JoS JOURNAL OF STROKE

Journal of Stroke 2023;25(2):303-306
https://doi.org/10.5853/jos.2023.00297

Letter to the Editor

Genotype–Phenotype Correlation of the *RNF213* R4810K Variant in Moyamoya Disease

Taedong Ok,[1,2] Yo Han Jung,[2,3] Kyung-Yul Lee[2,3]

[1]Department of Neurology, National Health Insurance Service Ilsan Hospital, Goyang, Korea
[2]Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[3]Severance Institute for Vascular and Metabolic Research, Yonsei University College of Medicine, Seoul, Korea

Dear Sir:

The R4810K variant of ring finger protein 213 (*RNF213*) was identified as a strong genetic susceptibility factor for moyamoya disease (MMD) in the East Asian population.[1,2] The *RNF213* R4810K variant is associated with significantly early age of onset and the severity of clinical disease phenotypes.[3-5] However, its association with various other clinical presentations and long-term patient outcomes has not been fully established.[6,7] This study aimed to investigate the influence of the *RNF213* R4810K variant on clinical phenotypes and long-term outcomes in Korean patients with MMD.

This retrospective study involved 311 Korean patients with MMD who had undergone *RNF213* genotyping at two tertiary university hospitals between January 2017 and August 2021. A flowchart for the selection of MMD with *RNF213* genotyping is shown in Supplementary Figure 1. The detailed methodology is described in the Supplementary Methods. Briefly, clinical manifestations including cerebral infarction, transient ischemic attack (TIA), intracranial hemorrhage/intraventricular hemorrhage (ICH/IVH), seizure, and angiographic characteristics including bilateral vasculopathy, posterior cerebral artery (PCA) involvement, and Suzuki grade were assessed at diagnosis of MMD. The association between the *RNF213* R4810K variant and clinical/angiographic characteristics at MMD diagnosis was investigated. Moreover, among patients with at least 3 months of follow-up, we evaluated the influence of the *RNF213* R4810K variant on long-term clinical outcomes and the results of revascularization after bypass surgery. This study was reviewed and approved by Severance Hospital Yonsei University Health System Institutional Review Board (3-2021-0443). The requirement for written informed consent was waived due to the retrospective study design.

The clinical and angiographic characteristics of 311 patients with MMD are summarized in Supplementary Table 1. The distribution of age peaked twice—at ages 5–9 and 45–49 years—with a higher frequency in the adult peak (Supplementary Figure 2A). Compared to adult MMD patients, pediatric MMD patients more frequently presented with ischemic manifestations and seizures and had a higher proportion of bilateral vasculopathy. The correlation between clinical characteristics and the *RNF213* R4810K variant in MMD is summarized in Table 1 and Supplementary Figure 3. The age at onset of homozygotes was significantly lower than those of heterozygotes and the wild-type (Supplementary Figure 2B). The proportion of patients who underwent revascularization surgery showed a dosage-dependent pattern of the variant, being the highest in homozygotes (60% in AA, 34% in GA, and 16% in GG; P for trend <0.001). Seizure as the initial clinical manifestation was more common in homozygotes than in heterozygotes or those with the wild-type variant (40% vs. 3%, P=0.03; 40% vs. 3%, P=0.06; respectively). Homozygotes were more susceptible to PCA involvement than heterozygotes and wild-type (80% vs. 20%, P=0.02; 80% vs. 10%, P<0.01; respectively). PCA involvement showed a dose-dependent pattern of the variant, being the highest in homozygotes (80% in AA, 20% in GA, and 10% in GG; P for trend <0.001). The results of the subgroup analysis of genotype–phenotype correlations for *RNF213* R4810K variant with the age at onset are described in the Supplementary Results, Supplementary Tables 2-4, and Supplementary Figure 3.

Among 311 MMD patients, 293 with at least 3 months of follow-up were analyzed for the association between the *RNF213* R4810K variant and long-term patient outcomes. During the me-

dian follow-up of 35 months after the diagnosis of MMD, 30 cases of cerebral infarction, 51 of TIA, 11 of ICH/IVH, and 2 deaths occurred (Supplementary Table 5). The risk of cerebral infarction after the diagnosis of MMD was approximately six times higher in homozygotes than in those with the wild-type variant (unadjusted hazard ratio, 6.38; 95% confidence interval 1.20–33.89; *P*=0.03) (Table 2). Among the 94 patients who underwent revascularization surgery, 99 hemispheres from 65 patients with MMD were included in this investigation (Supplementary Table 6). The increase in the caliber change ratios—defined as the ratio of postoperative caliber diameter to preoperative caliber diameter—for the superficial temporal artery was significantly higher in patients with the *RNF213* R4810K variant (median 1.27, interquartile range [IQR] 1.12–1.42) than in those with the wild-type variant (median 1.12, IQR 1.01–1.23; *P*=0.046) (Figure 1).

This study confirmed that the homozygous R4810K genotype is not only associated with an earlier onset of MMD, but also with seizures and PCA involvement. Previous studies have not demonstrated an association between the R4810K variant and seizures.[3,4,6] Additionally, the association between the R4810K variant and initial angiographic findings of MMD, such as bilaterality and PCA involvement, has not been fully established.[3,4,8] This is the most extensive study to assess the genotype–phenotype correlation of *RNF213* R4810K variant in Korean patients. We clarified that the homozygous R4810K variant of *RNF213* predicts the early onset of MMD and PCA involvement in Korean patients. Moreover, the R4810K variant was associated with seizures and influenced the clinical phenotype depending on the age at onset, indicating an extensive role of the *RNF213* R4810K variant in MMD.

Table 2. Correlation between clinical outcomes and the R4810K variant of *RNF213*

	GG (n=64)	GA (n=225)		AA (n=4)	
		HR (95% CI)	*P*	HR (95% CI)	*P*
TIA	Reference	0.87 (0.44–1.69)	0.67	1.16 (0.15–8.98)	0.89
Infarction	Reference	1.25 (0.48–3.27)	0.65	6.38 (1.20–33.89)	0.03
ICH/IVH	Reference	1.02 (0.21–4.85)	0.98	6.77 (0.57–80.72)	0.13
Death	Reference	0.16 (0.01–3.62)	0.25	2.11 (0.03–179.24)	0.74

RNF213, ring finger protein 213; GG, wild type; GA, heterozygote; AA, homozygote; TIA, transient ischemic attack; ICH/IVH, intracranial cerebral hemorrhage/intraventricular hemorrhage; PCA, posterior cerebral artery.

Table 1. Correlation of clinical characteristics with the R4810K genotype of *RNF213* in patients with moyamoya disease

Variable	GG (n=68)	GA (n=238)	AA (n=5)	*P*	*Post-hoc P*		
					GG vs. GA	GG vs. AA	GA vs. AA
Female sex	42 (62)	153 (64)	1 (20)	0.14			
Age at onset (yr)	37.7 [27.8, 47.3]	40.1 [22.7, 50.5]	4.3 [1.9, 9.5]	<0.001	>0.99	<0.001	<0.001
Age under 18	9 (13)	49 (21)	5 (100)	<0.001	0.52	<0.001	<0.001
Family history	2 (3)	44 (19)	0 (0)	<0.001	<0.001	>0.99	>0.99
Revascularization surgery*	11 (16)	80 (34)	3 (60)	0.01	0.02	0.40	>0.99
Clinical manifestation							
Infarction	16 (24)	44 (19)	2 (40)	0.26			
TIA	21 (31)	86 (36)	1 (20)	0.63			
ICH/IVH	1 (2)	23 (10)	0 (0)	0.07			
Seizure	2 (3)	6 (3)	2 (40)	0.01	>0.99	0.06	0.03
Incidental	9 (13)	40 (17)	0 (0)	0.60			
Others†	19 (28)	39 (16)	0 (0)	0.07			
Angiographic findings							
Bilateral vasculopathy	40 (59)	155 (65)	5 (100)	0.17			
PCA involvement*	7 (10)	48 (20)	4 (80)	<0.001	0.22	<0.01	0.02
Suzuki grade‡				0.34			
1–2	14 (26)	43 (25)	0 (0)				
3–4	28 (53)	108 (62)	2 (67)				
5–6	11 (21)	22 (13)	1 (33)				

Data are presented as n (%) as or median [interquartile range].
RNF213, ring finger protein 213; GG, wild type; GA, heterozygote; AA, homozygote; TIA, transient ischemic attack; ICH/IVH, intracranial cerebral hemorrhage/intraventricular hemorrhage; PCA, posterior cerebral artery.
*Revascularization surgery (*P*-value for trend <0.001), PCA involvement (*P*-value for trend <0.001); †Others: headache, dizziness, and syncope; ‡The Suzuki grade on the severe side was applied.

https://doi.org/10.5853/jos.2023.00297

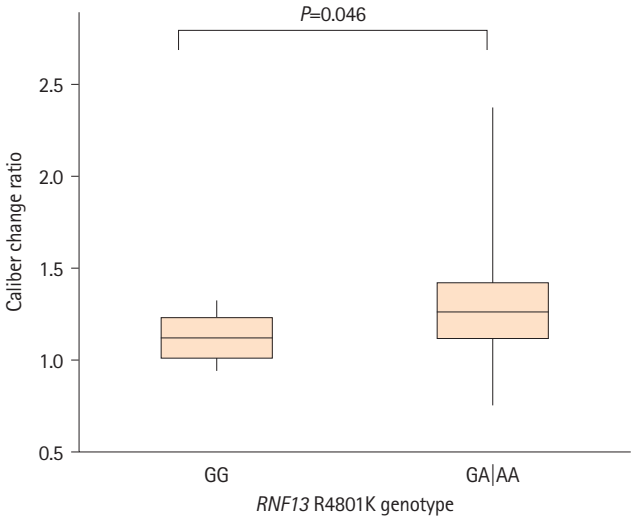

Figure 1. Association of postoperative collateral development and the *RNF213* R4810K variant in moyamoya disease. The caliber change ratios for the superficial temporal artery were compared between patients with the *RNF213* R4810K variant and those with the wild-type variant. *RNF213*, ring finger protein 213; GG, wild type; GA, heterozygote; AA, homozygote.

To our knowledge, this is the first study to demonstrate that the homozygous R4810K variant has a higher risk of future cerebral infarction than that of the wild-type, indicating that homozygotes are at high risk for later cerebral infarction, and more aggressive bypass surgery can be considered in these patients. Moreover, patients with the *RNF213* R4810K variant showed better revascularization outcomes than those of patients with the wild-type variant, as reported in previous studies.[8,9] Although the precise pathophysiological role of *RNF213* in MMD remains unclear, the present and previous studies' results support its role in angiogenic function.[2,10]

Our study had some limitations. Selection bias was unavoidable owing to its retrospective design. Only 8% of patients diagnosed with MMD underwent *RNF213* genotyping, and few homozygous patients were included. Moreover, rare variants of the *RNF213* gene were not analyzed.

In conclusion, the R4810K variant of *RNF213* strongly correlated with an earlier age of onset, seizure at presentation, PCA involvement, future cerebral infarction, and better development of collaterals after bypass surgery in patients with MMD. Our study suggests a broader genotype–phenotype correlation than was previously assumed and provides informative data on the role of *RNF213* in the clinical management of MMD.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2023.00297.

Funding statement

None

Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: TO, KYL. Study design: all authors. Methodology: TO, KYL. Data collection: TO. Investigation: TO, KYL.. Statistical analysis: TO, YHJ. Writing—original draft: TO. Writing—review & editing: all authors. Funding acquisition: KYL. Approval of final manuscript: all authors.

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Correspondence: Kyung-Yul Lee
Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea
Tel: +82-2-2019-3325
E-mail: kylee@yuhs.ac
https://orcid.org/0000-0001-5585-7739

Received: January 26, 2023
Revised: January 27, 2023
Accepted: January 27, 2023

Supplementary Methods

Study design and patient selection

This retrospective study included 311 Korean patients with moyamoya disease (MMD) who had undergone *RNF213* genotyping at two tertiary university hospitals between January 2017 and August 2021. MMD was diagnosed using digital subtraction angiography or magnetic resonance angiography (MRA) combined with a review of medical records. The diagnostic criteria for MMD were based on guidelines published by the Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis of Japan in 2012.[1] Patients with the following underlying diseases with similar angiographic findings were excluded: (1) atherosclerosis, (2) autoimmune disease, (3) history of cranial irradiation, (4) intracranial artery dissection, (5) von Recklinghausen's disease, (6) brain tumors, and (7) sickle cell disease. Patients were classified as having pediatric MMD when they had been diagnosed before 18 years of age. A flowchart for the selection of MMD with *RNF213* genotyping is shown in Supplementary Figure 1. Analysis of the R4810K variant of the *RNF213* gene (GenBank accession number NM_001256071.1) was performed using patients' blood samples. The analysis was conducted at a commercial laboratory (Seoul Clinical Laboratories, Yongin, South Korea).

Clinical and radiologic characteristics

Information on the patients' sex, age at onset, family history of MMD, revascularization surgery, primary clinical manifestation at diagnosis, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, history of current smoking, and angiographic findings was collected via a medical record review. A family history of MMD was obtained from patients' medical records or by interviewing patients or their main caretakers. The primary clinical manifestations at diagnosis were classified as cerebral infarction, transient ischemic attack (TIA), intracranial hemorrhage/intraventricular hemorrhage (ICH/IVH), seizure, incidental findings, and others (headache, dizziness, and syncope). The most severe neurological symptom was defined as the primary clinical manifestation if two or more symptoms were present. Bilateral vasculopathy, posterior cerebral artery involvement, and Suzuki grade, which are angiographic findings of MMD that are related to disease severity, were assessed.[2] The Suzuki grade on the severe side was applied. Angiographic findings and medical records were reviewed by a neurologist who was blinded to the *RNF213* genotyping results.

Evaluation of patient outcomes and results of revascularization after bypass surgery

To evaluate the influence of the *RNF213* R4810K variant on patient outcomes, clinical outcomes including TIA, cerebral infarction, ICH/IVH, and mortality of patients with at least 3 months of follow-up were collected by retrospective medical record review. The first event was evaluated for the same recurrent events. The follow-up period was defined as the period from the date of MMD diagnosis to the date of final observation.

Evaluation of the impact of the *RNF213* R4810K variant on the development of revascularization was performed as previously described by Kawabori et al.[3] Patients who performed revascularization with preoperative MRA performed within 1 year and postoperative MRA performed between 6 and 12 months after surgery were analyzed. MRA source images were used to quantitatively evaluate collateral development by measuring the caliber of the superficial temporal artery (STA). For either direct or indirect bypass, the calibers of the STA at the level of bifurcation of the frontal and parietal branches were compared. The caliber change ratio (CCR), defined as the ratio of the postoperative caliber diameter (mm) to the preoperative caliber diameter (mm), was compared among patients with GG, GA, and AA genotypes. The caliber of the basilar artery was used as the internal control.

Statistical analysis

Differences in the clinical and radiological characteristics of MMD patients with respect to the *RNF213* R4810K variant were assessed. Continuous variables were presented as means with standard deviations and were compared using analysis of variance. Categorical variables were presented as counts (percentage) and compared using the chi-square or Fisher's exact test. Multiple comparisons for *post hoc* analysis were adjusted using Bonferroni's method. Linear to linear analysis was used for trend analysis. Statistical significance was defined as a two-sided P-value <0.05.

To evaluate the influence of *RNF213* R4810K variant on patient outcomes, the hazard ratio was evaluated using a Cox proportional regression model. The correlation between the *RNF213* R4810K variant and the CCR for STA was compared using the Mann-Whitney test. Statistical analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC, USA) and the SPSS software (version 25.0; IBM Corp., Armonk, NY, USA).

Standard protocol approvals, registrations, and patient consent

This study was reviewed and approved by the Severance Hospital Yonsei University Health System Institutional Review Board (3-2021-0443). The requirement for written informed consent for participation was waived owing to this study's retrospective design.

Supplementary Results

Subgroup analysis of genotype–phenotype correlations for the *RNF213* R4810K variant upon age at onset

Among 248 adult MMD patients, 189 were heterozygous and none were homozygotes (Supplementary Table 2 and Supplementary Figure 3B). Heterozygotes had a family history of MMD (19% vs. 3%; $P<0.001$), underwent more revascularization surgeries (19% vs. 5%; $P=0.01$), and were more susceptible to posterior cerebral artery (PCA) involvement than were those with the wild type (22% vs. 9%; $P=0.02$). Cerebral hemorrhage as an initial clinical manifestation was significantly more common in heterozygotes than in those with the wild type (11% vs. 2%; $P=0.026$). The AA, GA, and GG genotypes did not differ significantly in other clinical presentations.

Among 63 pediatric MMD patients, 49 were heterozygous and 5 were homozygous (Supplementary Table 3 and Supplementary Figure 3C). Homozygotes were more susceptible to PCA involvement than were heterozygotes (80% vs. 14%; $P<0.001$). The AA, GA, and GG genotypes did not differ significantly in other clinical presentations.

The clinical characteristics were compared between pediatric and adult MMD patients among heterozygotes (Supplementary Table 4). Compared to adult MMD heterozygotes, pediatric MMD heterozygotes more frequently presented with TIA and underwent more revascularization surgeries. Moreover, pediatric MMD heterozygotes had a higher proportion of bilateral vasculopathy than did adult MMD heterozygotes. The AA, GA, and GG genotypes did not differ significantly in terms of Suzuki grades.

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https://doi.org/10.5853/jos.2023.00297

Supplementary Table 1. Clinical and angiographic characteristics of patients with moyamoya disease

	All (n=311)	Pediatric (n=63)	Adult (n=248)	*P*
Female sex	196 (63)	35 (56)	161 (65)	0.17
Age at onset (yr)	38.9 [23.6, 50.0]	7.8 [6.1, 11.6]	43.9 [35.1, 51.9]	<0.001
Family history	46 (15)	8 (13)	38 (15)	0.60
Revascularization surgery	94 (30)	56 (89)	38 (15)	<0.001
RNF213 genotype				<0.001
Wild type (GG)	68 (22)	9 (14)	59 (24)	
Heterozygote (GA)	238 (77)	49 (78)	189 (76)	
Homozygote (AA)	5 (2)	5 (8)	0 (0)	
Clinical manifestation				
Ischemic manifestation	170 (55)	46 (73)	124 (50)	0.001
TIA	108 (35)	39 (62)	69 (28)	<0.001
Infarction	62 (20)	7 (11)	55 (22)	0.05
ICH/IVH	24 (8)	2 (3)	22 (9)	0.19
Seizure	10 (3)	7 (11)	3 (1)	0.001
Incidental	49 (16)	0 (0)	49 (20)	<0.001
Others*	58 (19)	50 (20)	8 (13)	0.18
Angiographic findings				
Bilateral vasculopathy	200 (64)	54 (86)	146 (59)	<0.001
PCA involvement	59 (19)	13 (21)	46 (19)	0.71
Suzuki grade†				0.62
1–2	57 (25)	4 (17)	53 (26)	
3–4	138 (60)	16 (67)	122 (60)	
5–6	34 (15)	4 (17)	30 (15)	
Medical history				
Hypertension	92 (30)	0 (0)	92 (37)	<0.001
Diabetes mellitus	28 (9)	0 (0)	28 (11)	0.01
Dyslipidemia	70 (23)	0 (0)	70 (28)	<0.001
Coronary artery disease	6 (2)	0 (0)	6 (2)	0.61
Current smoker	38 (12)	0 (0)	38 (15)	0.001

Data are presented as n (%) or median [interquartile range].
RNF213, ring finger protein 213; TIA, transient ischemic attack; ICH/IVH, intracranial cerebral hemorrhage/intraventricular hemorrhage; PCA, posterior cerebral artery.
*Others: headache, dizziness, and syncope; †The Suzuki grade on the severe side was applied.

Supplementary Table 2. Genotype–phenotype correlation of the *RNF213* R4810K variant in adult moyamoya disease

Variable	GG (n=59)	GA (n=189)	*P*
Age at onset (yr)	39.2 [33.5, 48.5]	46.2 [35.8, 53.0]	0.05
Female sex	40 (68)	121 (64)	0.60
Family history	2 (3)	36 (19)	<0.001
Revascularization surgery	3 (5)	35 (19)	0.01
Clinical manifestation			
TIA	17 (29)	52 (28)	0.85
Infarction	16 (27)	39 (21)	0.30
ICH/IVH	1 (2)	21 (11)	0.03
Seizure	0 (0)	3 (2)	>0.99
Incidental	9 (15)	40 (21)	0.32
Others*	16 (27)	34 (18)	0.13
Angiographic findings			
Bilateral vasculopathy	33 (56)	113 (60)	0.60
PCA involvement	5 (9)	41 (22)	0.02
Suzuki grade†			0.38
1–2	13 (27)	40 (26)	
3–4	26 (53)	96 (62)	
5–6	10 (20)	20 (13)	

Data are presented as n (%) or median [interquartile range].
RNF213, ring finger protein 213; GG, wild type; GA, heterozygote; TIA, transient ischemic attack; ICH/IVH, intracranial cerebral hemorrhage/intraventricular hemorrhage; PCA, posterior cerebral artery.
*Others: headache, dizziness, and syncope; †The Suzuki grade on the severe side was applied.

Supplementary Table 3. Genotype–phenotype correlation of the *RNF213* R4810K variant in pediatric moyamoya disease

Variable	GG (n=9)	GA (n=49)	AA (n=5)	*P*	*Post-hoc P*		
					GG vs. GA	GG vs. AA	GA vs. AA
Female sex	2 (22)	32 (65)	1 (20)	0.01	0.08	>0.99	0.07
Age at onset (yr)	9.0 [7.8, 9.0]	7.7 [6.2, 11.6]	4.3 [1.9, 9.5]	0.60			
Age under 5	1 (11)	7 (14)	3 (60)	0.04	>0.99	0.28	0.11
Family history	0 (0)	8 (16)	0 (0)	0.51			
Revascularization surgery	8 (89)	45 (92)	3 (60)	0.14			
Clinical manifestation							
Infarction	0 (0)	5 (10)	2 (40)	0.14			
TIA	4 (44)	34 (69)	1 (20)	0.05			
ICH/IVH	0 (0)	2 (4)	0 (0)	>0.99			
Seizure	2 (22)	3 (6)	2 (40)	0.03	0.50	>0.99	0.06
Incidental	0 (0)	0 (0)	0 (0)	-			
Others*	3 (33)	5 (10)	0 (0)	0.15			
Angiographic findings							
Bilateral vasculopathy	7 (78)	42 (86)	5 (100)	0.67			
PCA involvement	2 (22)	7 (14)	4 (80)	<0.001	>0.99	0.27	<0.001
Suzuki grade†				0.72			
1–2	1 (25)	3 (18)	0 (0)				
3–4	2 (50)	12 (71)	2 (67)				
5–6	1 (25)	2 (12)	1 (33)				

Data are presented as n (%) or median [interquartile range].
RNF213, ring finger protein 213; GG, wild type; GA, heterozygote; AA, homozygote; TIA, transient ischemic attack; ICH/IVH, intracranial cerebral hemorrhage/intraventricular hemorrhage; PCA, posterior cerebral artery.
*Others: headache, dizziness, and syncope; †The Suzuki grade on the severe side was applied.

https://doi.org/10.5853/jos.2023.00297

Supplementary Table 4. Comparison between pediatric and adult moyamoya disease among *RNF213* R4810K heterozygotes

Variable	Pediatric (n=49)	Adult (n=189)	*P*
Female	32 (65)	121 (64)	0.87
Family history	8 (16)	36 (19)	0.66
Revascularization surgery	45 (92)	35 (19)	<0.001
Clinical manifestation			
TIA	34 (69)	52 (28)	<0.001
Infarction	5 (10)	39 (21)	0.09
ICH/IVH	2 (4)	21 (11)	0.14
Seizure	3 (6)	3 (2)	0.07
Incidental	0 (0)	40 (21)	<0.001
Others*	5 (10)	34 (18)	0.19
Angiographic findings			
Bilateral vasculopathy	42 (86)	113 (60)	0.001
PCA involvement	7 (14)	41 (22)	0.25
Suzuki grade†			0.65
1–2	3 (18)	40 (26)	
3–4	12 (71)	96 (62)	
5–6	2 (12)	20 (13)	

Data are presented n (%).
RNF213, ring finger protein 213; TIA, transient ischemic attack; ICH/IVH, intracranial cerebral hemorrhage/intraventricular hemorrhage; PCA, posterior cerebral artery.
*Others: headache, dizziness, and syncope; †The Suzuki grade on the severe side was applied.

Supplementary Table 5. Clinical Outcomes in patients with moyamoya disease and the R4810K variant of *RNF213*

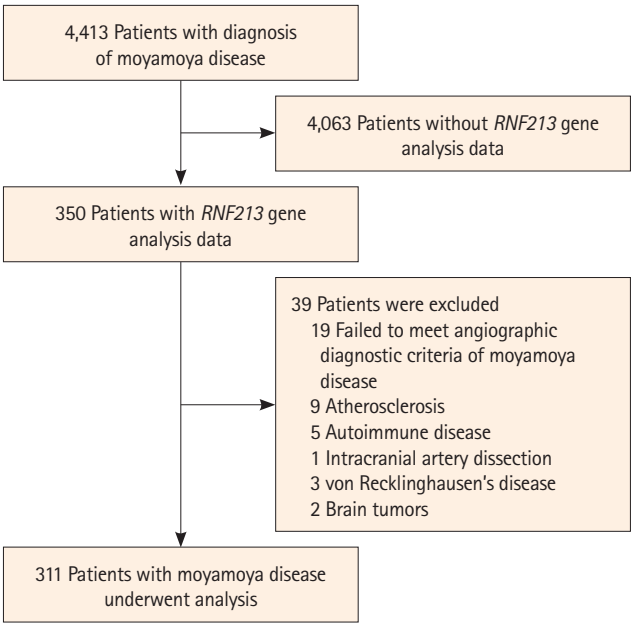
Variable	All (n=293)	GG (n=64)	GA (n=225)	AA (n=4)	*P*
Infarction	30 (10.2)	4 (6.3)	24 (10.7)	2 (50.0)	0.04
TIA	51 (17.4)	11 (17.2)	39 (17.3)	1 (25.0)	0.80
ICH/IVH	11 (3.8)	2 (3.1)	8 (36.7)	1 (25.0)	0.16
Death	2 (0.7)	1 (1.6)	1 (0.4)	0 (0.0)	0.41
FU period (mo)	34.9 [21.2–61.7]	29.3 [20.9–47.4]	36.8 [21.0–64.7]	53.5 [26.9–148.2]	0.13

Data are presented as n (%) or median [interquartile range].
RNF213, ring finger protein 213; GG, wild type; GA, heterozygote; AA, homozygote; TIA, transient ischemic attack; ICH/IVH, intracranial cerebral hemorrhage/intraventricular hemorrhage; PCA, posterior cerebral artery; FU, follow-up.

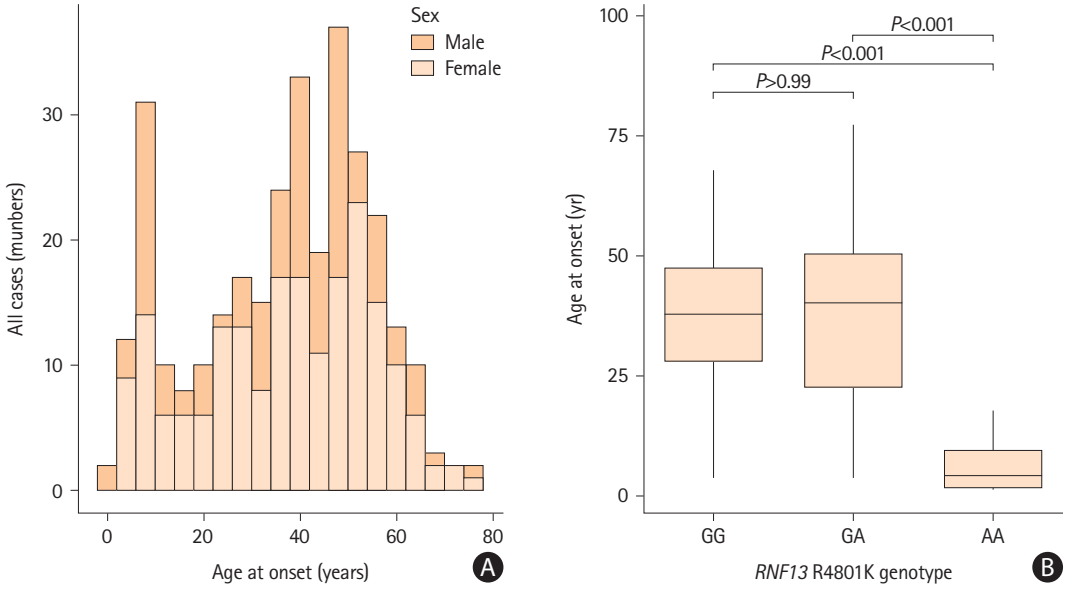
Supplementary Table 6. Characteristic of patients with revascularization surgery

	Number of hemispheres	Number of patients
Revascularization surgery	99	65
Direct	11	10
Indirect	88	55
RNF213 genotype		
Wild type (GG)	11	8
Heterozygote (GA)	85	55
Homozygote (AA)	3	2

RNF213, ring finger protein 213.

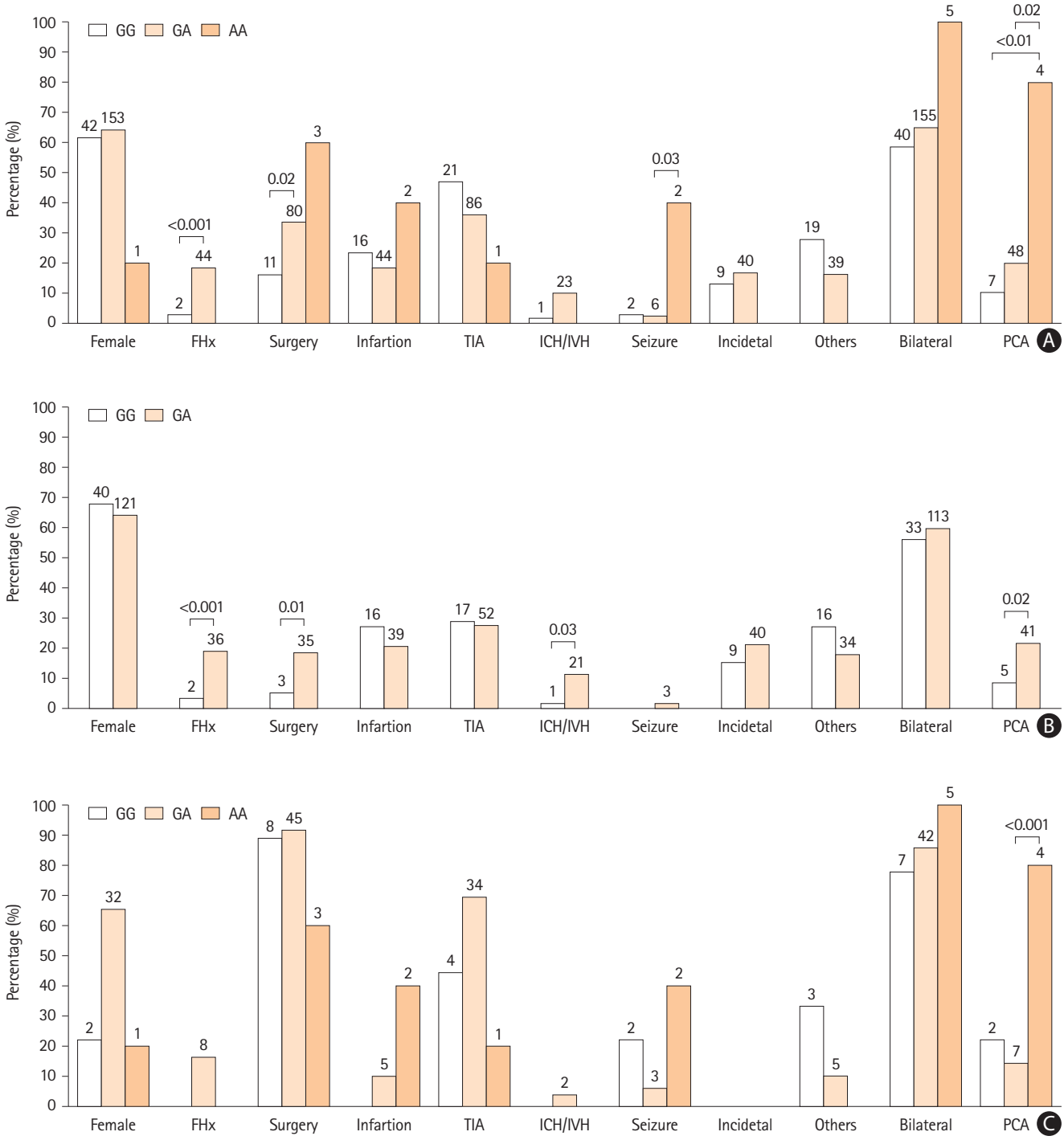


Supplementary Figure 1. Flowchart for the selection of moyamoya disease patients with ring finger protein 213 (*RNF213*) genotyping.



Supplementary Figure 2. Age distribution patterns in moyamoya disease and correlation between ring finger protein 213 (*RNF213*) R4810K genotype and age at onset. (A) Dual peak distribution of moyamoya disease. (B) A box plot of the age at onset among 3 groups of patients: homozygotes (AA), heterozygotes (GA), and wild types (GG) of *RNF213* R4810K variant.

https://doi.org/10.5853/jos.2023.00297



Supplementary Figure 3. Genotype–phenotype correlation of *RNF213* R4810K variant in moyamoya disease. (A) All patients with moyamoya disease. (B) Patients with adult moyamoya disease. (C) Patients with pediatric moyamoya disease. *RNF213*, ring finger protein 213; GG, wild type; GA, heterozygote; AA, homozygote; FHx, family history; TIA, transient ischemic attack; ICH/IVH, intracranial cerebral hemorrhage/intraventricular hemorrhage; PCA, posterior cerebral artery.