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The Correlation Between *MDR1* Gene Polymorphism and Clopidogrel Resistance in People of the Hui and Han Nationalities

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Abstract

To investigate the differences in the correlation between multidrug resistance protein 1 (*MDR1*) (*ABCB1*) gene polymorphism and clopidogrel resistance in patients of the Hui and Han nationalities with percutaneous coronary intervention (PCI). A total of 377 subjects (154 people of Hui nationality, 223 people of Han nationality) with PCI were enrolled in the study. Each patient's platelet aggregation rate was induced by adenosine diphosphate and measured using light turbidimetry. Based on the results, the patients were divided into two groups: a clopidogrel resistance (CR) group and a non-clopidogrel resistance (NCR) group. Restrictive fragment-length polymorphism polymerase chain reaction technology was then used to determine the genotype and alleles at two loci (C3435 T[rs1045642] and C1236 T[rs1128503]), calculate the frequencies of the genotype and alleles at these two loci, and conduct correlation analysis. The incidence rate of clopidogrel resistance was 23.4%, and the frequencies of the TT genotype and T allele at C3435 T for patients of both nationalities were significantly higher in the CR group than in the NCR group ($P < 0.05$). There were no significant differences between the two groups in genotype or allele frequency at C1236 T. There was a significant difference in the distribution of C1236 T polymorphism between the two nationalities ($P < 0.05$), but there was no significant difference between the two nationalities in C3435 T polymorphism. Patients with a T allele at *MDR1* C3435 T are more likely to show clopidogrel resistance, and no significant differences were identified in C3435 T gene polymorphism between the two nationalities.

Keywords

coronary heart disease, *MDR1* gene, clopidogrel resistance, gene polymorphism, ethnic differences

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Introduction

Coronary heart disease (CHD) is a cardiovascular disease that poses a serious threat to human health. Percutaneous coronary intervention (PCI) has become an important approach for the treatment of this disease. If there are no contraindications or high bleeding risks after PCI surgery, the administration of aspirin combined with clopidogrel, which acts as a $P2Y_{12}$ receptor inhibitor and an antiplatelet treatment (loading amount 300-600 mg, maintenance dose 75 mg daily), is recommended for 12 months. Recently, however, both domestic and international reports have identified significant individual variances in clopidogrel anti-platelet therapy: even after regular oral administration of the standard dose of clopidogrel, some patients experience a recurrence of myocardial infarction and stent thrombosis. This indicates a form of clopidogrel resistance[1] that increases the possibility of clinical cardiovascular adverse events in patients after PCI surgery.[2] After oral administration, clopidogrel needs to

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be converted into active products through a metabolic reaction via the liver CYP450 enzyme, and many other enzymes are also involved in this process. Therefore, it is currently believed that a poor response to clopidogrel is related to the polymorphism of genes in its metabolic pathway, including cytochrome *P450 2C19* (*CYP2C19*) and multidrug resistance protein 1 (*MDR1*). To date, research on *CYP2C19* has offered the clearest results,[3,4] while the results of studies on the *MDR1* gene have been inconsistent. The *MDR1* gene can encode the transporter P-glycoprotein of the small intestinal epithelium to regulate the absorption of clopidogrel. It has been reported that, among many single-nucleotide polymorphisms of *MDR1*, C1236 T and C3435 T may be related to the defects in P-glycoprotein.

Although there are many reports[5,6] regarding the wide variation of *MDR1* gene polymorphism between populations and races in different regions, there have been few studies involving the Hui population. The Hui people are, genetically, a relatively isolated nationality: the communities of this population live close together in the northwest of China, particularly in the Ningxia Hui Autonomous Region, and most people of Hui nationality are prohibited from marrying people from other ethnic groups. For these reasons, people of Hui nationality were selected as one of the populations for the present study.

This study enrolled patients of Hui or Han nationality with CHD who underwent PCI and received oral clopidogrel after the procedure. Their genotypes and alleles related to clopidogrel resistance were screened, the association between *MDR1* gene polymorphism and clopidogrel resistance was evaluated, and the differences between the results for the two nationalities were further analyzed. It is hoped that the study will have significant theoretical value in the individualized treatment of patients using clopidogrel.

Subjects and Methods

Subjects

A total of 377 patients who received PCI in the cardiology department at the General Hospital of Ningxia Medical University or the First People's Hospital of Yinchuan between May 2015 and January 2017 were enrolled, comprising 154 people of Hui nationality and 223 people of Han nationality.

The inclusion criteria for patients were as follows: (1) no interracial marriage within three generations and no consanguinity with other enrolled patients; (2) aged 18 to 80 years; (3) had received PCI treatment, with one or two stents implanted; (4) before the procedure, had received oral administration of enteric-coated aspirin 100 mg regularly for at least 1 week and clopidogrel bisulfate tablets (Plavix) 300 mg once daily, followed by an oral maintenance dose of 75 mg; and (5) had received oral dose of atorvastatin calcium tablets (40 mg daily) and undergone subcutaneous injection of low-molecular-weight heparin calcium according to body weight for anticoagulant therapy.

The exclusion criteria were as follows: (1) contraindications for anti-platelet therapy; (2) patient had previously received clopidogrel treatment or coronary artery bypass grafting/PCI surgery; (3) severe liver and kidney problems, digestive system diseases, acute and chronic blood system diseases, tumors or other end-stage diseases, or severe heart insufficiency; (4) patient had recently received platelet glycoprotein IIb/IIIa inhibitors; and (5) patient had simultaneously received orally administered rifampicin, erythromycin, and intervention with a proton pump inhibitor.

All participants in the study received professional training in compliance with the principle of voluntary participation. This study was conducted with the approval of the Ethics Committee of Yinchuan First People's Hospital. Written informed consent was obtained from all participants.

Collection of Samples and Clinical Data

Once a patient had been admitted, professionally trained medical personnel collected their general data and their biochemical indexes, including total cholesterol, triglyceride, high-density lipoprotein, fasting blood glucose, and uric acid.

Table 1. Comparison of General Data Between CR Group and NCR Group in Hui and Han Nationality.

	Hui		Han	
Items	CR	NCR	CR	NCR
(n = 40)	(n = 114)	(n = 63)	(n = 160)	
Age	59.13 ± 8.94	60.23 ± 8.71	61.63 ± 8.7	59.06 ± 9.33
Male/n(%)	26 (65.0)	92 (80.7)	45 (71.4)	112 (70.0)
Hypertension/n(%)	26 (65.0)	90 (78.9)	37 (58.7)	80 (50.0)
Diabetes/n(%)	16 (32.7)	50 (32.3)	49 (68.1)	63 (38.7)*
Smoking history/n(%)	14 (35.0)	43 (37.7)	27 (42.8)	74 (46.2)
BMI(Kg/m2)	27.22 ± 30.01	25.14 ± 3.21	26.79 ± 5.07	24.35 ± 3.11*
TG(mmol/L)	2.31 ± 1.79	1.81 ± 1.00	2.11 ± 1.09	1.54 ± 0.78*
CHOL(mg/dl)	3.73 ± 1.14	3.78 ± 2.45	3.97 ± 1.04	3.94 ± 1.15
FG(mmol/L)	7.45 ± 2.89	6.55 ± 2.89	7.37 ± 2.74	6.65 ± 2.81
UA(mmol/L)	321.07 ± 84.23	327.05 ± 90.06	291.81 ± 80.72	301.04 ± 84.45

Note: *: $P < 0.05$,the difference was statistically significant.
Abbreviations: BMI, body mass index; TG, triglyceride; CHOL, cholesterol; FG, Fasting blood glucose; UA, uric acid.

A Siemens ADVIA 2400 automatic biochemical analyzer (Siemens, Germany) was used to measure all biochemical indicators. The specific indicators used are shown in Table 1.

Platelet Function Assay

During the morning after the PCI procedure, 2 mL of fasting venous blood was collected from the patient in an ethylenediaminetetraacetic acid (EDTA) anticoagulation tube, and a further 2 mL was collected in a sodium citrate anticoagulation tube. The sample in the EDTA anticoagulation tube was centrifuged at 3500 r/min, and the middle and lower blood cells were extracted and stored in a refrigerator at −80 °C. The sodium citrate anticoagulation tube was sent to the First People's Hospital of Yinchuan City for platelet aggregation determination within 2 h. The platelet aggregation rate was measured using an LBY-NJ4 platelet aggregometer (Beijing Precil, China). Based on the results, the patients were divided into two groups, a clopidogrel resistance (CR) group and a non-clopidogrel resistance (NCR) group, with a platelet aggregation rate of ≥50% defined as clopidogrel resistance.[7]

Test Methods

Extraction of peripheral blood DNA: The stored blood samples were removed for extraction of the peripheral blood DNA using a Tiangen blood genomic DNA extraction kit (centrifugal column type; Tiangen, Beijing, China). The purity and concentration of the DNA samples were measured using a Nanodrop 2000 spectrophotometer (NanoDrop Technologies, LLC, Wilmington, Delaware, USA).

Polymerase chain reaction (PCR) amplification: Primers were synthesized by Sangon Biotech (Shanghai, China) following literature review. The C3435 T primer sequence was as follows: P1 = 5-TGCTGGTCCTGAAGTTGATCTGTGAAC-3′; P2 = 5′-ACATTAGGCAGTGACTCGATGAAGGCA-3′. The C1236 T primer sequence was as follows: P1 = 5′-TCTTTGTCACTTTATCCAGC-3′; P2 = 5′-TCTCACCATCCCCTCTGT-3′. The PCR reaction conditions were as follows: pre-denatured at 94 °C for 5 min, denatured at 94 °C for 30 s, annealed at 60 °C for 30 s, and extended at 72 °C for 1 min. The whole process was cycled 30 times and extended at 72 °C for 10 min.

Enzyme digestion: In accordance with previous research,[8–10] the restriction enzyme obtained at the C3435 T locus was *DpnII* (New England Biolabs [NEB], USA), and the restriction enzyme at the C1236 T locus was *Eco0109I* (NEB, USA). Binary logistic regression analysis was used to analyze the correlations between genotype, blood glucose, and clopidogrel resistance. A P value of <0.05 was considered statistically significant. The reaction systems were prepared as required and incubated at 37 °C for 15 min.

Statistical Processing

All analyses were conducted using SPSS 19.0 software. The measurement data were expressed as mean ± standard deviation, and the counting data were expressed as frequency values. The measurement data of the two groups were compared using t-testing, and the counting data were compared using χ^2 testing. The representativeness of samples was assessed using the Hardy–Weinberg equilibrium. Binary logistic regression analysis was used to analyze the correlations between genotype, blood glucose, BMI, age, gender, blood pressure, blood lipid levels, uric acid, smoking status, and clopidogrel resistance. A P value of <0.05 was considered statistically significant.

Results

Electrophoresis

It is currently thought that the mutation frequency of genes might vary for different populations: the same gene mutation may occur at varying intensities due to differences in environment. After enzyme digestion at the C1236 T locus of the *MDR1* gene, there was no enzyme digestion site for the T allele, and one enzyme digestion site was presented after mutation of T into C. The electrophoresis results were verified by sequencing. CC was cut into two fragments (379 and 123 bp, respectively), and CT was cut into three fragments (502, 379, and 123 bp, respectively). TT could not be cut, so there was just one fragment (502 bp).

After enzyme digestion at the C3435 T site of the *MDR1* gene, CT was cut into three fragments (248, 190, and 58 bp, respectively), and CC was cut into two fragments (190 and 58 bp, respectively). TT could not be recognized and cleaved by endonuclease, so there was only one fragment (248 bp). Although it seems that the C3435 T might have one more constitutive cleavage site for DpnII, after DNA sequencing, we found that the number and the length of the obtained RFLP fragments, especially the genotypes, would not be affected.

Genotype and Allele Frequency Distribution

There was no significant difference between the genotype and allele frequencies at the C3435 T locus (P > 0.05) for the Han and Hui CR groups or for the Han and Hui NCR groups, but there were significant differences in the frequencies at the C1236 T locus (P < 0.05).

There were significant differences between the genotype and allele frequencies of the polymorphism distribution at the C3435 T locus between the CR group and NCR group for both nationalities, with significantly higher frequency distributions of the TT genotype and T allele in the CR group than in the NCR group (P < 0.05). There were no significant differences in the genotype and allele frequencies at the C1236 T locus between the CR and NCR groups ($P > 0.05$; Table 2).

Table 2. Genotype and Allele Frequency Distribution in Each Group.

Polymorphic Gene	Groups (n)	Genotype Frequency			Allele Frequency	
		CC	CT	TT	C	T
C3435T	Hui CRgroup (40)	11 (28.6)	16 (36.7)	13 (34.7)	38 (46.9)	42 (53.1)
	Hui NCRgroup (114)	46 (44.5)	48 (37.4)	20 (18.1)[1)*]	140 (63.2)	88 (36.8)[5)*]
	Han CR group (63)	20 (31.9)	24 (38.9)	19 (29.2)	64 (51.4)	62 (48.6)
	Han NCR group (160)	77 (49.1)	66 (40.5)	17 (10.4)[2)*]	220 (69.3)	100 (30.7)[6)*]
C1236T	Hui CR group (40)	12 (24.5)	17 (34.7)	20 (40.8)	32 (41.8)	48 (58.2)
	Hui NCR group (114)	40 (25.8)	65 (41.9)	50 (32.3)	108 (46.8)	120 (53.2)
	Han CR group (63)	6 (9.7)	17 (27.8)	40 (62.5)[3)#]	29 (23.6)	97 (76.4)[7)#]
	Han NCR group (160)	19 (11.7)	57 (35.6)	84 (52.7)[4)#]	95 (29.4)	225 (70.6)[8)#]

Note: *: Comparison of CR group between the same Nationalities, $P < 0.05$[1)*] $X^2 = 6.998$, $P = 0.030$;[2)*] $X^2 = 14.221$, $P = 0.001$;[5)*] $X^2 = 8.185$, $P = 0.004$;[6)*] $X^2 = 13.918$, $P = 0.000$)

#: Compared with the same group of Hui nationality, $P < 0.05$ [3)#] $X^2 = 7.058$, $P = 0.029$;[4)#] $X^2 = 17.212$, $P = 0.000$;[7)#] $X^2 = 9.057$, $P = 0.003$;[8)#] $X^2 = 20.269$, $P = 0.000$)

Hardy–Weinberg Equilibrium Test

The Hardy–Weinberg balance test was performed on the genotypes of the Hui and Han subjects. All the results had P values of >0.05, indicating that the subjects within each nationality group came from the same large population with good representativeness.

*Logistic Regression Analysis of the Correlation Between **MDR1*** Gene Polymorphism and Clopidogrel Resistance

We introduced the following variables into the model for binary logistic regression analysis: clopidogrel resistance as the dependent variable; and a medical history of diabetes, fasting glucose, total cholesterol, body mass index (BMI), the C3435 T allele (introduced as a dummy variable compared with CC type), and C1236 T (introduced as a dummy variable compared with CC type) as the observed variables. The results indicated that 3435TT (odds ratio [OR] value = 2.307, OR 95% confidence interval [CI] = 1.010-2.879, $P = 0.005$) and diabetes history (OR value = 1.714, OR 95%CI = 1.013-2.907, $P = 0.038$) were independent risk factors for clopidogrel resistance, and no obvious correlations were found between any other factors and clopidogrel resistance.

Discussion

Clopidogrel is a widely used drug for CHD treatment and post-PCI antiplatelet therapy, but clopidogrel resistance can limit its clinical efficacy. However, different testing methods for clopidogrel resistance use different standards and definitions. Müller[11] defined clopidogrel resistance based on adenosine diphosphate-induced platelet aggregation decreasing by 10% or less compared with the baseline value in the 4 h after administration of 600 mg of clopidogrel. Barragan,[7] however, proposed defining clopidogrel resistance as a platelet aggregation rate greater than 50% after administration of 600 mg of clopidogrel. Different testing methods have also reported varying incidence rates of clopidogrel resistance, ranging between 4% and 31%.[12] The present study used the incidence rate of clopidogrel resistance obtained by Barragan (23.4%).

At present, the mechanism of clopidogrel resistance is unclear. While the interaction of patient compliance, dosage of medication, and drugs used may contribute to clopidogrel resistance, genetic factors may also affect the metabolism and absorption of active clopidogrel products. P-glycoprotein is expressed through the *MDR1* gene, which is involved in the regulation of the intestinal absorption of active clopidogrel products, so it may be related to the occurrence of clopidogrel resistance.

Gutierrez-Rubio's study[13] showed that the mutation rate of the *MDR1* gene is relatively high in people of Han nationality and that the distribution of the *MDR1* gene may vary between different groups. The frequency of a T mutation gene at the C3435 T locus was found to be higher in an Asian population than in an African population (Ghana 17%, Kenya 17%, Sudan 27%, Japan 39%, Caucasus 42%, India 62%), with an almost-zero frequency distribution of TT genotypes reported in the African population (Ghanaians 0%, Kenyans 4%, Sudanese 6%), which is significantly lower than for other groups.[14] In the present study, the TT genotype frequency was 18.3% and the T allele frequency was 38.7%; these figures are similar to the T-mutation-gene frequency at the C3435 T locus in the Japanese population. In our research, to identify any differences between people of Hui and Han nationalities, we analyzed findings for the subjects of these two nationalities separately. The results showed no significant difference in genotype frequency and allele frequency distribution between the two nationalities ($P > 0.05$). To date, there have been few studies on the C1236 T locus, although significant differences exist among different ethnic groups.[15] The analysis and comparison of the C1236 T locus CC, CT, and TT genotypes and C and T allele frequencies of the two groups in the present study indicate significant differences between the nationalities ($P < 0.05$).

Differing results have been reported regarding the correlation between the genetic polymorphism of the *MDR1* C3435 T locus and clopidogrel resistance. Multiple large-scale clinical trials[16,17] have shown that T mutation at the C3435 T site can reduce the rate of clopidogrel metabolism, reduce inhibition of platelet activity, and increase risk of thrombosis. In addition, it has been reported that wild-type C-gene carriers present the greatest risk of thrombosis.[18] In the present study, regardless of nationality, TT genotype and T allele frequencies were significantly higher in the CR group than in the NCR group ($P < 0.05$), indicating that T-site mutation may cause clopidogrel resistance. However, the results of a previous study on the association between the C1236 T site and clopidogrel resistance differ from these findings.[19] Some researchers have found that the CC wild type has a lower platelet inhibition rate than the CT + TT mutant type, but other domestic and international studies have identified no significant correlation between C1236 T and antiplatelet-drug resistance.[20] In the present study, no statistical difference was identified between the genotype and allele frequencies for the two nationalities, indicating that C1236 T polymorphism is related to clopidogrel resistance. However, the small sample size of the study was a limitation for the research process; therefore, further research with larger samples is required to confirm the correlation between C1236T-locus gene mutation and clopidogrel resistance.

Previous studies have shown that the pharmacodynamic effects of antiplatelet drugs are lower in patients with diabetes than in those without diabetes ($P < 0.05$),[18] and patients with myocardial infarction with blood glucose levels >8.5 mmol/L have generally shown a decreased reaction to clopidogrel.[21] It has therefore been suggested that blood glucose may have some influence on the occurrence of clopidogrel resistance. In the baseline data of the present study, among the patients of Han nationality, there was a significantly higher proportion of patients with diabetes in the CR group than in the NCR group; this is consistent with the findings of these previous studies. However, a similar discrepancy was not found among the patients of Hui nationality in our sample.

Many clinical studies have shown that obesity and hyperlipidemia are closely related to cardiovascular diseases such as hypertension and atherosclerosis. Doğan et al.[22] found a significantly increased incidence of clopidogrel resistance in patients with BMI > 30. Comparison of the baseline data in the present study identified significant differences between the two Han groups in cholesterol and BMI levels, which is consistent with the results of Doğan et al.'s study; however, significant differences were not found between the two Hui groups. The discrepancies in these results could be related to the different dietary habits of people of the Hui and Han nationalities; further studies with larger samples may report different results.

To further explore the correlation between *MDR1* genetic polymorphism and clopidogrel resistance in the present study, a multifactor logistic regression equation was applied. Clopidogrel resistance as the dependent variable, and the C3435 T and C1236 T genotypes (introduced as dummy variables compared with CC type) as independent variables, were introduced into the model for analysis. The results identified both a TT genotype at the C3435 T locus and diabetes as independent risk factors for clopidogrel resistance; the latter is consistent with the findings reported by Hochholzer.[23]

The present study's findings indicated a correlation between polymorphism of the C3435 T locus and clopidogrel resistance. The T allele may be a susceptibility gene for clopidogrel resistance, but the polymorphism of the C3435 T locus differed between patients of the Hui and Han nationalities. The occurrence of polymorphism of the C1236 T locus also differed between patients of the Hui and Han nationalities, but there was no obvious correlation of this factor with the occurrence of clopidogrel resistance. From a comprehensive analysis, considering that there may be linkage disequilibrium reactions at different loci in the same gene, we suggest that single-locus polymorphism may not change the coding protein performance.

The present study had some limitations. As the subjects were limited to residents of the Ningxia Hui Autonomous Region, the sample size was small. The dosage of clopidogrel was low, and the platelet aggregation rate level was not measured before medication was administered. In addition, there were multiple factors related to clopidogrel resistance in the baseline data, which may have affected the results. For further study and confirmation, future research should use larger samples and control for all influencing factors. The *MDR1* gene could also be associated with other genes related to clopidogrel metabolism for multigene correlation; this would offer increased opportunities to study the correlation between clopidogrel resistance and gene polymorphism, comprehensively clarify the relationship between clopidogrel resistance and *MDR1* gene polymorphism, and develop a basis for early intervention and prediction of clopidogrel resistance.

Conclusion

Patients with a T allele at *MDR1* C3435 T were found to be more likely to show clopidogrel resistance, and no significant differences in C3435 T gene polymorphism were identified between the Hui and Han nationality groups. Differences were identified in C1236 T gene polymorphism distribution between the two nationalities, but this factor showed no significant correlation with clopidogrel resistance. Finally, no significant difference was found between the two nationalities in terms of the correlation between *MDR1* gene polymorphism and clopidogrel resistance.

Ethics Approval and Consent to Participation

I confirm that I have read the Editorial Policy pages. This study was conducted with approval of the Ethics Committee of Yinchuan First People's Hospital. This study was conducted in accordance with the declaration of Helsinki. Written informed consent has been obtained from all participants.

Consent for Publication

All participants have signed documents with informed consent.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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