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ORIGINAL RESEARCH

Prospective Screening of Extracranial Systemic Arteriopathy in Young Adults with Moyamoya Disease

Tae Keun Jee, MD; Je Young Yeon, MD, PhD; Sung Mok Kim, MD; Oh Young Bang, MD, PhD; Jong-Soo Kim, MD, PhD; Seung-Chyul Hong, MD, PhD

BACKGROUND: *RNF213* is a major susceptibility gene for moyamoya disease (MMD), characterized by chronic progressive steno-occlusion of the intracranial arteries. However, coincidental extracranial arteriopathy is sporadically described in a few cases and in children with MMD.

METHODS AND RESULTS: This study prospectively enrolled 63 young adults (aged 20–49 years) without a known history of systemic vascular diseases who were confirmed to have definite (bilateral, n=54) or probable (unilateral, n=9) MMD, as per typical angiographic findings. Coronary and aorta computed tomography angiography was performed to characterize extracranial arteriopathy and investigate its correlation with clinical characteristics and MMD status, including the *RNF213* p.Arg4810Lys variation (c.14429G>A, rs112735431). Altogether, 11 of 63 patients (17%) had significant (>50%) stenosis in the coronary (n=6), superior mesenteric (n=2), celiac (n=2), renal (n=1), and/or internal iliac artery (n=1). One patient showed both mesenteric and iliac artery stenosis. Patients with extracranial arteriopathy were more likely to have diabetes mellitus and posterior cerebral artery involvement. Moreover, a higher prevalence of extracranial arteriopathy was observed in the presence of the *RNF213* p.Arg4810Lys variant (67% in homozygotes). After controlling for diabetes mellitus and posterior cerebral artery involvement, the p.Arg4810Lys variant was independently associated with extracranial arteriopathy (additive model; P=0.035; adjusted odds ratio, 4.57; 95% CI, 1.11–27.20).

CONCLUSIONS: Young adults with MMD may have concomitant extracranial arteriopathy in various locations. Patients with *RNF213* variants, especially the p.Arg4810Lys homozygous variant, should be screened for systemic arteriopathy.

Key Words: coronary artery disease ■ coronary artery stenosis ■ mesenteric ischemia ■ moyamoya disease ■ renal artery stenosis

Moyamoya disease (MMD) is characterized by chronic progressive steno-occlusion at the terminal portion of the internal carotid artery (ICA), the proximal portion of the anterior cerebral artery, and/or the middle cerebral artery, with concomitant abnormal collateral networks.[1] The pathogenesis of MMD remains unclear. However, *RNF213* has been identified as a major susceptibility gene for MMD.[2,3] Among East Asian individuals with MMD, 95% to 100% of familial cases, and 73% to 87% of nonfamilial cases had the founder variant of *RNF213*, p.Arg4810Lys (c.14429G>A, rs112735431).[2–4] Homozygosity for the *RNF213* p.Arg4810Lys variant, detected in 2% to 7% of cases in previous studies,[2–4] could predict early-onset and severe MMD.[4]

Several case reports have sporadically described extracranial systemic arteriopathy associated with MMD in the renal, pulmonary, celiac/mesenteric, and/or coronary arteries and even in the abdominal aorta.[5–7] Renal artery stenosis is the most commonly reported extracranial arteriopathy, with a prevalence of 5% to 8% in the pediatric MMD series.[8–10] Children with craniocervical and

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CLINICAL PERSPECTIVE

What Is New?

- Prospective screening of extracranial systemic arteriopathy in young adults with moyamoya disease revealed that 11 of 63 patients (17%) had significant (>50%) stenosis in the coronary, superior mesenteric, celiac, renal, and/or internal iliac artery.
- A higher prevalence of extracranial arteriopathy was observed in the presence of the RNF213 p.Arg4810Lys variant (8% in wild-types, 14% in heterozygotes, and 67% in homozygotes).

What Are the Clinical Implications?

- Patients with RNF213 variants, especially the p.Arg4810Lys homozygous variant, should be screened for systemic arteriopathy.

Nonstandard Abbreviations and Acronyms

CACTA	coronary and aorta computed tomography angiography
DSA	digital subtraction angiography
ECG	electrocardiography
ICA	internal carotid artery
MMD	moyamoya disease
PCA	posterior cerebral artery
PPAS	peripheral pulmonary artery stenosis

renal arteriopathy are considered to have a subtype of fibromuscular dysplasia, with or without moyamoya syndrome.[5,11] Systemic (ie, additional nonrenal or craniocervical) arteriopathy was also observed in 76% of children with pathologically proven fibromuscular dysplasia.[11] The pathological findings of these children were virtually indistinguishable from those observed in MMD.[11,12]

Peripheral pulmonary artery stenosis (PPAS) is a rare cause of pulmonary hypertension and is usually found in children with associated chromosomal syndromes.[13] Although isolated cases of PPAS have occasionally been reported in adolescents and adults, the cause of this disease remains unknown. Recently, homozygosity for the *RNF213* p.Arg4810Lys variant has been reported to be associated with PPAS in 4 adolescents with MMD.[13,14] Two of these 4 adolescents had concurrent renal and/or mesenteric arteriopathy.[13,14]

Coronary artery stenosis has been mostly described in young adults several years or decades after the diagnosis of MMD.[7,15,16] Previously, we reported that 21 (5%) of 456 adults with MMD had experienced unstable angina/myocardial infarction (n=10), stable angina (n=6), and variant angina with mild stenosis (n=5) at a median age of 44 years (range, 27–59 years).[17] Two of the 21 patients developed unstable angina/myocardial infarction before the diagnosis of MMD,[17] which prompted us to design this study. Up to this date, there have been no case–control studies elucidating the direct relationship between extracranial arteriopathy and MMD. The aim of this prospective study was to characterize extracranial arteriopathy in young adults with MMD and to investigate its correlation with clinical characteristics and MMD status, including the *RNF213* p.Arg4810Lys variation.

METHODS

Patient Selection

The data that support the findings of this study are available from the corresponding author upon reasonable request. This study was approved by the Institutional Review Board (2015-04-079). Consecutive patients who were admitted for digital subtraction angiography (DSA) evaluation of MMD between February 2016 and December 2018 were prospectively enrolled for co-evaluation of extracranial systemic arteriopathy using coronary and aorta computed tomography angiography (CACTA). The inclusion criteria were as follows: (1) definite and probable MMD based on the recent guidelines[1]; (2) young adults aged 20 to 49 years; (3) no known history of renal failure or severe contrast allergy; and (4) provision of informed consent by the patient.

Seventy-three patients were consecutively enrolled; 10 patients were excluded from the analysis because of the following reasons: (1) controversy in the MMD diagnosis, such as MMD associated with autoimmune diseases (moyamoya syndrome) and isolated middle cerebral artery or ICA occlusion with scanty collateral networks (n=6); (2) refusal of *RNF213* p.Arg4810Lys genotyping (n=3); and (3) known history of cardiac, renal, or systemic vascular diseases (n=1). The last patient had a history of angina and coronary stenting at the age of 39 years, 5 years before the MMD diagnosis. Therefore, this study included 63 young adults who had DSA-confirmed typical MMD and who underwent *RNF213* p.Arg4810Lys genotyping and CACTA to evaluate extracranial systemic arteriopathy at a presymptomatic stage.

Of the 63 study subjects, 48 were admitted for DSA confirmation of newly diagnosed MMD on magnetic resonance angiography. The remaining 15 patients were previously diagnosed with MMD or intracranial steno-occlusion and re-admitted for repeated DSA to investigate disease progression. Six of those 15 patients underwent revascularization surgery 8 to

138 months (mean, 67 months) before the re-admission. The DSA-confirmed diagnosis was definite (bilateral) MMD in 54 patients and probable (unilateral) MMD in 9 patients. The angiographic findings of the contralateral hemisphere were normal in 3 out of 9 patients with probable MMD, and mild middle cerebral artery abnormalities were observed in 3 patients, whereas nonvisualization of the anterior cerebral artery without ICA and middle cerebral artery abnormalities were observed in 3 patients.

Clinical and Radiological Assessment

Clinical information, including patient age at enrollment, sex, clinical presentation, family (first-degree relatives) history of MMD, and vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, and smoking status) were collected. All patients underwent standardized diagnostic tests that included routine blood tests (total cholesterol, high-density and low-density lipoprotein–cholesterol, etc.) and moyamoya work-ups (DSA, 3T magnetic resonance imaging of the brain, 3-dimensional time-of-flight magnetic resonance angiography, gadolinium-enhanced magnetic resonance angiography including cervical arteries, and perfusion imaging).

The presence of intracerebral hemorrhage or infarction was determined on computed tomography (CT) and magnetic resonance imaging. If an old infarction was found in patients presenting with nonspecific symptoms such as headache and dizziness, the patients were regarded as presenting with ischemic symptoms. DSA findings were classified according to Suzuki's 6 stages and dichotomized into early (Suzuki stage 0–3) and advanced (stage 4–6) MMD based on the hemisphere of higher Suzuki stages.[18] Involvement of the posterior cerebral artery (PCA), defined as significant (>50%) stenosis or occlusion with collateral networks, was also assessed by DSA. In 15 patients with progressed MMD, the DSA findings at the time of worsening were used for subsequent analysis.

A 128-section dual-source CT system (SOMATOM Definition Flash; Siemens Medical Solutions, Forchheim, Germany) was used for CACTA. A β-blocker (metoprolol, 50–100 mg) was administered orally 1 hour before CT in patients with heart rates higher than 65 beats per minute. Nitroglycerin (0.4 mg) was administered to all patients sublingually 1 minute before CT. CT imaging consisted of simultaneous coronary imaging using retrospective electrocardiography-gated helical mode and aorta imaging using prospective electrocardiography-gated high-pitch helical mode. Anatomic coverage for aorta imaging was from the level of the midclavicle to the symphysis pubis. The coronary, renal, celiac, superior mesenteric, internal iliac, and pulmonary arteries were evaluated. The degree of arterial stenosis was assessed using electronic calipers and classified as minimal (<25% stenosis on short-axis planes of arteries), mild (25%–50%), moderate (50%–70%), or severe (>70%). Only moderate or severe stenosis was regarded as significant (>50%) stenosis and was included in the analysis, considering the artifacts. The type of stenosis was determined as calcific or noncalcific.

In 10% to 24% of the population, the median arcuate ligament crosses the aorta at a lower level and subsequently compresses the celiac artery, with or without clinical significance.[19] Therefore, patients showing celiac artery stenosis were not considered to have true stenosis if the observed stenosis had any of the following CACTA findings of median arcuate ligament syndrome: (1) focal narrowing of the proximal celiac artery with poststenotic dilatation; (2) indentation on the superior aspect of the celiac artery; and (3) a hook-shaped contour of the celiac artery.[19] All CACTA findings were interpreted by a cardiovascular radiologist and reviewed again by the authors. Any differences were resolved by consensus.

RNF213 p.Arg4810Lys Genotyping

Genomic DNAs were prepared from peripheral blood leukocytes using the Wizard Genomic DNA Purification kit (Promega, Madison, WI). In order to genotype the p.Arg4810Lys variant (NM_001256071.1:c.14429G>A; rs112735431), exon 60 of *RNF213* was amplified using a primer: *RNF213*-e60-F, 5′-gctgcatcacaggaaatgac-3′ and *RNF213*-e60-R, 5′-aaggagtgagccgagtttga-3′. The polymerase chain reaction products were sequenced in a ABI 3730*xl* DNA Analyzer (Applied Biosystems, Foster City, CA) using a BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). The obtained sequence was compared with the reference sequence for *RNF213* (GenBank accession number NM_001256071.1).

Statistical Analysis

Statistical analyses were performed using SPSS Statistics Version 25.0 (IBM Corporation, Armonk, NY) and R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). The distribution between the 2 groups and the deviation from Hardy–Weinberg equilibrium were analyzed using the Fisher exact test. Correlations between explanatory variables and extracranial arteriopathy were determined by binary logistic regression analysis and the additive model was applied for the *RNF213* p.Arg4810Lys variant (G/G versus G/A versus A/A). Multivariate logistic regression analysis was performed using stepwise backward elimination with a significance level of 0.2 to stay in the

model. Odds ratio (OR) estimates and 95% CI were obtained for risk variables in the model. Firth's penalized likelihood adjustment was performed to solve a separation issue.[20] All *P* values were based on 2-sided comparisons, and *P* values <0.05 were considered statistically significant.

RESULTS

The clinicoradiological findings of 63 patients are summarized in Table 1. The median age of patients at the time of DSA and CACTA was 39 years (interquartile range, 31–43 years), and 43 (68%) patients were female. Of 63 patients included in this study, 51 patients (81%) presented with transient ischemic attacks or ischemic strokes, 7 patients (11%) with hemorrhagic strokes, and 5 patients (8%) with nonspecific symptoms such as headache and dizziness. Eight patients (13%) had a family history of MMD. Assuming that each patient had only 1 hemisphere of the higher Suzuki stages, 50 patients (79%) were categorized as having advanced MMD (Suzuki stage 4–6). Nine patients (14%) were diagnosed with probable (unilateral) MMD. Significant (>50%) stenosis (n=3) or occlusion (n=20) of the PCA was observed with collateral networks in 23 patients (37%), and 3 of them manifested bilateral PCA occlusion. The *RNF213* p.Arg4810Lys variant was identified in 50 patients (79%); 6 of them (9%) were homozygotes, and the remaining 44 (70%) were heterozygotes.

The evaluation CACTA screening of extracranial arteriopathy revealed that 11 out of 63 patients (17%) had asymptomatic, but significant (>50%) stenosis located in the coronary (n=6), superior mesenteric (n=2), celiac (n=2), renal (n=1), and/or internal iliac artery (n=1). One patient showed both mesenteric and iliac artery stenosis (Table S1). Three out of 6 patients with coronary stenosis had 5 severely stenotic lesions in the coronary branches, and none of these 5 lesions were calcific. Remarkably, 1 patient with severe coronary stenosis developed a non–ST-segment–elevation myocardial infarction just 1 day after urgent bypass surgery for recurrent PCA territory infarction (Figure 1). This patient underwent emergent percutaneous coronary intervention on the following day. The other 2 patients with severe coronary stenosis were referred to a cardiologist and were supervised under medical management after undergoing stress echocardiography.

Severe stenosis involving the proximal superior mesenteric artery was observed in 2 patients, who were homozygous for the *RNF213* p.Arg4810Lys variant. One of them developed a prominent arterio-arterial anastomosis between the superior and inferior

Table 1. Clinicoradiological Findings of the 63 Study Subjects

	All Patients (n=63)	Extracranial Arteriopathy		*P* Value
		Present (n=11, 17%)	Absent (n=52, 83%)	
Age, y	39.0 [31.5–42.9]	41.7 [36.0–43.7]	38.9 [29.6–42.7]	0.215
Female	43 (68)	6 (55)	37 (71)	0.304
Clinical presentation				0.827
Ischemic	51 (81)	10 (91)	41 (79)	
Hemorrhagic	7 (11)	1 (9)	6 (11)	
Nonspecific	5 (8)	0 (0)	5 (10)	
Family history of MMD	8 (13)	2 (18)	6 (12)	0.620
Hypertension	20 (32)	6 (55)	14 (27)	0.088
Diabetes mellitus	5 (8)	3 (27)	2 (4)	0.034
Hyperlipidemia	15 (24)	4 (36)	11 (21)	0.435
Smoking	11 (17)	3 (27)	8 (15)	0.389
Newly diagnosed MMD	48 (76)	9 (82)	39 (75)	1.000
Advanced MMD (Suzuki stage 4–6 in any hemisphere)	50 (79)	9 (82)	41 (79)	1.000
Probable (unilateral) MMD	9 (14)	2 (18)	7 (13)	0.650
PCA involvement	23 (37)	8 (73)	15 (29)	0.013
RNF213 p.Arg4810Lys				0.009
Wild-type, G/G	13 (21)	1 (9)	12 (23)	
Heterozygote, G/A	44 (70)	6 (55)	38 (73)	
Homozygote, A/A	6 (9)	4 (36)	2 (4)	

Data are shown as no. (%) or medians [interquartile ranges] where appropriate; *P* value derived from the Fisher exact test. MMD indicates moyamoya disease; and PCA, posterior cerebral artery.

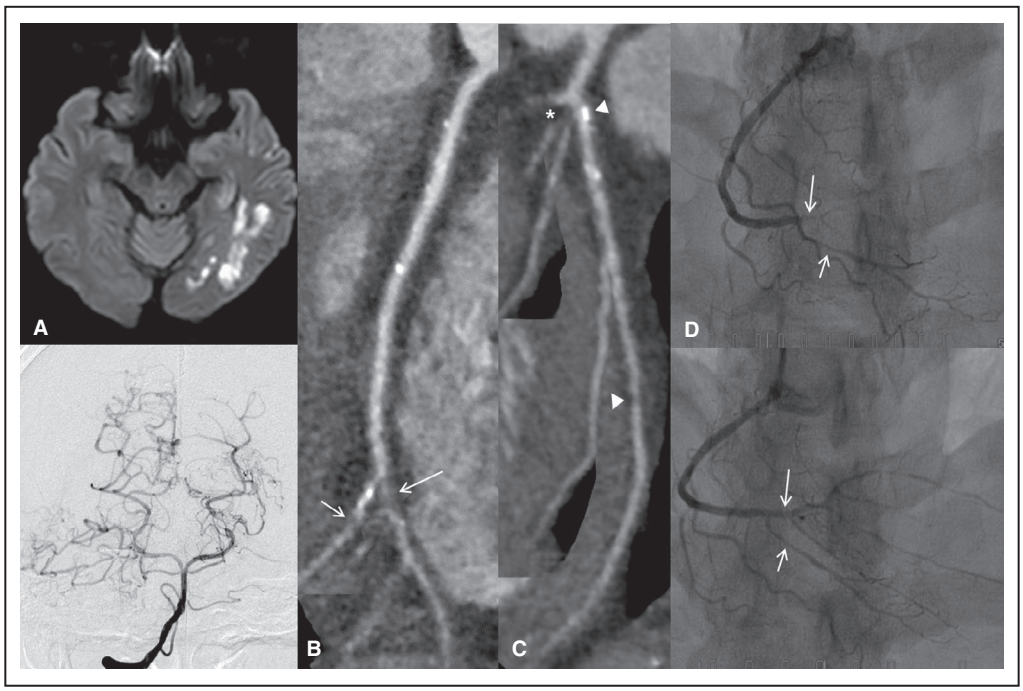

Figure 1. An example of coronary artery stenosis (M/45).
A, Acute infarction referable to the posterior cerebral artery involvement. **B** and **C**, Coronary and aorta computed tomography angiography showing a mild-to-severe coronary artery stenosis in multiple locations: the posterolateral branch (severe stenosis, long arrow), left anterior descending artery (mild stenosis, arrowheads), and ramus intermedius (severe stenosis, asterisk). **D**, Subsequent occlusion of the posterolateral branch and recanalization after balloon dilation (long arrow). This patient was heterozygous for the *RNF213* p.Arg4810Lys variant

mesenteric arteries, known as the arc of Riolan, and manifested moderate stenosis in the proximal internal iliac artery (Figure 2). Two patients exhibited moderate stenosis in the inferior aspect of the proximal celiac artery without a hook-shaped contour, which differed from typical or presumptive findings of the median arcuate ligament syndrome. Renal artery stenosis was found in only 1 patient, which was moderate unilateral stenosis in the proximal region. However, none of the 63 patients exhibited PPAS.

Compared with patients without extracranial arteriopathy (Table 1), those with extracranial arteriopathy were more likely to have diabetes mellitus (27% versus 4%, *P*=0.034) and PCA involvement (73% versus 29%, *P*=0.013). Moreover, a higher prevalence of extracranial arteriopathy was observed in the presence of the *RNF213* p.Arg4810Lys variant (67% in homozygotes, *P*=0.009). The correlation between the p.Arg4810Lys variant and extracranial arteriopathy, determined by binary logistic regression analysis, was statistically significant whether under the additive (G/G versus G/A versus A/A; *P*=0.009; OR, 5.64; 95% CI, 1.50–27.51) or recessive model (G/G + G/A versus A/A; *P*=0.004; OR, 12.12; 95% CI, 2.27–80.89). A multivariate logistic regression analysis was performed to further evaluate explanatory variables (Table 2). After controlling for family history of MMD, hypertension, diabetes mellitus, and PCA involvement, the p.Arg4810Lys variant was independently associated with extracranial arteriopathy (additive model; *P*=0.035; adjusted OR, 4.57; 95% CI, 1.11–27.20).

DISCUSSION

To our knowledge, this study is the first study that prospectively investigated extracranial systemic arteriopathy in young adults with typical MMD. We found that 11 (17%) out of 63 young adults (median age, 39 years) were asymptomatic with significant (>50%) stenosis in the coronary, superior mesenteric, celiac, renal, and/or internal iliac arteries. Coronary artery stenosis was the most common extracranial arteriopathy observed in 6 patients (10%). Although there has not been any directly comparable study reported previously, a prevalence of >50% coronary stenosis in the general population was reported to be 0.1% in a study consisting of 914 young adults aged 23 to 44 years (median age, 41 years) who underwent coronary CT angiography during a general medical check-up.[21] Other studies on 1000 to 2133 asymptomatic middle-aged adults

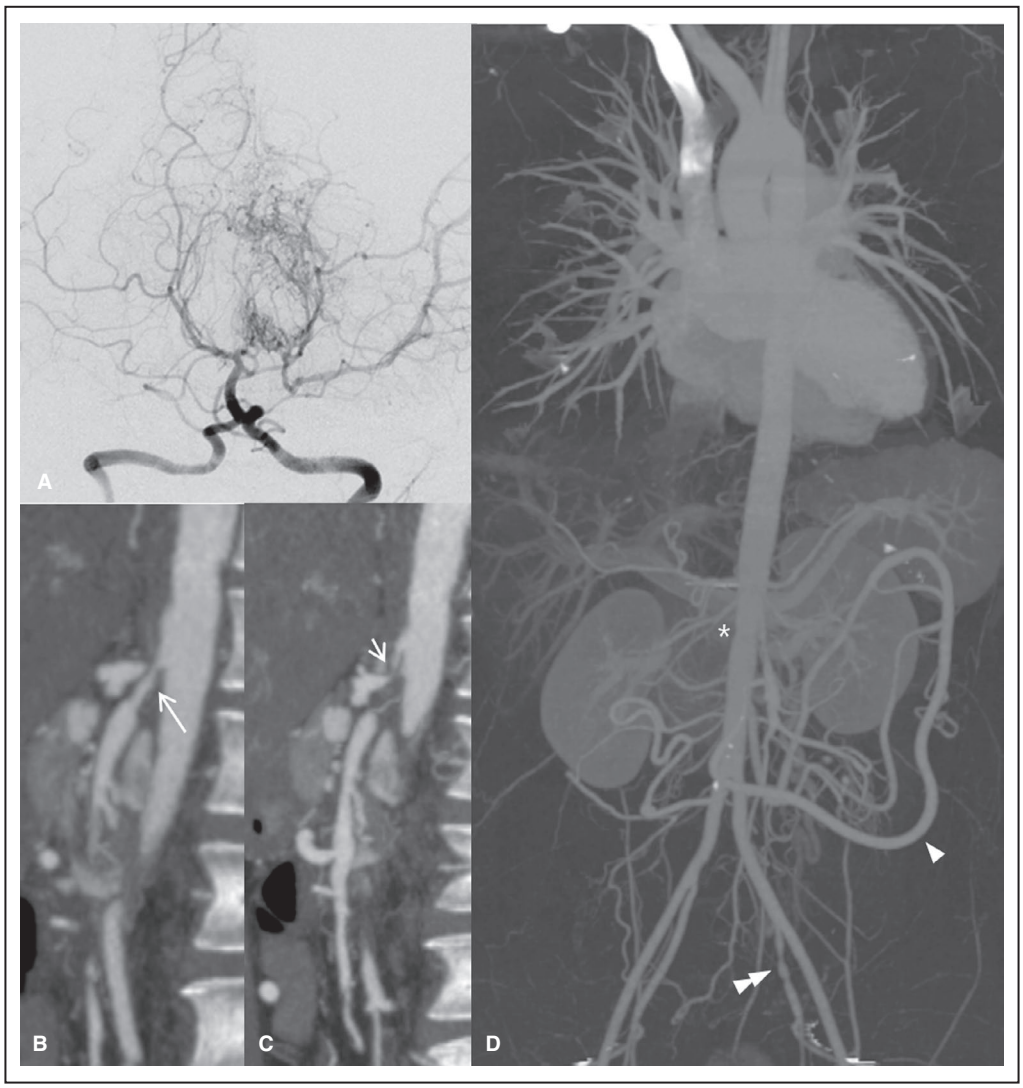

Figure 2. An example of superior mesenteric artery stenosis (F/42).
A, The posterior cerebral artery involvement on cerebral angiography. **B**, Coronary and aorta computed tomography angiography demonstrating a severe stenosis in the superior mesenteric artery (long arrow). **C**, Celiac artery stenosis was not regarded as a true stenosis, because it showed a hook-shaped contour with superior indentation (short arrow). **D**, A 3D-reconstructed image shows a prominent arterio-arterial anastomosis between the superior and inferior mesenteric arteries (the arc of Riolan, arrowhead), moderate stenosis in the left internal iliac artery (double arrowheads) and minimal narrowing of the infrarenal aorta (asterisk). There is no apparent stenosis in the pulmonary circulation. This patient was homozygous for the *RNF213* p.Arg4810Lys variant.

(mean age, 49–50 years) found that 1% to 5% of the patients had >50% coronary stenosis, depending on the vascular risk factors.[22,23] Considering that age is a strong risk factor for coronary stenosis,[21–23] >50% of asymptomatic coronary stenosis appears to be more prevalent in young adults with MMD than in the corresponding general population.

Superior mesenteric artery stenosis has rarely been described in patients with MMD.[5,24] It may cause chronic or acute-on-chronic mesenteric ischemia, resulting in abdominal pain and life-threatening bowel necrosis.[25] However, only a small subset of patients become symptomatic, because of the rich collateral networks from the celiac and inferior mesenteric artery. It has long been believed that significant steno-occlusion of at least 2 out of the 3 major visceral branches are required to compromise the overall mesenteric flow.[25] In this study, patients showing typical or presumptive findings of the median arcuate ligament syndrome (Figure 2) were not considered to have true celiac stenosis. As a result, only 2 patients had true celiac stenosis without evidence of external compression. These 2 patients were also unlikely to become symptomatic since they did not exhibit mesenteric stenosis.

Table 2. Logistic Regression Analysis of Explanatory Variables

	Univariate Analysis			Multivariate Analysis		
	P Value	OR	95% CI	*P* Value	aOR	95% CI
Age, y	0.203	1.05	0.97–1.16			
Female	0.277	0.49	0.13–1.82			
Family history of MMD	0.458	1.88	0.31–8.86	0.139	4.89	0.58–42.04
Hypertension	0.081	3.14	0.87–11.85	0.191	3.10	0.56–19.00
Diabetes mellitus	0.020	8.32	1.41–57.05	0.060	7.00	0.92–64.22
Hyperlipidemia	0.268	2.17	0.53–8.17			
Smoking	0.312	2.16	0.46–8.85			
PCA involvement	0.016	3.42	1.26–10.43	0.060	3.28	0.95–13.21
RNF213 p.Arg4810Lys (additive model)	0.009	5.64	1.50–27.51	0.035	4.57	1.11–27.20

aOR indicates adjusted odds ratio; MMD, moyamoya disease; OR, odds ratio; and PCA,posterior cerebral artery.

Renal artery stenosis is the most commonly reported extracranial arteriopathy, with a prevalence of 5% to 8% in pediatric MMD series.[8–10] Some patients present with renovascular hypertension for their initial symptoms in MMD, although others have renal artery stenosis and no hypertension.[8–10] In this study, only 1 patient (2%) showed renal artery stenosis. The patient had hypertension and was on antihypertensive medication before the MMD diagnosis. The relatively high prevalence reported in the pediatric MMD series might be attributable to the retrospective study design and the more severe course of childhood-onset MMD than that of adult-onset MMD. Involvement of the abdominal aorta and iliac artery in MMD has rarely been described.[6,26] We found 1 patient, who had superior mesenteric artery stenosis, and had concurrent iliac artery stenosis. Additionally, this patient manifested minimal narrowing of the infrarenal aorta (Figure 2).

The pathogenesis of MMD and associated extracranial arteriopathy remains unclear. Considering that 3 out of 5 patients with diabetes mellitus and 6 out of the 20 patients with hypertension had extracranial arteriopathy, premature atherosclerosis could be a possible explanation of these findings. However,

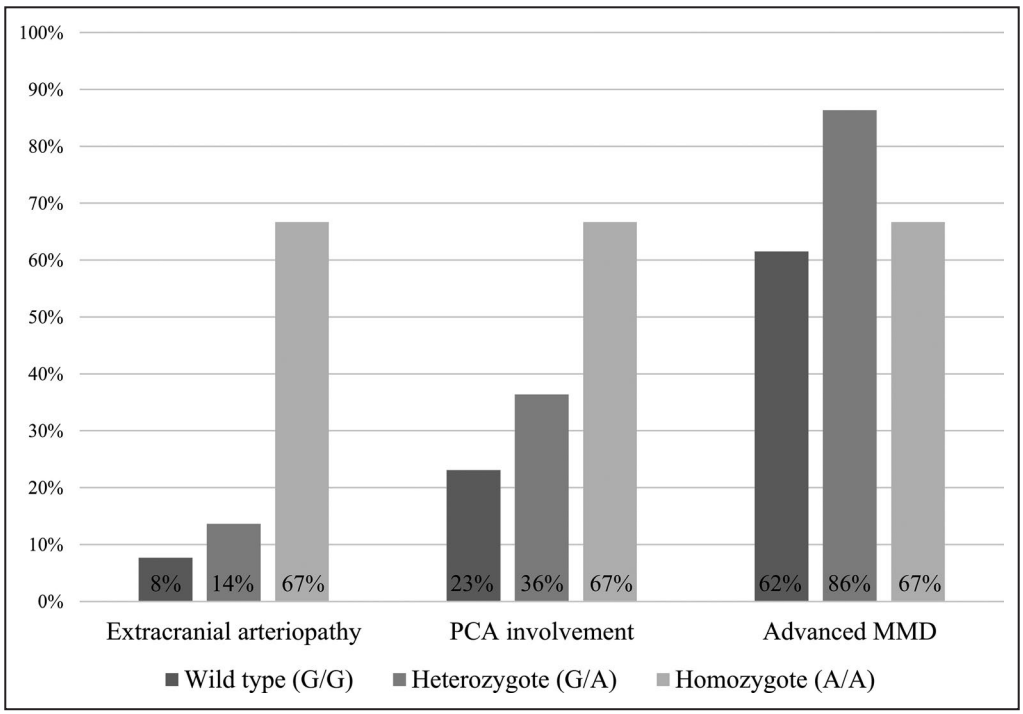

Figure 3. Prevalence of extracranial arteriopathy, posterior cerebral artery involvement, and advanced moyamoya disease with respect to the RNF213 p.Arg4810Lys status.
MMD indicates moyamoya disease; and PCA, posterior cerebral artery.

histopathology examination and morphometric analysis of the extracranial arteries from 13 autopsy cases with MMD revealed that these extracranial arteries exhibited intimal fibrous thickening similar to that exhibited by the intracranial arteries.[12] Intravascular ultrasound findings of noncalcified coronary stenosis in a young adult with MMD were intimal fibrous thickening with minimal lipid pooling, which differed significantly from those of the typical atherosclerotic plaques.[7]

Recently, the homozygosity of the *RNF213* p.Arg4810Lys variant has been reported to be associated with PPAS in 4 adolescents with MMD.[13,14] We could not find PPAS in any of our patients, including 6 homozygotes. Instead, 4 of the 6 homozygotes had stenosis involving the coronary, superior mesenteric, and/or internal iliac arteries. The prevalence of extracranial arteriopathy in homozygotes (67%) was significantly higher than in heterozygotes (14%) or wild-types (8%), indicating the gene–dosage effect (Figure 3). Some patients may develop extracranial arteriopathy before MMD.[13] Even in patients without MMD, the *RNF213* p.Arg4810Lys variant has been reported to be associated with intracranial atherosclerotic stenosis or coronary artery disease.[27,28] Altogether, *RNF213* could be a susceptibility gene for arteriopathy, which preferentially affects the intracranial arteries; however, it might involve almost every artery in the body at various times.

PCA involvement in MMD is generally associated with more advanced ICA stages and is a poor prognostic factor for representing MMD severity.[29] However, the side of PCA involvement is sometimes contralateral to the more advanced side of the ICA lesions (18% in 1 study),[30] and the prevalence is similar (≈30%) in both children and adults at the initial diagnosis.[29] Thus, PCA involvement may not be simply explained by ICA progression with aging. Although the correlation between PCA involvement and extracranial arteriopathy in MMD has rarely been described, 1 article reported that PCA involvement was observed in 5 of 6 children and young adults with concomitant MMD and renal artery stenosis.[8] In the present study, extracranial arteriopathy was more prevalent in patients with PCA involvement (35% versus 8%, P=0.013). However, PCA involvement did not reach statistical significance in the multivariate analysis (P=0.060; adjusted OR, 3.28; 95% CI, 0.95–13.21). This might be explained by the relationship between PCA involvement and *RNF213* variation. PCA involvement trended towards being related to the *RNF213* p.Arg4810Lys variant (additive model; P=0.090; OR, 2.29; 95% CI, 0.88–6.82), whereas advanced MMD (Suzuki stage 4–6 in any hemisphere) was not related to it (Figure 3). PCA involvement could be a surrogate marker of *RNF213*-related burdens.[4]

The present study included only adults with probably late-onset MMD without a known history of systemic vascular diseases. Selection bias associated with age restriction and difference in magnitude of vascular risk factors could have contributed to significant deviation from Hardy–Weinberg Equilibrium in the study subjects (P=0.002; observed/expected number of wild-types, 13/19.4; heterozygotes, 44/31.1; homozygotes, 6/12.4). The prevalence and distribution of extracranial arteriopathy may differ in children with early-onset MMD. The lack of significance noted for some comparisons could have been because of the small numbers analyzed. A case–control study using the same investigations in each group would be necessary to determine whether extracranial arteriopathy, such as coronary stenosis, is more prevalent in patients with MMD. Moreover, other variants of *RNF213* were not investigated, which may confer susceptibility to extracranial arteriopathy as a homozygous or compound heterozygous form.[31] Furthermore, invasive catheter angiography to validate CACTA findings was not performed in most patients, and peripheral artery stenosis could not be evaluated by CACTA.

Nevertheless, this is the first study that prospectively investigated extracranial arteriopathy in young adults with MMD and its correlation with MMD status, including the *RNF213* p.Arg4810Lys variation. Because asymmetrical involvement of bilateral ICAs and PCAs is common in MMD, involvement of the extracranial arteries varies significantly between patients. A longitudinal follow-up study would be required to investigate the development and progression of MMD-associated (probably *RNF213*-related) extracranial arteriopathy with clinical consequences and to understand the pathophysiological function of *RNF213* and other contributing factors.

Young adults with MMD may have concomitant extracranial arteriopathy in various locations. Patients with *RNF213* variants, especially the p.Arg4810Lys homozygous variant, should be screened for systemic arteriopathy.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Summary of the 11 Patients Manifesting Extracranial Arteriopathy.

Case No.	Sex	Age	DM	HTN	Hyper-lipidemia	BMI	*RNF213* variant†	PCA involve	Probable MMD	Coronary artery	Renal artery	Celiac artery	Superior mesenteric artery	Internal iliac artery
1	F	27	Y	N	N	19.6	hetero	N	Y			proximal (moderate)		
2	F	34	N	N	N	22.5	hetero	N	N			proximal (moderate)		
3	F	36	N	Y	N	26.8	hetero	Y	N	distal LM (moderate)				
4	M	36	N	N	Y	31.0	homo	N	N	RCA os (severe)				
5	M	39	N	Y	Y	22.1	wild	Y	N		proximal (moderate)			
6	F	42	N	N	N	21.3	homo	Y	Y				proximal (severe)	proximal (moderate)
7	M	43	Y	N	Y	27.7	hetero	N	N	mid-RCA (severe) PLSA (severe)				
8	F	43	N	Y	N	24.5	homo	Y	N				proximal (severe)	
9	M	44	N	Y	N	20.3	hetero	Y	N	LAD (moderate)				
10	M	45	Y	Y	Y	24.3	hetero	Y	N	PL (severe) PDA (moderate‡) LAD (moderate‡) RI (severe)				
11	F	50	N	N	N	21.3	homo	Y	N	proximal LAD (moderate)				

DM indicates diabetes mellitus; HTN, hypertension; BMI, body mass index; PCA, posterior cerebral artery; MMD, moyamoya disease; M, male; F, female; Y, yes; N, no; wild, wild type; hetero, heterozygote; homo, homozygote; p, proximal; d, distal; LM, left main; LCx, left circumflex; RCA, right coronary artery; os, ostium; PLSA, postero-lateral side artery; LAD, left anterior descending; D1, diagonal branch 1; PDA, posterior descending artery; PL, postero-lateral; RI, ramus intermedius. † p.Arg4810Lys variant of the *RNF213* gene; ǂ calcified stenosis