MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 3769-3776
DOI: 10.12659/MSM.895191

Received: 2015.07.01
Accepted: 2015.08.30
Published: 2015.12.03

Genetic Polymorphisms Analysis of Pharmacogenomic VIP Variants in Miao Ethnic Group of Southwest China

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AB 1,2,3,4 Tianbo Jin*
B 5 Ainiwaer Aikemu*
E 3,4 Mingxia Zhang
F 4 Tingting Geng
D 4 Tian Feng
G 1,2 Longli Kang
A 6 Manlin Luo

1 Key Laboratory of Molecular Mechanism and Intervention Research for Plateau Diseases of Tibet Autonomous Region, School of Medicine, Xizang Minzu University, Xianyang, Shaanxi, P.R. China
2 Key Laboratory of High Altitude Environment and Genes Related to Diseases of Tibet Autonomous Region, School of Medicine, Xizang Minzu University, Xianyang, Shaanxi, P.R. China
3 School of Life Sciences, Northwest University, Xi'an, Shaanxi, P.R. China
4 National Engineering Research Center for Miniaturized Detection Systems, Xi'an, Shaanxi, P.R. China
5 Department of Drug Analysis, Faculty of Pharmacy, Xinjiang Medical University, Urumqi, Xinjiang, P.R. China
6 Department of Blood Transfusion, Yunnan Province Second People's Hospital, Kunming, Yunnan, P.R. China

* Tian bo Jin and Ainiwaer Aikemu are joint first authors

Corresponding Author: Man lin Luo, e-mail: manlinluo@163.com

Source of support: This work was supported by the Major Training Program of Xizang Minzu University (No. 13myZP06), Natural Science Foundation of Xizang (Tibet) Autonomous Region (20152R-13-11), Major science and technology research projects of Xizang (Tibet) Autonomous Region (2015), and the National Natural Science Foundations (No. 81560516)

Background: Genetic polymorphisms have a potential clinical role in determining both inter-individual and inter-ethnic differences in drug efficacy, but we have not found any pharmacogenomics information regarding minorities, such as the Miao ethnic group. Our study aimed to screen numbers of the Miao ethnic group for genotype frequencies of VIP variants and to determine differences between the Miao and other human populations worldwide.

Material/Methods: In this study, we genotyped 66 Very Important Pharmacogene (VIP) variants selected from PharmGKB in 98 unrelated, healthy Miao individuals from the Guizhou province and compared our data with 12 other populations, including 11 populations from the HapMap data set and Xi'an Han Chinese.

Results: Using the χ^2 test, we found that the allele frequencies of the VDR rs1544410 and VKORC1 (rs9934438) variants in the Miao population are quite different from that in other ethnic groups. Furthermore, we found that genotype frequencies of rs1801133 (MTHFR) in the 13 selected populations are significantly different. Population structure and F-statistics (Fst) analysis show that the genetic background of the Miao is relatively close to that of Chinese in metropolitan Denver, CO, USA (CHD).

Conclusions: Our results help complete the information provided by the pharmacogenomics database of the Miao ethnic group and provide a theoretical basis for safer drug administration, which may be useful for diagnosing and treating diseases in this population.

MeSH Keywords: Ethnic Groups • Genetic Counseling • Genomic Structural Variation

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/895191

2257 3 1 32

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

The large variability among individuals in drug efficacy is a major challenge in current clinical practice, drug development, and drug regulation [1]. It has been suggested that genetic background may be responsible for the variation in response to therapy, and mounting evidence demonstrates that an individual's genetic makeup accounts for an estimated 20~95% of variability in drug disposition and effects [2,3]. Pharmacogenetics and pharmacogenomics elucidated the inherited nature of individual variation in drug response, with the goal of optimizing efficacy and safety through better understanding of human genetic variability and its influence on drug response, leading to personalized medicine [4,5].

The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB: *http://www.pharmgkb.org*) is a publicly available Web-based knowledge base created to aid researchers in understanding how genetic variation among individuals contributes to differences in reactions to drugs [6]. This information is presented in the form of Very Important Pharmacogene (VIP) summaries, pathway diagrams, and curated literature [7]. The PharmGKB currently contains information for more than 3000 drugs, 3000 diseases, and 26 000 genes with genotyped variants [8]. In total, it consists of 126 VIP variants that occur in 44 different genes and variously code for cytochrome P450 oxidases, drug targets, drug receptors, and drug transporters. The relationship between these VIP variants and their effect on drug-related toxicity as well as therapeutic benefit have been studied extensively [9].

Pharmacogenomic research in ethnic populations has great significance for the achievement of personalized drug treatment and development of new drugs. However, we have not found any pharmacogenomics information regarding minority groups, such as the Miao ethnic groups in southwest China. The Miao is an ethnic group mainly distributed in the southwest of China; they mostly live in Guizhou, Yunnan, and Sichuan provinces. It is one of China's largest ethnic groups, with a long history, distinct culture, and fine traditions. According to a 2000 census, the Miao have an approximate population of 9.6 million.

In the present study, we aimed to identify the allele frequencies of VIP variants in the Miao and to determine the difference in allele frequencies between the Miao and 12 other populations. Our goals were to identify differences and determine their extent and provide a theoretical basis for safer drug administration and better therapeutic treatment in the Miao population. The results of our study will extend our understanding of ethnic diversity and pharmacogenomics, and help clinicians triage patients for better individualized treatments.

Material and Methods

Study participants

We randomly recruited 98 unrelated, healthy Miao subjects from Guizhou province of China. The subjects selected were judged to be of good health and had exclusively Miao ancestry for at least the last 3 generations. We selected 96 unrelated Chinese Han individuals from Lantian county in Xi'an, Shaanxi province as one of our control groups. All subjects were healthy in terms of their medical history and physical examination. An explanation about the purpose and experimental procedures of the study were given to all individuals. Written informed consent was obtained from all subjects prior to sample donation, and the study protocol was performed in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics of Northwest University for Approval of Research Involving Human Subjects.

Variant selection and genotyping

We selected genetic variants from published polymorphisms associated with VIP variants from the Pharm GKB database, and excluded *loci* that could not be designed. We successfully genotyped 66 VIP variants selected from PharmGKB in 194 participants (98 Miao subjects and 96 Chinese Han controls). Genomic DNA was isolated from whole blood using the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Ltd. Xi'an, China) according to the manufacturer's protocol. DNA concentration was measured by NanoDrop 2000C (Thermo Scientific, Waltham, Massachusetts, USA). We used the Sequenom MassARRAY Assay Design 3.0 software (San Diego, CA, USA) to design Multiplexed SNP MassEXTEND assays [10]. Single-nucleotide polymorphism (SNP) genotyping used the standard protocol recommended by the manufacturer with a Sequenom MassARRAY RS1000 (San Diego, California, USA). Sequenom Typer 4.0 Software (San Diego, California, USA) was used to perform data management and analyze the SNP genotyping data, as described in a previous report [11].

HapMap genotype data

The genotype data of the 11 populations were downloaded from the International HapMap Project web site (HapMap_release127) at *http://hapmap.ncbi.nlm.nih.gov*. The 11 populations are as follows: (1) African ancestry in Southwest USA (ASW); (2) Utah, USA residents with Northern and Western European ancestry from the CEPH collection (CEU); (3) Han Chinese in Beijing, China (CHB); (4) Chinese in metropolitan Denver, CO, USA (CHD); (5) Gujarati Indians in Houston, Texas, USA (GIH); (6) Japanese in Tokyo, Japan (JPT); (7) Luhya in Webuye, Kenya (LWK); (8) Mexican ancestry in Los Angeles, California, USA

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

(MEX); (9) Maasai in Kinyawa, Kenya (MKK); (10) Toscani in Italy (TSI); and (11) Yoruba in Ibadan, Nigeria (YRI).

Data analysis

We used Microsoft Excel (Redmond, WA, USA) and SPSS 17.0 statistical packages (SPSS, Chicago, IL, USA) to perform statistical calculations. The validity of the frequency of each VIP variant in the Miao and Chinese Han data was tested by assessing the departure from HWE using an exact test. We calculated and compared the genotype frequencies of the variants in the Miao data with those in the 11 populations separately using the χ^2 test [12]. All p values obtained in this study were 2-sided, and Bonferroni adjustment for multiple tests was applied to the level of significance, which was set at $p<0.05/(66*12)$ [13]. Structure (version 2.3.4) software [14] was used to analysis the genetic structure of the 13 populations. We used Arlequin (version 3.1) software to calculate the value of Fst to infer the pairwise distance between populations [15].

Results

We successfully sequenced 66 VIP pharmacogenomic variant genotypes from 98 Miao individuals. The basic information about the selected VIP *loci* in Miao is listed in Table 1, including gene name and category, chromosome number and position, amino acid translation, and their allele frequencies in Miao.

We used the χ^2 test with the Bonferroni correction for multiple hypotheses and multiple comparisons, and we found 5, 7, 12, 13, 14, 15, 15, 16, 16, 19, 19, and 25 different *loci* in the frequency distributions when the Miao population was compared to the Xi'an Han, CHD, MEX, ASW, JPT, CHB, GIH, MKK, TSI, CEU, LWK, and YRI populations, respectively ($p \leq 6.3\times10^{-5}$). These VIP variants are mainly distributed in 23 genes; they mainly involve the cytochrome P450 superfamily, nuclear receptor family, G-protein-coupled receptor family, alcohol dehydrogenase family, adrenergic receptors family, ATP-binding cassette (ABC) transporters superfamily, and eag family. Genotype frequencies of *MTHFR, VDR,* and *VKORC1* in the Miao differed widely from those in the other 12 populations. We found that the rs1801133 was the most significantly different locus between the Miao ethnic group and the other populations (Table 2). Additionally, Rs698, Rs1805124, and Rs 1801131 were found to show a significant difference in the 11 HapMap populations.

Pairwise Fst values were calculated for all population comparisons across *loci*. As shown in Table 3, we found that pairwise Fst values for comparisons of the Miao population with the other 12 populations ranged from 0.01904 to 0.26192. Fst statistics [16] are measures of population differentiation. It is directly related to the variance in allele frequency among populations and to the degree of resemblance among individuals within populations. If Fst is small, it means that the allele frequencies within each population are similar; if it is large, it means that the allele frequencies are different. The value of Fst for the Miao and CHD populations was the smallest. We therefore conclude that the allele frequencies of the Miao and CHD are similar. We speculate that the genetic backgrounds of the Miao and CHD populations are similar.

We used a model-based clustering approach, as implemented in Structure, to infer population structure among the 13 populations. Different values ranging from 2 to 7 were assumed for K in Structure calculations. K=3 was selected, based on the estimated Ln Prob of Data and other recommendations of the Structure software manual. As shown in Figure 1, when the K value was equal to 3, individuals were independently assigned to 3 affinity groups (subpopulations 1: Miao, Xi'an Han, CHB, CHD, JPT; subpopulations 2: ASW, LWK, MKK, YRI; subpopulations 3: CEU, GIH, MEX, TSI) using the relative majority of likelihood to assign individuals to subpopulations. We tested additional values of K and obtained results suggesting that the genetic backgrounds of the Miao and CHD populations are similar.

Discussion

Individuals' differences in drug reactions can directly influence the efficacy and safety of the drug, and has become a worldwide problem in the treatment of some major diseases. However, it is almost impossible to predict whether a drug will be beneficial, lack efficacy, or cause serious adverse effects [17]. Because genetic variations play an important role in determining the metabolism of and reactions to some specific drugs in individual patients, in this study we genotyped the variants related to drug response (pharmacogenomics) in the Miao ethnic group and compared the genotype frequencies with those in 12 other populations. The χ^2 test results show that the allele frequencies of the *VDR* rs1544410 and *VKORC1* (rs9934438) variants in the Miao population are quite different from that in other ethnic groups. We found that genotype frequencies of rs1801133 (*MTHFR*) in the 13 selected populations are significantly different. Using Fst calculations and analysis of population structure, we also found that the genetic backgrounds of the Miao and CHD population are similar.

Methylenetetrahydrofolate reductase (MTHFR), located on chromosome 1 at 1p36.3, is an important enzyme involved in the folate metabolic pathway. Rs1801133 (677 C>T) is a significant variant of the MTHFR gene. In our present study, rs1801133 was found to be a significant variant that existed in the 13 selected populations. It has been widely reported that the polymorphism of rs1801133 is associated with many diseases,

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 1. Basic information about the selected variants and allele frequencies in the Miao ethnicity.

SNP ID	Genes	Category		Amino acid translation	Chromosome	Position	Allele		Allele frequencies	
		Family	Phase				A	B	A (%)	B (%)
rs1801131	MTHFR	Methylenetetrahydrofolate reductase	Phase I	Glu429Ala	1	11854476	C	A	1	0
rs1801133	MTHFR	Methylenetetrahydrofolate reductase	Phase I	Ala222Val	1	11856378	T	C	0.72	0.28
rs20417	PTGS2	Nuclear receptor	Others	–	1	186650320	G	C	1	0
rs689466	PTGS2	Nuclear receptor	Others	–	1	186650750	A	G	0.49	0.51
rs3918290	DPYD	–	Phase I	–	1	97915614	G	/	1	0
rs6025	F5	–	Others	Arg534Gln	1	169519049	C	A	1	0
rs890293	CYP2J2	Cytochrome P450	Phase I	–	1	60392494	G	T	0.34	0.66
rs4148323	UGT1A10	UDP–glucuronosyltransferase	Phase Ii	Gly71Arg	2	234669144	A	G	0.23	0.77
rs1065776	P2RY1	G–protein coupled receptor	Others	Ala19Ala	3	152553628	T	C	0.96	0.04
rs2046934	P2RY12	G–protein coupled receptor	Others	–	3	151057642	T	C	0.19	0.81
rs3814055	NR1I2	Nuclear receptor	Others	–	3	119500034	C	T	0.91	0.09
rs1805124	SCN5A	Sodium channel gene	Others	Pro1090Leu	3	38645420	G	A	0.85	0.15
rs6791924	SCN5A	Sodium channel gene	Others	Arg34Cys	3	38674699	G	/	1	0
rs7626962	SCN5A	Sodium channel gene	Others	Ser1103Tyr	3	38620907	G	/	1	0
rs975833	ADH1A	Alcohol dehydrogenase	Phase I	–	4	100201739	G	C	0.75	0.25
rs1229984	ADH1B	Alcohol dehydrogenase	Phase I	His48Arg	4	100239319	G	A	0.68	0.32
rs2066702	ADH1B	Alcohol dehydrogenase	Phase I	Arg370Cys	4	100229017	C	T	1	0
rs698	ADH1C	Alcohol dehydrogenase	Phase I	Ile350Val	4	100260789	A	G	0.95	0.05
rs1042713	ADRB2	Adrenergic receptors	Others	Ala222Val	5	148206440	G	A	0.48	0.52
rs1042714	ADRB2	Adrenergic receptors	Others	–	5	148206473	G	C	0.98	0.02
rs1800888	ADRB2	Adrenergic receptors	Others	Thr164Ile	5	148206885	C	T	1	0
rs17238540	HMGCR	–	Phase I	–	5	74619742	T	/	1	0
rs17244841	HMGCR	–	Phase I	–	5	74607099	A	/	0.99	0.01
rs3846662	HMGCR	–	Phase I	–	5	74615328	T	C	0.57	0.43
rs1142345	TPMT	Methyltransferase superfamily	Phase Ii	Tyr240Cys	6	18130918	G	A	0.99	0.01
rs1045642	ABCB1	ABC transporters	Others	Ile1145Ile	7	87138645	T	C	0.65	0.35
rs1128503	ABCB1	ABC transporters	Others	Gly412Gly	7	87179601	T	C	0.33	0.67
rs2066853	AHR	AHR	Others	Arg554Lys	7	17379110	G	A	0.52	0.48
rs12720441	KCNH2	Eag	Others	Arg444Trp	7	150647304	C	/	1	0
rs36210421	KCNH2	Eag	Others	Arg707Leu	7	150644428	G	T	1	0
rs3807375	KCNH2	Eag	Others	–	7	150667210	A	G	0.78	0.22
rs3815459	KCNH2	Eag	Others	–	7	150644394	A	G	0.73	0.27
rs2740574	CYP3A4	Cytochrome P450	Phase I	–	7	99382096	A	G	0.99	0.01
rs12721634	CYP3A4	Cytochrome P450	Phase I	Leu15Pro	7	99381661	T	/	1	0
rs4986909	CYP3A4	Cytochrome P450	Phase I	Pro416Leu	7	99359670	C	/	0.74	0.26
rs4986910	CYP3A4	Cytochrome P450	Phase I	Met445Thr	7	99358524	T	/	1	0
rs10264272	CYP3A5	Cytochrome P450	Phase I	Lys208Lys	7	99262835	C	/	1	0
rs1801252	ADRB1	Adrenergic receptors	Others	Ser49Gly	10	115804036	G	A	0.66	0.34
rs1799853	CYP2C9	Cytochrome P450	Phase I	Arg144Cys	10	96702047	C	T	1	0

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 1 continued. Basic information about the selected variants and allele frequencies in the Miao ethnicity.

SNP ID	Genes	Category		Amino acid translation	Chromosome	Position	Allele		Allele frequencies	
		Family	Phase				A	B	A (%)	B (%)
rs4244285	CYP2C19	Cytochrome P450	Phase I	Pro227Pro	10	96541616	G	A	0.32	0.68
rs4986893	CYP2C19	Cytochrome P450	Phase I	Trp212null	10	96540410	G	/	0.015	0.985
rs1138272	GSTP1	Glutathione S–transferase	Phase Ii	Ala114Val	11	67353579	T	C	1	0
rs1695	GSTP1	Glutathione S–transferase	Phase Ii	Ile105Val	11	67352689	A	G	0.889	0.121
rs1800497	DRD2	G-protein-coupled receptor	Others	Glu713Lys	11	113270828	T	C	0.59	0.41
rs6277	DRD2	G-rotein-coupled receptor	Others	Pro290Pro	11	113283459	G	A	0.985	0.015
rs5219	KCNJ11	Inward-rectifier potassium channel family	Others	Lys23Glu	11	17409572	C	T	0.939	0.061
rs11568820	VDR	Nuclear receptor	Others	–	12	48302545	G	A	0.54	0.46
rs1540339	VDR	Nuclear receptor	Others	–	12	48257326	G	A	0.78	0.22
rs1544410	VDR	Nuclear receptor	Others	–	12	48239835	G	A	0.99	0.01
rs2239185	VDR	Nuclear receptor	Others	–	12	48244559	T	C	0.78	0.22
rs9934438	VKORC1	VKORC1	Phase I	–	16	31104878	G	A	0.87	0.13
rs1801030	SULT1A1	Sulfotransferase	Phase Ii	Val223Met	16	28617485	A	/	1	0
rs3760091	SULT1A1	Sulfotransferase	Phase Ii	–	16	28620800	C	G	0.74	0.26
rs1801272	CYP2A6	Cytochrome P450	Phase I	Leu160His	19	41354533	T	/	1	0
rs28399433	CYP2A6	Cytochrome P450	Phase I	–	19	41356379	G	T	0.23	0.77
rs28399444	CYP2A6	Cytochrome P450	Phase I	Glu197Arg	19	41354190	A	/	1	0
rs28399454	CYP2A6	Cytochrome P450	Phase I	Val365Met	19	41351267	G	/	1	0
rs28399499	CYP2B6	Cytochrome P450	Phase I	Ile328Thr	19	41518221	T	/	1	0
rs3211371	CYP2B6	Cytochrome P450	Phase I	Arg487Cys	19	41522715	C	T	0.50	0.50
rs1051266	SLC19A1	Solute carrier	Others	His27Arg	21	46957794	G	A	0.57	0.43
rs4680	COMT	COMT	Phase Ii	Val158Met	22	19951271	A	G	0.79	0.21
rs16947	CYP2D6	Cytochrome P450	Phase I	–	22	42523943	G	A	0.05	0.95
rs28371706	CYP2D6	Cytochrome P450	Phase I	Thr107Ile	22	42525772	C	T	0.995	0.005
rs28371725	CYP2D6	Cytochrome P450	Phase I	–	22	42523805	G	A	0.05	0.95
rs5030656	CYP2D6	Cytochrome P450	Phase I	–	22	42524175	AAG	/	0.50	0.50
rs61736512	CYP2D6	Cytochrome P450	Phase I	Val136Met	22	42525134	C	/	1	0

such as breast cancer [18], colorectal cancer [19], and bladder cancer [20]. A previous meta-analysis demonstrated that the 677 C allele was significantly associated with breast cancer risk (OR=0.942, 95%CI = 0.898 to 0.988) when compared with the 677 T allele in the additive model [18]. In our study, the C allele frequency in Miao was somewhat high (28%) in our present study, suggesting that Miao have an intermediate susceptibility to breast cancer. Sohn et al. [21] demonstrated that the MTHFR 677T mutation decreased chemosensitivity of breast cancer cells to methotrexate (MTX), a common cancer chemotherapeutic agent. Cáliz et al. [22] also reported that the C677T polymorphism (rs1801133) was associated with increased MTX toxicity [odds ratio (OR) 1.42, 95% confidence interval (CI) 1.01–1.98, p=0.0428] in a Spanish rheumatoid arthritis population. These findings suggest that the MTHFR C677T polymorphism may be a useful pharmacogenetic determinant for providing rational and effectively tailored therapy for the Miao ethnic group.

Vitamin D receptor (VDR) gene maps to chromosome 12q13.11, whose function has been widely reported. It is an important regulator of the vitamin D pathway and a number of common single-nucleotide polymorphisms (SNP) have been identified in this gene [23]. Clinical evidence suggests that the VDR genotype could modify the efficacy of anti-osteoporotic treatments such as etidronate and alendronate in postmenopausal women [24]. Other studies have demonstrated that the SNP rs1544410 in VDR might modulate the risk of breast, skin, and

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 2. Significant variants in Miao compared to the twelve populations determined by Chi-square test.

SNP	Genes	Chi-square test p-value (after Bonferroni correction)											
		Xi'an Han	ASW	CEU	CHB	CHD	GIH	JPT	MEX	MKK	TSI	YRI	LWK
rs1042713	ADRB2	–	1.08E-05	–	3.37E-06	5.00E-07	–	–	–	1.35E-06	–	4.63E-05	4.83E-05
rs1042714	ADRB2	–	–	4.62E-18	7.97E-29	–	–	2.67E-28	–	–	–	1.92E-29	–
rs1045642	ABCB1	–	–	1.02E-10	–	–	2.39E-05	–	–	8.43E-06	–	1.21E-07	–
rs1051266	SLC19A1	–	–	3.05E-08	–	–	–	–	–	9.94E-12	–	2.11E-06	4.12E-08
rs1128503	ABCB1	–	6.40E-14	5.21E-07	–	–	–	–	–	3.60E-25	8.25E-06	1.01E-24	4.72E-23
rs1142345	TPMT	–	1.17E-32	–	–	–	–	–	–	–	–	–	8.35E-39
rs11568820	VDR	–	–	–	–	–	–	–	1.34E-07	9.98E-07	1.01E-07	1.52E-22	9.39E-11
rs1229984	ADH1B	–	–	–	1.35E-11	–	–	2.86E-10	–	–	–	–	–
rs1540339	VDR	–	1.15E-14	3.35E-13	–	–	4.27E-13	–	9.34E-09	1.64E-27	5.39E-13	3.91E-23	1.05E-24
rs1544410	VDR	3.80E-41	9.22E-32	1.44E-27	–	–	1.81E-29	4.34E-39	3.38E-29	2.03E-35	6.31E-28	2.01E-38	9.08E-36
rs1695	GSTP1	–	8.63E-09	–	–	–	2.39E-06	–	4.02E-10	6.13E-08	1.65E-05	5.05E-09	1.46E-14
rs1800497	DRD2	–	–	–	–	–	4.40E-10	–	–	6.38E-07	2.20E-13	–	1.32E-05
rs1801131	MTHFR	–	1.03E-15	3.89E-14	4.97E-18	6.97E-18	1.10E-09	5.32E-20	2.44E-14	1.50E-19	1.10E-12	1.35E-27	2.35E-20
rs1801133	MTHFR	2.75E-07	5.58E-20	9.97E-14	2.44E-05	7.81E-11	4.04E-20	2.99E-10	5.34E-06	2.44E-33	5.93E-06	9.64E-29	5.70E-26
rs1805124	SCN5A	–	1.03E-17	8.80E-28	6.45E-29	2.36E-30	9.16E-26	3.79E-28	3.71E-21	3.48E-22	4.53E-23	2.71E-24	2.47E-21
rs20417	PTGS2	–	–	6.78E-32	–	–	–	–	–	–	–	2.03E-26	–
rs2046934	P2RY12	–	–	6.28E-17	1.85E-18	–	–	6.41E-19	–	–	–	1.95E-20	–
rs2066702	ADH1B	–	2.52E-30	–	–	–	–	–	–	1.26E-52	–	2.09E-40	4.88E-40
rs2066853	AHR	–	–	6.29E-08	–	–	6.25E-13	–	1.60E-08	–	2.07E-14	–	–
rs2239185	VDR	–	–	–	8.08E-11	–	–	8.76E-06	–	–	–	–	–
rs28399454	CYP2A6	–	1.62E-33	–	–	–	–	–	–	–	–	4.13E-46	6.73E-41
rs28399499	CYP2B6	–	–	–	–	–	–	–	–	–	–	7.82E-45	1.50E-41
rs3760091	SULT1A1	5.37E-05	–	–	–	—	–	–	–	–	–	–	–
rs3807375	KCNH2	–	–	3.73E-16	–	–	1.30E-12	–	–	–	2.73E-14	–	–
rs3814055	NR1I2	–	–	3.96E-08	–	–	7.55E-12	–	–	–	5.27E-10	1.15E-05	1.18E-05
rs3815459	KCNH2	–	–	–	–	–	–	–	–	–	–	1.15E-08	–
rs3846662	HMGCR	–	1.11E-06	–	–	–	–	–	–	1.12E-09	–	4.95E-18	1.36E-16
rs4148323	UGT2A	–	–	–	1.54E-19	3.11E-20	1.09E-31	4.60E-23	4.52E-23	–	–	1.58E-28	–
rs4244285	CYP2C19	–	–	9.13E-07	5.07E-10	–	–	1.17E-08	–	–	–	8.56E-17	–
rs4680	COMT	9.20E-21	–	8.99E-07	–	–	3.32E-06	–	–	–	2.48E-07	–	–
rs4986909	CYP3A4	–	–	–	9.66E-39	–	–	3.55E-39	2.29E-30	–	–	2.20E-34	–
rs5219	KCNJ11	2.06E-05	–	–	–	–	–	–	–	–	–	–	–
rs6277	DRD2	–	–	4.12E-21	6.85E-30	–	–	–	–	–	–	–	–
rs689466	PTGS2	–	1.12E-09	–	–	–	2.92E-10	–	–	1.22E-26	6.81E-09	4.29E-16	1.69E-19
rs698	ADH1C	–	2.70E-23	1.14E-21	5.18E-34	1.07E-33	1.93E-28	1.37E-33	5.20E-23	6.93E-38	2.40E-25	1.32E-39	1.45E-31
rs975833	ADH1A	–	–	–	2.11E-15	–	–	1.00E-13	–	–	–	–	–
rs9934438	VKORC1	–	–	1.17E-07	9.85E-34	6.97E-33	–	2.70E-31	1.81E-08	–	2.42E-11	–	–

prostate cancers, as well as other forms [25,26]. One study reported that GA and AA genotypes of rs1544410 were associated with decreased cutaneous malignant melanoma (CMM) risk (odds ratio=0.78 and 0.75, respectively) compared with the GG genotype [26]. We found that the GG genotype frequency of rs1544410 in the Miao is very high, suggesting that the Miao should consider more aggressive screening for CMM.

The VKORC1 (vitamin K epoxide reductase complex, subunit 1) gene encodes the VKORC1 (vitamin K epoxide reductase)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 3. Pairwise Fst values between populations.

Population	Miao	Xi'an Han	ASW	CEU	CHB	CHD	GIH	JPT	LWK	MEX	MKK	TST	YRI
Miao	0.00000												
Xi'an Han	0.03382	0.00000											
ASW	0.20416	0.20827	0.00000										
CEU	0.1826	0.15671	0.13819	0.00000									
CHB	0.02257	0.00211	0.20498	0.15471	0.00000								
CHD	0.01904	0.00747	0.19789	0.14808	-0.0012	0.00000							
GIH	0.18045	0.17073	0.08734	0.02836	0.15889	0.15163	0.00000						
JPT	0.02566	0.01533	0.18516	0.14938	0.00547	0.00582	0.15292	0.00000					
LWK	0.25869	0.27541	0.01665	0.20017	0.26908	0.26468	0.14679	0.24248	0.00000				
MEX	0.13783	0.09328	0.11843	0.02856	0.10109	0.09437	0.05388	0.10439	0.1902	0.00000			
MKK	0.22133	0.23686	0.01934	0.14697	0.22869	0.22481	0.10441	0.19944	0.0145	0.1537	0.00000		
TSI	0.16704	0.13282	0.13316	0.0034	0.12909	0.1282	0.03023	0.12535	0.19757	0.02613	0.14577	0.00000	
YRI	0.26192	0.28092	0.01823	0.21784	0.27486	0.27251	0.15499	0.24575	0.00361	0.20902	0.01936	0.21334	0.00000

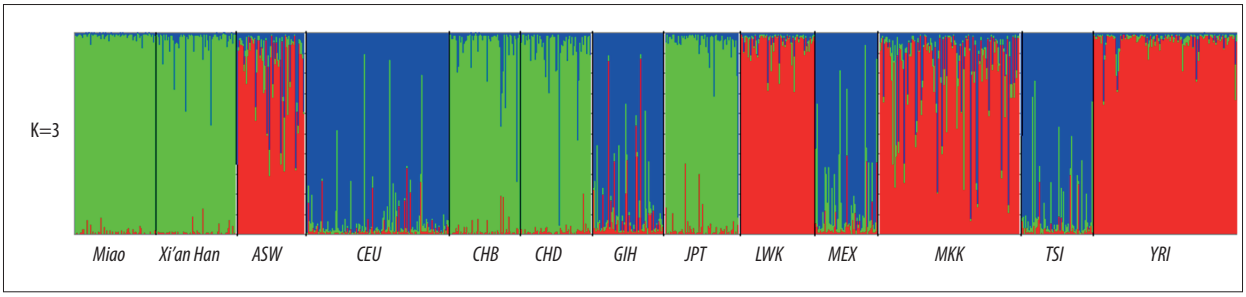

Figure 1. Bayesian clustering of genotypic samples from 13 populations. Each vertical bar denotes an individual and colors denote inferred clusters. Best model at K=3, where the proportion of each ancestral component in a single individual is represented by a vertical bar divided into 3 colors.

protein, which is considered a candidate gene for the variability in warfarin response, mainly including 3 common polymorphisms [27]. The C6484T (rs9934438), or 1173C>T (rs9934438), is a SNP in the first intron of VKORC1, which was the first SNP associated with the low-dose warfarin phenotype [28]. A previous study demonstrated that patients with the 1173T (rs9934438) allele require a lower warfarin dose (mean dose 24–26 mg/week) compared with 35 mg/week for the wild-type carriers [29]. In our study, the frequency of carriers of the allele T of rs9934438 is lower in the Miao population, suggesting that patients in this population will require a lower dose of warfarin.

Our study also demonstrated the correlation between the ethnic groups by Fst calculations and population structure analysis. The Structure plot (Figure 1) showed that the 13 ethnic groups were independently assigned into 3 affinity groups, suggesting they have a homogeneous genetic background. Genetic homogeneity among some populations separated by large geographic distances has been observed in migratory insects [30,31]. Our results are consistent with those findings, which could be explained by the migration theory described by Curry et al. [32].

Despite the current study possessing enough power, some limitations should be considered. First, the sample size of our study was relatively small, which may limit the statistical power. Second, the SNPs tested in our study were not large enough. Therefore, the association between these polymorphisms requires further investigation in a large sample before definitive conclusions can be drawn.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Conclusions

Our results provide the first pharmacogenomics information in the Miao population and illustrate the difference in selected genes between Miao and 12 other populations around the world. These results could be used to create individualized treatment strategies, including appropriate drugs and dosage selections for the Miao ethnic group.

Competing interests

The authors declare that they have no competing interests.

References:

1. Ma Q, Lu AY: Pharmacogenetics, pharmacogenomics, and individualized medicine. Pharmacol Rev, 2011; 63(2): 437–59
2. Marc J, Prezelj J, Komel R, Kocijancic A: VDR genotype and response to etidronate therapy in late postmenopausal women. Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 1999; 10(4): 303–6
3. Kalow W, Tang B, Endrenyi L: Hypothesis: comparisons of inter-and intra-individual variations can substitute for twin studies in drug research. Pharmacogenetics, 1998; 8(4): 283–89
4. Evans WE, McLeod HL: Pharmacogenomics – drug disposition, drug targets, and side effects. N Engl J Med, 2003; 348(6): 538–49
5. Crews KR, Hicks JK, Pui CH et al: Pharmacogenomics and individualized medicine: translating science into practice. Clin Pharmacol Ther, 2012; 92(4): 467–75
6. Whirl-Carrillo M, McDonagh E, Hebert J et al: Pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther, 2012; 92(4): 414–17
7. Sangkuhl K, Berlin DS, Altman RB, Klein TE: PharmGKB: understanding the effects of individual genetic variants. Drug Metab Rev, 2008; 40(4): 539–51
8. Evans WE, Relling MV: Pharmacogenomics: translating functional genomics into rational therapeutics. Science, 1999; 286(5439): 487–91
9. Gan GG, Phipps ME, Lee MM et al: Contribution of VKORC1 and CYP2C9 polymorphisms in the interethnic variability of warfarin dose in Malaysian populations. Ann Hematol, 2011; 90(6): 635–41
10. Gabriel S, Ziaugra L, Tabbaa D: SNP genotyping using the Sequenom MassARRAY iPLEX platform. Curr Protoc Hum Genet, 2009; Chapter 2 :Unit 2.12
11. Thomas RK, Baker AC, DeBiasi RM et al: High-throughput oncogene mutation profiling in human cancer. Nat Genet, 2007; 39(3): 347–51
12. Adamec C: [Example of the use of the nonparametric test. Test X2 for comparison of 2 independent examples.] Cesk Zdrav, 1964; 12: 613–19 [in Czech]
13. Song M-K, Lin F-C, Ward SE, Fine JP: Composite variables: when and how. Nurs Res, 2013; 62(1): 45–49
14. Falush D, Stephens M, Pritchard JK: Inference of population structure using multilocus genotype data: linked *loci* and correlated allele frequencies. Genetics, 2003; 164(4): 1567–87
15. Wright S: The genetical structure of populations. Annals of Eugenics, 1949; 15(1): 323–54
16. Weir BS, Cockerham CC: Estimating F-statistics for the analysis of population structure. Evolution, 1984; 1358–70
17. Roden DM, Altman RB, Benowitz NL et al: Pharmacogenomics: challenges and opportunities. Ann Intern Med, 2006; 145(10): 749–57
18. Li K, Li W, Dong X: Association of 677 C>T (rs1801133) and 1298 A>C (rs1801131) polymorphisms in the MTHFR gene and breast cancer susceptibility: a meta-analysis based on 57 individual studies. PloS One, 2014; 9(6): e71290
19. Teng Z, Wang L, Cai S et al: The 677C> T (rs1801133) polymorphism in the MTHFR gene contributes to colorectal cancer risk: a meta-analysis based on 71 research studies. PloS One, 2013; 8(2): e55332
20. Xu W, Zhang H, Wang F, Wang H: Quantitative assessment of the association between MHTFR C677T (rs1801133, Ala222Val) polymorphism and susceptibility to bladder cancer. Diagn Pathol, 2013; 8: 95
21. Sohn K-J, Croxford R, Yates Z et al: Effect of the methylenetetrahydrofolate reductase C677T polymorphism on chemosensitivity of colon and breast cancer cells to 5-fluorouracil and methotrexate. J Natl Cancer Inst, 2004; 96(2): 134–44
22. Cáliz R, Del Amo J, Balsa A et al: The C677T polymorphism in the MTHFR gene is associated with the toxicity of methotrexate in a Spanish rheumatoid arthritis population. Scand J Rheumatol, 2012; 41(1): 10–14
23. Tworoger SS, Gate MA, Lee I-M et al: Polymorphisms in the vitamin D receptor and risk of ovarian cancer in four studies. Cancer Res, 2009; 69(5): 1885–91
24. Otrock ZK, Mahfouz RA, Charafeddine KM et al: Vitamin D receptor genotypes and response to zoledronic acid therapy in thalassemia-induced osteoporosis. Ann Hematol, 2008; 87(11): 947–48
25. Raimondi S, Johanson H, Maisonneuve P, Gandini S: Review and meta-analysis on vitamin D receptor polymorphisms and cancer risk. Carcinogenesis, 2009; 30(7): 1170–80
26. Gandini S, Raimondi S, Gnagnarella P et al: Vitamin D and skin cancer: a meta-analysis. Eur J Cancer, 2009; 45(4): 634–41
27. Rost S, Fregin A, Ivaskevicius V et al: Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. Nature, 2004; 427(6974): 537–41
28. D'Andrea G, D'Ambrosio RL, Di Perna P et al: A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin. Blood, 2005; 105(2): 645–49
29. Wadelius M, Chen L, Downes K et al: Common VKORC1 and GGCX polymorphisms associated with warfarin dose. Pharmacogenomics J, 2005; 5(4): 262–70
30. Scott KD, Lawrence N, Lange CL et al: Assessing moth migration and population structuring in *Helicoverpa armigera* (*Lepidoptera: Noctuidae*) at the regional scale: example from the Darling Downs, Australia. Journal of Economic Entomology, 2005; 98(6): 2210–19
31. Llewellyn K, Loxdale H, Harrington R et al: Migration and genetic structure of the grain aphid (*Sitobion avenae*) in Britain related to climate and clonal fluctuation as revealed using microsatellites. Mol Ecol, 2003; 12(1): 21–34
32. Curry A: Coming to America. Nature, 2012; 485(7396): 30–32

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]