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]
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 300mg oral loading dose and then to continue at 75mg 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 4mL 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>C, 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 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,
Frequencies of the demographic 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/m², 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) |
| Cardiovascular disease      | 46 (8.1)    | 67 (11.0)  |
| 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 amldipine, nifedipine, amldipine besylate and hypoglycemic, antibiotics agents (Glimepiride, donepezil, acarbose, metformin, linagliptin, repaglinder, 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).

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.
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 < .001). However, as same as the genotype frequency, the significant difference was found in the A allele frequencies between Uygur patients 56.5% (33.4, 38.8) 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.

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.

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

CAD = coronary artery disease, NA = not available (not test).
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.[31] 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 reactivity 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.[13] 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 J] 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.[35] PON1 is therefore a key factor in the bioactivation and clinical activity of clopidogrel.[14] 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, therefore perhaps the varying prevalence of CAD results from unbalanced gender distributions in the 2 ethnic groups. Second, the observed ABCB1 C3435T variations 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 3 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 3 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.

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