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Genetic polymorphisms of pharmacogenomic VIP variants in the Lisu population of southwestern China

A cohort study

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Abstract

Pharmacogenomic studies of different ethnic or racial groups have been used to develop personalized therapies specific to subjects. This study aimed to identify the distribution differences of very important pharmacogenetic (VIP) variants between the Lisu population from southwestern China and other ethnic groups.

Eighty VIP variants in 37 genes were selected from the pharmacogenomic knowledge base (PharmGKB), and compared with genotype data of the Lisu population then compared with other 11 populations from the HapMap dataset and previously published data including Miao, Li, Deng, Sherpa, Lhoba, Tibetan, Kirghiz, Tajik, Mongol, Shaanxi Han ethnic, and Uygur populations.

VDR rs1540339, MTHFR rs1801131, P2RY1 rs701265, and PTGS2 rs689466 were significantly different between Lisu and 11 HapMap populations. ANKK1 rs1800497 was the least statistical significant locus among selected single nucleotide polymorphisms. In addition, genetic background of Lisu was strongly closest to Shaanxi Han ethnic cohort, and followed by Chinese in metropolitan Denver population based on population structure and F-statistics analyses.

Our results showed significant interethnic differences between Lisu and other populations, which will give useful information for prospective studies and better individualized treatments.

Abbreviations: ADP = adenosine diphosphate, ASW = African ancestry in Southwest United States, CEU = Utah, United States residents with Northern and Western European ancestry from the CEPH collection, CHB = Chinese Han in Beijing, CHD = Chinese in metropolitan Denver, CI = confidence interval, Fst = F-statistics, GIH = Gujarati Indians in Houston, JPT = Japanese in Tokyo, LWK = Luhya in Webuye, Kenya, MEX = Mexican ancestry in Los Angeles, CA, MKK = Maasai in Kinyawa, Kenya, MTHFR = 5,10-methylenetetrahydrofolate reductase, OR = odds ratio, PTGS2 = Prostaglandin endoperoxide synthase 2, T1DM = type 1 diabetes mellitus, TPMT = thiopurine-S-methyltransferase, TSI = Toscani in Italy, VDR = vitamin D receptor, VIP = very important pharmacogenomics, YRI = Yoruba in Ibadan, Nigeria.

Keywords: genetic polymorphisms, Lisu, pharmacogenomics, VIP variants

1. Introduction

It is well recognized that genetic polymorphisms are manifested fully involved in drug receptors, transporters, metabolism enzyme expression, and interindividual variability in drug pharmacokinetics or pharmacodynamics.[1] Existence of these polymorphisms may lead to significant individual differences in various therapeutic agents, causing serious adverse reactions or treatment failure. Pharmacogenomic research in different ethnic backgrounds can reveal the genetic characteristic differences at genetic level via determining the distribution of single nucleotide polymorphisms (SNPs), which are frequently used as markers of susceptibility, progression, prognosis of diseases, and interindividual variations in drug response or toxicity.[2]

Especially, certain important genes and genetic variations are called very important pharmacogenetic (VIP) variants, which have been extensively studied in various ethnic populations owing to their significant effects on drug treatment both at pharmacokinetic and pharmacodynamic levels.[3] For instance, the expression of CYP3A5 gene is proposed to be involved in altering vincristine toxicity, which is more frequently expressed in livers of African Americans (60%) than those of Caucasians (33%).[4] Thiopurine-S-methyltransferase (TPMT), a cytosolic enzyme, catalyzes the S-methylation of thiopurines into inactive compounds in response to thiopurine drug therapy.[5] McLeod showed that 6% to 10% patients of White population are heterozygous for the defective variants of TPMT, in comparison with ~2% to 3% Asian patients, resulting in null enzyme activity.[5] SLCO1B1, known as a member of solute carrier organic anion transporter family, have been performed in healthy

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Chinese individuals. Results showed that SLCO1B1*1B/*1B genotype was associated with reduced pharmacokinetic parameters after repaglinide treatment, such as decreasing of plasma concentration time curve and increasing clearance of repaglinide.[6] Together these findings, we can finally concluded that research on VIP variants contributes to ethnic differences in realizing personalized medicine.

The Lisus is an ethnic minority in China, most of whom primarily live in the Nujiang Lisu Autonomous Prefecture in northwestern Yunnan Province with some living in the Sichuan Province. Depending on the results of 6th population survey of China in 2010, the Lisus has an approximate population of more than 1.26 million. A study of evolutionary relationship of Lisu compared with other populations suggested that the Lisu ethnic group originated from a branch of the ancient Qiang, which was the most powerful nomadic tribe in the northwest of China.[7] In recent years, pharmacogenomic studies have been conducted on several ethnic groups in China.

Few studies have been performed on pharmacogenomic VIP in Lisu ethnic. Therefore, this present study was designed in order to provide information for personalized medicine by selecting and genotyping variants from the PharmGKB VIP database, which focused on published guidelines for dosage modification or drugs selection based on germ-line mutations in genes with pharmacokinetic or pharmacodynamic impact.[8] Specifically, we compared the genotype frequencies of VIP variants between the Lisu and other diverse populations based on HapMap database, and analyzed the genetic distance between Lisu and other ethnic groups in China including Miao,[9] Li,[10] Deng,[11] Sherpa,[12] Lhoba,[13] Tibetan,[14] Kyrhyz,[15] Tajik,[16] Mongol,[17] Shaanxi Han ethnic,[18] Uygur,[19] and 11 HapMap populations (Fig. 1). The results of our study will extend our understanding of ethnic diversity and pharmacogenomics, as well as provide useful information for prospective studies and better individualized treatments.

2. Materials and methods

2.1. Study participants

We randomly recruited 100 unrelated Lisu adults, including 50 males and 50 females from the Yunnan province of China. At entry into the study, all subjects had exclusive for at least 3 generations of Lisu ethnic ancestries and were judged to be healthy on the basis of medical history. Informed written consent was obtained from each subjects. Blood samples were collected, which was approved by the Clinical Research Ethics Committee of Northwest University and Xizang Minzu University. All procedures were performed in compliance with the ethical standards of the institution and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.[14]

2.2. Variant selection and genotyping

The database of Pharmacogenetics and Pharmacogenomic Knowledge (PharmGKB: http://www.pharmgkb.org), International HapMap Project (http://hapmap.ncbi.nlm.nih.gov), and previously published data were adopted for selecting variants. As the result, this approach finally yielded 80 variants located in 37 genes for genotyping. Genomic DNA was isolated from peripheral blood with GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMagLtd, Xi'an, China) according to the manufacturer's protocol, and DNA concentration was determined by NanoDrop 2000C spectrophotometer (Thermo Scientific, Waltham, MA).[14,15] Multiplex SNPs were designed by Sequenom MassARRAY Assay Design 3.0 software (San Diego, CA).[15] Genotyping of variants were performed in accordance with standard protocol recommended by manufacturer through the Sequenom MassARRAY RS1000. Sequenom Typer 4.0 software was used to manage and analyze SNP genotypic data as described in the previous report.[16]

2.3. Statistical analyses

Statistical analysis was performed with the usage of Microsoft Excel and statistical package of social sciences (SPSS) version 22 (SPSS, Chicago, IL) in order to determine whether variants were in Hardy–Weinberg equilibrium. All P values obtained in this study were 2-sided. Chi-squared test with Bonferroni correction was implemented to determine the statistical significance of variants' genotype frequencies between Lisu and other 11 HapMap populations. A P value $< .05/(77 \times 11)$ was considered statistically significant. HapMap populations involved in this study were an African-American population from the Southwest United States (ASW); individuals from Utah, United States with northern/western European ancestry (CEU); the Chinese Han in Beijing, China (CHB); the Chinese in metropolitan Denver, CO (CHD); the Japanese population in Tokyo, Japan (JPT); the Gujarati Indians in Houston, TX (GIH), the Luhya people in Webuye, Kenya (LWK); people of Mexican ancestry living in Los Angeles, CA (MEX); the Maasai people in Kinyawa, Kenya (MKK); Toscani in Italy (TSI); and Yoruba in Ibadan, Nigeria (YRI), respectively.[17] We used STRUCTURE 2.3.4 (Pritchard Lab, Stanford University, Stanford, CA) (http://pritchardlab.stanford.edu/software/structure_v.2.3.4.html) software to perform population genetic structure comparison that works well on small number of loci. Average number of pair-wise differences, pair-wise F-statistics (Fst) were calculated in Arlequin v3.5.1.3 (Institute of Ecology and Evolution, University of Bern, Bern, Switzerland) with the genotype data of these 80 VIP variants.[18,19] Afterward, we used the MAGE6 software combining with the Fst values to draw out the evolutionary tree of Lisu and 11 HapMap populations.

3. Results

A total of 80 VIP variants in 37 genes were selected from PharmGKB database and the basic characteristics of these variants in Lisu were shown in Table 1. Specific information obtained from Table 1 were detailed characteristics with regard to the gene name, position, nucleotide change, amino acid translation, genotype frequency, and calculated allele frequency distribution. The average sample call rate was above 98.2%, and genotype frequency at each polymorphic locus did not deviate significantly from Hardy–Weinberg expectations in the overall study cohort.

Table 2 shows the comparison of population pair-wise Fst between Lisu and other 11 HapMap populations. Fst distribution is directly related to the variance in allele frequency among subpopulations and is often used to quantify the overall genetic divergence between human populations.[20] According to the comparison results, the lowest Fst value (0.0185) was observed in CHD population, and the highest value was seen in YRI population, which indicated the greater divergence between them. Meanwhile, from Fig. 2, classification of the populations

Figure 1. A map of the world showing the geographical location of all the populations included in the study. ASW = African ancestry in Southwest United States, CEU = Utah, United States residents with Northern and Western European ancestry from the CEPH collection, CHB = Chinese Han in Beijing, CHD = Chinese in metropolitan Denver, GIH = Gujarati Indians in Houston, JPT = Japanese in Tokyo, LWK = Luhya in Webuye, Kenya, MEX = Mexican ancestry in Los Angeles, CA, MKK = Maasai in Kinyawa, Kenya, TSI = Toscani in Italy, YRI = Yoruba in Ibadan, Nigeria.

with their genetic relationships were inferred on phylogenetic trees constructed from Nei genetic distances between pairs of populations,[21] and these results confirmed the proximately phylogenetic relationship between Lisu and CHD populations as well.

Population structure analysis was further conducted to find out the similarity or differentiation among these populations, which based on the Bayesian clustering algorithm to assign the samples within a hypothetical K number of populations.[22] During data processing, we combined present and previously published data to perform genetic structure analysis using STRUCTURE 2.3.4 and assumed different K values ranging from 6 to 8. As shown in Fig. 3, 1 color represented 1 parental population cluster. Each individual was represented by a vertical column partitioned into different color segments. It could be obviously seen that the genetic background of Lisu population was strongly closest to Shaanxi Han ethnic, followed by population of CHD and CHB.

Multiple comparison of the distribution of genotype frequencies between Lisu and other 11 HapMap populations were shown in Table 3 based on the analysis of chi-squared test with the Bonferroni correction. The results showed that there were 14, 22, 1, 24, 25, 2, 20, 5, 19, 12, and 25 selected VIP variants with genotype frequencies in the Lisu that were significantly different from ASW, CEU, CHB, CHD, GIH, JPT, LWK, MEX, MKK, TSI, and YRI populations ($P < .05/[77 \times 11]$), respectively. We also found that rs1540339 located in vitamin D receptor (VDR) was the most significantly different locus between the Lisu and other populations. In addition, the distribution frequencies of rs1801131, rs701265, and rs689466 located in 5,10-methylenetetrahydrofolate reductase (MTHFR), P2RY1, and prostaglandin endoperoxide synthase 2 (PTGS2) genes in the Lisu population were quite different from them of the 11 HapMap populations, and rs1800497 located in ankyrin repeat and kinase domain containing 1 (ANKK1) is the least significant loci among the subjects.

4. Discussion

Pharmacogenomic studies of different ethnic or racial group have been used to develop personalized therapies for individuals with respect to the genotype distribution for purpose of maximum efficacy measurement with minimal adverse effects.[23] However, the relevant pharmacogenomic studies on Lisu ethnic minority population were seldom reported. This was a critical need for pharmacogenomic studies in order to improve the best treatment outcomes for Lisu individuals. In the current study, we examined the distribution of VIP variants genotype frequencies in a sample of Lisu ethnic group and compared the data with other human populations to identify the difference of distribution. The results presented herein suggested that the genetic background of the Lisu was similar to Shaanxi Han ethnic, followed by CHD population. In addition, the genotype frequencies of VDR rs1540339, MTHFR rs1801131, P2RY1 rs701256, as well as PTGS2 rs689466 variants were significantly different from them

Table 1

Basic characteristics of the selected very important pharmacogenomic variants from the PharmGKB database.

Gene	SNP	Chr	Allele		Position	Family	Phase*	Amino acid translation	Function	Allele frequencies		Lisu		
			A	B						A, %	B, %	AA	AB	BB
CYP3A5	rs10264272	7	C	T	99262835	Cytoome P450 superfamily	Phase I	Lys208Lys	Not Available	1	0	100	0	0
ADRB2	rs1800888	5	C	T	148206885	Adrenergic receptors family	Phase I	Thr164Ile	Missense	1	0	100	0	0
	rs1042713	5	G	A	148206440	Adrenergic receptors family	Phase I	Arg16Gly	Missense	0.435	0.565	19	49	32
	rs1042714	5	G	C	148206473	Adrenergic receptors family	Phase I	Gln27Glu	Missense	0.095	0.905	1	17	82
ABCB1	rs1128503	7	A	G	87179601	ATP-binding cassette (ABC) transporters superfamily	Others	Gly412Gly	Synonymous	0.51	0.49	28	46	26
	rs1045642	7	A	G	87138645	ABC transporters superfamily	Others	Ile1145Ile	Synonymous	0.31	0.69	10	42	48
	rs2032582	7	A	C	87160618	ABC transporters superfamily	Others	Ser893Ala	Missense	0.295	0.485	10	39	29
SLC19A1	rs1051266	21	T	C	46957794	Solute carrier family	Others	His27Arg	Missense	0.355	0.615	15	41	41
	rs12659	21	C	T	46951556	Solute carrier family	Others	Pro192Pro	Synonymous	0.585	0.365	41	35	19
P2RY1	rs1065776	3	C	T	152553628	G-protein coupled receptor family	Others	Ala19Ala	Synonymous	0.915	0.055	86	11	0
	rs701265	3	A	G	152554357	G-protein coupled receptor family	Others	Val262Val	Synonymous	0.67	0.33	41	52	7
VDR	rs10735810	12	A	G	48272895	Nuclear receptor family	Others	—	—	0.44	0.55	22	44	33
	rs11568820	12	C	T	48302545	Nuclear receptor family	Others	—	Not available	0.71	0.29	49	44	7
	rs1540339	12	C	T	48257326	Nuclear receptor family	Others	—	Intronic	0.4	0.6	14	52	34
	rs1544410	12	C	T	48239835	Nuclear receptor family	Others	—	Intronic	0.925	0.075	85	15	0
	rs2228570	12	T	C	48272895	Nuclear receptor family	Others	Met51Arg, Met51Lys, Met51Thr	Missense	0.57	0.43	34	46	20
	rs2239179	12	T	C	48257766	Nuclear receptor family	Others	—	Intronic	0	0	0	0	0
	rs2239185	12	G	A	48244559	Nuclear receptor family	Others	—	Intronic	0.71	0.29	48	46	6
	rs731236	12	A	G	48238757	Nuclear receptor family	Others	Ile352Ile	Synonymous	0.915	0.085	83	17	0
	rs7975232	12	C	A	48238837	Nuclear receptor family	Others	—	Intronic	0.71	0.29	48	46	6
UGT1A1	rs10929302	2	G	A	234665782	UDP-glucuronosyltransferase family	Phase II	—	5′ Flanking	0.93	0.07	86	14	0
	rs4124874	2	T	G	234665659	UDP-glucuronosyltransferase family	Phase II	—	5′ Flanking	0.76	0.24	57	38	5
	rs4148323	2	G	A	234669144	UDP-glucuronosyltransferase family	Phase II	Gly71Arg	Intronic	0.815	0.185	69	25	6
GSTP1	rs1138272	11	C	T	67353579	Glutathione S-transferase family	Phase II	Ala114Val	Missense	1	0	100	0	0
	rs1695	11	A	G	67352689	Glutathione S-transferase family	Phase II	Ile105Val	Missense	0.77	0.23	61	32	7
TPMT	rs1142345	6	T	C	18130918	Methyltransferase superfamily	Phase II	Tyr240Cys	Missense	0.96	0.01	95	2	0
	rs1800460	6	A	G	18139228	Methyltransferase superfamily	Phase II	Ala154Thr	Missense	1	0	100	0	0
	rs1800462	6	C	G	18143955	—	Others	Ala80Pro	Missense	0.97	0	97	0	0
ADH1B	rs1229984	4	T	C	100239319	Alcohol dehydrogenase	Phase I	His48Arg	Missense	0.365	0.625	10	53	36
	rs2066702	4	G	A	100229017	Alcohol dehydrogenase	Phase I	Arg370Cys	Missense	1	0	100	0	0
KCNH2	rs12720441	7	G	A	150647304	Eag family	Others	Arg444Trp	Missense	1	0	100	0	0
	rs3807375	7	C	T	150667210	Eag family	Others	—	Intronic	0.225	0.775	8	29	63
	rs36210421	7	G	T	150644428	Eag family	Others	Arg707Leu	Missense	1	0	100	0	0
CYP3A4	rs12721634	7	C	T	99381661	Cytoome P450 superfamily	Phase I	Leu15Pro	Missense	1	0	100	0	0
	rs4986909	7	G	A	99359670	Cytoome P450 superfamily	Phase I	Pro416Leu	Missense	1	0	100	0	0
	rs4986910	7	A	G	99358524	Cytoome P450 superfamily	Phase I	Met445Thr	Missense	1	0	100	0	0
	rs4986913	7	G	A	99358459	Cytoome P450 superfamily	Phase I	Pro467Ser	Missense	1	0	100	0	0
	rs2740574	7	A	G	99382096	Cytoome P450 superfamily	Phase I	—	5′ Flanking	1	0	100	0	0
CYP2D6	rs16947	22	A	G	42523943	Cytoome P450 superfamily	Phase I	—	Not available	0.8	0.2	60	40	0
	rs28371706	22	G	A	42525772	Cytoome P450 superfamily	Phase I	Thr107Ile	Missense	1	0	100	0	0
	rs28371725	22	A	G	42523805	Cytoome P450 superfamily	Phase I	—	Intronic	0.935	0.065	88	11	1
	rs5030656	22	—	AAG	42128174	Cytoome P450 superfamily	Phase I	—	Nonsynonymous	1	0	100	0	0
	rs59421388	22	C	T	42523610	Cytoome P450 superfamily	Phase I	Val287Met	Missense	1	0	100	0	0
	rs61736512	22	C	T	42525134	Cytoome P450 superfamily	Phase I	Val136Met	Intronic	1	0	100	0	0
HMGCR	rs17238540	5	G	T	74655498	—	Phase I	—	Intronic	1	0	100	0	0
	rs17244841	5	A	T	74642855	—	Phase I	—	Intronic	0.97	0.03	94	6	0
	rs3846662	5	A	G	74651084	3-Hydroxy-3-methylglutaryl-CoA reductase	Phase I	—	Intronic	0.495	0.505	25	49	26
CYP2C9	rs1799853	10	C	T	96702047	Cytoome P450 superfamily	Phase I	Arg144Cys	Missense	1	0	100	0	0
ANKK1	rs1800497	11	G	A	113270828	Ser/Thr protein kinase family	Phase I	Glu713Lys	Missense	0.62	0.38	38	48	14
NQO1	rs1800566	16	G	A	69711242	—	Others	Pro187Ser	Missense	0.685	0.315	45	47	8
SULT1A1	rs3760091	16	G	C	28609479	Sulfotransferase family	Phase II	—	5′ Flanking	0.65	0.35	35	60	5
	rs1801030	16	C	T	28617485	Sulfotransferase family	Phase II	Val223Met	Not available	0	1	0	0	100
MTHFR	rs1801131	1	T	G	11854476	Methylenetetrahydrofolate reductase family	Phase I	Glu429Ala	Missense	0.915	0.085	83	17	0
	rs1801133	1	G	A	11856378	Methylenetetrahydrofolate reductase family	Phase I	Ala222Val	Missense	0.565	0.435	38	37	25
ADRB1	rs1801253	10	G	C	115805056	Adrenergic receptors family	Phase I	Gly389Arg	Missense	0.27	0.73	9	36	55
CYP2A6	rs1801272	19	A	T	41354533	Cytoome P450 superfamily	Phase I	Leu160His	Missense	0	1	0	0	100
	rs28399433	19	G	T	41356379	Cytoome P450 superfamily	Phase I	—	5′ Flanking	0.79	0.21	64	30	6

(*continued*)

Table 1

(continued).

Gene	SNP	Chr	Allele A	Allele B	Position	Family	Phase*	Amino acid translation	Function	Allele frequencies A, %	Allele frequencies B, %	Lisu AA	Lisu AB	Lisu BB
	rs28399444	19	G	A	41354190	Cytoome P450 superfamily	Phase I	Glu197Ser, Glu197Arg	Frameshift	1	0	100	0	0
	rs28399454	19	C	T	41351267	Cytoome P450 superfamily	Phase I	Val365Met	Missense	1	0	100	0	0
SCN5A	rs1805124	3	T	C	38645420	Sodium channel gene family	Others	Pro1090Leu	Missense	0.725	0.275	50	45	5
	rs6791924	3	G	A	38674699	Sodium channel gene family	Others	Arg34Cys	Missense	1	0	100	0	0
	rs7626962	3	T	G	38620907	Sodium channel gene family	Others	Ser1103Tyr	Missense	1	0	100	0	0
P2RY12	rs2046934	3	G	A	151057642	G-protein coupled receptor family	Others	—	Intronic	0.245	0.755	9	31	60
AHR	rs2066853	7	G	A	17379110	—	Others	Arg554Lys	Missense	0.68	0.32	49	38	13
CYP2B6	rs28399499	19	T	C	41518221	Cytoome P450 superfamily	Phase I	Ile328Thr	Missense	1	0	100	0	0
	rs3745274	19	G	T	41512841	Cytoome P450 superfamily	Phase I	Gln172His	Missense	0.935	0.065	87	13	0
TS	rs34489327	18	—	/	663541	/	Others	—	Not available	1	0	100	0	0
NR1I2	rs3814055	3	C	T	119500035	Nuclear receptor family	Others	—	5′ Flanking	0.805	0.195	63	35	2
DPYD	rs3918290	1	C	T	97915614	Dihydropyrimidine dehydrogenase	Phase I	—	Donor	1	0	100	0	0
SLCO1B1	rs4149056	12	T	C	21331549	solute carrier family	Others	Val174Ala	Missense	0.975	0.025	95	5	0
COMT	rs4680	22	G	A	19951271	Catechol-O-methyltransferase	Phase II	Val158Met	5′ Flanking	0.75	0.25	59	32	9
CYP2C19	rs4986893	10	A	G	96540410	Cytoome P450 superfamily	Phase I	Trp212null	Stop codon	0.975	0.025	95	5	0
PTGIS	rs5629	20	G	T	48129706	Prostaglandin I2 (prostacyclin) synthase	Others	Arg373Arg	Synonymous	0.815	0.175	69	25	5
ALDH1A1	rs6151031	9	—	—	72953467	Aldehyde dehydrogenase 1 family	Others	—	5′ Flanking	0.995	0.005	99	1	0
DRD2	rs6277	11	G	A	113283459	G-protein coupled receptor family	Others	Pro290Pro	Synonymous	0.97	0.03	94	6	0
PTGS2	rs689466	1	T	C	186650751	Prostaglandin-endoperoxide synthase 2	Phase I	—	5′ Flanking	0.59	0.41	36	46	18
VKORC1	rs7294	16	C	T	31102321	Vitamin K epoxide reductase complex	Phase I	—	3′ UTR	0.965	0.035	93	7	0
	rs9923231	16	A	C	31096368	Vitamin K epoxide reductase complex	Others	—	5′ Flanking	0.995	0.005	99	1	0
	rs9934438	16	G	A	31104878	Vitamin K epoxide reductase complex	Phase I	—	Intronic	0.035	0.965	0	7	93
ADH1A	rs975833	4	G	C	100201739	Alcohol dehydrogenase family	Phase I	—	Intronic	0.36	0.64	8	56	36

SNP = single nucleotide polymorphism.

* Phase I and Phase II represent that the gene is involved in drug phase I metabolisms and drug phase II metabolisms, respectively.

in other ethnic groups. And rs1800497 located in ANKK1 was the least significantly loci among the subjects.

As the most significant locus in our data, VDR gene is implicated in regulation of vitamin D 1,25-dihydroxyvitamin D3 activity, and has extensive polymorphisms such as *Apa*I, *Bsm*I, *Fok*I, and *Taq*I sites.[24] Polymorphisms within VDR gene are associated with vitamin D levels, immunologic response, glucose metabolism, bone mineral density, and lung function in children, as well as, childhood asthma, insulin-dependent diabetes mellitus disease, and prostate cancer.[25] A association study between rs1540339 and type 1 diabetes mellitus (T1DM) ($P = .02$) showed that rs1540339 CT genotype was more frequent in the control group (47.7%) than patients (35.4%), thus conferring protection for T1DM.[26] In our data, nearly 1/2 of the Lisu individuals carried "CT" genotype, suggesting that the Lisus may have decreased susceptibility to T1DM, which is consistent with the results of the Li population, a ethnic group lived on Hainan Island in China.[10]

The gene MTHFR, located on the short arm of chromosome 1 (1p36.3), catalyzes the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate and is involved in DNA synthesis, repair, methylation, and folate metabolism.[27] The A to C transition at position 1298 (A1298C, rs1801131) results in amino acid changes from glutamate to alanine at codon position 429 and leads to reduced MTHFR activity.[28] Genetic polymorphisms in MTHFR gene may be linked to colorectal

Table 2

Distribution of pair-wise F-statistics distances among the 12 populations.

	Lisu	CHB	CHD	JPT	CEU	GIH	MEX	TSI	ASW	LWK	MKK	YRI
Lisu	0											
CHB	0.02011	0										
CHD	0.0185	−0.00161	0									
JPT	0.02125	0.00586	0.00761	0								
CEU	0.11711	0.13026	0.12708	0.11499	0							
GIH	0.1642	0.15697	0.15321	0.14338	0.03311	0						
MEX	0.07461	0.08424	0.07821	0.08033	0.02248	0.05258	0					
TSI	0.10839	0.11524	0.11626	0.10172	0.00012	0.04047	0.02447	0				
ASW	0.18902	0.1955	0.19394	0.17125	0.12124	0.08173	0.11144	0.12461	0			
LWK	0.26286	0.26654	0.26764	0.23703	0.18539	0.14618	0.18563	0.19061	0.01719	0		
MKK	0.22698	0.23189	0.23406	0.19985	0.13638	0.10553	0.15181	0.14253	0.01888	0.01336	0	
YRI	0.26826	0.26827	0.27045	0.23703	0.19138	0.14351	0.19235	0.1978	0.01513	0.00383	0.01359	0

ASW = African ancestry in Southwest United States, CEU = Utah, United States residents with Northern and Western European ancestry from the CEPH collection, CHB = Chinese Han in Beijing, CHD = Chinese in metropolitan Denver, GIH = Gujarati Indians in Houston, JPT = Japanese in Tokyo, LWK = Luhya in Webuye, Kenya, MEX = Mexican ancestry in Los Angeles, CA, MKK = Maasai in Kinyawa, Kenya, TSI = Toscani in Italy, YRI = Yoruba in Ibadan, Nigeria.

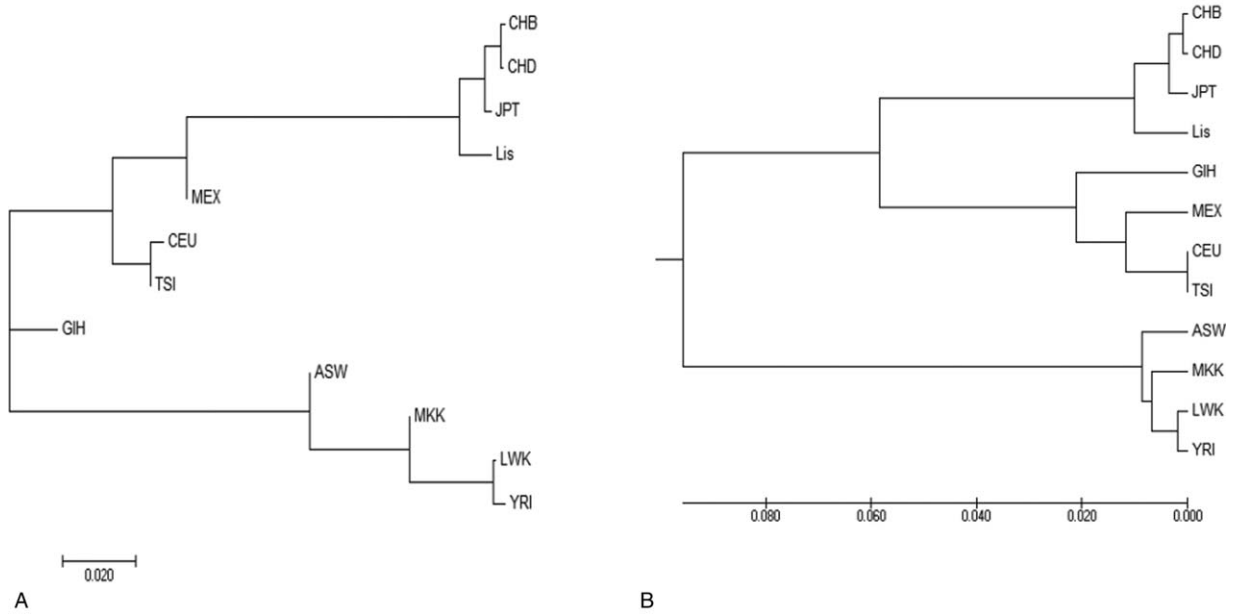

Figure 2. The phylogenetic trees between Lisu and other 11 HapMap ethnic groups. (A) Neighbor-Joining Tree. (B) UPGMA Tree.

Table 3

Significant very important pharmacogenomic variants in Lisus compared with the 11 HapMap populations after Bonferroni multiple adjustment.

	$P < .05/(77 \times 11)$										
SNP ID	**ASW**	**CEU**	**CHB**	**CHD**	**GIH**	**JPT**	**LWK**	**MEX**	**MKK**	**TSI**	**YRI**
rs10264272	—	—	—	*7.70E−31*	*2.01E−21*	—	*1.45E−12*	—	*8.82E−08*	—	*8.95E−09*
rs1042713	1.00E+00	1.44E−04	4.50E−01	—	—	6.29E−02	6.23E−01	1.51E−01	8.54E−01	8.63E−05	2.82E−01
rs1042714	—	*7.56E−10*	4.72E−01	*8.13E−10*	*1.06E−18*	5.88E−01	—	—	—	—	1.17E−01
rs1045642	1.40E−01	*2.26E−07*	1.22E−01	6.18E−03	1.55E−01	6.10E−03	—	2.94E−02	2.69E−04	1.03E−02	*4.82E−06*
rs1051266	1.55E−01	9.97E−02	5.09E−02	—	—	1.70E−03	*1.34E−10*	8.26E−01	*6.63E−15*	2.88E−01	*1.24E−08*
rs1065776	—	—	—	*1.60E−17*	*5.68E−26*	—	—	—	—	—	—
rs10735810	1.94E−04	8.08E−01	3.44E−01	—	—	4.93E−02	*1.07E−07*	4.70E−01	*1.71E−07*	4.92E−01	*8.80E−07*
rs10929302	—	*6.29E−06*	—	*1.71E−08*	*7.70E−13*	—	—	—	—	—	*1.66E−08*
rs1128503	*1.24E−06*	1.24E−01	1.14E−03	—	*1.29E−13*	3.22E−01	*2.68E−13*	3.63E−01	*3.87E−14*	2.86E−01	*1.91E−14*
rs1138272	—	—	—	—	—	—	—	6.47E−04	—	—	—
rs1142345	—	—	—	*2.80E−16*	*2.21E−19*	—	1.74E−04	1.48E−02	—	—	1.49E−01
rs11568820	*4.69E−11*	1.05E−01	3.21E−03	—	—	1.63E−03	*1.11E−23*	1.41E−01	*3.28E−21*	5.48E−01	*4.00E−37*
rs1229984	—	*1.85E−14*	*9.01E−10*	—	—	*1.74E−08*	—	—	—	—	*2.76E−14*
rs12659	—	—	—	—	—	—	—	—	—	—	—
rs12720441	—	—	—	—	—	—	—	—	—	—	—
rs12721634	—	—	—	*9.80E−37*	*3.44E−16*	—	—	—	—	—	—
rs1540339	*2.96E−08*	*6.05E−06*	5.49E−02	*3.98E−25*	1.54E−03	1.09E−02	*1.38E−17*	1.64E−03	*5.93E−18*	*9.61E−06*	*2.06E−14*
rs1544410	—	*1.17E−13*	—	—	—	—	*2.03E−05*	2.42E−04	*2.03E−11*	*2.48E−12*	*5.23E−07*
rs16947	—	—	—	2.85E−01	2.16E−03	—	—	—	—	—	—
rs1695	3.94E−04	1.12E−04	3.51E−01	—	—	3.50E−03	*4.81E−08*	*2.89E−06*	9.31E−03	1.31E−01	1.22E−03
rs17238540	—	—	—	—	—	—	—	—	—	—	—
rs17244841	—	—	—	—	—	—	—	—	—	—	—
rs1799853	—	—	—	—	—	—	—	—	—	—	—
rs1800460	—	—	—	—	—	—	—	—	—	—	—
rs1800462	—	—	—	*3.97E−22*	*1.48E−12*	—	—	—	—	—	—
rs1800497	7.11E−01	1.37E−04	5.29E−01	6.67E−02	5.05E−01	8.65E−01	9.43E−01	5.71E−01	8.58E−01	1.44E−03	8.04E−01
rs1800566	1.27E−01	6.60E−03	6.43E−04	—	—	7.44E−01	5.03E−03	3.05E−01	4.99E−04	1.04E−01	1.07E−02
rs1800888	—	—	—	—	—	—	—	—	—	—	—
rs1801030	—	—	—	*5.98E−36*	*3.57E−30*	—	—	—	—	—	—
rs1801131	1.97E−02	*5.31E−09*	9.18E−04	*2.97E−08*	3.26E−02	1.15E−02	1.45E−02	6.15E−03	*1.03E−05*	*8.67E−07*	4.60E−01
rs1801133	*7.32E−07*	6.45E−03	2.92E−01	—	—	5.11E−02	*2.18E−10*	1.88E−01	*2.21E−14*	7.27E−01	*7.46E−12*
rs1801253	—	6.56E−01	6.55E−01	—	—	9.19E−02	—	—	—	—	2.80E−02

(*continued*)

Table 3

(continued).

	$P < .05/(77 \times 11)$										
SNP ID	ASW	CEU	CHB	CHD	GIH	JPT	LWK	MEX	MKK	TSI	YRI
rs1801272	—	*1.80E−35*	—	*6.73E−41*	*7.70E−40*	*5.38E−32*	—	—	—	—	—
rs1805124	8.14E−01	3.17E−02	1.57E−04	*2.20E−05*	2.58E−01	1.32E−03	6.37E−01	3.55E−02	1.18E−01	3.95E−01	8.41E−01
rs2032582	*2.19E−06*	1.79E−01	8.04E−04	—	—	5.00E−03	*1.22E−15*	6.80E−01	*6.35E−12*	4.89E−01	—
rs2046934	—	3.06E−01	6.48E−01	—	—	3.42E−01	—	—	—	—	1.48E−01
rs2066702	*1.06E−10*	—	—	*1.06E−19*	*2.44E−05*	—	*4.08E−07*	—	—	—	*5.65E−15*
rs2066853	1.30E−01	*7.17E−07*	1.86E−01	—	—	1.74E−02	2.74E−03	1.79E−03	3.53E−01	*1.34E−06*	3.08E−02
rs2228570	—	—	—	2.04E−04	4.16E−01	—	—	—	—	—	—
rs2239179	—	—	—	—	—	—	—	—	—	—	—
rs2239185	—	—	1.85E−01	—	—	1.75E−01	—	—	—	—	*2.41E−05*
rs2740574	—	—	—	—	—	—	—	—	—	—	—
rs28371706	—	—	—	—	—	—	—	—	—	—	—
rs28371725	—	—	—	—	—	—	—	—	—	—	—
rs28399433	—	—	—	—	—	—	—	—	—	—	—
rs28399444	—	—	—	—	—	—	—	—	—	—	—
rs28399454	—	—	—	—	—	—	—	—	—	—	—
rs28399499	3.48E−04	—	—	—	—	—	—	—	1.68E−01	—	*2.04E−06*
rs34489327	—	—	—	—	—	—	—	—	—	—	—
rs36210421	—	—	—	*1.95E−07*	*2.09E−20*	—	—	—	—	—	—
rs3745274	*1.16E−06*	*3.16E−07*	5.90E−03	—	—	3.78E−03	*1.22E−08*	*3.64E−07*	*2.39E−13*	*2.36E−07*	*1.38E−14*
rs3760091	—	—	—	*3.62E−13*	1.51E−01	—	—	—	—	—	—
rs3807375	7.57E−02	*2.24E−14*	3.13E−01	*1.06E−16*	*3.55E−10*	8.30E−02	6.74E−01	4.73E−03	7.22E−02	*4.21E−14*	4.77E−01
rs3814055	4.21E−02	3.25E−03	5.61E−02	*1.82E−10*	*6.69E−16*	4.58E−02	2.71E−02	1.32E−01	7.74E−01	2.14E−04	1.50E−02
rs3846662	*9.06E−09*	2.59E−01	8.96E−01	—	*3.09E−22*	5.29E−01	*7.46E−20*	9.33E−02	*4.44E−13*	5.46E−01	*1.22E−21*
rs3918290	—	—	—	*3.13E−18*	*1.27E−33*	—	—	—	—	—	—
rs4124874	*1.56E−15*	*5.09E−05*	1.07E−01	1.23E−01	*8.88E−09*	1.34E−01	*1.66E−26*	*1.96E−05*	*2.73E−28*	6.18E−04	*1.56E−31*
rs4148323	—	*9.78E−06*	2.16E−02	3.03E−01	*1.67E−05*	2.10E−01	—	3.21E−03	—	—	*9.78E−06*
rs4149056	3.10E−01	*2.40E−05*	6.68E−05	*2.99E−13*	*2.32E−16*	6.33E−03	—	—	1.40E−03	*4.15E−08*	—
rs4680	8.37E−01	*2.55E−05*	5.69E−01	—	—	2.96E−01	2.54E−01	4.86E−02	7.01E−01	1.08E−04	1.31E−01
rs4986893	—	—	—	—	—	—	—	—	—	—	—
rs4986909	—	—	—	—	—	—	—	—	—	—	—
rs4986910	—	—	—	—	—	—	—	—	—	—	—
rs4986913	—	—	—	—	—	—	—	—	—	—	—
rs5030656	—	—	—	*2.37E−13*	*7.20E−13*	—	—	—	—	—	—
rs5629	9.32E−01	5.08E−01	9.88E−03	—	—	6.54E−02	2.55E−02	1.49E−01	7.87E−02	1.06E−03	3.58E−01
rs59421388	—	—	—	—	—	—	—	—	—	—	—
rs6151031	—	—	—	—	—	—	—	—	—	—	—
rs61736512	—	—	—	—	—	—	—	—	—	—	—
rs6277	—	*8.04E−22*	—	—	—	—	—	—	—	—	—
rs6791924	—	—	—	*2.61E−22*	*1.63E−07*	—	—	—	—	—	—
rs689466	*7.62E−07*	*7.62E−07*	1.98E−01	4.95E−03	4.11E−04	4.00E−01	*2.78E−15*	2.25E−02	*2.67E−21*	*7.72E−06*	*7.52E−12*
rs701265	*9.43E−09*	1.00E−03	2.08E−01	*2.77E−09*	*5.34E−12*	1.26E−01	*6.81E−18*	1.55E−02	*2.39E−17*	1.27E−04	*1.35E−19*
rs7294	*2.00E−18*	*3.89E−15*	—	—	*4.04E−11*	—	*5.77E−19*	*1.14E−10*	*4.80E−23*	*1.24E−13*	*2.28E−23*
rs731236	8.34E−04	*7.65E−13*	—	—	—	—	*3.04E−05*	2.06E−04	*1.15E−16*	*1.54E−11*	*5.05E−07*
rs7626962	—	—	—	*4.88E−15*	*7.05E−29*	—	—	—	—	—	1.24E−03
rs7975232	*4.32E−08*	*7.25E−08*	2.81E−01	—	—	3.76E−01	*5.59E−15*	1.15E−02	*1.06E−14*	*3.00E−08*	*9.36E−11*
rs975833	—	*2.93E−09*	4.26E−04	—	—	7.34E−03	—	—	—	—	*3.92E−10*
rs9923231	—	—	—	*7.03E−40*	*7.22E−10*	—	—	—	—	—	—
rs9934438	*4.60E−28*	*3.59E−26*	—	—	—	—	*2.94E−38*	*2.16E−18*	*1.52E−45*	*6.29E−22*	*1.95E−44*

ASW = African ancestry in Southwest United States, CEU = Utah, United States residents with Northern and Western European ancestry from the CEPH collection, CHB = Chinese Han in Beijing, CHD = Chinese in metropolitan Denver, GIH = Gujarati Indians in Houston, JPT = Japanese in Tokyo, LWK = Luhya in Webuye, Kenya, MEX = Mexican ancestry in Los Angeles, CA, MKK = Maasai in Kinyawa, Kenya, TSI = Toscani in Italy, YRI = Yoruba in Ibadan, Nigeria.

Italics indicates the locus with statistical significance ($P < .05/(77*11)$).

cancer, autoimmune diseases, and bronchodilator responsiveness.[27,28] Among Caucasians with rheumatoid arthritis, individuals carrying 1298 A allele had a frequency about 0.66, which was more likely to associate with the increase of antifolate drug methotrexate (MTX)-related adverse events (odds ratio [OR] = 15.86, 95% confidence interval [CI] = 1.51–167.01, $P = .021$) compared with A/A or A/G individuals.[29] In our study, the A allele frequency of rs1801131 in Lisu was particularly high (91%) and similar to YRI population, meaning that dose of drugs related to the MTHFR gene in Lisu can be analogous to that used for YRI patients, and patients with this genotype will require a lower dose of MTX to prevent the side effect.

The P2RY1 gene, coding for adenosine diphosphate (ADP)/adenosine triphosphate receptor, plays a crucial role in platelet activation.[30] Rs701265 (A1622G) in P2RY1 has been reported to be associated with increased platelet aggregation in response to ADP among White individuals.[31] Especially 1 study suggested

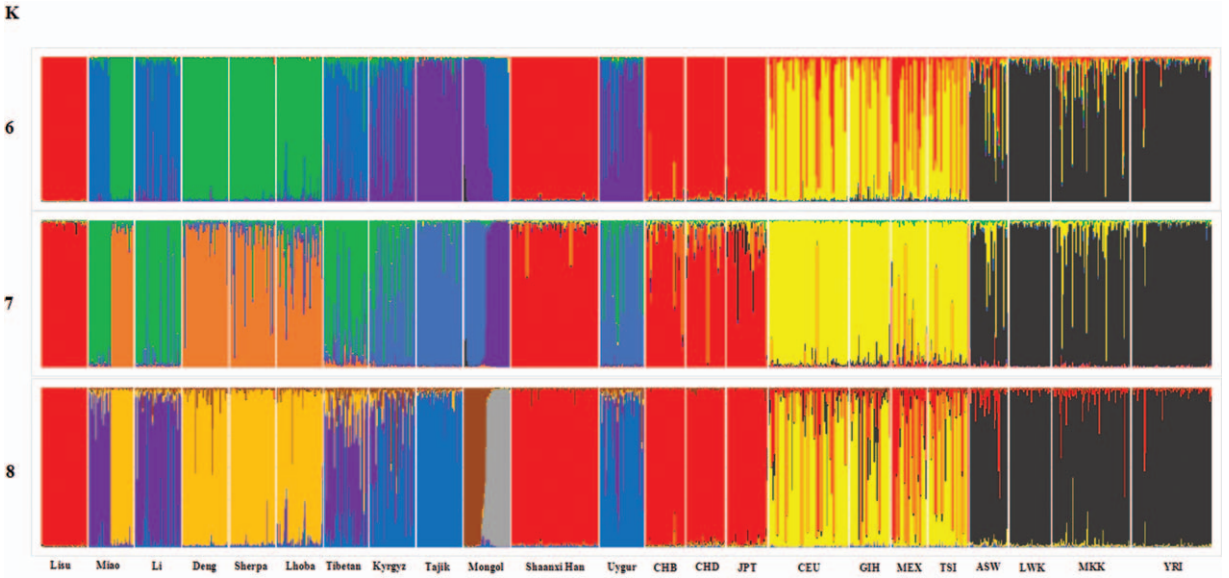

Figure 3. Bayesian clustering of genotypic samples from 23 populations. Each vertical bar denotes an individual, while colors denote inferred clusters. Note that colors are not universal between K = 6 and 8.

that the genotype frequencies of P2RY1 1622 GG carriers were presented with significantly higher risk of platelet aggregation than their 1622 AA or AG individuals.[32] We found that the GG genotype frequency of rs701265 was lower (0.7%) in the Lisu population, which suggested that Lisu people may have decreased susceptibility to platelet aggregation. And importantly, it can provide theoretical basis for medication guidance in ADP-induced platelet aggregation after aspirin treatment.

PTGS2 gene, which also known as cyclooxygenase 2 (COX-2), is located on chromosome 1q25.2-q25.3 and regulates the synthesis of prostaglandins modulates cell proliferation, apoptosis, and angiogenesis in a large proportion of adenoma and carcinoma tissues.[33] The rs689466 polymorphism also described as –1195G>A in PTGS2 was found associated with asthma in Australian Caucasians,[34] colorectal cancer in Norwegian cohorts,[33] and esophageal cancer in Han Chinese population.[35] A study carried out in the Chinese Han population showed that subjects carrying the 1195AA genotype had a 1.34-fold in intensifying risk of pancreatic cancer compared with subjects carrying the 1195GG genotype (95% CI = 1.12–1.60), and the 1195GA genotype had no such effect (OR = 1.14, 95% CI = 0.97–1.33).[36] Carriers with AA genotype (36%) versus GG genotype (18%) were observed in our subjects, which suggested that the screening of high-risk Lisu individuals with genotype AA should be pay more attention for prevention of pancreatic cancer at early stage.

As the least significant locus in our data, rs1800497 is located within exon 8 of the ANKK1 gene encoding a glutamate to lysine substitution at amino acid position 713 that may alter substrate binding specificity.[37] Presence of the rs1800497 T allele was linked to a 30% to 40% reduction of dopamine D2 receptor (DRD2) density in ventral striatum compared with homozygote of C allele.[38] In our study, C allele and T allele carriers had the frequency about 0.62 and 0.38, respectively, suggesting that carriers with T allele may require increased dopaminergic tone to achieve similar levels of reinforcement. Besides, the T allele polymorphism also found to be involved in traumatic brain injury treatment and citicoline dose-dependent effect for cognitive performance.[39] These findings may be useful in personalize treatment of these diseases based on individual's genetic makeup.

Our study also demonstrated the genetic background among the ethnic groups through Fst calculations, population structure, and evolutionary relationship analysis. The interpretation of genetic diversity among populations may be based on large geographic distances deriving from a series of prehistoric migrations or a common origin for the interpretation of similarity.[40,41] Our results showed a stronger correlation between Lisu and Shaanxi Han ethnic population, suggesting they had a homogeneous genetic background. Given ethnic disparities in genetic polymorphism and access to effective treatments for diseases, considerable studies of ethnic background in clinical trials and human laboratory may provide greater access to personalized treatments.

In summary, understanding the association between pharmacogenomics, ethnic diversity, and drug response is critical for the implementation of personalized medicine. Our findings were in agreement with previous studies and supposed to complement the data for the Lisu ethnic group in the pharmacogenomic database, as well as provide the basis for more effective and safer drug administration for the Lisus. Further investigation should focus on studies with larger sample sizes, in the hope that they will provide results of high clinical significance.

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