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, Dong, Sherpa, Lhoba, Tibetan, Kirghiz, Tajik, Mongol, Shaanxi Han ethnic, and Uygur populations. VDR rs1540339, MTHFR rs1801131, F2R1Y1 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, OI = confidence interval, Fst = F-statistics, GH1 = 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.\[6\] SLC01B1, known as a member of solute carrier organic anion transporter family, have been performed in healthy
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. 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. 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 germline mutations in genes with pharmacokinetic or pharmacodynamic impact. 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, Li, Deng, Sherpa, Lhoba, Tibetan, Kyrgyz, Tajik, Mongol, Shannxi Han ethnic, Uygur, 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 ancestors 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.

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 50 variants located in 37 genes for genotyping. Genomic DNA was isolated from peripheral blood with GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Ltd, Xi’an, China) according to the manufacturer’s protocol, and DNA concentration was determined by NanoDrop 2000C spectrophotometer (Thermo Scientific, Waltham, MA). Multiplex SNPs were designed by Sequenom MassARRAY Assay Design 3.0 software (San Diego, CA). 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.

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 × 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. We used STRUCTURE 2.3.4 (Pritchard Lab, Stanford University, Stanford, CA) (http://pritchardlab.stanford.edu/software/structure_v2.3.4.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. 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. 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
with their genetic relationships were inferred on phylogenetic trees constructed from Nei genetic distances between pairs of populations,\[21\] and these results confirmed the proximally 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, 3, 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-methyltetrahydrofolate 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 rs701265, 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 | A | B | Position | Family | Phase | Amino acid translation | Function | Allele frequencies | Lipid | Genotype |
|------|-----|-----|---|---|----------|--------|-------|------------------------|----------|---------------------|-------|----------|
| CYP2D6 | rs16947 | 22 | A | G | 42523943 | Cytoome P450 superfamily | Phase I | Lys208Lys | Not Available | 1 | 0 | 100 | 0 | 0 |
| MTHFR | rs1801131 | 1 | T | G | 11854476 | Methylenetetrahydrofolate reductase | Phase I | | | 0.31 | 0.69 | 10 | 42 | 48 |
| TPMT | rs1142345 | 6 | T | C | 18130918 | Methyltransferase superfamily | Phase II | Tyr240Cys | Missense | 0.96 | 0.04 | 95 | 2 | 0 |
| GSTP1 | rs1138272 | 11 | C | T | 67353579 | Glutathione S-transferase family | Phase II | Ala114Val | Missense | 0.95 | 0.05 | 86 | 11 | 0 |
| CYP2A6 | rs1801272 | 19 | A | T | 41354533 | Cytoome P450 superfamily | Phase I | Leu160His | Missense | 0 | 1 | 0 | 0 | 100 |
| ADRB1 | rs1801253 | 10 | G | C | 11580506 | Adrenergic receptors family | Phase I | Gly389Arg | Missense | 0.72 | 0.28 | 3 | 9 | 66 |
| CYP2A6 | rs1801259 | 22 | A | G | 87160818 | ABC transporters superfamily | Other | | | 0.29 | 0.71 | 10 | 90 | 10 |
| ABCB1 | rs1128503 | 7 | A | G | 87198601 | ATP-binding cassette (ABC) | Other | Gly4120y | Synonymous | 0.51 | 0.49 | 28 | 46 | 26 |

(continued)
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 Apal, BsmI, FokI, and TaqI sites. Polymorphisms within VDR gene are associated with vitamin D levels, immunoregulatory response, glucose metabolism, bone mineral density, and lung function in children, as well as, childhood asthma, insulin-dependent diabetes mellitus disease, and prostate cancer. A association study between rs1540339 and type 1 diabetes mellitus (T1DM) (P = 0.02) showed that rs1540339 CT genotype was more frequent in the control group (47.7%) than patients (35.4%), thus conferring protection for T1DM. 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, an ethnic group lived on Hainan Island in China.

The gene MTHFR, located on the short arm of chromosome 1 (1p36.3), catalyzes the irreversible conversion of 5,10-methylene tetrahydrofolate to 5-methyltetrahydrofolate and is involved in DNA synthesis, repair, methylation, and folate metabolism. A association between rs1540339 and type 1 diabetes mellitus (T1DM) (P = 0.02) showed that rs1540339 CT genotype was more frequent in the control group (47.7%) than patients (35.4%), thus conferring protection for T1DM. 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, an ethnic group lived on Hainan Island in China.

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### Table 1

| Gene   | SNP     | Chr | Position | Family | Phase | Amino acid translation | Function | Allele frequencies | Liu |
|--------|---------|-----|----------|--------|-------|------------------------|----------|-------------------|-----|
| rs28399444 | G A   | 19 | 43541960 | Cytochrome P450 superfamily | Phase I | Gly197Ser, Gly197Arg | Frameshift | 1 0 | 100 0 0 |
| rs28399454 | C T   | 19 | 43512676 | Cytochrome P450 superfamily | Phase I | Val368Met | Missense | 1 0 | 100 0 0 |
| rs1805124 | C T C | 3 | 38645439 | Sodium channel gene family | Others | Pro1096Leu | Missense | 0.725 0.275 | 50 45 5 |
| rs6791924 | G A   | 3 | 38674699 | Sodium channel gene family | Others | Arg340Gly | Missense | 1 0 | 100 0 0 |
| rs7626862 | C T G | 3 | 38620907 | Sodium channel gene family | Others | Ser1103 Tyr | Missense | 1 0 | 100 0 0 |
| rs2046934 | G A   | 3 | 151057624 | G-protein coupled receptor family | Others | — | Intrinsic | 0.245 0.755 | 31 60 |
| rs2066853 | G A   | 19 | 41512821 | Cytochrome P450 superfamily | Phase I | Ile328Thr | Missense | 1 0 | 100 0 0 |
| rs3745274 | G T   | 19 | 41512641 | Cytochrome P450 superfamily | Phase I | Gin172His | Missense | 0.935 0.065 | 87 13 0 |
| rs3449327 | C T   | 18 | 663541 | Nuclear receptor family | Others | — | Not available | 1 0 | 100 0 0 |
| rs3814055 | C T   | 3 | 11950035 | Nuclear receptor family | Others | — | 5’ Flanking | 0.805 0.195 | 63 35 2 |
| rs18915920 | C T | 1 | 97916514 | Dihydropyrimidine dehydrogenase | Phase I | — | Donor | 1 0 | 100 0 0 |
| rs4140056 | A B | 12 | 21331549 | Solute carrier family | Others | Val1744 Ala | Missense | 0.975 0.025 | 95 5 0 |
| rs6680 | C T | 19 | 17491271 | Catechol-O-methyltransferase | Phase II | Val158 Met | 5’ Flanking | 0.75 0.25 | 59 32 9 |
| rs4986993 | G T | 3 | 96540410 | Prostaglandin-endoperoxide synthase 2 | Phase I | Trp212 X | Stop Codon | 0.975 0.025 | 95 5 0 |
| rs6529 | G T | 20 | 48129706 | Prostaglandin D2 (prostaglandin) synthase | Others | Arg532Arg | Synonymous | 0.815 0.185 | 69 25 5 |
| rs671031 | G A | 7 | 7253467 | G-protein coupled receptor family | Others | Arg34 Cys | Missense | 1 0 | 100 0 0 |
| rs689466 | G C | 3 | 186650751 | Prostaglandin-endoperoxide synthase 2 | Phase I | — | 5’ Flanking | 0.59 0.41 | 36 46 18 |
| rs19274 | C T | 16 | 31096368 | Vitamin K epoxide reductase complex | Others | — | 3’ UTR | 0.965 0.035 | 93 7 0 |
| rs2932331 | C T | 16 | 31096388 | Vitamin K epoxide reductase complex | Others | — | 5’ Flanking | 0.995 0.005 | 99 1 0 |
| rs9934438 | G A | 16 | 31104878 | Vitamin K epoxide reductase complex | Others | — | Intrinsic | 0.035 0.965 | 0 7 93 |
| rs3745274 | C T | 19 | 41512641 | Cytochrome P450 superfamily | Phase I | Gin172His | Missense | 0.935 0.065 | 87 13 0 |

Table 2

| Liu | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|-----|---|---|---|---|---|---|---|
| CHB | 0.02011 | 0 | 0 | 0 | 0 | 0 | 0 |
| CHB | 0.0185 | 0.00061 | 0 | 0 | 0 | 0 | 0 |
| JPT | 0.11711 | 0.13026 | 0.12708 | 0.11499 | 0 | 0 | 0 |
| CEU | 0.1642 | 0.15697 | 0.15321 | 0.14388 | 0.03311 | 0 | 0 |
| MEX | 0.07461 | 0.08424 | 0.07821 | 0.08033 | 0.02248 | 0.05258 | 0 |
| TSI | 0.10839 | 0.11524 | 0.11626 | 0.1072 | 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 | 0.26296 | 0.26954 | 0.26764 | 0.23703 | 0.18539 | 0.14616 | 0.18563 | 0.19061 | 0.01719 | 0 |
| MKK | 0.2298 | 0.23198 | 0.23046 | 0.19985 | 0.19368 | 0.10533 | 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 |

**Table 1 (continued).**

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.

Liu = single nucleotide polymorphism.
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.

| SNP ID    | ASW | CEU | CHB | CHD | GIN | JPT | LWK | MEX | MKK | TSI | YRI |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| rs10264272 |     |     |     |     |     |     |     |     |     |     |     |
| rs1042713  |     |     |     |     |     |     |     |     |     |     |     |
| rs1042714  |     |     |     |     |     |     |     |     |     |     |     |
| rs1049842  |     |     |     |     |     |     |     |     |     |     |     |
| rs1051266  |     |     |     |     |     |     |     |     |     |     |     |
| rs12720441 |     |     |     |     |     |     |     |     |     |     |     |
| rs12721634 |     |     |     |     |     |     |     |     |     |     |     |
| rs140339   |     |     |     |     |     |     |     |     |     |     |     |
| rs144410   |     |     |     |     |     |     |     |     |     |     |     |
| rs16947    |     |     |     |     |     |     |     |     |     |     |     |
| rs1695     |     |     |     |     |     |     |     |     |     |     |     |
| rs17238540 |     |     |     |     |     |     |     |     |     |     |     |
| rs17244841 |     |     |     |     |     |     |     |     |     |     |     |
| rs1799853  |     |     |     |     |     |     |     |     |     |     |     |
| rs1800492  |     |     |     |     |     |     |     |     |     |     |     |
| rs1800497  |     |     |     |     |     |     |     |     |     |     |     |
| rs1800566  |     |     |     |     |     |     |     |     |     |     |     |
| rs1800888  |     |     |     |     |     |     |     |     |     |     |     |
| rs1801030  |     |     |     |     |     |     |     |     |     |     |     |
| rs1801131  |     |     |     |     |     |     |     |     |     |     |     |
| rs1801133  |     |     |     |     |     |     |     |     |     |     |     |
| rs1801253  |     |     |     |     |     |     |     |     |     |     |     |

P < .05/(77 x 11)

(continued)
Table 3 (continued).

| SNP ID  | ASW | CEU | CHB | CHD | GHR | JPT | LWK | MEX | MKK | TSI | YRI |
|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| rs1801272 |     |     |     |     |     |     |     |     |     |     |     |
| rs1805124 |     |     |     |     |     |     |     |     |     |     |     |
| rs2035282 |     |     |     |     |     |     |     |     |     |     |     |
| rs2048004 |     |     |     |     |     |     |     |     |     |     |     |
| rs2066702 |     |     |     |     |     |     |     |     |     |     |     |
| rs2066853 |     |     |     |     |     |     |     |     |     |     |     |
| rs2228570 |     |     |     |     |     |     |     |     |     |     |     |
| rs2239197 |     |     |     |     |     |     |     |     |     |     |     |
| rs2239198 |     |     |     |     |     |     |     |     |     |     |     |
| rs2740037 |     |     |     |     |     |     |     |     |     |     |     |
| rs2837172 |     |     |     |     |     |     |     |     |     |     |     |
| rs2839444 |     |     |     |     |     |     |     |     |     |     |     |
| rs2839454 |     |     |     |     |     |     |     |     |     |     |     |
| rs2839499 |     |     |     |     |     |     |     |     |     |     |     |
| rs3464937 |     |     |     |     |     |     |     |     |     |     |     |
| rs395210421 |     |     |     |     |     |     |     |     |     |     |     |
| rs3745274 |     |     |     |     |     |     |     |     |     |     |     |
| rs3760091 |     |     |     |     |     |     |     |     |     |     |     |
| rs3807375 |     |     |     |     |     |     |     |     |     |     |     |
| rs3814055 |     |     |     |     |     |     |     |     |     |     |     |
| rs3846622 |     |     |     |     |     |     |     |     |     |     |     |
| rs38913290 |     |     |     |     |     |     |     |     |     |     |     |
| rs4124874 |     |     |     |     |     |     |     |     |     |     |     |
| rs4148323 |     |     |     |     |     |     |     |     |     |     |     |
| rs4149056 |     |     |     |     |     |     |     |     |     |     |     |
| rs4680 |     |     |     |     |     |     |     |     |     |     |     |
| rs486893 |     |     |     |     |     |     |     |     |     |     |     |
| rs486909 |     |     |     |     |     |     |     |     |     |     |     |
| rs486910 |     |     |     |     |     |     |     |     |     |     |     |
| rs4869913 |     |     |     |     |     |     |     |     |     |     |     |
| rs5030065 |     |     |     |     |     |     |     |     |     |     |     |
| rs5629 |     |     |     |     |     |     |     |     |     |     |     |
| rs59421388 |     |     |     |     |     |     |     |     |     |     |     |
| rs6151031 |     |     |     |     |     |     |     |     |     |     |     |
| rs61736512 |     |     |     |     |     |     |     |     |     |     |     |
| rs6277 |     |     |     |     |     |     |     |     |     |     |     |
| rs6709124 |     |     |     |     |     |     |     |     |     |     |     |
| rs688466 |     |     |     |     |     |     |     |     |     |     |     |
| rs701265 |     |     |     |     |     |     |     |     |     |     |     |
| rs7294 |     |     |     |     |     |     |     |     |     |     |     |
| rs731238 |     |     |     |     |     |     |     |     |     |     |     |
| rs7629662 |     |     |     |     |     |     |     |     |     |     |     |
| rs7970232 |     |     |     |     |     |     |     |     |     |     |     |
| rs976233 |     |     |     |     |     |     |     |     |     |     |     |
| rs9932331 |     |     |     |     |     |     |     |     |     |     |     |
| rs9934438 |     |     |     |     |     |     |     |     |     |     |     |

$P < 0.05/(17 	imes 11)$

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, China, CHD = Chinese in metropolitan Denver, CHD = Gujarati Indians in Houston, JPT = Japanese in Tokyo, LWK = Luhya in Webuye, Kenya, MEX = Mexican ancestry in Los Angeles, CA, TSI = Tuscans in Italy, YRI = Yoruba in Ibadan, Nigeria.

Italics indicates the locus with statistical significance ($P < 0.05/(17 	imes 11)$).

cancer, autoimmune diseases, and bronchodilator responsiveness. 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] = 1.86, 95% confidence interval [CI] = 1.51–1.67, $P = 0.02$) compared with A/A or A/G individuals. In our study, the A allele frequency of rs1801131 in Lusia was particularly high (91%) and similar to YRI population, meaning that dose of drugs related to the MTHFR gene in Lusia 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.
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. 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 is 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. The rs689466 polymorphism also described as –1195G>A in PTGS2 was found associated with asthma in Australian Caucasians, colorectal cancer in Norwegian cohorts, and esophageal cancer in Han Chinese population. 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). 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. 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. 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. 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. 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 back-ground 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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