Association of ITGA2 Dual Site Variants with Recurrent Ischemic Events in Patients Undergoing Stenting for Symptomatic Intracranial Atherosclerotic Stenosis

Xingang Li[1], Yiwen Dong[1], Jiadan Ye[2], Sheng Cheng[1], Hongge Yang[1], Ze Li[1], Xuan Di[1], Xin Lou[3], and Ning Ma[4]

[1]Capital Medical University Affiliated Beijing Friendship Hospital
[2]Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital
[3]1st Medical Center of Chinese PLA General Hospital
[4]Beijing Tiantan Hospital

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Abstract

Objective: We aimed to investigate the relationship between gene polymorphisms and the occurrence of adverse clinical events following dual antiplatelet therapy in Patients with Symptomatic Intracranial Atherosclerotic Stenosis. **Methods**: A total of 195 patients were enrolled, categorized into 32 cases (those with clinical adverse events) and 163 controls (without events). Genotyping of 20 SNPs from 17 genes was executed. Statistical analyses (Fisher's exact test, logistic regression) were applied to determine associations. **Results**: The ITGA2 rs1126643 (C807T) and rs1062535 (G873A) polymorphisms were significantly correlated with adverse clinical events. Specifically, the mutant frequency of allele C (ITGA2 rs1126643) and allele G (ITGA2 rs1062535) was significantly higher in cases compared to controls (OR = 2.97, 95%CI = 1.702-5.172, P = 0.0001; OR = 3.27, 95%CI = 1.762-6.066, P = 0.0002, respectively). Other genotypes showed no significant differences between the groups. **Conclusion**: The ITGA2 C807T and G873A polymorphisms may elevate the risk of vascular events in Chinese patients. Detecting these polymorphisms may be valuable in identifying patients at risk of recurrent ischemic events.

Title

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Author list

Yiwen Dong[1], Jiadan Ye[2], Sheng Cheng[1], Hongge Yang[1], Ze Li[1], Xuan Di[1], Xin Lou[3], Xingang Li*[1], Ning Ma*[4,5]

Yiwen Dong, *dongyw1990@163.com*,[1] Department of Pharmacy, Beijing Friendship Hospital, Capital Medical University, Beijing, 100050, China

Jiadan Ye,*yejiadan0118@163.com*,[2] Department of Pharmacy, Fuwai Hospital, Chinese Academy of Medical Sciences, Beijing, 100037, China

Sheng Cheng,*chengsheng_08@sina.com*,[1] Department of Pharmacy, Beijing Friendship Hospital, Capital Medical University, Beijing, 100050, China

Hongge Yang, *oneestnn@126.com*,[1] Department of Pharmacy, Beijing Friendship Hospital, Capital Medical University, Beijing, 100050, China

Ze Li, *superlize@163.com*,[1] Department of Pharmacy, Beijing Friendship Hospital, Capital Medical University, Beijing, 100050, China

Xuan Di,*dixuan091400@163.com*,[1] Department of Pharmacy, Beijing Friendship Hospital, Capital Medical University, Beijing, 100050, China

Xin Lou,*louxin@301hospital.com.cn*,[3] Department of Radiology, The First Medical Center of Chinese PLA General Hospital, Beijing, China

Xingang Li,*lxg198320022003@163.com*,[1] Department of Pharmacy, Beijing Friendship Hospital, Capital Medical University, Beijing, 100050, China

Ning Ma,*maning_03@hotmail.com*,[4] Department of Interventional Neuroradiology, Beijing Tiantan Hospital, Capital Medical University, No. 119 South 4th Ring West Road, Fengtai District, Beijing 100070, China. [5]China National Clinical Research Center for Neurologic Diseases, Beijing, 100070, China

Corresponding authors

*Xingang Li, and Ning Ma contributed equally to this work and should be considered co-corresponding authors.

Abstract

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Methods : A total of 195 patients were enrolled, categorized into 32 cases (those with clinical adverse events) and 163 controls (without events). Genotyping of 20 SNPs from 17 genes was executed. Statistical analyses (Fisher's exact test, logistic regression) were applied to determine associations.

Results : The ITGA2 rs1126643 (C807T) and rs1062535 (G873A) polymorphisms were significantly correlated with adverse clinical events. Specifically, the mutant frequency of allele C (ITGA2 rs1126643) and allele G (ITGA2 rs1062535) was significantly higher in cases compared to controls (OR = 2.97, 95%CI = 1.702-5.172, P = 0.0001; OR = 3.27, 95%CI = 1.762-6.066, P = 0.0002, respectively). Other genotypes showed no significant differences between the groups.

Conclusion : The ITGA2 C807T and G873A polymorphisms may elevate the risk of vascular events in Chinese patients. Detecting these polymorphisms may be valuable in identifying patients at risk of recurrent ischemic events.

Keywords

Stroke, Ischemic, Dual antiplatelet therapy, Single nucleotide polymorphism, ITGA2

Introduction

As of the latest Global Burden of Disease (GBD) estimates for 2019, stroke ranks as the second largest global cause of death, significantly impacting public health, especially in low and middle-income countries [1]. GBD 2017 data indicates that the number of stroke-related deaths in China is approximately 2 million [2]. Effective management strategies for carotid artery stenosis encompass percutaneous transluminal angioplasty, stent implantation, post-surgery dual antiplatelet therapy with aspirin and clopidogrel, and proactive risk factor management to prevent recurrent ischemic events in stroke patients [3,4]. Concurrently, high therapeutic platelet reactivity has emerged as a predictor of major adverse cardiovascular events, influenced by factors including metabolism, genetics, clinical complications, and patient compliance [5].

The venerable drug, aspirin, cuts the relative risk of recurrent stroke by around 22% [6]. However, not all patients experience its antithrombotic effects, leading to a phenomenon known as "aspirin resistance,"

where platelet aggregation inhibition remains incomplete, potentially resulting in cardiovascular events post-administration [7]. In China, studies on cardiovascular and cerebrovascular diseases indicate that the rates of aspirin resistance, semi-resistance, and sensitivity stand at 15.4%, 4.6%, and 64.6% respectively [8], with some analyses reporting resistance rates up to 60% [7]. Clopidogrel, a prodrug, undergoes variable absorption and metabolism due to distinct bodily enzymes [6,8]. Consequently, gene mutations tied to these pathways can lead to differential patient reactions, flagging concerns of "clopidogrel resistance" [8,9]. Research has documented individual variability in clopidogrel's antiplatelet response, wherein inadequate or excessive response escalates the risks of ischemia and bleeding, respectively [9].

Post-absorption in the intestinal tract, aspirin swiftly hydrolyzes into salicylic acid and other compounds. It then undergoes an irreversible acetylation reaction with the active portion of the platelet COX serine residue, deactivating the enzyme and curtailing the arachidonic acid AA metabolism. This suppresses TXA2 generation, a known inducer of platelet aggregation, exerting an anticoagulant effect [7,10]. Clopidogrel's metabolic activation hinges on the hepatic cytochrome P450 system. Gene mutations such as ABCB1, CYP2C19 [11], CYP3A4, CYP3A5, PON1 [11], P2Y12 [11] and CES1[12], which play roles in its pharmacokinetic and pharmacodynamic pathways, influence its antiplatelet efficacy. Particularly, the CYP2C19 enzyme activity prominently affects clopidogrel's activation [13,14], with its intestinal absorption chiefly restrained by the activity of the P-glycoprotein intestinal efflux pump, encoded by the ABCB1 gene [15]. Grasping the ramifications of gene polymorphisms on dual antiplatelet therapy can bolster personalized clinical treatments.

Patients less responsive in producing anti-platelet aggregation effects tend to be more susceptible to drug resistance. In such cases, clinicians often advise switching to alternative medications or combining drugs [13]. With the pervasive utilization of dual antiplatelet therapy in combating cardiovascular and cerebrovascular diseases, and in the absence of alternative medicines, continuous monitoring of disease progression in potential resistance-risk individuals becomes imperative [9,16]. The expanding knowledge on the genetic underpinnings of stroke and cardiovascular ailments, powered by advances in genomic technologies, heralds the prospect of precision drug treatments. Pharmacogenetics offers a vision wherein a patient's genetic makeup guides clinicians in choosing the most effective therapy [17].

Materials and Methods

Study Population

We conducted a case-control study that enrolled ischemic stroke patients who underwent stenting for either extracranial or intracranial arterial stenosis at Beijing Tiantan Hospital, Capital Medical University. The inclusion criteria encompassed: 1) Confirmed diagnosis of ischemic cerebrovascular disease accompanied by 70% to 99% stenosis of major intracranial or extracranial arteries, as evidenced by DSA. 2) Initiation of a regimen consisting of clopidogrel (75 mg/day) and aspirin (100 mg/day) at least 5 days prior to enrollment. 3) Successful acquisition of informed consent. Patients were excluded if they had: 1) Contraindications to extracranial or intracranial stenting. 2) Known allergic reactions or contraindications to aspirin, clopidogrel, heparin, or any anesthetics. 3) Conditions like active peptic ulcer disease, bleeding tendencies, severe liver or kidney disorders. 4) Comorbid conditions potentially shortening life expectancy to less than a year. 5) Concurrent participation in a conflicting study.

Study Design

Demographic and clinical data were extracted from medical records, covering aspects such as gender, age, BMI, intracranial stent, smoking, alcohol consumption, hypertension, diabetes, or hyperlipidemia. Clopidogrel 75 mg and aspirin 100 mg were started by all patients at least 5 days before stenting. A 5 mL venous blood sample was taken from each patient a day before surgery for genotyping, preserved at -70°C. Seasoned neurointerventionalists undertook the stenting procedure. Post-surgery, patients were maintained on dual antiplatelet therapy for 90 days, transitioning thereafter to mono-antiplatelet therapy. Risk factors like hypertension, LDL levels, and lifestyle factors were actively managed. Primary endpoints included TIA, ischemic stroke, myocardial infarction, and vascular-related mortality. The researchers defined ischemic stroke as a new focal neurological deficit lasting at least 24 hours without bleeding on CT or MRI. They

defined TIA as a transient episode of neurological dysfunction caused by focal cerebral or retinal ischemia, lasting at least 10 minutes but resolving within 24 hours, regardless of DWI changes. Outcomes were tracked through follow-up visits or phone interviews at regular intervals within a year (1, 2, 3, 6 and 12 months). The researchers reviewed inpatient readmission records and outpatient records. Two independent physicians who were blinded to the subsequent course classified and adjudicated all clinical events. The patient pool was then bifurcated into a "case group" and a "control group" for comparison based on genotypes.

Genotyping

Frequently occurring genetic polymorphisms tied to aspirin and clopidogrel resistance were prioritized (detailed in **Table 1**). Genomic DNA from leukocytes in blood was extracted using the EZNA Blood DNA Midi Kit (Omega Bio-Tek, Norcross, GA, USA). Genotyping was performed by Boao Biotechnology Co., Ltd (Beijing, China) by MALDI-TOF mass spectrometry using the MassARRAY system (Sequenom, San Diego, CA, USA) according to the manufacturer's instructions. Sequenom Assay Design 3.1 software (Sequenom, San Diego, CA, USA) was used to design single-base extensions and PCR primers. Genotype calling was performed in real-time using MassARRAY RT software version 3.0.0.4 and analyzed using MassARRAY Typer software version 3.4 (Sequenom, San Diego, CA, USA). The analysis was repeated for quality control on randomly selected subgroups of 10% of cases and controls; reproducibility was 100%.

Statistical Analysis

Data were analyzed using the SPSS statistical package (version 17.0) and PLINK v1.07 software. Continuous variables underwent Student's t-test analysis and are articulated as mean +- SD. Pearson's χ test evaluated categorical data, whereas Fisher's exact test was reserved for instances of expected low cell frequencies. Genotype distributions were compared using Fisher's exact test (χ^2 test). The strength of genetic variant associations with primary outcomes was represented through ORs and 95% CIs, assessed via unconditional logistic regression. Haploview 4.1 software (Daly Lab, USA) was employed to define LD patterns and haplotype structures, with significance determined through the χ^2 test. A P-value below 0.05 was earmarked as statistically significant.

Results

Characteristics of the study population

Out of the total cohort, 195 patients were incorporated into the study. This comprised 32 cases (those experiencing significant clinical adverse events) and 163 controls (those without any adverse events).**Table 1** delineates the baseline characteristics of these patients. Out of the 32 adverse events documented, 11 were strokes (34.3%), 3 were angina episodes (9.4%), 4 were myocardial infarctions (12.5%), and 14 were TIAs (43.8%). Notably, the foundational characteristics of the case group mirrored those of the control group.

[Insert Table 1 here]

SNP selection and genotyping

For genotyping purposes, 20 SNPs derived from 17 genes were pinpointed. Detailed attributes of these SNPs, including their locations, presumed functions, along with the findings of MAF and HWE, are catalogued in**Table 2** . Here, MAF is indicative of the frequency of the rarest allele among our study's participants. Three SNPs - rs6787801 (LP2RY12), rs1045642 (ABCB1), and rs2307240 (CES1) - exhibited an MAF lower than 0.05. This discrepancy might arise due to the limited sample size. However, when consulting the HapMap database, all SNPs manifested MAFs exceeding 5%. Furthermore, the genotype distribution remained congruent with HWE ($P > 0.05$), signifying no noteworthy deviation for any SNP across the patient spectrum.

[Insert Table 2 here]

Association of recurrent ischemic events and genotypes

Table 3 chronicles the outcomes from both Fisher's exact test and logistic regression analysis juxtaposing cases and controls. When set against controls, the cases manifested a notably elevated mutant frequency for allele C (ITGA2 rs1126643) (OR = 2.97, 95%CI = 1.702-5.172, P = 0.0001) and allele G (ITGA2 rs1062535) (OR = 3.27, 95%CI = 1.762-6.066, P = 0.0002). No marked differences in other genotypes were discerned between the two groups (P > 0.05). The statistical power was assessed to determine if the non-significant outcomes truly stemmed from a lack of correlation within the sample or were attributable to insufficient statistical potency.

[Insert Table 3 here]

Haplotype analysis and association with event

The LD block and the haplotype structure were measured by D' and R^2, and the final LD analysis revealed two haplotypes in our patients. Two SNPs of rs41273215 and rs57731889 in PEAR1 are in Block 1, and rs1126643 and rs1062535 in ITGA2 are in Block 2 (**Figure 1**). The significance of any haplotypic association is shown in **Table 4** . In Block 2, the linked variant alleles were observed most frequently as the GC haplotype (frequency 0.700) and AT haplotype (frequency, 0.278). Both GC and AT haplotypes showed a significant impact on the recurrence of adverse events. No other haplotype was associated with the risk of clinical events

Discussion

This study aimed to determine the influence of gene polymorphisms on clinical adversities following dual antiplatelet therapy. Notably, the polymorphisms ITGA2 C807T (rs1126643) and G873A (rs1062535) were found to have a significant association with the onset of adverse clinical events. ITGA2, located on chromosome 5q23-31, encodes the GP Ia/IIa - a crucial platelet integrin receptor - with 807T/C situated in exon 7 and 873A/G within the intron of ITGA2. The GP Ia/IIa complex (integrin α2b1) of platelet glycoprotein receptors binds to exposed collagen, facilitating stable platelet adhesion and activation [18]. These connections trigger potent signaling cascades culminating in thrombosis. Existing literature reveals that platelet surface α2b1 levels correlate with the adhesive capacity and extent of platelets to collagen in the bloodstream [19]. A deficit in GP Ia/IIa, either congenital or acquired, can precipitate hemorrhagic tendencies, with SNPs in the ITAG2 gene modulating the expression of GP Ia/IIa [20].

The C807T has two alleles, C and T, resulting in three genotypes: CC, CT, and TT. Preliminary research indicated elevated GP Ia/IIa expression in individuals possessing the T allele, suggesting its thrombogenic potential. Consequently, patients with the CC genotype could be more receptive to aspirin and clopidogrel treatment compared to those with CT or TT genotypes [21,22]. Nonetheless, previous studies investigating the genetic links between glycoprotein gene polymorphism and ischemic stroke have produced mixed findings. The T allele, in contrast to the C allele, hasn't been linked with heightened cardiovascular event risks in patients with cardiovascular and cerebrovascular diseases undergoing aspirin and clopidogrel treatment [23,24]. The genetic polymorphism landscape of ITGA2 varies across populations. Despite expecting expression patterns of different Gplana/IIa genotypes to abide by straightforward Mendelian inheritance, the prevalent expression of the ostensibly low-risk CC/TT genotype in general European demographics implies its protective nature and potential pre-thrombotic advantage over TT/AA [25]. Beyond genetics, other clinical factors might modulate patients' responsiveness to aspirin and clopidogrel. A meta-analysis encompassing 15 studies with 2242 cases and 2408 controls identified a correlation between the ITGA2-C807T polymorphism and ischemic stroke susceptibility, specifically in Asians and in-patients, but this was absent in Caucasians and out-patients [26]. Additionally, evidence suggests that C807T mutations might elevate plasma lipid concentrations, amplifying stroke risk [27].

The G873A (rs1062535) polymorphism in the ITGA2 gene is characterized by a G>A transition. Certain studies postulate that patients with the GG genotype might experience reduced residual platelet reactivity upon aspirin and clopidogrel treatment in contrast to those with the AG or AA genotype. In our cohort, we observed a heightened risk association for clinical outcomes with allele G over allele A. Yet, some research counters this, suggesting no significant impact of the 873A locus polymorphism on adverse cardiovascular or cerebrovascular incidents [22].

In summary, the polymorphisms ITGA2 rs1126643 and rs1062535 could heighten the vulnerability to subsequent vascular incidents in Chinese patients diagnosed with either extracranial or intracranial occlusive conditions. Although our study did not identify the effects of previously documented pharmacogenetic-related SNPs involved in antiplatelet therapy, it's imperative to note the limited scope of our research. Hence, larger studies are essential for confirming these findings.

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Authors' contributions

Dong Yiwen: Conduct surveys, conduct statistical analysis, and write preliminary drafts; Ye Jiadan: Investigation, data management; Cheng Sheng: Methodology; Yang Hongge and Di Xuan: data collection; Li Ze: Data analysis; Lou Xin and Li Xingang: Project Management, Methodology, Resources, Writing Review; Ma Ning: Editor. The author has read and approved the final manuscript.

Xin Lou, Xingang Li, and Ning Ma contributed equally to this work and should be considered co-corresponding authors.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University (Ethics approval number: qx2012-012-01 and KY2014-051-01), and written informed consents were obtained from patients or their close relatives.

Consent for publication

We have obtained consent from participants/patients for publication.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Figure legend

Supplemental material: Diagram of the block structure of SNPs generated by Haploview. The numbers in the boxes are D' (upper panel) and R^2 (down panel) values, and the depth of red color showed computed pairwise D' and R^2.

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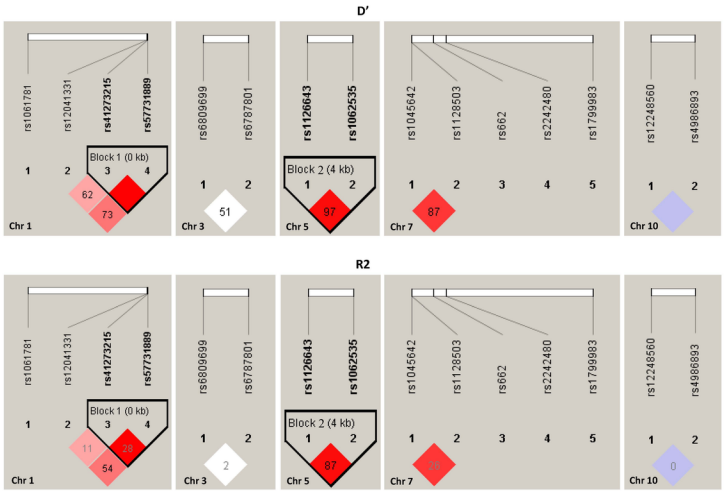

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