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ORIGINAL ARTICLES

Association of platelet glycoprotein Ia C807T polymorphism with ischemic stroke risk in young and elderly populations in Uzbekistan: A case-control study

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Abstract

Background: Ischemic stroke remains a significant health concern, with a growing incidence among younger populations. While traditional risk factors such as hypertension and smoking are well-documented, the genetic predisposition to stroke, particularly the role of GP Ia C807T polymorphism, is still debated. Given the limited genetic studies in Central Asia, investigating this polymorphism in Uzbekistan's young stroke patients is essential. *Objective:* This study aims to determine whether the GP Ia C807T polymorphism is associated with an increased risk of ischemic stroke in young individuals in Uzbekistan. *Methods:* A case-control study was conducted involving 90 ischemic stroke patients aged ≤50 years, 92 patients >50 years, and 168 healthy controls. Genomic DNA was extracted from venous blood samples, and genotyping was performed using PCR-RFLP analysis. Statistical comparisons were made using logistic regression, adjusting for confounding factors. *Results:* Hypertension and smoking were identified as significant risk factors for ischemic stroke in both young and elderly patients ($p<0.05$). However, no statistically significant association was observed between the GP Ia C807T polymorphism and ischemic stroke in either group ($p>0.05$). *Conclusion:* This study suggests that traditional risk factors, rather than genetic variations in GP Ia C807T, play a more prominent role in ischemic stroke development among young individuals in Uzbekistan. Further research incorporating larger cohorts and additional genetic markers is needed to clarify the genetic contribution to stroke susceptibility in this population.

Keywords: Ischemic stroke, GP Ia C807T polymorphism, genetic predisposition, young stroke, platelet adhesion, risk factors, Uzbekistan

INTRODUCTION

Stroke, as one of the leading causes of global mortality, poses a significant public health challenge.[1] Annually, over 17 million people experience a stroke worldwide, resulting in approximately 6 million deaths, which accounts for 10.8% of all global fatalities. Among various types of stroke, ischemic stroke constitutes 80% of cases, making it a primary cause of long-term disability and reduced quality of life. According to the World Health Organization (WHO), the economic burden of stroke represents 2%–4% of total healthcare costs globally[2,3], a figure projected to increase with the expected 23 million new stroke cases by 2030.[4]

Over the past 25 years, the prevalence and incidence of stroke have risen substantially. Recent global reports estimate a 40% rise in stroke incidence among individuals aged 20 to 54, particularly in low- and middle-income countries.[5,6] This shift highlights the growing impact of stroke on younger populations. Despite medical advances, only 20% of stroke survivors return to their prior occupational and functional

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status[7], which emphasizes the need for focused preventive strategies in high-risk groups.

In the context of Central Asia, particularly Uzbekistan, limited data exists on the burden and risk factors for stroke in the younger population. While traditional risk factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking are well-established[3], emerging evidence suggests that genetic predispositions also play a critical role, especially in early-onset ischemic strokes.[8,9] Recent studies suggest that stroke susceptibility is influenced by complex interactions between multiple genes and environmental factors

Among these, platelet glycoproteins involved in adhesion and thrombus formation have been extensively studied. The glycoprotein Ia/IIa complex (integrin α2β1), a major receptor for collagen on platelets, has garnered attention for its role in thrombogenesis. Individuals with the TT genotype exhibit increased receptor density, which may enhance platelet-collagen adhesion and thrombogenic potential.[10] The C807T polymorphism in the ITGA2 gene, encoding the α2 subunit of the integrin, has been associated with increased receptor expression and platelet adhesion. However, this association appears to vary significantly across ethnic groups.

The association between GPIa C807T polymorphism and ischemic stroke has been studied in diverse populations, but findings have been inconsistent. Several studies have reported a positive association, particularly among younger patients[11,13], while others found no correlation.[12,14,] These differences may stem from population-specific genetic backgrounds, environmental exposures, and lifestyle factors. For instance, positive associations have been reported in European cohorts[13], while studies from East Asia and South Asia have shown inconsistent or null findings.[11,12]

There is a significant gap in the literature regarding stroke genetics in Central Asia. The Uzbek population, with its unique admixture of Turkic, Persian, and East Asian ancestries, remains largely unstudied in this context. Understanding the role of genetic factors such as the GPIa C807T polymorphism in this population may provide insights into region-specific risk profiles and support tailored stroke prevention efforts.

Therefore, this study aims to determine whether the GP Ia C807T polymorphism is associated with an increased risk of ischemic stroke in young individuals in Uzbekistan. We hypothesize that individuals carrying the TT genotype may have increased platelet activity, potentially elevating their stroke risk.

METHODS

This case-control study was conducted with the approval of the Institutional Ethics Committee of the Multidisciplinary clinic of the Tashkent Medical Academy, Khorezm regional multidisciplinary clinic, Namangan regional multidisciplinary clinic (Approval No. 226/2022). Written informed consent was obtained from all participants before enrollment, and the study adhered to the ethical principles outlined in the Declaration of Helsinki.

Study design and setting

The study was performed between October 2022 and February 2024 at the Multidisciplinary Clinic of the Tashkent Medical Academy, Khorezm regional multidisciplinary clinic, and Namangan regional interdisciplinary clinic. A total of 90 first-time hospitalized ischemic stroke patients aged ≤ 50 years (young stroke group) and 92 ischemic stroke patients aged > 50 years (elderly stroke group) were recruited from the Neurology Ward and Intensive Care Unit. Additionally, 168 age- and sex-matched healthy controls were selected from individuals attending the hospital's outpatient department for routine check-ups.

The inclusion criteria were: Young stroke group: Patients aged ≤ 50 years with first-time ischemic stroke, confirmed via imaging studies (CT or MRI); Elderly stroke group: Patients aged > 50 years with first-time ischemic stroke, confirmed via imaging studies (CT or MRI); Control group: Healthy individuals matched for age and sex, with no history of stroke or other vascular diseases.

The exclusion criteria were: Patients with intracerebral hemorrhage, subarachnoid hemorrhage, cerebral venous thrombosis, vasculitis, myocardial infarction, transient ischemic attacks, and previous history of stroke; Individuals with incomplete medical records or refusal to provide informed consent.

Diagnostic Procedures

Stroke was defined as an acute episode of focal (or global) neurological dysfunction that persists for more than 24 hours or leads to death, with no apparent causes other than of vascular origin. All patients underwent a brain

CT or MRI to confirm the diagnosis of ischemic stroke. Echocardiography and extracranial duplex ultrasound were performed based on the attending neurologist's discretion to assess potential cardioembolic or large vessel disease. Echocardiography and extracranial duplex scanning were conducted on individuals with cardiovascular issues and obesity, as prescribed by a neurologist.

Control selection and data collection

Healthy control participants were selected at random from the hospital's outpatient department. Inclusion criteria ensured they were free from stroke, myocardial infarction, or peripheral arterial disease. Participants fasted for a minimum of 8 hours before blood collection.

Baseline demographic information, including age, sex, hypertension, diabetes mellitus, hyperlipidemia, smoking status, and prior vascular incidents (myocardial infarction, angina, claudication, and amputation), was documented for all participants. Clinical histories were obtained through structured interviews conducted by trained research staff.

Sample collection and analysis

Fasting venous blood samples (10 mL) were collected from all participants within 7 days following the acute stroke event and stored in EDTA-coated tubes to prevent coagulation. Genomic DNA was isolated from peripheral blood leukocytes using the conventional phenol-chloroform extraction method. The concentration and purity of extracted DNA were evaluated spectrophotometrically (NanoDrop 2000, Thermo Scientific), and DNA integrity was verified by 1% agarose gel electrophoresis. Genotyping of the *ITGA2* C807T (rs1126643) polymorphism was performed using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) technique. The following oligonucleotide primers were used to amplify the target region of the *ITGA2* gene: Forward primer: 5′-CAG GGC TGG AAA TGA ACT GCA-3′; Reverse primer: 5′-AGG GCA GGG AGA GGA TAA GGA-3′. The resulting PCR amplicons (268 bp) were digested with MspI restriction endonuclease (New England Biolabs, USA) at 37°C for 4 hours. Digestion products were separated on a 3% agarose gel stained with ethidium bromide and visualized under ultraviolet (UV) illumination. The presence of the wild-type C allele yielded two fragments of 188 bp and 80 bp, while the mutant T allele remained uncut, producing a single 268 bp fragment. All genotyping procedures were performed at the Molecular Biology Laboratory of the Tashkent medical academy. Laboratory personnel conducting the genotyping were blinded to the clinical status (case/control) of the samples to ensure objectivity and reduce bias.

Statistical analysis

Descriptive statistics were presented as means and standard deviations for continuous variables and proportions for categorical variables. Comparisons between groups were performed using the Student's t-test for continuous variables and the chi-square test for categorical variables. Logistic regression analysis was employed to evaluate the association between genetic polymorphisms and stroke risk, adjusting for potential confounders such as age, sex, hypertension, diabetes mellitus, and smoking. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated to measure the strength of associations. A p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS software (version 27.0).

RESULTS

Baseline characteristics

The baseline characteristics of the study population, comprising 350 participants, are summarized in Table 1. The study included 90 young ischemic stroke patients ($\leq$ 50 years), 92 elderly ischemic stroke patients ($>$ 50 years), and 168 healthy controls, evenly divided into two age-matched subgroups (84 individuals aged $\leq$ 50 years and 84 individuals aged $>$ 50 years). The mean age of the young stroke group was 42.6 ± 6.5 years, while the elderly stroke group's mean age was 69.4 ± 9.7 years. Male participants predominated in both groups, accounting for 75.8% of young and 62.1% of elderly stroke cases.

Among the young stroke group, hypertension (52.2%, $p = 0.006$) and smoking (36.5%, $p = 0.012$) were identified as significantly more frequent compared to controls. Diabetes mellitus and hypercholesterolemia showed no significant association with ischemic stroke in this age group ($p > 0.05$). Conversely, in the elderly stroke group, hypertension (68.5%, $p < 0.001$), diabetes mellitus (35.9%, $p = 0.017$), and

Table 1: Baseline characteristics of the study population

Characteristic	Young Patients (n=90)	Controls (n=84)	p-value	Elderly Patients (n=92)	Controls (n=84)	p-value
Hypertension (%)	52.2 (47/90)	34.5 (29/84)	0.006	68.5 (63/92)	34.5 (29/84)	<0.001
Smoking (%)	36.5 (33/90)	20.2 (17/84)	0.012	39.1 (36/92)	20.2 (17/84)	0.026
Diabetes Mellitus (%)	18.9 (17/90)	14.3 (12/84)	0.214	35.9 (33/92)	14.3 (12/84)	0.017
Hypercholesterolemia (%)	27.8 (25/90)	26.2 (22/84)	0.621	28.3 (26/92)	26.2 (22/84)	0.741
Positive Family History (%)	21.1 (19/90)	20.2 (17/84)	0.472	15.2 (14/92)	20.2 (17/84)	0.701

smoking (39.1%, p = 0.026) were all identified as significant risk factors.

Genotype and allele frequencies of GPIa C807T

The genotype distribution and allele frequencies for the GPIa C807T polymorphism are presented in Table 2. In the young group, the T allele frequency was 29.3% among stroke patients and 26.8% among controls; however, this difference was not statistically significant (p = 0.573). Similarly, in the elderly group, the T allele frequency was 33.7% among stroke patients compared to 30.4% among controls (p = 0.653).

Logistic regression analysis

Logistic regression analysis revealed that hypertension and smoking were independent risk factors for ischemic stroke in both age groups. Among young patients, the odds ratio (OR) for hypertension was 2.58 (95% CI: 1.34–4.93, p = 0.003), while for smoking, it was 2.99 (95% CI: 1.38–6.55, p = 0.006). In the elderly group, the OR for hypertension was 3.88 (95% CI: 2.03–7.39, p < 0.001), and for smoking, it was 2.49 (95% CI: 1.32–4.69, p = 0.004). The GPIa C807T polymorphism was not significantly associated with ischemic stroke risk in either group (p > 0.05).

DISCUSSION

This study provides valuable insights into the association between the GPIa C807T polymorphism and ischemic stroke risk in a Central Asian cohort. Using logistic regression analysis, we evaluated the influence of this genetic variation alongside conventional risk factors. Our findings confirmed that hypertension and smoking were significantly more prevalent among stroke patients compared to healthy controls in both younger (≤50 years) and older (>50 years) age groups. Additionally, diabetes mellitus was a notable risk factor among elderly stroke patients. However, our results did not support the hypothesis that the GPIa C807T polymorphism is an independent risk factor for

Table 2: Genotype and allele frequencies of GPIa C807T in stroke patients and controls

Group	Genotype Distribution (CC/CT/TT)	Total Patients (n)	T Allele Frequency (%)	T Allele Count	p-value
Young Patients (≤ 50)	47 (52.2%) / 33 (36.7%) / 10 (11.1%)	90	29.3	53/180	0.573
Controls (≤ 50)	45 (53.6%) / 32 (38.1%) / 7 (8.3%)	84	26.8	45/168	
Elderly Patients (> 50)	40 (43.5%) / 36 (39.1%) / 16 (17.4%)	92	33.7	62/184	0.653
Controls (> 50)	42 (50.0%) / 34 (40.5%) / 8 (9.5%)	84	30.4	51/168	

Table 3: Logistic regression analysis of risk factors for ischemic stroke

Risk Factor	Young Group (≤ 50 years)	p-value	Elderly Group (> 50 years)	p-value
Hypertension	OR = 2.58 (95% CI: 1.34–4.93)	0.003	OR = 3.88 (95% CI: 2.03–7.39)	<0.001
Smoking	OR = 2.99 (95% CI: 1.38–6.55)	0.006	OR = 2.49 (95% CI: 1.32–4.69)	0.004
Diabetes Mellitus	OR = 1.50 (95% CI: 0.70–3.34)	0.291	OR = 3.19 (95% CI: 1.58–6.65)	0.003
GPIa C807T Polymorphism	OR = 1.17 (95% CI: 0.67–2.11)	0.643	OR = 1.20 (95% CI: 0.69–2.19)	0.594

ischemic stroke in either group (p=0.643 for young patients, p=0.594 for elderly patients).

Our results align with those of Liu *et al*. (2016), who performed a comprehensive meta-analysis and reported that while GP Ia C807T is associated with ischemic stroke in some populations, the effect size varies widely depending on ethnicity.[10] In particular, Asian populations often show weaker or non-significant associations compared to European populations. Carlsson *et al*. (1999) found a strong association among younger European patients, suggesting a possible ethnicity-age interaction.[13] However, Cole *et al*. (2003) and subsequent studies in East Asia reported null findings, emphasizing the need for population-specific research.[14] These discrepancies may stem from differing genetic architectures, environmental exposures, and lifestyle factors among ethnic groups.

In our study, conducted in a genetically diverse population with Turkic, Persian, and East Asian ancestry, we did not find a statistically significant association between the polymorphism and stroke. This further supports the hypothesis that the role of GP Ia C807T may be modulated by population-specific factors. Therefore, regional studies like ours fill a critical gap in the literature and highlight the importance of ethnic diversity in genetic epidemiology.

Our results align with several studies indicating that population-specific genetic and environmental interactions play a crucial role in stroke pathogenesis. The absence of a significant association between the C807T polymorphism and ischemic stroke in our cohort may be explained by various factors, including dietary habits, healthcare access, and the prevalence of other genetic variants within the population. These factors could modulate platelet function and thrombotic risk, potentially obscuring the effect of the GPIa C807T polymorphism.

Table 4 summarizes previously published studies investigating the relationship between GP Ia C807T and ischemic stroke across various ethnicities. This table includes sample size, ethnic background, outcome, and observed associations. Our study is included in the table for contextual comparison.

This study provides a foundation for further research into the genetic predisposition to ischemic stroke in Uzbekistan and the broader Central Asian region. One notable limitation of our study was the lack of complete subtyping of ischemic stroke using standardized classification systems such as TOAST. Subtype-specific analysis is particularly relevant when investigating genetic or hemostatic factors such as platelet glycoproteins, which are more likely to be implicated in large artery atherosclerosis and small vessel occlusion rather than cardioembolic stroke. Future research should aim to incorporate systematic stroke subtyping, alongside the inclusion of larger, multi-center cohorts. Moreover, the application of advanced genomic methodologies—such as genome-wide association studies (GWAS)—will allow for a more comprehensive identification of stroke-related genetic variants. Additionally, exploring gene-environment interactions may offer deeper insights into stroke risk modification and contribute to the development of personalized prevention strategies for high-risk individuals.

In conclusion, our findings reinforce the significance of modifiable risk factors, particularly hypertension and smoking, in stroke prevention. However, the absence of a genetic link with GPIa C807T in this population highlights the need for broader genetic screening and more tailored public health strategies. By addressing both genetic and environmental determinants, we can make strides in reducing the burden of ischemic stroke in Central Asia.

Table 4: Summary of studies investigating GP Ia C807T and ischemic stroke risk across populations

Study	Population	Sample Size	T Allele Frequency (%)	Association with Stroke	OR (95% CI)	Notes
Carlsson *et al*. (1999)13	Germany (young adults)	397	40	Yes	3.02 (1.20–7.61)	Independent risk factor only in ≤50 yrs
Liu *et al*. (2016, meta-analysis)10	Mixed (Asia, Europe)	5200+	Varies (20–40%)	Yes (in Asians)	1.31 (1.1–1.54)	Heterogeneous results
Nikolopoulos *et al*. (2006)12	Greece	1848	36.3	No	1.11 (0.82–1.5)	Not significant
de Oliveira *et al*. (2007)15	Brazil	140	61	No	1.38 (0.69-2.74)	First study in Latin America
Zhang *et al*. (2012)16	China	338	30-33	No	0.16 (0.59-2.32)	Not significant
Current Study (2025)	Uzbekistan	350	29.3	No	1.17 (0.67–2.11)	First in Central Asia

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DISCLOSURE

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