Genetic polymorphisms of pharmacogenomic VIP variants in Chinese Lisu population

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Abstract

Introduction

The specificity of drug therapy in individuals and races has promoted the development and improvement of pharmacogenomics and precision medicine. While there is a few cognition on the minorities in China, especially in Lisu nationality from the Yunnan Province. Therefore, we performed the research to improve the role of pharmacogenomics in the Lisu population from the Yunnan province of China.

Materials and Methods

In our study, 54 variants of very important pharmacogenes (VIPs) selected from the PharmGKB database were genotyped in 199 unrelated and healthy Lisu adults from the Yunnan province of China, and then, genotyping data wtih χ^2 test were analyzed.

Results

We compared our date with those of other 26 populations from the 1000 Genomes Project, and acquired that the Lisu ethnicity is similar with the CDX(Chinese Dai in Xishuangbanna, China) and CHS(Southern Han Chinese, China). Furthermore, rs776746 (*CYP3A5*), rs1805123 (*KCNH2*), rs4291 (*ACE*), rs1051298 (*SLC19A1*) and rs1065852 (*CYP2D6*) were deemed as the most varying loci. The MAF of “G” at rs1805123 (KCNH2) in the Lisu population was the largest with the value of 51.0%.

Conclusions

Our results show that there are significant differences in SNP (single nucleotide polymorphism) loci, supplementing the pharmacogenomic information of the Lisu population in Yunnan province, China, and can provide a theoretical basis for individualized medication in the future.

Introduction

Pharmacogenomics is one of the emerging methods to precise medicine, tailoring drug selection, and dose to the patient’s genetic features[1]. The domain of pharmacogenomics is designed to predict the drug response in patients before medication administration and to expose the biological underpinnings of drug response. Its adhibition are promised to improve therapeutic outcome, enable targeted drug administration, and informed drug development[2]. More and more pharmacogenomic information can now guide clinicians to elect the safest and most effective medications for individual patients from the very first prescription[3].

Precise medical care, also known as personalized medicine, is a kind of treatment that patients are classified into different subtypes with their genome, biochemistry, behavior science, or even in response to a particular treatment[4]. Studies have shown that the difference of individual reaction in drug response are largely concluded by genetic polymorphisms[5]. The changes in genotype would cause mutations in drug metabolism, leading to different responses to drugs in different populations, which is closely influenced to the effect of drug therapy. These genetic variants are known as very important pharmacogenetic (VIP) variants[6]. It has been reported that some countries have initially applied the research results of pharmacogenomic VIP variants to precise drug therapy[7], which has led to a major step forward in pharmacogenomics research.

Pharmacogenetics and pharmacogenomics knowledge are based on PharmGKB (http://www.pharmgkb.org), which has focused on curating knowledge. At present, more complex relationships between genes, variants, drugs, diseases, and pathways are captured[8]. The PMT (Pharmacogenetics of Membrane Transporters) database

(http://pharmacogenetics.ucsf.edu/) mainly contains some information about genetic polymorphisms of membrane transporter genes associated with drug reactions[9].

The Lisu ethnicity, is one of the China's 55 ethnic minorities. According to the sixth national census in 2010, there are 1.26 million Lisu people in China, including more than 730,000 in Yunnan province. There are differences in traditions, history and culture between the Lisu people and other ethnics since the Lisu ethnicity originated from the descendants of the ancient Diqiang people, which is considered to be a possible and reasonable factor leading to the genetic and/or other aspects.

In our experiment, 54 VIP variants were selected from PharmGKB in 199 members of Lisu people from Yunnan. Chi-square test was used to compare genotype frequency with those of 26 other ethnic groups. A growing number of studies have demonstrated that pharmacogenomic information holds the promise of creating personalized medical systems[10],which can select more appropriate drugs and the doses according to a patient's genetic profile or individual needs[11, 12]. Hence, we hope to find out the differences of genetic variation among disparate ethnic groups and provide theoretical basis for personalized medical treatment of the Yunnan Lisu population.

Materials And Methods

Study participants

This study contained 199 unrelated volunteers from the Lisu ethnic group in Yunnan, China. An eligible subject for this study must met with the following criteria: a) The individuals have at least the past three generations of particular Lisu descents. b) All subjects are healthy and free of other diseases. Then, through the Han and Dai people are making progress in culture and economy, the Lisu ethnicity still sustain their distinctive,cultures,features. Therefore, they were taken as a representative sample of Lisu ethnic group with deemed as ancestry and environmental exposure. The experimental samples were voluntarily taken 5mL of blood.

Ethics statement

All subjects were both verbally informed and signed a document about the purpose and steps of the study. Blood samples were collected in the light of the study protocol ratification by the Clinical Research Ethics of Xizang Minzu University. Our study was conformed to the legislations of Department of Health and Human Services (DHHA) for the protection of human research subjects, absolutely.

Variants selection and genotyping

Genetic variants were chosen from published polymorphisms related to VIP variants from the PharmGKB database. After ruled out the loci without designed absolutely, there were eventually left 54 SNPs which located on 27 genes. We extracted genomic DNA from peripheral blood (5mL) in accordance with the direction of GoldMag Whole Blood Genomic DNA Isolation Kit (Xi'an GoldMag Biotechnology, China). Then the DNA concentration was measured using a NanoDrop 2000C spectrophotometer (Thermo Scientific, Waltham, MA, USA). We designed primers for amplification and extension reactions with Agena MassARRAY Assay Design 3.0 Software[13]. We used Agena Mass ARRAY RS1000 (San Diego, California, USA) to implemented genotyping of SNPs in the guidance of operation manual. Agena Typer 4.0 software (USA) was used to manage and analyze the experimental data (USA)[14].

1000 Genomes Project data

The genotype distribution frequencies of 57 VIP loci in 26 populations were downloaded from the 1000 Genomes Project and were presented as follows: (1) Chinese Dai in Xishuangbanna, China (CDX), (2) Han Chinese in Bejing, China (CHB), (3) Southern Han Chinese, China (CHS), (4) Japanese in Tokyo, Japan (JPT), (5) Kinh in Ho Chi Minh City, Vietnam (KHV),

(6) African Caribbeans in Barbados (ACB), (7) African ancestry in the southwestern USA (ASW), (8) Esan in Nigeria (ESN), (9) Gambian in Western Divisions, The Gambia (GWD), (10) Luhya in Webuye, Kenya (LWK), (11) Mende in Sierra Leone (MSL), (12) Yoruba in Ibadan, Nigeria (YRI), (13) Colombian in Medellin, Colombia (CLM), (14) Mexican Ancestry in Los Angeles, Colombia (MXL), (15) Peruvian in Lima, Peru (PEL), (16) Puerto Rican in Puerto Rico (PUR), (17) Utah residents with Northern and Western European ancestry (CEU), (18) Finnish in Finland (FIN), (19) British in England and Scotland (GBR), (20) Iberian populations in Spain (IBS), (21) Toscani in Italy (TSI), (22) Bengali in Bangladesh (BEB), (23) Gujarati Indian in Houston, Texas (GIH), (24) Indian Telugu in the UK (ITU), (25) Punjabi in Lahore, Pakistan (PJL), and (26) Sri Lankan Tamil in the UK (STU). Data mentioned above were all from the 1000 Genomes Project(http://www.1000genomes.org/).

Statistical analyses

Microsoft Excel and SPSS 20.0 statistical packages (SPSS, Chicago, IL) were used to carry out Hardy-Weinberg equilibrium (HWE) and chi-square tests. Precise testing was used to evaluate whether the genotype frequency of each SNP in the Lisu people was out of the HWE equilibrium. All the computed p values in our study were calculated two-sided and Bonferroni's multiple adjustment was used for correction. While $p < 0.05$ were viewed significant before correcting, statistically. To wake the deviated detection rate of multiple tests, we indicated that $p < 0.05/(54\times27)$ was typically significant after Bonferroni's multiple adjustments. The SNP allele frequencies of other races worldwide were successfully acquired from the Ensemble database (https://asia.ensembl.org/index.html).

Results

We successfully sequenced 54 VIP pharmacogenomic variant genotypes selected from the PharmGKB in 199 members of the Lisu ethnicity. The PCR primers used for the selected variants are listed in **Supplementary table 1**. Table 1 shows not only the basic characters of the candidate SNPs within 27 genes, but also the SNPs such as the chromosomal position, functional consequence, location, gene type, and minor allele frequency (MAF). The genes mentioned above are belong to cytochrome P450 superfamily, ATP-binging cassette (ABC) transporters superfamily, alcohol dehydrogenase family, G-protein coupled receptor family, solute carrier family, nuclear receptor family, and sulfotransferase family.

Table 1
Basic information of the selected VIP variants from the PharmGKB database in Lisu population.

SNP ID	Chromosome	BP	Functional Consequence	Genes	Genotype			MAF
					AA	AB	BB	
rs11572325	1	59896030	intron variant	*CYP2J2*	0	25	174	0.063
rs10889160	1	59896449	intron variant	*CYP2J2*	0	49	150	0.123
rs890293	1	59926822	upstream transcript variant	*CYP2J2*	0	16	183	0.040
rs1760217	1	97137438	genic downstream transcript variant, intron variant	*DPYD*	16	83	99	0.290
rs1801160	1	97305364	coding sequence variant, genic downstream transcript variant, intron variant, missense variant	*DPYD*	2	11	185	0.038
rs1801159	1	97515839	coding sequence variant, genic downstream transcript variant, intron variant, missense variant	*DPYD*	5	59	134	0.174
rs1801265	1	97883329	non coding transcript variant, intron variant, coding sequence variant, 5 prime UTR variant, missense variant	*DPYD*	2	40	157	0.111
rs5275	1	186673926	3 prime UTR variant	*PTGS2*	4	44	151	0.131
rs20417	1	186681189	upstream transcript variant, non coding transcript variant	*PTGS2*	0	3	196	0.008
rs12139527	1	201040054	missense variant, coding sequence variant, intron variant	*CACNA1S*	0	13	186	0.033
rs3850625	1	201047168	coding sequence variant, missense variant	*CACNA1S*	0	23	176	0.058
rs2306238	1	237550803	intron variant	*RYR2*	21	78	100	0.302
rs2231142	4	88131171	coding sequence variant, missense variant	*ABCG2*	4	43	150	0.129
rs2231137	4	88139962	coding sequence variant, missense variant	*ABCG2*	52	99	44	0.521
rs698	4	99339632	coding sequence variant, non coding transcript variant, missense variant	*ADH1C*	4	50	144	0.146
rs776746	7	99672916	intron variant, splice acceptor variant, genic downstream transcript variant, downstream transcript variant	*CYP3A5*	38	0	161	0.191
rs2242480	7	99763843	intron variant	*CYP3A4*	18	88	92	0.313

MAF: minor allele frequencies

SNP ID	Chromosome	BP	Functional Consequence	Genes	Genotype			MAF
					AA	AB	BB	
rs1805123	7	150948446	missense variant, coding sequence variant, genic downstream transcript variant	*KCNH2*	4	194	0	0.510
rs4646244	8	18390208	upstream transcript variant, genic upstream transcript variant, intron variant	*NAT2*	6	55	137	0.169
rs4271002	8	18390758	upstream transcript variant, genic upstream transcript variant, intron variant	*NAT2*	6	68	123	0.203
rs1041983	8	18400285	coding sequence variant, synonymous variant	*NAT2*	32	79	86	0.363
rs1801280	8	18400344	missense variant, coding sequence variant	*NAT2*	3	36	160	0.106
rs1799929	8	18400484	coding sequence variant, synonymous variant	*NAT2*	3	36	160	0.106
rs1799930	8	18400593	missense variant, coding sequence variant	*NAT2*	6	54	137	0.168
rs1208	8	18400806	missense variant, coding sequence variant	*NAT2*	3	36	160	0.106
rs1799931	8	18400860	missense variant, coding sequence variant	*NAT2*	9	62	128	0.201
rs1495741	8	18415371	None	*NAT2*	51	81	60	0.477
rs2115819	10	45405641	intron variant	*ALOX5*	2	35	161	0.098
rs12248560	10	94761900	upstream transcript variant	*CYP2C19*	0	9	189	0.023
rs4244285	10	94781859	coding sequence variant, synonymous variant	*CYP2C19*	37	83	76	0.401
rs1057910	10	94981296	missense variant, coding sequence variant	*CYP2C9*	1	10	188	0.030
rs7909236	10	95069673	upstream transcript variant	*CYP2C8*	2	19	178	0.058
rs17110453	10	95069772	upstream transcript variant	*CYP2C8*	23	83	93	0.324
rs3813867	10	133526101	non coding transcript variant, upstream transcript variant	*CYP2E1*	1	24	174	0.065
rs2031920	10	133526341	non coding transcript variant, upstream transcript variant	*CYP2E1*	1	26	172	0.070
rs6413432	10	133535040	intron variant	*CYP2E1*	0	19	180	0.048
rs2070676	10	133537633	intron variant	*CYP2E1*	12	45	142	0.173

MAF: minor allele frequencies

SNP ID	Chromosome	BP	Functional Consequence	Genes	Genotype			MAF
					AA	AB	BB	
rs5219	11	17388025	missense variant, stop gained,5 prime UTR variant, intron variant, coding sequence variant	*KCNJ11*	0	111	88	0.279
rs1801028	11	113412762	missense variant, coding sequence variant	*DRD2*	0	6	193	0.015
rs2306283	12	21176804	missense variant, coding sequence variant	*SLCO1B1*	14	97	87	0.316
rs4516035	12	47906043	upstream transcript variant	*VDR*	0	14	185	0.035
rs762551	15	74749576	intron variant	*CYP1A2*	20	100	77	0.355
rs2472304	15	74751897	intron variant	*CYP1A2*	7	62	129	0.192
rs750155	16	28609251	5 prime UTR variant, intron variant, genic upstream transcript variant, upstream transcript variant	*SULT1A1*	46	71	77	0.420
rs1800764	17	63473168	None	*ACE*	24	101	71	0.380
rs4291	17	63476833	upstream transcript variant	*ACE*	0	190	8	0.480
rs4267385	17	63506395	None	*ACE*	10	79	109	0.250
rs2108622	19	15879621	missense variant, coding sequence variant	*CYP4F2*	8	63	127	0.199
rs3093105	19	15897578	missense variant,coding sequence variant	*CYP4F2*	0	198	0	0.500
rs8192726	19	40848591	intron variant	*CYP2A6*	12	80	102	0.268
rs1051298	21	45514912	intron variant,3 prime UTR variant	*SLC19A1*	1	156	40	0.401
rs1051296	21	45514947	intron variant,3 prime UTR variant	*SLC19A1*	38	103	54	0.459
rs1131596	21	45538002	missense variant,5 prime UTR variant,synonymousvariant, genic upstream transcript variant,coding sequence variant	*SLC19A1*	23	110	65	0.394
rs1065852	22	42130692	intron variant, missense variant, coding sequence variant	CYP2D6	35	158	1	0.588

MAF: minor allele frequencies

We performed a comparison using χ^2 analysis to seek differences in genotype frequency distribution of the variants between Lisu and the other 26 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, GIH, ITU, PJL, and STU). Table 2 exposes the most significant SNPs in Lisu people compared with the other 26 populations after corrected, while the total is shown in **Supplementary table 2**. Before corrected ($p < 0.05$), we found that there were 25, 28, 27, 29, 27, 42, 34, 41, 41, 41, 39, 42, 38,

32, 33, 34, 37, 40, 35, 37, 40, 30, 35, 37, 38, and 40 varying SNPs in the Lisu population compared to the other 26 ethnic groups, respectively. While after being the Bonferroni's multiple adjustment ($p < 0.05/ (54\times27)$), these numbers became 6, 12, 10, 12, 12, 27, 26, 31, 31, 29, 28, 29, 24, 20, 23, 26, 27, 26, 25, 26, 27, 20, 27, 26, 25, and 25 in Lisu people compared to the other 26 ethnic groups which has been listed previously, respectively. The results revealed that GWD and ESN were the two biggest dissimilar populations with Lisu people of Yunnan Province and were similar with the East Asian population, especially in the CDX and CHS populations. Definitely, the remarkable difference SNPs of the Lisu nationality with the other 26 populations are listed below *CYP2D6* rs1065852, *CYP3A5* rs776746, *KCNH2* rs1805123, *ACE* rs4291, and *SLC19A1* rs1051298.

Table 2
Significant SNPs in Lisu people compared to the 26 populations with Bonferroni's multiple correction

Genes	PTGS2	CYP3A5	KCNH2	ALOX5	ACE	SLC19A1	CYP2D6
SNP ID	rs20417	rs776746	rs1805123	rs2115819	rs4291	rs1051298	rs1065852
CDX	/[a]	**2.78E-22**[b]	**3.72E-49**	1.90E-03	**1.30E-23**	**3.89E-11**	**6.88E-14**
CHB	/	**4.53E-20**	**1.30E-60**	**2.96E-07**	**7.80E-29**	**1.67E-13**	**1.47E-11**
CHS	/	**1.73E-20**	**4.82E-60**	2.81E-03	**1.96E-24**	**5.18E-07**	**3.82E-15**
JPT	/	**1.52E-23**	**6.47E-59**	**2.41E-05**	**2.71E-20**	**1.02E-11**	**5.44E-21**
KHV	/	**7.02E-23**	**8.93E-51**	1.66E-03	**2.68E-28**	**3.11E-09**	**8.89E-10**
ACB	**3.92E-27**	**6.41E-36**	**1.30E-62**	**1.12E-43**	**4.36E-22**	**9.72E-11**	**4.36E-41**
ASW	**2.79E-24**	**2.23E-33**	**4.34E-51**	**2.89E-31**	**9.08E-22**	**1.00E-10**	**2.65E-37**
ESN	**1.00E-35**	**2.00E-40**	**3.22E-65**	**3.55E-43**	**1.14E-23**	**2.63E-10**	**4.51E-49**
GWD	**1.76E-25**	**3.68E-38**	**2.52E-67**	**4.68E-47**	**7.45E-20**	**3.79E-14**	**2.58E-47**
LWK	**1.73E-22**	**1.52E-37**	**3.02E-64**	**7.82E-39**	**3.36E-28**	**5.85E-13**	**6.95E-57**
MSL	**4.04E-34**	**2.13E-36**	**3.53E-62**	**6.55E-38**	**2.48E-19**	**1.75E-10**	**2.00E-38**
YRI	**4.05E-31**	**1.20E-42**	**3.57E-67**	**6.41E-46**	**1.25E-28**	**1.62E-10**	**1.50E-47**
CLM	**1.33E-17**	**1.28E-15**	**7.72E-36**	**2.26E-21**	**1.28E-22**	**2.02E-13**	**2.10E-37**
MXL	**3.85E-17**	**4.47E-19**	**2.65E-37**	**9.53E-16**	**1.09E-26**	**9.65E-22**	**1.30E-36**
PEL	**3.74E-15**	**5.84E-12**	**1.37E-49**	**1.63E-09**	**1.59E-34**	**4.55E-20**	**1.16E-49**
PUR	**7.58E-17**	**3.37E-16**	**8.59E-35**	**9.95E-20**	**2.89E-22**	**2.04E-13**	**9.95E-40**
CEU	**2.28E-13**	**1.57E-08**	**3.43E-30**	**1.10E-29**	**8.56E-24**	**6.81E-16**	**2.04E-29**
FIN	**8.68E-08**	**8.66E-09**	**6.84E-39**	**1.57E-24**	**2.68E-18**	**1.47E-13**	**3.18E-41**
GBR	**1.14E-10**	**2.35E-09**	**8.64E-34**	**9.05E-24**	**7.19E-25**	**4.08E-19**	**1.20E-30**
IBS	**8.50E-12**	**2.45E-10**	**2.85E-33**	**2.64E-25**	**1.27E-21**	**4.50E-15**	**1.58E-38**
TSI	**8.74E-15**	**9.57E-10**	**1.13E-30**	**3.50E-26**	**1.06E-24**	**6.24E-15**	**1.73E-34**
BEB	**1.02E-13**	**1.39E-23**	**4.28E-27**	**5.75E-21**	**2.21E-22**	**4.59E-10**	**1.93E-30**

EAS East Asian, AFR African, AMR American, EUR European, SAS South Asian, CDX Chinese Dai in Xishuangbanna, CHB Han Chinese in Bejing, China, CHS Southern Han Chinese, China, JPT Japanese in Tokyo,Japan, KHV Kinh in Ho Chi Minh City, Vietnam, ACB African Caribbeans in Barbados, ASW African ancestry in the southwestern USA,ESN Esan in Nigeria, GWD Gambian in Western Divisions, The Gambia, LWK Luhya in Webuye, Kenya, MSL Mende in Sierra Leone, YRI Yoruba in Ibadan, CLM Nigeria,Colombian in Medellin, Colombia ,MXL Mexican Ancestry in Los Angeles, Colombia, PEL Peruvian in Lima, Peru, PUR Puerto Rican in Puerto Rico, 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, GIH Gujarati Indian in Houston, Texas, ITU Indian Telugu in the UK,PJL Punjabi in Lahore, Pakistan, STU Sri Lankan Tamil in the UK

[a] Result of the calculation was meaningless.

[b] Bold indicated that after adjustment $p < 0.05/ (54*27)$ the locus has statistically significant.

$p < 0.05/ (54*27)$ indicates statistical significance.

Genes	PTGS2	CYP3A5	KCNH2	ALOX5	ACE	SLC19A1	CYP2D6
GIH	**8.10E-14**	**4.57E-22**	**3.29E-36**	**2.14E-28**	**1.38E-21**	**4.31E-11**	**2.35E-40**
ITU	**5.92E-13**	**1.47E-22**	**1.55E-30**	**9.55E-26**	**1.24E-28**	**4.89E-11**	**7.72E-38**
PJL	**8.44E-18**	**1.07E-20**	**2.62E-34**	**7.74E-21**	**2.47E-23**	**2.68E-11**	**6.22E-46**
STU	**4.06E-16**	**5.06E-22**	**3.47E-33**	**2.38E-18**	**3.07E-22**	**5.93E-13**	**2.68E-41**

EAS East Asian, AFR African, AMR American, EUR European, SAS South Asian, CDX Chinese Dai in Xishuangbanna, CHB Han Chinese in Bejing, China, CHS Southern Han Chinese, China, JPT Japanese in Tokyo,Japan, KHV Kinh in Ho Chi Minh City, Vietnam, ACB African Caribbeans in Barbados, ASW African ancestry in the southwestern USA,ESN Esan in Nigeria, GWD Gambian in Western Divisions, The Gambia, LWK Luhya in Webuye, Kenya, MSL Mende in Sierra Leone, YRI Yoruba in Ibadan, CLM Nigeria,Colombian in Medellin, Colombia ,MXL Mexican Ancestry in Los Angeles, Colombia, PEL Peruvian in Lima, Peru, PUR Puerto Rican in Puerto Rico, 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, GIH Gujarati Indian in Houston, Texas, ITU Indian Telugu in the UK,PJL Punjabi in Lahore, Pakistan, STU Sri Lankan Tamil in the UK

[a] Result of the calculation was meaningless.

[b] Bold indicated that after adjustment $p < 0.05/ (54*27)$ the locus has statistically significant.

$p < 0.05/ (54*27)$ indicates statistical significance.

Many pharmacogenetic polymorphisms, to some extent, differ in frequency among populations[15]. Figure 1 shows the MAF of significant polymorphisms situated in the Lisu and the other 26 populations. For instance, the allele “A” of rs1065852 locus (*CYP2D6*) was 36.1–66.2%, of which 58.8% was in Lisu. The allele “G” at rs1805123 (*KCNH2*) was much lower in African, ranging from 0 to 4.1%, and the Lisu was 51.0%, which was the largest value. In summary, the allelic distribution is diverse in the midst of individual races, which figures that some otherness is affected by genetic backgrounds.

Discussion

Many people expect that expanding knowledge of genetic variants related to disease risk and drug response will revolutionize clinical medicine, thereby making personalized medicine based on pharmacogenomics a reality. Based on this progress, treatments tailored to the genomes in ethnicity even in individuals are also within our reach[11]. In our study, we selected from antecedently published polymorphisms and analyzed *CYP2D6, CYP3A5, KCNH2, ACE* and *SLC19A1* within the Lisu population in Yunnan.

Cytochrome P450 (CYP) enzymes are responsible for the metabolism and disposal of many drugs, among which CYP2D6 and CYP3A4 subtypes have the highest activities and are highly expressed in the liver and extrahepatic organs, such as gastrointestinal tract[16, 17]. The gene “cytochrome P450, family 2, subfamily D, polypeptide 6” (*CYP2D6*), situate at chromosome 22q13.1, is one of the pivotal enzymes for the generation of the potent active metabolites of tamoxifen, “endoxifen”, and “4-hydroxytamoxifen”, and its gene polymorphism will have a significant effect on enzyme activity [18, 19]. *CYP2D6*, although representing only approximately 5% of the active P450 in human liver, metabolizes 20–25% of known drugs containing antidepressants, anti-arrhythmics, antipsychotics, β-blockers and tamoxifen[20], and also may increase drug-drug interactions (DDIs) when drugs are 2D6 substrates[21]. *CYP2D6* substrates are also the first-line medications in psychiatry, scholars[22] have proposed it before that the *CYP2D6* genotype has a great influence on the blood concentration of aripiprazole, while the *CYP3A* genotypes and *CYP3A4* expression have a small or even negligible effect on aripiprazole clearance. Iloperidone elimination was detected to be expressively impacted by the *CYP2D6* rs1065852 variants[23]. Hence, the mutation of *CYP2D6* gene may lead to poisoning or no response under normal dose of drugs, which affects the treatment outcomes and costs[24].

There are different alleles for *CYP3A5*, indicating its genetic polymorphism: the *CYP3A5*1* allele expresses active *CYP3A5*, while the *CYP3A5*3* allele (a central variant) expresses an inactive form of *CYP3A5*[25]. An increasing number of examples show that *CYP3A5* polymorphism can affect the pharmacokinetics and metabolism of *CYP3A* substrates, involving the immunosuppressant tacrolimus[26, 27], the anticancer drug vincristine[28], alfentanil[29], and maraviroc[30, 31]. The intrinsic tacrolimus clearance rate of the *CYP3A5* enzyme was only half that of *CYP3A4*, in vitro[32]. *CYP3A5* is 9–14 times more efficient at clearing vincristine than *CYP3A4* is[33]. *CYP3A5* also involved in the overall metabolism of eplerenone and plays a more important role in the expression of 21-hydroxyacrylone formation[34]. Moreover, the polymorphic of *CYP3A5* has been referred to be figured in the regulation of blood pressure[35] as following. The *CYP3A5*3/*3* genotype attracted a greater reduction in blood pressure of Chinese hypertensive patients with amlodipine treatment because the metabolism of amlodipine is faster and *CYP3A* enzyme activity is higher in subjects with the *CYP3A5*3/*3* genotype[36].

Genetic polymorphisms in human ether-a-go-go-related gene (*KCNH2 or* hERG) which codes for the potassium channels, are associated with sensitivity to channel-related drugs and many complex diseases[37]. It has been reported that *KCNH2* has a small intron region that may be a susceptibility site for schizophrenia[38] and the gene variations might predict the efficacy of an antipsychotic drug in given patients[39]. However, antipsychotic drugs, which can increase the risk of QT prolongation and sudden cardiac death by block *KCNH2* channel, has been thought to be an “anti-target”[40]. Surprisingly, paliperidone, the principal metabolite of risperidone, as well as other atypical antipsychotics, such as aripiprazole, olanzapine, and clozapine, showed no distinction in the efficacy of block for the individual *KCNH2* channel isoforms. Meanwhile, based on the data from this study, scholars estimated that approximately 7% schizophrenia patients who have slow risperidone metabolism and the risk genotypes would do better when treated with risperidone than with other antipsychotic[41]. Then, there are many other drugs that share the same mechanism. For example, oral administration of methadone aconitine and rosiglitazone were blocked *KCNH2* potassium channels in a dose-dependent manner, respectively[42–44], as well as nelfinavir, lopinavir, saquinavir and ritonavir in vitro[45]. Thomas et al.[46] suggested that the α1-inhibitors, such as prazosin, terazosin, and doxazosin, directly blocked *KCNH2*, and the susceptivity was affected by the mutation of *KCNH2* (1956, C.T). Additionally, there was a study revealed that the hypotensive functions of azelnidipine and nitrendipine were not enough patent in wildtype carriers when compared with “T” allele carriers *KCNH2* (1956, C.T) in patients with essential hypertensions (EH) [47]. In reality, almost all drugs that induce long QT syndrome have a blocking effect on *KCNH2*[48]. Remarkably, among Lisu people, the MAF (G) of rs1805123 with in *KCNH2* gene was 0.51, which is different from other frequencies among most of the other populations, suggesting that we should pay more attention to QT prolongation-related diseases in Lisu people.

In one study, the role of *ACE* insertion/deletion (I/D) polymorphism in the blood pressure response to diuretics (hydrochlorothiazide 25mg) was investigated. It was found that the blood pressure hypertensive patients with the D/D genotype with a significant correlation was lowered by 3.8mm Hg, while the mean arterial pressure of I/I genotype was lowered by about 10mm Hg[49]. Cicoira, M., et al.[50] hypothesizeded that the influence of spironolactone treatment on left ventricular systolic function and remoulding may in part rely on *ACE* genotype. A randomized controlled trial indicated that carriers of the D allele and patients with DD genotype responded expressively better to sertraline than to fluoxetine. Therefore, although, it was not significant, the TT genotype of rs4291 were more responsive to sertraline[51].

The folate carrier *SLC19A1* is a folate-organic phosphate antiporter to transports folates[52], whose expression was observably associated with drug sensitivity. A study in polymorphism and expressions of folate pathway genes revealed that *SLC19A1* expression were connected with the sensitivity of some drugs (antifolates, nitrosoureas, thiopurines, and DACH-platinum drugs) in the NCI-60 cancer cell lines[53]. From previous researches, we know that *SLC19A1* inhibitors, as we all know, the methotrexate and sulfasalazine, are first line treatments in rheumatoid arthritis(RA)[54–56]. Methotrexate also works against cancer by interfering with the folate pathway to exerting its cytotoxic effects. Methotrexate can be used to treat a variety of systemic diseases, and however, amounts of prospective study are still need to judge the effect of genetic variant in *SLC19A1* on risk of methotrexate treatment failure, as well as determining whether dosing adjustment to methotrexate based on *SLC19A1* genotype in order to improve overall therapeutic effect[57].

Conclusion

At present, there is little pharmacogenomic information on the Lisu population in Yunnan, and our study will make progress on it. Especially, the dose of Iloperidone in Lisu psychiatric population deserves further study. This study aimed to provide a basis for more accurate drug use and better treatment in the Lisu population. However, there are still some limitations in our experiment, such as the small sample size thereforel, we hope to conduct this study in a larger sample to ensure the accuracy of the experiment. In addition, we look forward to developing new therapeutic pathways for humans based on these findings.

Abbreviations

DHHA, Department of Health and Human Service; EAS East Asian, AFR African, AMR American, EUR European, SAS South Asian, CDX Chinese Dai in Xishuangbanna, CHB Han Chinese in Bejing, China, CHS Southern Han Chinese, China, JPT Japanese in Tokyo,Japan, KHV Kinh in Ho Chi Minh City, Vietnam, ACB African Caribbeans in Barbados, ASW African ancestry in the southwestern USA,ESN Esan in Nigeria, GWD Gambian in Western Divisions, The Gambia, LWK Luhya in Webuye, Kenya, MSL Mende in Sierra Leone, YRI Yoruba in Ibadan, CLM Nigeria,Colombian in Medellin, Colombia ,MXL Mexican Ancestry in Los Angeles, Colombia, PEL Peruvian in Lima, Peru, PUR Puerto Rican in Puerto Rico, 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, GIH Gujarati Indian in Houston, Texas, ITU Indian Telugu in the UK,PJL Punjabi in Lahore, Pakistan, STU Sri Lankan Tamil in the UK;HWE, Hardy-Weinberg Equilibrium;SNP, single nucleotide polymorphism; VIP, Very Important Pharmacogenes

Declarations

Ethics approval

This study was approved by the Human Research Ethics Committee of Xizang Minzu University in accordance with the tenets of the Declaration of Helsinki.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the Figshare repository, [https://doi.org/10.6084/m9.figshare.15161781] and [https://doi.org/10.6084/m9.figshare.15506451].

Conflict interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceptualization, Hongyan Lu; methodology, Shishi Xing and Dandan Li; software, Yuliang Wang and Zhanhao Zhang; data curation, Tianbo Jin; writing, review and editing, Li Wang and Shishi Xing.

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Consent for publication

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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Figures

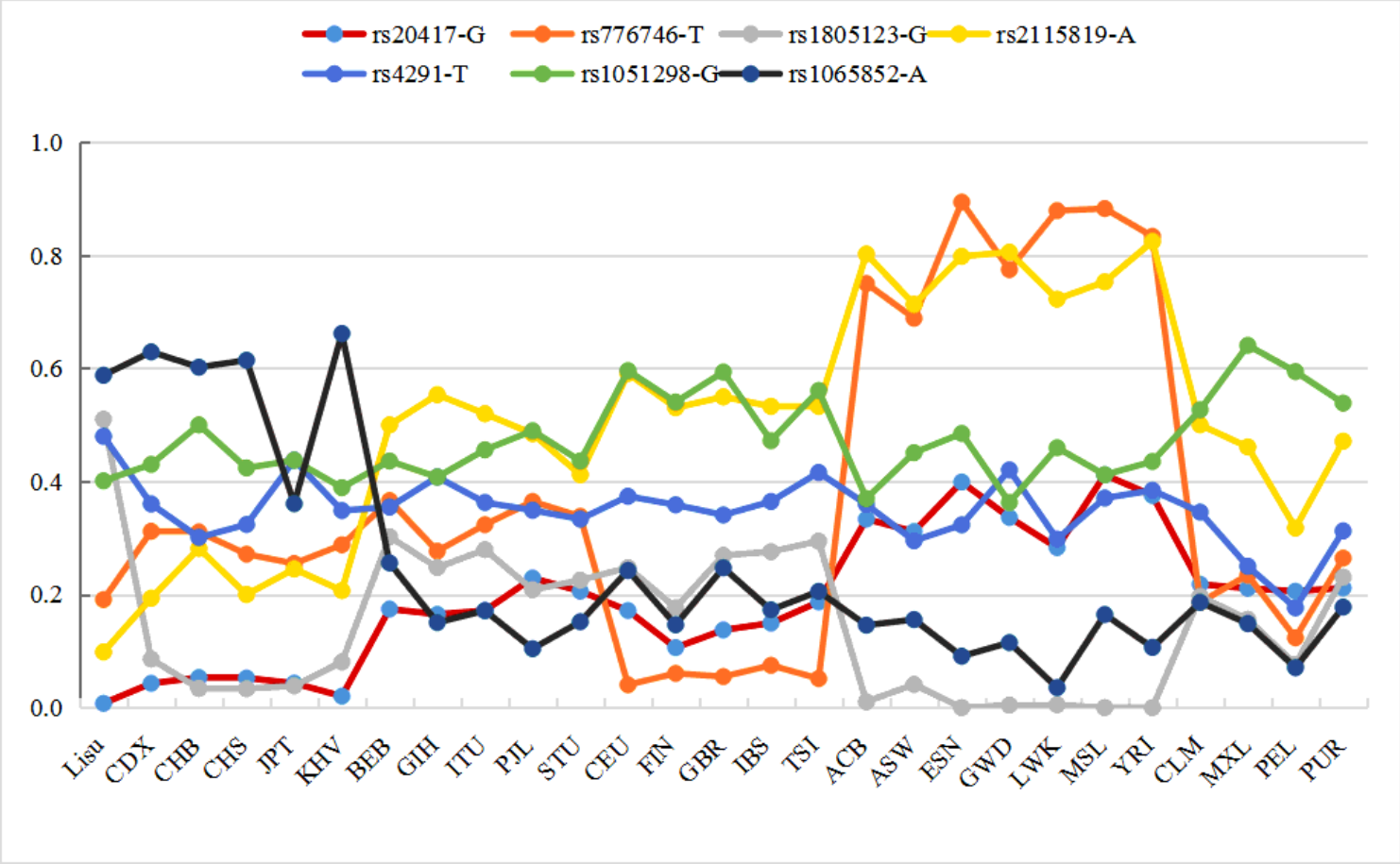

Figure 1

Minor allele frequencies of significant polymorphisms in 27 populations.

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