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CYP2C19, PON1, and ABCB1 gene polymorphisms in Han and Uygur populations with coronary artery disease in Northwestern Xinjiang, China, From 2014 Through 2019

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Abstract

The morbidity of coronary artery disease (CAD) in the Uygur population of Xinjiang was much higher than the national average. Clopidogrel is the most commonly used medication worldwide in dual antiplatelet therapy for CAD, and the response of clopidogrel is affected by *CYP2C19*, *PON1*, and *ABCB1* genetic polymorphisms. The distribution of *CYP2C19*17*, *ABCB1*, and *PON1* genetic polymorphisms in Han and Uygur populations with CAD of Xinjiang has not been investigated.

This study aimed to investigate the frequencies of *CYP2C19*, *PON1*, and *ABCB1* genetic polymorphisms, and to identify the metabolizer phenotype of *CYP2C19* in Han and Uygur populations with CAD in Northwestern Xinjiang, China. We identified 602 Han and 527 Uygur patients from 2014 through 2019 and studied genotypes for selected allele polymorphisms using sequencing by hybridization.

There were significantly different allele frequencies and genotype frequencies between the 2 ethnic groups in terms of *CYP2C19*2, *3, *17*, *ABCB1* and *PON1*, ($P < .05$). For *CYP2C19*17*, the frequency of *TT* genotype was 2.5% in Uygur patients, but it was undetectable in Han patients. In both the intermediate and poor metabolizer groups, the genotypes polymorphisms *CYP2C19*2, *3, *17* were significantly less common in Uygur patients than in Han patients ($P < .001$). By contrast, the proportion of ultra-metabolizers as defined by *CYP2C19*2, *3, *17* polymorphisms significantly higher in Uygur patients (18.6%) than in Han patients (1.7%, $P < .001$). The *CYP2C19*2* frequency was significantly different between Han patients and Han healthy groups ($P < .001$), while the *CYP2C19*3* frequency was significantly different between Uygur patients and Uygur healthy groups ($P < .001$).

Our study supports the notion of interethnic differences in terms of *CYP2C19*, *PON1*, and *ABCB1* polymorphisms and *CYP2C19* genotype-defined clopidogrel metabolic groups. These finding could provide valuable data and insights into personalized CAD treatment for the Uygur and Han populations in Xinjiang.

Abbreviations: CAD = coronary artery disease, EMs = extensive metabolizers, IMs = intermediate metabolizers, PMs = poor metabolizers, UMs = ultra-metabolizers.

Keywords: *ABCB1*, *CYP2C19*, ethnicity, polymorphisms, *PON1*

1. Introduction

Coronary artery disease (CAD) is emerging as the major cause of mortality in China. CAD has both genetic and environmental components.[1] The Uygur populations live primarily in the Xinjiang autonomous region, encompassing vast territory in a multi-ethnic province in Northwest China.[2] By 2011, the Uygur population had reached 10,069,347 (6th population survey of China, 2011). In 2012, the morbidity of CAD in the Uygur population of Xinjiang was 24.2%, much higher than the national average (7.2%).[3]

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TW and TZ contributed equally to this work and should be considered co-first authors.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Clopidogrel is the most commonly used medication worldwide in dual antiplatelet therapy for CAD. It is employed as therapy for acute coronary syndrome, emergency or elective percutaneous intervention, angina pectoris, myocardial infarction, and stable coronary heart disease. Gene polymorphisms associated with clopidogrel resistance, and known genes that affect clopidogrel response, include *CYP2C19, ABCB1*, and *PON1*.[4–6]

Clopidogrel is an orally-administered prodrug that requires biotransformation into its active antiplatelet form by hepatic cytochrome p450 (*CYP*) isoenzymes. Polymorphisms of the *CYP2C19* gene have been identified to be strong predictors of clopidogrel resistance.[7] Patients with loss-of-function allele variants (*CYP2C19*2* and *CYP2C19*3*) are at risk for thromboembolic events.[8] The *CYP2C19* gain-of-function allele (**17*) is associated with increased catalytic activity.[7]*ABCB1* encodes an efflux transporter p-glycoprotein expressed in the intestine that modulates clopidogrel absorption. *PON1* encodes the enzyme paraoxonase-1 that participates in the esterification of clopidogrel and its subsequent inactivation.[9]

The distribution of *CYP2C19*17*, *ABCB1*, and *PON1* genetic polymorphisms in Han and Uygur populations with CAD of Xinjiang has not been investigated. Early detection for purposes of preventing CAD progression in Xinjiang populations is important. The primary aims of our study were to evaluate the frequencies of *CYP2C19*, *PON1*, and *ABCB1* polymorphisms and to identify the *CYP2C19* genotype-defined clopidogrel metabolic groups in these 2 ethnic groups. The goal was to develop individualized medication guides for patients with CAD in Uygur and Han populations in Xinjiang.

2. Materials and methods

2.1. Study population

From July 5, 2014, to August 31, 2019, we identified 1129 patients (527 Uygur, 602 Han) at People's Hospital of Xinjiang Uygur Autonomous Region. Of the 527 Uygur patients, the mean age was 57.3 ± 9.4 years (range: 27–79 years), and 424 (80.5%) were male. Of the 602 Han patients, the mean age was 59.6 ± 10.2 years (range: 23–80 years), and 487 (80.9%) were male.

Consecutive patients were assessed based on the following inclusion criteria:

(1) age >18 years;
(2) diagnosis of CAD;
(3) planned treatment with clopidogrel: patients with either acute coronary syndrome or undergoing percutaneous intervention were allowed to receive clopidogrel at a 300 mg oral loading dose and then to continue at 75 mg once daily;
(4) no contraindications to clopidogrel;
(5) living in the Xinjiang province of China;
(6) no history of intermarriage with other ethnic groups within 3 generations.

2.2. Ethical approval of the study protocol

The purpose and experimental procedures of the study were explained to all patients, who gave informed written consent prior to the study. All patients explicitly provided permission for genotyping as well as for collection of relevant clinical data. The study was conducted according to the standards of the Declaration of Helsinki and was approved by The Ethics Committees of People's Hospital of Xinjiang Uygur Autonomous Region (Urumqi, China).

2.3. Blood sampling

Blood samples were obtained from a peripheral vein and were collected in 4 mL vacuum tubes containing EDTA (BD). Samples were stored at -20°C until analysis.

2.4. Genotyping

Genomic DNA was extracted from whole blood samples using the Puregene Blood Core Kit (Huaxia Times, China). *CYP2C19*2 (681G>A, rs4244285)*, *CYP2C19*3 (636G>A, rs4986893)*, *CYP2C19*17 (−806C>T, rs12248560)*, *ABCB1 (3435C>T, rs1045642)*, and *PON1 (Q192R, rs662)* were genotyped according to the manufacturer's instructions using sequencing by hybridization (Realtime qPCR, Xi'an Tianlong Science & Technology Co Ltd, China).

2.5. CYP2C19 genotype-defined clopidogrel metabolic groups

Patients were categorized by genotype-defined clopidogrel metabolic groups based on *CYP2C19*2, *3*, and **17* genotypes, according to the Dutch Pharmacogenetics Working Group guidelines for clopidogrel and *CYP2C19*. Patients with at least 1 *CYP2C19*2* or *CYP2C19*3* allele variant were classified as loss-of-function allele carriers. Those with at least 2 *CYP2C19*2* or *CYP2C19*3* allele variants (**2/*2*, **2/*3*, or **3/*3*) were classified as poor metabolizers (PMs). Patients with 1 *CYP2C19*2* or *CYP2C19*3* allele variant (**1/*2*,**1/*3*), or 1 *CYP2C19*17* allele variant with 1 (**2* or **3*) allele variant (**2/*17* or **3/*17*) were classified as intermediate metabolizers (IMs). Patients without a **2*, **3*, or **17* allele variant (**1/*1*) were classified as extensive metabolizers (EMs). Patients with at least 1 **17* allele variant (**1/*17* or **17/*17*) were classified as ultra-metabolizers (UMs).

2.6. Statistical analysis

The chi-square test was used for comparative analysis of the allele and genotype frequencies for the *CYP2C19*, *ABCB1*, and *PON1* polymorphisms. We also analyzed the the *CYP2C19* genotype-defined clopidogrel metabolic groups frequency in Han and Uygur populations with CAD. The correspondence of the distribution of the genotype frequencies to the Hardy-Weinberg equilibrium was conducted using the Chi-square test. 95% confidence intervals and other statistical analyses were carried out using the SPSS 19.0 (version 4.0.100.1124, SPSS Inc). $P < .05$ was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics

Patients included in this study were more likely to have complications such as diabetes, hypertension, dyslipidemia and cerebrovascular disease. The body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) were 28.0 ± 3.6 in Uygur patients and 26.1 ± 3.2 in Han patients. In addition to clopidogrel, some patients also received antihypertensive agents (metoprolol, bisoprolol, captopril, benazepril,

Table 1

Demographic and clinical characteristics of the study patients in 2 ethnic groups.

demographic characteristics	Uygur N = 527	Han N = 602
Age (yr, mean ± SD)	57.3 ± 9.4	59.6 ± 10.2
Male sex, N%	424 (80.5)	487 (80.9%)
BMI (kg/m^2, mean ± SD)	28.0 ± 3.6	26.1 ± 3.2
comorbidities, N%		
Hypertension	359 (68.1)	395 (65.6)
Diabetes	203 (38.5)	224 (37.2)
Dyslipidemia	348 (66.0)	393 (65.3)
Cerebrovascular disease	48 (9.1)	67 (11.10)
pharmacological treatments, N%		
Antihypertensive agents	440 (83.5)	487 (80.1)
Antidiabetes agents	198 (37.6)	199 (33.1)
Lipid-lowering agents	498 (94.5)	534 (88.7)

BMI = body mass index, SD = standard deviation.

fosinopril, losartan potassium, irbesartan, valsartan amlodipine, nifedipine, amlodipine besylate and hypoglycemic), antidiabetes agents (Glimepiride, donepezil, acarbose, metformin, linagliptin, repaglinide, insulin) and lipid-lowering agents (atorvastatin, rosuvastatin, pravastatin, simvastatin, ezemeb). All results are displayed in Table 1.

3.2. Hardy-Weinberg equilibrium analysis

Distributions of allelic frequencies of the 4 single nucleotide polymorphisms (SNPs) were all in Hardy-Weinberg equilibrium in both ethnic groups ($P > .05$), except that of the *ABCB1 (3435C>T, rs1045642)* ($P < .05$) in Uygur patients.

3.3. The CYP2C19 allele and genotype frequency

For the *CYP2C19*2* polymorphism, Uygur patients had a lower *AA* genotype frequency 5.5% (3.6, 7.4) and lower *GA* genotype frequency 30.4% (26.5, 34.3) than did the Han patients: 11.3% (8.8, 13.8) and 42.2% (38.3, 46.1), respectively ($P < .001$). The allele frequencies of the *A* alleles were 20.7%(18.3, 23.1) in Uygur patients and 32.4%(29.8, 35.0) in Han patients, the difference was significant ($P < .001$).

For the *CYP2C19*3* polymorphism, the *AA* genotype was not present in any of the patients recruited in this study. The *GG* and *GA* genotype frequencies were 92.8% (90.6, 95.0) and 7.2% (5.0, 9.4) in Uygur patients, respectively. In Han patients, the frequencies were 8.0% (85.4, 90.6) and 12.0% (9.4, 14.6), respectively. There were significantly different allele and genotype frequencies between the 2 ethnic groups ($P < .01$).

Table 2

Allele and genotype frequencies of *CYP2C19* in 2 ethnic groups.

Polymorphisms	Han patients (N = 602) N, N% (95% CI)	Uygur patients (N = 527) N, N% (95% CI)	*P* value
CYP2C19*2			
GG	280/ 46.5 (42.5, 50.5)	338 /64.1 (60.0, 68.2)	< .001
GA	254/42.2 (38.3, 46.1)	160/ 30.4 (26.5, 34.3)	
AA	68/11.3 (8.8, 13.8)	29 /5.5 (3.6, 7.4)	
A allele	390/32.4 (29.8, 35.0)	218/20.7 (18.3, 23.1)	< .001
G allele	814/67.6 (65.0, 70.2)	836/79.3 (62.0, 69.8)	
CYP2C19*3			
GG	530/88.0 (85.4, 90.6)	489/92.8 (90.6, 95.0)	.007
GA	72/12.0 (9.4, 14.6)	38/ 7.2 (5.0, 9.4)	
AA	/	/	
A allele	72/6.0 (4.7, 7.3)	38/3.6 (2.5, 4.7)	.009
G allele	1132/94.0 (92.7, 95.3)	1016/96.4 (95.3, 97.5)	
CYP2C19*17			
CC	579/96.2 (94.7, 97.7)	407/77.2 (73.6, 80.8)	< .001
CT	23/3.8 (2.3, 5.3)	107/20.3 (16.9, 23.7)	
TT	/	13/2.5 (1.2, 3.8)	
T allele	23/1.9 (1.1, 2.7)	133/12.6 (10.6, 14.6)	< .001
C allele	1181/98.1 (97.3, 98.9)	921/87.4 (85.4,89.4)	

95% CI = 95% confidence intervals.

The frequency of the *CYP2C19*17 CT* genotype was significantly higher in Uygur patients 20.3% (16.9, 23.7) than in Han patients 3.8% (2.3, 5.3), ($P < .001$). The frequency of the *TT* genotype was 2.5% (1.2, 3.8) in Uygur patients, but *TT* was not detected among Han patients. The allele frequency of the *T* alleles was 12.6% (10.6, 14.6) in Uygur patients, significantly higher than those of Han patients 1.9% (1.1, 2.7), ($P < .001$). All results are displayed in Table 2.

3.4. Frequencies of the CYP2C19 genotype-defined clopidogrel metabolic groups distribution according to 2 ethnic groups

Based on the *CYP2C19* genetic polymorphism, the metabolic groups were classified into 4 groups: EMs, IMs, PMs, and UMs. The frequencies of EMs among Han and Uygur patients were 37.7% (33.8, 41.6) and 40.6% (36.4, 44.8), the difference was not significant ($P = .319$). The IMs in the Han and Uygur patients occurred at 45.2% (41.2, 49.2) and 34.0% (30.0, 38.0), respectively. The frequencies of PMs within the Han and Uygur patients were 15.4% (12.5, 18.3) and 6.8% (4.7, 8.9), respectively. Both the IMs and PMs were significantly lower in Uygur patients than in Han Uygur patients ($P < .001$). Contrary to IMs and PMs, the proportion of UMs individuals was significantly higher in Uygur patients 18.6% (15.3, 21.9) than in Han patients 1.7% (0.7, 2.7), ($P < .001$). All results are displayed in Table 3.

Table 3

Frequencies of the *CYP2C19* genotype-defined clopidogrel metabolic groups distribution according to 2 ethnic groups.

Metabolizer Phenotype	Observed genotypes	Han patients (N = 602) N, N% (95% CI)	Uygur patients (N = 527) N, N% (95% CI)	*P* value
EMs	*1/*1	227/37.7 (33.8, 41.6)	214/40.6 (36.4, 44.8)	.319
IMs	*1/*2, *1/*3, *2/*17, *3/*17	272 /45.2 (41.2, 49.2)	179/34.0 (30.0, 38.0)	< .001
PMs	*2/*2, *2/*3, *3/*3	93 /15.4 (12.5, 18.3)	36 /6.8 (4.7, 8.9)	< .001
UMs	*1/*17, *17/*17	10 /1.7 (0.7, 2.7)	98 /18.6 (15.3, 21.9)	< .001

95% CI = 95% confidence intervals, EMs = extensive metabolizers, IMs = intermediate metabolizers, PMs = poor metabolizers, UMs = ultra-metabolizers.

Table 4

Allele and genotype frequencies of *ABCB1* in 2 ethnic groups.

Polymorphisms	Han patients (N = 602) N, N% (95% CI)	Uygur patients (N = 527) N, N% (95% CI)	*P* value
CC	240 /39.9 (36.0, 43.8)	176 /33.4 (29.4, 37.4)	.001
CT	263 /43.7 (39.7, 47.7)	216/41.0 (36.8, 45.2)	
TT	99/16.4 (13.4, 19.4)	135/25.6 (21.9, 29.3)	
T allele	461/38.3 (35.6, 41.0)	486/46.1 (43.1, 49.1)	< .001
C allele	743/61.7 (59.0, 64.4)	568/53.9 (50.9, 56.9)	

95% CI = 95% confidence intervals.

3.5. The ABCB1 allele and genotype frequency

For the *ABCB1* allele, the *CC, TT* and *CT* genotype frequencies were 33.4% (29.4, 37.4), 25.6% (21.9, 29.3) and 41.0% (36.8, 45.2) in Uygur patients, respectively. In Han patients, the frequencies were 39.9% (36.0, 43.8), 16.4% (13.4, 19.4) and 43.7% (39.7, 47.7), respectively. There were significantly different genotype frequencies between the 2 ethnic groups ($P = .001$). The allele frequencies of the *T* alleles were 46.1% (43.1, 49.1) in Uygur patients and 38.3% (35.6, 41.0) in Han patients, respectively. The allele frequency of the *T* alleles was significantly higher in Uygur patients than in Han patients, ($P < .001$). All results are displayed in Table 4.

3.6. The PON1 allele and genotype frequency

For the *PON1* allele, the Uygur patients had lower *GG* genotype frequencies for 18.2% (14.9, 21.5) than did the Han patients 42.2% (38.3, 46.1), but higher *GA* and *AA* genotype frequencies (50.7%, 31.1%, respectively) than did the Han patients (43.4% and 14.4%, respectively). All differences in the genotype frequencies were significant ($P < 0.001$). However, as same as the genotype frequency, the significant difference was found in the *A* allele frequencies between Uygur patients 56.5% (53.5, 59.5) and Han patients 36.1% (33.4, 38.8), ($P < .001$). All results are displayed in Table 5.

3.7. The prevalence of CYP2C19*2, *3, *17, ABCB1 and PON1 polymorphisms in general population for 2 ethnic groups.

Frequencies of the *CYP2C19*2, *3, *17* alleles were 24.7%, 3.3%, and 1.2% in Han healthy groups and 16.1%, 9.4%, and undetected in Uygur healthy groups, respectively. Frequency of the *ABCB1* allele was 43.6% in Han healthy groups and 59.5% in Uygur healthy groups. Frequency of the *PON1*allele was 36.3% in Han healthy groups and undetected in the Uygur healthy groups. The *CYP2C19*2* frequency was significantly different between Han patients and Han healthy groups (Table 6, $P < .001$). Other allele frequencies showed no significant difference between Han patients and Han healthy groups (Table 6, $P > .05$ for all). The *CYP2C19*3* frequency was significantly different between Uygur patients and Uygur healthy groups (Table 7, $P < .001$). The *ABCB1* allele frequencies showed no significant difference between Uygur patients and Uygur healthy groups (Table 7, $P > .05$. All results are displayed in Tables 6 and 7.

Table 5

Allele and genotype frequencies of *PON1* in 2 ethnic groups.

Polymorphisms	Han patients (N = 602) N, N% (95% CI)	Uygur patients (N = 527) N, N% (95% CI)	*P* value
GG	254/42.2 (38.3, 46.1)	96 /18.2 (14.9, 21.5)	< .001
GA	261/43.4 (39.4, 47.4)	267/50.7 (46.4, 55.0)	
AA	87/14.4 (11.6, 17.2)	164/31.1 (27.1, 35.1)	
A allele	435/36.1 (33.4, 38.8)	595/56.5 (53.5, 59.5)	< .001
G allele	769/63.9 (61.2, 66.6)	459/43.5 (40.5, 46.5)	

95% CI = 95% confidence intervals.

Table 6

The prevalence of *CYP2C19*2, *3, *17, ABCB1* and *PON1* polymorphisms in Han patients with CAD and Han healthy groups.

Allele	Allele frequency (%) Han patients	Han healthy groups	*P* value	References
CYP2C19	N = 602	N = 384		10
*2	32.4	24.7	<.001	
*3	6	3.3	.706	
*17	1.9	1.2	.158	
ABCB1	N = 602	N = 39		11
	38.3	43.6	.351	
PON1	N = 602	N = 146		12
	36.1	36.3	.956	

CAD = coronary artery disease.

3.8. Allele frequencies of CYP2C19*17 in comparison with other ethnic groups with CAD

We further compared allele frequencies of *CYP2C19*17* in the study populations (Uygur patients and Han patients) and various ethnic groups of Chinese in other areas of China, as well as Russian, German, Polish, American, Turks, and Italian populations. We found that the allele frequency of *CYP2C19*17* in Uygur patients was significantly higher than that of Chinese in other areas of China ($P < .05$) and were significantly lower than those of Russians in Northern Siberia, Polish, and American populations ($P < .05$). Furthermore, the allele frequency of *CYP2C19*17* was significantly lower ($P < .05$) for Han patients than for other ethnic groups except Chinese in other areas of China ($P > .05$). All results are displayed in Table 8.

Table 7

The prevalence of *CYP2C19*2, *3, *17, ABCB1,* and *PON1* polymorphisms in Uygur patients with CAD and Uygur healthy groups.

Allele	Allele frequency (%) Uygur patients	Uygur healthy groups	*P* value	References
CYP2C19	N = 527	N = 103		10
*2	20.7	16.1	.125	
*3	3.6	9.4	<.001	
*17	12.6	NA	/	
ABCB1	N = 527	N = 37		11
	46.1	59.5	.026	
PON1	N = 527	NA	/	
	56.5	/	/	

CAD = coronary artery disease, NA = not available (not test).

Table 8

Allele frequencies of *CYP2C19*17* comparison with other ethnic groups with CAD.

population	N	Allele frequency of *CYP2C19*17* (%)	References
Uygur	527	12.6	Current study
Han	602	1.9	
Chinese	325	0.9[a]	**13**
Chinese	196	1.3 [a]	**14**
Russians in Northern Siberia	87	33.3[ab]	15
Russians in Central Siberia	222	17.1[b]	
Russians in Eastern Siberia	122	22.2[b]	
Russians in Moscow region	81	15.4[b]	
German	1524	22.9[b]	16
Polish	211	27.0[ab]	17
American	321	25.8[ab]	18
Turks	347	15.9[b]	19
Italian	448	19.5[b]	20

CAD = coronary artery disease.

[a] $P < .05$, compared with the data of Uygur patients in the current study.

[b] $P < .05$, compared with the data of Han patients in the current study.

4. Discussion

Clopidogrel itself has no biological activity. Its response variability is linked to its 2 bioactivation steps by *CYP* enzymes: enteric drug transporters, and paraoxonase enzymes.[21] The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate to its platelet P2Y12 receptor with subsequent adenosine diphosphate -mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Clopidogrel is metabolized into 15% active metabolite and 85% inactive metabolite by the P450 system. The polymorphic isoenzyme *CYP2C19* plays an important part in genetic diversity.[22] Interpersonal differences in metabolic activities may be reflected in drug pharmacokinetics as well as in therapeutic outcomes of *CYP2C19* substrates.[23]

In our study, we assessed 5 SNPs in 3 genes (*ABCB1*, *PON1*, and *CYP2C19*) that affect the metabolism and activation of clopidogrel. We measured allele frequencies in a prospective cohort of 1129 patients (602 Han and 527 Uygur) with CAD. The genotype frequencies of *CYP2C19*2* were significantly different between the 2 ethnic groups ($P < .001$). Similar to *CYP2C19*2*, the *CYP2C19*3* allele frequencies of the *A* alleles were significantly lower in Uygur patients than in Han patients ($P < .001$). Some studies have shown that the *CYP2C19*2* and *CYP2C19*3* loss-of-function alleles are associated with a marked decrease in platelet response to clopidogrel in unstable patients.[24–26]

*CYP2C19*17* has been linked to a superior response to clopidogrel but an increased risk of bleeding.[16] We found that the frequency of the *T* allele was 12.6% in Uygur patients, significantly higher than the 1.9% in Han patients ($P < .001$). While previous studies analyzed *CYP2C19* genetic polymorphisms in Han Chinese populations,[27,28] few studies focused on Uygur populations. Ethnic differences have been reported regarding the allelic and genotype frequencies of *CYP2C19*17* and *CYP2C19*2*.[29,30] To date, the *CYP2C19*2* and *CYP2C19*3* polymorphism in Han and Uygur patients with CAD in the Kashi area of Xinjiang have been reported, but the *CYP2C19*17* allele was not.[31]

We compared CYP2C19*17 polymorphisms in current study populations (Uygur and Han patients) with various global ethnic groups.[13–20] Our analysis in those groups found that the allele frequencies of *CYP2C19*17* in Uygur patients were significantly higher than those of Chinese in other areas of China ($P < .05$) and were significantly lower than those of Russians in Northern Siberia, Polish, and American groups ($P < .05$). Additionally, the *CYP2C19*17* allele frequencies identified in Uygur populations were most similar to those of Russians in Central Siberia, Russians in Eastern Siberia, Russians in Moscow region, German, Turks, and Italian patients. Furthermore, allele frequencies of *CYP2C19*17* were significantly lower ($P < .05$) in the Han patients than in other ethnic groups except that for Chinese in other areas of China ($P > .05$). Our results provide new data regarding the genetic polymorphisms of the *CYP2C19* gene in Uygur patients, the ethnic and living areas were the key factors that affected *CYP2C19* polymorphism distribution.

Genetic variants have been identified in *CYP2C19* that alter clopidogrel active metabolite formation. On the basis of their abilities to metabolize *CYP2C19* substrates, individuals may be classified as EMs, IMs, PMs, or UMs.[18,21,32] We found both the IMs and PMs were significantly lower in Uygur patients than in Han Uygur patients ($P < .001$), hence, the different incidences of clopidogrel resistance in the 2 ethnicities. The key finding was that the proportion of UMs individuals was significantly higher in Uygur patients (18.6%) than in Han patients (1.7%, $P < .001$). Guidelines recommend that Clopidogrel dosage be tailored according to label-recommended dosage and administration.[33] Our data suggest that future versions of clopidogrel guidelines will incorporate consideration of metabolizer groups.

The *ABCB1* gene encodes MDR1, responsible for intestinal absorption of many molecules including clopidogrel.[34] Patients with a *T* allele at *C3435T* were at a greater risk of cardiovascular events than were non-carriers during clopidogrel treatment.[35,36] *ABCB1 C3435T* genotyping should be another parameter taken into account when determining dosing of clopidogrel.[37] In the present study, the allele frequency of the *T* alleles was significantly higher in Uygur patients than in Han patients, ($P < .001$). In contrast, Park JJ et al. showed that genetic variation in *ABCB1 C3435T* drug transporter did not play a major role in clopidogrel OPR, at least not in Asians.[21] Although these discrepancies remain controversial, the present study provided data for further clinical study which not limited to clopidogrel absorption.

Paraoxonase-1 (*PON1*) is a hepatic protein involved in the conversion of clopidogrel to its active metabolite.[38] *PON1* is therefore a key factor in the bioactivation and clinical activity of clopidogrel.[4] We found the significant differences were seen in genotype and allele frequencies for *PON1 (Q192R)* between the ethnicities. There have been reports that *PON1* genetic variants did not affect clopidogrel on-treatment platelet reactivity in Korean patients.[39] Whether *PON1* variants affected clopidogrel activity and CAD risks remains an area of active investigation. We were able to provide experimental data to more reliably predict the effects of *PON1* variants in Uygur and Han patients.

We also found *CYP2C19*2, *3, *17, ABCB1* and *PON1* polymorphisms in healthy groups in both ethnic groups in the literature.[10–12] The *CYP2C19*2* frequency was significantly different between Han patients and Han healthy groups ($P < .0001$), while the *CYP2C19*3* frequency was significantly different between Uygur patients and Uygur healthy groups ($P < .0001$). To our knowledge, this was the first study that

assessed the *CYP2C19*17*, *ABCB1*, and *PON1* gene polymorphisms among Han and Uygur patients with CAD in Xinjiang Province.

In summary, we found interethnic differences in terms of *CYP2C19*, PON1, and *ABCB1* polymorphisms and *CYP2C19* genotype-defined clopidogrel metabolic groups. This study may provide valuable insights into the genetic polymorphisms affecting clopidogrel metabolism among minority groups. Ideally, we would create a database on which to launch further functional research. Our efforts aim eventually to determine the most effective and safe individualized CAD therapies for various ethnic groups in Xinjiang.

5. Limitations

There were several limitations in our study. First, because the study was designed for patients with CAD, there was no genetic frequency control for healthy individuals. Gender is a non-modifiable risk factor of CAD,[40] therefore perhaps the varying prevalence of CAD results from unbalanced gender distributions in the 2 ethnic groups. Second, the observed *ABCB1 C3435T* distributions deviated from Hardy-Weinberg equilibrium in Uygur patients. It may be the case that ancestors of some Uygur patients were intermarried with different nationalities prior to 3 generations, but no information regarding this possibility was available. Finally, the results of our study only suggested 5 major SNPs that altered the metabolism and activation of clopidogrel in 2 ethnic groups. Thus, we would like to suggest further study with larger sample sizes to better define correlations with these 5 SNPs in order to create a more reliable group representative of Uygur patients. We believe that investigation of the association between genotypes and clinical outcomes in both Han and Uygur CAD patients is warranted.

Author contributions

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