Pharmacogenomics and Personalized Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Analysis of Very Important Pharmacogenomics Variants in the Chinese Lahu Population

Pharmacogenomics and Personalized Medicine downloaded from https://www.dovepress.com/
For personal use only.

Yujing Cheng[1,*]
Qi Li[1,*]
Xin Yang[1]
Heng Ding[2]
Wanlu Chen[1]
Run Dai[1]
Chan Zhang[1]

[1]Department of Blood Transfusion, First People's Hospital of Yunnan, Kunming City, 650021, Yunnan Province, People's Republic of China; [2]Blood Station of Honghe State Center, Honghe Prefecture City, 661100, Yunnan Province, People's Republic of China

*These authors contributed equally to this work

Background: Genetic polymorphism, obviously, has a potential clinical role in determining differences in drug efficacy; however, there are no reports about the pharmacogenomic information of the Lahu population. Therefore, our research aimed to screen the genotypic frequencies of the very important pharmacogenomics (VIP) mutations and determined the differences between Lahu and the other 11 populations.

Methods: Agena MassARRAY (AgenaMassARRAY) single nucleotide polymorphism (SNP) genotyping technique was used to detect 81 VIP mutations of pharmacogenomics genes in Lahu, and their genotypic frequencies were compared with the other major 11 populations. Chi-square tests were used to identify different loci among these populations. Finally, the genetic structure and pairwise Fst values of Lahu and the other 11 populations were analyzed.

Results: We found that the distribution of allele frequencies within different pharmacogenes in Lahu showed significantly different with other populations. Additionally, the pairwise F-statistics (Fst) values and genetic structure revealed the variants in the Lahu population as well were mostly related to the Han Chinese in Beijing, China (CHB) and the Japanese population in Tokyo, Japan (JPT) genetically.

Conclusion: This study will provide a theoretical basis for safe drug use and help to establish the appropriate individualized treatment strategies in the Lahu population.

Keywords: pharmacogenomics, population genetics, Lahu population, VIP variants

Introduction

Pharmacogenomics is an organic combination of molecular pharmacology and gene function. Researchers use information from the entire genome to identify and describe the genetic basis and genetic influence of patients on drug therapy. As the most common type of genetic variation among people, single nucleotide polymorphisms (SNPs) constitute the basis of pharmacogenetics, which means the monogenic variants, which alter the drug response. Most importantly, the SNPs of drug metabolic enzymes and drug transporter genes are important determinants of variation among individual drug metabolites and of human therapeutic responses and disease susceptibility.[1,2] What is more, individual differences in drug reactions and side effects are a major challenge in clinical pharmacology. Therefore, identifying these polymorphisms and understanding how they affect drug response and genetic disease trends are the key to drug genetics research.[3] Pharmacogenomics can enhance the outcome of treatment by adopting pharmacogenomic testing to maximize drug efficacy and minimize the risk of serious adverse events.[4] The most well-known pharmacogenes are cytochrome P450 genes, encoding Phase 1 cytochrome P450 (CYP) or Phase 2 drug-metabolizing enzymes, transporters, drug

Correspondence: Chan Zhang
First People's Hospital of Yunnan, #157 Jinbi Road, Kunming, Yunnan, 650021, People's Republic of China
Email zhangchanyzt@163.com

Received: 11 June 2021
Accepted: 7 September 2021
Published: 1 October 2021

© 2021 Cheng et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

targets, or human leukocyte antigen (HLA) alleles and predicting drug efficacy or toxicity.[5] CYP2C19*2 (rs4244285), CYP2C19*3 (rs4986893), and CYP2C19*17 (rs12248560) have been studied commonly. One study showed that CYP2C19*2 is the most common variant of the reduced function allele, accounting for more than 95% of the African whites and blacks, and more than 75% of the Asian population.[6] Yi et al found that there was at least one allele with impaired CYP2C19 function, and the main prognostic risk was three times higher in clopidogrel carriers than in non-carriers,[7] suggesting that the failure of clopidogrel antiplatelet drug therapy may be related to CYP2C19 gene mutation. These very important pharmacogenomics (VIP) genes have been summarized in the Pharmacogenomics Knowledge Base (PharmGKB; http://www.pharmgkb.org). A South Korean survey showed that preemptive genotyping can help many people avoid adverse drug reactions, suggesting that pharmacogenomics is promising.[8] Exploring the VIP variants among different races is an acceptable way to find suitable drugs for patients or specific populations.

Lahu, distributed in 31 provinces, autonomous regions and municipalities directly under the Central Government in China, is an ancient ethnic group evolved from the Ancient Qiang people in Gansu and Qinghai provinces, whose population in total is 485,966. In the process of ethnic development, Lahu moved to the current Yunnan province and Southeast Asia, such as Myanmar and Thailand. In Yunnan, they mainly lived in Lancang and Shuangjiang counties near the border, with nearly 447,600 people, accounting for 98.66% of the total population of the Lahu ethnic group.[9] The Lahu have not only their own unique genetic characteristics but also their own lifestyle patterns, particularly in terms of traditional practices related to the use of alcohol.[10] However, the pharmacogenomic VIP variants in Lahu people are seldom reported. The study of drug genome in rare and population-specific mutation groups, such as the Lahu, is of great significance to the realization of individualized drug therapy and the development of new drugs. We hope our findings could conduce to the supplement of pharmacogenomic data and support the clinical application of personalized medication in the Lahu population.

In this study, the genotype frequencies of 81 VIP variants in the Lahu population and 11 major HapMap populations were compared and analyzed statistically. Finally, Fst pairwise comparisons and Bayesian clustering analysis were applied to analyze the Lahu population genetics.

Materials and Methods

Subjects

We randomly collected a sample of 100 unrelated Lahu healthy adults aged 25–55 years from the Department of Physical examination, Yunnan First People's Hospital and drew blood samples. The participants, who must reach several detailed inclusion criteria, were considered to be eligible. What is more, all individuals were at least three generations of Lahu paternal ancestor without any known ancestry from other ethnicities. The exclusion criteria were as follows: with the presence of chronic cancer, contagious disease, drugs or alcohol addiction, with severe heart, liver, and kidney dysfunction, immune disorders, pregnancy, or lactation. We have obtained informed consent and blood samples from the volunteers according to the study protocol approved by the Ethics Committee of the Yunnan First People's Hospital. The sample size and the proportion were determined through G*Power 3.1.9.2 software.[11]

The study was approved by the Ethics Committee of the Yunnan First People's Hospital (YYLH054) and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all volunteers in the study.

Selection and Genotyping of VIP Variants

In the current study, we screened the genetic variants related to VIP variants from the PharmGKB database (https://www.pharmgkb.org/) with the minor allele frequency (MAF) > 0.05, Hardy–Weinberg equilibrium (HWE) > 0.05, and call rate > 0.95. The loci that could not be designed were excluded. Ultimately, a total of 81 genetic variants located in 45 genes were selected. The fresh blood samples were stored at −80°C. According to the manufacturer's standard procedure, genomic DNA was isolated using GoldMag-Mini Genomic DNA Purification Kit (GoldMag Ltd. Xi'an, China). The DNA concentration and purity were performed using Nanodrop 2000.

(Thermo Scientific, Waltham, MA, USA) and agarose electrophoresis. The MassARRAY Assay Design 3.0 software (San Diego, California, USA) was applied to design amplification primers for the selected variants.[12] The Agena MassARRAY RS1000 (SanDiego, California, USA) was utilized to perform genotype following the manufacturer's protocol (San Diego, California, USA). Finally, we used Agena Typer 4.0 software for data management and analysis.[3,13]

Statistical Analyses

Microsoft Excel and SPSS 19.0 statistical packages (SPSS, Chicago, IL) were applied to perform HWE and chi-square tests. HWE was assessed using chi-square test and $p < 0.05$ indicated the disequilibrium of HWE. All genotype frequencies of variants in the Lahu population and the other 11 populations from HapMap (http://hapmap.ncbi.nlm.nih.gov) were calculated and compared using the chi-square test. The other 11 people included the Han Chinese in Beijing, China (CHB); Gambian in Western Divisions, The Gambia (GWD); the Japanese population in Tokyo, Japan (JPT); British in England and Scotland (GBR); a northwestern European population (CEU); the Tuscan people of Italy (TSI); the Luhya people in Webuye, Kenya (LWK); African ancestry in the southwestern USA (ASW); Mexican Ancestry in Los Angeles, California (MXL); the Gujarati Indians in Houston, Texas, USA (GIH); Indian Telugu in the UK (ITU). All *p* values in this study were two-sided. Then, we reduced the false discovery rate of multiple testing by Bonferroni's multiple comparison adjustment. When *p* values were less than 0.05/(81*11), it was considered to be statistically significant.

F-statistics (Fst) and structure analyses were usually adopted in population genetic studies. In this study, the Arlequin v3.5 program was used to calculate global Fst along with the pairwise Fst among all the populations using the loci, which were polymorphic at the 5% level.[14] Therefore, we could estimate the pairwise distances between the populations. The diversity of population genetic structures was analyzed through Structure (version 2.3.4) software in 12 populations.[15,16]

Results

Identification of VIP Variants

In this study, 81 genetic variants were selected for investigation in the Lahu population, which was based on previously published VIP variants from the PharmGKB database. The VIP variants were distributed in 45 genes. Basic characteristics of these selected variants in the Lahu population are listed in Table 1.

Statistical Analyses

Chi-square test was performed for significant difference assessment on genotype frequency distribution of 81 loci among Lahu people and the other 11 populations from HapMap project, which are demonstrated in Table 2. On the one hand, compared to the 11 groups (CHB, GWD, JPT, GBR, CEU, TSI, ASW, LWK, GIH, ITU, and MXL) without adjustment ($p < 0.05$), the number of significantly different variants in the Lahu was 32, 59, 32, 49, 52, 54, 51, 55, 51, 52, and 49, respectively. In these 81 different SNPs, the genotype frequencies distribution in thiopurine S-methyltransferase (*TPMT*) rs1142345 and vitamin K epoxide reductase complex subunit 1 (*VKORC1*) rs9934438 were found to be different in the Lahu population when compared to the other 11 ethnic groups. After adjustment using the Bonferroni correction ($p < 0.05/(81*11)$), there were 5, 49, 6, 38, 39, 40, 40, 46, 39, 34, and 22 loci of significant differences between Lahu and the other 11 populations, respectively. The significance of rs1142345 and rs9934438 still existed between Lahu and the other 11 populations. After adjustment, the results also exhibited that GWD was the most different population compared with Lahu, with the number of 49 distinct SNPs loci, followed by LWK with the number of 46 distinct SNPs loci. It was also noteworthy that the different loci between CHB, JPT and the Lahu were the least. However, according to the statistics, the frequencies of alcohol dehydrogenase 1C (*ADH1C*) rs698, glutathione S-transferase pi 1 (*GSTP1*) rs1695, cytochrome P450 family 2 subfamily A member 6 (*CYP2A6*) rs28399433 were distinct from that of CHB groups, respectively. On the other hand, in addition to the above loci, we also found that the genotype distribution of potassium voltage-gated channel subfamily H member 2 (KCNH2) rs3807375 was significantly different between Lahu and JPT.

Then, we performed linkage disequilibrium (LD) analysis using Haploview to define blocks and haplotypes. In the vitamin D receptor (VDR) gene, we found LD blocks in Lahu, CHB, JPT, GBR, CEU, TSI, GIH, ITU, and MXL, and however, there was no strong linkage between GWD, ASW, and LWK (Figure 1). Haplotype constitutions and frequencies showed that Lahu was differed from the other 11 populations. These findings, which are in accordance with the results, are shown in Table 2.

Analyses of Genetic Background

The Fst values were calculated with the help of Arlequin 3.5 to demonstrate the pairwise difference. With a detailed and comprehensive estimate and assessment for different population pairs, we figured out the magnitude of the differentiation among all the 12 geographic populations (0 means no divergence, and 1 indicates complete separation). As shown in Table 3, pairwise Fst values between Lahu and the other 11 HapMap groups measured the

Table 1 Basic Characteristics Selected Variants in the Lahu

Chromosome	Gene	Position	SNP	Functional Consequence	Alleles (A/B)	Freq.A	Freq.B
1	MTHFR	11794419	rs1801131	Missense	G/T	0.20	0.80
1	MTHFR	11796321	rs1801133	Missense	A/G	0.32	0.68
1	CYP2J2	59926822	rs890293	Upstream variant 2KB	A/C	0.02	0.98
1	DPYD	97450058	rs3918290	Splice donor variant	T/C	0.00	1.00
1	DPYD	97515839	rs1801159	Intron variant, missense	C/T	0.27	0.74
1	DPYD	97883329	rs1801265	Intron variant, missense, nc transcript variant, utr variant 5 prime	G/A	0.17	0.83
1	F5	169549811	rs6025	Missense	T/C	0.00	1.00
1	PTGS2	186673926	rs5275	utr variant 3 prime	G/A	0.24	0.76
1	PACERR	186681189	rs20417	nc transcript variant, upstream variant 2KB	G/C	0.01	0.99
1	PACERR	186681619	rs689466	Downstream variant 500B, upstream variant 2KB	C/T	0.42	0.58
2	LOC100286922	233757013	rs4124874	Intron variant, upstream variant 2KB	G/T	0.39	0.62
2	LOC100286922	233757136	rs10929302	Intron variant, upstream variant 2KB	A/G	0.07	0.93
2	UGT1A1	233760498	rs4148323	Intron variant, missense	A/G	0.20	0.80
3	SCN5A	38603929	rs1805124	Missense	C/T	0.07	0.93
3	SCN5A	38633208	rs6791924	Missense	A/G	0.00	1.00
3	NR1I2	119781188	rs3814055	Upstream variant 2KB, utr variant 5 prime	T/C	0.22	0.79
3	MED12L	151339854	rs2046934	Intron variant	G/A	0.23	0.77
3	P2RY1	152835839	rs1065776	Synonymous codon	T/C	0.03	0.97
3	P2RY1	152836568	rs701265	Synonymous codon	G/A	0.41	0.59
4	ADH1A	99280582	rs975833	Intron variant	G/C	0.28	0.72
4	ADH1B	99307860	rs2066702	Missense	A/G	0.00	1.00
4	ADH1C	99339632	rs698	Missense, nc transcript variant	C/T	0.21	0.79
5	HMGCR	75347030	rs17244841	Intron variant	A/T	1.00	0.00
5	HMGCR	75355259	rs3846662	Intron variant	G/A	0.44	0.56

5	ADRB2	148826877	rs1042713	Missense	G/A	0.36	0.64
5	ADRB2	148826910	rs1042714	Missense	G/C	0.01	0.99
6	TPMT	18130687	rs1142345	Missense	T/C	0.99	0.01
7	AHR	17339486	rs2066853	Missense	A/G	0.26	0.74
7	ABCB1	87509329	rs1045642	Synonymous codon	A/G	0.46	0.55
7	ABCB1	87550285	rs1128503	Synonymous codon	G/A	0.36	0.64
7	CYP3A4	99784473	rs2740574	Upstream variant 2KB	C/T	0.00	1.00
7	KCNH2	150970122	rs3807375	Intron variant	C/T	0.44	0.56
8	NAT2	18390208	rs4646244	Intron variant, upstream variant 2KB	A/T	0.34	0.66
8	NAT2	18390758	rs4271002	Intron variant, upstream variant 2KB	C/G	0.26	0.75
8	NAT2	18400344	rs1801280	Missense	C/T	0.09	0.92
8	NAT2	18400484	rs1799929	Synonymous codon	T/C	0.09	0.92
8	NAT2	18400806	rs1208	Missense	G/A	0.09	0.92
8	NAT2	18400860	rs1799931	Missense	A/G	0.25	0.75
10	CYP2C19	94761900	rs12248560	Upstream variant 2KB	T/C	0.00	1.00
10	CYP2C19	94780653	rs4986893	Stop gained	A/G	0.13	0.87
10	CYP2C19	94781859	rs4244285	Synonymous codon	A/G	0.35	0.65
10	CYP2C9	94981296	rs1057910	Missense	C/A	0.05	0.96
10	CYP2C8	95069673	rs7909236	Upstream variant 2KB	T/G	0.07	0.93
10	CYP2C8	95069772	rs17110453	Upstream variant 2KB	C/A	0.39	0.62
10	CYP2E1	133537633	rs2070676	Intron variant	G/C	0.08	0.92
11	GSTP1	67585218	rs1695	Missense	G/A	0.37	0.63
11	GSTP1	67586108	rs1138272	Missense	T/C	0.00	1.00
11	ANKK1	113400106	rs1800497	Missense	A/G	0.44	0.56

(*Continued*)

https://doi.org/10.2147/PGPM.S324410

Table 1 (Continued).

Chromosome	Gene	Position	SNP	Functional Consequence	Alleles (A/B)	Freq.A	Freq.B
11	DRD2	113412737	rs6277	Synonymous codon	A/G	0.03	0.97
11	DRD2	113412762	rs1801028	Missense	C/G	0.02	0.98
12	SLCO1B1	21130388	rs4149015	Upstream variant 2KB	A/G	0.06	0.94
12	SLCO1B1	21176804	rs2306283	Missense	A/G	0.22	0.78
12	SLCO1B1	21178615	rs4149056	Missense	C/T	0.05	0.95
12	VDR	47844974	rs731236	Synonymous codon	G/A	0.03	0.97
12	VDR	47845054	rs7975232	Intron variant	A/C	0.29	0.71
12	VDR	47846052	rs1544410	Intron variant	T/C	0.07	0.93
12	VDR	47850776	rs2239185	Intron variant	A/G	0.29	0.71
12	VDR	47863543	rs1540339	Intron variant	C/T	0.23	0.77
12	VDR	47863983	rs2239179	Intron variant	C/T	0.21	0.79
12	VDR	47872384	rs3782905	Intron variant	C/G	0.13	0.87
12	VDR	47906043	rs4516035	Upstream variant 2KB	C/T	0.02	0.98
12	None	47908762	rs11568820	None	T/C	0.40	0.60
15	CYP1A2	74749576	rs762551	Intron variant	C/A	0.28	0.72
16	SULT1A1	28609479	rs3760091	Intron variant, upstream variant 2KB	G/C	0.37	0.63
16	PRSS53	31091000	rs7294	Upstream variant 2KB, utr variant 3 prime	T/C	0.17	0.83
16	VKORC1	31093557	rs9934438	Intron variant	G/A	0.18	0.82
16	NQO1	69711242	rs1800566	Missense	A/G	0.38	0.62
19	CYP4F2	15879621	rs2108622	Missense	T/C	0.13	0.88
19	CYP2A6	40848591	rs8192726	Intron variant	A/C	0.11	0.89
19	CYP2A6	40848628	rs1801272	Missense	T/A	0.02	0.98
19	CYP2A6	40850474	rs28399433	Upstream variant 2KB	C/A	0.15	0.86
19	CYP2B6	41016810	rs3211371	Downstream variant 500B, missense, utr variant 3 prime	T/C	0.50	0.50

20	PTGIS	49513169	rs5629	Stop gained, synonymous codon	T/G	0.22	0.78
21	SLC19A1	45514912	rs1051298	Intron variant, utr variant 3 prime	A/G	0.46	0.54
21	SLC19A1	45514947	rs1051296	Intron variant, utr variant 3 prime	C/A	0.46	0.54
21	SLC19A1	45537880	rs1051266	Missense, utr variant 5 prime	T/C	0.36	0.64
21	SLC19A1	45538002	rs1131596	Synonymous codon, utr variant 5 prime	A/G	0.62	0.39
22	COMT	19963748	rs4680	Missense, upstream variant 2KB	A/G	0.30	0.70
22	CYP2D6	42127608	rs59421388	Missense, synonymous codon, upstream variant 2KB	T/C	0.00	1.00
22	CYP2D6	42127803	rs28371725	Intron variant, upstream variant 2KB	T/C	0.12	0.88
22	CYP2D6	42129132	rs61736512	Intron variant, missense, upstream variant 2KB	T/C	0.00	1.00

genetic divergence based on the genetic polymorphism data, which were variously ranged from 0.02782 to 0.23350. When Fst value is less than 0.15, there is no genetic differentiation between the two populations. Compared to other populations, the results showed that the lowest level (Fst = 0.02782) existed between the Lahu and CHB populations, followed by the JPT (Fst = 0.03449) and GIH (Fst = 0.114). The LWK population showed the greatest divergence (Fst = 0.2335).

The Bayesian-based structure analysis showed us complementary methods for patterns of genetic similarity and differentiation of the total 12 populations, which works well for 81 loci in the current study. The most suitable K value was observed at 3. The proportion of each ancestor in a single individual was represented with a vertical bar, which was divided into three colors. In Figure 2, the BAR diagram showed that individuals sampled in Lahu were close to the clustering of people with CHB people.

Discussion

There is increasing interest in pharmacogenomics because of genetic variations leading to each person's different metabolism of and reactions to some drugs. As is known to all, race is an important factor leading to large differences in drug metabolism, treatment response, and toxicity among individuals.[17] In our results, we genotyped the pharmacogenomic VIP variants in the Lahu population and determined the differences between Lahu and the other 11 populations. We found that 32, 59, 32, 49, 52, 54, 51, 55, 51, 52, and 49 of the selected variants in the Lahu population significantly differed from those of CHB, GWD, JPT, GBR, CEU, TSI, ASW, LWK, GIH, ITU, and MXL, respectively. These results suggest that the Lahu ethnic group has genetic heterogeneity that distinguishes it from other ethnic groups. Interestingly, the difference of loci genotype frequencies between CHB, JPT and Lahu was the least. Additionally, the pairwise Fst values and genetic structure also revealed that the variants in the Lahu were mostly similar to the JPT and CHB populations genetically.

Nonetheless, we found that compared to the other 11 populations, *TPMT* rs1142345 was significantly different in Lahu people. Pharmacogenomics studies have shown that genetic polymorphisms in *TPMT* are variable and that *TPMT* activity is regulated by genetic polymorphisms, which is also the cause of adverse drug reactions.[18] The *TPMT* genotype has been considered as an indicator of the initial dose of thiopurine drugs,[19] and race-specific

https://doi.org/10.2147/PGPM.S324410 DovePress

Table 2 Different VIP Variants Loci in the Lahu Compared with the 11 Populations After Bonferroni's Multiple Adjustment

Gene	SNP-ID	$p < 0.05/(81*11)$										
		CHB	GWD	JPT	GBR	CEU	TSI	ASW	LWK	GIH	ITU	MXL
MTHFR	rs1801131	0.6849	0.0070	0.6849	0.0007	0.0016	0.0044	0.9460	0.6015	***9.33E-08***	***1.87E-10***	0.6546
MTHFR	rs1801133	0.0024	***3.20E-12***	0.0024	0.7684	0.8032	0.0016	***4.61E-05***	***2.63E-10***	***5.49E-05***	***3.65E-08***	0.0094
CYP2J2	rs890293	0.2596	***2.80E-08***	0.2596	0.1756	–	–	***2.12E-07***	***2.21E-07***	–	0.0495	–
DPYD	rs3918290	–	–	–	–	–	–	–	–	–	–	–
DPYD	rs1801159	0.6304	***4.42E-07***	0.6304	0.0519	0.0099	0.5508	0.0334	0.4394	***3.16E-05***	***9.00E-09***	0.4038
DPYD	rs1801265	0.0028	***1.61E-13***	0.0028	0.8394	0.8211	0.1765	***2.81E-11***	***1.01E-14***	***2.15E-05***	***2.15E-04***	0.0499
F5	rs6025	–	–	–	–	0.0167	–	–	–	–	–	–
PTGS2	rs5275	0.0168	***3.43E-15***	0.0168	0.2943	0.0003	0.1896	***2.57E-10***	***3.47E-16***	0.0006	0.0020	0.0308
PACERR	rs20417	0.0001	***1.31E-25***	6.07E-05	***9.23E-12***	***5.75E-14***	***2.82E-15***	***8.95E-25***	***9.32E-23***	***5.91E-15***	***1.64E-13***	***1.83E-18***
PACERR	rs689466	0.1498	***8.66E-18***	0.1498	***7.59E-06***	***1.40E-06***	***6.91E-07***	***3.80E-07***	***1.83E-19***	***1.32E-10***	***6.55E-10***	0.0074
LOC100286922	rs4124874	0.0081	***1.01E-36***	0.0081	0.8923	0.5139	0.3397	***1.13E-12***	***1.40E-27***	***1.45E-06***	***6.94E-06***	0.0310
LOC100286922	rs10929302	–	***1.17E-16***	–	***2.15E-07***	***1.76E-13***	***2.69E-08***	***1.34E-14***	***8.50E-18***	***4.06E-21***	***2.36E-18***	***5.16E-14***
UGT1A10	rs4148323	0.2194	***4.64E-12***	0.2194	***4.61E-10***	***8.53E-11***	***1.61E-11***	***1.35E-06***	***8.53E-11***	***9.94E-09***	***1.81E-09***	***9.78E-06***
SCN5A	rs1805124	0.0225	***3.64E-16***	0.0225	***7.78E-07***	0.0001	***7.13E-08***	***1.73E-07***	***3.48E-12***	***3.04E-06***	***1.10E-10***	0.0069
SCN5A	rs6791924	–	***2.00E-14***	–	–	–	–	–	***8.16E-15***	–	–	–
NR1I2	rs3814055	0.3176	0.0018	0.3176	***5.31E-05***	0.0067	0.0008	0.0857	0.0787	***2.93E-06***	0.0006	0.0062
MED12L	rs2046934	0.6725	0.0007	0.6725	0.7739	0.4479	0.0052	0.0934	0.0008	0.0007	***3.62E-06***	0.0123
P2RY1	rs1065776	–	***1.32E-19***	–	–	0.1784	0.3752	***2.75E-10***	***2.73E-12***	–	***1.25E-08***	–
P2RY1	rs701265	0.0079	***5.36E-22***	0.0079	***2.13E-10***	***1.14E-08***	***1.79E-09***	***1.65E-06***	***6.28E-18***	***3.46E-06***	***2.76E-06***	5.97959E-05
ADH1A	rs975833	0.0982	***2.93E-26***	0.0982	***1.81E-23***	***2.27E-24***	***7.13E-23***	***1.37E-18***	***8.90E-29***	***1.37E-07***	0.0007	***5.10E-29***
ADH1B	rs2066702	–	***1.52E-12***	–	–	–	–	***7.85E-18***	–	–	–	–
ADH1C	rs698	***7.26E-06***	***7.45E-04***	***7.26`E-06***	***1.44E-06***	***5.63E-10***	0.0201	0.2570	0.0541	0.1455	0.2145	0.0509
HMGCR	rs17244841	-	***8.63E-65***	-	***1.06E-63***	***1.95E-65***	***3.18E-66***	***3.48E-57***	***1.84E-64***	-	-	***7.77E-58***

HMGCR	rs3846662	0.1962	***7.93E-33***	0.1962	0.4358	0.9355	0.9305	***3.02E-16***	***3.60E-33***	***2.86E-06***	0.0169	0.9571
ADRB2	rs1042713	0.0214	0.0385	0.0214	***6.57E-06***	***1.11E-09***	***1.27E-08***	0.2285	0.0038	***2.20E-05***	8.01E-05	0.0046
ADRB2	rs1042714	-	***2.68E-08***	-	***6.90E-34***	***1.55E-36***	***4.70E-34***	***9.95E-08***	***3.31E-18***	***4.16E-19***	***6.14E-13***	***8.72E-09***
TPMT	rs1142345	***1.56E-65***	***7.13E-66***	***1.56E-65***	***2.80E-61***	***4.36E-63***	***1.55E-65***	***1.48E-53***	***2.25E-59***	***3.70E-64***	***8.09E-65***	***5.26E-55***
AHR	rs2066853	0.0087	***4.66E-06***	0.0087	***3.80E-05***	***7.27E-06***	***1.07E-05***	0.1338	***1.76E-07***	***7.17E-05***	0.0051	0.0094
ABCB1	rs1045642	0.0350	***6.93E-11***	0.0350	0.1975	0.0261	0.4327	***9.52E-08***	***1.40E-13***	0.0147	0.0015	0.9044
ABCB1	rs1128503	0.1754	***4.90E-27***	0.1754	***3.67E-06***	***3.55E-06***	***5.21E-07***	***4.82E-19***	***5.52E-31***	0.2013	0.4434	0.0019
CYP3A4	rs2740574	-	***4.21E-64***	-	-	-	-	***1.73E-51***	***6.09E-60***	-	-	-
KCNH2	rs3807375	-	***1.73E-07***	***8.22E-06***	***4.58E-08***	***9.80E-06***	***1.73E-06***	0.0022	***3.08E-09***	0.0004	***2.07E-05***	0.6611
NAT2	rs4646244	0.0009	0.0014	0.0009	0.0140	0.3181	0.3332	0.2172	0.0544	0.6579	0.3230	***1.73E-05***
NAT2	rs4271002	0.0723	***1.41E-10***	0.0723	0.0520	***7.27E-07***	0.0430	0.0044	***8.58E-06***	0.0034	7.72E-05	0.2957
NAT2	rs1801280	0.0300	***1.01E-12***	0.0300	***1.45E-20***	***1.60E-18***	***1.71E-19***	***7.06E-09***	***8.92E-15***	***1.00E-12***	***4.60E-13***	***4.70E-13***
NAT2	rs1799929	0.0300	***1.47E-09***	0.0300	***4.22E-19***	***3.32E-18***	***1.71E-19***	***2.47E-06***	***2.78E-12***	***2.96E-10***	***6.34E-11***	***1.58E-12***
NAT2	rs1208	0.0300	***1.69E-20***	0.0300	***2.70E-19***	***5.00E-17***	***5.32E-20***	***1.22E-11***	***9.64E-21***	***1.00E-12***	***1.15E-13***	***6.61E-17***
NAT2	rs1799931	0.0162	***6.78E-13***	0.0162	***2.03E-10***	***3.15E-13***	***3.14E-12***	***8.10E-06***	***1.44E-12***	***3.55E-08***	***5.94E-08***	0.0279
CYP2C19	rs12248560	-	***1.18E-21***	-	***2.79E-21***	***1.15E-20***	***1.33E-19***	***1.48E-17***	***1.46E-15***	***7.28E-12***	***3.94E-12***	***5.71E-09***
CYP2C19	rs4986893	0.0095	***5.23E-07***	0.0095	***7.56E-06***	***2.85E-06***	***1.08E-06***	0.0003	***3.76E-05***	***6.81E-06***	***5.37E-06***	0.0002
CYP2C19	rs4244285	0.4105	***2.05E-08***	0.4105	***1.90E-06***	***1.03E-07***	***3.73E-11***	***3.73E-05***	0.0022	0.2001	0.5652	***4.58E-06***
CYP2C9	rs1057910	-	-	-	-	-	0.1068	-	-	0.0005	0.0248	-
CYP2C8	rs7909236	0.2181	-	0.2181	***1.33E-06***	***4.93E-10***	0.0001	-	-	***3.11E-08***	***1.40E-06***	***1.92E-10***
CYP2C8	rs17110453	0.5292	***6.02E-27***	0.5292	***1.26E-11***	***1.53E-13***	***4.64E-13***	***2.85E-16***	***1.86E-24***	0.0806	0.3722	***9.57E-09***
CYP2E1	rs2070676	0.0001	***2.37E-40***	0.0001	0.7921	0.0115	0.0003	***4.38E-25***	***1.27E-43***	0.0515	0.0015	0.0306
GSTP1	rs1695	***1.26E-05***	0.0003	***1.26E-05***	0.3247	0.4896	0.1296	0.2429	0.0036	0.2995	0.4442	0.0006
GSTP1	rs1138272	-	-	-	-	-	-	-	-	-	-	6.82029E-05

(*Continued*)

https://doi.org/10.2147/PGPM.S324410

Table 2 (Continued).

Gene	SNP-ID	$p < 0.05/(81*11)$										
		CHB	GWD	JPT	GBR	CEU	TSI	ASW	LWK	GIH	ITU	MXL
ANKK1	rs1800497	0.9333	0.0513	0.9333	***3.39E-06***	***7.02E-07***	***2.79E-06***	0.8065	0.0882	0.0022	0.3197	0.1703
DRD2	rs6277	-	0.1737	-	***1.60E-35***	***9.18E-37***	***8.88E-45***	***2.99E-05***	-	***1.64E-20***	***2.85E-22***	***3.16E-15***
DRD2	rs1801028	0.0983	-	0.0983	-	0.2920	-	-	-	***2.79E-10***	-	-
SLCO1B1	rs4149015	0.0385	0.0006	0.0385	0.1190	0.5077	0.4303	0.0550	0.2497	0.7721	0.5153	0.2353
SLCO1B1	rs2306283	0.9604	0.4582	0.9604	***4.64E-19***	***1.67E-16***	***1.74E-19***	0.6967	0.0913	***1.37E-07***	***2.33E-05***	***3.91E-15***
SLCO1B1	rs4149056	0.0007	0.0045	0.0007	0.0002	7.39E-05	***1.37E-09***	0.6318	0.2800	0.2469	0.7585	0.2271
VDR	rs731236	-	***5.09E-16***	-	***1.57E-19***	***2.31E-30***	***1.56E-28***	***2.07E-13***	***1.29E-16***	***6.98E-21***	***3.17E-33***	***7.10E-10***
VDR	rs7975232	0.9252	***2.15E-15***	0.9252	0.0006	***9.00E-11***	***1.24E-10***	***3.82E-10***	***9.57E-19***	***1.33E-07***	***2.64E-13***	0.0359
VDR	rs1544410	-	***3.12E-07***	-	***4.45E-14***	***6.08E-23***	***1.28E-20***	***7.10E-09***	***3.65E-09***	***4.12E-23***	***1.50E-30***	0.0002
VDR	rs2239185	0.9122	***6.08E-11***	0.9122	0.0004	***1.86E-11***	***6.13E-11***	***2.07E-06***	***5.33E-14***	***1.15E-07***	***6.02E-15***	0.0270
VDR	rs1540339	0.4823	***1.53E-30***	0.4823	***3.83E-14***	***1.09E-20***	***6.51E-19***	***8.80E-21***	***4.25E-36***	***1.05E-18***	***3.70E-24***	***4.60E-13***
VDR	rs2239179	0.5287	0.2834	0.5287	0.0054	***3.96E-11***	***1.41E-06***	0.0008	0.0010	***2.76E-11***	***5.76E-18***	0.1391
VDR	rs3782905	0.7474	0.1133	0.7474	0.0037	***1.81E-09***	***1.18E-08***	0.0333	0.0062	0.0004	***1.17E-08***	0.0465
VDR	rs4516035	-	-	-	***1.22E-30***	***4.01E-27***	***5.64E-33***	***2.11E-05***	-	***9.81E-13***	***5.38E-13***	***1.56E-16***
None	rs11568820	0.0042	***3.79E-40***	0.0042	***2.29E-06***	***5.98E-07***	***5.81E-06***	***2.94E-12***	***1.81E-29***	0.0238	9.27E-05	***1.24E-09***
CYP1A2	rs762551	0.1140	0.0035	0.1140	0.9717	0.9008	0.0442	0.1393	***1.93E-07***	***2.43E-05***	0.0002	0.4248
SULT1A1	rs3760091	0.2385	0.9878	0.2385	0.7667	0.4910	0.0016	0.7226	0.7652	0.0002	0.2869	0.0625
PRSS53	rs7294	0.0001	***4.67E-12***	0.0001	***9.47E-10***	0.0003	***1.39E-05***	***3.89E-10***	***1.13E-10***	***4.36E-29***	***1.25E-37***	0.0001
VKORC1	rs9934438	**3.29463E-05**	***2.30E-51***	***3.29E-05***	***8.52E-24***	***5.84E-18***	***9.24E-16***	***1.86E-34***	***3.66E-53***	***8.27E-39***	***1.52E-45***	***5.57E-13***
NQO1	rs1800566	0.0033	***3.89E-07***	0.0033	0.0001	***8.48E-06***	0.0040	0.0001	***2.42E-06***	0.1776	0.8636	0.8644
CYP4F2	rs2108622	0.0040	0.0650	0.0040	0.0001	0.0016	***1.11E-07***	0.3779	0.5558	***1.83E-14***	***2.40E-12***	0.0003
CYP2A6	rs8192726	0.0396	0.2028	0.0396	0.0481	0.0828	0.1709	0.9164	0.6684	0.3413	0.9189	0.1496
CYP2A6	rs1801272	-	-	-	0.0016	0.0003	***2.46E-05***	0.1054	-	0.0512	-	0.0231

CYP2A6	rs28399433	***1.52E-05***	-	***1.52E-05***	***4.25E-05***	-	-	0.0508	0.0216	0.0026	0.0014	-
CYP2B6	rs3211371	-	-	-	***4.95E-46***	***6.39E-50***	***7.46E-49***	-	-	-	***1.06E-50***	-
PTGIS	rs5629	0.1823	***2.46E-05***	0.1823	0.3970	0.9328	0.0132	0.2800	0.0005	0.4016	0.9687	0.1124
SLC19A1	rs1051298	0.5280	***4.10E-05***	0.5280	0.1800	0.3496	0.8507	0.1978	0.1180	0.0079	0.1941	0.0341
SLC19A1	rs1051296	0.3014	0.6567	0.3014	0.1731	0.3626	0.7741	0.8344	0.1013	0.2798	0.9925	0.0330
SLC19A1	rs1051266	0.0227	***5.65E-18***	0.0227	0.0647	0.1370	0.0869	0.0003	***1.06E-12***	0.7523	0.5757	0.1027
SLC19A1	rs1131596	0.1040	***3.87E-17***	0.1040	0.4546	0.0551	0.3251	***4.00E-05***	***8.55E-15***	0.5542	0.6345	0.3417
COMT	rs4680	0.3271	0.1218	0.3271	***2.22E-07***	8.28E-05	0.0003	0.1128	0.9426	0.0004	0.0002	0.0805
CYP2D6	rs59421388	-	-	-	-	-	-	0.0013	***8.16E-15***	-	-	-
CYP2D6	rs28371725	0.0086	0.0000	0.0086	0.2853	0.4283	0.0214	0.0090	0.0063	0.6276	0.4518	0.0066
CYP2D6	rs61736512	-	-	-	-	-	-	0.0013	***8.16E-15***	-	-	-
Different SNPs		5	49	6	38	39	40	40	46	39	34	22

Note: Bold italics indicates that after adjustment $p < 0.05/(81*11)$ the locus has statistically significant.

Abbreviations: ASW, African ancestry in southwestern USA; CEU, Utah residents with Northern and Western European ancestry; CHB, Han Chinese in Beijing, China; GIH, Gujarati Indians in Houston, Texas, USA; JPT, Japanese in Tokyo, Japan; LWK, Luhya people in Webuye, Kenya; TSI, Toscans in Italy; GWD, Gambian in Western Divisions, The Gambia; GBR, British in England and Scotland; ITU, Indian Telugu in the UK; MXL, Mexican Ancestry in Los Angeles, Colombia.

https://doi.org/10.2147/PGPM.S324410

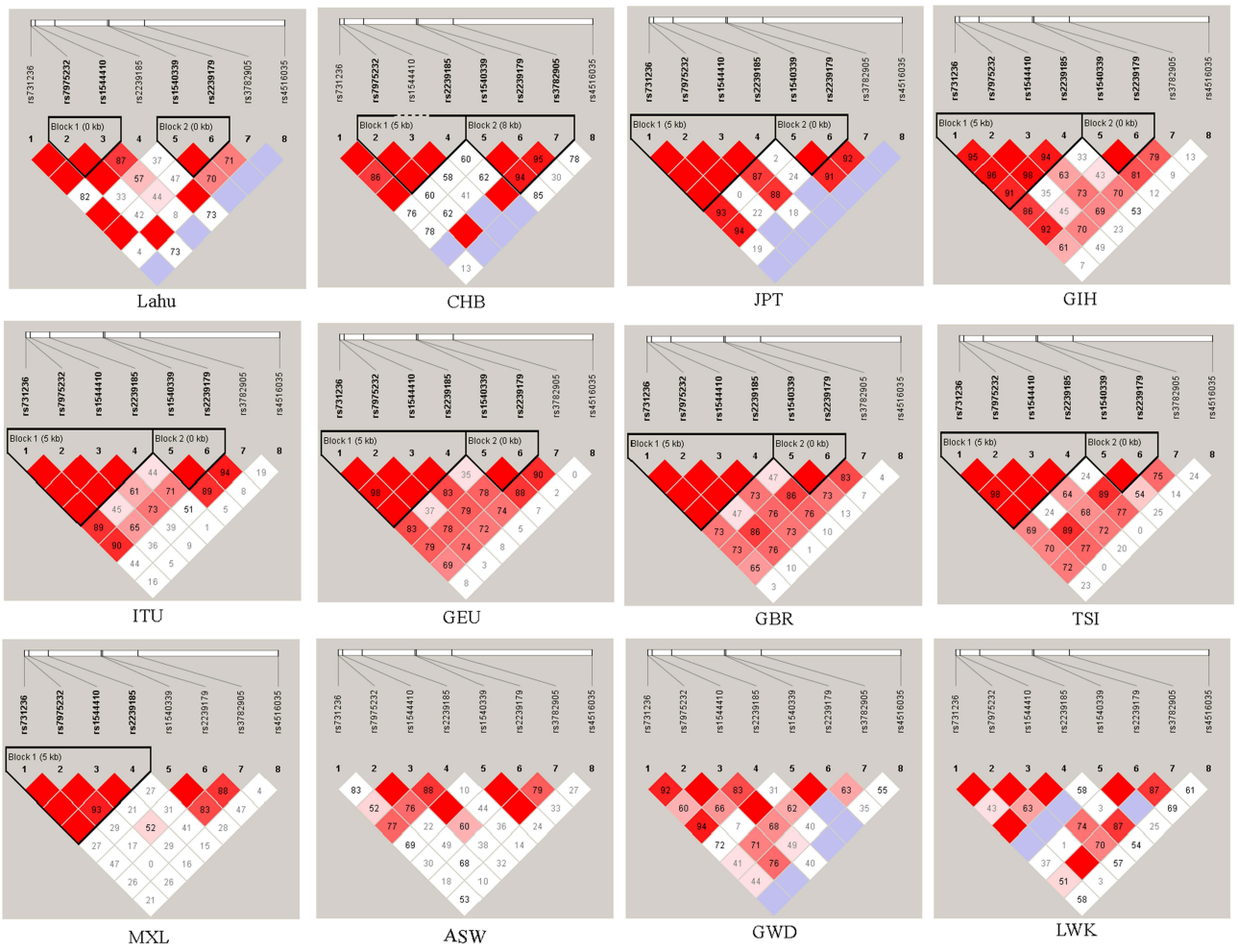

Figure 1 LD analysis of the VDR in each of the twelve populations. LD is displayed by standard color schemes with bright red for very strong LD (LOD>2, D′ =1), pink red (LOD> 2, D′ <1), blue (LOD< 2, D′ =1) for intermediate LD, and white (LOD<2, D′ <1) for no LD.

differences in *TPMT* activity and mercaptopurine metabolism have been observed.[20] African ancestry is associated with the lower *TPMT* activity, and some studies have reported a higher prevalence of *TPMT* variants in blacks.[21,22] The CC genotype carrying the TPMT*3C (c.719 T>C, rs1142345) variant is susceptible to the toxicity of the

Table 3 Estimates of Pairwise Fst Among the 12 Population

	Lahu	CHB	JPT	GIH	ITU	CEU	GBR	TSI	ASW	GWD	LWK	MXL
Lahu	0											
CHB	0.0278	0										
JPT	0.0345	0.0045	0									
GIH	0.1140	0.1277	0.1155	0								
ITU	0.1350	0.1511	0.1383	0.0045	0							
CEU	0.1354	0.1491	0.1396	0.0384	0.0443	0						
GBR	0.1239	0.1404	0.1330	0.0371	0.0484	0.0040	0					
TSI	0.1270	0.1333	0.1254	0.0405	0.0477	0.0040	0.0047	0				
ASW	0.1668	0.1784	0.1639	0.0879	0.1001	0.1150	0.1191	0.1118	0			
GWD	0.2263	0.2388	0.2213	0.1469	0.1602	0.1825	0.1882	0.1790	0.0118	0		
LWK	0.2335	0.2430	0.2264	0.1440	0.1565	0.1772	0.1860	0.1741	0.0134	0.0055	0	
MXL	0.0939	0.0916	0.1079	0.1072	0.0997	0.0515	0.0490	0.0636	0.0399	0.0672	0.0304	0

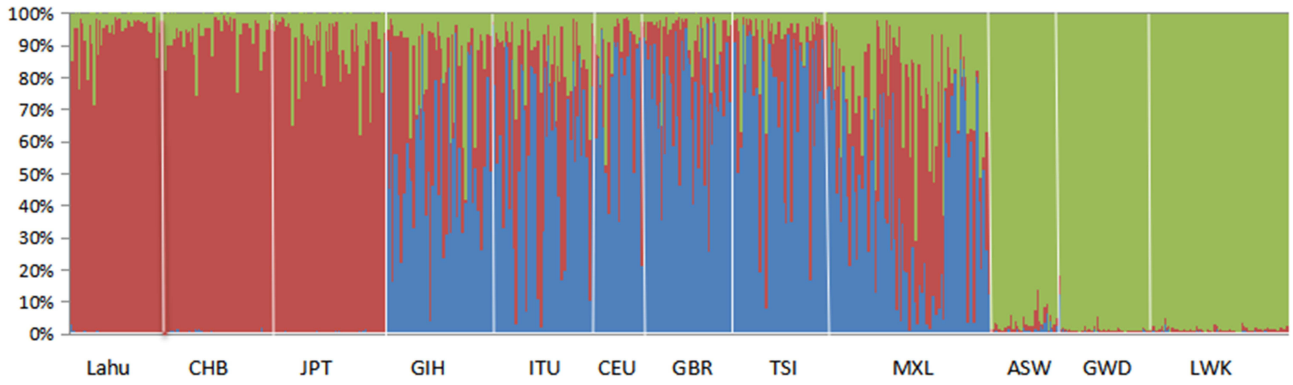

Figure 2 Results of STRUCTURE analyses (K=3) among 12 populations. Most suitable K value is 3.

standard dose of 6-mercaptopurine. A high-frequency CC genotype of the TPMT*3C variant was found in traditional indigenous people in the Amazon region.[23] Compared with the other 11 populations, *TPMT* rs1142345 variants in the Lahu population are statistically different. The C allele is associated with mercaptopurine exposure in children with leukemia when compared with the T allele. The relationship between the polymorphism of rs1142345 and the risk of acute lymphoblastic leukemia has been widely reported.[23,24] The personalized medication (mercaptopurine) for acute lymphoblastic leukemia of the Lahu ethnic group is worthy of attention.

Furthermore, we found that *VKORC1* rs9934438 (A>G) was significantly different in Lahu compared to the other 11 populations as well. A common variant of the vitamin K epoxide reductase complex subunit 1 (VKORC1) gene has also been strongly associated with inter-individual warfarin dosing variability[25,26] The warfarin dose of patients from Southern Italy GG genotype carriers at rs9934438 was significantly higher than that of AA genotype carriers or GA genotype patients.[26] In different populations, such as the whites and Asians, the *VKORC1* polymorphism has showed a sustained and significant effect on the warfarin response, accounting for 11% to 32% of the dose variation[27,28] More attention should be paid to warfarin and related agents in the Lahu population.

Our research further found that differences in gene frequency of *ADH1C* rs698, *CYP2A6* rs28399433, and *GSTP1* rs1695 between the Lahu and the CHB. Their polymorphism has been reported to be closely related to alcohol metabolism,[29] tobacco metabolism,[30] and carcinogen metabolism.[31] What is more, there are population differences, especially in Asia with the other states. Lahu and CHB were found to be two close populations. However, our study implied that individual medications in clinical practice should also be considered separately in the Lahu population.

In conclusion, the VIP variation detected in Lahu group is different from those of the other 11 populations. Determination of the allele distribution and frequencies of VIP variants in such a minority group would provide a theoretical basis for the safer drug administration and much better therapeutic effects. Our results first provide a basic overview of VIP in Lahu groups, and it is hoped that these data will help to develop the population-specific pharmacogenetics studies. However, this study still has limitations. Presently, the sample size is small. A large number of samples were needed to provide strong evidence for the results, to provide a broad overview of better efficacy and safer drug strategies for the Lahu people, and to influence the rational drug selection and the dosage of the Lahu people. Finally, we hope to help optimize personalized treatment strategies.

Abbreviations

VIP, very important pharmacogenomics; SNP, single nucleotide polymorphism; Fst, F-statistics; CHB, the Han Chinese in Beijing, China; GWD, Gambian in Western Divisions, the Gambia; JPT, the Japanese population in Tokyo, Japan; GBR, British in England and Scotland; CEU, the northwestern European population; TSI, the Tuscan people of Italy; ASW, African ancestry in the southwestern USA; LWK, the Luhya people in Webuye, Kenya; MXL, Mexican Ancestry in Los Angeles, California; GIH, the Gujarati Indians in Houston, Texas, USA; ITU, Indian Telugu in the UK.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the Yunnan First People's Hospital (YYLH054) and was

performed in accordance with the Declaration of Helsinki. All participants agreed to participate and signed informed consent.

Acknowledgments

The authors thank all the participants in this study. We are also grateful to the hospital staff who contributed to the sample and data collection. Yujing Cheng and Qi Li are co-first authors of this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Applied Basic Research Foundation of Yunnan Province (CN) [grant number: 2017FE468 (−125) and 202001AY070001-111], the Open Project of the Clinical Medicine Center of the First People's Hospital of Yunnan Province [grant number: 2021LCZXXF-XY12] and CAMS Innovation Fund for Medical Sciences (CIFMS) [grant number: 2016-I2M-3-024].

Disclosure

The authors report no conflicts of interest in this work.

References

1. Owen RP, Klein TE, Altman RB. The education potential of the pharmacogenetics and pharmacogenomics knowledge base (PharmGKB). *Clin Pharmacol Ther*. 2007;82(4):472–475. doi:10.1038/sj.clpt.6100332
2. Badary OA. Pharmacogenomics and COVID-19: clinical implications of human genome interactions with repurposed drugs. *Pharmacogenomics J*. 2021;21(3):275–284. doi:10.1038/s41397-021-00209-9
3. He Y, Yang H, Geng T, et al. Genetic polymorphisms of pharmacogenomic VIP variants in the lhoba population of southwest China. *Int J Clin Exp Pathol*. 2015;8(10):13293–13303.
4. Ma JD, Lee KC, Kuo GM. Clinical application of pharmacogenomics. *J Pharm Pract*. 2012;25(4):417–427. doi:10.1177/0897190012448309
5. Ventola CL. Role of pharmacogenomic biomarkers in predicting and improving drug response: part 1: the clinical significance of pharmacogenetic variants. *P t*. 2013;38(9):545–560.
6. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(7):2064–2089. doi:10.1161/STR.0b013e318296aeca
7. Yi X, Lin J, Zhou J, et al. The secondary prevention of stroke according to cytochrome P450 2C19 genotype in patients with acute large-artery atherosclerosis stroke. *Oncotarget*. 2018;9(25):17725–17734. doi:10.18632/oncotarget.24877
8. Kim GJ, Lee SY, Park JH, et al. Role of preemptive genotyping in preventing serious adverse drug events in South Korean patients. *Drug Saf*. 2017;40(1):65–80. doi:10.1007/s40264-016-0454-5
9. Guo F. Genetic polymorphism of 17 autosomal STR loci in the Lahu ethnic minority from Yunnan Province, Southwest China. *Forensic Sci Int Genet*. 2017;31:e52–e3. doi:10.1016/j.fsigen.2017.08.002
10. Singkorn O, Apidechkul T, Putsa B, et al. Factor associated with alcohol use among Lahu and Akha hill tribe youths, northern Thailand. *Subst Abuse Treat Prev Policy*. 2019;14(1):5. doi:10.1186/s13011-019-0193-6
11. Faul F, Erdfelder E, Lang AG, et al. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39(2):175–191. doi:10.3758/BF03193146
12. Gabriel S, Ziaugra L, Tabbaa D. SNP genotyping using the Sequenom massARRAY iPLEX platform. *Curr Protoc Hum Genet*. 2009;60. doi:10.1002/0471142905.hg0212s60
13. 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
14. Excoffier L, Laval G, Schneider S. Arlequin (version 3.0): an integrated software package for population genetics data analysis. *Evol Bioinform Online*. 2007;1:47–50.
15. Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. *Genetics*. 2000;155(2):945–959. doi:10.1093/genetics/155.2.945
16. Evanno G, Regnaut S, Goudet J. Detecting the number of clusters of individuals using the software STRUCTURE: a simulation study. *Mol Ecol*. 2005;14(8):2611–2620. doi:10.1111/j.1365-294X.2005.02553.x
17. Chowbay B, Zhou S, Lee EJ. An interethnic comparison of polymorphisms of the genes encoding drug-metabolizing enzymes and drug transporters: experience in Singapore. *Drug Metab Rev*. 2005;37(2):327–378. doi:10.1081/DMR-28805
18. Otterness D, Szumlanski C, Lennard L, et al. Human thiopurine methyltransferase pharmacogenetics: gene sequence polymorphisms. *Clin Pharmacol Ther*. 1997;62(1):60–73. doi:10.1016/S0009-9236(97)90152-1
19. Schaeffeler E, Fischer C, Brockmeier D, et al. Comprehensive analysis of thiopurine S-methyltransferase phenotype-genotype correlation in a large population of German-Caucasians and identification of novel TPMT variants. *Pharmacogenetics*. 2004;14(7):407–417. doi:10.1097/01.fpc.0000114745.08559.db
20. Cooper SC, Ford LT, Berg JD, et al. Ethnic variation of thiopurine S-methyltransferase activity: a large, prospective population study. *Pharmacogenomics*. 2008;9(3):303–309. doi:10.2217/14622416.9.3.303
21. Hon YY, Fessing MY, C H PUI, et al. Polymorphism of the thiopurine S-methyltransferase gene in African-Americans. *Hum Mol Genet*. 1999;8(2):371–376. doi:10.1093/hmg/8.2.371
22. Jones CD, Smart C, Titus A, et al. Thiopurine methyltransferase activity in a sample population of black subjects in Florida. *Clin Pharmacol Ther*. 1993;53(3):348–353. doi:10.1038/clpt.1993.31
23. Cardoso de Carvalho D, Pereira Colares Leitão L, Mello Junior FAR, et al. Association between the TPMT*3C (rs1142345) polymorphism and the risk of death in the treatment of acute lymphoblastic leukemia in children from the Brazilian Amazon Region. *Genes*. 2020;11(10):1132. doi:10.3390/genes11101132
24. Yang JJ, Landier W, Yang W, et al. Inherited NUDT15 variant is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia. *J Clin Oncol*. 2015;33(11):1235–1242. doi:10.1200/JCO.2014.59.4671

25. Limdi NA, Wadelius M, Cavallari L, et al. Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups. *Blood*. 2010;115(18):3827–3834. doi:10.1182/blood-2009-12-255992
26. D'andrea G, D'ambrosio RL, DI PERNA P, et al. A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin. *Blood*. 2005;105(2):645–649. doi:10.1182/blood-2004-06-2111
27. Limdi NA, Arnett DK, Goldstein JA, et al. Influence of CYP2C9 and VKORC1 on warfarin dose, anticoagulation attainment and maintenance among European-Americans and African-Americans. *Pharmacogenomics*. 2008;9(5):511–526. doi:10.2217/14622416.9.5.511
28. Veenstra DL, You JH, Rieder MJ, et al. Association of vitamin K epoxide reductase complex 1 (VKORC1) variants with warfarin dose in a Hong Kong Chinese patient population. *Pharmacogenet Genomics*. 2005;15(10):687–691. doi:10.1097/01.fpc.0000174789.77614.68
29. Li D, Zhao H, Gelernter J. Further clarification of the contribution of the ADH1C gene to vulnerability of alcoholism and selected liver diseases. *Hum Genet*. 2012;131(8):1361–1374. doi:10.1007/s00439-012-1163-5
30. Tanner JA, Zhu AZ, Claw KG, et al. Novel CYP2A6 diplotypes identified through next-generation sequencing are associated with in-vitro and in-vivo nicotine metabolism. *Pharmacogenet Genomics*. 2018;28(1):7–16. doi:10.1097/FPC.0000000000000317
31. Kassogue Y, Diakite B, Kassogue O, et al. Genetic polymorphism of drug metabolism enzymes (GSTM1, GSTT1 and GSTP1) in the healthy Malian population. *Mol Biol Rep*. 2020;47(1):393–400. doi:10.1007/s11033-019-05143-5

Pharmacogenomics and Personalized Medicine Dovepress

Publish your work in this journal

Pharmacogenomics and Personalized Medicine is an international, peer-reviewed, open access journal characterizing the influence of genotype on pharmacology leading to the development of personalized treatment programs and individualized drug selection for improved safety, efficacy and sustainability. This journal is indexed on the American Chemical Society's Chemical Abstracts Service (CAS). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/pharmacogenomics-and-personalized-medicine-journal