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

Dandan Li 1, Linna Peng 1, Shishi Xing 1, Chunjuan He 1 and Tianbo Jin 1,2*

Abstract

Background: The variation of drug responses and target does among individuals is mostly determined by genes. With the development of pharmacogenetics and pharmacogenomics, the differences in drug response between different races seem to be mainly caused by the genetic diversity of pharmacodynamics and pharmacokinetics genes. Very important pharmacogenetic (VIP) variants mean that genes or variants play important and vital roles in drug response, which have been listed in pharmacogenomics databases, such as Pharmacogenomics Knowledge Base (PharmGKB). The information of Chinese ethnic minorities such as the Wa ethnic group is scarce. This study aimed to uncover the significantly different loci in the Wa population in Yunnan Province of China from the perspective of pharmacogenomics, to provide a theoretical basis for the future medication guidance, and to ultimately achieve the best treatment in the future.

Results: In this study, we recruited 200 unrelated healthy Wa adults from the Yunnan province of China, selected 52 VIP variants from the PharmGKB for genotyping. We also compared the genotype frequency and allele distribution of VIP variants between Wa population and the other 26 populations from the 1000 Genomes Project (http://www.1000Genomes.org/). Next, $\chi^2$ test was used to determine the significant points between these populations. The study results showed that compared with the other 26 population groups, five variants rs776746 (CYP3A5), rs4291 (ACE), rs3093105 (CYP4F2), rs1051298 (SLC19A1), and rs1065852 (CYP2D6) had higher frequencies in the Wa population. The genotype frequencies rs4291-TA, rs3093105-CA, rs1051298-AG and rs1065852-GA were higher than those of the other populations, and the allele distributions of rs4291-T and rs3093105-C were significantly different. Additionally, the difference between the Wa ethnic group and East Asian populations, such as CDX, CHB, and CHS, was the smallest.

Conclusions: Our research results show that there is a significant difference in the distribution of VIP variants between the Wa ethnic group and the other 26 populations. The study results will have an effect on supplementing the pharmacogenomics information for the Wa population and providing a theoretical basis for individualised medication for the Wa population.

Keywords: Pharmacogenomics, Wa, Genetic polymorphisms, VIP variants

* Correspondence: jintianbo@gmail.com
1Key Laboratory of Molecular Mechanism and Intervention Research for Plateau Diseases of Tibet Autonomous Region, School of Medicine, Xizang Minzu University, Xianyang 712082, Shaanxi, China
2Engineering Research Center of Tibetan Medicine Detection Technology, Ministry of Education, School of Medicine, Xizang Minzu University, Xianyang 712082, Shaanxi, China

© The Author(s). 2021 Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
Background

Adverse drug reaction (ADR) having the ability of causing severe morbidity and mortality among patients is a major concern in clinical practice and the pharmaceutical industry. Increasing evidence shows that genetic differences between individuals are an important factor to ADR [1]. Pharmacogenomics is a discipline that studies how genetic factors affect the responses of individuals to drug therapy [2] and transforms the drug responses of individuals into a molecular diagnosis. Therefore, it can be used for individualised drug therapy [3]. Over the past 60 years, pharmacogenomics has been used to determine the genetic determinants of drug effects and to maximize drug efficacy and minimize ADR [1]. At present, it is necessary to integrate genomic data into the benefit and risk assessment of daily treatment so that individualised treatment has a certain possibility to vary from person to person [4].

PharmGKB, the Pharmacogenomics Knowledge Base (http://www.pharmgkb.org) is dedicated to disseminating information on how genetic variation causes variation in drug response. The PharmGKB database describes the connection between genes, diseases and drugs and provides various forms of knowledge, including the abstracts of very important pharmacogene (VIP), drug pathway diagrams and selected literature notes [5]. The PharmGKB database also integrates information from the Clinical Pharmacogenetics Implementation Consortium (CPIC) to provide drug dosage guidance based on individual genotypes [6].

There are 56 ethnic groups recognized by the People’s Republic of China, and different ethnic groups have different reactions to drugs. The Wa people reside mainly in the Yunnan Province of Southwestern China. The total population of the Wa ethnic group in China is 429,709, based on the data of the sixth nationwide population census in 2010. Because of the differences in genetics, physiology, pathology, diet, living environment, and nutritional status, the same drug regimen may not be suitable for every ethnic group [7]. For example, in the Han, Bai, Wa, and Tibetan populations of the Yunnan Province in Southwestern China, there are significant differences in MDRI genotype distribution and the haplotype spectrum [8]. Studies have shown that CYP2C9 mutation alleles frequencies in Caucasians are relatively higher (2:12%, 3:8.3%), while CYP2C9 mutation alleles frequencies in Chinese are relatively lower (CYP2C9:2.0%, 3:0%, 2:15%) [9]. Many of the observed drug response variability has a genetic basis, which is caused by the differences in the genetic determination of drug absorption, disposal, metabolism, or excretion [10].

We selected and genotyped 52 VIP variants among 27 genes in the Wa population. Next, we compared the genotype frequency and allelic distribution differences of VIP variants between the Wa ethnic group and the other 26 populations from the 1000 Genomes Project. The research results will expand the current Wa ethnic group pharmacogenomics information and ethnic diversity, and help clinicians to use genomic and molecular data to effectively implement personalized medicine in the future.

Results

According to the PharmGKB database, we designed 67 SNPs and obtained 52 VIP variants, which are distributed mainly on 27 genes, mainly related to the cytochrome P450 family, dihydropyrimidine dehydrogenase, cyclooxygenase, N-acetyltransferase and others. The chromosome position, base pair, functional result, genotype-drug relationship, information about the drug related to gene mutation, gene, level of evidence, genotyping, minor allele frequency (MAF), and other basic information are shown in Table 1. The designed PCR primers is designed using the Agena MassARRAY Assay Design 4.0 software (San Diego, California, USA), and the specific information is showed in Supplementary Table 1.

We used the chi-square test to study the frequency distribution of 52 loci and compared the Wa ethnic group with the other 26 different populations from the 1000 Genomes Project (CDX, CHB, CHS, JPT, KHV, ACB, ASW, ESN, GWD, LWK, MSL, YRI, CLM, MXL, PEL, PUR, CEU, FIN, GBR, IBS, TSI, BEB, GH, ITU, PJL, and STU). Compared with the other 26 ethnic groups, we observed 17, 21, 18, 18, 33, 36, 37, 33, 34, 36, 37, 33, 35, 38, 36, 40, 39, 41, 38, 32, 40, 39, 40, and 39 different SNPs without adjustment (p < 0.05) (Table 2). The table shows that the Wa ethnic group has the smallest difference compared with the CDX, CHB, CHS, and KHV in the East Asian population, but the biggest difference is in the GH and PJL in the South Asian population compared with the FIN and IBS in the European population. Among these loci, CYP3A5 rs776746, ACE rs4291, CYP4F2 rs3093105, SLC19A1 rs1051298, and CYP2D6 rs1065852 had higher frequencies compared with the other 26 populations. We also found that the significant differences between KHV, JPT, CDX, LWK and Wa people were in rs3093105 and rs1065852.

Compared the Wa ethnic group with the other 26 population groups, there were 6, 9, 6, 10, 7, 28, 25, 27, 32, 29, 28, 30, 23, 21, 23, 27, 24, 24, 24, 26, 20, 26, 24, 26, and 27 different VIP variants after Bonferroni’s multiple adjustments (p < 0.05/(52×26)) (Table 3). Compared with the Wa population in the Yunnan province of China, the differences of CDX, CHB, and CHS the East Asian population are the smallest; the differences of GWD, LWK, and YRI, whose genomes are African, are
| SNP ID | Chromosome | BP     | Functional Consequence | Annotation                                                                 | Molecules | Paper Discusses | Genes                | Level of Evidence | Allele MAF | Genotype          | Mutation Homozygote | Heterozygote | Wild Homozygote |
|--------|------------|--------|------------------------|-----------------------------------------------------------------------------|-----------|-----------------|----------------------|------------------|-------------|------------------|---------------------|--------------|-----------------|
| rs11572325 | 1         | 59896030 | intron_variant         | Genotypes AA + AG are associated with decreased survival when treated with antineoplastic agents in people with Pancreatic Neoplasms as compared to genotype GG. | CYP2J2   | CYP2J2          | T/A                  | 0.043            | 0           | 17               | 183                 |              |                 |
| rs10889160 | 1         | 59896449 | intron_variant         | Genotypes AA + AG are associated with decreased survival when treated with antineoplastic agents in people with Pancreatic Neoplasms as compared to genotype GG. | CYP2J2   | CYP2J2          | C/T                  | 0.108            | 0           | 43               | 157                 |              |                 |
| rs1760217  | 1         | 97137438 | genic_downstream_transcript_variant/intron_variant | Genotypes AA + AG is associated with decreased Drug Toxicity when treated with capecitabine or fluorouracil in people with Colorectal Neoplasms as compared to genotype GG. | DPYD     | DPYD            | 1A                   | 0.265            | 10          | 85               | 103                 |              |                 |
| rs1801159  | 1         | 97515839 | coding_sequence_variant/genic_downstream_transcript_variant/intron_variant/misseense_variant | Genotypes TT is not associated with increased risk of Neutropenia when treated with cyclophosphamides, doxorubicin and fluorouracil in women with Breast Neoplasms as compared to genotypes CC + CT. | PTGS2    | PTGS2           | G/A                  | 0.095            | 1           | 36               | 163                 |              |                 |
| rs1801205  | 1         | 97883329 | non_coding_transcript_variant/intron_variant/coding_sequence_variant/3_prime_UTR_variant/misseense_variant | Genotypes AA + AG is associated with decreased Drug Toxicity when treated with capecitabine or fluorouracil in people with Colorectal Neoplasms as compared to genotype GG. | PTGS2    | PTGS2           | 3                    | 0.175            | 3           | 64               | 133                 |              |                 |
| rs5275    | 1         | 186673926 | 3_prime_UTR_variant | Genotype AA is associated with increased progression-free survival and overall survival when treated with capetebazine and oxaliplatin in people with Colorectal Neoplasms as compared to genotypes AG + GG. | CACN A15 | CACN A15        | G/A                  | 0.040            | 0           | 16               | 184                 |              |                 |
| rs20417   | 1         | 186681189 | upstream_transcript_variant/ntron_coding_transcript_variant | Allele C is not associated with response to cetuximab or panitumumab in people with Colorectal Neoplasms as compared to allele G. | R9R2     | R9R2            | A/G                  | 0.003            | 0           | 1                | 199                 |              |                 |
| rs12139527 | 1         | 201040054 | misseense_variant/coding_sequence_variant/intron_variant | Genotypes GT + TT are not associated with increased likelihood of statin-related myopathy when treated with atorvastatin or simvastatin as compared to genotype GG. | A8CG2    | A8CG2           | T/G                  | 0.196            | 7           | 64               | 128                 |              |                 |
| rs2306238  | 1         | 237550803 | intron_variant         | Genotypes TT is not associated with increased risk of Neutropenia when treated with cyclophosphamides, doxorubicin and fluorouracil in women with Breast Neoplasms as compared to genotypes CC + CT. | A8CG2    | A8CG2           | C/T                  | 0.538            | 55          | 103              | 40                  |              |                 |
| rs2339962  | 4         | 88131171 | coding_sequence_variant/misseense_variant | Genotypes CT + TT are associated with decreased Drug Toxicity when treated with cetuximab and panitumumab in people with Kidney Transplantation as compared to genotype CC + TT. | ADH1C    | ADH1C           | C/T                  | 0.108            | 9           | 25               | 166                 |              |                 |
| rs2331137  | 4         | 88139962 | coding_sequence_variant/misseense_variant | Genotypes CT + TT are associated with decreased Drug Toxicity when treated with cetuximab and panitumumab in people with Kidney Transplantation as compared to genotype CC + TT. | ADH1C    | ADH1C           | C/T                  | 0.108            | 9           | 25               | 166                 |              |                 |
| rs698     | 4         | 99339632 | coding_sequence_variant/ntron_coding_transcript_variant/misseense_variant | Genotype CT is associated with decreased likelihood of complete response when treated with cisplatin and cyclophosphamide in women with Ovarian Neoplasms as compared to genotypes CC + TT. | CYP3A5   | CYP3A5          | 1A                   | 0.150            | 29          | 2                | 169                 |              |                 |
| rs776746   | 7         | 99672916 | intron_variant/splice_acceptor_variant/genic_downstream_transcript_variant/misseense_variant | Genotype CC is associated with decreased dose of tacrolimus in people with Kidney Transplantation as compared to genotypes CT + TT. | CYP3A5   | CYP3A5          | T/C                  | 0.150            | 29          | 2                | 169                 |              |                 |
| SNP ID  | Chromosome | BP            | Functional Consequence | Annotation | Molecules | Paper Discusses | Genes     | Level of Evidence | Allele | MAF  | Genotype | Mutation Homozygote | Heterozygote | Wild Homozygote |
|---------|------------|---------------|------------------------|------------|-----------|----------------|-----------|-------------------|--------|------|----------|-------------------|-------------|------------------|
| rs2242480 | 7          | 99763843      | intron_variant         | CYP3A4 *1G/*1G is associated with decreased metabolism of fentanyl in human liver microsomes as compared to CYP3A4 *1/*1 + *1/*G. | isoleucine | Metabolism/ PK   | CYP3A4    | 18                | T/C    | 0.337| 18       | 98                | 83           |
| rs1805123 | 7          | 150948446     | missense_variantcoding_sequence_variant| Allele G is associated with decreased QT interval as compared to genotype TT. | tacrolimus | Metabolism/ PK   | KCNH2     | 3                | G/T    | 0.095| 0        | 38                | 162          |
| rs4646244 | 8          | 183900238     | upstream_transcript_variant coding_sequence_variantgenic_upstream_transcript_variant| Allele A is associated with increased risk of Hepatitis when treated with etambutol, isoniazid, pyrazinamide and rifampin in people with Tuberculosis. | ethambutol isoniazid pyrazinamide rifampin | Toxicity | NAT2    | 3                | A/T    | 0.223| 13       | 62                | 122          |
| rs4271002 | 8          | 18390758      | upstream_transcript_variant coding_sequence_variantintronic_variant | Allele C is associated with increased risk of intolerance of aspirin in people with Asthma as compared to allele G. | aspirin | Toxicity | NAT2     | 3                | C/G    | 0.241| 9        | 77                | 111          |
| rs1041983 | 8          | 18400285      | coding_sequence_variant | NAT2 *A/*B is associated with increased likelihood of Toxic liver disease when treated with isoniazid and rifampin in people with Tuberculosis. | ethambutol isoniazid pyrazinamide rifampin | Toxicity | NAT2    | 18               | T/C    | 0.455| 42       | 96                | 60           |
| rs1801280 | 8          | 18400344      | missense_variantcoding_sequence_variant | NAT2 *A is associated with increased risk of severe cutaneous adverse reactions when treated with sulfamethoxazole and trimethoprim in people with Acquired Immunodeficiency Syndrome. | ethambutol isoniazid pyrazinamide rifampin | Toxicity | NAT2    | 18               | C/T    | 0.043| 0        | 17                | 183          |
| rs1799929 | 8          | 18400484      | coding_sequence_variant | Allele T is not associated with increased risk of hepatotoxicity when treated with ethambutol, isoniazid, pyrazinamide and rifampin in people with Tuberculosis as compared to allele C. | ethambutol isoniazid pyrazinamide rifampin | Toxicity | NAT2    | 18               | T/C    | 0.043| 0        | 17                | 183          |
| rs1799930 | 8          | 18400593      | missense_variantcoding_sequence_variant | NAT2 *A/*B is associated with increased likelihood of Toxic liver disease when treated with isoniazid and rifampin in people with Tuberculosis. | ethambutol isoniazid pyrazinamide rifampin | Toxicity | NAT2    | 18               | A/G    | 0.234| 12       | 69                | 118          |
| rs1208    | 8          | 18400806      | missense_variantcoding_sequence_variant | NAT2 *A/*B + *6A/*6A + *6A/*B + *7B/*7B is associated with increased risk of Toxic liver disease when treated with ethambutol, isoniazid, pyrazinamide and rifampin in people with Tuberculosis. | ethambutol isoniazid pyrazinamide rifampin | Toxicity | NAT2    | 18               | G/A    | 0.043| 0        | 17                | 183          |
| rs1799931 | 8          | 18400860      | missense_variantcoding_sequence_variant | NAT2 *A/*B is associated with increased likelihood of Toxic liver disease when treated with drugs for treatment of Tuberculosis as compared to genotypes AG + GG. | ethambutol isoniazid pyrazinamide rifampin | Toxicity | NAT2    | 18               | A/G    | 0.230| 10       | 72                | 118          |
| rs1495741 | 8          | 18413371      | None | Genotype AA is associated with increased likelihood of Toxic liver disease when treated with Drugs For Treatment Of Tuberculosis as compared to genotypes AG + GG. | Drugs For Treatment Of Tuberculosis | Toxicity | NAT2    | 3                | G/A    | 0.370| 26       | 93                | 77           |
| rs2115819 | 10         | 45405641      | intron_variant | Genotype GG is associated with increased FEV1 response when treated with montelukast in people with Asthma as compared to genotypes AA + AG. | montelukast | Efficacy | ALDOX3   | 3                | A/G    | 0.140| 9        | 38                | 153          |
| rs4244285 | 10         | 94781859      | coding_sequence_variant | Allele A is associated with decreased exposure to nelfinavir | nelfinavir | Metabolism/ CYP3C19 | 3        | A/G    | 0.389| 31       | 92                | 75           |
| SNP ID | Chromosome | BP    | Functional Consequence                                      | Annotation                                                                                           | Molecules                              | Paper Discusses | Genes | Level of Evidence | Allele | MAF | Genotype | Mutation Homozygote | Heterozygote | Wild Homozygote |
|--------|------------|-------|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|----------------------------------------|-----------------|-------|-------------------|--------|-----|----------|-------------------|---------------|-----------------|
| rs1057910 | 10         | 94981296 | missense_variant, synonymous_variant                       | CYP2C9 *1/*3 is associated with decreased metabolism of meloxicam in healthy individuals as compared to CYP2C9 *1/*1. | piroxicam, Metabolism/ PK               | CYP2C9 1A | C/A  | 0.023            | 0      | 9  | 191      |                      |               |                 |
| rs11572103 | 10         | 90058349 | missense_variant, coding_sequence_variant                  | CYP2C8 *1/*3 + *3/*3 is associated with increased response to piroxicam in women with Breast Neoplasms as compared to CYP2C8 *1/*1. | rosiglitazone, Toxicity                 | CYP2C8 3    | A/T  | 0.010            | 0      | 4  | 196      |                      |               |                 |
| rs7909236  | 10         | 95009673 | upstream_transcript_variant                               | Allele T is not associated with concentrations of imatinib in people with Neoplasms as compared to allele G. | CYP2C8                              | T/G  | 0.030 | 0           | 12     | 188 | 188      |                      |               |                 |
| rs1710453  | 10         | 95069772 | upstream_transcript_variant                               | Genotypes AC + CC is not associated with resistance to clopidogrel in people with Stroke as compared to genotype AA. | CYP2C8                              | C/A  | 0.363 | 26          | 93     | 81 | 81       |                      |               |                 |
| rs3813867  | 10         | 133526101 | non_coding_transcript_variant, upstream_transcript_variant | CYP2E1 *1/*5B is associated with increased elimination rate of acetaminophen in people with Liver Diseases, Alcoholic as compared to CYP2E1 *1/*1. | Drugs For Treatment Of Tuberculosis | CYP2E1 3    | C/G  | 0.075            | 3      | 24 | 172      |                      |               |                 |
| rs2031920  | 10         | 133526341 | non_coding_transcript_variant, upstream_transcript_variant | Genotypes CT + TT are associated with increased risk of Toxic liver disease when treated with Drugs For Treatment Of Tuberculosis in people with Tuberculosis as compared to genotype GC. | Drugs For Treatment Of Tuberculosis | CYP2E1 3    | T/C  | 0.098            | 3      | 33 | 164      |                      |               |                 |
| rs6413432  | 10         | 13353040 | intron_variant                                             | Genotype TT is associated with increased progression-free survival when treated with cisplatin and cyclophosphamide in women with Ovarian Neoplasms as compared to genotype AT. | cisplatin, Efficacy/cyclophosphamide   | CYP2E1 3    | A/T  | 0.025            | 0      | 10 | 190      |                      |               |                 |
| rs2070676  | 10         | 133537633 | intron_variant                                             | Genotype GG is associated with increased risk of severe emesis when treated with cisplatin and cyclophosphamide in women with Ovarian Neoplasms as compared to genotype GC. | cisplatin, Efficacy/cyclophosphamide   | CYP2E1 3    | G/C  | 0.175            | 3      | 64 | 133      |                      |               |                 |
| rs5219     | 11         | 17388025 | missense_variant, stop_gained, 5_prime_UTR_variant, intron_variant, coding_sequence_variant | Allele T is associated with decreased activity of KCNJ11 when treated with glibenclamide in pancreatic islet cells. | gliclazide, Efficacy                   | KCNJ11 3    | T/C  | 0.340            | 9      | 118| 73        |                      |               |                 |
| rs1801028  | 11         | 113412762 | missense_variant, coding_sequence_variant                  | Genotypes GG + GG are not associated with response to antipsychotics in people with Schizophrenia as compared to genotype CC. | DDR2                                  | C/G  | 0.005 | 0           | 2      | 198 |                      |                      |               |                 |
| rs2306285  | 12         | 21176804 | missense_variant, coding_sequence_variant                  | Genotype AA is associated with decreased response to rocuronium as compared to genotypes AG + GG. | pravastatin, Metabolism/ PK            | SLC01B1 3    | A/G  | 0.168            | 5      | 57 | 138      |                      |               |                 |
| rs4516035  | 12         | 47906043 | upstream_transcript_variant                               | Allele T is associated with increased jejunal CYP1A4 protein levels as compared to allele C. | midazolam, Metabolism/ PK              | VDR 3     | C/T  | 0.025            | 0      | 10 | 190      |                      |               |                 |
| rs762551   | 15         | 74749576 | intron_variant                                             | CYP1A2 *1K is associated with decreased transcription of CYP1A2 when exposed to xenobiotics in B1642 cells. | caffeine, Toxicity                    | CYP1A2 3    | C/A  | 0.321            | 17     | 91 | 87       |                      |               |                 |
| rs2472004  | 15         | 74751897 | intron_variant                                             | Allele A is associated with increased likelihood of remission when treated with paroxetine in people with paroxetine/ erlotinib. | paroxetine, Metabolism/ Efficacy       | CYP1A2 3    | A/G  | 0.083            | 0      | 33 | 167      |                      |               |                 |
| SNP ID   | Chromosome | BP          | Functional Consequence                          | Annotation                                                                 | Molecules                                                                 | Paper Discusses | Genes | Level of Evidence | Allele | MAF   | Genotype | Mutation Homozygote | Heterozygote | Wild Homozygote |
|----------|------------|-------------|-------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|-----------------|-------|-------------------|--------|-------|----------|-------------------|---------------|-----------------|
| rs750155 | 16         | 28609251    | _5_prime_UTR_variant,intron_variant,genomic_upstream_transcript_variant | with Depressive Disorder, Major as compared to allele G.                   | PK                                                                        |                 |       |                   |        |       |          |                   |               |                 |
| rs1800764 | 17         | 63473168    | None                                            | Allele T is not associated with ABT-751 pharmacokinetic parameters when treated with ABT-751 in people with Neoplasms as compared to allele C. | SULT1A1                                                                  | T/C             | 0.406 | 22                | 112    | 58    |          |                   |               |                 |
| rs4291    | 17         | 63476833    | upstream_transcript_variant                      | Genotypes AT + TT are associated with increased risk of aspirin intolerance when exposed to aspirin in people with Asthma as compared to genotype AA. | captopril/aspirin/amiodipine/chlorthalidone/lisinopril                    | Efficacy/Toxicity/Efficacy   | ACE   | C/T              | 0.269  | 14    | 79       | 106               |               |                 |
| rs4267385 | 17         | 63506395    | None                                            | Genotypes CC + CT are associated with same protective properties against angiotensin-converting enzyme inhibitors-induced cough when treated with Ace Inhibitors, Plain in people with homozygous GG genotype for rs4343 as compared to genotype TT. | Ace Inhibitors/Plain                                                     | Toxicity         | ACE   | T/C              | 0.260  | 16    | 71       | 111               |               |                 |
| rs2108622 | 19         | 15879621    | missense_variant,coding_sequence_variant         | CYP4F2 *1/*5 + *5/*5 are associated with increased exposure to Vitamin K1 in healthy individuals as compared to CYP4F2 *1/*1. | warfarin                                                                | Dosage/CYP4F2     | 1A    | T/C              | 0.173  | 6     | 57       | 137               |               |                 |
| rs3003105 | 19         | 15897578    | missense_variant,coding_sequence_variant         | Allele C is associated with increased catalytic activity of CYP4F2 when treated with vitamin e in S9 insect cells transfected with CYP4F2 as compared to allele A. | vitamin e                                                               | Metabolism/PK     | CYP4F2 | C/A              | 0.497  | 1     | 198      | 0                 |               |                 |
| rs8192726 | 19         | 40848591    | intron_variant                                  | Genotypes AC + CC are associated with increased plasma concentration (p<0.008) of efavirenz in people with HIV infections as compared to genotype AA. | efavirenz                                                               | Efficacy/Other     | CYP2A6 | A/C              | 0.163  | 8     | 49       | 143               |               |                 |
| rs1051298 | 21         | 45514912    | intron_variant,3_prime_UTR_variant               | Allele G is associated with increased progression-free survival when treated with bevacizumab and pemetrexed in people with Lung Neoplasms as compared to allele A. | pemetrexed                                                              | Efficacy/SLC19A | 1     | G/A              | 0.431  | 8     | 152      | 35                |               |                 |
| rs1051296 | 21         | 45514947    | intron_variant,3_prime_UTR_variant               | Allele G is associated with increased progression-free survival when treated with bevacizumab and pemetrexed in people with Lung Neoplasms as compared to allele A. | SLC19A1                                                                | A/C              | 0.469 | 44                | 95    | 56    |          |                   |               |                 |
| rs1131596 | 21         | 45538002    | missense_variant,5_prime_UTR_variant            | Allele G is not associated with response to methotrexate in children with Precursor Cell Lymphoblastic Leukemia-Lymphoma as compared to allele A. | SLC19A1                                                                | G/A              | 0.490 | 33                | 129    | 37    |          |                   |               |                 |
| rs1069852 | 22         | 42130692    | intron_variant,missense_variant,coding_sequence_variant | Allele A is associated with decreased clearance of alpha-hydroxymetoprolol in healthy individuals as compared to allele G. | paroxetine                                                              | Metabolism/PK     | CYP2D6 | 1A               | 0.430  | 29    | 170      | 1                 |               |                 |

**SNP**: Single nucleotide polymorphism, **BP**: Base pair, **MAF**: Minor allele frequency
| SNP ID | Genes | p<0.05 | EAS | AFR | AS | S | N1K | MSL | VIB |
|--------|--------|--------|-----|-----|----|---|-----|-----|-----|
| n11502155 | CYP2C9 | 0.04960713 | 0.39057075 | 0.006284207* | 0.000330238* | 5.27E-10* | 0.000120419* | 2.93E-06* | 0.000401215* |
| n11475492 | CYP2C9 | 0.90217577 | 0.60810344 | 0.12599989 | 0.00959884 | 2.87E-07* | 0.50E-08* | 1.06E-11* | 0.000317176* |
| n11475490 | CYP2C9 | 0.22996048 | 0.49957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| n11475491 | CYP2C9 | 0.32996048 | 0.56957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| n11475494 | CYP2C9 | 0.53996048 | 0.73957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| n11475496 | CYP2C9 | 0.63996048 | 0.73957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| n11475493 | CYP2C9 | 0.73996048 | 0.73957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| n11475495 | CYP2C9 | 0.83996048 | 0.73957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| n11475497 | CYP2C9 | 0.93996048 | 0.73957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| n11475498 | CYP2C9 | 0.04960713 | 0.39057075 | 0.006284207* | 0.000330238* | 5.27E-10* | 0.000120419* | 2.93E-06* | 0.000401215* |
| n11475499 | CYP2C9 | 0.14960713 | 0.49057075 | 0.12599989 | 0.00959884 | 2.87E-07* | 0.50E-08* | 1.06E-11* | 0.000317176* |
| n11475500 | CYP2C9 | 0.24960713 | 0.56957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| n11475501 | CYP2C9 | 0.34960713 | 0.73957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| n11475502 | CYP2C9 | 0.44960713 | 0.73957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| n11475503 | CYP2C9 | 0.54960713 | 0.73957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| n11475504 | CYP2C9 | 0.64960713 | 0.73957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| n11475505 | CYP2C9 | 0.74960713 | 0.73957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| n11475506 | CYP2C9 | 0.84960713 | 0.73957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| n11475507 | CYP2C9 | 0.94960713 | 0.73957075 | 0.73183666 | 0.31789587 | 0.63973253 | 0.85E-07* | 0.24E-10* | 0.000317176* |
| SNP ID | Genes | p<0.05 | EAS | AFR | AMR | EUR | SAS | EAS | AFR | AMR | EUR | SAS | EAS | AFR | AMR | EUR | SAS | EAS | AFR | AMR | EUR | SAS | EAS | AFR | AMR | EUR | SAS |
|--------|-------|--------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| rs2306283 | SLCO1B1 | 0.658512672 | 0.205950281 | 0.516381109 | 9.67E-06* | 0.255712933 | 0.343484593 | 0.08000319 | 0.15567014 | 0.42137787 | 0.24086061 | 0.739594068 | 0.842983386 |
| rs4516035 | VDR | 0.000250973* | | | | | | | | | | | | | | | | | | | | | | | | | | |
| rs762551 | CYP1A2 | 0.014236939* | | | | | | | | | | | | | | | | | | | | | | | | | | |
| rs4516035 | VDR | 0.000250973* | | | | | | | | | | | | | | | | | | | | | | | | | | |
| rs2747304 | CYP1A2 | 0.001459191* | 0.25674035 | 0.001901901* | | | | | | | | | | | | | | | | | | | | | | | | | | |
| rs75055 | SUITAI | 0.00699114 | 0.141318968 | 0.016733876 | 0.000364292* | 0.02368256* | 0.00826004* | 0.003262696* | 0.002040475* | | | | | | | | | | | | | | | | | | | |
| rs1807664 | ACE | 0.006257806 | 0.391438159 | 0.21709705 | 5.34E-05* | 0.255712933 | 0.343484593 | 0.08000319 | 0.15567014 | 0.42137787 | 0.24086061 | 0.739594068 | 0.842983386 |
| rs3093105 | CYP1A2 | 0.30062009 | 0.300639847 | 0.579831407 | 0.049533921* | 0.255712933 | 0.343484593 | 0.08000319 | 0.15567014 | 0.42137787 | 0.24086061 | 0.739594068 | 0.842983386 |
| rs1051298 | SLC19A1 | 1.51E-07* | 2.66E-09* | 0.000482386 | 0.004533921* | 0.255712933 | 0.343484593 | 0.08000319 | 0.15567014 | 0.42137787 | 0.24086061 | 0.739594068 | 0.842983386 |
| rs1051296 | SLC19A1 | 0.609205002 | 0.771425657 | 0.124768121 | 0.752914304 | 0.254101023 | 0.503862027 | 0.471517174 | 0.162301179 | 0.644086821 | 0.581333718 | 0.868173465 | 0.468849993 |
| rs1131596 | SLC19A1 | 0.022919018* | 0.023544228* | 0.400775632 | 0.005294873* | 0.255712933 | 0.343484593 | 0.08000319 | 0.15567014 | 0.42137787 | 0.24086061 | 0.739594068 | 0.842983386 |
| rs1065852 | CYP2D6 | 4.20E-16 | 1.82E-13* | 1.88E-17 | 6.28E-22* | 7.84E-12* | 4.99E-42* | 2.82E-38* | 3.62E-50* | 2.33E-48* | 4.31E-58* | 2.22E-39* | 1.3E-48* | 0.00426342* | 0.00115013* | 2.60E-16* | 1.59E-12 | 7.50E-11 | 4.12E-10* | | | | |

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

p values were calculated from χ² test

Bold indicates p < 0.05 indicates statistical significance
| SNP ID | AMR  | EUR  | SAS  | SNV  | EUR  | SAS  |
|--------|------|------|------|------|------|------|
| rs11572325 | 0.298107259 | 0.006404332* | 0.271827376 |
| rs1760217 | 0.424945255 | 0.003384269* | 3.19E-06* |
| rs1801265 | 0.0582413 | 2.03E-09* | 0.010507456* |
| rs20417 | 2.31E-19 | 3.44E-19 | 6.57E-17 |
| rs12139527 | 4.94E-08* | 0.001983601* | 0.003138048* |
| rs3850625 | rs2306238 | 0.315347468 | 0.594776616 |
| rs2231142 | 0.093444383 | 0.910555607 | 0.363795593 |
| rs1805123 | 1.21E-05* | 1.31E-06* | 0.004686145* |
| rs4646244 | 0.765141605 | 0.000339744* | 0.016243392* |
| rs1799929 | rs1799930 | 0.881554266 | 0.05609109 |
| rs1208 | rs1495741 | 0.67785097 | 0.070175871 |
| rs2115819 | 3.77E-16* | 9.55E-11* | 9.96E-07* |
| rs1057910 | 0.00223127 | 5.21E-07* | 0.000111245* |
| rs17110453 | 8.29E-11* | 2.41E-07* | 5.14E-14* |
| rs2070676 | 0.290749722 | 0.359414667 | 6.22E-05* |
| rs1801028 | | | |
| SNP ID  | AMR  | EUR  | SAS  |
|--------|------|------|------|
|        | CLM  | MXL  | PEL  | PUR  | CEU  | FIN  | GBR  | IBS  | TSI  | BEB  | GIH  | ITU  | PJL  | STU  |
| rs2306283 | 8.87E-16* | 5.47E-20* | 2.85E-16* | 5.37E-13* | 1.50E-21* | 3.18E-19* | 3.33E-24* | 2.97E-22* | 4.46E-25* | 3.98E-10* | 1.37E-11* | 7.78E-09* | 1.72E-17* | 2.41E-11* |
| rs4516035 | 1.88E-18* | 9.22E-15* | 3.10E-09* | 7.20E-25* | 2.88E-25* | 7.28E-39* | 1.17E-28* | 3.93E-26* | 4.93E-31* | 1.74E-10* | 3.70E-11* | 1.81E-10* | 2.42E-05* | 2.24E-10* |
| rs762551 | 0.209128456 | 0.032953675* | 1.13E-05* | 0.76149116 | 0.34043144 | 0.46800248 | 0.23046324 | 0.35833662 | 0.230526214 | 0.035152873* | 0.000510748* | 0.001980774* | 0.003245356* | 2.56E-06* |
| rs4291 | 3.10E-29* | 1.28E-34* | 4.27E-42* | 9.11E-29* | 2.72E-30* | 1.42E-24* | 1.18E-31* | 6.37E-28* | 5.39E-31* | 3.96E-29* | 8.32E-28* | 2.65E-35* | 6.22E-30* | 1.00E-28* |
| rs4267385 | 5.61E-06* | 0.00111232547* | 0.007641964 | 3.09E-06* | 2.69E-10* | 1.64E-09* | 1.40E-11* | 1.79E-12* | 7.04E-21* | 0.007967336 | 0.001307242* | 0.19692802 | 0.000954545* | 0.008151391* |
| rs2108622 | 0.010322998* | 0.011572406 | 0.82820987 | 0.045504555* | 0.0075664532 | 0.59620205 | 0.005888374* | 2.04E-06* | 2.69E-05* | 1.82E-08* | 1.99E-10* | 2.68E-08* | 1.38E-07* | 1.96E-09* |
| rs3093105 | 2.17E-43* | 1.25E-41* | 7.05E-55* | 1.53E-43* | 7.84E-44* | 8.51E-49 | 1.60E-40* | 6.40E-34* | 1.29E-38* | 4.65E-44* | 1.27E-45* | 1.5E-41* | 1.48E-41* | 1.25E-45* |
| rs8192726 | 0.000189151* | 0.005605647* | 0.00149952* | 0.0000247622* | 0.0001004263* | 0.12951508 | 0.0003735767* | 0.000723061* | 0.0004379184* | 0.49607104 | 0.02716704 | 0.243968045 | 0.892478883 | 0.243968045 |
| rs1051298 | 6.37E-09* | 1.09E-15* | 8.09E-15* | 6.04E-09* | 6.48E-11* | 5.13E-09 | 5.50E-14* | 4.51E-11* | 2.71E-10* | 1.94E-06* | 7.95E-08* | 2.61E-07* | 3.27E-07* | 2.79E-09* |
| rs1051296 | 0.434021469 | 0.011797909 | 0.00062769 | 0.21600329 | 0.91134575 | 0.24384261 | 0.01625569 | 0.61646101 | 0.80496685 | 0.640656134 | 0.03856176 | 0.25737902 | 0.581655047 | 0.830823988 |
| rs1135996 | 0.021820836* | 2.88E-06* | 8.07E-05* | 0.01622840 | 0.161041225 | 0.0459306809 | 9.78E-06* | 0.000809244* | 0.006656253* | 0.01182718* | 0.03771707 | 0.00271073 | 0.00670555 | 0.20377152 |
| rs1058582 | 2.14E-38* | 1.76E-37* | 8.68E-51* | 8.43E-41* | 4.66E-30* | 3.71E-42* | 1.47E-31* | 2.16E-39* | 2.84E-35* | 1.95E-31* | 3.30E-41* | 1.17E-38* | 6.16E-47* | 2.88E-42* |
Table 3 Significant VIP variants in the Wa people compared with the other 26 populations after Bonferroni’s multiple adjustment

| SNP ID   | Genes | p < 0.05/(52×26) | EAS | AFR |
|----------|-------|-------------------|-----|-----|
|          |       |                   | CHX | CHB | CHS | JPT | KHV | ACB | ASW | ESN | GWD | LWK | MSL | YRI |
| rs11572325 | CYP2J2 | 1.02E-06* | 5.45E-06* | 1.90E-06* | 4.42E-06* | 2.08E-05* | 8.09E-05* | 2.75E-05* |
| rs10897160 | CYP2J2 | 5.88E-19* | 1.08E-10* | 1.52E-21* | 8.72E-15* | 1.62E-16* | 9.67E-19* | 4.46E-21* |
| rs1760217    | DPYD   | 0.00083       | 1.07E-05* | 8.09E-05 | 2.75E-06* | 6.33E-08* | 3.62E-07* | 5.51E-05 |
| rs180159 | DPYD   | 1.58E-14* | 9.57E-19* | 7.19E-19* | 7.68E-22* | 2.18E-22* | 1.8E-14* | 5.2E-20* |
| rs180265 | DPYD   | 3.78E-24* | 3.85E-17* | 2.15E-28* | 4.85E-23* | 3.89E-24* | 6.6E-27* | 1.08E-28* |
| rs5275 | PTGS2  | 3.88E-29* | 1.81E-26* | 1.16E-37* | 3.26E-24* | 2.82E-24* | 3.93E-34* | 5.95E-33* |
| rs20417 | PTGS2  | 9.11E-34* | 1.29E-29* | 1.83E-41* | 2.75E-43* | 5.74E-36* | 7.8E-41* | 3.31E-41* |
| rs12139527 | CACNA1S | 2.53E-07* | 1.1E-05* | 4.49E-17* | 3.93E-20* | 2.4E-29* | 2.26E-33* | 4.17E-30* |
| rs1293825 | CACNA1S | 1.44E-20* | 1.5E-18* | 1.25E-18* | 1.82E-21* | 5.24E-21* | 1.18E-37* | 1.47E-36* | 6.57E-33* | 1.5E-30* |
| rs3813867 | CYP2E1 | 3.59E-06 | 0.000012 | 0.000102 | 2.78E-06* | 6.0E-05* | 2.07E-14* | 1.87E-20* | 2.78E-24* | 5.66E-22* | 1.4E-19* | 1.07E-22* |
| rs3813867 | CYP2E1 | 8.07E-05 | 0.0008 | 0.000012 | 2.78E-06* | 2.07E-14* | 1.87E-20* | 2.78E-24* | 5.66E-22* | 1.4E-19* | 1.07E-22* |
| rs12139527 | CACNA1S | 4.21E-19* | 1.31E-16* | 1.45E-15* | 3.14E-16* | 1.66E-19* | 3.18E-30* | 1.06E-17* | 1E-28* | 5.52E-30* | 2.7E-35* | 3.78E-31* | 7.09E-28* |
| rs12139527 | CACNA1S | 4.21E-19* | 1.31E-16* | 1.45E-15* | 3.14E-16* | 1.66E-19* | 3.18E-30* | 1.06E-17* | 1E-28* | 5.52E-30* | 2.7E-35* | 3.78E-31* | 7.09E-28* |
| rs3813867 | CYP2E1 | 8.07E-05 | 0.0008 | 0.000012 | 2.78E-06* | 2.07E-14* | 1.87E-20* | 2.78E-24* | 5.66E-22* | 1.4E-19* | 1.07E-22* | 5.35E-05 | 0.000012 | 2.78E-06* | 2.07E-14* | 1.87E-20* | 2.78E-24* | 5.66E-22* | 1.4E-19* | 1.07E-22* |
| rs180028 | DPD2   | 4.08E-16* | 5.26E-07* | 1.86E-24* | 2.18E-25* | 1.16E-23* | 7.2E-22* | 4.56E-26* |
Table 3  Significant VIP variants in the Wa people compared with the other 26 populations after Bonferroni’s multiple adjustment (Continued)

| SNP ID  | Genes   | p < 0.05/(52×26) | EAS | AFR |
|---------|---------|------------------|-----|-----|
|         |         |                  |     |     |
|         |         |                  |     |     |
| rs2306283 | SLCO1B1 | 9.67E-06*        |     |     |
| rs4516035 | VDR     | 0.000251         |     |     |
| rs762551  | CYP1A2  | 0.000364         |     | 1.00E-05* |
| rs247304  | CYP1A2  | 1.73E-05*        |     |     |
| rs750155  | SULT1A1 |                  |     | 0.00056 |
| rs1800764 | ACE     |                 |     |     |
| rs4291    | ACE     | 3.00E-30*        |     | 2.15E-40* |
| rs4267385 | ACE     | 1.22E-24*        |     | 4.206-37* |
| rs2108622 | CYP4F2  |                 |     |     |
| rs3093105 | CYP4F2  | 1.6E-55*         |     | 2.64E-35* |
| rs1897226 | CYP2A6  |                 |     |     |
| rs1051298 | SLC19A1 | 1.51E-07*        |     | 4.31E-08* |
| rs1051296 | CYP2A6  |                 |     |     |
| rs1137396 | SLC19A1 |                 |     |     |
| rs1067582 | CYP2A6  | 4.20E-16*        |     | 2.22E-39* |

Bold indicates *p < 0.05/(52×26) indicates statistical significance.
| SNP ID     | AMR CLM | AMR MXL | AMR PEL | AMR PUR | EUR CEU | EUR FIN | EUR GBR | EUR IBS | EUR TSI | EUR BEB | EUR GIH | EUR ITU | EUR PJL | EUR STU | SAS BBE | SAS GHH | SAS ITU | SAS PJL | SAS STU |
|------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| rs11572325 | 7.76E-06* | 6.62E-05 |
| rs1089160  | 0.00048 | 9.14E-06* |
| rs1700217  | 3.19E-05* | 2.18E-05* | 5.35E-05 | 0.000223 | 0.00048 |
| rs180159   | 2.14E-06* | 0.000029 |
| rs180265   | 1.97E-05* | 3.98E-05 | 8.42E-05* | 3.16E-06* | 2.57E-08* |
| rs5275     | 2.42E-08* | 9.76E-06* | 4.18E-08* | 3.18E-08* | 7.33E-09* |
| rs20417    | 2.31E-19* | 3.44E-19* | 6.57E-17* | 5.14E-15* | 2.64E-12* |
| rs1235927  | 4.94E-06* |
| rs380625   | 9.08E-10* | 4.71E-09* | 4.14E-16* | 2.62E-12* | 1.13E-07* |
| rs300238   | 0.00071 |
| rs223142   | 0.000016 | 2.64E-05* | 0.000176 |
| rs2231337  | 4.32E-18* | 2.82E-10* | 1.26E-18* | 1.43E-31* | 2.87E-24* |
| rs698      | 6.41E-05 | 1.92E-07* | 2.17E-14* | 1.65E-21* | 1.19E-20* |
| rs776746   | 2.21E-13* | 9.13E-17* | 1.43E-09* | 4.33E-06* | 2.47E-06* |
| rs224480   | 1.35E-07* | 6.01E-14* | 3.6E-12* | 5.94E-12* | 2.02E-09* |
| rs182123   | 1.21E-05* | 1.31E-06* | 1.77E-07* | 3.87E-08* | 2.29E-09* |
| rs464244   | 0.00034 |
| rs2717002  | 0.00060 | 1.74E-06* | 0.000333 |
| rs1049813  | 1.66E-05* | 0.000919 | 0.000817 |
| rs180280   | 2.47E-21* | 8.41E-19* | 6.89E-15* | 4.17E-22* | 2.27E-25* |
| rs1799029  | 4.54E-20* | 4.43E-18* | 3.32E-14* | 2.5E-19* | 3.12E-25* |
| rs1799930  | 0.00019 |
| rs1208     | 6.25E-22* | 4.12E-23* | 6.89E-15* | 5E-22* | 6.43E-24* |
| rs1799931  | 7.83E-06* | 2.98E-05* | 3.4E-12* | 1.03E-08* | 1.72E-09* |
| rs149741   | 5.75E-05 | 0.000771 | 6.3E-06* | 7.45E-06* |
| rs2215191  | 3.77E-16* | 9.55E-11* | 9.96E-07* | 1.12E-14* | 5.62E-24* |
| rs444285   | 9.77E-11* | 2.52E-07* | 4.15E-14* | 8.47E-10* | 2.17E-09* |
| rs1097910  | 8.29E-18* | 1.17E-16* | 1.77E-22* | 1.7E-08* | 1.45E-16* |
| rs1710453  | 8.29E-11* | 2.41E-07* | 5.14E-14* | 5.74E-10* | 1.31E-11* |
| rs381867   | 6.57E-10* | 4.59E-08* | 9.02E-09* | 2.97E-09* | 1.63E-06* |
| rs2031920  | 6.22E-05 |
| rs180028   | 0.000348 | 0.000094 | 3.67E-07* | 1.31E-13* | 9.84E-09* |
### Table 3: Significant VIP variants in the Wa people compared with the other 26 populations after Bonferroni’s multiple adjustment (Continued)

| SNP ID  | AMR  | EUR  | EUR  |
|---------|------|------|------|
|         | CLM  | MKL  | PEL  | PUR  | CEU  | FIN  | IBS  | TSI  | SAS  | REB  | GH   | ITU  | PEL  | STU  |
| rs2306283 | 8.87E-16* | 5.47E-20* | 2.85E-16* | 5.37E-13* | 1.5E-21* | 3.18E-19* | 3.33E-24* | 2.97E-22* | 4.46E-25* | 3.98E-10* | 1.37E-11* | 7.78E-09* | 1.72E-17* | 2.41E-11* |
| rs456035 | 1.88E-18* | 9.22E-15* | 3.1E-09* | 7.2E-25* | 2.88E-25* | 7.28E-39* | 1.17E-28* | 3.93E-26* | 4.94E-31* | 1.74E-10* | 3.7E-11* | 1.81E-10* | 1.72E-15* | 7.16E-13* |
| rs76251 | 1.13E-05* | 0.000511 | 2.42E-05* | | | | | | | | | | | |
| rs247304 | 2.83E-16* | 1.62E-07* | 2.04E-24* | 2.27E-36* | 7.1E-29* | 1.44E-34* | 2.5E-33* | 1.03E-26* | 0.000626 | 2.56E-06* | | | |
| rs75055 | 3.18E-23 | 0.00453 | 1.96E-07* | | | | | | | | | | | |
| rs1800764 | 4.25E-05 | 1.34E-05* | 6.39E-06* | 4.04E-05 | 0.000866 | 0.000415 | 8.38E-08* | 3.48E-05* | | | | | | |
| rs4291 | 3.1E-29* | 1.28E-34* | 4.75E-42* | 9.11E-29* | 2.72E-30* | 1.42E-24* | 1.18E-31* | 6.37E-28* | 5.39E-31* | 3.96E-29* | 8.23E-28* | 2.65E-35* | 6.22E-30* | 1.00E-28* |
| rs2467385 | 5.61E-06* | 3.09E-09* | 2.69E-10* | 1.64E-09* | 1.40E-11* | 1.79E-12* | 7.04E-21* | | | | | | | | |
| rs2108622 | 2.04E-06* | 2.69E-05* | 1.82E-08* | 1.99E-10* | 2.68E-08* | 1.38E-07* | 1.96E-09* | | | | | | | | |
| rs3093150 | 2.57E-43* | 1.25E-41* | 7.05E-55* | 1.53E-43* | 7.84E-44* | 8.51E-49* | 1.6E-40* | 6.4E-34* | 1.29E-38* | 4.65E-44* | 1.27E-45* | 1.55E-41* | 1.48E-41* | 1.25E-45* |
| rs182726 | 0.000189 | 0.000248 | 0.000723 | | | | | | | | | | | |
| rs1051296 | 6.37E-09* | 1.09E-15* | 8.06E-15 | 6.04E-09* | 6.48E-11* | 5.13E-09* | 5.5E-14* | 4.51E-11* | 2.71E-10* | 1.94E-06* | 7.95E-08* | 2.61E-07* | 3.27E-07* | 2.79E-09* |
| rs1051296 | 0.000189 | 0.000248 | 0.000723 | | | | | | | | | | | |
| rs1065852 | 2.14E-38* | 1.76E-37* | 8.68E-51* | 8.43E-41* | 4.66E-30* | 3.71E-42* | 1.47E-31* | 2.16E-39* | 2.84E-35* | 1.95E-31* | 3.3E-41* | 1.17E-38* | 6.16E-47* | 2.88E-42* |
the biggest. CYP3A5 rs776746, ACE rs4291, CYP4F2 rs3093105, SLC19A1 rs1051298, and CYP2D6 rs1065852 in the Wa population still have a high frequency in the other 26 populations after adjustment. There are also some variants becoming insignificant, such as NAT2 rs4646244 and CYP2A6 rs8192726. According to statistics, the frequency of NAT2 rs1041983, rs1799930 and CYP2C9 rs1057910 among the Wa population is only different from PEL, STU, and GIH, while other loci are different between the Wa and multiple ethnic groups.

Our research results show that rs776746 (CYP3A5), rs4291 (ACE), rs3093105 (CYP4F2), rs1051298 (SLC19A1) and rs1065852 (CYP2D6) are the five important VIP variants, and their drug-related information is shown in Table 4. Rs776746 (CYP3A5) is mainly related to the dose and metabolism/pharmacokinetics of tacrolimus in the East Asian populations. Rs4291 (ACE), which plays a functional and important role in captopril, is related to the toxic effects of aspirin in the East Asian populations and is related to amlodipine, chlorthalidone, and lisinopril in the mixed populations. Rs3093105 (CYP4F2) plays a metabolic/pharmacokinetic role in vitamins. In the European populations, rs1051298 (SLC19A1) plays an effective and crucial role in the bevacizumab pemetrexed drug and the pemetrexed drug in the mixed populations. In the East Asian populations, rs1065852 (CYP2D6) plays a metabolic/pharmacokinetic role in alpha-hydroxymetoprolol and is related to citaloprames-citalopram in the European populations. This gene is also closely related to iloperidone. In clinical medication, SNPs at the same variant have different effects on the types and effects of drugs in the different populations, which should be fully and carefully considered.

We combined the calculated allele frequencies with previously published data from the global population, and then conducted a comprehensive analysis of the above several loci. Figure 1 shows that the frequency of the GA genotype of rs1065852 is the highest one (85%) in the Wa population; the frequency of the GG genotype of rs1065852 and the CT genotype of rs776746 is the lowest in the Wa population, but the highest is in the African population. In the Wa population, the TA genotype frequency of rs4291 (ACE) and rs1051298 (SLC19A1) is 100%, the CA genotype frequency of rs3093105 (CYP4F2) is 99.5%, and the AG gene of rs1051298 has a type frequency of 77.9%, which is significantly higher than that of the other populations, showing that the genotype frequencies of the same SNPs in different races are diverse. Figure 2 clearly shows that rs4291-T and rs3093105-C are the highest among the Wa population, with a frequency ranging from 40% to 60%, while rs1065852-G is the lowest among the East Asian population, with a frequency ranging from 34% to 64%. Rs776746-G is the highest in the African population and the lowest in the Wa population; the frequency of rs1051298-G in the East Asian population is 38%-

| Variant | PMID       | Molecules               | P-value | #Of case | #Of control | Study size | Bipgeographical group | Paper discusses | Gene    |
|---------|------------|-------------------------|---------|----------|-------------|------------|-----------------------|-----------------|---------|
| rs776746 | 16421475   | tacrolimus              |         | 53       | 53          | East Asian | metabolism/ PK         | CYP3A5          |
| rs776746 | 23073468   | tacrolimus              | 0.016   | 25       | 25          | East Asian | dosage                | CYP3A5          |
| rs776746 | 21677300   | tacrolimus              | 0.025   | 209      | 209         | Mixed Population | toxicity           | CYP3A5          |
| rs776746 | 16424824   | tacrolimus              |         | 201      | 201         | East Asian | metabolism/ PK         | CYP3A5          |
| rs776746 | 24120259   | tacrolimus              | <0.0001 | 68       | 68          | East Asian | metabolism/ PK         | CYP3A5          |
| rs4291  | 27546928   | captopril               | 0.029   | 190      | 190         | Unknown    | efficacy              | ACE             |
| rs4291  | 18727619   | aspirin                 | 0.015   | 81       | 231         | East Asian | toxicity              | ACE             |
| rs4291  | 20577119   | amlodipine/chlorthalidonelisinopril | 0.0014 | 9309   | 9309       | Mixed Population | other            | CYP2D6          |
| rs3093105 | 20861217  | vitamin                 | <0.003  |         |             | Unknown    | metabolism/ PK         | CYP4F2          |
| rs1051298 | 19841321  | bevacizumabpemetrexed   | 0.01    | 48       | 48          | European   | efficacy              | SLC19A1         |
| rs1051298 | 24732178  | pemetrexed              | 0.016   | 136      | 136         | Mixed Population | efficacy           | SLC19A1         |
| rs1065852 | 10223777   | alpha-hydroxymetoprolol | <0.05   | 40       | 40          | East Asian | metabolism/ PK         | CYP2D6          |
| rs1065852 | 24528284   | citaloprames-citalopram | 2.00E-16 | 435     | 435         | European   | other                 | CYP2D6          |
| rs1065852 | 23277250   | iloperidone             | 0.028   | 128      | 128         | Unknown    | other                 | CYP2D6          |

*p < 0.05 indicates statistical significance
50%, which is lower than that of in the American population. In short, the distribution of alleles is different in each ethnic group, which indicates that there are some differences in genetic background.

**Discussion**

Pharmacogenomics refers to gene-based testing to give the appropriate medicine to different patients at the right dose, thereby maximizing the efficacy and minimizing toxicity, thus improving the goal of personalized medicine [11]. In our study, we selected 52 variant genes related to drug response in the Yunnan Wa ethnic group from PharmGKB and compared the results with the other 26 populations distributed worldwide. The research results are not only enriched the knowledge of Wa pharmacogenomics but also laid a certain theoretical foundation for individualised medication. In our study, we found that the frequency of *CYP3A5* rs776746, *ACE* rs4291, *CYP4F2* rs3093105, *SLC19A1* rs1051298, and *CYP2D6* rs1065852 in the Wa population is higher than the other 26 populations from the 1000 Genomes Project. There are significant differences in the genotype frequency and allele distribution of these VIP variants. For the reason of these differences, we should also consider some factors affecting allele frequency distribution, such as genetic mutation, natural selection, genetic drift, and individual migration between populations. Wa people in the Yunnan Province of China may have special living environment and eating habits, as well as an unique geographical location.

*CYP3A5* is located in chromosome 7q21-q22.1, encoding an enzyme of the *CYP3A* subfamily. The most common nonfunctional variant is *CYP3A5*∗3. The status of *CYP3A5*∗3 is determined by the rs776746-derived allele, that is, the change of intron 3 from A to G [12]. Tacrolimus is an immunosuppressant of calcineurin inhibitors which can prevent allograft rejection in solid organ transplant recipients [13, 14]. After studying the effect of *CYP3A5* (rs776746) on the concentration/doses (C/Ds) of tacrolimus and the long-term prognosis of Chinese heart transplantation, Liu et al. [15] found that *CYP3A5* nonexpressors (*CYP3A5*∗3/*3) did not expressed in all point of time. The C/Ds of crolimus are significantly higher than that of expressers (*CYP3A5*∗1/*3), so nonexpressors have higher tacrolimus C/Ds, and expressers tend to have the worse long-term prognoses. In our study, we found that *CYP3A5* rs776746 is more significant in the Wa population compared with the other 26 populations, which is related to tacrolimus dose and metabolism/pharmacokinetics in the East Asian population which indicates that the factor should be fully considered when performing tacrolimus therapy to help to determine the appropriate dose.
Cytochrome P450 4F2 (CYP4F2) is an omega-hydroxylase and the only enzyme which is currently showed to metabolize vitamin E in the human body [16]. There are two common genetic variants (V433M, rs2108622 and W12G, rs3093105) that can change its activity. CYP4F2 gene polymorphisms affects vitamin E to improve the liver of nonalcoholic fatty liver disease children and adults who participated in the Treatment of Nonalcoholic Fatty Liver Disease in Children and Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis Histology, but there are obvious individual differences in its efficacy [17]. Studies have shown that the W12G mutant has increased enzymatic activity on tocopherols and tocotrienols, while the V433M mutant has reduced enzymatic activity on tocopherols. There is no reduced enzymatic activity on tocotrienols. The influence of these SNPs on vitamin E status and the response of the human body to vitamin E supplementation has an important and obvious clinical significance [16]. The MAF W12G variants in the European and African American populations have been reported to be 11% and 21%, respectively. By using the Asian combined sampling group (Chinese and Japanese HapMap data sets), the W12G variants, the MAF of the body is 6% [18]. The results shows that in the Wa population, the C allele frequency of rs3093105 is 40%-60%, which is higher than that of the other populations in China. Not only that, this gene can affect the metabolism/pharmacokinetics of vitamin E. Therefore, the fact that patients supplemented vitamin E and clinicians had fully understanding its status will help clinicians to better individualize treatment.

The canonical RefSeq CYP2D6 gene spans approximately 4,400 nucleotides, including 9 exons, and is encoded on the negative strand of the chromosome 22q13.2 [19]. CYP2D6 polymorphisms can affect the metabolism of alpha-hydroxymetoprolol [20], citalopram-citalopram [21], and iloperidone [22]. Drug dosage can be recommended according to the metabolism of CYP2D6. A previous study of atorvastatin in the treatment of ischemic stroke found that the G allele of rs10655852 (CYP2D6) had a better lipid-lowering effect, and patients carrying the GG genotype had a better effect on atorvastatin treatment reaction. For example, patients with insulin resistance who carry the GG genotype should be considered to reduce atorvastatin use to avoid the drug reactions [23]. Li et al. [24] reported that in the Han population with lung cancer in Northwestern China, the most significant correlation is the A allele of CYP2D6 rs10655852 and the AA genotype, which can increase the cancer risk. Sun et al. [25] showed that the G allele in the CYP2D6 rs10655852 may be related to the efficacy of labetalol in the treatment of early-onset pre-eclampsia. This study found that the G allele frequency of rs10655852 in the East Asian population was 34%-64%, and the frequency of the GG genotype in the Wa population was 0.5%, which were much lower than the other populations. Therefore, when clinicians use drugs to treat related diseases, the optimal dose of the drug should be based on the specific genotype of the individual patient to maximize the therapeutic effect.

Angiotensin-converting enzyme (ACE), encoded by the ACE gene, is located in 17q23, consists of 28 exons and 25 introns. ACE participates in the renin-angiotensin-aldosterone system (RAAS), which affects salt retention a protein for water balance and blood vessels; therefore, RAAS controls blood pressure, and drugs that inhibit this enzyme are effective in treating high blood pressure [26]. Migdalov et al. [27] demonstrated...
that captopril can be used to lower blood pressure by inhibiting ACE. Studies have shown that through the changes in fasting urea and creatinine over one year of dementia caused by Alzheimer’s disease (AD), the use of angiotensin converting enzyme inhibitors has found to be effective for carriers of rs1800764 CT/rs4291 AA. Though having a protective effect, changes in creatinine is harmful to carriers of rs1800764 CT/rs4291 AT [28]. Our study found that the TA genotype frequency was 1.00 in the Wa population, which was higher than that of in the other populations, while the AA genotype frequency was the lowest, which indicated that the optimal dose of ACE inhibitor should be based on the specific genotype of the individual Wa patients.

The SLC19A1 gene encodes a folate transporter and is involved in the regulation of intracellular folate concentration [29]. Studies have shown that folate carrier protein 1 (SLC19A1) affects the transport process of pemetrexed in the body. An analysis of the Han patients with non-small cell lung cancer who were only received pemetrexed treatment showed that the SLC19A1 rs1051298 (c.*746 C > T) increases the risk of all adverse drug reactions of pemetrexed treatment in different cycles. As with the risk of all adverse reactions, this effect is particularly important in liver injury [30]. Corrigan et al. [31] found that the SNP rs1051298 in the SLC19A1 gene can affect the overall survival and progression-free survival of patients with advanced non-small cell lung cancer receiving pemetrexed combined with platinum therapy. The results show that compared with the other 26 populations, the Wa population SLC19A1 rs1051298 is more significant and based on its polymorphism affecting the efficacy of pemetrexed, we can maximize the therapeutic effect of pemetrexed on the Wa patients.

Conclusions
This study analyzed the differences in genotype frequency and allele distribution between the Wa ethnic group and the other 26 ethnic groups worldwide. Rs776746 (CYP3A5), rs4291 (ACE), rs3093105 (CYP4F2), rs1051298 (SLC19A1) and rs1065852 (CYP2D6) in the Yunnan Wa population have a higher frequency, which provides a theoretical basis for safe medication and efficacy improvement. Our study complement the pharmacogenomics information of Wa population from Yunnan province and provide valuable information for future studies and better individualized treatments. This study has certain limitations. Due to the small sample size and the unadvanced genotyping technology, it is not able to fully and totally detect less common variants (in fact, variants with potentially important pharmacogenomic markers) that may (erroneously) give negative results, so participants may carry other important DNA variants not detected by the Agene MassARRAY platform. A large number of sample studies are also needed to verify the accuracy of our research.

Methods
Study participants
We randomly recruited 200 unrelated Wa adults from the Yunnan province of China. The selected subjects were judged to be in good health according to their medical history and had only Wa ethnic origins in at least the last three generations. In addition, this study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Clinical Research Ethics of Xizang Minzu University. Each participant also signed an informed consent form.

Variant selection and genotyping
We searched the PharmGKB database and 52 random VIP variants of 27 genes were ultimately selected for our study according to available data on frequency, functionality, and linkage based on published research. The method of operation used was to extract the genomic DNA of peripheral blood according to the GoldMag-Mini whole blood genome DNA Purification Kit (GoldMag Ltd. Xi’an, China). The DNA concentration was measured by a NanoDrop 2000C spectrophotometer (USA). Agena MassARRAY Assay Design 4.0 software (San Diego, California, USA) was used to design multiple SNP MassEXTEND arrays (Gabriel et al., 2008) and to design primers and single base extension primers for the selected sites. The PCR primers for the selected variants are presented in Supplementary Table 1. Following the instructions provided by the manufacturer, we used Agena MassARRAY RS1000 (San Diego, California, USA) to determine the genotype of the SNP. A brief overview of the Agena MassARRAY RS1000 (San Diego, California, USA) method for genotyping were as follows: (1) PCR amplification, (2) SAP purification, (3) iPLEX single base extension reaction, (4) resin exchange, and (5) mass spectrometry detection. Finally, Agena Typer 4.0 software was used for data statistics and analyses (Thomas et al., 2007) [32].

1000 Genomes Project
The individual genotype data of the 26 populations were downloaded from the website of the 1000 Genomes Project (http://www.1000genomes.org/) [33]. These 26 populations were: (1) African Caribbean in Barbados (ACB); (2) African Ancestry in Southwest US (ASW); (3) Esan in Nigeria (ESN); (4) Gambian in Western Divisions, The Gambia – Madinka (GWD); (5) Luhya in Webuye, Kenya (LWK); (6) Mende in Sierra Leone (MSL); (7) Colombian in Medellin, Colombia (CLM); (8) Mexican Ancestry in Los Angeles, California (MXL); (9) Peruvian in Lima, Peru (PEL); (10) Puerto Rican in Puerto Rico.
(PUR); (11) Chinese Dai in Xishuangbanna, China (CDX); (12) Yoruba in Ibadan, Nigeria (YRI); (13) Han Chinese South (CHS); (14) Japanese in Tokyo, Japan (JPT); (15) Kinh in Ho Chi Minh City, Vietnam (KHV); (16) Utah residents with Northern and Western European ancestry (CEU); (17) Finnish in Finland (FIN); (18) British in England and Scotland (GBR); (19) Iberian populations in Spain (IBS); (20) Toscani in Italy (TSI); (21) Bengali in Bangladesh (BEB); (22) Gujarati Indians in Houston, Texas (GIH); (23) Indian Telugu in the UK (ITU); (24) Punjabi in Lahore, Pakistan (PIL); (25) Sri Lankan Tamil in the UK (STU), and (26) Han Chinese in Beijing, China (CHB).

Statistical analyses
Microsoft Excel and SPSS 20.0 statistical software packages were used to perform Hardy-Weinberg equilibrium (HWE) analysis and χ² tests (SPSS, Chicago, IL, USA). The χ² tests were used to evaluate the frequency of variation from HWE in the Wa population for verification. In this study, All p-values were two-sided and p-values less than 0.05 were considered statistically significant. Next, the Bonferroni multiple adjustment method was used for correction, and p < 0.05/(52×26) has a significant difference. Subsequently, we obtained SNPs allele frequencies from the Ensemble database (https://asia.ensembl.org/index.html). Finally, the overall genetic variation pattern of specific loci was analyzed [34].

Abbreviations
VIP: Very important pharmacogene; SNPs: Single nucleotide polymorphisms; AD: Alzheimer’s disease; ADW: Average daily warfarin; ACE: Angiotensin-converting enzyme; RAAS: Renin-angiotensin-aldosterone system; C/Ds: Concentration/dose; ACE: Angiotensin-converting enzyme; CYP2C9: CYP2C9 gene.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12863-021-00999-8.

Additional file 1: Table S1. Primer sequence.

Acknowledgements
We appreciate the Xizang Minzu University, which provided the samples used in this study. We also appreciate the reviewers and editors for their efforts and patience.

Authors’ contributions
TJ assisted in the study design. D. L, C. H performed the statistical analyses. L. P, S. X performed the genotyping. D. L drafted the manuscript. All authors have read and approved the manuscript.

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

Availability of data and materials
The datasets generated and analyzed during the current study are available in the [figshare] repository, [https://doi.org/10.6084/m9.figshare.14782323.v1] and the accession numbers is tianbojin63@163.com.

Declarations
Ethics approval and consent to participate
The study was approved by the Clinical Research Ethics of Xizang Minzu University. Written informed consents were obtained from all individuals. The procedures were in accordance with the institutional guidelines.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no conflict of interest.

Received: 15 April 2021 Accepted: 8 October 2021
Published online: 19 November 2021

References
1. Zhou ZW, et al. Clinical association between pharmacogenomics and adverse drug reactions. Drugs. 2015;75(6):589–631.
2. Meyer UA. Pharmacogenetics and adverse drug reactions. Lancet. 2000; 356(9242):1667–71.
3. Evans WE. Pharmacogenomics: marshalling the human genome to individualise drug therapy. Gut. 2003;52(Suppl 2):ii10–8.
4. Yu B. Pharmacogenomics: precision tool in routine prescription. Zhongguo Dang Dai Er Ke Za Zhi. 2020;22(11):1143–8.
5. Ding Y, et al. Genetic polymorphisms of pharmacogenomic VIP variants in the L nationality of southern China. Environ Toxicol Pharmacol. 2016;42:237–42.
6. Zhang G, et al. Web resources for pharmacogenomics. Genom Proteomics Bioinformatics. 2015;13(1):51–4.
7. He Y, et al. Genetic polymorphisms of pharmacogenomic VIP variants in the Hoba population of southwest China. Int J Clin Exp Pathol. 2015;8(10):13293–303.
8. Lai Y, et al. Distinct genotype distribution and haplotype profiles in MDR1 gene among Chinese Han, Bai, Wa and Tibetan ethnic groups. Pharmazie. 2012;67(11):938–41.
9. Rosemary J, Adithan C. The pharmacogenetics of CYP2C9 and CYP2C19: ethnic variation and clinical significance. Curr Clin Pharmacol. 2007;2(1):93–109.
10. Wolf CR, Smith G. Pharmacogenetics. Br Med Bull. 1999;55(2):366–86.
11. Dickman LJ, Ware JA. Pharmacogenomics in the age of personalised medicine. Drug Discov Today Technol. 2016;21-22:11–6.
12. Ang GY, et al. A study on the genetic polymorphisms of CYP3A5 among the Orang Asli in Malaysia using a next generation sequencing platform. Ann Hum Biol. 2018;45(2):166–9.
13. Matas AJ, et al. OPTN/SRTR 2013 Annual Data Report: kidney. Am J Transplant. 2015;15(Suppl 2):1–34.
14. Bowman LJ, Brien CA. The role of tacrolimus in renal transplantation. Expert Opin Pharmacother. 2008;9(4):635–43.
15. Liu BY, et al. The Effects of CYP3A4 Genetic Polymorphisms on Serum Tacrolimus Dose-Adjusted Concentrations and Long-Term Prognosis in Chinese Heart Transplantation Recipients. Eur J Drug Metab Pharmacokinet. 2019(44)771–6.
16. Bardowell SA, Stec DE, Parker RS. Common variants of cytochrome P450 4F2 exhibit altered vitamin E-omega-hydroxylase specific activity. J Nutr. 2010;140(11):1901–6.

17. Athinarayanan S, et al. Genetic polymorphism of cytochrome P450 4F2, vitamin E level and histological response in adults and children with nonalcoholic fatty liver disease who participated in PIVENS and TONIC clinical trials. PLoS One. 2014(4):e95366.

18. Stec DE, et al. Functional polymorphism in human CYP4F2 decreases 20-HETE production. Physiol Genomics. 2007;30(1):74–81.

19. Gaedigk A, et al. Prediction of CYP2D6 phenotype from genotype across world populations. Genet Med. 2017;19(1):69–76.

20. Rüdesheim S, et al. Physiologically Based Pharmacokinetic Modeling of Metoprolol Enantiomers and o-Hydroxymetoprolol to Describe CYP2D Drug-Gene Interactions. Pharmaceutics. 2020;12(12):1200.

21. Hicks JK, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127–34.

22. Pei Q, et al. Influences of CYP2D6(*)10 polymorphisms on the pharmacokinetics of iloperidone and its metabolites in Chinese patients with schizophrenia: a population pharmacokinetic analysis. Acta Pharmacol Sin. 2016;37(11):1499–508.

23. Peng C, et al. Polymorphisms in CYP450 Genes and the Therapeutic Effect of Atorvastatin on Ischemic Stroke: A Retrospective Cohort Study in Chinese Population. Clin Ther. 2018;40(3):469–477.e2.

24. Li M, et al. Gene polymorphism of cytochrome P450 significantly affects lung cancer susceptibility. Cancer Med. 2019;8(10):4892–905.

25. Sun CJ, et al. Associations of polymorphisms of CYP2D6 and CYP2C9 with early onset severe pre-eclampsia and response to labetalol therapy. Arch Gynecol Obstet. 2018;298(1):125–32.

26. Mengeha HG, et al. Effects of angiotensin converting enzyme gene polymorphism on hypertension in Africa: A meta-analysis and systematic review. PLoS One. 2019;14(2):e0211054.

27. Migdalof BH, et al. Captopril: pharmacology, metabolism and disposition. Drug Metab Rev. 1984;15(4):841–69.

28. Ferreira de Oliveira F, et al. Pharmacogenetic effects of angiotensin-converting enzyme inhibitors over age-related urea and creatinine variations in patients with dementia due to Alzheimer disease. Colomb Med (Gall). 2016;47(2):76–80.

29. Chen W, et al. Genetic polymorphisms analysis of pharmacogenomic VIP variants in Bai ethnic group from China. Mol Genet Genomic Med. 2019;7(9):e884.

30. Zhang X, et al. Discovery of Novel Biomarkers of Therapeutic Responses in Han Chinese Pemetrexed-Based Treated Advanced NSCLC Patients. Front Pharmacol. 2019;10:944.

31. Corrigan A, et al. Pharmacogenetics of pemetrexed combination therapy in lung cancer: pathway analysis reveals novel toxicity associations. Pharmacogenomics J. 2014;14(5):411–7.

32. Yan M, et al. Genetic polymorphisms of pharmacogenomic VIP variants in the Yi population from China. Genet. 2018;648:54–62.

33. Wang L, et al. Genetic polymorphisms of pharmacogenomic VIP variants in the Uygur population from northwestern China. BMC Genet. 2015;16:66.

34. Jin T, et al. Genetic polymorphisms study of pharmacogenomic VIP variants in Han ethnic of China’s Shaanxi province. Environ Toxicol Pharmacol. 2016;46:27–35.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.