ORIGINAL ARTICLE

Genetic analysis of pharmacogenomic VIP variants in the Blang population from Yunnan Province of China

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Abstract

Background: Genetic polymorphisms in numerous pharmacogenetics studies were regarded as the essential factors involved in the response to or metabolism of drugs. These genetic variants called very important pharmacogenetic (VIP) variants played a role in drugs metabolism, which have been summarized in the PharmGKB database. In this study, we genotyped 80 VIP variants from the PharmGKB in 100 members of Blang volunteers from Yunnan province.

Methods: Based on the PharmGKB database, we genotyped 80 VIP variants loci located in 47 genes. We used χ² tests to evaluate the significant loci between Blang and the other populations, including ASW, CEU, CHB, CHD, GIH, JPT, LWK, MEX, MKK, TSI, and YRI. The global variation distribution of the significant variants was observed from the ALlele FREquency Database. And then, we used F-statistics (Fst), genetic structure, and phylogenetic tree analyses to ascertain the genetic affinity among 12 populations.

Results: Comparing the Blang with the other 11 populations from the HapMap Project, the statistical results revealed that rs3814055 (NC_000003.12:g.119781188C>T) of nuclear receptor subfamily 1 group I member 2 (NR1I2, OMIM# 603,065) was the most significant variant, followed by rs1540339 (NC_000012.12:g.47863543C>T) of vitamin D receptor (VDR, OMIM#601,769). Furthermore, we found that genotype frequency of rs3814055 in the Blang was closer to the populations distributed in Miao. And genetic structure and F-statistics indicated that the Blangs had a relatively closer affinity with CHD, CHB, and JPT populations. In addition, the Han nationality in Shaanxi was closer to it.

Conclusions: Our results will complement the pharmacogenomics information of the Blang ethnic group and provide a theoretical basis for safer drug administration for Blang.

KEYWORDS
Blang, genetic polymorphism, pharmacogenomics, VIP variants
1 | INTRODUCTION

Personalized medicine (Jain, 2009) simply means selection of a best treatment suited for a person on a comprehensive consideration of each patient's characteristics. Its scope is more wider, including pharmacogenetics, pharmacogenomics, and so forth. Pharmacogenomics, a crucial foundation for the development of personalized medicine and patient medication management, enables therapy more precisely.

Furthermore, the Pharmacogenomics Knowledge Base (PharmGKB: http://www.pharmgkb.org) is an extremely useful resource for explaining the gene–drug–disease relationships, more importantly, supporting personalized medicine projects. Recently, a large number of pharmacogenomics studies focused on genetic variations considered to be involved in response to or metabolism of drugs (Evans & McLeod, 2003). These genetic variations also called very important pharmacogenetic (VIP) variants (Peters & McLeod, 2008). At present, there were a total of 246 VIP variants located in 66 genes, which have been summarized in the PharmGKB database.

Numerous studies have elucidated that the importance of ethnicity is great in influencing the frequencies of gene variants. There are 56 ethnic minorities in China, including the Blang ethnic group. The Blang nationality has a population of 91,882 (the fifth national census statistics in 2000), most of whom live in Mount Blang, Xiding, Bada, Mengman, and Daluo areas of Menghai County in Xishuangbanna Dai Autonomous Prefecture of Yunnan province of Southwest China. The others distribute in Lincang, Simao, and Baoshan areas (Wang, Hu et al., 2008a). The areas they live in are mild climate and rich products. They are mainly engaged in agricultural production, especially tea planting, which is the origin of the famous Pu'er tea.

This study aims to determine the Blang's genotype and allele frequencies distribution of pharmacogenetic variants. And we compare Blang with the 11 HapMap populations, including the Chinese Han in Beijing, China (CHB); the Chinese of metropolitan Denver, Colorado, USA (CHD); the Japanese in Tokyo, Japan (JPT); a residents population in Utah with Northern and Western European Ancestry (CEU); the Gujarati Indians in Houston, Texas, USA (GIH); people with Mexican ancestry living in Los Angeles, California, USA (MEX); the Tuscan people of Italy (TSI); a population of African ancestry in the southwestern USA (ASW); the Luhya people in Webuye, Kenya (LWK); the Maasai people in Kinyawa, Kenya (MKK); and the Yoruba in Ibadan, Nigeria (YRI). All p values of less than 0.05 obtained in this study were two-sided and Bonferroni’s multiple tests were used to calculate the level of significance. After Bonferroni's

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

All participants were informed both in writing and verbally to the procedures and purpose of the study and signed informed consent documents. The study protocol was approved by the Clinical Research Ethics Committee of Xizang Minzu University. It is in accordance with the Department of Health and Human Services (DHHS) regulations for human research subject protection.

2.2 | Study participants

We randomly recruited about 100 unrelated, healthy Blang people from the Yunnan Province of China. Each participant has undergone rigorous screening criteria. None of the subjects had any diseases including self-reported cancer history and other diseases. Moreover, despite the influence of the Han and Dai people whose economy and culture development are relatively rapid, they still maintain the characteristics of the nation. They can be seen as representatives of the Blang population.

2.3 | Variant selection and genotyping

We chose 80 VIP variants loci located in 47 genes from the PharmGKB database. Genomic DNA was extracted from peripheral blood sample using the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Ltd. Xi’an, China) according to the manufacturer’s protocol. NanoDrop 2000C spectrophotometer (Thermo Scientific, Waltham, MA) was used to measure the DNA concentration. We utilized the Sequenom MassARRAY Assay Design 3.0 Software (San Diego, CA) to design Multiplexed SNP MassEXTEND assays (Gabriel, Ziaugra, & Tabbaa, 2009) and genotyped the variants using Sequenom MassARRAY RS1000 (San Diego, CA). Based on the Sequenom Typer 4.0 software (San Diego, CA) used in previous research (He et al., 2015; Jin, Aikemu et al., 2015a; Jin, Yang et al., 2015b; Thomas et al., 2007), we completed data management and analyses.

2.4 | Statistical analyses

We performed χ² tests and Hardy–Weinberg equilibrium (HWE) analysis by the Microsoft Excel (Redmond, WA) and SPSS 19.0 statistical software platform (SPSS, Chicago, IL). The genotype frequencies of 80 variants in the Blang population were separately compared with those of the other populations, including the Chinese Han in Beijing, China (CHB); the Chinese Han in Beijing, China (CHB); the Japanese in Tokyo, Japan (JPT); a residents population in Utah with Northern and Western European Ancestry (CEU); the Gujarati Indians in Houston, Texas, USA (GIH); people with Mexican ancestry living in Los Angeles, California, USA (MEX); the Tuscan people of Italy (TSI); a population of African ancestry in the southwestern USA (ASW); the Luhya people in Webuye, Kenya (LWK); the Maasai people in Kinyawa, Kenya (MKK); and the Yoruba in Ibadan, Nigeria (YRI). All p values of less than 0.05 obtained in this study were two-sided and Bonferroni’s multiple tests were used to calculate the level of significance. After Bonferroni's
multiple adjustment, we attempted to discover significantly different sites \((p < [0.05/(80 \times 11)])\). Subsequently, we downloaded significant SNP allele frequencies from the ALlele FREquency Database (http://alfred.med.yale.edu, ALFRED) and analyzed the global genetic variation patterns from the HapMap database (Gibbs et al., 2003).

### 2.5 Population genetic structures analysis

In view of the genetic structure of human populations, we used Structure 2.3.4 (Pritchard Lab, Stanford University, USA) (http://pritchardlab.stanford.edu/software/structure_v.2.3.4.html) to observe the variation of the selected VIP variants. On the basis of the Bayesian clustering algorithm approach, we performed structural analysis to assign the samples within a hypothetical \(K\) number of populations hypothesized by Pritchard, Stephens, and Donnelly (2000). The MCMC analyses for each structure analysis \((K = 3–10)\) was run for 10,000 steps after an initial burn-in period of 10,000 steps. And we used \(\Delta K\) to calculate to identify the most likely number of clusters by STRUCTURE HARVESTER (Evanno, Regnaut, & Goudet, 2005). Moreover, Wright's \(F\)-statistics is the most widely used descriptive statistics in population and evolutionary genetics. (Wright, 1931). We used the program Arlequin version 3.1 to calculate the \(Fst\) values to deduce the pairwise distance between populations. Besides, neighbor-joining method was used to group them in several clusters based on the genetic distance.

### 3 RESULTS

#### 3.1 Basic information of the VIP variants

We selected 80 VIP variants from PharmGKB database in 100 members of the Blang population.

The selected single-nucleotide polymorphisms (SNPs) of PCR primers (listed in Table S1) were designed by the Sequenom MassARRAY Assay Design 3.0 Software. The basic information of the selected variants has been shown in Table 1, including the genes name, their positions, the nucleotide change, the amino acid translation, the allele frequencies, and the genotype frequencies of Blang and the like.

#### 3.2 Analyses of 80 loci among 12 populations

The average variants call rate of the results was over 95%. All selected loci meet the HWE. Using chi-square test, we compared the Blangs and the 11 populations of the genotype frequencies distribution of 80 loci. Before adjustment \((p < 0.05)\), we found that some loci were different (not shown). When compared to the 11 groups (ASW, CEU, CHB, CHD, GIH, JPT, LWK, MEX, MKK, TSI, and YRI) and Blang without adjustment, the number of significantly different variants in the Blang population was 23, 30, 17, 30, 30, 21, 26, 21, 25, 22, and 35, respectively (data no shown). After adjustment \((p < [0.05/(80 \times 11)])\), listed in Table 2, there were 15, 20, 6, 25, 25, 7, 19, 7, 20, 15, and 26 loci of significant differences between Blang and the 11 populations, respectively. While there were contrasts in the two sets of data, there were also similarities. It was also noteworthy that the different loci between CHB and the Blang were the least.

However, through a comparison of before and after adjustment, the distribution of rs1801133 (HGVS: NM_001330358.1:c.788C>T) and rs4680 (HGVS: NM_000754.3:c.472G>A) in populations has changed. After correction for multiple tests, rs1801133 became less significant in ASW, JPT, LWK, MEX, MKK, TSI, YRI, except CHB. Besides, rs4680 were detected significant differences between CEU, MEX, TSI, and Blang. In the populations of ASW, CHB, JPT, LWK, MKK, and YRI, its differences disappeared. Nonetheless, some variants varied little, not even a bit, such as rs11568820, rs1544410, and so forth.

After analysis of Table 2, significant variants in some genes were distributed in every population, such as VDR and NR1I2. There were rs10735810, rs11568820, rs1540339, rs1544410, rs2228570, rs2239179, rs2239185, rs731236, rs7975232 distributed in VDR (vitamin D receptor), which encodes the nuclear hormone receptor for vitamin D3. Although failing to make amino acid changed, rs1540339 was also very significant among the nine populations except CHB, JPT, and MEX. Although rs2228570 (HGVS: NM_000376.2:c.2 T>G) was, the only one SNP changing amino acid, located in exon 2 of VDR, it was still prominent in the CHD.

Although rs3814055 in NR1I2 changed little, significant differences still existed. We downloaded the associated data of rs3814055 from the website (http://alfred.med.yale.edu). As seen from the Figures 1 and 2, the frequency of the Blangs of rs3814055 from the website (http://alfred.med.yale.edu). As seen from the Figures 1 and 2, the frequency of the Blangs was closer to the populations distributed in East Asia, especially Miao. On the whole, the frequencies of the allele C of rs3814055, ranged from 67% to 94%, were higher in East Asia than the other populations. The Blang population was the highest among them, so attention should be paid to its allele C.

#### 3.3 The relationship between 23 populations

We used Structure 2.3.1 Software to analyze the genetic structure of the 23 populations in order to further identify the relationships between them throughout the world. Different \(K\) values ranging from 2 to 10 were hypothetically in structure analysis. And, the results of \(K = 2,3\) among global populations and the results of \(K = 3,4\) ethnic groups from China
| SNP      | Gene               | Full name                                             | Chr       | Allele | Position   |
|----------|--------------------|-------------------------------------------------------|-----------|--------|------------|
| rs1045642 | ABCB1              | ATP binding cassette subfamily B member 1             | chr7      | A      | 87,138,645 |
| rs1128503 | ABCB1              | ATP binding cassette subfamily B member 1             | chr7      | A      | 87,179,601 |
| rs2032582 | ABCB1              | ATP binding cassette subfamily B member 1             | chr7      | A      | 87,160,618 |
| rs975833  | ADH1A              | alcohol dehydrogenase 1A (class I), alpha polypeptide | chr4      | G      | 100,201,739|
| rs1229984 | ADH1B              | alcohol dehydrogenase 1B (class I), beta polypeptide  | chr4      | T      | 100,229,017|
| rs2066702 | ADH1B              | alcohol dehydrogenase 1B (class I), beta polypeptide  | chr4      | G      | 100,229,017|
| rs1801253 | ADRB1              | adrenoceptor beta 1                                   | chr10     | G      | 115,805,056|
| rs1042713 | ADRB2              | adrenoceptor beta 2                                   | chr5      | G      | 148,206,440|
| rs1042714 | ADRB2              | adrenoceptor beta 2                                   | chr5      | G      | 148,206,473|
| rs1800888 | ADRB2              | adrenoceptor beta 2                                   | chr5      | C      | 148,206,885|
| rs2066853 | AHR                | aryl hydrocarbon receptor                            | chr7      | G      | 17,379,110 |
| rs6151031 | ALDH1A1            | aldehyde dehydrogenase 1 family member A1            | chr9      | —      | 72,953,467 |
| rs1800497 | ANKK1              | ankyrin repeat and kinase domain containing 1        | chr11     | G      | 113,270,828|
| rs4680    | COMT               | catechol-O-methyltransferase                          | chr22     | G      | 19,951,271 |
| rs1801272 | CYP2A6             | cytochrome P450 family 2 subfamily A member 6        | chr19     | A      | 41,354,533 |
| rs28399433| CYP2A6             | cytochrome P450 family 2 subfamily A member 6        | chr19     | G      | 41,356,379 |
| rs28399444| CYP2A6             | cytochrome P450 family 2 subfamily A member 6        | chr19     | G      | 41,354,190 |
| rs28399454| CYP2A6             | cytochrome P450 family 2 subfamily A member 6        | chr19     | C      | 41,351,267 |
| rs28399499| CYP2B6             | cytochrome P450 family 2 subfamily B member 6        | chr19     | T      | 41,518,221 |
| rs3745274 | CYP2B6             | cytochrome P450 family 2 subfamily B member 6        | chr19     | G      | 41,512,841 |
| rs4986893 | CYP2C19            | cytochrome P450 family 2 subfamily C member 19       | chr10     | A      | 96,540,410 |
| rs1799853 | CYP2C9             | cytochrome P450 family 2 subfamily C member 9        | chr10     | C      | 96,702,047 |
| rs16947   | CYP2D6             | cytochrome P450 family 2 subfamily D member 6        | chr12     | A      | 42,523,943 |
| rs28371706| CYP2D6             | cytochrome P450 family 2 subfamily D member 6        | chr12     | G      | 42,525,772 |
| rs28371725| CYP2D6             | cytochrome P450 family 2 subfamily D member 6        | chr12     | G      | 42,523,805 |
| rs5030656 | CYP2D6             | cytochrome P450 family 2 subfamily D member 6        | chr12     | —      | 42,128,174 |
| rs59421388| CYP2D6             | cytochrome P450 family 2 subfamily D member 6        | chr12     | C      | 42,523,610 |
| rs61736512| CYP2D6             | cytochrome P450 family 2 subfamily D member 6        | chr12     | C      | 42,523,134 |
| rs12721634| CYP3A4             | cytochrome P450 family 3 subfamily A member 4        | chr7      | C      | 99,381,661 |
| rs2740574 | CYP3A4             | cytochrome P450 family 3 subfamily A member 4        | chr7      | A      | 99,382,096 |
| rs4986909 | CYP3A4             | cytochrome P450 family 3 subfamily A member 4        | chr7      | G      | 99,359,670 |
| rs4986910 | CYP3A4             | cytochrome P450 family 3 subfamily A member 4        | chr7      | A      | 99,358,524 |
| rs4986913 | CYP3A4             | cytochrome P450 family 3 subfamily A member 4        | chr7      | G      | 99,358,459 |
| rs10264272| CYP3A5             | cytochrome P450 family 3 subfamily A member 5        | chr7      | C      | 99,262,835 |
| rs3918290 | DPYD               | dihydropyrimidine dehydrogenase                      | chr1      | C      | 97,915,614 |
| rs6277    | DRD2               | dopamine receptor D2                                  | chr11     | G      | 113,283,459|
| rs1138272 | GSTP1              | glutathione S-transferase pi 1                        | chr11     | C      | 67,353,579 |
| rs1695    | GSTP1              | glutathione S-transferase pi 1                        | chr11     | A      | 67,352,689 |
| Amino Acid Translation | Function      | Allele A | Allele B |
|------------------------|---------------|----------|----------|
| Ile1145Ile             | Synonymous    | 0.335    | 0.665    |
| Gly412Gly              | Synonymous    | 0.590    | 0.410    |
| Ser893Ala              | Missense      | 0.378    | 0.622    |
| —                      | Intrinsic     | 0.365    | 0.635    |
| His48Arg               | Missense      | 0.035    | 0.965    |
| Arg370Cys              | Missense      | 1.000    | 0.000    |
| Gly389Arg              | Missense      | 0.350    | 0.650    |
| Arg16Gly               | Missense      | 0.395    | 0.605    |
| Gln27Glu               | Missense      | 0.050    | 0.950    |
| Thr164Ile              | Missense      | 1.000    | 0.000    |
| Arg554Lys              | Missense      | 0.845    | 0.155    |
| —                      | Missense      | 0.953    | 0.047    |
| Glu713Lys              | Missense      | 0.720    | 0.280    |
| Val158Met              | Missense      | 0.860    | 0.140    |
| Leu160His              | Missense      | 0.000    | 1.000    |
| —                      | Missense      | 0.200    | 0.800    |
| —                      | Frameshift    | 0.000    | 1.000    |
| Val365Met              | Missense      | 1.000    | 0.000    |
| Ile328Thr              | Missense      | 1.000    | 0.000    |
| Gln172His              | Missense      | 0.485    | 0.515    |
| Trp212null             | Stop Codon    | 0.025    | 0.975    |
| Arg144Cys              | Missense      | 1.000    | 0.000    |
| Arg296Cys              | Missense      | 0.210    | 0.790    |
| Thr107Ile              | Missense      | 1.000    | 0.000    |
| —                      | Intron        | 0.130    | 0.870    |
| Val338Met              | Missense      | 1.000    | 0.000    |
| Val136Met              | Missense      | 1.000    | 0.000    |
| Leu15Pro               | Missense      | 0.000    | 1.000    |
| —                      | Missense      | 1.000    | 0.000    |
| Pro415Leu              | Missense      | 1.000    | 0.000    |
| Met444Thr              | Missense      | 1.000    | 0.000    |
| Pro466Ser              | Missense      | 1.000    | 0.000    |
| Lys208Lys              | Synonymous    | 1.000    | 0.000    |
| —                      | Missense      | 1.000    | 0.000    |
| Pro319Pro              | Synonymous    | 0.975    | 0.025    |
| Ala114Val              | Missense      | 1.000    | 0.000    |
| Ile105Val              | Missense      | 0.740    | 0.260    |

(Continues)
| SNP      | Gene               | Full name                                      | Chr | Allele | Allele | Position      |
|----------|--------------------|-----------------------------------------------|-----|--------|--------|---------------|
| rs17238540 | HMGCR             | 3-hydroxy-3-methylglutaryl-CoA reductase       | chr5 | G      | T      | 74,655,498   |
| rs17244841 | HMGCR             | 3-hydroxy-3-methylglutaryl-CoA reductase       | chr5 | A      | T      | 74,642,855   |
| rs3846662  | HMGCR             | 3-hydroxy-3-methylglutaryl-CoA reductase       | chr5 | A      | G      | 74,651,084   |
| rs12720441 | KCNH2             | potassium voltage-gated channel subfamily H   | chr7 | G      | A      | 150,647,304  |
| rs36210421 | KCNH2             | potassium voltage-gated channel subfamily H   | chr7 | G      | T      | 150,644,428  |
| rs3807375  | KCNH2             | potassium voltage-gated channel subfamily H   | chr7 | C      | T      | 150,667,210  |
| rs1801131  | MTHFR             | methylenetetrahydrofolate reductase           | chr1 | T      | G      | 11,854,476   |
| rs1801133  | MTHFR             | methylenetetrahydrofolate reductase           | chr1 | G      | A      | 11,856,378   |
| rs1800566  | NQO1              | NAD(P)H quinone dehydrogenase 1               | chr16| G      | A      | 69,711,242   |
| rs3814055  | NR1I2             | nuclear receptor subfamily 1 group I member 2 | chr3 | C      | T      | 119,500,035  |
| rs1065776  | P2RY1             | purinergic receptor P2Y1                      | chr3 | C      | T      | 152,553,628  |
| rs1800566  | PTGS2             | prostaglandin-endoperoxide synthase 2         | chr1 | T      | C      | 186,650,751  |
| rs6791924  | SCN5A             | sodium voltage-gated channel alpha subunit 5  | chr3 | T      | C      | 38,645,420   |
| rs7626966  | SCN5A             | sodium voltage-gated channel alpha subunit 5  | chr3 | G      | T      | 38,620,907   |
| rs1051266  | SLC19A1           | solute carrier family 19 member 1             | chr21| T      | C      | 46,957,794   |
| rs12659    | SLC19A1           | solute carrier family 19 member 1             | chr21| C      | T      | 46,951,556   |
| rs4149056  | SLC19A1           | solute carrier family 19 member 1             | chr12| T      | C      | 21,331,549   |
| rs1801030  | SULT1A1           | sulfotransferase family 1A member 1           | chr16| C      | T      | 28,617,485   |
| rs3760091  | SULT1A1           | sulfotransferase family 1A member 1           | chr16| G      | C      | 28,609,479   |
| rs1142345  | TPMT              | thiopurine S-methyltransferase                | chr6 | T      | C      | 18,130,918   |
| rs1800460  | TPMT              | thiopurine S-methyltransferase                | chr6 | A      | G      | 18,139,228   |
| rs1800462  | TPMT              | thiopurine S-methyltransferase                | chr6 | C      | G      | 18,143,955   |
| rs34489327 | TS                | thymidylate synthetase                        | chr18| Del    |        |               |
| rs10929302 | UGT1A1            | UDP glucuronosyltransferase family            | chr2 | G      | A      | 234,665,782  |
| rs4124874  | UGT1A1            | UDP glucuronosyltransferase family 1 member A1| chr2 | T      | G      | 234,665,659  |
| rs4148323  | UGT1A1            | UDP glucuronosyltransferase family 1 member A1| chr2 | G      | A      | 234,669,144  |
| rs10735810 | VDR               | vitamin D (1,25-dihydroxyvitamin D3) receptor| chr12| A      | G      | 48,272,895   |
| rs11568820 | VDR               | vitamin D (1,25-dihydroxyvitamin D3) receptor| chr12| C      | T      | 48,302,545   |
| rs1540339  | VDR               | vitamin D (1,25-dihydroxyvitamin D3) receptor| chr12| C      | T      | 48,257,326   |
| rs1544410  | VDR               | vitamin D (1,25-dihydroxyvitamin D3) receptor| chr12| C      | T      | 48,239,835   |
| rs2228570  | VDR               | vitamin D (1,25-dihydroxyvitamin D3) receptor| chr12| T      | C      | 48,272,895   |
| rs2239179  | VDR               | vitamin D (1,25-dihydroxyvitamin D3) receptor| chr12| T      | C      | 48,257,766   |
| rs2239185  | VDR               | vitamin D (1,25-dihydroxyvitamin D3) receptor| chr12| G      | A      | 48,244,559   |
| rs731236   | VDR               | vitamin D (1,25-dihydroxyvitamin D3) receptor| chr12| A      | G      | 48,238,757   |
| Amino Acid Translation | Function     | Allele A | Allele B | AA  | AB  | BB  | HWE   |
|-------------------------|--------------|----------|----------|-----|-----|-----|-------|
| —                      | Splice acceptor | 0.000    | 1.000    | 0   | 0   | 100 | —     |
| —                      | Intronic     | 0.929    | 0.071    | 87  | 8   | 3   | 0.001 |
| —                      | Intronic     | 0.465    | 0.535    | 22  | 48  | 29  | 0.968 |
| Arg784Trp              | Missense     | 1.000    | 0.000    | 100 | 0   | 0   | —     |
| Arg1047Leu             | Missense     | 1.000    | 0.000    | 99  | 0   | 0   | —     |
| —                      | Intronic     | 0.200    | 0.800    | 6   | 28  | 66  | 0.458 |
| Glu429Ala              | Missense     | 0.795    | 0.205    | 65  | 29  | 6   | 0.544 |
| Ala222Val              | Missense     | 0.770    | 0.230    | 62  | 30  | 8   | 0.31  |
| Pro187Ser              | Missense     | 0.595    | 0.405    | 32  | 55  | 13  | 0.369 |
| —                      | 5'‐UTR       | 0.940    | 0.060    | 88  | 12  | 0   | 0.816 |
| Ala19Ala               | Synonymous   | 0.875    | 0.125    | 64  | 19  | 1   | 0.953 |
| Val262Val              | Synonymous   | 0.695    | 0.305    | 45  | 49  | 6   | 0.297 |
| —                      | Intronic     | 0.085    | 0.915    | 0   | 17  | 83  | 0.65  |
| Arg373Arg              | Synonymous   | 0.885    | 0.115    | 77  | 23  | 0   | 0.43  |
| —                      | —            | 0.596    | 0.404    | 36  | 46  | 17  | 0.941 |
| His558Arg              | Missense     | 0.890    | 0.110    | 81  | 16  | 3   | 0.188 |
| Arg34Cys               | Missense     | 1.000    | 0.000    | 100 | 0   | 0   | —     |
| Ser1103Tyr             | Missense     | 0.000    | 1.000    | 0   | 0   | 100 | —     |
| His27Arg               | Missense     | 0.436    | 0.564    | 13  | 56  | 25  | 0.123 |
| Pro232Pro              | Synonymous   | 0.556    | 0.444    | 25  | 59  | 14  | 0.094 |
| Val174Ala              | Missense     | 0.965    | 0.035    | 93  | 7   | 0   | 0.936 |
| Val223Met              | Missense     | 0.000    | 1.000    | 0   | 0   | 100 | —     |
| —                      | Intronic     | 0.355    | 0.645    | 6   | 59  | 35  | 0.016 |
| Tyr240Cys              | Missense     | 0.985    | 0.015    | 95  | 3   | 0   | 0.988 |
| Ala154Thr              | Missense     | 0.000    | 1.000    | 0   | 0   | 100 | —     |
| Ala80Pro               | Missense     | 0.000    | 1.000    | 0   | 0   | 98  | —     |
| —                      | 3'‐UTR       | 1.000    | 0.000    | 100 | 0   | 0   | —     |
| —                      | Intronic     | 0.880    | 0.120    | 78  | 20  | 2   | 0.869 |
| —                      | Intronic     | 0.530    | 0.470    | 32  | 42  | 26  | 0.292 |
| Gly71Arg               | Missense     | 0.845    | 0.155    | 71  | 27  | 2   | 0.954 |
| Met1Thr                | Missense     | 0.571    | 0.429    | 28  | 57  | 14  | 0.22  |
| —                      | —            | 0.196    | 0.804    | 4   | 21  | 49  | 0.694 |
| —                      | Intronic     | 0.340    | 0.660    | 13  | 42  | 45  | 0.814 |
| —                      | Intronic     | 0.975    | 0.025    | 94  | 5   | 0   | 0.967 |
| Met1Thr                | Missense     | 0.575    | 0.425    | 29  | 57  | 14  | 0.251 |
| —                      | Intronic     | 0.000    | 0.000    | 0   | 0   | 0   | —     |
| —                      | Intronic     | 0.695    | 0.305    | 43  | 53  | 4   | 0.044 |
| Ile352Ile              | Synonymous   | 0.975    | 0.025    | 95  | 5   | 0   | 0.968 |

(Continues)
TABLE 1 (Continued)

| SNP       | Gene          | Full name                                              | Chr | Allele | Position |
|-----------|---------------|---------------------------------------------------------|-----|--------|----------|
| rs7975232 | VDR           | vitamin D (1,25-dihydroxyvitamin D3) receptor          | chr12 | C   | A       | 48,238,837  |
| rs7294    | VKORC1        | vitamin K epoxide reductase complex subunit 1           | chr16 | C   | T       | 31,102,321  |
| rs9923231 | VKORC1        | vitamin K epoxide reductase complex subunit 1           | chr16 | A   | C       | 31,096,368  |
| rs9934438 | VKORC1        | vitamin K epoxide reductase complex subunit 1           | chr16 | G   | A       | 31,104,878  |

Notes: SNP: single-nucleotide polymorphism; HWE: Hardy–Weinberg equilibrium. The GenBank reference of the above genes were as follows: ABCB1 (NC_000007.14), ADH1A (NC_000004.12), ADH1B (NC_000004.12), ADRB1 (NC_000010.11), ADRB2 (NC_000005.10), AHR (NC_000007.14), ALDH1A1 (NC_000009.12), ANKK1 (NC_000110.10), COMT (NC_000022.11), CYP2A6 (NC_000019.10), CYP2B6 (NC_000019.10), CYP2C19 (NC_000010.111), CYP2C9 (NC_000010.11), CYP2D6 (NC_000022.11), CYPI4A4 (NC_000007.14), CYP3A5 (NC_000007.14), DPYD (NC_000001.11), DRD2 (NC_000011.10), GSTP1 (NC_000011.10), HMGCR (NC_000005.10), KCNH2 (NC_000007.14), MTHFR (NC_000001.11), NQO1 (NC_000016.10), NR1I2 (NC_000033.12), P2RY12 (NC_000003.12), PTGIS (NC_000020.11), PTGS2 (NC_000001.11), SCN5A (NC_000003.12), SLC19A1 (NC_000021.9), SLC21A1 (NC_000012.12), SULT1A1 (NC_000016.10), TPMT (NC_000006.10), UGT1A1 (NC_000002.12), VDR (NC_000012.12), VKORC1 (NC_000016.10).

TABLE 2 Significant VIP variants in the Blangs compared with the 11 populations after Bonferroni's multiple adjustment

| SNP ID  | Gene | $p < 0.05/ (80*11)$ |
|---------|------|---------------------|
| rs1045642 | ABCB1 | 0.059 2.873E−06 0.277 0.024 |
| rs1128503 | ABCB1 | 2.072E−09 0.005 0.072 — |
| rs2032582 | ABCB1 | 1.486E−06 0.161 0.001 — |
| rs975833 | ADH1A | — 3.544E−08 0.001 — |
| rs12298984 | ADH1B | — — 3.393E−25 — |
| rs2066702 | ADH1B | 1.065E−10 — — 1.056E−19 |
| rs1801253 | ADRB1 | 0.785 0.217 — — 0.365 |
| rs342713 | ADRB1 | 0.258 4.559E−07 0.481 — |
| rs342714 | ADRB2 | — 1.530E−12 — 8.438E−14 |
| rs800888 | ADRB2 | — — — — |
| rs2066843 | AHR | 1.696E−05 0.181 1.202E−06 — |
| rs6151031 | ALDH1A1 | 0.107 0.144 0.025 0.000 |
| rs18000497 | ANKK1 | 0.002 2.205E−11 0.000 — |
| rs4680 | COMT | 0.002 1.205E−11 0.000 — |
| rs1801272 | CYP2A6 | — 1.805E−35 — 6.726E−41 |
| rs28399433 | CYP2A6 | — — — — |
| rs28399444 | CYP2A6 | — — — — |
| rs28399454 | CYP2A6 | — — — — |
| rs28399499 | CYP2B6 | 0.000 — — — |
| rs3745374 | CYP2B6 | 0.000 1.314E−06 1.166E−10 — |
| rs4986893 | CYP2C19 | — — — — |
| rs1799853 | CYP2C9 | — — — — |
| rs16947 | CYP2D6 | — — — 0.248 |
| rs2837106 | CYP2D6 | — — — — |
| rs2837125 | CYP2D6 | — — — — |
| rs5036056 | CYP2D6 | — — — 2.373E−13 |
| rs59421388 | CYP2D6 | — — — — |
| Amino Acid Translation | Function | Allele A | Allele B | Blang | AA | AB | BB | HWE |
|------------------------|----------|----------|----------|-------|----|----|----|-----|
| —                      | Intrinsic| 0.695    | 0.305    | 43    | 53 | 4  | 0.044 |
| —                      | 3’-UTR   | 0.874    | 0.126    | 75    | 23 | 1  | 0.87 |
| —                      | Intrinsic| 1.000    | 0.000    | 100   | 0  | 0  | —   |
| —                      | Intrinsic| 0.125    | 0.875    | 1     | 23 | 76 | 0.876 |

Notes: SNP: single-nucleotide polymorphism; HWE: Hardy–Weinberg equilibrium. The GenBank reference of the above genes were as follows:

- **ABCB1** (NC_000007.14)
- **ADH1A** (NC_000004.12)
- **ADH1B** (NC_000004.12)
- **ADRB1** (NC_000010.11)
- **ADRB2** (NC_000005.10)
- **AHR** (NC_000007.14)
- **ALDH1A1** (NC_000009.12)
- **ANKK1** (NC_000011.10)
- **COMT** (NC_000022.11)
- **CYP2A6** (NC_000019.10)
- **CYP2B6** (NC_000019.10)
- **CYP2C19** (NC_000010.11)
- **CYP2C9** (NC_000010.11)
- **CYP2D6** (NC_000022.11)
- **CYP3A4** (NC_000007.14)
- **CYP3A5** (NC_000007.14)
- **DPYD** (NC_000001.11)
- **DRD2** (NC_000011.10)
- **GSTP1** (NC_000011.10)
- **HMGCR** (NC_000005.10)
- **KCNH2** (NC_000007.14)
- **MTHFR** (NC_000001.11)
- **NQO1** (NC_000016.10)
- **NR1I2** (NC_000003.12)
- **P2RY1** (NC_000003.12)
- **P2RY12** (NC_000003.12)
- **PTGIS** (NC_000020.11)
- **PTGS2** (NC_000001.11)
- **SCN5A** (NC_000003.12)
- **SLC19A1** (NC_000021.9)
- **SLCO1B1** (NC_000012.12)
- **SULT1A1** (NC_000016.10)
- **TPMT** (NC_000006.12)
- **TS** (NC_000018.10)
- **UGT1A1** (NC_000002.12)
- **VDR** (NC_000012.12)
- **VKORC1** (NC_000016.10).
| SNP ID     | Gene     | $p < 0.05$ (80°11) | ASW | CEU | CHB | CHD |
|-----------|----------|--------------------|-----|-----|-----|-----|
| rs61736512 | CYP2D6   | —                  | —   | —   | —   | —   |
| rs12721634 | CYP3A4   | —                  | —   | —   | —   | 9.801E−37 |
| rs2740574  | CYP3A4   | —                  | —   | —   | —   | —   |
| rs4986909  | CYP3A4   | —                  | —   | —   | —   | —   |
| rs4986910  | CYP3A4   | —                  | —   | —   | —   | —   |
| rs4986913  | CYP3A4   | —                  | —   | —   | —   | —   |
| rs10264272 | CYP3A5   | —                  | —   | 7.700E−31 | 2.008E−21 | 1.445E−12 | 8.823E−08 | 8.948E−09 |
| rs3918290  | DPYD     | —                  | —   | —   | —   | 3.132E−18 |
| rs6277     | DRD2     | —                  | 1.663E−22 | —   | —   |
| rs1138272  | GSTP1    | —                  | —   | —   | —   | —   |
| rs1695     | GSTP1    | 0.003              | 0.003 | 0.231 | —   | —   |
| rs17238540 | HMGCRC   | —                  | —   | —   | —   | —   |
| rs17244841 | HMGCRC   | —                  | —   | —   | —   | —   |
| rs3846662  | HMGCRC   | 1.111E−07          | 0.084 | 0.994 | —   | —   |
| rs12720441 | KCNH2    | —                  | —   | —   | —   | —   |
| rs36210421 | KCNH2    | —                  | —   | —   | —   | 2.249E−07 |
| rs3807375  | KCNH2    | 0.042              | 5.814E−16 | 0.172 | 3.093E−18 |
| rs1801131  | MTHFR    | 0.458              | 0.006 | 0.439 | 0.013 | —   | —   |
| rs1801133  | MTHFR    | 0.013              | 0.076 | 1.559E−05 | —   | —   |
| rs1800566  | NQO1     | 0.001              | 2.084E−06 | 0.135 | —   | —   |
| rs3814055  | NR1I2    | 1.029E−07          | 9.604E−11 | 2.269E−07 | 1.593E−19 |
| rs1065776  | P2RY1    | —                  | —   | —   | —   | 2.296E−11 |
| rs701265   | P2RY1    | 1.620E−09          | 0.007 | 0.293 | 5.222E−08 |
| rs2046934  | P2RY12   | —                  | 0.001 | 0.010 | —   | —   |
| rs5629     | PTGIS    | 0.124              | 0.006 | 0.003 | —   | —   |
| rs689466   | PTGS2    | 1.039E−06          | 1.169E−06 | 0.175 | 0.007 | —   | —   |
| rs1805124  | SCN5A    | 0.003              | 0.008 | 0.194 | 1.046E−15 |
| rs6791924  | SCN5A    | —                  | —   | —   | 2.606E−22 |
| rs7626962  | SCN5A    | —                  | —   | —   | 4.880E−15 |
| rs1051266  | SLC19A1  | 0.531              | 0.818 | 0.056 | —   | —   |
| rs12659    | SLC19A1  | —                  | —   | —   | —   | —   |
| rs4149056  | SLCO1B1  | 0.382              | 0.000 | 0.000 | 4.768E−12 |
| rs1801030  | SULT1A1  | —                  | —   | —   | 5.982E−36 |
| rs3760091  | SULT1A1  | —                  | —   | —   | 1.349E−12 |
| rs1142345  | TPMT     | —                  | —   | —   | 1.031E−15 |
| rs1800460  | TPMT     | —                  | —   | —   | —   | —   |
| rs1800462  | TPMT     | —                  | —   | —   | 2.714E−22 |
| rs34489327 | TS       | —                  | —   | —   | —   | —   |
| rs10929302 | UGT1A1   | —                  | 0.002 | 0.592 | 2.608E−05 |
| rs4124874  | UGT1A1   | 8.170E−06          | 0.630 | 0.0002 | 2.226E−07 |
| rs4148323  | UGT1A1   | —                  | 2.428E−05 | 0.108 | 0.536 | —   | —   |
| rs10735810 | VDR      | 1.259E−10          | 0.001 | 0.003 | —   | —   |
| rs11568820 | VDR      | 0.133              | 2.969E−22 | 4.962E−08 | —   | —   | —   |

**TABLE 2 (Continued)**
| SNP ID | Gene     | GIH   | JPT   | LWK   | MEX   | MKK   | TSI   | YRI   |
|--------|----------|-------|-------|-------|-------|-------|-------|-------|
| 3.439E-16 | UGT1A1 | —     | —     | —     | —     | —     | —     | —     |
| 1.259E-10 |       |       |       |       |       |       |       |       |
| 1.039E-06 |       |       |       |       |       |       |       |       |
| 1.166E-12 |       |       |       |       |       |       |       |       |
| ASW     | CEU     | CHB   | CHD   |       |       |       |       |       |
| p       | < 0.05/  |       |       |       |       |       |       |       |
| 2.428E-05 |       |       |       |       |       |       |       |       |
|        | 2.969E-22 |       |       |       |       |       |       |       |
|        | 4.962E-08 |       |       |       |       |       |       |       |
|        | 0.630    | 0.0002 |       |       |       |       |       |       |
|        | 5.814E-16 |       |       |       |       |       |       |       |
|        | 0.084    | 0.994  | —     |       |       |       |       |       |
|        | 3.093E-18 |       |       |       |       |       |       |       |
|        | 3.132E-18 |       |       |       |       |       |       |       |
|        | 3.034E-13 |       |       |       |       |       |       |       |
|        | 0.266    | 6.247E-19 | 0.052 | 8.827E-19 | 0.001 |       |       |       |
|        | 0.020    |       |       |       |       |       |       |       |
|        | 0.008    |       |       |       |       |       |       |       |
|        | 0.001    | 0.0002 | 0.002 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
|        | 2.198E-08 |       |       |       |       |       |       |       |
|        | 1.283E-07 |       |       |       |       |       |       |       |
|        | 0.018    | 8.244E-09 | 0.059 | 9.767E-13 | 0.181 |       |       |       |
|        | 0.391E-15 |       |       |       |       |       |       |       |
|        | 0.024    |       |       |       |       |       |       |       |
|        | 0.365E-30 |       |       |       |       |       |       |       |
|        | 0.255    |       |       |       |       |       |       |       |
|        | 8.286E-19 |       |       |       |       |       |       |       |
|        | 0.001    | 0.034  |       |       |       |       |       |       |
|        | 1.166E-12 |       |       |       |       |       |       |       |
|        | 4.574E-09 |       |       |       |       |       |       |       |
|        | 3.725E-18 |       |       |       |       |       |       |       |
|        | 0.000    | 0.769  | 0.007 |       |       |       |       |       |
|        | 4.321E-07 | 1.916E-15 | 0.299 | 3.465E-15 | 0.000 |       |       |       |
|        | 1.086E-07 | 0.061  | 8.376E-15 | 0.618 | 7.171E-18 | 0.701 |       |       |

(Continues)
were shown in Figure 3. The cluster analysis indicated that when $K = 3$, the group was divided into three subgroups (subgroups 1: Blang, CHB, CHD, JPT, SX Han; subgroups 2: CEU, GIH, MEX, TSI, Deng, Sherpa, Lhoba, Kyrgyz, Tajik, Uygur; subgroups 3: ASW, LWK, MKK, YRI, Miao, Li, Tibet, Mongol) based on relative majority of likelihood to assign individuals to subgroups. The results indicated that Blang had a relatively closer affinity with CHB, CHD, and JPT. In accordance with the Table 2, the results were confirmed. Likewise, when comparing ethnic groups within China, we found that Blang was closer to SX Han.

Based on genetic structure, we further assessed the genetic relationship among 12 populations by using pairwise Fst values (Table 3). As mentioned in it, it was clear that the differences between CHB, CHD, JPT, and Blang (Fst = 0.04728, 0.04259, and 0.04914, respectively) were smaller. The smaller the Fst value, the more similar they were. The results indicated that the Blang and the other three groups had a
relatively closer affinity, followed by MEX. As presented by the phylogenetic tree (Figure 4) about 12 populations in the same Fst-based way, the results were verified again.

4 DISCUSSION

There is increasing interested in personalized medicine, because of genetic variations leading to each person’s different metabolism of and reactions to some drugs. In our results, we genotyped the pharmacogenomic VIP variants in the Blang population. The conclusion was that that NR1I2 rs3814055 was the most significant variant among the 12 selected populations, followed by VDR rs1540339. Using genetic structure analysis and Fst values, we also concluded that the genetic backgrounds of the Blang were similar to CHB.

Pregnane X, encoded by the gene NR1I2, belongs to the nuclear hormone receptor superfamily, whose major role is to promote the detoxification and clearance of drugs and toxic xenobiotics from the body as a transcription factor (Bertilsson et al., 1998). And some CYPs (Ding et al., 2015; Jin, Zhang, Shi et al., 2016a; Jin, Zhang, Geng et al., 2016b; Shan et al., 2016; Zhang et al., 2016) regulated by PXR/NR1I2 were associated with phase I metabolism in human. Moreover, some studies (Lown et al., 1997; Shimada, Yamazaki, Mimura, Inui, & Guengerich, 1994) illustrated that SNPs in PXR may be a main reason to the differences in drug reactions and the induction of CYP3A4. Rs3814055, localized in the 5’ untranslated region (UTR) of NR1I2, has already attracted the attention of many researchers, for both disease risk and pharmacogenomics impact. Numerous studies showed that the frequency of rs3814055 in the NR1I2 gene varied according to different populations. The frequency of this variation in a Chinese Han population was 0.218 (Wang et al., 2007), 0.39 for Caucasians (Zhang et al., 2013), 0.21 for Asians (King et al., 2007), 0.50 for Europeans (King et al., 2007), 0.36 for the Dutch (Bosch et al., 2006), and 0.34 for African Americans (Thomas et al., 2007). In our previous studies, the frequency of the rs3814055 SNP variant in the Lhoba population and in the Miao population were 0.101 and 0.09 (He et al., 2015; Jin, Aikemu et al., 2015a), respectively. In our study about the Blangs, the allele T frequency of rs3814055 was 0.06 (Figures 1 and 2). In a Chinese Han Population, upregulated CYP3A4 expression was due to the frequency of rs3814055 (−25,385 T) (Zhang et al., 2001), demonstrating that it was similar to that of Lhoba and Miao. Yet it was still lower than the other populations. Additionally, another report has shown that the allele C linked to Inflammatory Bowel Diseases (IBD) in a European population (Martínez et al., 2010). However, the haplotype TCC of rs3814055/rs6784598/rs2276707

| GIH     | JPT  | LWK  | MEX  | MKK  | TSI  | YRI  |
|---------|------|------|------|------|------|------|
| 1.452E−05 | 0.284 | 4.490E−19 | 0.000 | 2.537E−20 | 1.931E−07 | 1.484E−16 |
| 0.110   | 0.161 | —    | —    | —    | —    | —    |
| 0.000   | 0.553 | 1.328E−10 | 0.000 | 3.526E−14 | 4.204E−06 | 9.144E−15 |
| 1.328E−10 | 0.551 | 1.212E−34 | 1.623E−11 | 6.354E−37 | 9.903E−14 | 1.557E−42 |

| SNP ID | Gene       | rs3814055 | rs1540339 | rs7294 | rs7975232 | rs2239185 | rs2239179 | rs1540339 |
|--------|------------|-----------|-----------|--------|-----------|-----------|-----------|-----------|
| 4.496E−11 | VDR       | 2.436E−07 | 1.511E−08 | 3.289E−08 | 6.439E−19 | —         | —         | —         |
| 1.172E−09 | VDR       | 1.135E−07 | 1.109E−40 | 9.321E−19 | 6.552E−26 | —         | —         | —         |
**FIGURE 2**  Rs3814055 frequencies in different populations of the world. NA, North America; SA, South America; S, Siberia; O, Oceania

**FIGURE 3**  Analysis the genetic structure between Blang and the 23 populations. K denotes the possible numbers of parental population clusters. Each vertical bar represents a person, dividing into color sections. K = 2, 3 were used to assess the genetic relationship between Blang and 11 global populations. And the genetic relationship between 11 ethnic groups from China and Blang were evaluated by K = 3, 4. ASW: ASW: a population of African ancestry in southwestern USA; CEU: a residents population in Utah with Northern and Western European Ancestry; CHB: the Chinese Han in Beijing, China; CHD: Chinese in Metropolitan Denver, Colorado, USA; GIH: Gujarati Indians in Houston, Texas, USA; JPT: Japanese in Tokyo, Japan; LWK: Luhya people in Webuye, Kenya; MEX: people with Mexican ancestry in Los Angeles, California, USA; MKK: Maasai people in Kinyawa, Kenya; TSI: Toscans in Italy; YRI: Yoruba in Ibadan, Nigeria; SX Han, Shaanxi Han. A: Comparing the Blangs with the other 11 populations from the International HapMap Project, Blang was closer to CHB, CHD, and JPT. B: The Han nationality in Shaanxi was very close to the Blangs within China.
functioned as a whole in risk assessment for ulcerative colitis (UC) in Spanish population. In addition, Kurzawski M et al revealed that there were significant differences in tacrolimus concentrations between patients with different NR1I2 rs3814055: C > T genotypes (Kurzawski, Malinowski, Dziiewanowski, & Drozdzik, 2017). And Zazuli et al. (2015) found that, in Indonesian patients with tuberculosis, the TT genotype of rs3814055 had a significantly greater risk of antituberculosis drug-induced liver injury than those of CC genotype.

The SNP rs1540339 is situated in the intron region of VDR. Previous studies have demonstrated that rs1540339 was related to the susceptibility of type 1 diabetes mellitus (T1DM) (Wang et al., 2014), colorectal cancer (Wang, Li, & Zhou, 2008b), and so on. The other study drew the same conclusion that the variant involved in T1DM prevention (Wang, Li et al., 2008b). Jin TB et al. reported that the frequency of rs1540339 T in the Li population was higher than the allele C, indicating that the Li group had lower sensitivity to T1DM. In our study, the allele frequencies of rs1540339 C/T in the Blang were 34% and 66%, respectively. So we guess that the Blang may have lower susceptibility to T1DM.

Considering the above results, ethnicity is an important factor for the frequency distribution and the genotype of rs3814055 can be used as a marker for detecting IBD and UC. And the Blang may have a lower susceptibility to T1DM.

### Table 3

|       | Bul | CHB | CHD | JPT | CEU | GIH | MEX | MKK | NDA | YRI |
|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Bul   | 0   | 0.0427 | 0.0016 | 0   | 0   | 0.0764 | 0.0162 | 0   | 0   | 0.0331 |
| CHB   | 0.0427 | 0   | 0.0016 | 0   | 0   | 0.0764 | 0.0162 | 0   | 0   | 0.0331 |
| CHD   | 0   | 0   | 0.0016 | 0   | 0   | 0.0764 | 0.0162 | 0   | 0   | 0.0331 |
| JPT   | 0   | 0   | 0.0016 | 0   | 0   | 0.0764 | 0.0162 | 0   | 0   | 0.0331 |
| CEU   | 0.0162 | 0.0764 | 0.0016 | 0   | 0   | 0.0764 | 0.0162 | 0   | 0   | 0.0331 |
| GIH   | 0.0162 | 0.0764 | 0.0016 | 0   | 0   | 0.0764 | 0.0162 | 0   | 0   | 0.0331 |
| MEX   | 0.0162 | 0.0764 | 0.0016 | 0   | 0   | 0.0764 | 0.0162 | 0   | 0   | 0.0331 |
| MKK   | 0.0162 | 0.0764 | 0.0016 | 0   | 0   | 0.0764 | 0.0162 | 0   | 0   | 0.0331 |
| NDA   | 0   | 0   | 0.0016 | 0   | 0   | 0.0764 | 0.0162 | 0   | 0   | 0.0331 |
| YRI   | 0   | 0   | 0.0016 | 0   | 0   | 0.0764 | 0.0162 | 0   | 0   | 0.0331 |

**Notes:** ASW, a population of African ancestry in the southwestern USA; CEU, a residents population in Utah with Northern and Western European Ancestry; CHB, the Chinese Han in Beijing, China; CHD, the population of metropolitan Denver, Colorado, USA; GIH, the Gujarati Indians in Houston, Texas, USA; JPT, the Japanese population in Tokyo, Japan; LWK, the Luhu Man in Luhu, Gambia, West Africa; LWK, the Luhu Man in Luhu, Gambia, West Africa; MKK, the Maasai people in Kenya; NDA, the North American descendant; TSI, the Tuscan people of Italy; YRI, the Yoruba in Ibadan, Nigeria.
and provide some help for the development of personalized medicine.

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DISCLOSURE

The authors have no conflicts of interest to declare.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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