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Effect of 106PEAR1 and 168PTGS1 genetic polymorphisms on recurrent ischemic stroke in Chinese patient

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Abstract

The impact of genetic polymorphisms on the occurrence of recurrent ischemic stroke (RIS) is not fully understood. This study was aimed to examine the relationships among the 106PEAR1 and 168PTGS1 polymorphisms and RIS.

This was a single-center, retrospective, case-control study of patients seen in consultation between March 2016 and December 2016 at the Shandong Provincial Hospital. The 106PEAR1 (G>A) and 168PTGS1 (−842A>G) polymorphisms were determined by fluorescence in situ hybridization.

There were 56 patients with RIS and 137 with initial stroke. Compared with the initial group, the RIS group showed lower LDL-C levels ($P = .04$). 168PTGS1 (−842A>G) did not meet the Hardy–Weinberg equilibrium. The AA genotype of the 106PEAR1 (G>A) polymorphism was more frequent in the RIS group (17.9% vs 5.8%, $P = .009$). The A allele also showed a higher frequency than the G allele in the RIS group ($P = .02$). The multivariable logistic regression analysis showed that 106PEAR1 (G>A) (OR = 3.24, 95%CI: 1.04–10.14, $P = .04$) and lipid-lowering agents (OR = 9.18, 95%CI: 4.48–18.84, $P < .001$) were independently associated with RIS.

The polymorphism at 106PEAR1 (G>A) was independently associated with RIS in Chinese patients. The assessment of genetic polymorphisms in the prediction of RIS warrants further investigation in order to improve patient management and prognosis after a first ischemic stroke.

Abbreviations: AR = aspirin resistance, CRP = C-reactive protein, CT = computed tomography, DBP = diastolic blood pressure, FISH = fluorescence in situ hybridization, HCY = homocysteine, HDL-C = high-density lipoprotein cholesterol, IS = ischemic stroke, LDL-C = low-density lipoprotein cholesterol, MRI = magnetic resonance imaging, PEAR1 = Platelet endothelial aggregation receptor-1, PTGS1 = prostaglandin-endoperoxide synthase 1, RIS = recurrent ischemic stroke, SBP = systolic blood pressure, SD = standard deviation, TC = total plasma cholesterol, TG = triglycerides, TIA = transient ischemic attack, TOAST = Trial of Org 10172 in Acute Stroke Treatment.

Keywords: genetic polymorphisms, ischemic stroke, PEAR1, recurrence

1. Introduction

Stroke is the second leading cause of mortality worldwide and is the most common cause of long-term disability.[1,2] Recurrent ischemic stroke (RIS) is common and it is associated with poor prognosis in patients with acute ischemic stroke (IS).[3] In China, with a population of 1.4 billion, the annual stroke death toll is approximately 1.6 million and stroke has superseded heart diseases as the major cause of death.[4] The 1-year risk of RIS has been reported to vary from 3.6% to 12% in Western countries.[5] In China, the risk of RIS can be as high as 7.0% to 21.4%.[6,7] RIS is associated with severe consequences including long-term disability and death.[8] Nevertheless, the factors leading to higher risk of RIS are still poorly understood. If we could predict the recurrence the stroke, some appropriate preventive measures could be taken in patients at higher risk, reducing disability and mortality from RIS.[9–11]

Aspirin therapy is the mainstay approach to reduce the risk of RIS and other ischemic events. Nevertheless, some patients with IS will experience RIS despite taking aspirin,[12] which is known as aspirin resistance (AR). A number of potential genetic and environmental factors may lead to AR.[13] Some studies have shown that antiplatelet drug resistance was associated with RIS,[12,14] but the association between genetic polymorphisms and RIS has not been adequately evaluated.

Platelet endothelial aggregation receptor-1 (PEAR1) is a platelet transmembrane protein that is activated by platelet-to-platelet contact and agonist stimulation. Activated PEAR1 sends signals to enhance and stabilize platelet thrombin through the functionality of GPIIb/IIIa.[15,16] Some clinical trials have shown that genetic variations in PEAR1 are important determinants of platelet reactivity during aspirin treatment.[17] Furthermore,

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polymorphisms in the prostaglandin-endoperoxide synthase 1 (PTGS1) gene may contribute to AR,[18–21] but it is controversial.[22–25]

Therefore, the aim of the present study was to examine the relationships between RIS and the 106PEAR1 and 168PTGS1 polymorphisms. The results could help identify individuals at high risk of RIS.

2. Methods

2.1. Study design and patients

This was a single-center, retrospective, case-control study of patients seen in consultation between March 2016 and December 2016 at the Shandong Provincial Hospital. The study was approved by the ethics committee of the Shandong Provincial Hospital. Informed consent was waived by the committee because of the retrospective nature of the study.

The inclusion criteria were:

1. acute IS or transient ischemic attack (TIA) by computed tomography (CT) or magnetic resonance imaging (MRI) according to the World Health Organization criteria[26];
2. within 14 days after onset; and
3. the symptoms reflected the infarct area. Patients who had cardioembolism, trauma, vascular malformations, brain tumors, cerebral hemorrhage, or congenital brain disorders were excluded.

The patients were divided into the RIS and initial stroke groups according to whether there was a previous history of IS at admission. The subtypes of ischemic stroke were categorized according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[27] RIS was defined as a new cerebrovascular event that met one of the following criteria[28]:

1. the event resulted in a neurological deficit that was clearly different from that of the index stroke;
2. the event involved a different anatomic site or vascular territory from that of the index stroke; or
3. the event was of a stroke subtype different from that of the index stroke.

Baseline data were collected from the medical charts using the reports of the face-to-face interviews performed at admission by trained neurologists. Collected data also included age, gender, and histories of smoking, drinking, hypertension, and diabetes. Biochemistry was based on the fasting blood samples that were obtained in the morning of the second day of admission, and included triglycerides (TG), total plasma cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), homocysteine (HCY) and C-reactive protein (CRP).

Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg. Hypertension was graded as grade 1 (SBP 140–159 mmHg or DBP 90–99 mmHg), grade 2 (SBP 160–179 mmHg or DBP 100–109 mmHg), and grade 3 (SBP ≥180 mmHg or DBP ≥110 mmHg).[29,30]

2.2. Genotyping

Blood samples with EDTA were used for genotyping. The 2 SNPs were 106PEAR1 (G>A) and 168PTGS1 (−842A>G). Genotyping was performed routinely using fluorescence in situ hybridization (FISH) by Shandong Provincial Hospital Pharmacy Department using a fluorescence detection system (TL998A, Tianlong, Xi'an, China). The white blood cells were enriched by centrifugation using 150 μl of whole blood in 1.2 ml of NH_4Cl, at 500 to 700 × g for 5 minutes at room temperature. The precipitate was resuspended in 1 ml of NH_4Cl and the mixture was centrifuges again at 500 to 700 × g for 5 minutes at room temperature. The nucleic acid extraction kit (Sino-Era Jiyin Tech Co., ltd., Beijing, China) was used to extract the DNA, as per the manufacturer's instructions. The FISH reagent (Sino-Era Jiyin Tech Co., ltd., Beijing, China) was added to 1.5 μl of sample and the samples were read by the device, as per the manufacturer's instructions.

2.3. Statistical analysis

The Hardy–Weinberg equilibrium was tested for the 106PEAR1 (G>A) and 168PTGS1 (−842A>G) polymorphism using the chi-square test. Continuous variables were presented as means ± standard deviation (SD) and compared using the Student's *t* test. Categorical variables were reported as counts (percentages) and the chi-square test was used to compare the groups. Multivariable logistic regression analysis (step-wise backward method) was used to identify independent predictors for RIS ($P < .10$). All statistical analyses were performed using SPSS 20.0 (IBM, Armonk, NY). Two-tailed $P < .05$ was considered statistically significant.

3. Results

3.1. Characteristics of the patients

A total of 193 patients with IS were included and divided into the initial stroke group (n = 137, 71.0%) and the RIS group (n = 56, 29.0%). The demographic and clinical characteristics of the participants are summarized in Table 1. There were no differences between the 2 groups regarding age, gender, smoker, alcohol use, blood pressure, diabetes, HDL-C, TG, HCY, and CRP. Compared with the initial group, the RIS group showed

Table 1

Characteristics of the patients.

	Recurrent stroke (n = 56)	Initial stroke (n = 137)	*P*
Age (yr)	64.9 ± 8.9	62.5 ± 10.7	.137
Sex, male, n (%)	43 (76.8)	86 (62.8)	.061
Smoker, n (%)	21 (37.5)	58 (40.9)	.535
Alcohol use, n (%)	22 (39.3)	57 (41.6)	.766
Blood pressure, n (%)			.483
Normal	12 (21.4)	44 (32.1)	.457
Grade 1	4 (7.1)	11 (8.0)	
Grade 2	9 (16.1)	16 (11.7)	
Grade 3	31 (55.4)	66 (48.2)	
Diabetes, n (%)	15 (26.8)	38 (27.7)	.893
Lipid-lowering agents	39 (69.6)	27 (19.7)	<.05
Total cholesterol, mmol/L	4.31 ± 1.21	4.67 ± 1.07	.052
HDL cholesterol, mmol/L	1.22 ± 1.20	1.07 ± 0.24	.161
LDL cholesterol, mmol/L	2.66 ± 0.96	2.95 ± 0.86	.042
Triglycerides, mmol/L	1.52 ± 0.80	1.61 ± 0.84	.496
Homocysteine	15.78 ± 8.65	15.82 ± 10.96	.976
C-reactive protein	4.83 ± 9.30	6.20 ± 18.65	.601

Table 2

Hardy–Weinberg equilibrium test.

Gene name (SNP)	Allele frequency	Genotypes frequency	P
106PEAR1 (G>A)	G (0.67); A (0.33)	GG (0.42);AG (0.48);AA (0.09)	.25
168PTGS1 (−842A>G)	A (0.96); G (0.04)	AA (0.94);AG (0.04);GG (0.02)	<.05

lower LDL-C levels ($P = .042$). In the RIS group, 45 patients were receiving antiplatelet drugs before admission and 39 patients were receiving lipid-lowering drugs. In the initial stroke group, 27 patients were receiving lipid-lowering drugs before admission.

3.2. Genotypes

Table 2 shows that 168PTGS1 (−842A>G) did not meet the Hardy–Weinberg equilibrium ($P < .05$). Genotype results for 106PEAR1 (G>A) are reported in Table 3. The distribution of the 106PEAR1 (G>A) polymorphism was significantly different between the 2 groups ($P = .023$). The AA genotype was more frequent in the RIS group (17.9% vs 5.8%). The A allele also showed a higher frequency than the G allele in the RIS group ($P = .023$).

3.3. Association of the 106PEAR1 (G>A) polymorphism and other factors with RIS by multivariable analysis

The multivariable logistic regression analysis showed that 106PEAR1 (G>A) (OR = 3.243, 95%CI: 1.037–10.143, $P = .043$) and lipid-lowering agents (OR = 9.183, 95%CI: 4.476–18.841, $P < .001$) were independently associated with RIS (Table 4). After adjustment for lipid-lowering agents and LDL-C, AA in the recessive model (OR = 3.857, 95%CI: 1.047–14.209, $P = .042$) was independently associated with RIS. In the codominant model, GA at 106PEAR1 (G>A) (OR = 0.235, 95%CI: 0.059–0.934, $P = .040$) was independently associated with RIS. The dominant model was not statistically significant (Table 5).

4. Discussion

The impact of genetic polymorphisms on the occurrence of RIS is not fully understood. Therefore, this study aimed to examine the relationships among the 106PEAR1 and 168PTGS1 polymorphisms and RIS. The results suggest that the polymorphism at 106PEAR1 (G>A) was independently associated with RIS in Chinese patients. The assessment of genetic polymorphisms in the prediction of RIS warrants further investigation in order to improve patient management and prognosis after a first ischemic stroke.

Table 3

Genotypes and alleles in 2 groups.

106PEAR1 (G>A)	Genotype	Recurrent stroke (n = 56)	Initial stroke (n = 137)	P
Genotype				.023
	GG	19 (33.9%)	63 (46.04%)	
	AG	27 (48.2%)	66 (48.2%)	
	AA	10 (17.9%)	8 (5.8%)	
Allele				.023
	A	47 (41.96%)	82 (29.93%)	
	G	65 (58.04%)	192 (70.07%)	

Table 4

Association of the 106PEAR1 polymorphism with RIS by multivariable analysis.

	Adjusted OR	95%CI	P
106PEAR1 (G>A)	3.243	1.037–10.143	.043
Lipid-lowering agents	9.183	4.476–18.841	<.001

PEAR1 is a platelet transmembrane protein that play an important role in platelet reactivity and endothelial function.[15,31] The PEAR1 gene comprises 23 exons and 22 introns and its protein participates in extracellular protein-protein interactions.[32] Genetic variations in the PEAR1 gene have been repeatedly reported to affect platelet aggregation in both the presence and absence of antiplatelet therapy.[33] The roles of PEAR1 polymorphisms in platelet aggregation have been revealed in some studies. Lewis et al[34] showed that in aspirin-treated patients, carriers of the A allele of rs12041331 in the PEAR1 gene had significantly increased risk of myocardial infarction compared with GG homozygotes. Wurtz et al[17] showed that the A allele of rs12041331 was associated with reduced platelet aggregation and increased platelet activation with coronary artery disease. Yao et al[35] showed that PEAR1 polymorphisms influenced the response to clopidogrel and aspirin in Chinese patients with cardiovascular diseases. Nevertheless, the role of PEAR1 polymorphisms on the risk of RIS remains mostly unknown. In the present study, the AA genotype of 106PEAR1 (G>A) was found to have a significant association with RIS by multivariable analysis. This is supported by Zhang et al[36] who showed that PEAR1 polymorphisms could be used to guide the use of clopidogrel and aspirin. On the other hand, a previous study showed that PEAR1 polymorphisms were not associated with AR.[37] Discrepancies among studies may be due to a number of factors. The 3 studies did not examine exactly the same polymorphisms and some differences were observed in the distribution of the polymorphisms among the studies. This could be explained by differences in populations since the present study was performed in a population from Northeast China, while Peng et al[37] studied a population from Southeast China, and Zhang et al[36] studied an Eastern China population. Finally, the 3 studies used different approaches for the detection of the polymorphisms

Most of the variants in PTGS1 are present at low frequency, which makes it difficult to detect the true association. Since aspirin therapy is effective to reduce the risk of recurrent stroke and other ischemic events, PTGS1 genetic susceptibility may contribute to AR,[18–21] and thus modify the prognosis of cardiovascular diseases.[38–40] A recent study[38] in China identified an association of rs1330344 in the PTGS1 gene with poor vascular outcomes in patients with extracranial or intracranial stents, but this is controversial.[22–25,41] These inconsistencies may be due to the population characteristics, different SNP allele frequencies, and possible gene-environment interactions. Indeed, Cai et al[42] showed that an interaction between the PTGS1 gene and smoking might in part reflect the heterogeneity in the prognosis of patients with IS treated with aspirin. Therefore, smoking should be considered when examining the influence of this polymorphism on RIS. Nevertheless, in the present study, 168PTGS1 (−842A>G) was not associated

Table 5

Association of the 106PEAR1 (G>A) polymorphism with recurrence of ischemic stroke.

			Univariable			Multivariable	
Genetic models	**Genotype**	**Crude OR**	**95% CI**	***P***	**Adjusted OR***	**95% CI**	***P***
Dominant model							
	GG	1.00					
	GA/AA	1.658	0.868–3.167	.126	1.518	0.763–3.021	.234
Recessive model							
	GG/GA	1.00					
	AA	3.505	1.304–9.422	.013	3.857	1.047–14.209	.042
Codominant model							
	GG	1.00					
	GA	0.241	0.083–0.698	.009	0.235	0.059–0.934	.040
	AA	0.327	0.117–0.918	.034	0.282	0.073–1.093	.067

Adjusted for lipid-lowering agents and LDL-C.

with RIS. The main reason was probably because this polymorphism did not respect the Hardy–Weinberg equilibrium in our population of patients.

In the present study, the RIS group showed lower LDL-C levels and a higher frequency of lipid-lowering drugs than the initial stroke group, which may seem contradictory to the known risk factors for IS.[1,2] This could be explained by the possibility that those patients had additional risk factors for stroke or more comorbidities, and that they were more aggressively treated. Low LDL-C levels could be associated with increased stroke severity, resulting in poor outcomes and mortality,[43] but this is controversial.[44] Nevertheless, additional studies are necessary to examine this issue.

Our study has some limitations that should be considered when interpreting the results. First, the results may have possible bias due to the relatively small sample size and additional patients need to be included to emphasize statistical differences. Second, this study investigated Chinese Han patients, which may not represent other ethnic population. Third, no healthy control group was included as this was a study of the differences in SNPs between patients with first stroke and those with recurrent stroke. Fourthly, this study only investigated 2 variants in the PEAR1 and 168PTGS1 genes. Several other gene polymorphisms may be associated with RIS. Therefore, future studies should involve multiple populations, a larger sample size, and a larger set of genetic variants.

The present study showed that the AA genotype at 106PEAR1 (G>A) might be an independent risk factor for RIS. There was no association of the 168PTGS1 (−842A>G) polymorphism with RIS. These findings need to be confirmed in future studies. Admittedly, further studies may also reveal different conclusions. The assessment of genetic polymorphisms in the prediction of RIS warrants further investigation in order to improve patient management and prognosis after a first ischemic stroke.

Author contributions

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