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ORIGINAL RESEARCH

Prevalence of *CYP2C19* Variants in Patients with Cardiovascular Disease from the Yunnan-Guizhou Plateau in Southwestern China

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Background and Purpose: The CYP2C19 enzyme is essential for activation of the antiplatelet drug clopidogrel. Genetic variations in CYP2C19 are known to influence individual drug responses. Here, differences in *CYP2C19* alleles, genotypes, and phenotypes in patients with cardiovascular disease from the Yunnan-Guizhou Plateau were systematically surveyed to provide a reference for appropriate treatment approaches.

Methods: The *CYP2C19*2, *3*, and **17* variants were determined by RT-qPCR in 1934 patients with cardiovascular disease from 10 different areas of the Yunnan-Guizhou Plateau. Clinical data were analyzed using χ^2 tests.

Results: The proportions of the *CYP2C19*1, *2, *3*, and **17* alleles in the study cohort were 64.94, 29.81, 4.42, and 0.83%, respectively, while the frequencies of nine observed genotypes (**1/*17, *1/*1, *2/*17, *3/*17, *1/*2, *1/*3, *2/*2, *2/*3, *3/*3*) were 1.03, 42.09, 0.57, 0.05, 38.73, 5.95, 8.89, 2.53, and 0.16%, respectively. Four metabolic phenotypes were found in the population, namely, rapid (1.03%), normal (42.09%), intermediate (45.29%), and poor (11.58%) metabolizers. Regional differences in allele and phenotype distribution were observed.

Conclusion: These results represent the first comprehensive profile of *CYP2C19* variants in patients with cardiovascular disease from the Yunnan-Guizhou Plateau, offering a valuable genetic reference for the selection of optimal treatment strategies.

Keywords: plateau, clopidogrel, *CYP2C19*, allele, genotype, phenotype

Introduction

Cardiovascular disease (CVD) contributes markedly to worldwide mortality and disability, especially ischemic heart disease (IHD) and stroke.[1] Clopidogrel, a prescribed antiplatelet drug, blocks adenosine diphosphate-induced platelet aggregation through specific and irreversible binding to the P2Y12 purinergic receptor on platelet surfaces. It is widely used in the treatment of conditions such as acute coronary syndromes, post-percutaneous coronary intervention (PCI) management, and ischemic stroke.[2–4] However, pharmacodynamic responses to the drug vary considerably, with between 4 and 30% of individuals showing poor responses, thus reducing the efficacy of the treatment and raising the likelihood of adverse events.[5] On the other hand, clopidogrel treatment, while preventing thrombus formation, can induce severe bleeding if platelet inhibition is excessive.[6]

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Genetic factors account for approximately 75% of this variability.[7] Cytochrome P450 (CYP) enzymes are members of a large polymorphic superfamily (approximately 57 enzymes in humans) that are responsible for metabolizing >80% of clinical drugs.[8,9] CYP2C19 is the principal enzyme responsible for catalyzing two sequential biotransformation steps essential for clopidogrel bioactivation.[10,11] The genetic polymorphisms thus lead to significant phenotypic variations in CYP2C19 activity and influence the metabolism of clopidogrel.[12] Differences in enzyme activity are used to classify the population into ultrarapid metabolizer (UM), rapid metabolizer (RM), normal metabolizer (NM), intermediate metabolizer (IM), and poor metabolizer (PM). Homozygous *CYP2C19*17* forms (*CYP2C19 *17/*17*) are classified as UM. Individuals carrying normal and a gain-of-function alleles (*CYP2C19 *1/*17*) fall into the RM category, while NM is represented by two normal alleles (*CYP2C19 *1/*1*) and IM represents a normal and a non-functional allele or a non-functional and a gain-of-function allele (*CYP2C19*1/*2, CYP2C19*1/*3, CYP2C19*2/*17, CYP2C19*3/*17*). The presence of two non-functional alleles (*CYP2C19*2/*3, CYP2C19*2/*2, CYP2C19*3/*3*) represents PM.[13] The Pharmacogenetic Variation Consortium (PharmVar) recognizes 39 different *CYP2C19* alleles, of which *CYP2C19*1, *2, *3*, and **17* are the most clinically relevant.[14] *CYP2C19*2* and**3* are loss-of-function alleles that impair the enzyme's ability to convert clopidogrel to its active metabolite, resulting in an increased risk of cardiovascular events.[15] However, the gain-of-function allele, *CYP2C19*17*, enhances responsiveness to clopidogrel by enhancing the transcriptional activity of CYP2C19 substrates, increasing the risk of bleeding. The US Food and Drug Administration (FDA) advises the identification of individuals with genotypic variants affecting clopidogrel metabolism to modify their treatment strategies.[16] There is marked variability in *CYP2C19* polymorphisms among different ethnic groups and geographical regions.[17]

The Yunnan-Guizhou Plateau in Southwest China, characterized by an average elevation exceeding 2,000 meters and home to several ethnic minorities (eg, the Yi, Miao, and Hui peoples), is predisposed to distinctive pharmacogenetic profiles due to high altitude, resulting in hypoxic conditions and intense ultraviolet radiation, together with the diverse genetic backgrounds of its multiethnic populations. Although there have been numerous reports on *CYP2C19* polymorphisms in various parts of China, to date, nothing is known about *CYP2C19* polymorphisms in the Yunnan-Guizhou Plateau. Here, the proportions of the *CYP2C19**2, *CYP2C19**3, and *CYP2C19**17 variants were assessed in the Yunnan-Guizhou Plateau population for the prediction of metabolizer phenotypes as a reference for drug therapy.

Materials and Methods

Subjects

Overall, 2065 unrelated patients who had undergone genetic screening for *CYP2C19* variants in the Kunming Medical University Affiliated Qujing Hospital between April 2017 and April 2023 were selected. Of these, after the exclusion of individuals who had not been born in the Yunnan-Guizhou Plateau region or whose birthplace was unknown, 1934 (741 female and 1193 male) aged on average 64 years (range, 19–95) were enrolled. These patients were from 10 different areas of the Yunnan-Guizhou Plateau (Qilin, Zhanyi, Malong, Xuanwei, Fuyuan, Luliang, Huize, Luoping, Shizong, and Guizhou). The research protocol conformed to the guidelines outlined in the Declaration of Helsinki. The study was approved by the ethics committee of the First People's Hospital of Qujing (No. 20170223.01). All participants provided written informed consent.

DNA Extraction

Genomic DNA was extracted from 3 mL of blood in ethylene diamine tetraacetic acid tubes with a TIANamp Blood DNA Kit (Tiangen Biotech Co., Ltd., Beijing, China), as directed.

CYP2C19 Allele Testing

The presence of the *CYP2C19*2, CYP2C19*3*, and *CYP2C19*17* alleles was examined using a Human *CYP2C19* Gene Detection Kit (Youzhiyou Co., Ltd., Wuhan, China), based on a PCR fluorescence probe method. The kit included three PCR reactions corresponding to the *CYP2C19*2, *3*, and **17* alleles with each reaction solution containing FAM-labeled wild-type, VIC-labeled mutant, and ROX-labeled internal standard probes. Two microliters of sample DNA, positive and negative controls, were mixed in a 20μL reaction solution. Amplification and fluorescence analysis was performed on

a Bio-Rad CFX96 Real-Time System. The cycling conditions were UNG digestion at 37°C for 10 min, predenaturation for 5 min at 95°C, 40 denaturation cycles at 95°C for 15 seconds, and extension at 62°C for 60 seconds. The fluorescence signals were collected during the extension phase of the PCR cycle.

When the FAM channel showed an amplification curve, but the VIC did not, the genotype was recorded as wild homozygous. When amplification curves were observed in both channels, the genotype was described as heterozygous, and when only the VIC channel showed an amplification curve, the genotype was recorded and homozygous mutant.

Statistical Analysis

Excel and IBM SPSS Statistics 23.0 were used for data analyses. Differences in allele and genotype frequencies among the different areas and different populations were examined with chi-square tests with $p < 0.05$ considered significant. The Hardy-Weinberg equilibrium for the alleles was assessed using chi-square tests.

Results

The proportions of the *CYP2C19*1, *2, *3*, and **17* alleles in the Yunnan-Guizhou Plateau were observed to be in Hardy-Weinberg equilibrium with no marked differences in observed and expected values ($p>0.05$) nor between male and female participants ($p>0.05$).

Allele Frequencies

The proportions of *CYP2C19*1, CYP2C19*2, CYP2C19*3*, and *CYP2C19*17* in the study cohort were 64.94, 29.81, 4.42, and 0.83%, respectively. The distributions in the allele proportions in Qilin, Zhanyi, Malong, Xuanwei, Fuyuan, Luliang, Huize, Luoping, Shizong, and Guizhou are summarized in Table 1. The frequency of *CYP2C19*1* in Luliang was significantly greater than in Malong ($p=0.00$, $\chi^2=14.865$) while that of *CYP2C19*1* frequency was markedly greater in Zhanyi relative to Malong ($p=0.026$, $\chi^2=4.935$) and Huize ($p=0.022$, $\chi^2=5.245$), and *CYP2C19*2* was lower in Zhanyi than in Malong ($p=0.035$, $\chi^2=4.428$) and Huize ($p=0.006$, $\chi^2=7.423$). The *CYP2C19*3* frequencies in the 10 areas were essentially similar ($p>0.05$, χ^2test). *CYP2C19*17* was not found in Luoping, and its frequency in Malong was significantly greater than that in Qilin ($p=0.032$, $\chi^2=4.640$), Zhanyi ($p=0.009$, $\chi^2=6.821$), Xuanwei ($p=0.039$, $\chi^2=4.244$), and Fuyuan ($p=0.012$, $\chi^2=6.328$). This comprehensive analysis revealed pronounced regional heterogeneity in *CYP2C19* allele frequencies across the Yunnan-Guizhou Plateau. These findings address the paucity of *CYP2C19* genetic data in the high-altitude populations of southwestern China. The frequency of *CYP2C19*17* (0.83%) is the lowest reported among East Asian populations to date, emphasizing its unique pharmacogenomic profile in the Yunnan-Guizhou Plateau cohort.

Genotype Frequencies and Metabolic Phenotypes

Nine different genotypes were identified. These were **1/*17* (20, 1.03%), **1/*1* (814, 42.09%), **2/*17* (11, 0.57%), **3/*17* (1, 0.05%), **1/*2* (749, 38.73%), **1/*3* (115, 5.95%), **2/*2* (172, 8.89%), **2/*3* (49, 2.53%), and **3/*3* (3, 0.16%), respectively. The distribution of these genotypes in different regions of the Yunnan-Guizhou Plateau is shown in Figure 1. *CYP2C19*1/*17* was not observed in Zhanyi and Luoping. *CYP2C19*1/*1* was higher in Qilin ($p=0.043$, $\chi^2=4.076$), Zhanyi ($p=0.029$, $\chi^2=4.792$), Xuanwei ($p=0.038$, $\chi^2=4.290$), Fuyuan ($p=0.047$, $\chi^2=3.955$), and Luliang ($p=0.022$, $\chi^2=5.216$) compared with Huize. The frequency of *CYP2C19*1/*3* in Zhanyi was greater than that in Qilin ($p=0.016$, $\chi^2=5.794$), Xuanwei ($p=0.048$, $\chi^2=3.895$), and Luliang ($p=0.047$, $\chi^2=3.929$), while *CYP2C19*3/*17* was only found in Qilin. The *CYP2C19*2/*2* frequency was greater in Xuanwei ($p=0.024$, $\chi^2=5.111$), and Luliang ($p=0.044$, $\chi^2=4.057$) compared with that in Zhanyi, while *CYP2C19*3/*3* was only found in Qilin and Fuyuan.

The metabolic phenotypes identified were RM (1.03%), NM (42.09%), IM (45.29%), and PM (11.58%) in the overall cohort, and UM was not found. The results for the different areas are shown in Figure 2. RM was not observed in either Zhanyi or Luoping, while the proportion of PM in Shizong was far higher than that seen in Zhanyi ($p=0.046$, Fisher's exact test). The combined prevalence of PM and IM was 56.87% in the overall cohort, with Huize demonstrating a markedly elevated proportion of 69.12%. These results underscore the importance of region-specific pharmacogenetic screening to tailor antiplatelet therapy regimens in geographically diverse populations, particularly among multiethnic communities residing in the Yunnan-Guizhou Plateau.

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Table 1 CYP2C19 Allele Distributions in the Yunnan-Guizhou Plateau

Alleles	Qilin	Zhanyi	Malong	Xuanwei	Fuyuan	Luliang	Huize	Luoping	Shizong	Guizhou	Total
	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)
*1	952 65.12 (62.67–67.56)	282 68.12 (63.61–72.62)	118 59.00 (52.12–65.88)	358 64.39 (60.40–68.38)	328 66.13 (61.95–70.31)	164 66.67 (60.73–72.60)	78 57.35 (48.93–65.77)	100 64.10 (56.49–71.71)	54 61.36 (50.99–71.74)	78 68.42 (59.76–77.08)	2512 64.94 (63.44–66.45)
*2	434 29.69 (27.34–32.03)	105 25.36 (21.15–29.57)	67 33.50 (26.90–40.10)	172 30.94 (27.08–34.79)	144 29.03 (25.02–33.04)	74 30.08 (24.31–35.85)	51 37.50 (29.26–45.74)	48 30.77 (23.45–38.09)	27 30.68 (20.85–40.51)	31 27.19 (18.90–35.49)	1153 29.81 (28.37–31.25)
*3	62 4.24 (3.21–5.27)	26 6.28 (3.93–8.63)	9 4.50 (1.60–7.40)	22 3.96 (2.33–5.58)	22 4.44 (2.62–6.25)	7 2.85 (0.75–4.94)	6 4.41 (0.92–7.91)	8 5.13 (1.63–8.63)	5 5.68 (0.75–10.61)	4 3.51 (0.08–6.94)	171 4.42 (3.77–5.07)
*17	14 0.96 (0.46–1.46)	1 0.24 (−0.23–0.72)	6 3.00 (0.62–5.38)	4 0.72 (0.01–1.42)	2 0.40 (−0.16–0.96)	1 0.41 (−0.39–1.21)	1 0.74 (−0.74–2.19)	ND	2 2.27 (−0.90–5.45)	1 0.88 (−0.86–2.62)	32 0.83 (0.54–1.11)

Abbreviations: N, number; F, frequency; CI, confidence interval; ND, not detected.

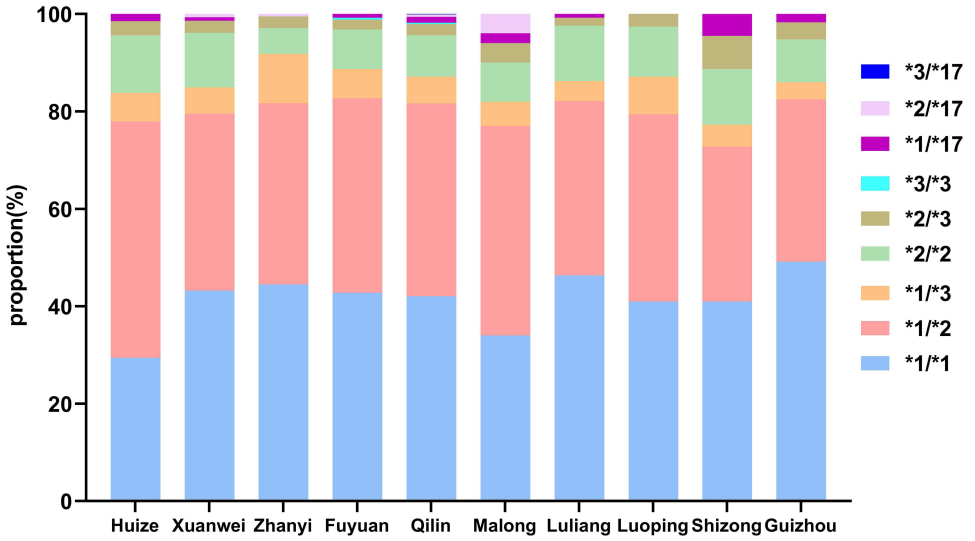

Figure 1 Distribution of CYP2C19 genotype frequencies in different areas of the Yunnan-Guizhou Plateau.

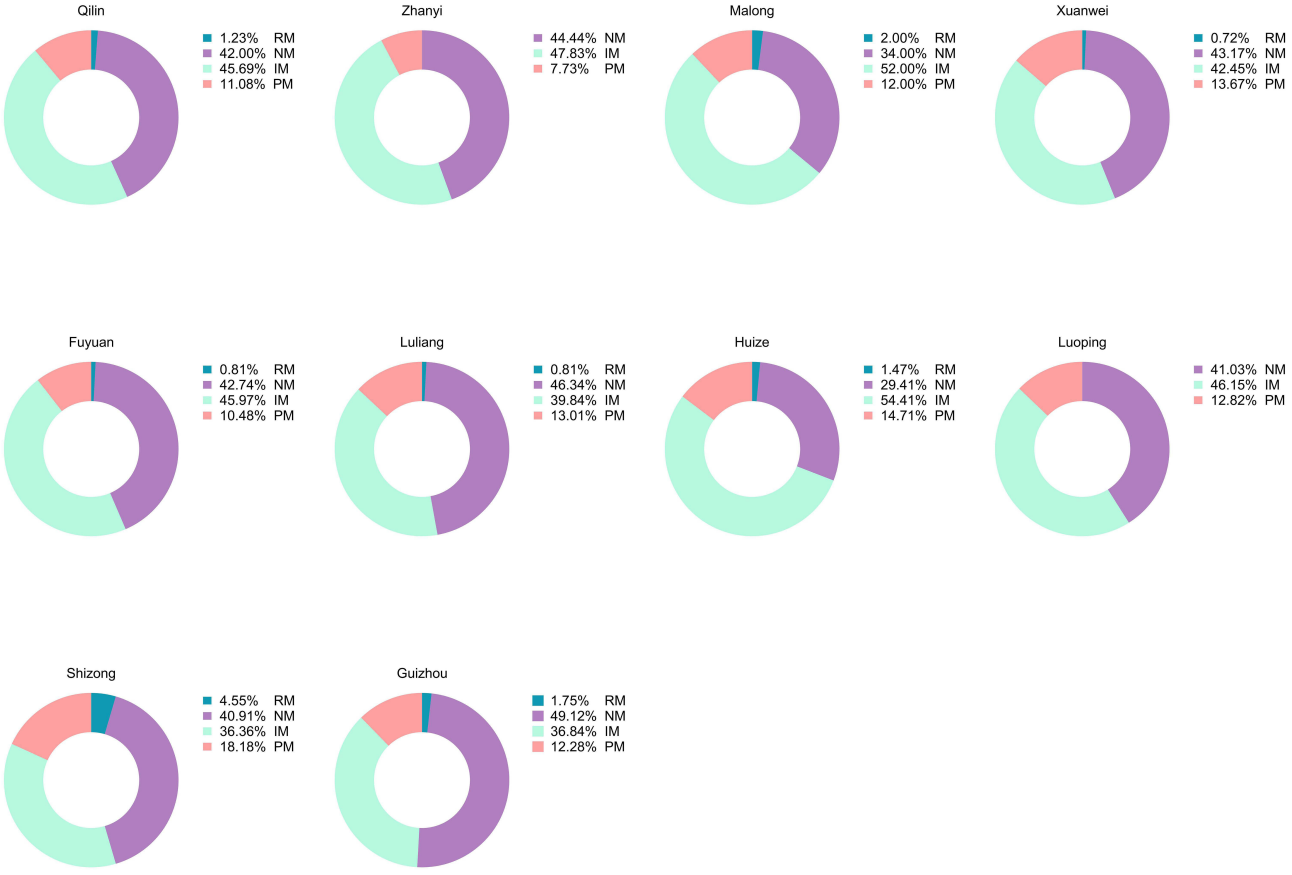

Figure 2 Comparisons of metabolic phenotypes identified in different areas of the Yunnan-Guizhou Plateau.

Discussion

CYP2C19 polymorphisms have a significant influence of the therapeutic efficacy of clopidogrel due to altered metabolic activation, increasing the susceptibility to bleeding. *CYP2C19* polymorphisms differ across ethnicities and regions. Although many studies have been conducted on *CYP2C19* alleles, genotypes, and predicted metabolism phenotypes in various

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populations around the world, there is no available information on *CYP2C19* polymorphisms in the Yunnan-Guizhou Plateau population. Thus, the present results fill a gap in the pharmacogenomic data of high-altitude, multi-ethnic populations, and suggest the importance of appropriate antiplatelet therapy strategies for patients with cardiovascular disease within this unique ethnogeographical context.

Here, 4 *CYP2C19* alleles were investigated and 9 genotypes were identified. The proportions of the *CYP2C19* alleles in individuals of different ethnicities are shown in Table 2. It has been found that *CYP2C19*1* proportions are lower in Asia compared to Caucasian and African populations, with India showing only 42%. The *CYP2C19**2 allele was more common in Asians (11.2–40.2%),[18–31] with the lowest frequency seen in Caucasians (8.7–20.5%).[32–37] The *CYP2C19**2 proportion found here was markedly greater ($p<0.05$) than the proportions documented in African, Caucasian, and some Asian populations (ie, Iranian, Saudi Arabian).[38,39] The present data on the *CYP2C19**2 allele approximate those of other Asian populations.[18–20,23,24,26–28] *CYP2C19*3* is uncommon in individuals of Caucasian and African origin (0.04% and 0.037%, respectively) but is more common in Asians (2–9%).[40–42] The observed frequency of this allele (4.42%) was significantly lower than that reported in the low-altitude Foshan cohort ($p<0.05$), highlighting altitude-related differences in the distribution of *CYP2C19* polymorphisms. *CYP2C19*2* and *CYP2C19*3* are both associated with loss-of-function, and account for over 90% of functionally deficient *CYP2C19* alleles. The *CYP2C19*2* mutation (rs4244285, c.681G > A), situated in the coding region of exon 5, results in a cryptic splice site that leads to a shift in the mRNA reading frame

Table 2 Comparison of CYP2C19 Alleles Among Different Populations

Populations	Sample Size	Allele Frequency (%)				References
		*1	*2	*3	*17	
Yunnan-Guizhou Plateau	1934	64.94	29.81	4.42	0.83	Present study
Chinese Ningxia	1050	63.2	31.7	4.5	2.1**	[18]
Chinese Foshan	1231	63.89	30.46	5.65*	_	[19]
Chinese Hakka	2982	64.2	30.8	5.0	_	[20]
Chinese Han	831	64.0	30.0	5.0	1.0	[21]
Chinese Hui	85	60.6	30.6	5.9	2.9*	[21]
Chinese Uygur	352	61.2	22.0**	3.1	13.6**	[21]
Chinese Kazakh	69	63.8	18.8*	6.5	10.9**	[21]
Chinese Mongolian	280	72.0*	24.0**	4.0	_	[22]
Korean	271	60.0*	28.4	10.1**	1.5	[23]
Japanese	265	57.9*	27.9	12.8*	1.3	[24]
Vietnamese	100	76.0*	20.5*	2.5	1.0	[25]
Thai	1051	63.0	27.0	6.0*	4.0**	[26]
Malaysian	142	66.0	28.0	6.0	_	[27]
Burmese	127	66.0	30.0	4.0	_	[28]
Indian	87	42.0**	40.2*	0	17.9**	[29]
Iranian	180	65.3	13.1**	0	21.6**	[30]
Saudi Arabian	201	62.9	11.2**	_	25.7**	[31]
Caucasians						
Mexican Americans	346	90.2**	9.7**	0.1**	_	[32]
Italian	360	88.9**	11.1**	0	_	[33]
Colombian	189	91.3**	8.7**	0	_	[34]
Roma	500	79.5**	20.5**	0	_	[35]
Hungarian	370	87.4**	12.6**	0	_	[35]
Faroese	311	81.8**	18.8**	0	_	[36]
Belgian	121	90.9**	9.1**	0	_	[37]
Africans						
Bantu Tanzanians	251	81.5**	17.9**	0.6**	_	[38]
Venda	76	78.3*	21.7	0	_	[39]
Zimbabwean	84	86.9**	13.1**	0	_	[39]

Notes: *p <0.05; **p<0.01; -: not reported.

and yields a catalytically inactive truncated protein lacking the heme-binding region.[43] The *CYP2C19*3* mutation (rs4986893, c.636G > A) in exon 4 creates a stop codon at residue 212, resulting in a truncated and inactive protein.[44] Loss-of-function variants are linked to marked reductions in clopidogrel effectiveness.[45] The allele frequencies in our cohort were similar to those observed in Chinese Han populations ($p>0.05$).

Unlike *CYP2C19*2* and *3, the *CYP2C19*17* proportions are extremely low in East Asia (2%) while being most common (33%) in Central Europe,[9] with 25.7% in Saudi Arabia,[31] 18.2% in Africa, and 15.8% in Caucasians.[46] The frequency of *CYP2C19*17* in the present cohort was only 0.83%, lower than that in other East Asian populations. The *CYP2C19*17* variant (rs12248560, c. −806C>T), discovered by Sim et al in 2006, occurs in the 5′-flanking region of the promoter and enhances transcription.[47] This mutation increases the metabolism of *CYP2C19* substrates, leading to excessive platelet inhibition and an elevated risk of bleeding.[48] The remarkably low frequency of the *CYP2C19*17* allele (0.83%) in this population is a potential reflection of evolutionary adaptation to the hypoxic conditions of high-altitude environments. These results further underscore the necessity of region-specific pharmacogenomic studies.

CYP2C19 genetic polymorphisms have marked effects on the therapeutic effectiveness of clopidogrel, and predicting phenotypes by the identification of *CYP* polymorphisms is helpful in clinical practice. The metabolic phenotypes identified here were largely IM, with the identified proportions of RM, NM, IM, and PM being 1.03, 42.09, 45.29, and 11.58%, respectively, and resembling those documented in Chinese Han populations.[21] The proportion of *CYP2C19* RM found here was lower than that found for African American (23.74%), Americans (13.64%), Central/South Asians (18.57%), and Europeans (27.12%), as listed in the PharmGKB data. However, the proportions of poor metabolizers in the study population were higher than those reported in African Americans (4.05%), Americans (1.48%), and Europeans (2.38%).[11] The distribution of the metabolic phenotypes was also found to vary across different areas. The frequency of PM in Shizong in the south was far higher than that seen in Zhanyi in the north of the Yunnan-Guizhou Plateau, while the proportion of RM in Shizong was observed to be the highest overall, but this phenotype was not found in Zhanyi in the north. The reason for these differences may be due to inter-ethnic genetic diversity, in addition to geographical distance. People living in Zhanyi belong to the Han, Yi, and Hui ethnic groups with some small ethnic settlements, while 35 ethnic minorities live together in the Shizong region. Further evidence is needed to confirm this speculation. Studies have demonstrated that poor metabolism is associated with reduced levels of active clopidogrel, while ultrarapid metabolizers have an increased likelihood of bleeding. Both clinical ineffectiveness and bleeding risk are serious issues in the use of clopidogrel. The high prevalence of IM and PM in this region (56.87%) emphasizes the need for genotype-guided antiplatelet strategies. In areas where *CYP2C19* genotyping is unavailable, alternative therapies that are independent of *CYP2C19* metabolism should be prioritized to reduce the incidence of thrombotic events.

There are also some limitations to our study. First, due to limitations in research conditions, the sample sizes were small in several remote areas. Second, this study primarily characterized *CYP2C19* polymorphisms in the Yunnan-Guizhou Plateau region, and we did not investigate clinical treatment outcomes in relation to phenotype. Finally, further studies with large sample sizes are needed to investigate *CYP2C19* polymorphisms among different ethnic groups.

Conclusion

In summary, this study investigated the frequency distributions of *CYP2C19* alleles in patients with cardiovascular disease from the Yunnan-Guizhou Plateau using a large-scale cohort of 1,934 individuals, providing the first comprehensive pharmacogenomic profile for this high-altitude, multi-ethnic population. Significant regional heterogeneity was observed in the prevalence of *CYP2C19* alleles, genotypes, and metabolic phenotypes across the plateau. The proportions of alleles and phenotypes were comparable to those of Chinese Han populations. These results provide a theoretical basis for the selection of appropriate treatment strategies to reduce the risk of adverse cardiovascular events.

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Disclosure

The authors report no conflicts of interest in this work.

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