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BRIEF COMMUNICATION

Role of the *RNF213* Variant in Vascular Outcomes in Patients With Intracranial Atherosclerosis

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BACKGROUND: The *RNF213* (*ring finger protein 213* gene) variant R4810K is a susceptibility allele not only for Moyamoya disease (MMD) but also for intracranial atherosclerosis (ICAS) in East Asian populations. We hypothesized that this variant would affect the distribution of ICAS and recurrence of cerebrovascular events.

METHODS AND RESULTS: We conducted a prospective study of patients with ICAS and MMD using high-resolution magnetic resonance imaging and *RNF213* R4810K genotyping. Patients were included in the ICAS group when relevant plaques existed on high-resolution magnetic resonance imagingand in the MMD group when they carried the variant and high-resolution magnetic resonance imaging showed no plaques but characteristic features of MMD. We compared clinical and neuroimaging features of patients with ICAS-*RNF213*+ with patients with ICAS-*RNF213*– and of patients with MMD. Of 477 patients, 238 patients were in the ICAS group and 239 were in the MMD group. Among patients with ICAS, 79 patients (33.2%) were in the ICAS-*RNF213*+ group and 159 (66.8%) in the ICAS-*RNF213*– group. Tandem lesions were significantly more common in the ICAS-*RNF213*+ group than in the ICAS-*RNF213*– group (40.3% versus 72.2%, $P<0.001$), and their distributions were similar between the ICAS-*RNF213*+ and MMD groups. The presence of the R4810K variant (hazard ratio [HR], 3.203; 95% CI, 1.149–9.459; $P=0.026$) and tandem lesions (≥3) (HR, 8.315; 95% CI, 1.930–39.607; $P=0.005$) were independently associated with recurrent cerebrovascular events.

CONCLUSIONS: Patients with ICAS carrying the *RNF213* R4810K variant showed clinical and imaging features distinct from patients with ICAS without the variant, suggesting that the R4810K variant plays a role in intracranial atherosclerosis in East Asian patients.

Key Words: intracranial atherosclerosis ■ Moyamoya disease ■ RNF213 variant

Both intracranial atherosclerosis (ICAS) and Moyamoya disease (MMD) are prevalent in East Asian populations. The R4810K (p.Arg4810Lys) polymorphism in the gene encoding the *RNF213* (*ring finger protein 213*) at chromosome 17q25.1 is the strongest genetic susceptibility factor for MMD in East Asian populations.[1] Recently, the R4810K variant was reported to be associated with non-MMD disorders, such as intracranial atherosclerosis and systemic vasculopathy.[2] Japanese and Korean investigators reported that this variant was present in about a quarter of patients with intracranial steno-occlusive lesions without signs of MMD[3,4] and with high-resolution magnetic resonance imaging (HR-MRI)-confirmed ICAS.[5] A recent large population study in Japan that evaluated the R4810K variant in various stroke subtypes showed that only large artery disease was associated with this variant.[6]

However, the role of the *RNF213* R4810K variant in patients with ICAS is unknown. In this study, we

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hypothesized that this variant may affect the distribution of atherosclerotic plaques and the outcome of patients with ICAS. Thus, we compared the distribution of intracranial plaques on HR-MRI and the occurrence of recurrent stroke depending on the presence or absence of this variant.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Selection

We prospectively studied consecutive patients with ICAS and MMD (ClinicalTrials.gov Identifier, NCT02074111). We included patients (1) aged ≥18 years with ≥50% stenosis or occlusion on distal portions of the internal carotid artery (dICA) and/or proximal middle cerebral artery (MCA) disease on MRA, regardless of the presence or absence of neurological symptoms, (2) and who underwent both HR-MRI and *RNF213* R4810K genotyping. Identification of *RNF213* variant was performed as described elsewhere.[5,7] We excluded patients with (1) potential sources of cardioaortic embolism; (2) extracranial atherosclerosis with significant (≥50%) stenosis of the relevant cervical carotid artery; (3) other stroke mechanisms (coagulopathy, vasculitis, arterial dissection, etc); (4) prior ischemic event in vascular territory that was associated with intracranial large artery disease; or (5) incomplete evaluations. All symptomatic cases were hospitalized for the management of acute stroke, whereas most patients with asymptomatic cases were seen in the outpatient clinic after intracranial vessel stenosis diagnosis by medical check-up or non-stroke symptoms. The local institutional review board approved this study (approval number, 2016-08-064) and registered on ClinicalTrials.gov (NCT02074111). All patients or their guardians provided informed consent for participation.

MRI Protocol and Analysis

HR-MRI images were analyzed to evaluate the vessel walls. Details of the HR-MRI parameters are described elsewhere.[7] Two participating neurologists (H.J.K. and E.-H.C.) independently analyzed the characteristics: outer diameter, wall remodeling, morphology of the stenotic portion (dichotomous as eccentric or concentric), and basal collateral structure. We evaluated vessel walls of MCA and dICA at the site of maximal stenosis or just proximal to the occlusion on 3-dimensional time-of-flight MRA and bilateral dICAs immediately after branching ophthalmic arteries. If the stenotic portion of the vessel wall showed consistent thickness of the circumference on a cross-sectional image of the vessel, the wall stenosis was considered to be concentric; if not, eccentric. Eccentric plaques were defined as localized plaques surrounding <75% of the vessel wall. If there were ≥2 flow void signals present in the basal ganglia on the 3-dimensional time-of-flight source image, these were considered to be collateral vascular structures.[8]

Tandem lesions were defined as cases in which a steno-occlusive lesion of ≥50% on the M1 or M2 segment of the MCA, A1, or A2 segment of the anterior cerebral artery, dICA, P1 or P2 segment of the posterior cerebral artery, basilar artery, and vertebral artery accompanied the index (M1 and/or dICA) lesion.

Patient Groups

Based on the results of HR-MRI and genetic analyses, patients were classified into 1 of 3 groups. Patients were assigned to the ICAS group when eccentric wall thickness, with/without eccentric enhancement suggesting the presence of plaques, was observed on HR-MRI. The ICAS group was subclassified as R4810K carriers (ICAS-*RNF213*+ group) and non-carriers (ICAS-*RNF213*– group), depending on the presence or absence of the R4810K variant. The diagnosis of MMD was made when all 3 of following criteria were met: negative remodeling, ≥2 flow void signals present in the basal ganglia in 3-dimensional time-of-flight MRA source images, and presence of the R4810K variant. To compare the angiographic feature of ICAS and MMD with identical genetic variant, as well, of the patients with MMD group were recruited only R4810K carrier. We compared the clinical and neuroimaging features of carrier patients with ICAS R4810K (ICAS-*RNF213*+ group) with non-carrier patients with ICAS (ICAS-*RNF213*– group) and with patients with MMD.

All patients with symptomatic ICAS were followed up for >3 months. Any cerebrovascular events, either in the same vascular territory or in the vascular territory related to tandem stenotic lesions, were evaluated.

Statistical Analysis

Fisher exact test or the χ^2 test was used to analyze the categorical variables. Differences in the continuous variables were evaluated using Student *t*-test and the Wilcoxon rank sum test. Independent factors for tandem stenotic lesions were evaluated using logistic regression. A multivariate logistic regression analysis

model was used to evaluate the independent factors for tandem stenotic lesion after adjusting for sex, age, vascular risk factors, and genetic mutation. The Cox proportional hazards model was used to calculate the hazard ratios (HRs), 95% CI, and *P* values with adjustments for sex, age, and vascular risk factors. The recurrence rate was compared using Kaplan–Meier curve analysis and log-rank test. All statistical analyses were performed in SPSS (version 23.0, IBM, Chicago, IL) and open-source statistical package R version 3.6.3 (R Project for Statistical Computing, Vienna, Austria) with the "coxphf" package (https://cran.r-project.org/web/packages/coxphf/index.html).

RESULTS

General Characteristics

Among the 477 patients, 238 (49.9%) patients were considered to have ICAS and 239 (50.1%) to have MMD. Among the patients with ICAS, 79 (33.2%) were R4810K carriers and 159 (66.8%) were non-carriers.

Patients' characteristics are summarized in the Table. The MMD-*RNF213*+ group had younger patients and more women than the ICAS-*RNF213*+ group. Although not significant, ICAS-*RNF213*– group had many vascular risk factors, followed by the ICAS-*RNF213*+ and MMD-*RNF213*+ groups. Family history

Table. Comparison of Clinical and Angiographic Features Among the Groups

	ICAS *RNF213* R4810K Non-Carrier (n=159)	ICAS *RNF213* R4810K Carrier (n=79)	MMD *RNF213* R4810K Carrier (n=239)	*P* Value*	*P* Value†
Age, y	54.57±10.47	52.87±10.37	47.63±12.67	0.241	<0.001
Men	83 (52.5%)	40 (50.6%)	75 (31.4%)	0.857	0.002
Hypertension	78 (49.4%)	34 (43.0%)	87 (36.4%)	0.404	0.292
Diabetes mellitus	35 (22.2%)	13 (16.5%)	30 (12.6%)	0.326	0.379
Hyperlipidemia	82 (51.9%)	35 (44.3%)	73 (30.5%)	0.311	0.025
Current smoker	21 (13.3%)	9 (11.4%)	14 (5.9%)	0.381	0.100
Body mass index	24.94±3.01	25.39±3.37	25.08±3.71	0.310	0.651
Family history of MMD	2 (1.3%)	7 (8.9%)	40 (16.7%)	0.004	0.087
Presence of tandem lesion					
Any (number of tandems ≥1)	64 (40.3%)	57 (72.2%)	221 (92.5%)	<0.001	<0.001
MMD-related lesion‡	52 (32.7%)	51 (64.6%)	221 (92.5%)	<0.001	<0.001
Accompanying plaque§	49 (94.2%)	39 (76.5%)	0 (0.0%)	0.011	<0.001
No. of tandems				<0.001	<0.001
0	95 (59.7%)	22 (27.8%)	18 (7.5%)		
1	27 (17.0%)	21 (26.6%)	19 (7.9%)		
2	15 (9.4%)	21 (26.6%)	34 (14.2%)		
≥3	22 (13.8%)	15 (19.0%)	168 (70.3%)		
Degree of stenosis				0.167	<0.001
50%–69% stenosis	27 (17.0%)	18 (22.8%)	9 (3.8%)		
70%–99% stenosis	64 (40.3%)	37 (46.8%)	50 (20.9%)		
Occlusion	68 (42.8%)	24 (30.4%)	180 (75.3%)		
Symptom				0.511	0.769
Asymptomatic case	54 (34.0%)	31 (39.2%)	87 (36.4%)		
Symptomatic case	105 (66.0%)	48 (60.8%)	152 (63.6%)		
Stroke recurrence in symptomatic cases	6 (5.7%)	9 (18.8%)	25 (16.4%)	0.012	0.816
Medication in symptomatic cases					
Antiplatelet treatment	103 (98.1%)	47 (97.9%)	135 (88.8%)	0.941	0.055
Statin	96 (91.4%)	45 (93.8%)	88 (57.9%)	0.620	<0.001

MMD indicates Moyamoya disease; ICAS, intracranial atherosclerosis; and *RNF213, ring finger protein 213 gene*.
*Comparison between intracranial atherosclerosis-*RNF213* R4810K carrier and intracranial atherosclerosis-*RNF213* R4810K non-carrier groups.
†Comparison between intracranial atherosclerosis-*RNF213* R4810K carrier and Moyamoya disease-*RNF213* R4810K carrier groups.
‡Tandem lesions located at the terminal portion of internal carotid artery, proximal middle cerebral artery, and proximal anterior cerebral artery.
§Plaque in Moyamoya disease-related tandem lesions.

of MMD was observed in 8.9% of patients in the ICAS-*RNF213*+ group and in 16.7% of those with MMD, but rarely in patients in the ICAS-*RNF213*– group (1.3%, *P*<0.05).

Differences in Angiographic Findings Between the 3 Groups

Figure 1 shows the distribution of stenotic lesions (index and tandem stenotic lesions) in the 3 groups. The number of tandem stenotic lesions differed among the groups. Tandem stenosis was the most prevalent in patients with MMD (92.5%), followed by ICAS-*RNF213*+ (72.2%), and fewer with ICAS-*RNF213*– (40.3%) had tandem stenotic lesions (*P*<0.001). Tandem lesions were more commonly located at the predilection site of MMD involvement (such as the dICA and proximal MCA, or anterior cerebral artery) in the ICAS-*RNF213*+ group than in the ICAS-*RNF213*– group (64.6% versus 32.7%, *P*<0.001). Moreover, most patients with ICAS-*RNF213*– showed plaques on tandem lesions, whereas negative remodeling without plaques was observed on HR-MRI in about one fourth of the tandem lesions of patients with ICAS-*RNF213*+ (*P*=0.011).

After adjusting for age and vascular risk factors, younger age, hypertension, current smoking status, and R4810K carrier status were independently associated with tandem stenotic lesions (*P*<0.05 for all cases) (Table S1).

Stroke Recurrence in Symptomatic ICAS

Patients with symptomatic ICAS were followed for 50.73±33.8 months (median 45 months; interquartile range, 3–133 months). Recurrent cerebrovascular events were more frequently observed in patients with ICAS-*RNF213*+ than in patients with ICAS-*RNF213*– (5.7% versus 18.8%; *P*=0.012). After adjusting for age, vascular risk factors, and degree of stenosis, R4810K carrier status (HR, 2.814; 95% CI, 0.947–8.367) and multiple (≥3) tandem lesions (HR, 4.612; 95% CI, 1.288–16.509) were independently associated with recurrent cerebrovascular events (Table S2). The Kaplan–Meier curves for stroke recurrence depending on R4810K carrier status and the number of tandem lesions are shown in Figure 2.

DISCUSSION

Tandem stenotic lesions were almost 2-fold more prevalent in patients with ICAS with the R4810K variant than in those without this variant, despite similar vascular risk factor profiles between these 2 groups. Interestingly, about two thirds of tandem lesions were located at the MMD predilection sites. Vascular progression related to this MMD-associated genetic variant could be associated with anatomic factors and related hemodynamic status. A recent study showed that endothelial shear stress was related to the progression of MMD.[9] In addition, HR-MRI did not demonstrate plaques on tandem lesions in one fourth of patients with ICAS with the variant, whereas plaques were observed in most patients with ICAS without the variant. The outer diameter of the tandem MCA and dICA lesions in the ICAS-*RNF213*+ group were significantly smaller than the tandem lesions in the ICAS-*RNF213*- group (data not shown), and the outer diameter was not related to the presence or absence of plaque. These results suggest the possibility of a mixture of atherosclerosis pathology and Moyamoya pathology in the ICAS-*RNF213*+. Our study showed that recurrent cerebrovascular events were more

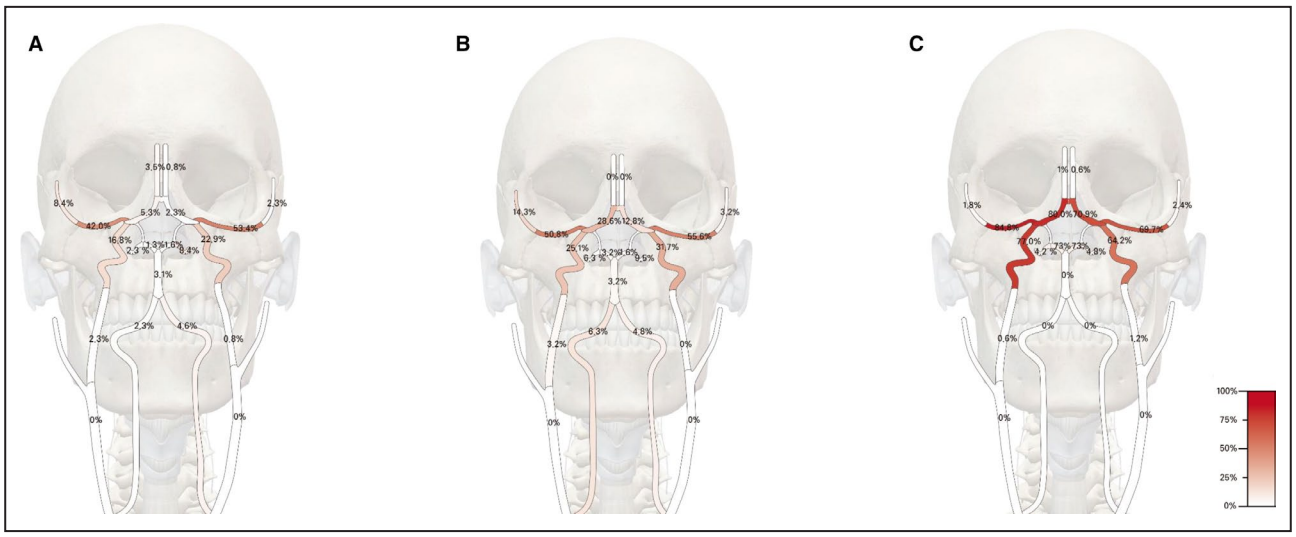

Figure 1. Distribution of stenotic lesions in (A) intracranial atherosclerosis without the *RNF213 (ring finger protein 213 gene)* R4810K variant, (B) intracranial atherosclerosis with the variant, and (C) Moyamoya disease.

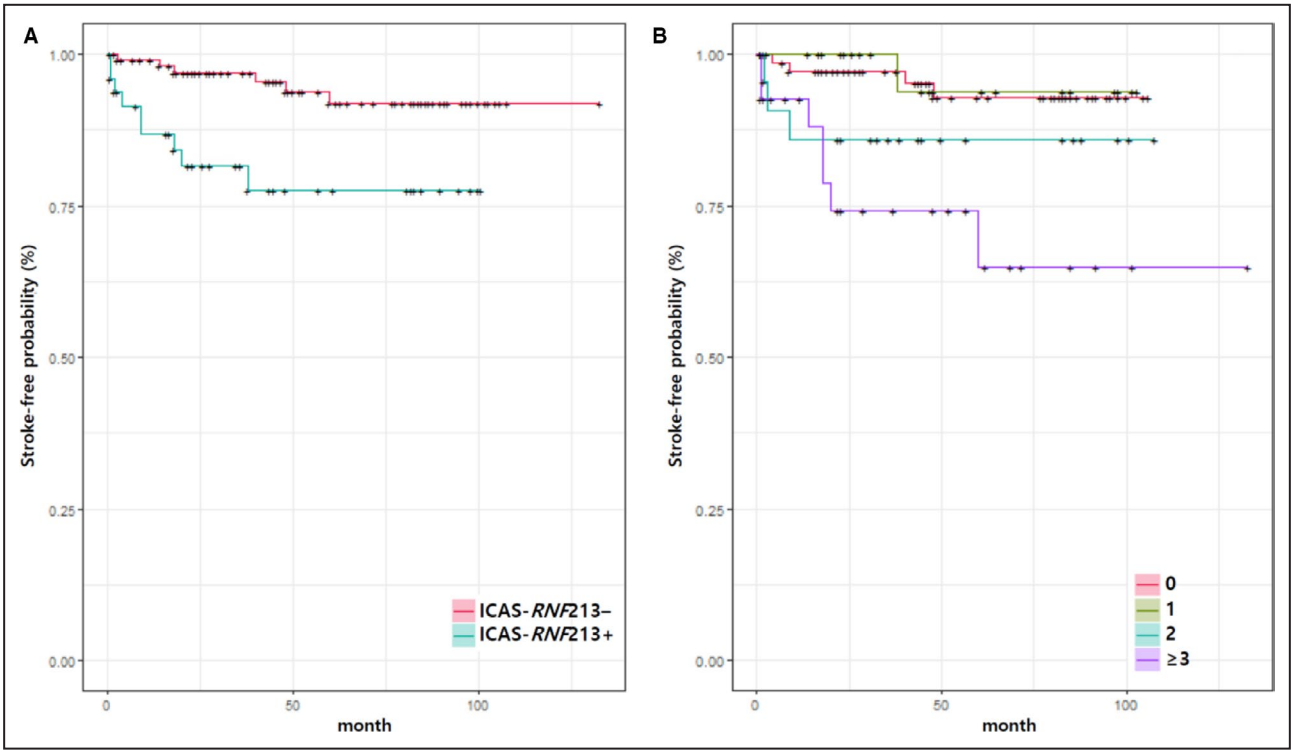

Figure 2. Kaplan–Meier survival curves for recurrent cerebrovascular events in patients with symptomatic intracranial atherosclerosis.
Probability of remaining stroke-free based on (**A**) the presence of the *RNF213 (ring finger protein 213 gene)* R4810K variant (log-rank test *P*=0.0039) and (**B**) the number of tandem stenotic lesions (log-rank test *P*=0.0044). ICAS indicates intracranial atherosclerosis; and *RNF213, ring finger protein 213 gene*.

common in patients with ICAS with the R4810K variant, despite similar vascular risk factor profile and degrees of stenosis. Possible explanations include the increased atherosclerotic burden (tandem stenotic lesions) and hemodynamic compromise. A recent hemodynamic study showed that in the presence of intracranial atherosclerosis, the variant predisposes smaller intracranial arteries to hemodynamic compromise.[7]

This study has some limitations. First, being a single-center study, the sample size was limited. However, this study involved a large series of prospective cases that were diagnosed by HR-MRI and *RNF213* R4810K genotyping. Second, the results of this study cannot be extrapolated to populations other than the East Asian population. In White and South Asian populations, the *RNF213* R4810K variant has not been reported and several other *RNF213* variants were recently reported.[10] In addition, participants in this study are not representative of the general population with intracranial stenosis, as they were from a single tertiary referral center where stenting and bypass surgery are routinely performed for ICAS and MMD, respectively. Third, serial follow-up HR-MRI was not conducted in this study. Further prospective HR-MRI studies are needed to demonstrate the impact of this mutation over time on vessel wall features. Lastly, in the present study, the ICAS and MMD were identified based on HR-MRI, not histological data. However, *RNF213* R4810K variant analysis was performed for all patients to improve diagnostic accuracy, and only cases with characteristic HR-MRI findings of ICAS and MMD were included.

To conclude, our study showed that about one third of patients with ICAS carried the *RNF213* R4810K variant, and those patients showed clinical and imaging features distinct from those of non-carrier patients with ICAS, suggesting that this variant modifies disease in individuals with atherosclerotic vascular pathology in East Asian patients. Further prospective studies are necessary to confirm our results.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Factors associated with the tandem lesions among 238 patients with intracranial atherosclerosis.

	Univariate		Multivariate	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*
Age at diagnosis	1.034 (1.003-1.066)	**<0.05**	1.032 (1.002-1.063)	**<0.05**
Vascular risk factor				
Male sex	0.681 (0.364-1.275)	0.230	0.682 (0.365-1.276)	0.231
Hypertension	2.586 (1.361-4.915)	**<0.05**	2.560 (1.387-4.725)	**<0.05**
Diabetes mellitus	2.723 (1.243-5.967)	<**0.05**	2.704 (1.238-5.909)	**<0.05**
Hyperlipidemia	0.819 (0.446-1.506)	0.521	0.816 (0.444-1.498)	0.816
Current smoker	3.808 (1.446-10.030)	**<0.05**	3.240 (1.274-8.235)	**<0.05**
Body mass index	1.049 (0.945-1.163)	0.370	1.047 (0.945-1.161)	0.380
Genetic factors				
*RNF*213 variant (+)	5.541 (2.787-11.017)	**<0.05**	5.705 (2.907-11.194)	**<0.05**
Family history of MMD	1.226 (0.225-6.689)	0.814		

*RN*F213, *Ring Finger Protein 213*; MMD, moyamoya disease.

Table S2. Multivariate analysis of possible predictors of stroke recurrence in symptomatic intracranial atherosclerosis.

	Crude HR		Adjusted HR	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	0.986 (0.934-1.042)	0.627		
Hypertension	1.164 (0.349-3.885)	0.805		
Diabetes mellitus	2.034 (0.646-6.408)	0.225		
Hyperlipidemia	1.098 (0.383-3.147)	0.862		
Current smoker	1.676 (0.403-6.960)	0.477		
Body mass index	1.005 (0.841-1.201)	0.953		
Stenosis degree				
50-69%	reference			
70-99%	0.986 (0.219-4.428)	0.985		
Occlusion	1.427 (0.306-6.666)	0.651		
*RNF*213 variant	4.800 (1.610-14.311)	0.005	3.203 (1.149-9.459)	0.026
Number of tandem lesions				
0	reference			
1	0.481 (0.047-4.879)	0.536	0.716 (0.070-4.038)	0.722
2	3.338 (0.559-19.939)	0.186	3.628 (0.658-20.386)	0.134
≥3	7.653(1.597-36.661)	0.011	8.315 (1.930-39.607)	0.005

Adjustment for age, sex, vascular risk factors, stenosis degree, *RNF*213 variant, and number of tandems.

*RN*F213, *Ring Finger Protein 213*; HR, hazard ratio