

A Study on the Correlation Between MDR1 Polymorphism and Clopidogrel Resistance in Hui Patients Treated with Percutaneous Coronary Intervention

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Objective: This study assesses the correlation between MDR1 gene polymorphism and clopidogrel resistance (CR) in Hui patients with coronary heart disease (CHD) who were treated with percutaneous coronary intervention (PCI).

Methods: The study includes 204 Ningxia Hui patients with CHD who were treated with PCI. These patients were divided into two groups: those who with CR and others were non-clopidogrel resistant (NCR), according to the results of the patients' platelet aggregation rate, which was tested by adenosine diphosphate-induced turbidimetry on the second postoperative day. C3435T and C1236T genotypes and alleles were tested by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: The CR rate was 24.0%, and there were 3 genotypes of C3435T and C1236T. For C3435T, the distribution frequency of the 3435TT genotype and T allele was significantly higher in the CR group than in the NCR group. For C1236T, no significant difference was found between the two groups.

Conclusion: Hui patients who had CHD were treated with PCI. CR was most likely to occur in those who had the T allele of MDR1 in gene C3435T.

Keywords: coronary heart disease, MDR1 gene, clopidogrel resistance, gene polymorphism, platelet aggregation rate

Background

Coronary heart disease (CHD) is a major cardiovascular condition that threatens human health and requires percutaneous coronary intervention (PCI) treatment. Postoperative aspirin combined with clopidogrel antiplatelet therapy can effectively reduce adverse events such as stent thrombosis.¹⁻⁴ However, some patients have clopidogrel resistance (CR), which can lead to thromboembolisms.⁵ Genetic factors are a major mechanism for the occurrence of CR and are related to region, race and population.

The MDR1 gene encodes the protein P-glycoprotein, which has a molecular weight of approximately 170,000. P-glycoprotein is a membrane transporter depended on adenosine triphosphate (ATP)⁶ and is widely distributed in many excretory organs and protective tissues in the human bodies. P-glycoprotein is closely related to the concentration of drugs in body. Clopidogrel can inhibit platelet aggregation, but its intestinal absorption is regulated by P-glycoprotein. Thus, P-glycoprotein has an important effect on the in vivo concentration of clopidogrel.

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Currently, the MDR1 genetic markers C1236T and C3435T are the research hotspots.^{7,8} However, studies on the correlation between the MDR1 gene and clopidogrel are mostly limited to the Han population, and no such studies have been conducted on Hui population. Therefore, the present studies selected the genotype and allele related to CR in Hui patients who had CHD and received PCI and evaluated the correlation between the MDR1 gene polymorphism and CR.

Research Object and Methods

Patients

The studies include 204 patients (130 males and 74 females, 63.7% vs 36.3%) who range from 18 to 80 years old. These patients have been diagnosed with CHD and had accepted PCI treatment for the first time in Yinchuan First People's Hospital between May 2015 and January 2017.

The inclusion group patients were required to have neither ethnic intermarriage within 3 generations nor related by blood. During their PCI treatment, the patients would receive 1 to 2 stent implantations, long-term oral administration of 100 mg of aspirin (Bayer), and one 300 mg dose of clopidogrel (Sanofi), followed by a maintenance dose of 75 mg daily. Patients also received 40 mg atorvastatin calcium tablets (Pfizer) and a subcutaneous injection of low-molecular-weight heparin according to their weight. Patients were excluded if they were averse to platelet therapy or had pre-existing medical conditions: a previous coronary artery bypass graft or PCI, severe liver or kidney disease, digestive system diseases, acute and chronic

hematological diseases, tumors or other end-stage diseases, or severe cardiac insufficiency. Patients would also be excluded if they recently took platelet glycoprotein IIb/IIIa inhibitors, oral rifampin Li Fuping, erythromycin, or proton pump inhibitors. Participation in the study was voluntary. Patients have signed informed consent, and their treatments have been overseen by trained medical personnel.

Diagnostic Criteria

Diagnostic criteria for CHD: The World Health Organization and the Chinese Medical Association (2007) issued the guidelines for diagnosis and treatment of CHD, including involvement of the left main stem, circumflex branch, or anterior descending branch confirmed by coronary angiography and diagnosis of stenosis of more than 50% in the main coronary artery or its branches.

Clopidogrel resistance: CR patients had a platelet aggregation rate of more than 50%; Non-clopidogrel resistant (NCR) patients had a rate below 50%.^{9,10}

Research Methods

Collect General Information

With admission, the general clinical data of patients were collected by trained medical personnel (Table 1).

Collect Peripheral Blood Samples

EDTA anticoagulant tubes and sodium citrate anticoagulant tubes were used to collect 2 mL specimens of fasting venous blood in the morning of the first postoperative day. The blood samples in the EDTA anticoagulant tube were centrifuged at 3500 rpm, and DNA was extracted from the middle and lower

Table 1 Comparison of General Clinical Data Between Group CR and Group NCR

Subjects	CR Group (n=49)	NCR Group (n=155)	T/X ² value	P value
Man/cases (%)	28 (57.1)	102 (65.8)	1.209	0.272
Age (years)	60.73±9.94	61.52±9.01	-0.516	0.606
Hypertension/cases (%)	27 (55.1)	94 (60.6)	0.474	0.491
Diabetes/cases (%)	16 (32.7)	50 (32.3)	0.003	0.959
Smoking/cases (%)	15 (30.6)	45 (29.0)	0.045	0.832
BMI (Kg m ⁻²)	25.22±3.57	25.05±3.39	0.303	0.762
Systolic pressure (mmHg)	129.47±22.06	134.02±22.39	-1.244	0.215
Diastolic pressure (mmHg)	76.61±14.10	80.22±12.67	-1.690	0.093
Triglyceride (mmol L ⁻¹)	2.13±1.42	1.87±1.23	1.236	0.218
Cholesterol (mg dL ⁻¹)	3.93±1.24	3.98±2.55	-0.131	0.896
High density lipoprotein (mmol L ⁻¹)	0.99±0.21	0.93±0.21	1.771	0.078
Fasting blood glucose (mmol L ⁻¹)	6.95±2.89	6.15±2.19	2.041	0.043*
Uric acid (mmol L ⁻¹)	321.27±86.32	327.20±92.06	-0.248	0.804
Number of stents (Pieces)	1.30±0.46	1.33±0.47	-0.306	0.760

Note: *P < 0.05 was statistically significant.

portions of the tubes after -80°C refrigeration. The blood in the sodium citrate tube was used to determine the platelet aggregation rate 2 hours after collection.

Experimental Methods

Extraction of DNA from peripheral blood: Blood samples were extracted and preserved, and a TIANGEN kit was used to extract genomic DNA from the peripheral blood.

Polymerase chain reaction (PCR) amplification: Primer sequences for C3435T and for C1236T were designed according to the literature:¹¹

- C3435T primer sequence: P1: 5-TGCTGGTCCTG AAGTTGATCTGTGAAC-3', P2: 5'-ACATTAGGCAGTGAAGGCA-3'
- C1236T primer sequence: P1: 5'-TCTTTGTCA CTTTATCCAGC-3', P2: 5'-TCTCACCATCCCCTC TGT-3'.

PCR reaction conditions: DNA materials were pre-denatured at 94°C for 5 minutes, denatured for 30 seconds at 94°C , annealed at 60°C , extended at 72°C for one minute. This thermal cycling was repeated 30 times. The procedure was then extended at 72°C for 10 minutes. The primer sequence was compounded by Shanghai Biotechnology Co., Ltd.

Restriction enzyme digestion: The restriction endonuclease of the C3435T locus was DpnII, and the restriction endonuclease of the C1236T locus was Eco0109I; the reaction system was incubated for 15 minutes at 37°C .

The platelet aggregation test: The blood samples in the sodium citrate anticoagulant tube were centrifuged at a speed of 300–500 RPM for 5 mins, then drew the upper plasma to make the Platelet-rich plasma (PRP) and counted the number of platelet. The rest blood were centrifuged at a speed of 3000

RPM for 10 mins to make the Platelet-poor plasma (PPP). And 300 ul PRP and PPP were put into the platelet aggregation instrument (LBY-NJ4) to determine the relative platelet concentration. Finally, 3 ul ADP was added to determine the maximum platelet aggregation rate.

Statistical Methods

SPSS 19.0 software was used to analyze the data. The measurement data were expressed as mean \pm standard deviation, while counting data were expressed in frequencies. A χ^2 -test was used to measure the data of the 2 groups, and a t -test was used to compare the groups' measurement data. Logistic regression analysis showed the correlation between the CR, genotype, blood sugar, and other factors. A value of $P < 0.05$ was considered statistically significant.

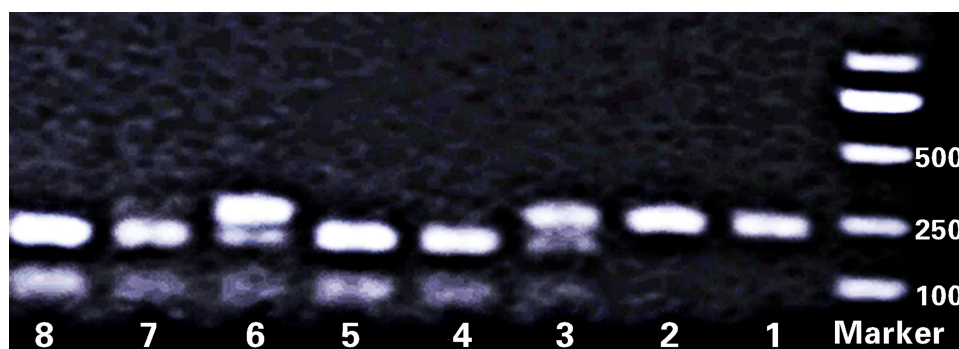
Results

Comparison of General Clinical Data

Table 1 shows the patients' general clinical data.

Electrophoretic Results

After the MDR1 gene C1236T site was cleaved, the CC type was cut into 379 bp and 123 bp, and 2 fluorescent bands were visible, while the CT type was cut into 502 bp, 379 bp, and 123 bp, and 3 fluorescent bands were visible. However, the TT type could not be cleaved; hence, only one fluorescent band (502 bp) was observed. After the C3435T site was cleaved, the CT type was cut into 248 bp, 190 bp, and 58 bp, and 2 fluorescent bands were visible, while the CC type was cut into 190 bp and 58 bp, and one fluorescent band was visible. However, the TT type could not be cut by endonuclease identification; hence, only one fluorescent band (248 bp) was visible (Figure 1).



Note: 1 and 2 are TT; 3 and 6 are CT; 4, 5, 7, and 8 are CC.

Figure 1 Electrophoresis of the restriction enzyme cleaved product of C3435T.

Table 2 Comparison of Genotype Frequencies and Allelic Frequencies of C3435T Between CR and NCR Groups

C3435T	Genotype, n (%)					Allele, n (%)			
	CC	CT	TT	X ² value	P value	C	T	X ² value	P value
CR group	14 (28.6)	18 (36.7)	17 (34.7)	6.998	0.030*	46 (46.9)	52 (53.1)	8.185	0.004*
NCR group	69 (44.5)	58 (37.4)	28 (18.1)			196 (63.2)	114 (36.8)		

Note: *P < 0.05 was statistically significant.

Genotype and Allele Frequency Distribution

Significant differences were seen in the distribution of the C3435T genotype and allele, respectively, between the CR and NCR groups ($P < 0.05$, Table 2). On the other hand, the C1236T genotype and allele frequencies showed no crucial differences when the CR and NCR groups were compared ($P > 0.05$, Table 3).

The Hardy–Weinberg Balance Test

The Hardy–Weinberg equilibrium test was performed on the genotype distribution of the subjects' MDR1 gene C1236T and C3435T loci. For the C1236T locus, the CR group scored $X^2 = 1.857$, $P = 0.395$, and the NCR group had $X^2 = 1.884$, $P = 0.390$. For the C3435T locus: The CR group had $X^2 = 1.507$, $P = 0.471$, and the NCR group scored $X^2 = 2.882$, $P = 0.237$. The P -values of both groups were greater than 0.05, indicating these subjects were from the same large group with good representation.

The Correlation Between MDR1 Gene Polymorphism and Clopidogrel Resistance

A two-element logistic regression analysis was performed with CR as the dependent variable. The independent variables included diabetes, fasting blood glucose levels, hypertension history, total cholesterol, body mass index, and C3435T and C1236T alleles (that were compared with the CC type, which acted as a dummy variable). The 3435TT locus (odds ratio [OR] = 2.992, $P = 0.010$) and fasting blood glucose levels

(OR = 2.479, $P = 0.001$) were independent risk factors for CR, while other factors were not correlated with CR.

Discussion

Since the specific criteria for CR are not consistent, different studies have been using different methods to measure platelet function, which makes the incidence of CR vary. The overall incidence of CR has been reported to be within 4%–31%.^{12,13} In the present studies, we used the method defined by Barragan¹⁴ to test the platelet aggregation rate of 204 patients. According to Barragan, a value of more than 50% was defined as CR, and the patients received 600 mg of clopidogrel 6 hours before the operation. The incidence of CR was 24%, which was consistent with the above findings. Other studies have shown that taking 600 mg of clopidogrel after 4 hours can be effective; taking 300 mg can induce the strongest effect after 24 hours; and a dose of 75 mg/d can inhibit platelet aggregation for 3–7 days after the operation.¹⁵ The subjects in our study underwent elective PCI surgery, and a 300 mg dose of clopidogrel was given after 4 hours, followed by a dose of 75 mg/d for maintenance. Although this was not strictly in accordance with the treatment protocol of 600 mg, this dose could also reach a steady state and inhibit platelet action.

Previous studies showed that the allele distribution and C3435T locus were significantly different when Asian and African¹⁶ were compared. The allele frequencies of locus T in African population in Ghana, Kenya, Sudan, and other African countries were 17%, 17%, and 27%, respectively, which were significantly lower than those in the

Table 3 Comparison of Genotype Frequencies and Allelic Frequencies of C1236T Between CR and NCR Groups

C1236T	Genotype, n (%)					Allele, n (%)			
	CC	CT	TT	X ² value	P value	C	T	X ² value	P value
CR group	12 (24.5)	17 (34.7)	20 (40.8)	1.306	0.521	41 (41.8)	57 (58.2)	0.732	0.392
NCR group	40 (25.8)	65 (41.9)	50 (32.3)			145 (46.8)	165 (53.2)		

Caucasus region (42%), India (62%), and among other Asian population.¹⁶ However, the TT genotype frequency in the African population was nearly zero (0% in Ghana, 4% in Kenya, and 6% in Sudan), which was observably lower than that in other population.¹⁷

This shows that the distribution of polymorphism is different among population depending on their races and regions. In the studies of healthy Han subjects conducted by Kim,¹⁸ the frequencies of the CC, CT, and TT types in C3435T were 35.1%, 49%, and 15.9%, respectively. In our present studies, among the 204 Hui patients, the CC, CT, and TT genotypes accounted for 40.7%, 37.3%, and 22.1%, respectively, and the C and T alleles accounted for 59.3% and 40.7%, respectively. Compared to the results reported by Kim, there was no significant difference in genotype distributions ($P > 0.05$), suggesting there is no significant difference in C3435T polymorphism between the Hui and Han peoples.

In the present studies on Hui patients, the CC, CT, and TT genotype frequencies of the C1236T loci were 25.5%, 40.2%, and 34.3%, respectively, which were all significantly different compared to the Han population¹⁹ whose CC, CT and TT genotype frequencies were 14.4%, 38%, and 47.6%, respectively; $P < 0.05$. This suggests that C1236T polymorphism exists not only in different regions but divergent ethnic groups.

Different genetic polymorphisms of the MDR1 C3435T locus have different impacts on CR. Studies have shown that patients with MDR1 CT or TT mutations have a higher rate of clinical endpoint events compared to those who carry the CC wild-type genes. Furthermore, several large clinical trials have shown that subjects with the C3435T locus TT mutant gene have lower rates of clopidogrel metabolism and inhibited platelet activities and, thereby, have an increasing risk of thromboembolic events.^{9,20} In addition, the present studies found that the TT genotypes and T alleles of the C3435T locus were dominant in the CR group, while the CC genotypes and C alleles were dominant in the NCR group.

The differences between these 2 groups are statistically significant ($P = 0.004$), which suggest the mutation of the T locus may lead to CR, which is consistent with the results of the above studies. It is also reported that subjects who carries the wild-type C3435T locus have the maximum risk of a thromboembolism event,²¹ which may due to the different functions of the alleles and the subsequent activity of encoding functional proteins. Due to the

different frequencies of alleles in different races and regions, there are differences in the activities in coding functional proteins. For the C1236T site, Sibbing²² found that the CC wild type had a lower platelet inhibition rate when compared to the CT+TT mutant. Furthermore, other domestic and foreign studies did not reveal a significant correlation between C1236T and antiplatelet drug resistance.²³ The polymorphism of this locus was not associated with CR in the present studies.

A study has shown that patients with myocardial infarction whose blood glucose level is higher than 8.5 mmol/l are usually low in response to clopidogrel and prone to clopidogrel resistance,²⁴ which is consistent with the results of the present study. The different levels of fasting blood glucose between the 2 groups may interfere with the relationship between genetic polymorphism and CR. Hence, this variable should be controlled in future large-sample studies in order to reduce the impact of these interference factors on the results.

In order to clarify the correlation between MDR1 gene polymorphism and CR, a multivariate logistic regression equation was used for the analysis. Taking CR as the dependent variable, the C3435T and C1236T genotypes (compared with the CC types, which acted as a dummy variable) were the model's independent variables. The results revealed that the TT genotype of the C3435T locus was an independent risk factor for CR (OR = 2.992, $P = 0.010$, 95% CI: 1.301–6.880). In addition, fasting blood glucose was also an independent risk factor for CR ($P = 0.001$, OR = 2.479, 95% CI: 1.438–4.274), which is consistent with the report of Hochholzer.²⁵

In the present studies, we found that the MDR1 C3435T locus T allele mutation was associated with CR in Hui patients who had got PCI-treated CHD, but there was no significant relationship between the C1236T genetic polymorphism and CR in this patient group. However, due to the restriction of conditions, the platelet levels were not measured before drugs were taken. Meanwhile, the sample size was too small to be workable. Hence, these results need to be further confirmed by multi-center studies with larger sample sizes and higher experimental standards. Nevertheless, CR may be identified through genetic studies, which provide a theoretical basis for the individualization, safety, and rationale of clinical medication protocols for patients suffering from CHD after PCI.

Data Sharing Statement

We declared that materials described in the manuscript, including all relevant raw data, will be freely available to any scientists who wish to use them for non-commercial purposes without breaching participants' confidentiality.

Ethics Approval and Consent to Participation

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.

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Disclosure

The authors declare that they have no competing interests.

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