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Prevalence of RNF213 rs112735431 Genetic Polymorphism in Non-Cardioembolic Ischemic Cerebrovascular Disease: A Cross-Sectional Study in Thai Patients

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Ischemic stroke · RNF213 · rs112735431 · Thailand · Moyamoya disease

Abstract
Introduction: Moyamoya disease (MMD) and non-MMD intracranial cerebral artery stenosis (ICAS) have been linked to the RNF213 rs112735431 gene in Korean and Japanese populations. This cross-sectional study investigates the prevalence of the RNF213 rs112735431 gene in non-cardioembolic ischemic stroke (NCIS) among Thai patients. ***Methods:*** A cross-sectional investigation was conducted on patients aged 18 years or older admitted to King Chulalongkorn Memorial Hospital between June 2015 and March 2016 with acute NCIS. ICAS and extracranial carotid artery stenosis (ECAS) were assessed through computer tomography angiography or magnetic resonance angiography. Blood samples were collected, and Sanger sequencing was performed. ***Results:*** Among 234 acute NCIS cases, 113 exhibited ICAS, 12 had ECAS, 20 had both, and 89 had neither. The RNF213 rs112735431 gene variant was detected in 2 patients, both heterozygous A/G. The frequency of the RNF213 rs112735431 variant was 0.9% (2/234; 95% CI: 0–2.1%) in acute NCIS patients and 1.8% (2/113; 95% CI: 0–4.2%) in ICAS. All individuals with the RNF213 variant were males with hypertension, diabetes mellitus, dyslipidemia, and ICAS, without a family history of ischemic stroke. ***Conclusion:*** This study reveals that the RNF213 rs112735431 gene variant is uncommon among Thai NCIS patients, suggesting a discrepancy in the prevalence of this genetic variation between Thai and other Eastern Asian populations.

Introduction

Variability in the distribution of cervicocerebral artery stenosis across different racial and ethnic groups has been well documented [1, 2]. Beyond traditional atherosclerotic risk factors, the influence of genetic factors on the specific sites of cervicocerebral artery stenosis has

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garnered increasing attention [3]. A notable example of progressive intracranial stenotic vasculopathy is Moyamoya disease (MMD) [4]. Notably, studies conducted in Japan and Korea have identified the RNF213 rs112735431 gene as a susceptibility factor for both MMD and non-MMD-related intracranial artery stenosis [5–9].

Given the potential impact of genetic factors on the manifestation of cervicocerebral artery stenosis, it becomes imperative to explore these associations within diverse populations. This study specifically endeavors to contribute to this knowledge base by investigating the prevalence of the RNF213 rs112735431 variant in cases of acute non-cardioembolic ischemic stroke within the unique context of the Thai population. Understanding the genetic underpinnings of cervicocerebral artery stenosis in different ethnic groups is crucial for advancing our comprehension of the complex interplay between genetics and vascular pathology, offering insights that may have implications for tailored diagnostic and therapeutic approaches in distinct populations.

Methods

Study Population

This cross-sectional study included Thai patients with acute non-cardioembolic ischemic stroke who were aged 18 years or older, who were admitted to King Chulalongkorn Memorial Hospital between June 1, 2015, and March 31, 2016. Patients were consecutively recruited. After informed consent was provided, baseline data were gathered. Blood samples for routine blood chemistry and genetic analyses were collected prospectively. This study was approved by the Local Ethics Committee from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB No. 99/2558). Written informed consent to participate in the study has been obtained from all adult participants and all vulnerable participants' parent/legal guardian/next of kin.

Imaging Analysis

Computer tomography (CT) (Ingenuity, Philips, USA) and/or magnetic resonance imaging (MAGNETOM Aera 1.5T, Germany) of the brain were performed in all studied patients. For vascular study, the computer tomography angiography (CTA) (Ingenuity, Philips, USA) and/or the magnetic resonance angiography (MAGNETOM Aera 1.5T, Germany) of the brain were performed.

From the vascular study, significant intracranial cerebral artery stenosis (ICAS) was defined as ≥50% stenosis in at least one of the following intracranial segments: internal carotid artery/vertebral artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, and basilar artery. Patients exhibiting ≥50% stenosis in the extracranial part of the ICA or vertebral artery were categorized as having significant extracranial artery stenosis. We defined the percent stenosis of intracranial and extracranial arteries by standardized methods, according to the Warfarin-Aspirin Symptomatic Intracranial Disease Trial and the North American Symptomatic Carotid Endarterectomy Trial, respectively [10, 11]. Using a handheld digital caliper, neuroradiologists and neurologists independently measured the vessel diameters on CTA or magnetic resonance angiography images.

For variable comparisons, patients with acute ischemic stroke or TIA were grouped into two categories: those with intracranial artery stenosis and those with extracranial artery stenosis. Patients with both significant extracranial and ICAS were specifically categorized as having extracranial cerebral artery stenosis.

The diagnostic criteria for definitive MMD, as outlined by the Research Committee on Spontaneous Occlusion of the Circle of Willis in Japan, encompass angiographic findings such as (1) stenosis or occlusion of the terminal portion of the intracranial ICA or proximal portions of anterior cerebral artery or middle cerebral artery. (2) Development of abnormal vascular networks near the occlusive or stenotic lesions. (3) Bilateral presence of criteria (1) and (2) [12].

Study Outcomes

The primary study outcome is the prevalence of the RNF213 rs112735431 genetic polymorphism in the studied patients. Secondary outcomes include the prevalence of genetic polymorphism on the RNF213 rs112735731 gene in patients with intracranial artery stenosis. The association of the gene variant with the outcome of ischemic stroke and the age at the onset of the first ischemic stroke was also evaluated. Data on stroke outcomes at discharge, including the Barthel Index (BI), modified Rankin Scale (mRS), NIH Stroke Scale (NIHSS), and the duration of hospital stay, were collected.

Identification of RNF213 rs112735431 Gene Variant

Genomic DNA was extracted from peripheral blood leukocyte by standard procedure with phenol-chloroform extraction. The extracted DNA was quantified by spectrophotometry technique to guarantee purification of the DNA product. For RNF213 genotyping, DNA was amplified using two primers: 5′TTT GCT GTC TAG CAA GGA TGA 3′ and 5′TTA GGC TAT AGA GCA CCC ATC A 3′. Each amplification reaction contained 1 μg of leukocyte DNA, 1 pmol/μL of

Table 1. Baseline characteristics of non-embolic ischemic stroke patients

Baseline characteristics	Patients (N = 234)
Age, years	62.5±14.4
≤45 years, *n* (%)	35 (15.0)
>45 years, *n* (%)	199 (85.0)
Male, *n* (%)	135 (57.7)
Diabetes mellitus, *n* (%)	77 (32.9)
Hypertension, *n* (%)	154 (65.8)
Dyslipidemia, *n* (%)	115 (49.1)
Coronary heart disease, *n* (%)	19 (8.1)
Previous history of ischemic stroke/TIA, *n* (%)	65 (21.8)
BMI, kg/m^2	25.0±6.8
Obesity, *n* (%)	10 (4.3)
Smoker, *n* (%)	70 (29.9)
Family history of stroke/TIA, *n* (%)	6 (2.6)

Continuous variables are presented as mean ± standard deviation. Nominal variables are presented as absolute number and percent. TIA, transient ischemic attack; BMI, body mass index.

each primer, 10% dimethyl sulfoxide, and 1 unit of Taq polymerase as well as 1 unit of dNTP in a final volume of 20 μL. Each reaction mixture was heated at 95°C for 5 min, denatured at 95°C for 45 s, annealed at 50°C for 45 s, and extended at 72°C for 45 s, after which it was cooled at 72°C for 7 min and rested at 4°C for 5 min. The PCR products were measured for size by agarose gel electrophoresis and treated with ExoSAP-IT (USP, Cleveland, OH) according to the protocols supplied by the manufacturer and sent for direct sequencing to First BASE Inc., Singapore. The DNA sequencing used was the Sanger-Coulson technique, which was then compared with established human RNF213 sequences (GenBank Accession No. NM_001256071.2).

Statistics

Given the absence of prior studies on the prevalence of the RNF213 rs112735431 gene variant in Thailand, a pilot study was conducted from February 1, 2015, to February 28, 2015. Among 15 admitted ischemic stroke patients, the observed prevalence of the RNF213 rs112735431 variant was 6.7%. With a designated type 1 error of 5% and a precision of 3%, the estimated sample size required for the main study was determined to be more than 196 patients.

Data analysis was carried out using SPSS (SPSS Statistics for Windows, Version 17.0, SPSS Inc., USA) and Stata (Stata Statistical Software, Version 13.0, StataCorp LP, USA). For analytical statistics, Pearson χ^2 was employed for qualitative variables, while the unpaired t test was applied for quantitative variables. The Mann-Whitney U test was utilized for ordinal scale data and non-parametric data. A p value <0.05 was deemed statistically significant in the analysis.

Results

From June 1, 2015, to March 31, 2016, a total of 234 patients met the eligibility criteria and underwent genetic testing. Table 1 provides the baseline demographics and clinical characteristics of the patients. According to the TOAST classification, 60.7% exhibited large artery atherosclerosis, 23.9% was small vessel occlusion, 14.1% was stroke of undetermined etiology, and 1.3% was stroke of other determined etiology. Within the large artery atherosclerosis subgroup, 77.4% presented with intracranial arterial stenosis.

Within the entire cohort, 2 patients exhibited heterozygosity for the RNF213 rs112735431 gene, yielding an overall prevalence rate of 0.9% (2/234; 95% CI: 0–2.1%) among acute non-embolic ischemic stroke patients and 1.8% (2/113; 95% CI: 0–4.2%) among patients with intracranial artery stenosis. No homozygous gene variants were observed. There were 3 patients who were diagnosed to have MMD, clinically. None of them exhibited the RNF213 rs112735431 gene.

Clinical characteristics and treatment outcomes of the 234 patients with the wild-type and heterozygous

Table 2. Clinical characteristics and treatment outcomes of the patients with RNF213 rs112735431 among 234 patients with acute non-cardioembolic ischemic stroke

	RNF213	RNF213	*p* value
	Wild-type (*n* = 232)	G/A or A/A (*n* = 2)	
Age, years[a]	62.4±14.4	66.5±6.4	0.69
Age at the onset of first ischemic stroke, years[a]	61.5±14.2	57.5±7.80	0.69
Gender, male, *n* (%)[b]	133 (57.3)	2 (100)	0.50
Family history of ischemic stroke, *n* (%)[b]	6 (2.6)	0 (0)	1.0
Vascular risk factor, *n* (%)[b]			
Hypertension	152 (65.5)	2 (100)	0.55
Diabetes mellitus	75 (32.3)	2 (100)	0.11
Dyslipidemia	113 (48.7)	2 (100)	0.24
Angiographic findings, *n* (%)[b]			
Distal ICA or proximal MCA or proximal ACA stenosis	91 (39.2)	2 (100)	0.16
Basal collaterals	7 (3.0)	1 (50)	0.07
Bilateral involvement	3 (1.3)	0 (0)	–
Number of diagnostic criteria met, *n* (%)[b, c]			
0	140 (60.3)	0 (0)	–
1	87 (37.5)	1 (50)	1.00
2	2 (0.9)	1 (50)	0.03
All 3	3 (1.3)	0 (0)	–
Severity of stroke[d]			
GCS at the admission	15	15	0.66
mRS at the admission	2	4	0.11
NIHSS at the admission	4	5	0.85
Barthel index at the admission	75	70	0.95
Treatment outcome			
Length of stay, day[a]	7.8±8.5	5.0±2.8	0.65
NIHSS at discharge[d]	3	3	0.92
mRS at discharge[d]	1	4	0.07
Barthel index at discharge[d]	95	50	0.09

Continuous variables are presented as mean ± standard deviation. Nominal variables are presented as absolute number and percent. ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; GCS, Glasgow Coma Scale; mRS, modified Rankin scale; NIHSS, National Institutes of Health stroke scale. [a]Unpaired *t* test compared RNF 213 wild-type group with RNF213 variant group. [b]Fisher's exact test compared RNF213 wild-type group with RNF213 variant group. [c]Diagnostic criteria of MMD by the Research Committee on Spontaneous Occlusion of the Circle of Willis in Japan. [d]Mann-Whitney test compared RNF213 wild-type group with RNF213 variant group.

genotype of RNF213 rs112735431 are shown in Table 2, Figures 1 and 2. Notably, all patients with the RNF213 rs112735431 gene had hypertension, diabetes, and dyslipidemia. Additionally, none of these individuals had a family history of ischemic stroke.

Discussion

Our study revealed that the RNF213 rs112735431 mutation is rare in the Thai non-cardioembolic stroke population. More importantly, the prevalence of RNF213 rs112735431 in the intracranial artery stenosis group in Thai patients is lower than that reported in previous studies in Japanese and Korean populations [6, 8]. Studies in Japan and Korea indicated frequencies of 5.3–24.4% and 21.4–22.6%, respectively, for RNF213 rs112735431 among patients with intracranial artery stenosis without MMD [7, 8, 13–17].

Contrary to expectations based on previous studies in Japan and Korea, the carrier rate of RNF213 p.R4810K in Chinese intracranial artery stenosis, without MMD was 0.54–7.54 which is comparable to our results [18–20]. However, no study has explored the prevalence of RNF213 rs112735431 in intracranial artery stenosis

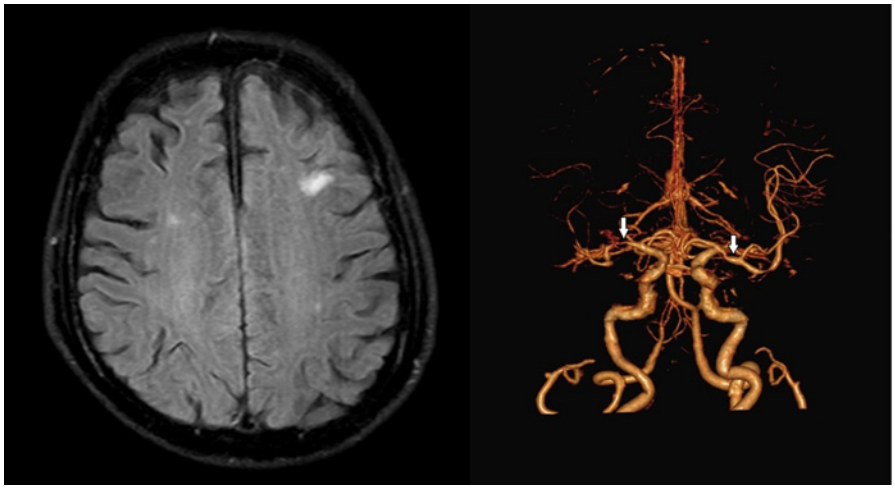

Fig. 1. Magnetic resonance imaging. T2W/FLAIR hyperintense lesions were detected at cortical and subcortical area of bilateral frontal lobes. CTA demonstrated narrowing of the bilateral proximal middle cerebral arteries (white arrow).

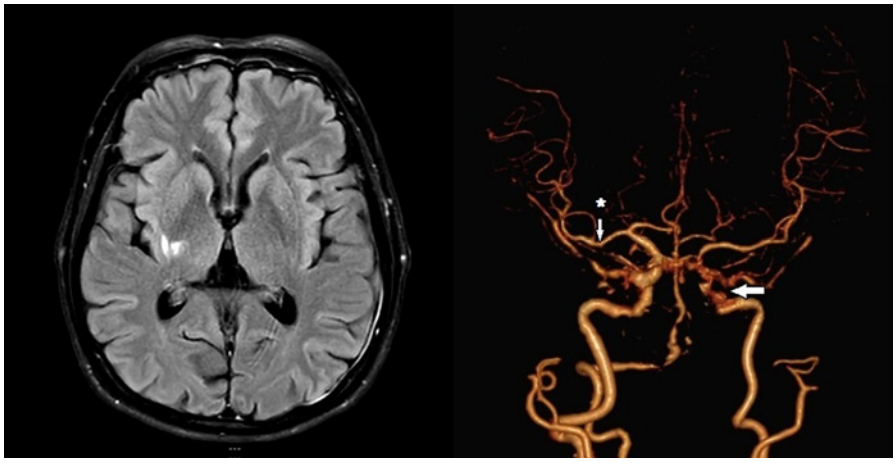

Fig. 2. Magnetic resonance imaging. T2W/FLAIR hyperintense lesions were detected at right lentiform nucleus and posterior limb of internal capsule. CTA demonstrated narrowing of the right middle cerebral artery (white arrow with asterisk) and the left distal internal carotid artery (white arrow). Bilateral vertebral arteries were severe stenosis.

without MMD within the Southeast Asian population. Table 3 demonstrates the comparison of prevalence of the RNF213 rs112735431 variant in non-MMD intracranial artery stenosis with ischemic stroke patients in previous studies in Japan, Korea, China, and our study.

This rarity in Thai patients may be attributed to the lower prevalence of MMD in Thailand compared to Japan and Korea [9]. Furthermore, our study suggests that ICAS in the Thai population may be associated with different genetic polymorphisms not assessed in this study. Recent meta-analyses proposed an association between rs112735431 and an increased risk of MMD among Japanese, Korean, and Chinese populations, while MMD in non-Asian populations was associated with rs397514563 [21–23].

Interestingly, two cases with the RNF213 rs112735431 gene variant did not meet the definite diagnosis of MMD and had many atherosclerotic risk factors. This raises challenges in determining the exact mechanism of their ischemic stroke. Previous data from a study by Okazaki suggested an association between RNF213 rs112735431 genetic variant and large atheromatous disease. Whether the RNF213 rs112735431 gene variant in these cases is related to intracranial artery stenosis or is a coincidental finding remains uncertain [16].

Highlighting three cases that met the definite diagnosis of MMD, we did not find the RNF213 rs112735431 gene variant. This observation suggests that MMD in the Thai population may be linked to other genetic polymorphisms.

Despite these insights, our study has limitations. The exclusive focus on the RNF213 rs112735431 gene variant may have overlooked other genetic variants, such as rs138130613, in some intracranial artery stenosis patients. Future genetic studies on intracranial stenotic ischemic stroke patients in the Thai population should explore additional genetic variants. Furthermore, the absence of a control group hinders definitive conclusions regarding the

Table 3. Comparison of prevalence of the RNF213 rs112735431 variant in non-MMD disease intracranial artery stenosis with ischemic stroke patients in previous studies

Author and reference	Year	Country	Sample size		Genotype[a]		Prevalence, %		OR (95% CI)
			stroke	Control	stroke	control	stroke	control	
Miyawaki et al. [6]	2013	Japan	84	110	64/20/0	108/2/0	23.81	1.82	16.88 (3.82–74.58)
Shinya et al. [14]	2017	Japan	104	100	94/10/0	98/2/0	9.62	2.00	5.21 (1.11–24.42)
Kamimura et al. [15]	2019	Japan	70	0	53/17/0	–	24.28	–	–
Okazaki et al. [24]	2019	Japan	1,757	29,206	1,664/93/0	28,818/388/0	5.30	1.33	3.58 (2.55–5.03)
Bang et al. [8]	2016	Korea	234	83	184/50/0	82/1/0	21.37	1.20	22.28 (0.43–10.73)
Park et al. [17]	2017	Korea	31	100	24/7/0	98/2/0	22.58	2.00	14.58 (2.85–74.69)
Zhang et al. [18]	2017	China	715	507	709/6/0	505/2/0	0.84	0.39	2.14 (0.43–10.63)
Xue et al. [19]	2017	China	114	268	106/8/0	267/1/0	7.54	0.37	20.15 (2.49–163.08)
Zhou et al. [20]	2022	China	10,381	–	10,325/56/0	–	0.54	–	–
Travanichakul et al. (this study)	2024	Thailand	110	60	108/2/0	–	1.81	–	–

[a]Genotype presented as wild-type/heterozygous/homozygous.

association of the RNF213 rs112735431 mutation with ischemic stroke. Subsequent genetic studies in the normal Thai population are essential. Finally, the discrepancy in the frequency of RNF213 mutations between the pilot study and the present study indicates the possibility of sampling bias. Recommendations include conducting tests in other institutes in Thailand and enrolling larger sample sizes consecutively in future studies.

Conclusion

We conclude that the RNF213 rs112735431 gene variant is not responsible for most cases of intracranial arterial stenosis in Thailand. The complexity of genetic factors influencing this condition in the Thai context warrants further investigation and underscores the need for a more comprehensive understanding of the unique genetic landscape in this population. Further genetic epidemiology studies with larger sample sizes, multi-center studies, and whole genome sequencing on Thai ischemic stroke patients are needed.

Statement of Ethics

This study protocol was reviewed and approved by the Local Ethics Committee from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB no 99/2558). Written informed consent to participate in the study has been obtained from all adult participants and all vulnerable participants' parent/legal guardian/next of kin.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: N. Suwanwela and S. Travanichakul; methodology: S. Travanichakul; identification of gene variant: T. Snabboon, N. and Houngngam; drafting the article: S. Travanichakul; review and editing: N. Kijpaisalratana, A. Chutinet, and N. Suwanwela; and supervision: N. Suwanwela. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. There are no separate or additional files. Further inquiries can be directed to the corresponding author.

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