.49E-38**
1.72E-13	**1.78E-06**	2.44E-03	**5.15E-14**	**1.09E-14**	**4.56E-13**	**3.25E-12**	**9.62E-12**	**4.06E-17**	**2.53E-09**	**2.56E-13**	**6.97E-11**	**1.27E-09**	**9.22E-09**
2.72E-28	**1.77E-33**	**4.86E-41**	**7.35E-28**	**2.28E-29**	**1.16E-23**	**1.08E-30**	**4.98E-27**	**4.26E-30**	**3.76E-28**	**6.58E-27**	**2.23E-34**	**5.37E-29**	**8.21E-28**
3.38E-09	**2.86E-05**	3.72E-01	**5.61E-11**	**1.90E-12**	**8.53E-12**	1.67E-14	**3.12E-15**	**1.67E-24**	4.82E-01	5.48E-05	5.94E-02	**2.46E-05**	1.62E-03
2.88E-04	1.54E-03	2.06E-01	**7.88E-05**	8.67E-03	2.43E-02	**4.99E-04**	**2.80E-09**	**1.41E-06**	**6.00E-11**	**6.61E-13**	**2.18E-10**	**6.11E-10**	**9.78E-12**
5.66E-44	**1.39E-42**	**1.35E-55**	**1.54E-44**	**1.21E-44**	**1.84E-49**	-	**7.51E-35**	**1.34E-39**	**6.52E-45**	**1.47E-46**	**1.85E-42**	**3.34E-42**	**2.80E-46**
6.33E-06	**6.22E-04**	**8.59E-05**	**7.64E-06**	**4.51E-05**	1.60E-01	**1.13E-05**	**2.79E-05**	**2.94E-04**	1.23E-01	2.95E-01	2.20E-02	2.34E-01	2.20E-02
7.46E-18	**4.53E-25**	**1.55E-24**	**1.90E-17**	**2.01E-18**	**1.54E-17**	**2.72E-23**	**5.20E-22**	**1.00E-18**	**4.21E-16**	**1.89E-18**	**4.75E-17**	**3.15E-16**	**3.93E-20**
9.92E-09	**1.92E-15**	**2.65E-15**	**3.14E-09**	**1.12E-10**	**8.19E-09**	**8.43E-14**	**1.17E-10**	**1.40E-10**	**8.78E-06**	**5.30E-07**	**4.94E-09**	**7.81E-09**	**8.11E-09**
1.43E-09	**1.98E-14**	**1.99E-12**	**1.82E-09**	**5.01E-06**	**1.35E-08**	**5.87E-15**	**1.13E-12**	**1.30E-10**	**7.51E-08**	**1.48E-09**	**4.33E-10**	**5.09E-12**	**3.51E-11**
5.66E-44	**1.58E-39**	**9.87E-53**	**7.74E-47**	**2.41E-34**	**1.99E-45**	**2.51E-38**	**3.61E-43**	**1.34E-39**	**4.53E-39**	**1.68E-43**	**1.02E-41**	**1.23E-48**	**2.80E-46**

Table 3 The Minor Allele Frequency Distribution of Seven SNPs Among 27 Populations

Geographic Region	Population	rs750155-C	rs1800764-C	rs4291-A	rs1051298-G	rs1051296-A	rs1131596-A	rs1065852-A
EAS	Blang	0.233	0.183	0.503	0.458	0.435	0.488	0.500
	CDX	0.500	0.366	0.640	0.430	0.425	0.538	0.629
	CHB	0.602	0.311	0.699	0.500	0.490	0.476	0.602
	CHS	0.486	0.333	0.676	0.424	0.424	0.533	0.614
	JPT	0.639	0.447	0.563	0.438	0.438	0.543	0.361
	KHV	0.535	0.348	0.652	0.389	0.399	0.540	0.662
SAS	BEB	0.750	0.390	0.645	0.436	0.483	0.390	0.256
	GIH	0.636	0.451	0.592	0.408	0.471	0.393	0.150
	ITU	0.716	0.407	0.637	0.456	0.539	0.397	0.172
	PJL	0.682	0.391	0.651	0.490	0.516	0.422	0.104
	STU	0.794	0.377	0.667	0.436	0.495	0.431	0.152
EUR	CEU	0.566	0.470	0.626	0.596	0.596	0.429	0.242
	FIN	0.505	0.449	0.641	0.540	0.540	0.455	0.146
	GBR	0.560	0.434	0.659	0.593	0.593	0.401	0.247
	IBS	0.579	0.425	0.636	0.472	0.477	0.523	0.173
	TSI	0.589	0.505	0.584	0.561	0.565	0.449	0.206
AFR	ACB	0.578	0.854	0.641	0.370	0.427	0.724	0.146
	ASW	0.631	0.787	0.705	0.451	0.533	0.623	0.156
	ESN	0.682	0.919	0.677	0.485	0.551	0.646	0.091
	GWD	0.735	0.942	0.580	0.363	0.509	0.774	0.115
	LWK	0.636	0.874	0.702	0.460	0.475	0.763	0.035
	MSL	0.659	0.953	0.629	0.412	0.482	0.741	0.165
	YRI	0.667	0.944	0.616	0.435	0.514	0.722	0.106
AMR	CLM	0.489	0.457	0.654	0.527	0.527	0.495	0.186
	MXL	0.492	0.313	0.750	0.641	0.641	0.352	0.148
	PEL	0.165	0.224	0.824	0.594	0.600	0.371	0.071
	PUR	0.582	0.462	0.688	0.538	0.543	0.438	0.178

Note: Loci with minor allele frequency (MAF) > 0.05 could be considered into this study.

Abbreviations: EAS, East Asian; SAS, South Asian; EUR, European; AFR, African; AMR, American; CDX, Chinese Dai in Xishuangbanna, China; CHB, Han Chinese in Beijing, China; CHS, Southern Han Chinese, China; JPT, Japanese in Tokyo, Japan; KHV, Kinh in Ho Chi Minh City, Vietnam; BEB, Bengali in Bangladesh; GIH, Gujarati Indian in Houston, Texas; ITU, Indian Telugu in the UK; PJL, Punjabi in Lahore, Pakistan; STU, Sri Lankan Tamil in the UK; CEU, Western European ancestry; FIN, Finnish in Finland; GBR, British in England and Scotland; IBS, Iberian populations in Spain; TSI, Toscani in Italy; ACB, African Caribbeans in Barbados; ASW, African Ancestry in Southwest USA; ESN, Esan in Nigeria; GWD, Gambian in Western Divisions, The Gambia; LWK, Luhya in Webuye, Kenya; MSL, Mende in Sierra Leone; YRI, Yoruba in Ibadan, Nigeria; CLM, Colombian in Medellin, Colombia; MXL, Mexican Ancestry in Los Angeles, Colombia; PEL, Peruvian in Lima, Peru; PUR, Puerto Rican in Puerto Rico.

Reduced folate carrier protein 1 (RFC1), encoded by *SLC19A1*, is a high-capacity, bidirectional transporter of 5-methyl-tetrahydrofolate and thiamine monophosphate. RFC1 is involved in the uptake, homeostasis, folate deficiency as well as the transportation and sensitivity of antifolate chemotherapeutic agents, such as methotrexate.[48–50] The SNPs rs1051298 and rs1051296 are intron variants, and rs1131596 is the missense variant of *SLC19A1*. Scholars have postulated genotype (AA + AG) of rs1051298 to be associated with reduced overall survival upon treatment with pemetrexed in people with non-small-cell lung cancer or mesothelioma compared with that with genotype GG.[51] In addition, allele G of rs1051298 has been reported to be associated with longer progression-free survival after treatment with bevacizumab and pemetrexed in patients with lung neoplasms compared with that with allele A of rs1051298.[52] Besides, the SNP rs1051296 is associated with higher plasma concentrations of methotrexate in pediatric patients with acute lymphoblastic leukemia.[53] Evidence suggests that rs1131596 variants have a positive effect on methotrexate toxicity.[54] Research has shown that the SNP rs1131596-G is not associated with alteration of the concentration or side-effects of methotrexate treatment compared with that of the SNP rs1131596-A in Chinese children with precursor cell lymphoblastic leukemia/lymphoma and people with rheumatoid arthritis.[55] In our study, the genotype distribution of rs1051298, rs1051296,

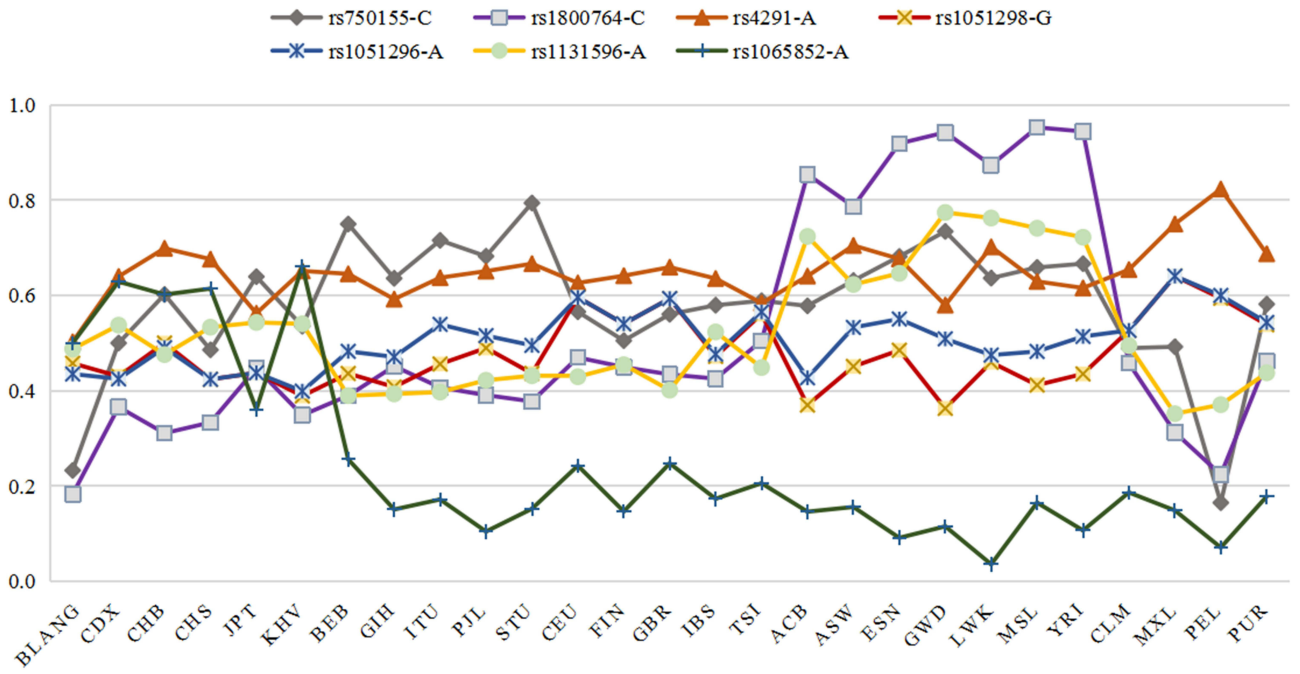

Figure 1 The minor allele frequency (MAF) distribution of seven significantly different SNPs between Blang population and other 26 populations. The value of the Y axis represents the MAF.

and rs1131596 in the Blang population was significantly different from that of the other 26 populations. MAF analyses showed that rs1051298 (*SLC19A1*), and rs1051296 (*SLC19A1*) showed relatively less fluctuation between the Blang population and the other 26 populations, even though the MAF of rs1131596 (*SLC19A1*) in the AFR population showed a distinct difference when compared with that of the Blang population. These observations suggested that pharmacogenomic research of variants of rs1051298, rs1051296 and rs1131596 may help to provide guidance for individualized drug use for the Blang population.

CYP2D6, encoded by *CYP2D6*, is an enzyme of the cytochrome P450 superfamily. It is involved in the metabolism of ≤25% of drugs in common use in the clinic.[56] Debrisoquine and sparteine are *CYP2D6* variation-related drugs.[57] The genetic variation of *CYP2D6* has been reported to be closely related to the metabolism of antipsychotic, antiarrhythmic and antiepileptic drugs.[58–60] The SNP rs1065852 is an intron variant of *CYP2D6*. It is related to alteration of the encoded amino acids of CYP2D6 protein, reduction of CYP2D6 activity and to have a "poor metabolizer" phenotype.[61] In addition, the genotype GG of rs1065852 (*CYP2D6*) is a factor of increased corrected QT (QTc) interval after treatment with iloperidone in people suffering from schizophrenia.[61] The distribution of rs1065852 (*CYP2D6*) has been shown to be significantly different in a Zhuang population as compared with that in 11 other ethnic groups by Liu et al.[3] In the present study, the genotype distribution of rs1065852 (*CYP2D6*) was different in the Blang population when compared with that in all other ethnic groups except for the LWK population, and the MAF distribution showed the largest fluctuation between the Blang population and SAS, EUR, AFR and AMR populations. Hence, the different corrected QTc interval may occur in schizophrenia patients of Blang ethnicity upon treatment with iloperidone. All the above evidence indicated the non-negligible roles of CYP2D6 (rs1065852) in effective drug usage and normal drug metabolism in Blang individuals.

We provided information on the genetic polymorphisms of VIP variants in the Blang population from Yunnan Province. Nevertheless, the sample size was small: a much larger sample size is needed to verify our results.

Conclusions

The genotype distribution of five SNPs (rs750155 (*SULT1A1*), rs4291 (*ACE*), rs1051298 (*SLC19A1*), rs1051296 (*SLC19A1*) and rs1131596 (*SLC19A1*)) was significantly different in the Blang population compared with that in the other 26 populations tested. Two SNPs

(rs1800764 (*ACE*) and rs1065852 (*CYP2D6*)) showed a significantly different genotype distribution in the Blang population as compared with all other populations tested except for PEL and LWK populations, respectively. The MAF of rs1065852 (*CYP2D6*) and rs750155 (*SULT1A1*) showed the largest fluctuation between the Blang population and SAS, EUR, AFR and AMR populations. Our data can provide theoretical guidance for safe and efficacious personalized drug use in the Blang population.

Abbreviations

VIPs, very important pharmacogenes; BP, Blang population; GD, genotype distribution; CDX, Chinese Dai in Xishuangbanna, China; CHB, Han Chinese in Beijing, China; CHS, Southern Han Chinese, China; JPT, Japanese in Tokyo, Japan; KHV, Kinh in Ho Chi Minh City, Vietnam; BEB, Bengali in Bangladesh; GIH, Gujarati Indian in Houston, Texas; ITU, Indian Telugu in the UK; PJL, Punjabi in Lahore, Pakistan; STU, Sri Lankan Tamil in the UK; CEU, Western European ancestry; FIN, Finnish in Finland; GBR, British in England and Scotland; IBS, Iberian populations in Spain; TSI, Toscani in Italy; ACB, African Caribbeans in Barbados; ASW, African Ancestry in Southwest USA; ESN, Esan in Nigeria; GWD, Gambian in Western Divisions, The Gambia; LWK, Luhya in Webuye, Kenya; MSL, Mende in Sierra Leone; YRI, Yoruba in Ibadan, Nigeria; CLM, Colombian in Medellin, Colombia; MXL, Mexican Ancestry in Los Angeles, Colombia; PEL, Peruvian in Lima, Peru; PUR, Puerto Rican in Puerto Rico; LD, linkage disequilibrium; MTX, methotrexate; SULT1A1, sulfotransferase family 1A member 1; ACE, angiotensin I-converting enzyme; SLC19A1,solute carrier family 19 Member 1; CYP2D6, cytochrome P450 family 2 subfamily D member 6; VKORC, vitamin K epoxide reductase complex; CYP2C9, cytochrome P450 family 2 subfamily C member 9; DRD2, dopamine receptor D2; RFC1, reduced folate carrier protein 1; PCR, polymerase chain reaction; MAF, minor allele frequency; SNP, single-nucleotide polymorphism; PharmGKB, Pharmacogenomics Knowledge Base; SAS, South Asian; EUR, European; AFR, African; AMR, American.

Data Sharing Statement

All relevant data are available within the manuscript. Scholars interested in other information from this study should contact the corresponding author.

Ethics Approval and Consent to Participate

All experiments were conducted in accordance with the Declaration of Helsinki 1964 and its later amendments. Each participant provided written informed consent before study commencement. The study protocol was approved (2019-12) by the Ethics Committee of Xizang Minzu University.

Acknowledgments

We express our thanks to all study participants. We also thank the clinicians and hospital staff who worked on sample/data collection in this study.

Author Contributions

This work was performed in collaboration between all authors. YLW and LNP carried out the draft and improvement of the manuscript. HYL, ZHZ and SSX designed the tables and figures. DDL and CJH performed the SNP genotyping analysis. TBJ and LW conceived of the study, worked on associated data collection and statistical analysis, participated in the coordination and funded of the study. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. YLW and LNP contributed equally to this article. Yuliang Wang and Linna Peng are co-first authors.

Funding

The study was supported by the Talent Development Supporting Project entitled Tibet-Shaanxi Himalaya of Xizang Minzu University (2020 Plateau Scholar), Major Science and Technology Research Projects of Xizang (Tibet) Autonomous Region (2015XZ01G23), and Natural Science Foundation of Tibet Autonomous Region (2015ZR-13-19).

Disclosure

The authors declare that they have no competing interests.

References

1. Kalow W, Tang BK, Endrenyi L. Hypothesis: comparisons of inter- and intra-individual variations can substitute for twin studies in drug research. *Pharmacogenetics*. 1998;8(4):283–289. doi:10.1097/00008571-199808000-00001

2. Zhou SF, Liu JP, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. *Drug Metab Rev*. 2009;41(2):89–295. doi:10.1080/03602530902843483
3. Liu Y, Li H, Cao K, et al. Genetic variation of pharmacogenomic VIP variants in Zhuang nationality of southern China. *Pharmacogenomics J*. 2021;21(1):60–68. doi:10.1038/s41397-020-0177-y
4. He C, Peng L, Xing S, Li D, Wang L, Jin T. Population genetic difference of pharmacogenomic VIP variants in the Tibetan population. *Pharmgenomics Pers Med*. 2021;14:1027–1040. doi:10.2147/PGPM.S316711
5. Cecchin E, Stocco G. Pharmacogenomics and personalized medicine. *Genes*. 2020;11(6):679–683. doi:10.3390/genes11060679
6. Barbarino JM, Whirl-Carrillo M, Altman RB, Klein TE. PharmGKB: a worldwide resource for pharmacogenomic information. *Wiley Interdiscip Rev Syst Biol Med*. 2018;10(4):1–13.
7. Bader LA, Elewa H, Novelli G. The impact of genetic and non-genetic factors on warfarin dose prediction in MENA region: a systematic review. *PLoS One*. 2016;11(12):1–15. doi:10.1371/journal.pone.0168732
8. Kim GJ, Lee SY, Park JH, Ryu BY, Kim JH. Role of preemptive genotyping in preventing serious adverse drug events in south Korean patients. *Drug Safe*. 2017;40(1):65–80. doi:10.1007/s40264-016-0454-5
9. Arbitrio M, Scionti F, Di Martino MT, et al. Pharmacogenomics biomarker discovery and validation for translation in clinical practice. *Clin Transl Sci*. 2021;14(1):113–119. doi:10.1111/cts.12869
10. Wang B, Hu W, Wang J, et al. HLA-DPB1 polymorphism in Blang and Puyi ethnic groups of southwest China inferred from sequence-based typing. *Tissue Antigens*. 2008;71(1):81–84. doi:10.1111/j.1399-0039.2007.00963.x
11. Zeng WM, Yang J, Dong YL, et al. The frequency distribution of flavin-containing monooxygenase 3 mutant alleles in 28 populations from Yunnan. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*. 2003;20(4):318–321.
12. Li L, Zhang Y, Wang W, et al. Allele frequencies of 20 autosomal STR loci for 207 unrelated individuals of the Blang people in China. *Int J Legal Med*. 2020;134(3):987–988. doi:10.1007/s00414-019-02192-0
13. Zhang C, Guo W, Cheng Y, et al. Genetic analysis of pharmacogenomic VIP variants in the Blang population from Yunnan Province of China. *Mol Genet Genom Med*. 2019;7(5):1–17. doi:10.1002/mgg3.574
14. Rosmarin D, Palles C, Pagnamenta A, et al. A candidate gene study of capecitabine-related toxicity in colorectal cancer identifies new toxicity variants at DPYD and a putative role for ENOSF1 rather than TYMS. *Gut*. 2015;64(1):111–120. doi:10.1136/gutjnl-2013-306571
15. Fritsche E, Baek SJ, King LM, Zeldin DC, Eling TE, Bell DA. Functional characterization of cyclooxygenase-2 polymorphisms. *J Pharmacol Exp Ther*. 2001;299(2):468–476.
16. Pan R, Qi X, Wang F, Chong Y, Li X, Chen Q. Correlations of calcium voltage-gated channel subunit alpha1 A (CACNA1A) gene polymorphisms with benign paroxysmal positional vertigo. *Med Sci Monit*. 2019;25:946–951. doi:10.12659/MSM.912359
17. Klein A, Lillis S, Munteanu I, et al. Clinical and genetic findings in a large cohort of patients with ryanodine receptor 1 gene-associated myopathies. *Hum Mutat*. 2012;33(6):981–988. doi:10.1002/humu.22056
18. Saloner R, Paolillo EW, Kohli M, et al. Genetic variation in alcohol dehydrogenase is associated with neurocognition in men with HIV and history of alcohol use disorder: preliminary findings. *J Neurovirol*. 2020;26(2):214–225. doi:10.1007/s13365-019-00825-z
19. Li L, Shen C, Yao Z, Liang J, Huang C. Genetic variants of potassium voltage-gated channel genes (KCNQ1, KCNH2, and KCNE1) affected the risk of atrial fibrillation in elderly patients. *Genet Test Mol Biomarkers*. 2015;19(7):359–365. doi:10.1089/gtmb.2014.0307
20. Song Y, Qi X, Liu X. N-acetyltransferase 2 polymorphism is associated with bladder cancer risk: an updated meta-analysis based on 54 case-control studies. *Gene*. 2020;757:1–39.
21. Stoffel M, Espinosa R, Powell KL, Philipson LH, Le Beau MM, Bell GI. Human G-protein-coupled inwardly rectifying potassium channel (GIRK1) gene (KCNJ3): localization to chromosome 2 and identification of a simple tandem repeat polymorphism. *Genomics*. 1994;21(1):254–256. doi:10.1006/geno.1994.1253
22. Parry DA, Smith CE, El-Sayed W, et al. Mutations in the pH-sensing G-protein-coupled receptor GPR68 cause amelogenesis imperfecta. *Am J Hum Genet*. 2016;99(4):984–990. doi:10.1016/j.ajhg.2016.08.020
23. Collins KS, Metzger IF, Gufford BT, et al. Influence of uridine diphosphate glucuronosyltransferase family 1 member A1 and solute carrier organic anion transporter family 1 member B1 polymorphisms and efavirenz on bilirubin disposition in healthy volunteers. *Drug Metab Dispos*. 2020;48(3):169–175. doi:10.1124/dmd.119.089052
24. Zimmer V, Liebe R, Lammert F. Nuclear receptor variants in liver disease. *Dig Dis*. 2015;33(3):415–419. doi:10.1159/000371695
25. Arslan S, Silig Y, Pinarbasi H. Sulfotransferase 1A1 Arg(213)His polymorphism and prostate cancer risk. *Exp Ther Med*. 2011;2(6):1159–1162. doi:10.3892/etm.2011.334
26. Muminovic Umihanic M, Babic R, Kravic N, et al. Associations between polymorphisms in the solute carrier family 6 member 3 and the myelin basic protein gene and posttraumatic stress disorder. *Psychiatr Danub*. 2019;31(2):235–240. doi:10.24869/psyd.2019.235
27. Cambien F, Evans A. Angiotensin I converting enzyme gene polymorphism and coronary heart disease. *Eur Heart J*. 1995;16(Suppl K):13–22. doi:10.1093/eurheartj/16.suppl_K.13
28. Gabriel S, Ziaugra L, Tabbaa D. SNP genotyping using the Sequenom massARRAY iPLEX platform. *Curr Protocols Human Genet*. 2009;Chapter 2:Unit2.12.
29. Thomas RK, Baker AC, Debiasi RM, et al. High-throughput oncogene mutation profiling in human cancer. *Nat Genet*. 2007;39(3):347–351. doi:10.1038/ng1975
30. Nowell S, Falany CN. Pharmacogenetics of human cytosolic sulfotransferases. *Oncogene*. 2006;25(11):1673–1678. doi:10.1038/sj.onc.1209376
31. Daniels J, Kadlubar S. Pharmacogenetics of SULT1A1. *Pharmacogenomics*. 2014;15(14):1823–1838. doi:10.2217/pgs.14.134
32. Carlini EJ, Raftogianis RB, Wood TC, et al. Sulfation pharmacogenetics: SULT1A1 and SULT1A2 allele frequencies in Caucasian, Chinese and African-American subjects. *Pharmacogenetics*. 2001;11(1):57–68. doi:10.1097/00008571-200102000-00007
33. Kim KA, Lee SY, Park PW, Ha JM, Park JY. Genetic polymorphisms and linkage disequilibrium of sulfotransferase SULT1A1 and SULT1A2 in a Korean population: comparison of other ethnic groups. *Eur J Clin Pharmacol*. 2005;61(10):743–747. doi:10.1007/s00228-005-0989-3
34. Moyer AM, de Andrade M, Weinshilboum RM, Miller VM. Influence of SULT1A1 genetic variation on age at menopause, estrogen levels, and response to hormone therapy in recently postmenopausal white women. *Menopause (New York, NY)*. 2016;23(8):863–869. doi:10.1097/GME.0000000000000648
35. Innocenti F, Ramírez J, Obel J, et al. Preclinical discovery of candidate genes to guide pharmacogenetics during Phase I development: the example of the novel anticancer agent ABT-751. *Pharmacogenet Genomics*. 2013;23(7):374–381. doi:10.1097/FPC.0b013e3283623e81
36. de Oliveira FF, Bertolucci PH, Chen ES, Smith MC. Brain-penetrating angiotensin-converting enzyme inhibitors and cognitive change in patients with dementia due to Alzheimer's disease. *JAD*. 2014;42(Suppl 3):S321–4. doi:10.3233/JAD-132189
37. Rahimi Z. ACE insertion/deletion (I/D) polymorphism and diabetic nephropathy. *J Nephropathol*. 2012;1(3):143–151. doi:10.5812/nephropathol.8109

38. Jeffrey LP. Progression of cardiovascular damage: the role of renin-angiotensin system blockade. *Am J Cardiol*. 2010;1 (Suppl105):1–11.
39. de Oliveira FF, Chen ES, Smith MC, Bertolucci PHF. Pharmacogenetics of angiotensin-converting enzyme inhibitors in patients with Alzheimer's disease dementia. *Curr Alzheimer Res*. 2018;15(4):386–398. doi:10.2174/1567205014666171016101816
40. Rebaï M, Kharrat N, Ayadi I, Rebaï A. Haplotype structure of five SNPs within the ACE gene in the Tunisian population. *Ann Hum Biol*. 2006;33(3):319–329. doi:10.1080/03014460600621977
41. Kharrat N, Abdelmouleh W, Abdelhedi R, Alfadhli S, Rebai A. The linkage disequilibrium pattern of the angiotensin converting enzyme gene in Arabic and Asian population groups. *Ann Hum Biol*. 2012;39 (6):538–540. doi:10.3109/03014460.2012.713509
42. Ding P, Yang Y, Ding S, Sun B. Synergistic association of six well-characterized polymorphisms in three genes of the renin-angiotensin system with breast cancer among Han Chinese women. *JRAAS*. 2015;16(4):1232–1239. doi:10.1177/1470320314542828
43. Su SL, Yang HY, Wu CC, et al. Gene-gene interactions in renin-angiotensin-aldosterone system contributes to end-stage renal disease susceptibility in a Han Chinese population. *Sci World J*. 2014;2014:1–10.
44. Miners S, Ashby E, Baig S, et al. Angiotensin-converting enzyme levels and activity in Alzheimer's disease: differences in brain and CSF ACE and association with ACE1 genotypes. *Am J Transl Res*. 2009;1(2):163–177.
45. Kim TH, Chang HS, Park SM, et al. Association of angiotensin I-converting enzyme gene polymorphisms with aspirin intolerance in asthmatics. *Clin Exp Allergy*. 2008;38(11):1727–1737. doi:10.1111/j.1365-2222.2008.03082.x
46. Ezzidi I, Mtiraoui N, Kacem M, Chaieb M, Mahjoub T, Almawi WY. Identification of specific angiotensin-converting enzyme variants and haplotypes that confer risk and protection against type 2 diabetic nephropathy. *Diabetes Metab Res Rev*. 2009;25(8):717–724. doi:10.1002/dmrr.1006
47. Ferreira de Oliveira F, Berretta JM, Suchi Chen E, Cardoso Smith M, Ferreira Bertolucci PH. Pharmacogenetic effects of angiotensin-converting enzyme inhibitors over age-related urea and creatinine variations in patients with dementia due to Alzheimer disease. *Colombia medica (Cali, Colombia)*. 2016;47(2):76–80. doi:10.25100/cm.v47i2.2188
48. Dixon KH, Lanpher BC, Chiu J, Kelley K, Cowan KH. A novel cDNA restores reduced folate carrier activity and methotrexate sensitivity to transport deficient cells. *J Biol Chem*. 1994;269(1):17–20. doi:10.1016/S0021-9258(17)42301-5
49. Westerhof GR, Schornagel JH, Kathmann I, et al. Carrier- and receptor-mediated transport of folate antagonists targeting folate-dependent enzymes: correlates of molecular-structure and biological activity. *Mol Pharmacol*. 1995;48(3):459–471.
50. Ifergan I, Jansen G, Assaraf YG. The reduced folate carrier (RFC) is cytotoxic to cells under conditions of severe folate deprivation. RFC as a double edged sword in folate homeostasis. *J Biol Chem*. 2008;283(30):20687–20695. doi:10.1074/jbc.M802812200
51. Corrigan A, Walker JL, Wickramasinghe S, et al. Pharmacogenetics of pemetrexed combination therapy in lung cancer: pathway analysis reveals novel toxicity associations. *Pharmacogenomics J*. 2014;14 (5):411–417. doi:10.1038/tpj.2014.13
52. Adjei AA, Mandrekar SJ, Dy GK, et al. Phase II trial of pemetrexed plus bevacizumab for second-line therapy of patients with advanced non-small-cell lung cancer: NCCTG and SWOG study N0426. *J Clin OIncol*. 2010;28(4):614–619. doi:10.1200/JCO.2009.23.6406
53. Wang SM, Sun LL, Wu WS, Yan D. MiR-595 suppresses the cellular uptake and cytotoxic effects of methotrexate by targeting SLC19A1 in CEM/C1 cells. *Basic Clin Pharmacol Toxicol*. 2018;123(1):8–13. doi:10.1111/bcpt.12966
54. Chatzikyriakidou A, Georgiou I, Voulgari PV, Papadopoulos CG, Tzavaras T, Drosos AA. Transcription regulatory polymorphism −43T>C in the 5′-flanking region of SLC19A1 gene could affect rheumatoid arthritis patient response to methotrexate therapy. *Rheumatol Int*. 2007;27(11):1057–1061. doi:10.1007/s00296-007-0339-0
55. Liu SG, Gao C, Zhang RD, et al. Polymorphisms in methotrexate transporters and their relationship to plasma methotrexate levels, toxicity of high-dose methotrexate, and outcome of pediatric acute lymphoblastic leukemia. *Oncotarget*. 2017;8(23):37761–37772. doi:10.18632/oncotarget.17781
56. Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. *Pharmacol Ther*. 2007;116(3):496–526.
57. Evans DA, Harmer D, Downham DY, et al. The genetic control of sparteine and debrisoquine metabolism in man with new methods of analysing bimodal distributions. *J Med Genet*. 1983;20(5):321–329. doi:10.1136/jmg.20.5.321
58. Jürgens G, Andersen SE, Rasmussen HB, et al. Effect of routine cytochrome P450 2D6 and 2C19 genotyping on antipsychotic drug persistence in patients with schizophrenia: a randomized clinical trial. *JAMA Netw Open*. 2020;3(12):1–12. doi:10.1001/jamanetworkopen.2020.27909
59. Hamm BS, Rosenthal LJ. Psychiatric aspects of chloroquine and hydroxychloroquine treatment in the wake of Coronavirus disease-2019: psychopharmacological interactions and neuropsychiatric sequelae. *Psychosomatics*. 2020;61(6):597–606. doi:10.1016/j.psym.2020.06.022
60. López-García MA, Feria-Romero IA, Serrano H, et al. Influence of genetic variants of CYP2D6, CYP2C9, CYP2C19 and CYP3A4 on antiepileptic drug metabolism in pediatric patients with refractory epilepsy. *Pharmacolog Rep*. 2017;69(3):504–511. doi:10.1016/j.pharep.2017.01.007
61. Potkin SG, Preskorn S, Hochfeld M, Meng X. A thorough QTc study of 3 doses of iloperidone including metabolic inhibition via CYP2D6 and/or CYP3A4 and a comparison to quetiapine and ziprasidone. *J Clin Psychopharmacol*. 2013;33(1):3–10. doi:10.1097/JCP.0b013e31827c0314