JACC: ASIA VOL. 3, NO. 4, 2023

ORIGINAL RESEARCH

Amplified Risk of Intracranial Artery Stenosis/Occlusion Associated With *RNF213* p.R4810K in Familial Hypercholesterolemia

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ABSTRACT

BACKGROUND The *RNF213* p.R4810K variant is associated with moyamoya disease in East Asian individuals and increases the risk of developing intracranial major artery stenosis/occlusion (ICASO) that affects anterior circulation. Meanwhile, 0.5% to 2.5% of asymptomatic East Asian individuals also carry this variant. As such, additional factors are likely required to develop ICASO in variant carriers. Familial hypercholesterolemia (FH) is a common genetic disorder in Japan that has a significant associated risk of developing premature coronary atherosclerosis; however, the relationship between ICASO and FH remains unknown.

OBJECTIVES This study aimed to determine if FH facilitates *RNF213* p.R4810K carriers to develop ICASO.

METHODS We enrolled patients with FH who had undergone brain magnetic resonance angiography at our hospital from May 2005 to March 2020. The *RNF213* p.R4810K variant, and *LDLR* and *PCSK9* mutations were genotyped. ICASO lesions in the brain magnetic resonance angiogram were analyzed.

RESULTS Six *RNF213* p.R4810K variant carriers were identified among 167 patients with FH (*LDLR*, n = 104; *PCSK9*, n = 22). Five of the carriers (83.3%) exhibited ICASO in the anterior circulation; a significant difference in ICASO frequency was observed between the variant carriers and noncarriers ($P = 0.025$). The median number of stenotic or occluded arteries in the anterior circulation was also significantly larger in the variant carriers (3 vs 1, $P = 0.01$); however, did not differ between patients with FH with *LDLR* and *PCSK9* mutations.

CONCLUSIONS Patients with FH exhibit increased prevalence and severity of ICASO associated with *RNF213* p.R4810K. Gene mutations for FH may confer an increased risk of ICASO in *RNF213* p.R4810K carriers. (JACC: Asia 2023;3:625–633)

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 7, 2022; revised manuscript received February 23, 2023, accepted March 18, 2023.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2023.03.011

JACC: ASIA, VOL. 3, NO. 4, 2023
AUGUST 2023:625–633

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

FH = familial hypercholesterolemia

ICASO = intracranial major artery stenosis/occlusion

LAA = large-artery atherosclerosis

LDL-C = low-density lipoprotein cholesterol

LDLR = LDL receptor

MMD = moyamoya disease

MRA = magnetic resonance angiography

PCSK9 = proprotein convertase subtilisin/kexin type 9

The RING finger protein 213 (*RNF213*) p.R4810K variant is a susceptibility gene for moyamoya disease (MMD) in East Asian individuals.[1] Approximately 80% of Japanese patients with MMD harbor this variant.[1-3] However, it has rarely been reported in Whites, with a maximum allele frequency of 0.0006.[4,5] The *RNF213* gene encodes AAA + ATPase units and the RING finger domain that acts as an E3 ubiquitin ligase.[6] The p.R4810K variant lies at the C-terminus of RNF213, downstream of the RING finger domain[7] and reportedly has an important role in the development of intracranial major artery stenosis/occlusion (ICASO), despite not meeting the diagnostic criteria for MMD.[5,8-10] We previously reported that the *RNF213* p.R4810K variant is associated with ICASO in the anterior circulation of 70 Japanese patients with early-onset stroke.[8] Furthermore, the variant poses a strong genetic risk for cerebral infarction, especially large-artery atherosclerosis (LAA), based on the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification (OR of total ischemic stroke, 1.91; LAA, 3.58), among 46,958 Japanese subjects.[5] Thus, the variant is regarded as one of the most significant genetic risk factors for ICASO in the anterior circulation, not only in patients with MMD, but also in non-MMD patients. Radiologically, patients with ICASO who are carriers of the variant have a smaller outer diameter of intracranial arteries, contrary to conventional LAA showing positive remodeling.[11] Therefore, *RNF213* p.R4810K suggests a new disease entity: *RNF213*-related vasculopathy. However, considering that asymptomatic carriers also exist in 0.5% to 2.5% of the East Asian general population,[1,3] several additional factors, such as environmental and genetic factors, are also likely involved in the development of MMD or ICASO. However, these factors remain to be elucidated.

Familial hypercholesterolemia (FH) is one of the most common genetic disorders in Japan. Its prevalence is approximately 1:500 in Japanese[12] and 1:200 to 1:250 in White individuals.[13] FH is characterized by the early-onset elevation of low-density lipoprotein cholesterol (LDL-C) levels, skin and tendon xanthomas, and premature coronary artery disease (CAD). It is caused by loss of function mutations in the LDL receptor (*LDLR*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*), or apolipoprotein B (*APOB*) gene.[14] Although FH is known to confer an extremely high risk of developing early-onset CAD,[14] the relationship between cerebrovascular diseases and FH is not well understood.[15-18] Two longitudinal observational studies have reported that FH, or a high LDL-C level per se, does not confer an increased risk of ischemic stroke.[13,19] Although FH has been regarded as a monogenic disease induced by the aforementioned genetic mutations, an alternative emerging concept suggests that FH is an oligogenic or polygenic disease. This is based on the recent advancement of comprehensive genetic analyses, which show that multiple common genetic variants could confer accumulation of small effects to elevate LDL-C levels and induce premature CAD with different severities in concert with the conventional FH genetic mutations.[20,21]

We hypothesized that the genetic mutations responsible for FH facilitate *RNF213* p.R4810K carriers to develop ICASO.

METHODS

STUDY DESIGN. This was a single-center, cross-sectional study performed at the National Cerebral and Cardiovascular Center in Japan. The study was approved by the Research Ethics Committee of the National Cerebral and Cardiovascular Center (approval number: M17-056, M24-080). Written informed consent was obtained from all individuals between May 2005 and March 2020. We investigated the medical records of patients diagnosed with FH based on guidelines from the Japan Atherosclerosis Society. Patients who fulfilled at least 2 clinical characteristic criteria were enrolled. The criteria included: 1) untreated LDL-C level ≥180 mg/dL; 2) tendon/skin xanthomas; and 3) familial history of FH or premature CAD in second-degree relatives.[22] Patients were required to have undergone brain magnetic resonance angiography (MRA). We also performed genotyping of *RNF213* p.R4810K and mutations in *LDLR* and *PCSK9*. The physical findings, past medical history, familial history, blood tests, and brain MRA images were collected from the medical records of all patients. The diagnosis of ICASO was made based on findings from the brain MRA. Two well-trained neurologists (K.N. and A.T.) reviewed ICASO in the internal carotid artery, M1-M2 segment of a middle cerebral artery, and A1 segment of an anterior cerebral artery in the anterior circulation, and the basilar artery in the posterior circulation. More specifically, they reported the detection of stenosis or occlusion, and defined mild, moderate, and

TABLE 1 Baseline Characteristics of Patients With FH

	RNF213 p.R4810K Noncarriers (n = 161)	*RNF213* p.R4810K Carriers (n = 6)	*P* Value
Age at MRA testing, y	62.1 ± 16.4	46.5 ± 19.4	0.045[a]
Male	76 (47.2)	2 (33.3)	0.69[b]
Smoking	62 (38.5)	3 (50.0)	0.68[b]
Hypertension	63 (39.1)	3 (50.0)	0.68[b]
Diabetes mellitus	28 (17.4)	0	0.59[b]
PMH of ischemic stroke	18 (11.2)	0	>0.99[b]
PMH of intracerebral hemorrhage	2 (1.2)	0	>0.99[b]
PMH of coronary artery disease	66 (41.0)	0	0.082[b]
Tendon xanthomas	116 (73.9)	5 (83.3)	0.514[b]
LDLR mutation	100 (62.1)	4 (66.7)	>0.99[b]
PCSK9 mutation	21 (13.0)	1 (16.7)	0.58[b]
LDL-C at first visit, mg/dL	209.9 ± 72.6	249.3 ± 87.1	0.261[a]
LDL-C–lowering drugs	68 (42.2)	1 (16.7)	0.42
Statins	51 (31.7)	0	>0.99[b]
Fibrates	1 (0.6)	0	>0.99[b]
PCSK9 inhibitors	0	0	-

Values are mean ± SD or n (%). [a]t-test; [b]Fisher exact test.

FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; *LDLR* = low-density lipoprotein receptor; MRA = magnetic resonance angiography; *PCSK9* = proprotein convertase subtilisin/kexin type 9; PMH = past medical history.

TABLE 2 Comparison of ICASO Frequency and the Number of Arteries With ICASO in the Anterior Circulation

	RNF213 p.R4810K Noncarriers (n = 161)	*RNF213* p.R4810K Carriers (n = 6)	*P* Value
ICASO in the anterior circulation	56 (34.8)	5 (83.3)	0.025[a]
Number of arteries with ICASO in the anterior circulation	1 (1–2)	3 (2–6)	0.01[b]

Values are n (%) or median (IQR). [a]Fisher exact test. [b]Mann-Whitney *U*-test.

ICASO = intracranial major artery stenosis/occlusion.

severe stenosis, and occlusion as ICASO, based on a previously described method.[23] In this evaluation, the neurologists were blinded to any genetic or clinical information about the patients.

DNA ANALYSIS. Genotyping of *RNF213* p.R4810K was performed using a fully automated gene analysis system (LightCycler 96, Roche). The reference sequences used for the *LDLR* and *PCSK9* genes were NM_000527.4 and NM_174936.3, respectively. Genomic DNA was extracted from the patients' whole blood using an automated DNA extraction machine (QIAsymphony, QIAGEN). All coding regions and exon-intron boundary sequences of the *LDLR* and *PCSK9* genes were examined as described previously.[24] Multiplex ligation-dependent probe amplification was performed to detect large rearrangements of the *LDLR* gene using a P062B LDLR MLPA kit (MRC Holland).

STATISTICAL ANALYSIS. Data were summarized as mean ± SD or median (IQR) values for continuous variables and as percentages for categorical variables. Fisher exact test or Mann-Whitney *U*-test was performed to evaluate differences in the categorical or discrete variables. The Mann-Whitney *U*-test or *t*-test was performed to evaluate differences in continuous variables between groups, as appropriate. To identify significant predictors for the development of ICASO in patients with FH, univariable and multivariable logistic regression models were constructed. Because of the small number of *RNF213* p.R4810K carriers, exact-like inferences in logistic regression models were also built using the "elrm" package[25] of the statistical software R (version 4.0.5, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing). The multivariable model was adjusted for age, sex, diabetes mellitus, and hypertension as potential confounders for cerebrovascular events. ORs with 95% CIs were calculated. All reported *P* values were 2-tailed, and $P < 0.05$ was considered statistically significant. All analyses were performed using the SPSS (version 27, IBM) and R statistical software (version 4.0.5).

RESULTS

BASELINE CLINICAL CHARACTERISTICS. Among the 167 patients diagnosed with FH who underwent brain MRA, all patients were Japanese, and the average age at MRA testing was 61 years. *LDLR* and *PCSK9* mutations were observed in 104 and 22 patients, respectively. The *RNF213* p.R4810K variant was identified in 6 patients with FH (3.6%), none of whom had

TABLE 3 The Distribution of ICASO in the Anterior Circulation in Patients With FH

	RNF213 p.R4810K Noncarriers (n = 161)	*RNF213* p.R4810K Carriers (n = 6)	OR	95% CI Lower	95% CI Upper	*P* Value[a]
ICA	24 (14.9)	3 (50)	29.96	1.09	5.71	0.054
A1	27 (16.8)	3 (50)	25.92	0.95	4.96	0.072
M1	15 (9.3)	4 (66.7)	8.44	0.88	19.47	0.002
M2	19 (11.8)	5 (83.3)	337.7	4.14	37.37	< 0.001

Values are n (%) unless otherwise indicated. [a]Fisher exact test.

A1 = A1 segment of an anterior cerebral artery; ICA = internal carotid artery; ICASO = intracranial major artery stenosis/occlusion; M1 = M1 segment of a middle cerebral artery; M2 = M2 segment of a middle cerebral artery.

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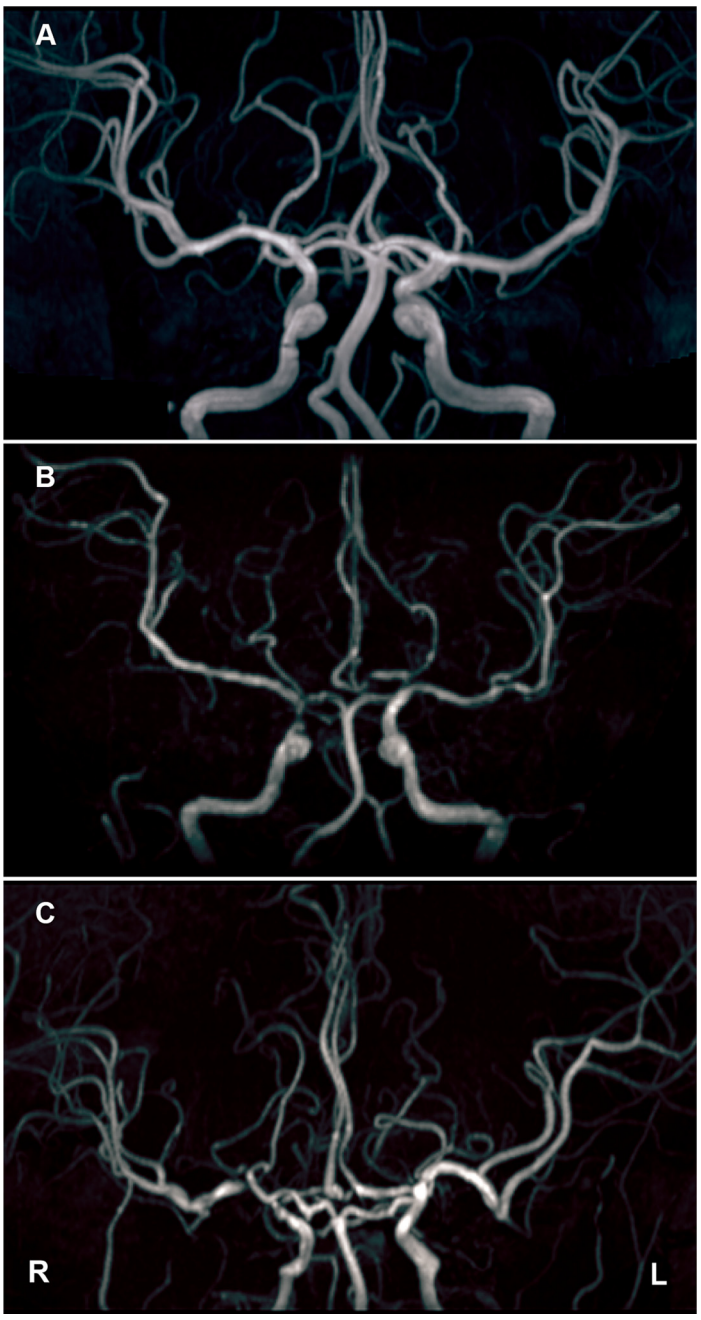
FIGURE 1 ICASO Severity in the *RNF213* p.R4810K Carriers



Representative MRA showing different ICASO severity. **(A)** A 29-year-old man carrying *LDLR* mutation showed no ICASO lesion (patient 5 in Supplemental Table 1). **(B)** A 45-year-old woman carrying *LDLR* mutation showed 6 ICASO lesions (patient 2 in Supplemental Table 1). **(C)** A 76-year-old woman carrying *PCSK9* mutation showed 7 ICASO lesions (patient 1 in Supplemental Table 1). Three patients did not exhibit moyamoya angiopathy. ICASO = intracranial major artery stenosis/occlusion; L = left; *LDLR* = low-density lipoprotein receptor; MRA = magnetic resonance angiography; *PCSK9* = proprotein convertase subtilisin/kexin type 9; R = right.

experienced any cerebrovascular events. No significant differences in sex, hypertension, diabetes mellitus, administration of LDL-C-lowering drugs, smoking, past history of ischemic/hemorrhagic stroke and CAD, or genetic mutations for FH were observed between the *RNF213* p.R4810K carriers and noncarriers. The mean age at MRA testing for the *RNF213* p.R4810K carriers was significantly younger than that of the noncarriers (Table 1).

PREVALENCE AND SEVERITY OF ICASO IN THE ANTERIOR AND POSTERIOR CIRCULATION BETWEEN THE RNF213 p.R4810K CARRIERS AND NONCARRIERS. ICASO in the anterior circulation was more frequently observed in the *RNF213* p.R4810K carriers than in the noncarriers among the 167 patients with FH (5 of 6 carriers, 83.3% vs 56 of 161 noncarriers, 34.8%; $P = 0.025$) (Table 2). Among the patients with ICASO, the median number of stenotic or occluded arteries in the anterior circulation was significantly larger in the variant carriers than in the noncarriers (3 [IQR: 2-6] vs 1 [IQR: 1-2]; $P = 0.01$).

Moreover, the variant carriers had a larger prevalence of ICASO with diffuse involvement of the anterior circulation than the noncarriers (Table 3). In particular, the prevalence of ICASO in M1 and M2 was significantly higher in the variant carriers (M1: 4 of 6 [66.7%] vs 15 of 161 [9.3%], $P = 0.002$; M2: 5 of 6 [83.3%] vs 19 of 161 [11.8%], $P < 0.001$). We also investigated ICASO in the posterior circulation. We found that 5 noncarriers had basilar artery stenosis, whereas none of the carriers had basilar artery stenosis, which suggests that the variant is not associated with basilar artery involvement as far as FH is concerned. A summary of the clinical information for all RNF213 p.R4810K carriers is shown in Supplemental Table 1, and three representative cases are shown in Figure 1.

The logistic regression analysis showed that carrying *RNF213* p.R4810K was a significant predictor for ICASO development in the anterior circulation after correction for age at MRA, sex, diabetes mellitus, and hypertension in the patients with FH (logistic regression: OR: 22.53; 95% CI: 2.71-502.54; $P = 0.011$; exact-like inference: OR: 5.44; 95% CI: 1.10-∞; $P = 0.019$) (Table 4).

INFLUENCES OF LDLR AND PCSK9 MUTATIONS ON ICASO. Apart from the *RNF213* p.R4810K carriers, those with *LDLR* and/or *PCSK9* mutations exhibited no significant difference in ICASO prevalence, or the median number of stenotic or occluded arteries (Supplemental Tables 2 and 3).

TABLE 4 Logistic Regression Analysis of the Factors Associated with ICASO in the Anterior Circulation

	Univariable Analysis (Logistic Regression)				Multivariable Analysis (Logistic Regression)				Univariable Analysis (Exact-Like Inference)				Multivariable Analysis (Exact-Like Inference)			
		95% CI				95% CI				95% CI				95% CI		
	OR	Lower	Upper	*P* Value	OR	Lower	Upper	*P* Value	OR	Lower	Upper	*P* Value	OR	Lower	Upper	*P* Value
RNF213 p.R4810K	9.38	1.47	181.97	0.043	22.53	2.71	502.54	0.011	5.79	0.98	Infinity	0.026	5.44	1.10	Infinity	0.019
Diabetes mellitus	2.33	1.02	5.388	0.044	1.90	0.76	4.81	0.17	2.84	1.07	9.90	0.035	1.82	0.67	7.03	0.25
Hypertension	2.33	1.23	4.49	0.010	1.82	0.86	3.94	0.12	5.86	1.22	382.30	0.007	2.04	0.73	9.47	0.23
Male	0.50	0.26	0.96	0.038	0.46	0.22	0.95	0.038	0.42	0.07	1.04	0.048	0.18	0.01	0.98	0.043

Multivariable analysis was adjusted for age at magnetic resonance angiography testing.
ICASO = intracranial major artery stenosis/occlusion.

DISCUSSION

This study defined the pathogenetic impact of genetic mutations for FH on the prevalence and severity of ICASO in *RNF213* p.R4810K variant carriers. FH patients carrying the *RNF213* p.R4810K suffered from a higher prevalence of ICASO than the noncarriers in anterior circulation (83.3% vs 34.8%). They were further affected by a larger number of affected arteries than patients with FH who did not carry the variant. Meanwhile, the prevalence of asymptomatic ICASO was detected in only 5.9% (166 of 2,807) of the participants in a study of Japanese subjects who had never experienced neurological diseases including stroke,[26] and in only 3.3% (46 of 1,349) in a Japanese population-based cohort study.[27] Furthermore, the prevalence of ICASO in asymptomatic *RNF213* p.R4810K variant carriers was 23.5%.[28] Therefore, our findings reflect an add-on effect of FH on *RNF213* p.R4810K-associated ICASO. However, the underlying mechanisms remain unknown. Nevertheless, 2 plausible explanations may account for the observed results. First, the combinatorial control of gene expression could have generated a greater magnitude of ICASO development associated with *RNF213* p.R4810K. Owing to advances in genome analyses, the effects of polygenic changes on developing diseases have gradually been elucidated.[29-32] Although the influence of individual single nucleotide polymorphisms is weak, the accumulation of multiple common single nucleotide polymorphisms contributes to disease susceptibility. For example, the phosphatase domain containing paladin 1 gene mutation overlaid with *RNF213* variants may act synergistically in 2 affected White European families who develop MMD.[33] Polygenic risk scores predict the prevalence of cardiovascular disease in patients with FH.[20] Oligogenic patients with FH who carry damaging variants of both conventional FH genes and LDL-altering accessory genes, including adenosine triphosphate-binding cassette subfamily G member 5/8, apolipoprotein E, and LDL receptor adaptor protein 1 gene variants, have higher LDL-C levels than those carrying classical monogenic FH genes. Genes such as *LDLR*, *PCSK9*, and *APOB* carry conventional mutations.[21] Similarly, our study showed that the mutations responsible for FH, such as *LDLR* and *PCSK9* mutations, may have additional, or synergistic effects with *RNF213* p.R4810K in developing and aggravating ICASO. However, carriers of double mutations in *LDLR* and *PCSK9*, despite severe hypercholesterolemia, did not show severe ICASO, supporting the notion that the interaction between *RNF213* p.R4810K and FH-associated mutations affects cerebral arteries. Thus, the mechanisms by which the oligogenic changes promote the development of ICASO with significant frequency require further investigation.

Changes in the environmental factors surrounding patients with FH may also exacerbate *RNF213* p.R4810K-associated ICASO (**Central Illustration**). As previously stated, it remains controversial whether FH or elevated LDL-C leads to cerebrovascular diseases.[13,19] However, both FH and carriage of *RNF213* p.R4810K may accelerate endothelial damage, increasing the probability of developing cerebrovascular diseases. Cerebral arterial walls in patients with FH are exposed to long-standing high concentrations of LDL-C, which induce endothelial damage and resultant atherosclerotic plaques. Circulating LDL-C enters the intima by passive diffusion[34] or transcytosis through certain transporters, especially in the brain.[35] With the latter mechanism, LDL-C can enter endothelial cells through transcytosis with LDL receptor, activin receptor-like kinase 1, or scavenger receptor B1, as well as caveolin 1, and LDL-C particles are transferred to the opposite side of the cell.[35]

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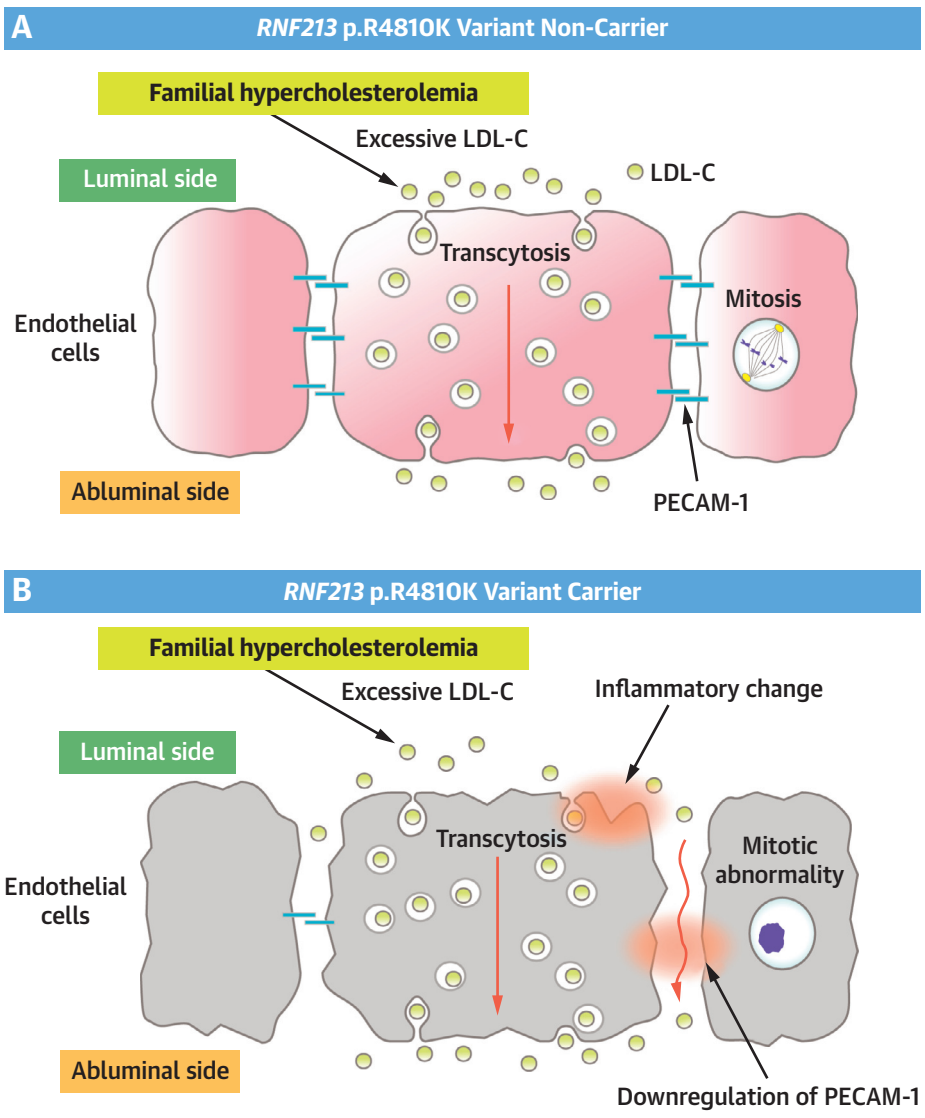
CENTRAL ILLUSTRATION ***RNF213*** **p.R4810K and Familial Hypercholesterolemia in the Development of Intracranial Major Artery Stenosis/Occlusion**



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Circulating excessive low-density lipoprotein cholesterol (LDL-C) may enter the intima by transcytosis, promoting cerebrovascular endothelial damage in patients with familial hypercholesterolemia (FH) even without the *RNF213* p.R4810K variant **(A)**. The *RNF213* p.R4810K variant may induce mitotic abnormality, downregulate platelet endothelial cell adhesion molecule-1 (PECAM-1) with resultant increase of blood-brain barrier permeability, and enhance cerebrovascular endothelial inflammatory change due to lymphocyte transmigration, further aggravating endothelial damage and blood-brain barrier disruption in patients with FH **(B)**.

Monocytes concurrently migrate toward the intima and differentiate into macrophages. The macrophages then phagocytose the LDL and transform into lipid-laden foam cells, ultimately leading to the formation of atherosclerotic plaques.[19,34,36] In addition, RNF213 plays an important role in regulating endothelial function.[37,38] RNF213-deficient human cerebrovascular endothelial cells are involved in endothelial inflammatory changes, such as downregulated platelet endothelial cell adhesion molecule-1 and enhanced lymphocyte transmigration. These elevate the blood-brain barrier permeability.[38] Moreover, mice overexpressing vascular endothelial cell-specific *Rnf213* p.R4757K

(the human P4810K allelic ortholog) are more vulnerable to hypoxic stimuli with reduced cerebral blood flow and lower angiogenic activity, implying that endothelial damage is involved in the pathogenesis of *RNF213* p.R4810K-associated MMD or ICASO.[39,40] Furthermore, vascular endothelial cells differentiated from the induced pluripotent stem cells of *RNF213* p.R4810K carriers exhibit mitotic abnormality.[41] Dyslipidemia is likely to increase the risk and be a modifiable risk factor for cerebrovascular events in asymptomatic Japanese patients with MMD,[42] suggesting that dyslipidemia is an additional risk in *RNF213* p.R4810K-associated ICASO.

Although premature CAD is a characteristic of FH, in this study some of the patients with FH carrying the *RNF213* p.R4810K variant developed cerebrovascular diseases such as ICASO; however, none suffered CAD (**Table 1**). This prompted us to investigate what contributed to the development of cerebrovascular diseases, rather than CAD in FH. As many as 83.3% of the *RNF213* p.R4810K carriers were found to possess ICASO (**Table 2**). Provoked inflammation associated with mutated RNF213 in cerebrovascular endothelial cells indicated previously may lead to blood-brain barrier dysfunction via endothelial damage, and the impaired permeability of the blood-brain barrier is crucially responsible for developing ICAS.[38] Hence, the *RNF213* p.R4810K variant likely confers susceptibility to ICASO, thus, explaining the higher frequency of the variant in patients with ICASO[28] compared with CAD[43] (23.5% vs 3.9%). This may also explain why patients with FH carrying the variant had ICASO, not CAD.

STUDY LIMITATIONS. The number of patients with FH with *RNF213* p.R4810K was relatively small. FH is an autosomal dominant inherited disorder, and the frequency of *RNF213* p.R4810K carriers in Japanese patients is only 0.5% to 2.5%, making it difficult to recruit sufficient participants.

The known *APOB* c.10580 G>A: p.Arg3527Gln mutation was not genotyped in this study, as its allele frequency is 0.0001 in the Japanese population. Its frequency is also low in Japanese patients with FH, and it has not been detected in other East Asian populations.[44-47]

As we used the historical cohort with non-FH subjects,[28] a direct comparison was not conducted between the prevalence of ICASO in FH and non-FH subjects with the *RNF213* p.R4810K variant.

Due to the cross-sectional nature of this study, it focused primarily on elucidating the association between the *RNF213* p.R4810K mutation and ICASO in patients with FH.

CONCLUSIONS

FH confers a significantly greater risk of ICASO in the anterior circulation among *RNF213* p.R4810K variant carriers. Genetic interactions between *RNF213* and FH-related genes may underlie this increased risk. Randomized clinical trials may be considered to determine whether statin treatment can prevent the progression of intracranial artery stenosis in *RNF213* p.R4810K variant carriers.

ACKNOWLEDGMENTS The authors thank Enago (https://www.enago.jp) for the English language review.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was supported by the Japan Agency for Medical Research and Development (Grant Nos. JP21ek0210120 and JP21ek0210126) (Dr Ihara) and the Takeda Medical Research Foundation, Suzuken Memorial Foundation, and Koyanagi Foundation (Dr Hattori). Dr Yoshimoto is supported by lecture fees from Takeda Pharmaceutical and Nippon Boehringer Ingelheim. Dr Ihara has received lecture fees from Daiichi Sankyo and Eisai; and grants from Panasonic, Bristol Myers Squibb, and Shimadzu Corporation, outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with FH carrying the *RNF213* p.R4810K variant suffer from a higher prevalence and severity of ICASO in the anterior circulation. As a concept of oligogenic disease, genetic interactions between *RNF213* p.R4810K and FH-related genes may facilitate the development of ICASO. Alternatively, the exacerbation of endothelial injuries and the resultant development of ICASO may be induced by the overlap of *RNF213* p.R4810K and long-standing dyslipidemia, as RNF213 is a key regulator of cerebral endothelium integrity, and dyslipidemia is a conventional risk factor for endothelial injury. Hence, FH may serve as an additional exacerbating factor for the development of *RNF213* p.R4810K-associated ICASO.

TRANSLATIONAL OUTLOOK: Randomized clinical trials may be considered to determine whether LDL-C–lowering treatment may prevent the progression of ICASO in *RNF213* p.R4810K variant carriers.

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KEY WORDS familial hypercholesterolemia, genetic interaction, genetic mutation, intracranial artery stenosis/occlusion, *RNF213* p.R4810K

APPENDIX For supplemental tables, please see the online version of this paper.