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Genetic polymorphisms in very important pharmacogenomic (VIP) variants in the Tibetan population

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ABSTRACT. Genetic polymorphisms of very important pharmacogenomic (VIP) variants are important for personalized medicine. However, these have not been extensively studied in the Tibetan population. In this study, 82 VIP variants were detected in the Tibetan and Han (HAN) populations from northwestern China. Subsequently, we compared the differences between the Tibetan population and ten populations, including the HAN, Japanese in Tokyo (JPT), Mexican ancestry in Los Angeles (MEX), Toscans in Italy (TSI), African ancestry in Southwest USA (ASW), Luhya in California Webuye, Kenya (LWK), Gujarati Indians in Houston, Texas (GIH), Maasai in Kinyawa, Kenya (MKK), Yoruba in Ibadan, Nigeria (YRI),

and Utah residents with Northern and Western European ancestry from the CEPH collection (CEU). Using the χ^2 test, we identified differences in the frequency distribution of 4, 4, 7, 10, 11, 11, 13, 15, 19, and 20 loci in the Tibetan population, compared to the HAN, JPT, MEX, TSI, ASW, LWK, GIH, MKK, YRI, and CEU populations, respectively [$P < 0.05/(82*10)$]. rs2115819, rs9934438, and rs689466, located in the *ALOX5* (arachidonate 5-lipoxygenase), *VKORC1* (vitamin K epoxide reductase complex, subunit 1) and *PTGS2* (prostaglandin-endoperoxide synthase 2) genes, respectively, in the Tibetan population were different from those in most of the populations. Our results complement the information provided by the database of pharmacogenomics on Tibetan people, and provide an avenue for personalized treatment in the Tibetan population.

Key words: *ALOX5*; *VKORC1; PTGS2*; Pharmacogenomics; SNP

INTRODUCTION

Single nucleotide polymorphisms (SNPs) in genes encoding drug metabolizing enzymes and drug transporters are the essential determinants of inter-individual variability in drug metabolism, and, consequently, treatment response as well as disease susceptibility in humans. Pharmacogenetics is the study of how genetic variations in individual genes can cause different reactions to a given drug (Owen et al., 2007). The variability in therapeutic response, severe toxicity, and unpredictable efficacy are the major challenges of drug therapy, particularly anticancer treatments (Wood et al., 2003). The drug and its dosage can be selected prior to clinical treatment, and personalized therapeutics promoted, by combining the genetic constitution of a patient with pharmacogenomics (Becquemont et al., 2011). The very important pharmacogene (VIP gene) has been summarized in the Pharmacogenomics Knowledge Base (PharmGKB; http://www.pharmgkb.org). These VIP variants are genetic variants deemed most important in relation to drug response by PharmGKB. In total, there are 126 VIP variants that occur in 44 different genes coding for cytochrome P450 oxidases, drug targets, receptors, and transporters. The relationship between these VIP variants and their effect on drug-related toxicity as well as therapeutic benefits have been studied extensively (Sangkuhl et al., 2008).

Tibetans, with a population of 6,282,187 (according to the sixth population survey of China in 2010), live mostly in the Tibet Autonomous Region on the Tibetan Plateau, with some groups also residing in the Qinghai, Gansu, Sichuan, and Yunnan provinces of China. Tibetans mostly live in compact communities in highlands and mountainous regions. The Tibetan population comprises one of the largest ethnic groups in China, with a long history in and effecting a lasting impact on the culture and tradition of the region. A study of genomic variations in Tibetan people suggested that a majority of the Tibetan gene pool may have diverged from that of the Han population around 3000 years ago (Yi et al., 2010). However, there are possibilities of much earlier human inhabitation of Tibet (Yuan et al., 2007), and these early residents may have contributed to the modern Tibetan gene pool.

In this study, we have attempted to identify the genotype frequencies of 82 VIP variants selected from 41 genes from the Tibetan population and to determine the difference in genotype frequencies between the Tibetan and the Han populations of northwestern China and 9 other populations from the HapMap_release127 data. Our results serve to complement the information being provided currently by the database of pharmacogenomics on the Tibetan ethnic group, and could help devise new strategies for optimization of drug therapy for each individual patient.

MATERIAL AND METHODS

Study participants

We recruited 96 random unrelated Tibetan and Han adults from the Tibet Autonomous Region and northwest of China, respectively. The subjects selected were judged to be of good health and had exclusive Tibetan or Han ancestry for at least the past 3 generations. Blood samples were taken from the subjects according to the study protocol, which was approved by the Clinical Research Ethics of Northwest University. Signed informed consent forms were also obtained from all participants enrolled in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Variant selection and genotyping

Genomic DNA was extracted from the peripheral blood obtained from the subjects using the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Ltd., Xi'an, China) according to the manufacturer protocols. The 82 VIP variants selected from among 41 genes were genotyped using the protocol recommended by the manufacturer of a MassARRAY RS1000 (Sequenom, San Diego, CA, USA). The SNP genotyping data was managed and analyzed using the Sequenom Typer 4.0 software (Thomas et al., 2007).

Statistical analyses

The χ^2 test was performed on the SPSS (v.18.0) statistical software platform (SPSS Inc., Chicago, IL, USA). The genotype frequencies of the variants in the Tibetan population were compared separately with those in the ten populations using the χ^2 test. All P values obtained in this study were two-sided, and Bonferroni's multiple adjustment was applied to the level of significance, which was set at $P < 0.05/(82*10)$. We attempted to discover significantly different sits using the χ^2 test. Subsequently, we analyzed the global patterns of genetic variation frequency at the specific loci. The SNP allele frequencies were obtained from the ALlele FREquency Database (http://alfred.med.yale.edu).

RESULTS

Basic information regarding the 82 VIP loci selected is summarized in Table 1. These VIP loci were distributed in the 41 genes, and were mainly involved in theATP-binding cassette transporter superfamily, and the alcohol dehydrogenase, adrenergic receptors, G-protein coupled receptor, solute carrier, and nuclear receptor families, and the cytochrome P450 superfamily.

Using the χ^2 test, we identified differences in the frequency distribution of the 4, 4, 7, 10, 11, 11, 13, 15, 19, and 20, loci in the Tibetan population, compared to the Han, Japanese in Tokyo (JPT), Mexican ancestry in Los Angeles, Toscans in Italy, African ancestry in Southwest USA, Luhya in California Webuye, Kenya, Gujarati Indians in Houston, Texas, Maasai in Kinyawa, Kenya, Yoruba in Ibadan, Nigeria, and Utah residents with Northern and Western European ancestry from the CEPH collection populations, respectively (following Bonferroni adjustments). rs2115819, rs9934438, and rs689466 located in the *ALOX5*, *VKORC1*, and *PTGS2* genes, receptively, were different in the Tibetan population compared to most of the other populations (Table 2).

For global analysis, we compared the frequencies of *ALOX5* (rs2115819 C allele) and

Table 1. Basic characteristics of variants selected.

SNP ID	Genes	Categories		Alleles		Amino acid translation
		Family	Phase	A	B	
rs1045642	*ABCB1*	ATP-binding cassette (ABC)	Others	T	C	Ile1145Ile
rs1128503	*ABCB1*	Transporter superfamily	Others	T	C	Gly412Gly
rs975833	*ADH1A*	Alcohol dehydrogenase family	Phase I	G	C	-
rs2066702	*ADH1B*		Phase I	C	T	Arg370Cys
rs1229984	*ADH1B*		Phase I	G	A	His48Arg
rs698	*ADH1C*		Phase I	A	G	Ile350Val
rs1801252	*ADRB1*	Adrenergic receptor family	Phase I	G	A	Ser49Gly
rs1042713	*ADRB2*		Phase I	G	A	Arg16Gly
rs1042714	*ADRB2*		Phase I	G	C	Gln27Glu
rs1800888	*ADRB2*		Phase I	C	T	Thr164Ile
rs2066853	*AHR*		Others	G	A	Arg554Lys
rs2115819	*ALOX5*	Lipoxygenase gene family	Others	T	C	-
rs4680	*COMT*		Phase II	A	G	Val158Met
rs28399454	*CYP2A6*	Cytochrome P450 superfamily	Phase I	G	A	Val365Met
rs28399444	*CYP2A6*		Phase I	AA	-	Glu197Ser,Glu197Arg
rs1801272	*CYP2A6*		Phase I	T	A	Leu160His
rs28399433	*CYP2A6*		Phase I	G	T	-
rs8192726	*CYP2A6*		Phase I	G	T	-
rs28399499	*CYP2B6*		Phase I	T	C	Ile328Thr
rs3211371	*CYP2B6*		Phase I	C	T	Arg487Cys
rs4986893	*CYP2C19*		Phase I	G	A	Trp212null
rs4244285	*CYP2C19*		Phase I	G	A	Pro227Pro
rs17110453	*CYP2C8*		Phase I	A	C	-
rs1799853	*CYP2C9*		Phase I	C	T	Arg144Cys
rs59421388	*CYP2D6*		Phase I	C	T	Val287Met
rs28371725	*CYP2D6*		Phase I	G	A	-
rs16947	*CYP2D6*		Phase I	G	A	-
rs61736512	*CYP2D6*		Phase I	C	A/G/T	Val136Met
rs28371706	*CYP2D6*		Phase I	C	T	Thr107Ile
rs2070676	*CYP2E1*		Phase I	G	C	-
rs890293	*CYP2J2*		Phase I	G	T	-
rs4986910	*CYP3A4*		Phase I	T	C	Met445Thr
rs4986909	*CYP3A4*		Phase I	C	T	Pro416Leu
rs12721634	*CYP3A4*		Phase I	T	C	Leu15Pro
rs10264272	*CYP3A5*		Phase I	C	T	Lys208Lys
rs3918290	*DPYD*		Phase I	G	A	-
rs1801159	*DPYD*		Phase I	A	G	Ile543Val
rs1801160	*DPYD*		Phase I	G	A	Val732Ile
rs6277	*DRD2*	G-protein coupled receptor family	Others	C	T	Pro290Pro
rs1800497	*ANKK1*	Ser/Thr protein kinase family	Phase I	C	T	Glu713Lys
rs2227983	*EGFR*	Epidermal growth factor family	Others	G	T/C/A	Arg521Thr, Arg521Met, Arg521Lys
rs28929495	*EGFR*		Others	G	T/A	Gly719Cys Gly719Ser
rs6025	*F5*		Others	G	A	Arg534Gln
rs1050828	*G6PD*		Phase I	A	C/T	Asn156Asp
rs1695	*GSTP1*	Glutathione S-transferase family	Phase II	A	G	Val68Met
rs1138272	*GSTP1*		Phase II	T	C	Ala114Val
rs17244841	*HMGCR*		Phase I	A	T	-
rs3846662	*HMGCR*		Phase I	T	C	-
rs17238540	*HMGCR*		Phase I	T	G	-
rs3815459	*KCNH2*	Eag family	Others	A	G	-
rs36210421	*KCNH2*		Others	G	T	Arg707Leu
rs12720441	*KCNH2*		Others	C	T	Arg444Trp
rs3807375	*KCNH2*		Others	A	G	-
rs5219	*KCNJ11*	Inward-rectifier potassium channel family	Others	C	T	Lys23Glu
rs1801131	*MTHF*R	Methylenetetrahydrofolate reductase family	Phase I	C	A	Glu429Ala
rs1801133	*MTHFR*		Phase I	T	C	Ala222Val
rs3814055	*NR1I2*	Nuclear receptor family	Others	C	T	-
rs1065776	*P2RY1*	G-protein coupled receptor family	Others	T	C	Ala19Ala
rs701265	*P2RY1*		Others	G	A	Val262Val
rs2046934	*P2RY1*		Others	T	C	-
rs20417	*PTGS2*		Phase I	G	C	-
rs689466	*PTGS2*		Phase I	A	G	-
rs7626962	*SCN5A*	Sodium channel gene family	Others	G	T	Ser1103Tyr
rs1805124	*SCN5A*		Others	G	A	Pro1090Leu

Continue on next page

Table 1. Continued.

SNP ID	Genes	Categories		Alleles		Amino acid translation
		Family	Phase	A	B	
rs6791924	*SCN5A*		Others	G	A	Arg34Cys
rs12659	*SLC19A1*	Solute carrier family	Others	C	T	Pro192Pro
rs1051266	*SLC19A1*		Others	G	A	His27Arg
rs1131596	*SLC19A1*		Others	T	C	-
rs1801030	*SULT1A1*	Sulfotransferase family	Phase II	A	G	Val223Met
rs3760091	*SULT1A1*		Phase II	C	G	-
rs1142345	*TPMT*	Methyltransferase superfamily	Phase II	G	A	Tyr240Cys
rs4148323	*UGT1A1*	UDP-glucuronosyltransferase family	Phase II	A	G	Gly71Arg
rs7975232	*VDR*	Nuclear receptor family	Others	C	A	-
rs1544410	*VDR*		Others	G	A	-
rs2239185	*VDR*		Others	T	C	-
rs1540339	*VDR*		Others	G	A	-
rs2239179	*VDR*		Others	A	G	-
rs3782905	*VDR*		Others	C	G	-
rs2228570	*VDR*		Others	T	C	Met51Arg,Met51Lys,Met51Thr
rs11568820	*VDR*		Others	G	A	-
rs9934438	*VKORC1*		Phase I	G	A	-
rs7294	*VKORC1*		Phase I	G	A	-

A: reference allele. B: other allele.

Table 2. Significant variants in the Tibetan population compared to the HAN, JPT, MEX, TSI, GIH, LWK, ASW, GIH, MKK, YRI, and CEU populations.

rs ID	Gene	P values against four populations[a]									
		HAN	JET	MEX	TSI	LWK	ASW	GIH	MKK	YRI	CEU
rs1045642	*ABCB1*	-	-	-	-	-	-	1.28E-05	2.67E-05	4.10E-07	-
rs1128503	*ABCB1*	-	-	-	-	2.85E-19	8.69E-11	-	8.38E-21	1.13E-20	-
rs975833	*ADH1A*	-	-	-	-	-	-	-	-	1.21E-05	2.21E-05
rs1229984	*ADH1B*	6.81E-17	7.36E-15	-	-	-	-	-	-	-	-
rs698	*ADH1C*	-	-	-	-	-	-	-	-	-	6.42E-13
rs1042714	*ADRB1*	-	-	-	-	-	-	-	-	-	1.45E-07
rs1045642	*ADRB1*	-	-	-	-	-	-	-	-	-	4.98E-06
rs1801252	*ADRB1*	-	1.33E-26	-	-	-	-	-	-	2.99E-29	-
rs1042714	*ADRB2*	-	1.15E-20	-	-	-	-	-	-	-	-
rs2066853	*AHR*	-	-	-	2.61E-06	-	-	4.15E-05	-	-	1.66E-06
rs2115819	*ALOX5*	-	-	2.89E-06	2.20E-09	5.20E-20	1.32E-15	4.79E-11	1.60E-17	7.59E-26	3.18E-15
rs2070676	*CYP2E1*	-	-	-	-	9.18E-21	1.05E-10	-	2.32E-18	1.26E-20	-
rs6277	*DRD2*	-	-	-	-	-	-	-	-	-	3.32E-18
rs1050828	*G6PD*	-	-	-	-	-	-	-	-	3.23E-08	-
rs1695	*GCTP1*	-	-	-	-	-	-	-	-	-	4.76E-05
rs1695	*GSTP1*	-	-	9.98E-08	-	1.06E-08	-	-	-	-	-
rs3846662	*HMGCR*	-	-	-	-	3.33E-26	2.13E-13	2.57E-05	7.12E-19	2.19E-28	-
rs3807375	*KCNH2*	-	-	-	1.44E-12	-	-	4.62E-11	-	-	1.39E-12
rs1801133	*MTHFR*	1.53E-05	-	-	-	-	-	-	5.10E-08	-	-
rs3814055	*NR1I2*	-	-	-	5.89E-05	-	-	-	-	-	-
rs701265	*P2RY1*	-	-	-	-	9.66E-25	2.36E-14	-		5.16E-27	-
rs701265	*P2RY1*	-	-	-	-	-	-	-	3.64E-27	-	-
rs20417	*PTGS2*	-	-	-	-	-	-	-	-	5.56E-23	4.07E-28
rs689466	*PTGS2*	-	-	-	5.30E-06	1.88E-16	1.81E-07	2.02E-07	1.10E-22	1.39E-12	1.31E-07
rs1051266	*SLC19A1*	1.19E-05	-	6.89E-07	-	-	-	4.86E-06	-	-	-
rs12659	*SLC19A1*	1.42E-05	-	-	-	-	-	-	-	-	-
rs4148323	*UGT1A1*	-	-	1.37E-06	-	-	-	5.86E-11	-	3.89E-10	3.89E-10
rs1540339	*VDR*	-	-	3.72E-07	4.13E-11	5.54E-22	1.57E-12	4.41E-11	8.70E-25	1.23E-20	1.28E-11
rs1544410	*VDR*	-	-	-	3.95E-13	-	-	9.24E-15	2.24E-12	4.43E-08	2.22E-14
rs2239179	*VDR*	-	-	-	9.67E-05	-	-	4.14E-07	5.95E-06	-	1.57E-05
rs3782905	*VDR*	-	3.75E-24	-	-	-	-	-	-	2.95E-22	4.30E-19
rs7975232	*VDR*	-	-	-	3.72E-05	-	3.37E-05	-	2.97E-10	4.86E-07	6.88E-05
rs11568820	*VDR*	-	-	3.70E-05	-	7.54E-16	3.17E-05		9.56E-12	4.33E-29	5.61E-07
rs7294	*VKORC1*	-	-	-	-	1.78E-11	5.96E-12	3.61E-25	5.65E-15	1.46E-15	3.59E-08
rs9934438	*VKORC1*	-	-	2.23E-12	1.43E-14	7.71E-35	6.31E-26	8.66E-29	1.41E-37	1.40E-42	1.25E-18

[a]Bonferroni's multiple adjustment was applied to the level of significance, which was set at $P < 0.05/(82*10)$. ''-'' = not significant. HAN = Han Chinese in northwest China; JPT = Japanese in Tokyo, Japan; MEX = Mexican ancestry in Los Angeles, California; TSI = Toscans in Italy; LWK = Luhya in Webuye, Kenya; ASW = African ancestry in Southwest USA; GIH = Gujarati Indians in Houston, Texas; MKK = Maasai in Kinyawa, Kenya; YRI = Yoruba in Ibadan, Nigeria (West Africa); CEU = Utah residents with Northern and Western European ancestry from the CEPH collection.

PTGS2 (rs689466 A allele) in the Tibetan population to previously published data for a total of 50 population samples. The frequency data is displayed graphically in Figure 1, with the population samples arranged “geographically” from Africa to South America. The frequency of expression of rs2115819 was seen to be high in eastern Asia and lower in Africa. However, the frequency of rs689466 was higher in Africa than in eastern Asia.

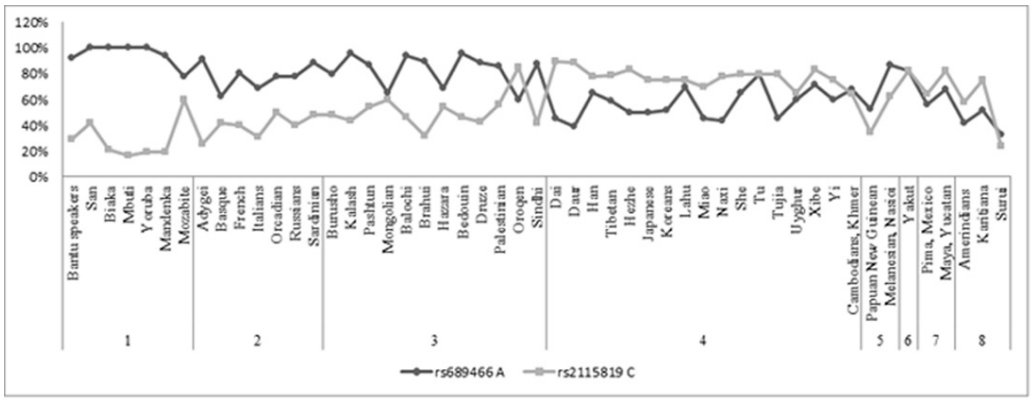

Figure 1. *PTGS2* rs689466 and *ALOX5* rs2115819 frequencies in populations from different regions of the world. Descriptions of the specific samples, full references, and allele frequencies are available in ALFRED. 1 = Africa, 2 = Europe, 3 = Asia, 4 = East Asia, 5 = Oceania, 6 = Siberia, 7 = North America, and 8 = South America.

DISCUSSION

In this study, we identified the genotype frequencies of 82 VIP variants selected from 41 genes in the Tibetan population, and compared the genotype frequencies to those in 10 different populations. Our results showed that many the expression of VIP variants in the Tibetan population was significant differently from that in other populations. Among these variants, rs2115819, rs689466, and rs9934438 were significantly differentially expressed in the Tibetan people, compared to the ten populations, except the Han population from northwest China and JPT. This result showed the similarities in the genetic backgrounds of the Tibetan, Chinese, and Japanese populations.

rs2115819 is an intronic SNP of the *ALOX5* gene, which encodes arachidonate 5-lipoxygenase, a cystolic enzyme that catalyzes the two-step conversion of arachidonic acid to leukotriene A4 (Kalayci et al., 2006). It is positively associated with increased FEV_1 (forced expiratory volume in one second) response to montelukast therapy. The CC homozygotes of the rs2115819 SNP had a significantly higher FEV_1 response to montelukast at 6 months of treatment compared to the TT homozygotes and heterozygotes (Lima et al., 2006). This SNP is also part of a 4-SNP haplotype associated with increased asthma exacerbation during the 6 months of montelukast treatment, relative to that seen in the placebo group (Lima et al., 2006). The frequency of the C allele is higher in the Tibetan population than in other populations, especially that of Africa. This result may suggest that the Tibetan may show a better response to montelukast treatment.

The rs689466 variant is found in the promoter of the *PTGS2* (prostaglandin-endoperoxide synthase 2) gene, which codes for prostaglandin G/H synthase-2 (Geiger et al., 2011). Previous studies have associated the rs689466 expression with many diseases, such as asthma (Shi et

al., 2008; Ho and Chew, 2010), breast cancer (Dai et al., 2014), and pancreatic cancer (Zhao et al., 2009). The A variant of rs689466 (-1195 G>A) creates a v-Myb-binding site in the promoter that increases transcription (Zhang et al., 2005; Agundez et al., 2014), and is also significantly associated with increased risk of cancers of the digestive system, especially among the Asian populations (Dong et al., 2010). Asian individuals with the G allele have higher blood pressure (Iwai et al., 2004; Jin et al., 2008). Given the side effects of some non-steroidal anti-inflammatory drugs (NSAIDs), such as the elevation of blood pressure, this will be an interesting variant to study in the future. The G allele frequency is slightly higher in the Tibetan population; because of this, we suggest that the Tibetan population should pay more attention on their diet and lifestyle to prevent hypertension, and be aware of the side effect of some NSAIDs.

rs9934438 is located in the *VKORC1* gene. This gene encodes the vitamin K epoxide reductase protein, which is a key enzyme in the vitamin K cycle (Rost et al., 2004). Previous studies have suggested that the carriers of the TT genotype show a better response to warfarin (oral anticoagulant) than the carriers of the CC or CT genotypes (D'Andrea et al., 2005; Wang et al., 2008). The genotype frequencies of rs9934438 in the Tibetan population (detected in our study) were higher than those seen in populations from other continents; this indicated that the Tibetan population must pay closer attention to the warfarin dosage (relative to the *VKORC1* gene). The distribution of genotype frequencies of VIP variants is altered among different human populations. The differences in genotype frequencies can determine the response to specific drugs in individual patients. Our results complement the currently available data on the Tibetan ethnic group in the pharmacogenomics database; in addition, our data provides a basis for safer and more effective drug administration in the Tibetan population. However, our sample size of Tibetan people was relatively small, and our results must be validated in a larger sample set.

Conflicts of interest

The authors declare no conflict of interest.

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