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The association between the ring finger protein 213 gene R4810K variant and intracranial major artery stenosis/occlusion in the Han Chinese population and high-resolution magnetic resonance imaging findings

Sufang Xue, Weiyang Cheng, Wanqian Wang[1], Xiaowei Song[2], Jian Wu[2], Haiqing Song

Abstract:

BACKGROUND AND PURPOSE: The ring finger protein 213 (RNF213) gene R4810K variant, a susceptibility locus for moyamoya disease (MMD), has recently been identified to be associated with intracranial major artery stenosis/occlusion (ICASO) without satisfying the diagnostic criteria of MMD in the Japanese population. However, further studies are needed to determine whether this variant is associated with ICASO in other populations and whether R4810K variant-related ICASO could be categorized as MMD. The aim of this study is to elucidate whether the R4810K variant was associated with ICASO among the Han Chinese population and potential histopathology of R4810K variant-related ICASO.

MATERIALS AND METHODS: We conducted a case–control study to evaluate association and performed high-resolution (HR) magnetic resonance imaging (MRI) to investigate arterial wall feature of ICASO. The R4810K variant was genotyped in 114 ICASO patients and 268 controls. Then, patients with R4810K variant-related ICASO were subjected to HR MRI examination and presumptively diagnosed based on the characteristics thus observed.

STATISTICAL ANALYSIS: The relationship between R4810K variant and ICASO was evaluated by Fisher's exact test with odds ratios (OR) and 95% confidence interval (CI).

RESULTS: The R4810K variant was associated with ICASO and increased the risk for ICASO ($P < 0.01$; OR: 20.2; 95% CI: 2.5–163.11). Presumptive MMD was diagnosed in all female patients with R4810K variant. However, presumptive intracranial atherosclerotic stenosis was diagnosed in one of three males harboring this variant.

CONCLUSIONS: The R4810K variant is a genetic risk factor for ICASO among the Han Chinese population and that R4810K variant-related ICASO should be identified as MMD in female but not uncertain in male patients.

Keywords:

High-resolution magnetic resonance imaging, intracranial major artery stenosis/occlusion, ring finger protein 213 gene

Departments of Neurology and [1]Radiology, Xuanwu Hospital of Capital Medical University, [2]Department of Neurology, Beijing Tsinghua Changgung Hospital, Beijing, China

Address for correspondence:
Dr. Haiqing Song, Changchun Street No. 45, Xicheng District, Beijing, China.
E-mail: songhaiqing@xwh.ccmu.edu.cn

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Introduction

Intracranial major artery stenosis/occlusion (ICASO) is a common and important stroke subtype and more common in Asian patients.[1] The most common cause of ICASO is atherosclerosis acquired through factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking.

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Especially in younger adults, ICASO predominantly involves major intracranial arteries in the anterior circulation including the middle cerebral artery (MCA) and the internal carotid artery (ICA).[2] Its prevalence has racial disparities and is known to be much higher in non-Caucasians, particularly Asian populations,[3] suggesting a genetic basis for the development of ICASO. Moyamoya disease (MMD) is a rare cerebrovascular condition that occurs primarily in Asian populations.[4] MMD is characterized by stenosis and occlusion around the terminal portions of the internal carotid arteries and the formation of abnormal vascular networks at the base of the brain. Familial MMD cases have been reported to occur in siblings or in a parent and offspring. In monozygotic twins, the concordance rate is close to 80%.[5] The difference in MMD prevalence among races as well as the familial segregation provides evidence for a genetic predisposition to the disease. Due to these similarities between ICASO and MMD, it has been hypothesized that the pathogenetic bases of these two diseases are closely related.

Ring finger protein 213 (RNF213) has been identified as a susceptibility gene for MMD in East Asian populations, especially with the R4810K (rs112735431) mutation.[6,7] Interestingly, studies of Japanese and Korean populations found that the R4810K variant was also significantly associated with ICASO without satisfying the diagnostic criteria of MMD, and a few studies have reported that adult ICASO patients with that RNF213 variant may develop MMD in later years.[8-11] Thus, it has been proposed that RNF213 R4810K variant-related ICASO should be identified and categorized as MMD based on its genetic background.[8,9] However, more studies are needed to confirm this hypothesis. Especially, direct pathological study of the affected MCA from patients with RNF213 R4810K variant-related ICASO would be very helpful to verify the hypothesis. However, obtaining pathological tissue of affected MCA of patients by biopsy is very difficult in clinical work.

Previous studies revealed that the association of R4810K with MMD is genetically heterogeneous among different geographic and ethnic populations in East Asia.[12] Whether the association between RNF213 R4810K and ICASO is applicable to other populations is unclear.

In addition, high-resolution magnetic resonance imaging (MRI) (HR-MRI) can delineate the arterial wall from the lumen and the surrounding perivascular structures and identify the contrast enhancement of the arterial wall.[13-15] Several studies have shown that HR-MRI can differentiate MMD from atherosclerotic plaque on the stenotic segment.[16-18] Thus, use of HR-MRI on RNF213 R4810K variant-related ICASO can potentially elucidate its histopathology.

To elucidate whether the RNF213 R4810K mutation was associated with ICASO patients without satisfying the diagnostic criteria of MMD among the Han Chinese population and potential pathogenesis of RNF213 R4810K variant-related ICASO, we first examined the RNF213 R4810K mutation in ICASO patients compared to normal healthy participants among the Han Chinese population. Then, we performed HR MRI on patients with RNF213 R4810K variant-related ICASO.

Materials and Methods

Subjects

A total of 114 patients with ICASO but not MMD were recruited from the patients who were hospitalized at the Department of Neurology, Xuanwu Hospital, Capital Medical University, from October 2012 to February 2016. Diagnosis of the stenosed or occluded intracranial major artery was based on magnetic resonance (MR) or computed tomography (CT) angiography findings or conventional digital subtraction angiography (DSA) interpreted by ≥1 radiologist and one neurologist. The ICASO group showed partial stenosis or occlusion of the major intracranial artery in the anterior circulation and did not satisfy MMD criteria. Especially, most of the patients did not satisfy MMD criteria because of lack of typical moyamoya vessels. Patients with extracranial vascular stenosis and obvious steno-occlusive lesions in the basilar or vertebral arteries were excluded from the study. In addition, no patient had any signs of cardiac embolism, dissection, vasculitis, or any of the other syndromes that cause ICASO. At the same time, 268 normal healthy persons were also recruited from outpatients in this period as controls. Cranial CT/MRI and cerebral artery examination did not find any cerebrovascular lesion in the controls; thus, cerebral artery is not apparent abnormal in the normal group. All the participants were Han Chinese and gave consent to participate in this study for sample collection and subsequent analysis.

Genotype identification of ring finger protein 213 R4810K polymorphisms

Peripheral blood samples were obtained from all enrolled participants. Genomic DNA was extracted from peripheral blood lymphocytes by standard phenol/chloroform extraction methods. Primers were designed to amplify the target region spanning R4810K to identify RNF213 polymorphisms. The polymerase chain reaction (PCR) primer sequences for R4810K were as follows: Forward 5′-GCTGGTAAAGTTCCTGCCTG-3′ and reverse 5′-CTGTTCCCCTATGCAGTGATC-3′. The expected PCR product size was 194 bp, and the optimal primer Tm was 57°C. After 30 cycles of standard PCR, the sequence of PCR products was analyzed by direct

sequencing, and the genotype with respect to the polymorphisms was analyzed with Applied Biosystems® Sequence Scanner version 1.0.

High-resolution-magnetic resonance imaging protocol and analysis

We examined patients with RNF213 R4810K variant-related ICASO using a 3.0-T MR imager (Magnetom Verio; Siemens, Erlangen, Germany) and a 32-channel head coil. A standard MRI protocol was used that included pre- and post-Gd-DTPA contrast three-dimensional (3D) sampling perfection with application-optimized contrasts using different flip angle evolutions (SPACE) and 3D time-of-flight (TOF) MR angiographic sequences. The 3D TOF MR angiograms were acquired using the following parameters: repetition time ms/echo time ms, 20/3.6; field of view, 220 mm × 220 mm; slice thickness, 0.7 mm; and voxel size 0.7 mm × 0.7 mm × 0.7 mm. The 3D SPACE MRI were acquired using the following parameters: repetition time ms/echo time msec, 900/15; field of view, 170 mm × 170 mm; slice thickness, 0.53 mm; and voxel size 0.5 mm × 0.5 mm × 0.5 mm.

All HR-MRI images were analyzed by two experienced reviewers blinded to clinical details and were diagnosed by consensus. They analyzed characteristics including outer diameter, wall thickness, concentricity, signal intensity, enhancement and distribution of the stenotic portion, and collateral vascular structures adjacent to the stenosis position. These characteristics were evaluated using the parameters previously described[16-18] and were used to make a presumptive diagnosis according to previously reported methods.[14,16-20] Several examples follow: (1) an intracranial atherosclerotic stenosis (CAS) diagnosis was based on HR-MRI findings showing eccentric plaque with heterogeneous signals and enhancement. (2) An MMD diagnosis was based on HR-MRI findings showing concentric, homogeneous shrinkage of the vessel wall and diffuse concentric enhancement on the affected segment and collateral vascular structures. (3) Other possibilities included a presumptive dissection diagnosis, which was based on HR-MRI showing a dissecting flap or eccentric wall thickening associated with T1-bright wall components representing an intramural hematoma.

Statistical analysis

SPSS 17.0 software was used in data analysis. We performed statistical analysis using the two-tailed *t*-test for continuous variables and the Chi-square test for discrete variables. The relationship of the R4810K variant with each phenotype was evaluated by Fisher's exact test with odds ratios (OR) and 95% confidence interval (CI). In addition, the independent risk of the R4810K variant for ICASO was evaluated using multivariate logistic regression. $P < 0.05$ was considered statistically significant.

Results

General characteristics of subjects

Basic subject characteristics are listed in Table 1. Some participants within this group had atherosclerotic features associated with a history of hypertension, dyslipidemia, and diabetes mellitus, while younger patients had fewer risk factors for atherosclerosis. Compared with the control group, rates of diabetes mellitus and smoking were elevated in the ICASO group. Of 114 patients with ICASO, isolated MCA or isolated ICA lesions were observed in 84 patients, whereas 16 patients had lesions involving a combination of the MCA, terminal ICA, and proximal anterior cerebral artery (ACA). Fourteen had multiple lesions involving the MCA, terminal ICA, ACA, or proximal posterior cerebral artery. Approximately 31.58% of patients possessed bilateral vessel lesions.

Association of ring finger protein 213 R4810K with intracranial major artery stenosis/occlusion

Genotype distributions for the RNF213 R4810K variant were in Hardy–Weinberg equilibrium among normal controls. The genotype frequencies of R4810K in the two groups are shown in Table 2. The RNF213 R4810K variant was observed in 8 (7.02%) patients with ICASO. All patients with the RNF213 R4810K variant were heterozygotes. The patients with RNF213 R4810K variant-related non-MMD ICASO included five females and three males. Clinical and vascular characteristics of these patients are shown in Table 3. In contrast, the RNF213 R4810K variant was found in only one (0.37%) healthy control ($n = 268$). The RNF213 R4810K variant had significant associations with ICASO and increased the risk for ICASO ($P = 0.005$; OR: 20.2; 95% CI: 2.5–163.11). After logistic multivariate analysis, the R4810K variant was still an independent risk factor for ICASO ($P = 0.008$; OR: 18.1; 95% CI: 2.1–145.9).

Table 1: General characteristics of patients with intracranial major artery stenosis/occlusion and controls

Subjects	ICASO	Control
Age (years), (mean±SD)	46.0±9.14	43.0±8.72
Male sex, *n* (%)	90 (78.9)	197 (73.5)
Hypertension, *n* (%)	52 (45.6)	111 (41.4)
Diabetes mellitus, *n* (%)	18 (15.8)	20 (7.5)
Dyslipidemia, *n* (%)	46 (40.4)*	88 (32.8)
Smoking, *n* (%)	62 (54.4)#	70 (26.1)
Drinking, *n* (%)	44 (38.6)	60 (22.4)
Symptomatic, *n* (%)	102 (89.5)	0

Compared with the control group, *$P<0.05$; #$P<0.01$. ICASO: Intracranial major artery stenosis/occlusion, SD: Standard deviation

Table 2: The genotype frequencies of the ring finger protein 213 R4810K variant in intracranial major artery stenosis/occlusion and controls

Group	*n*	Genotype		Univariate		Multivariate	
		AG	GG	*P*	OR (95% CI)	*P*	OR (95% CI)
ICASO	114	8	106	0.005	20.2 (2.5-163.11)	0.008	18.1 (2.1-145.9)
Control	268	1	267				

ICASO: Intracranial major artery stenosis/occlusion, CI: Confidence interval, OR: Odds ratio

Table 3: Clinical and vascular characteristics of patients with ring finger protein 213 variant-related intracranial major artery stenosis/occlusion

Patient	Gender	Age (year)	Family history of MMD	Vascular risk factors	Clinical symptoms	Manifestation in MRI/CT	Vascular abnormality in CTA/MRA/DSA
1	Male	52	No	Hypertension Smoking Drinking	Dizziness, numbness of the left limbs	Lacunar infarction in the right basal ganglia and corona radiata	Severe stenosis in intracranial vessel of right ICA
2	Male	54	No	Hypertension Smoking Drinking	No symptoms	Infarction in the bilateral centrum semiovale	Moderate stenosis in M1 segment of left MCA
3	Female	45	No	Hypertension	Dizziness	Normal	Occlusion of the left MCA
4	Female	58	No	Hypertension Dyslipidemia	No symptoms	Spotty cerebral ischemic lesions in both lateral ventricles	Severe stenosis of the right MCA with multiple irregular blood vessels in the corresponding level
5	Male	41	No	Smoking Drinking	Weakness of the left limbs	Infarction in the left basal ganglia and left temporal lobe, parietal lobe and insula	Occlusion of the left MCA
6	Female	42	No	Dyslipidemia	Episodic left upper limb numbness and weakness	Spotty cerebral ischemic lesions in right centrum ovale	Occlusion of the right MCA
7	Female	51	No	Dyslipidemia	Dizziness	Normal	Severe stenosis of the right MCA
8	Female	54	No	Hypertension	Episodic weakness in the right limbs	Normal	Severe stenosis in M1 segment of left MCA

ICA: Internal carotid artery, MCA: Middle cerebral artery, CTA: Computed tomography angiography, MRA: Magnetic resonance angiography, DSA: Digital subtraction angiography, MMD: Moyamoya disease, MRI: Magnetic resonance imaging, CT: Computed tomography

High-resolution-magnetic resonance imaging findings on patients with ring finger protein 213 R4810K variant-related intracranial major artery stenosis/occlusion

One of the male patients did not undergo HR-MRI examination due to a heart stent, and another male patient refused HR-MRI examination because of severe neurological impairment. Six of eight patients (including all five females and one male) with RNF213 R4810K variant-related ICASO completed HR-MRI image scanning. HR-MRI images in the five female patients displayed blunted obliteration of the vessel lumen without eccentric plaque, while the affected site demonstrated concentric, homogeneous shrinkage of the vessel wall and multiple spring-like vascular structures [Figure 1a-e]. A presumptive MMD diagnosis based on HR-MRI findings was given to these five female patients. Conversely, eccentric plaque with heterogeneous signals and enhancement was revealed on HR-MRI images in the male patient [Figure 1f-j], and he was, therefore, given a presumptive CAS diagnosis.

Discussion

The major findings of this study were as follows: (a) RNF213 R4810K is a prevalent genetic variant associated with ICASO in the Han Chinese population. (b) All female patients with RNF213 variant-related ICASO presented characteristic features of MMD on HR MRI, and one male patient had signs of atherosclerotic disease but not MMD.

In recent years, significant progress had been made in understanding the genetics of MMD. A genome-wide linkage analysis and exome analysis identified RNF213 as the strongest susceptibility gene for MMD in East Asian populations.[6,7] However, there is genetic heterogeneity among these different ethnic populations. RNF213 R4810K variant was found to be strongly associated with MMD in the Japanese and Korean populations though to a lesser extent in the Chinese population.[12,21]

Miyawaki *et al.* suggested that a particular subset of Japanese patients with intracranial stenosis harbors a genetic variant associated with MMD. In their studies, 22%–24% of ICASO patients were found to possess the

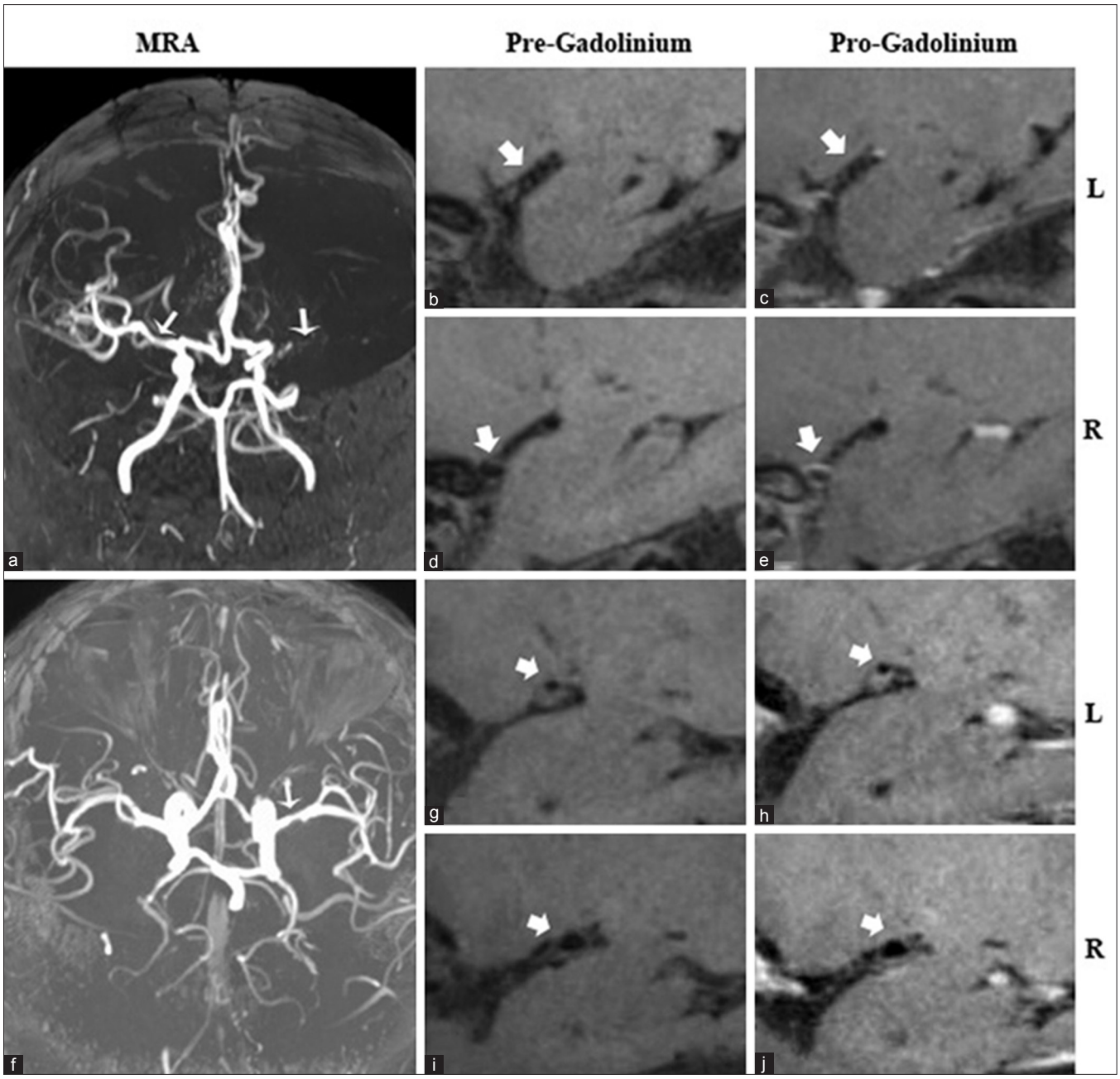

Figure 1: (a-e) Patient 1. (a) Occlusion in M1 segment of the left middle cerebral artery with irregular blood vessels in the corresponding level and slight stenosis in M1 segment of right middle cerebral artery. (b and c) Disappearance of M1 segment in left middle cerebral artery and replacement by multiple thin round vascular structures; (d and e) Slightly concentric, homogeneous shrinkage of vessel wall with concentric enhancement in M1 segment of right middle cerebral artery. (f-j) Patient 5. (f) Moderate stenosis in M1 segment of left middle cerebral artery; (g and h) Eccentric plaque with heterogeneous enhancement signals on the affected part of the left middle cerebral artery; (i and j) Normal blood vessel lumen of the right middle cerebral artery

RNF213 R4810K mutation.[8,9] In another study in a Korean population, this genetic variant was prevalent in 1/2 of patients with two criteria for MMD diagnosis as well as 1/4 of patients with one criterion who were diagnosed with ICAS.[10] Patients in this study experienced focal or lateralizing symptoms within the MCA distribution and had 50% stenosis or occlusion at the terminal portions of the ICA and/or proximal ACA and/or MCA on conventional or MR angiography. Thus, the results of this study are consistent with the reports from Miyawaki *et al*.

Due to considerable genetic heterogeneity among ethnic populations, we analyzed the association of the RNF213 R4810K variant with ICASO with case–control study in the Han Chinese population. As shown in Table 1, diabetes mellitus and smoking were twice as common in patients with ICASO versus controls. It was not strange because diabetes mellitus and smoking were risks for large artery intracranial occlusive disease, which was supported by several studies.[22,23] Our results supported that the R4810K mutation was still an independent risk

factor for ICASO after logistic multivariate analysis and the prevalence of this variant in the subset of patients was 5% in our cohort. This frequency was significantly lower than those from the Japanese and Korean populations. A similar phenomenon was reported for the frequency of RNF213 R4810K in MMD.[12] Our data also support that the genetic background of ICASO in Han Chinese is distinct from that in Japanese and Korean populations. It is possible that there are novel RNF213 gene variants or other genes related to ICASO in Han Chinese.

Management of conventional acquired risk factors, aggressive medical management (including antiplatelet therapy and statins), and stent placement (in selected patients) are important for preventing stroke in patients with atherosclerotic ICASO.[24,25] However, no current treatments can stop or reverse MMD progression. The role of stenting in MMD is also uncertain due to a high rate of symptomatic restenosis/occlusion.[24,25] Bypass surgery remains the mainstay treatment for MMD[26,27] but is not recommended for atherosclerotic ICASO.[28] Therefore, differentiation of MMD from atherosclerotic ICASO is important for treating patients with intracranial occlusive disease. Miyawaki *et al*. proposed the existence of a new entity of ICASO that is caused by the RNF213 R4810K variant and should be categorized as MMD based on its genetic background.[8,9] Screening for the RNF213 R4810K mutation among ICASO patients might be helpful to differentiate MMD from atherosclerotic ICASO, though more studies are needed to validate this hypothesis.

One patient harboring the RNF213 R4810K variant who met only one MMD diagnosis criterion but had a family history of MMD showed characteristic features of MMD on HR-MRI in a Korean population as previously described.[10] It is unclear whether most patients with RNF213 variant ICASO show MMD characteristics when examined by HR-MRI. Interestingly, all five female patients with RNF213 variant-related ICASO had a presumptive MMD diagnosis based on HR-MRI findings. In contrast, the only male patient who was examined by HR-MRI produced results that supported an atherosclerotic disease diagnosis. Routine vascular imaging examination, including CTA, MRA, and even DSA, is difficult to distinguish the pathological changes of atherosclerosis and MMD, especially smog-like vessels are not obvious in the early stage or late stage of MMD. HR-MRI is helpful to distinguishing between these two conditions but is not widely used in clinical work at present. Our results indicated that screening female patients with RNF213 R4810K variant ICASO might be helpful to differentiate MMD from atherosclerotic ICASO. However, this same diagnostic value was not immediately clear with our small cohort of male patients. Of course, this claim requires more data support. The exact mechanism by which an abnormality in RNF213 leads to MMD is still unknown. A study generated RNF213-deficient mice (RNF213-/-) to investigate whether they developed MMD. The results showed mice lacking the RNF213 gene did not spontaneously develop MMD, indicating that a functional loss of RNF213 did not sufficiently induce MMD.[29] The RNF213 genetic variant may be just a risk for vascular fragility, making vessels more vulnerable to hemodynamic stress and secondary insults, or facilitating the formation of basal collaterals in the setting of large intracranial arterial stenosis.[30] In addition, MMD is significantly more prevalent among females,[31,32] suggesting potential gender susceptibility. Thus, it is possible that combined effect of the RNF213 R4810K gene variant and female gender could lead to pathogenesis of MMD.

This study has some notable limitations. Because the prevalence of the R4810K variant in the Han Chinese population is very low, the sample size of patients with RNF213 variant-related ICASO on whom to perform HR-MRI examination is limited. Second, because most of the patients had no apparent sign of further interventional or surgical treatment, the DSA examination was not performed in most patients; thus, we lack the DSA data to support the HR-MRI findings. Third, although HR-MRI is helpful to determine the histopathology of RNF213 variant-related ICASO, it is an indirect pathological method, and a presumptive MMD diagnosis based on these findings needs to be confirmed by follow-up. Finally, participants in our study may not necessarily be representative of the general population with intracranial stenosis, as this is a single-center study at a tertiary hospital.

Conclusions

Our data indicate that RNF213 R4810K is a genetic risk variant for ICASO in the Han Chinese population. Screening RNF213 R4810K variant is useful to differentiate MMD-associated ICASO from atherosclerotic ICASO among female patients with RNF213 mutations, though its value in males is uncertain. Further studies with following up would be very interesting if that cohort (MMD + criteria and ICASO) was also included with ages, Suzuki classification, etc., to determine if a faster progression with the gene mutation is noted.

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Conflicts of interest

There are no conflicts of interest.

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