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The correlation between recurrent risk and CYP2C19 gene polymorphisms in patients with ischemic stroke treated with clopidogrel for prevention

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Abstract

Background: To explore the correlation between recurrent risk and CYP2C19 gene polymorphisms in patients with ischemic stroke (IS) treated with clopidogrel for prevention.

Methods: A total of 289 patients with IS treated with clopidogrel regularly were enrolled in this study, and stroke recurrence of all patients were recorded by follow-up. The correlation between CYP2C19 gene polymorphism and stroke recurrence in patients taking clopidogrel regularly was analyzed.

Results: After a mean follow-up period of 6 months, there were 289 patients who took clopidogrel regularly, and 41 of which occurred recurrent stroke. Patients of poor metabolizer and intermediate metabolizer had higher risk of recurrent stroke comparing with patients of extensive metabolize, and the odds ratios were 2.88 (95% confidence interval [CI] 1.31–6.33, $P = .068$) and 3.00 (95% CI 1.09–8.22, $P = .027$), respectively. The recurrence risk of *2 (G681A)A allele carriers was 3.30 times that of G allele carriers ($P = .0065$). The recurrence rate of stroke in patients carrying heterozygous and homozygous *2 allele mutant was 1.96 times ($P = .071$) and 3.30 times ($P = .012$) that of patients with wild-type genes. Multifactor logistic regression analysis result indicated carrying loss of function (LOF) allele was an independent risk factor of stroke recurrence.

Conclusion: For patients with IS treated with clopidogrel regularly for secondary prevention, poor metabolizer, and intermediate metabolizer patients had higher risk of recurrent stroke comparing with extensive metabolize ones. Carrying CYP2C19 LOF allele is an independent risk factor of stroke recurrence in patients with IS.

Abbreviations: CI = confidence interval, IS = ischemic stroke, LOF = loss of function, NIHSS = National Institutes of Health Stroke scale, OR = odds ratio.

Keywords: CYP2C19, gene polymorphism, clopidogrel, stroke, recurrence

1. Introduction

Stroke is common and often leads to disabling events worldwide, and it has become the 1st cause of morbidity and mortality in China.[1] Oral antiplatelet therapy is a widely used secondary prevention strategy for noncardiogenic ischemic stroke (IS).[2] Clopidogrel is recommended as an antiplatelet drug for secondary prevention of IS. As a precursor, clopidogrel must pass through the liver cytochrome P450 enzyme to be metabolized into the active product and then play the role of antiplatelet aggregation, among which CYP2C19 plays the most important role.[3] Studies have demonstrated that the polymorphism of CYP2C19 gene is closely related to the degree of platelet inhibition of clopidogrel, and the extensive metabolizer (EM) type has a higher platelet inhibition rate than the intermediate metabolizer (IM) type and slow metabolizer.[4] Asians seem to have a higher probability of carrying a loss of function (LOF) CYP2C19 allele (e.g., CYP2C19*2 or CYP2C19*3) than persons of either African or Caucasian ethnicity.[5] In our study, the correlation between recurrent risk and CYP2C19 gene polymorphisms in patients with IS treated with clopidogrel for prevention was investigated in Han patients with IS.

2. Methods

2.1. Patient recruitment

This was a retrospective study for patients admitted to the inpatient department of neurology of the First Affiliated Hospital of Shantou University Medical College due to IS and regularly followed up by 1 stroke neurologist and 1 pharmacist (SQC and GHL) between January 2015 and January 2018. This study was approved by the Institutional Review Board of the First Affiliated

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Hospital of Shantou University Medical College, and all patients provided written informed consent before the collection of their blood samples.

The inclusion criteria: an acute IS confirmed by computed tomography or magnetic resonance imaging within 1 week of onset and it meets the diagnostic criteria of IS; after clinical judgment, clopidogrel treatment was suitable for patients with secondary prevention. The exclusion criteria: patients with clotting disorders or other blood disorders; patients with serious heart, liver, and kidney diseases; patients received proton pump inhibitors; acute IS caused by cardioembolism. The onset time was defined as the time patients were last known to be without neurologic symptoms. Clinical data were obtained from the electronic medical record and existing paper charts of each patient. Based on the physician's discretion, patients with transient ischemic attacks or IS received 75 mg clopidogrel after the onset of symptoms daily. Clopidogrel was administered to the study patients within 2 hours after initial imaging.

2.2. Parameters studied

Patient-related factors like gender, age, weight, hypertension, diabetes, current smoking, drinking, liver function, renal function, hyperlipidemia, hyperhomocysteinemia, atrial fibrillation, coronary heart disease, carotid plaque, CYP2C19 metabolic genotype of clopidogrel, NIHSS score at enrollment, Barthel score at enrollment, and drug therapy during follow-up (Statins, angiotensin-converting enzyme inhibitors/angiotensin receptor antagonist [ACEI/ARB], β-blocker, calcium antagonist), recurrence of IS.

2.3. CYP2C19 genotyping

Whole blood was obtained for CYP2C19 genotyping with the CYP2C19 genotyping kit (Shanghai, China) (DNA Microarray) in accordance with the manufacturer's instructions. The CYP2C19 genotyping kit can identify the CYP2C19*2 and *3 variations. The CYP2C19 genotype was classified into 3 phenotypic groups: EMs (*1/*1), IMs (*1/*2 or *1/*3), and poor metabolizers (PMs; *2/*2, *3/*3, or *2/*3).

2.4. Endpoint events and follow-up methods

Endpoint event: recurrent IS. Follow-up methods: patients were followed up every 3 months through inpatient and outpatient service, telephone, mobile APP, etc. Patients' medication status, the occurrence of endpoint events, and the time of occurrence were recorded.

2.5. Statistical analysis

Patient-related factors were assessed using Pearson Chi-squared test or the Student *t* test. Variables individually found to have a significant association with recurrence were then analyzed using multivariable logistic regression. Statistical significance was attributed for *P*-value $<.05$. All calculations were performed with SPSS 22.0 software.

3. Results

3.1. Characteristics of the patients

A total of 289 patients met the inclusion and exclusion criteria, including 159 (63.98%) with CYP2C19 mutant gene (carrying CYP2C19*2 and/or *3 allele) and 130 without mutant gene (carrying CYP2C19*1/*1 allele). After a mean follow-up period of 6 months, patients were regularly treated with clopidogrel for secondary prevention. There were 168 males and 221 females, mean age 66.60 ± 10.90, range 25 to 91. There were no significant differences in demographic or baseline clinicopathologic features between mutant gene group and without mutant gene group. The detailed information of the patients is summarized in Table 1.

Table 1

Baseline characteristics of the study patients.

	Total (n = 289)	Mutant gene group (n = 159)	Without mutant gene group (n = 130)	*P*-value
Men, n (%)	168 (58.1%)	92 (57.9%)	76 (58.5%)	.918
Age, yrs	66.60 ± 10.90	65.82 ± 10.20	67.55 ± 11.67	.179
Weight, kg	59.02 ± 7.50	59.04 ± 7.09	59.00 ± 7.99	.969
Abnormal liver function, n (%)	9 (3.1%)	2 (1.3%)	7 (5.4%)	.083
Abnormal renal function, n (%)	30 (10.4%)	20 (12.6%)	10 (7.7%)	.175
Hypertension, n (%)	208 (72.0%)	114 (71.7%)	94 (72.3%)	.909
Diabetes, n (%)	111 (38.4%)	61 (38.4%)	50 (38.5%)	.987
Hyperlipidemia, n (%)	76 (26.3%)	38 (23.9%)	38 (29.2%)	.306
Hyperhomocysteinemia, n (%)	79 (27.7%)	41 (26.1%)	38 (29.7%)	.503
Current smoking, n (%)	91 (33.1%)	53 (35.3%)	38 (30.4%)	.387
Drinking, n (%)	34 (12.5%)	19 (12.8%)	15 (12.1%)	.870
Atrial fibrillation, n (%)	19 (6.6%)	11 (6.9%)	8 (6.2%)	.794
Coronary heart disease, n (%)	22 (7.6%)	10 (6.3%)	12 (9.2%)	.348
Carotid plaque, n (%)	201 (70.0%)	117 (74.1%)	84 (65.1%)	.100
NIHSS score at enrollment	5.78 ± 5.22	6.60 ± 5.82	4.79 ± 4.22	.053
Barthel score at enrollment	58.44 ± 24.37	56.81 ± 25.07	60.44 ± 23.43	.218
Drug therapy during follow-up				
Statins, n (%)	267 (92.4%)	153 (96.2%)	114 (87.7%)	.060
ACEI/ARB, n (%)	74 (25.6%)	41 (25.8%)	33 (25.4%)	.938
β-Blocker, n (%)	21 (7.3%)	15 (9.4%)	6 (4.6%)	.116
Calcium antagonist, n (%)	153 (52.9%)	83 (52.2%)	70 (53.8%)	.780

ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor antagonist

Table 2

Hardy–Weinberg equilibrium test for CYP2C19 genotype.

	Genotype frequency							
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	χ^2	*P*-value
Actual frequency	130	102	17	31	9	0		
Theoretical frequency, %	43.00	19.60	29.50	8.90	1.35	0.20	2.44	.30
Theoretical frequency	124.27	56.64	8.53	25.72	3.90	0.58		

3.2. CYP2C19 genotype distribution

Among patients, 130 cases was identified as EM (CYP2C19*1/*1), 119 cases as IM (CYP2C19*l/*2 or *1/*3), 40 cases as PM (CYP2C19*2/*2 or *2/*3 or *3/*3), and Hardy–Weinberg equilibrium test was no significant difference ($P=.30$). The detailed information is summarized in Table 2.

3.3. Metabolizer and allele frequency of CYP2C19 association with recurrent stroke

There were 8 cases of PM in the recurrent IS group and 32 cases in the nonrecurrence group. Among IM, 23 patients had recurrent stroke and 96 patients had no recurrent stroke. Results compared with EM, stroke recurrence rate both in IM and PM had significant difference ($P<.05$). The detailed information is summarized in Table 3.

The frequency of patients with *2 (G681A) A alleles in the recurrence group and the nonrecurrence group was 42.68% and 27.82%. Compared with G allele, the odds ratios (ORs) was 3.30, $P=.0065$. Patients with *2 mutant heterozygotes allele (CYP2C19*1/*2, *2/*3) who suffered a recurrence of stroke were 1.96 times vs those with the wild type, $P=.071$. Patients with *2 mutant homozygous allele (CYP2C19*2/*2) were 3.30 times who suffered a recurrence of stroke vs those with wild type, $P=.012$. Compared with the wild-type G allele, there was no statistically significant difference in the risk of stroke recurrence. The detailed information is summarized in Table 4.

3.4. Relationship between stroke risk factors, LOF CYP2C19 allele, and risk of stroke recurrence

Patients who suffered stroke recurrence were more likely to LOF CYP2C19 alleles (75.6% vs 51.6%, $P=.004$), hypertension (85.4% vs 69.8%, $P=.040$), hyperhomocysteinemia (46.3% vs 24.6%, $P=.007$), drug therapy during follow-up (ACEI/ARB; 43.9% vs 22.6%, $P=.006$). The detailed information is summarized in Table 5.

In the multivariable logistic regression model adjusting for LOF CYP2C19 alleles, hypertension, hyperhomocysteinemia, drug therapy during follow-up (ACEI/ARB) found to be significantly associated with LOF CYP2C19 alleles (OR = 3.13; 95% CI 1.446–6.770; $P=.004$) and hyperhomocysteinemia (OR = 2.61; 95% CI 1.287–5.296; $P=.008$). It indicated that LOF CYP2C19 alleles and hyperhomocysteinemia were the independent risk factors. The detailed information is summarized in Table 6.

4. Discussion

A total of 289 patients with IS treated with clopidogrel regularly for secondary prevention were included in this study. Stroke

Table 3

CYP2C19 genotype association with recurrent ischemic stroke.

CYP2C19 genotype	Recurrent group (n = 41), %	Nonrecurrence group (n = 248), %	OR (95% CI)	*P*-value
Extensive metabolizer, n (%)	10 (24.39)	120 (48.39)		
Intermediate metabolizer, n (%)	23 (56.10)	96 (38.71)	2.88 (1.31–6.33)	.0068
Poor metabolizer, n (%)	8 (19.51)	32 (12.90)	3.00 (1.09–8.22)	.027

Table 4

CYP2C19 genotype and the frequency of allele association with recurrent ischemic stroke.

Allele	Recurrent group, n (%)	Nonrecurrence group, n (%)	OR (95% CI)	*P*-value
CYP2C19*2 (681G>A)				
GG	14 (34.14)	133 (53.63)		
GA	19 (46.34)	92 (37.10)	1.96 (0.94–4.11)	.071
AA	8 (19.52)	23 (9.27)	3.30 (1.25–8.76)	.012
G (*1)	47 (57.32)	358 (72.18)		
A (*2)	35 (42.68)	138 (27.82)	3.30 (1.25–8.76)	.0065
CYP2C19*3 (636G>A)				
GG	37 (90.24)	226 (91.13)		
GA	4 (9.76)	22 (8.87)	1.11 (0.36–3.41)	.85
AA	0	0	–	–
G (*1)	78 (95.12)	474 (95.56)		
A (*2)	4 (4.88)	22 (4.44)	1.15 (0.37–3.30)	.86

CI = confidence interval, OR = odds ratio.

Table 5

Clinical and procedural characteristics of patients based on recurrent ischemic stroke.

Risk factors	Total	Recurrent group, n (%)	Nonrecurrence group, n (%)	*P*-value
N	289	41	248	
Men, n (%)	168 (58.1%)	27 (65.9%)	141 (56.9%)	.279
Age, yr	66.60 ± 10.90	66.88 ± 11.10	66.55 ± 10.89	.860
Weight, kg	59.02 ± 7.50	60.10 ± 7.90	58.84 ± 7.43	.321
LOF CYP2C19 alleles	159 (55.0%)	31 (75.6%)	128 (51.6%)	.004
Abnormal liver function, n (%)	9 (3.1%)	3 (7.3%)	6 (2.4%)	.121
Abnormal renal function, n (%)	30 (10.4%)	4 (9.8%)	26 (10.5%)	1.000
Hypertension, n (%)	208 (72.0%)	35 (85.4%)	173 (69.8%)	.040
Diabetes, n (%)	111 (38.4%)	17 (41.5%)	94 (37.9%)	.730
Hyperlipidemia, n (%)	76 (26.3%)	11 (26.8%)	65 (26.2%)	1.000
Hyperhomocysteinemia, n (%)	79 (27.7%)	19 (46.3%)	60 (24.6%)	.007
Current smoking, n (%)	91 (33.1%)	14 (34.1%)	77 (32.9%)	.859
Drinking, n (%)	34 (12.5%)	2 (4.9%)	32 (13.8%)	.130
Atrial fibrillation, n (%)	19 (6.6%)	4 (9.8%)	15 (6.0%)	.325
Coronary heart disease, n (%)	22 (7.6%)	0 (0.0%)	22 (8.9%)	.053
Carotid plaque, n (%)	201 (70.0%)	24 (58.5%)	177 (72.0%)	.098
NIHSS score at enrollment	5.78 ± 5.22	5.35 ± 3.53	5.88 ± 5.52	.679
Barthel score at enrollment	58.44 ± 24.37	59.03 ± 21.14	58.35 ± 24.86	.877
Statins, n (%)	267 (92.4%)	38 (92.7%)	229 (92.3%)	1.000
ACEI/ARB drugs, n (%)	74 (25.6%)	18 (43.9%)	56 (22.6%)	.006
β-Blocker, n (%)	21 (7.3%)	2 (4.9%)	19 (7.7%)	.749
Calcium antagonist, n (%)	153 (52.9%)	24 (58.5%)	129 (52.0%)	.501

ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor antagonist, LOF = loss of function.

recurrence rate in patients with CYP2C19 LOF allele is higher than that of patients without mutant gene. What's more, CYP2C19 genetic polymorphism has a significant influence on the pharmacokinetics of clopidogrel. Multifactor logistic regression analysis result indicated carrying LOF allele was an independent risk factor of stroke recurrence.

At present, many studies have confirmed that CYP2C19 gene mutation was associated with clopidogrel resistance at home and abroad. However, most studies have focused on coronary atherosclerotic heart disease, and there are few studies on the correlation between CYP2C19 gene polymorphism and stroke.[6] In 1 study, 625 patients with acute IS given clopidogrel for secondary prevention were enrolled. The results showed that patients carried CYP2C19*2/*3 LOF allele had a higher incidence of composite vascular events (vascular death, nonfatal IS, and nonfatal myocardial infarction) than those without mutant gene.[7] The above results indicate that the CYP2C19 genotype plays an important role in secondary prevention of IS and CYP2C19 LOF allele was an independent risk factor of stroke recurrence, which was consistent with the results of our study.

In our study, patients with CYP2C19 LOF allele accounted for 55.02%, which was similar to previous reports and much higher than white people and black people.[8] China is a country with a large number of stroke patients, with about 3 million FIS patients every year.[9] According to the data of Chinese stroke registration survey, the recurrence rate of IS within 6 months after onset was as high as 16%. Therefore, the study on the relationship between CYP2C19 gene polymorphism and stroke recurrence was of great significance for reducing the risk of stroke recurrence. Meta-analysis we conducted suggested that carriers of the CYP2C19 allele LOF may be associated with attenuated response to clopidogrel after IS (total risk ratio 2.14; 95% CI 1.73–2.65; $P < .00001$; Fig. 1).[10–24] The current studies were consistent with our study.

According to the results of our study, the screening of CYP2C19 gene polymorphisms for patients was meaningful for guiding clinical individualized antiplatelet therapy. On the basis of the genotype of CYP2C19, adjusting antiplatelet drug therapy, such as increasing the drug dose, combining drugs or using new antiplatelet drugs (ticagrelor, plagre, etc) may be a potential solution to clopidogrel resistance, but it has not been fully evaluated.[25–27] Adjusting the dose of antiplatelet drugs according to the results of platelet function test also did not seem to improve the prognosis of patients.

Our study has the following shortcomings. First, the subjects of our study were mainly the local Han population in Chaoshan, China, and only CYP2C19*1/*2/*3 allele, the most common CYP2C19 gene, was detected. Second, the sample size is relatively

Table 6

Multivariable logistic regression analysis of association between recurrent ischemic stroke and LOF CYP2C19 alleles, hypertension, hyperhomocysteinemia, ACEI/ARB drugs.

Risk factors	*B*	Wald	OR	95% CI	*P*-value
LOF CYP2C19 alleles	1.141	8.39	3.13	1.446–6.770	.004
Hypertension	0.69	2.63	2.16	0.849–5.478	.106
Hyperhomocysteinemia	0.72	4.55	2.61	1.287–5.296	.008
ACEI/ARB drugs	0.544	2.59	1.72	0.888–3.344	.107

ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor antagonist, CI = confidence interval, LOF = loss of function, OR = odds ratio.

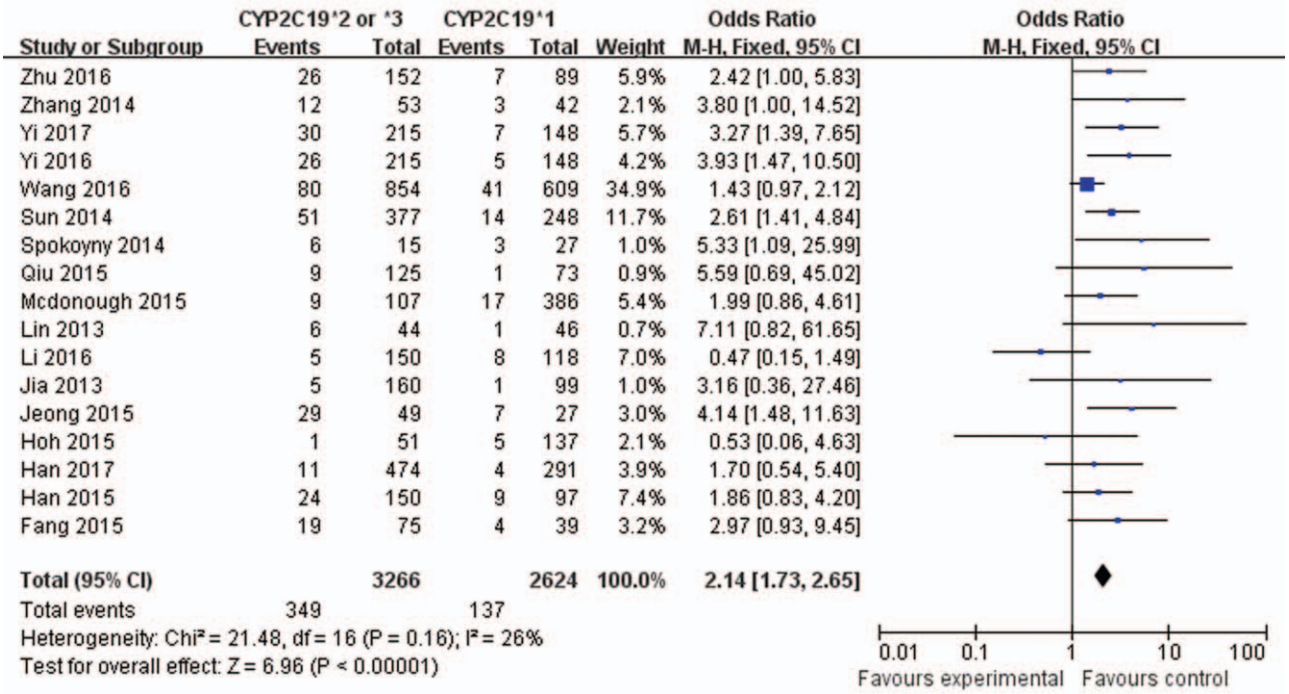

Figure 1. Risk of stroke for acute ischemic stroke or transient ischemic attack patients with any copy of CYP2C19*2, *3, to wild-type *1.

small. According to the results of the present study, carrying the CYP2C19 LOF allele is an independent risk factor for stroke recurrence after clopidogrel therapy in patients with IS. However, more studies are needed on the adjustment of antiplatelet therapy in IS patients with CYP2C19 LOF allele.

5. Conclusion

In summary, CYP2C19 LOF alleles could reduce the responsiveness of clopidogrel. For patients of IS treated with clopidogrel regularly for secondary prevention, PM and IM patients had higher risk of recurrent stroke comparing with EM ones.

Author contributions

Conceptualization: Guohua Liu, Sufang Yang, Siqia Chen.
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