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Platelet glycoprotein IIb/IIIa polymorphism HPA-3 b/b is associated with increased risk of ischemic stroke in patients under 60 years of age

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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Background:

The role of genetic risk factors in ischemic stroke is unclear. Platelet glycoprotein IIb/IIIa (GpIIb-IIIa) has been implicated in the pathogenesis of ischemic stroke. We sought to evaluate the relationship between the GpIIb/IIIa complex gene polymorphism and ischemic stroke.

Material/Methods:

We investigated the association of the GpIIb/IIIa complex gene polymorphism with stroke risk in 306 patients with acute ischemic stroke and 266 control subjects by determining the GpIIb and GpIIIa genotype from leukocyte DNA by polymerase chain reaction (PCR) followed by *FokI* and *SrfI* digestion, respectively.

Results:

Compared with controls, more patients presented with coronary heart disease, hypertension, smoking history, and diabetes. In addition, the patients had higher levels of cholesterol and glucose compared with the control subjects. All donors in the GpIIIa (n=572) group expressed the GpIIIa PI^{Al} (*HPA-1 aa*) phenotype. There were no significant differences between the *HPA-3* genotype (GpIIb) patient distribution (*aa*=39.9%, *ab*=41.4%, *bb*=28.7%) and healthy control subjects (*aa*=36.1%, *ab*=35.0%, *bb*=28.9%) (*P*=0.580). Among study participants <60 years, there was a significant difference in the *HPA-3* genotype distributions of patients (*aa*=42.9%, *ab*=19.8%, *bb*=37.4%) and healthy control subjects (*aa*=43.3%, *ab*=38.8%, *bb*=17.9%) (*P*=0.007). Furthermore, *HPA-3 b/b* increased the risk of ischemic stroke >2-fold (*P*=0.008).

Conclusions:

The GpIIb Ile/Ser⁸⁴³ gene polymorphism is associated with ischemic stroke among young and middle-aged adults (<60 years), especially males. The GpIIIa PI^{Al} phenotype has no relationship to ischemic stroke.

key words:

platelets • glycoprotein IIb/IIIa • polymorphism • ischemic stroke

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BACKGROUND

Stroke is the leading cause of adult disability and remains the third most common cause of death in industrialized nations [1]. In the US and Canada, thrombolysis is the only approved therapy during the acute stroke phase [2]; however, thrombolysis therapy has a narrow therapeutic window of 3 hours (up to 6 hours) because intravenous administration of t-PA within 3 hours after the onset of stroke has been shown to increase the probability of a favorable outcome [3]. In the US, fewer than 5% of patients with acute ischemic stroke receive t-PA, primarily because of a delay in hospital presentation, and are outside the 3-hour window [4]. In addition, the limitations of tissue plasminogen activators (t-PA) are well-known [5], and few stroke patients are recommended for this treatment.

Known risk factors for stroke include smoking, heart failure, atrial fibrillation, advanced age, dyslipidemia, hypertension, and diabetes mellitus. The single nucleotide polymorphism (SNP) *rs12425791* of nerve injury-induced protein-2 gene polymorphism was reported in Chinese Han patients with ischemia stroke [6]. However, the role of genetic risk factors in ischemic stroke remains largely undefined [7]. Platelet glycoprotein IIb/IIIa (GpIIb-IIIa), a membrane receptor for fibrinogen and von Willebrand factor, has been implicated in the pathogenesis of cerebral infarction. The genes encoding the platelet IIb and IIIa glycoprotein are located on chromosome 17, lying within a 260-kb fragment in the region 17q21 to 22 with GpIIb 3' to GpIIIa [8]. Several point mutations in the genes that encode GpIIb and GpIIIa result in disorders of platelet binding. Human platelet antigen-3 (*HPA-3*) (*Bak^a*/*Bak^b*) is a common polymorphism of platelet GpIIb, resulting from a thymine (T) to guanine (G) base change coding for an isoleucine-to-serine substitution at position 843 of the GpIIb heavy chain [8]. A transversion or exchange from thymine (T) to cytosine (C) was found at codon 33 of the GpIIIa, resulting in a Leu³³ (*HPA-1a*, *PI¹¹*) to Pro (*HPA-1b*, *PI¹²*) change [9].

Therefore, we carried out a study to evaluate the relationship between the GpIIb/IIIa complex gene polymorphism and ischemic stroke, and to provide a possible basis for preventing and treating ischemic stroke.

MATERIAL AND METHODS

Patients

From May 2008 and June 2010, we recruited patients with acute ischemic stroke who were admitted to the Neurology Department of Shanghai Sixth People's Hospital, Shanghai Jiao Tong University, Shanghai, China. Patient inclusion criteria were ≥ 18 years of age, and a clinical diagnosis of primary acute ischemic stroke. Ischemic stroke was diagnosed by a neurologist according to the World Health Organization (WHO) criteria [10] and confirmed by computed tomographic (CT) scan and/or conventional magnetic resonance imaging (MRI) of the brain. A cerebral CT scan or MRI was performed to exclude patients who had an intracranial hemorrhage. Patient exclusion criteria included other intracranial pathologies (eg, tumor, infection). Control subjects were included if they showed no neurological symptoms, and had no pathological findings on cranial CT or MRI, and if the stenosis of the cervical artery and vertebral artery was $<30\%$ by ultrasound examination.

The study protocol was approved by the local institutional review board, including the consent procedures, data security processes, and genotyping protocols. This study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the study subjects or their legal guardians.

Polymerase chain reaction (PCR)

Genomic DNA was isolated from 1 mL EDTA anticoagulated blood by protein salting and ethanol extraction of DNA as described by Miller et al. [11]. Oligonucleotide primers selected for the polymerase chain reaction (PCR) were used to amplify those parts of the genomic DNA that contain the polymorphic sequences corresponding to the *HPA-1* and *HPA-3* alleles. The *HPA-3* polymorphism, which is a substitution of Ile843Ser as a result of a T-to-G change in the *GpIIb* gene, was detected by PCR amplification of a 253-bp fragment with use of the forward primer (5'-CTC AAG GTA AGA GCT GGG TGG AAG AAA GAC-3') and the reverse primer (5'-CTC ACT ACG AGA ACG GGA TCC TGA AGC CTC-3'). The *HPA-1* polymorphism, which is a substitution of Leu33Pro as a result of a T-to-C change in the *GpIIIa* gene, was detected by PCR amplification of a 338-bp fragment with use of the forward primer (5'-CTG CAG GAG GTA GAG AGT CGC CAT AG-3') and the reverse primer (5'-CTC CTC AGA CCT CCA CCT TGT GCT CT -3') [12].

PCR was performed on 1 μ g genomic DNA template in a total volume of 50 μ L with 50 pmol of the appropriate primers and 2.5 units of *Taq* DNA polymerase. For *GpIIb*, 40 cycles of PCR were run at 96°C for 90 seconds, 60.5°C for 90 seconds, and 72°C for 3 minutes; for *GpIIIa*, 37 cycles of PCR were run at 94°C for 50 seconds, 57.5°C for 85 seconds, and 72°C for 110 seconds.

Restriction-enzyme digestion

Restriction-enzyme digestion of the PCR products were performed under conditions recommended by the manufacturers with 4 units *FokI* (SibEnzyme) and 10 units *ScrFI* (MBI Fermentas) for determination of *HPA-3* and *HPA-1* genotype, respectively. For *HPA-3*, the presence of Ile at position 843 resulted in the cleavage of the 253-bp fragment into a 126- and 127-bp fragment, whereas the presence of Ser was characterized by the uncleaved 253-bp fragment. Genotypes were classified as *aa* (Ile, Ile), *ab* (Ile, Ser) and *bb* (Ser, Ser); for *HPA-1*, the presence of Leu at position 33 resulted in the cleavage of the 338-bp fragment into a 214-, 46- and 78-bp fragment, respectively, whereas the presence of Pro resulted in the cleavage of the 338-bp fragment into a 77-, 137-, 46- and 78-bp fragment, respectively. Genotypes were classified as *aa* (Leu, Leu), *ab* (Leu, Pro) and *bb* (Pro, Pro) [12]. The PCR products of GpIIb and GpIIIa were analyzed by 1.6% agarose gel electrophoresis and visualized with ethidium bromide. The digests were analyzed by 2.2% agarose gel electrophoresis and visualized with ethidium bromide. Fragments were visualized by use of the Multi Genius Bio Imaging System (Dell).

Statistical analysis

Data are expressed as mean \pm standard deviation (s.d.). Student's T test was used to compare differences between groups. Categorical variables were compared by means of

Table 1. Characteristics of study participants with acute ischemic stroke and healthy control subjects.

	Patients	Control subjects	P
Age, y	69.55±11.36	67.89±7.11	0.192
SBP, mmHg	143.61±15.78	134.17±20.18	0.003
DBP, mmHg	85.84±8.48	83.32±10.28	0.270
Cholesterol, mmol/L	5.23±0.84	4.81±1.14	0.002
TGs, mmol/L	1.67±0.82	1.53±0.91	0.183
Glu, mmol/L	6.54±2.12	5.68±1.57	0.001
Smoking	199 (65.0%)	85 (32.0%)	0.000
CAD, n (%)	88 (28.8%)	32 (12.0%)	0.003
Diabetes, n (%)	59 (19.3%)	16 (6.0%)	0.004
Hypertension, n (%)	221 (72.2%)	107 (40.2%)	0.000

CAD – coronary artery disease; DBP – diastolic blood pressure; Glu – glucose; SBP – systolic blood pressure; TGs – triglyceride.

the χ^2 test or Fisher's exact test. Logistic regression analysis was used to analyze all classic risk factors together with the genotype on ischemic stroke. All statistical analyses were performed with SPSS 11.5 software. P values <0.05 were considered statistically significant.

RESULTS

Characteristics of study patients and control subjects

A total of 306 patients with ischemic stroke met the eligibility criteria and were included in the study; 266 control subjects were also recruited. Demographic characteristics of the patients and control subjects are presented in Table 1. There were 165 males and 141 females in the stroke patient group and 136 males and 130 females in the control group. The mean age of stroke patients was 69.55±11.36 years (range, 35–96 years) and the mean age of control subjects was 67.89±7.11 years (range, 42–97 years). No statistically significant difference was observed between the 2 groups. Compared with controls, more patients presented with coronary heart disease, hypertension, smoking history, and diabetes. In addition, patients had higher levels of cholesterol and glucose compared with the control subjects.

The patterns of enzyme-digested PCR products of *GpIIb* or *GpIIIa* gene

The PCR products for a portion of the *GpIIb* and *GpIIIa* genes generated from genomic DNA of different individuals are shown in Figures 1 and 2. For the *HPA-3(aa)* phenotype, the 2 fragments after cleavage differed so little that they appeared as a single band in the gel. For the *HPA-1* system, the expected fragments of 46 bp and 78 bp were too low in weight to be reliably detected by gel electrophoresis. All donors in the *GpIIIa* (n=572) expressed the *GpIIIa* PI^{A1} (*HPA-1 aa*) phenotype. These results were confirmed by subsequent sequencing of the PCR product.

The genotype between the patients and the control subjects

There were no significant differences in the *HPA-3* genotype distributions of patients (*aa*=39.9%, *ab*=41.4%, *bb*=28.7%)

and healthy control subjects (*aa*=36.1%, *ab*=35.0%, *bb*=28.9%) ($P=0.580$, Table 2).

The genotype between patients and control subjects with age under 60 years

Because age has been shown to influence the incidence of ischemic stroke, we further analyzed the clinical and genotyping data in study patients with acute ischemic stroke and healthy control subjects who were <60 years. The 2 groups showed no statistically significant difference in age, cholesterol, and glucose levels except that the ischemic stroke patients had significantly higher levels of triglycerides (Table 3).

There was a significant difference in the *HPA-3* genotype distributions of patients (*aa*=42.9%, *ab*=19.8%, *bb*=37.4%) and healthy control subjects (*aa*=43.3%, *ab*=38.8%, *bb*=17.9%) ($P=0.007$, Table 4).

In a logistic regression model comparing ischemic stroke patients to control subjects aged <60 years, the *HPA-3 b/b* genotype was significantly associated with ischemic stroke ($P=0.000$). We further found that the presence of *HPA-3 b/b* significantly increased the risk of ischemic stroke >2-fold ($P=0.008$, Table 5).

In addition, the *HPA-3 b/b* genotype might be a stronger risk factor for stroke among males ($P=0.032$) compared with females ($P=0.184$). As to the genotype (*aa+ab*) and *bb* in males, the presence of *HPA-3 b/b* increased the risk of ischemic stroke >2-fold (OR=2.194, 95%CI 1.177~4.091).

DISCUSSION

Platelets play an important role in the pathogenesis of thromboembolic diseases, and the possibility of inherited platelet risk factors for acute thrombosis is intriguing and especially important in assessing clinical risk and in prophylactic and therapeutic interventions. Platelet thrombosis is mediated by several platelet membrane receptor complexes, including glycoprotein Ib/IX, glycoprotein Ia/IIa, and glycoprotein IIb/IIIa [13]. *GpIIb/IIIa*, the Ca^{2+} -dependent receptor for fibrinogen on the surface of platelets, which consists of α_{IIb} subunits (*GpIIb*) and β_3 subunits (*GpIIIa*),

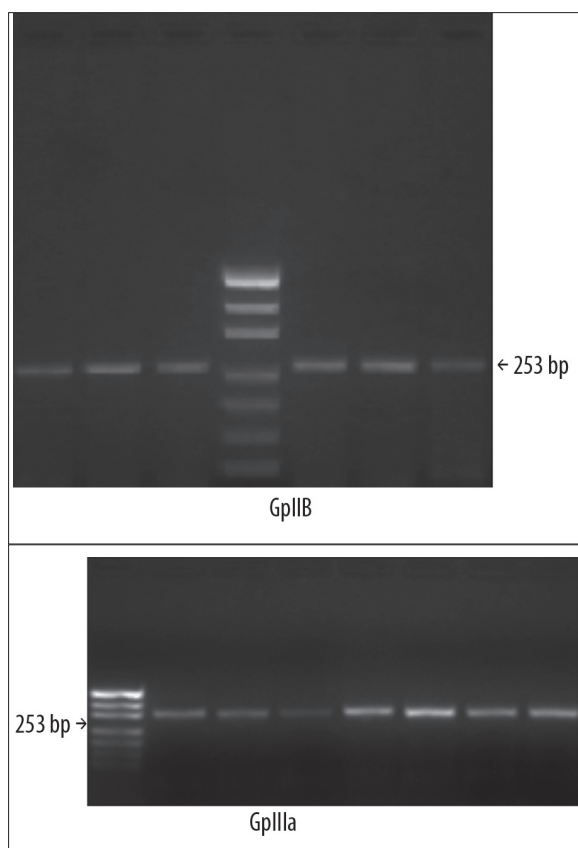


Figure 1. PCR products of GpIIb and GpIIIa DNA, pUC19 (MspI) fragments were used as standard. Analysis was performed on 1.6% agarose gel.

is the platelet integrin thought to mediate the fibrinogen-dependent common pathway of platelet aggregation [14]. The platelet GpIIb/IIIa receptors play an important role in thrombus formation.

Carlsson et al. demonstrated that the *HPA-1b* genotype was slightly more frequent in patients than in healthy blood donors [15]. In a rather small and limited study, GpIIb/IIIa $PI^{A1/A2}$ polymorphism was shown to be associated with atherothrombotic stroke in young patients [16] and in young white women [17]. Some studies indicate that there was a smoking-by-genotype association with the risk of lacunar infarcts and with survival. Among younger (55 to 69 years) stroke patients, smokers carrying the PI_{A2} allele were at a higher risk ($P=0.024$) of lacunar infarcts than were non-carrier smokers [18]. One study suggested that homozygosity for the *HPA-1b* ($P<0.001$) alleles was more prevalent in stroke patients than in control subjects [19]. Our study showed that there were no significant differences between patients and the control subjects for the *aa*, *ab*, and *bb* of *HPA-3* genotypes ($P=0.580$).

Previous studies indicated that various risk factors related with ischemic stroke include smoking, dyslipidemia, hypertension, diabetes, transthoracic echocardiographic abnormalities, and advanced age [18,20]. Hence, we further analyzed patients with acute ischemic stroke who were <60 years for a comparison according to the World Health Organization definition of the elderly. The present

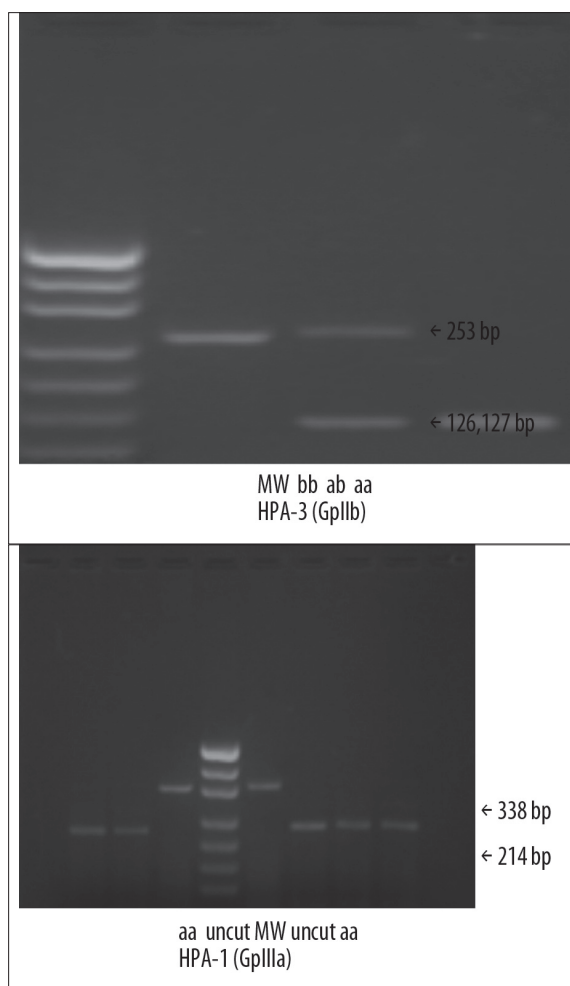


Figure 2. Analysis of *HPA-1* and *HPA-3* by PCR-RFLP using *ScrFI* and *FokI* endonuclease respectively, on 2.2% agarose gel. pUC19 (MspI) fragments were used as molecular weight (MW) standards.

results indicated that in this patient subgroup, the genotype ($P=0.007$) and triglycerides ($P=0.003$) between the patients and the control subjects were statistically significantly different. The *HPA-3 b/b* genotype in patients was significantly higher than in control subjects ($P=0.008$). The *HPA-3 b/b* genotype was a stronger risk factor for ischemic stroke among males ($P=0.032$) than females ($P=0.184$). As for the *HPA-1* system, all donors expressed the GpIIIa PI_{A1} (*HPA-1 a/a*) phenotype, suggesting that the GpIIIa PI_{A1} phenotype has no relationship with cerebral infarction in Chinese patients. The *HPA-3 b/b* genotype was significantly associated with ischemic stroke.

Drugs that inhibit platelet function are widely used to decrease the risk of arterial occlusion in patients with atherosclerosis. There are 3 families of anti-platelet agents with proven clinical efficacy: (1) cyclooxygenase inhibitors, such as aspirin; (2) adenosine diphosphate (ADP) receptor antagonists, such as ticlopidine and clopidogrel; and (3) glycoprotein IIb/IIIa antagonists. Antagonists of platelet membrane GpIIb/IIIa inhibit the final common step in platelet aggregation, which involves the binding of adhesive proteins to GpIIb/IIIa or integrin $\alpha_{IIb}\beta_3$, which is essential for

Table 2. The genotype of *HPA-3* between the patients and the control subjects.

	aa	ab	bb	X2	P
Patients (n,%)	122 (39.9%)	96 (31.4%)	88 (28.7%)	1.090	0.580
Control subjects (n,%)	96 (36.1%)	93 (35.0%)	77 (28.9%)		

Table 3. Characteristics of study participants with acute ischemic stroke and healthy control subjects (age <60 years).

	Patients (n=91)	Control subjects (n=67)	P
Age, years	51.55±7.36	52.27±4.62	0.697
SBP, mmHg	134.32±16.92	129.18±12.41	0.258
DBP, mmHg	82.95±10.31	77.05±11.38	0.078
Cholesterol, mmol/L	4.98±1.14	5.03±0.78	0.865
TGs, mmol/L	2.01±0.91	1.25±0.64	0.003
Glu, mmol/L	6.29±2.24	5.25±1.59	0.083
Smoking	57 (62.6%)	41 (61.2%)	0.870
CAD, n (%)	16 (17.6%)	8 (11.9%)	0.376
Diabetes, n (%)	11 (12.1%)	6 (9.0%)	0.610
Hypertension, n (%)	28 (30.8%)	19 (28.4%)	0.860

CAD – coronary artery disease; DBP – diastolic blood pressure; Glu – glucose; SBP – systolic blood pressure; TGs – triglyceride.

Table 4. The genotype distribution of *HPA-3* between patients and control subjects (age <60 years).

	aa	ab	bb	X2	P
Patients (n,%)	39 (42.9%)	18 (19.8%)	34 (37.4%)	10.033	0.007
Control Subjects (n,%)	29 (43.3%)	26 (38.8%)	12 (17.9%)		

Table 5. The genotype (*aa+ab*) and *bb* of *HPA-3* between patients and control subjects (age <60 years).

	Patients (n,%)	Control subjects (n,%)	X2	P
aa+ab (n,%)	57 (62.6%)	55 (82.1%)	7.075	0.008
bb (n,%)	34 (37.4%)	12 (17.9%)		

platelet-to-platelet bridging. GpIIb/IIIa antagonists that are available for clinical use are: (1) abciximab, a humanized murine monoclonal antibody IIb/IIIa receptor antagonist; (2) 2 non-peptide compounds, tirofiban and lamifiban; and (3) eptifibatid, a peptide based on a snake venom sequence and presumably a mimetic of the r-chain peptide of fibrinogen [21]. Some research has shown that GpIIb/IIIa antagonists had no positive effect on stroke size and functional outcome, but increased the incidence of ischemic cerebral hemorrhage [22]; however, other studies have shown that the combination of a thrombolytic and a GpIIb/IIIa antagonist may have a synergistic effect on recanalization efficiency, which may improve clinical outcome and lower the risk of ischemic cerebral hemorrhage [23]. In patients

with acute ischemic stroke, a dose-escalation study demonstrated that the GpIIb/IIIa inhibitor abciximab is safe when given as a 0.25 mg/kg bolus and 0.125 mg/kg/min infusion. The Emergent Stroke Treatment Trial (ABESTT) study suggested that compared with rt-PA given within a 3-hour window, abciximab may be more effective and had a better safety profile in treating acute stroke [24,25]. Systemic combined thrombolysis with rt-PA and tirofiban seems to be a feasible treatment in acute stroke [26]. In the EPIC study, there was no difference in the occurrence of hemorrhagic or non-hemorrhagic strokes between patients treated with abciximab or placebo [27,28]. A more recent study examining polymorphism of the human thromboxane synthase (CYP5A1) gene in stroke patients indicated that allelic

prevalence of the CYP5A1 exon 12 might be associated with particular characteristics of stroke patients [29]. It is obvious that ischemic stroke is a heterogeneous disease, and a single approach to treatment will necessarily fail in some patients. Hence, a patient-specific individualized medicine approach or combining a variety of drugs, each chosen based on the patient's likely mechanism of stroke, may increase the chance of recanalization.

One limitation of our study was that we did not investigate the treatment effects of different genotypes for ischemic stroke patients, which will be addressed in our future studies. Our study suggests that more research should be carried out on GpIIb/IIIa receptor antagonist, especially GpIIb antagonist, for ischemic stroke in young and middle-aged patients.

CONCLUSIONS

We found that platelet glycoprotein IIb/IIIa polymorphism *HPA-3 b/b* is associated with increased risk of ischemic stroke in patients younger than 60 years of age.

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