REVIEW ARTICLE

Moyamoya Disease and Spectrums of *RNF213* Vasculopathy

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Abstract
Moyamoya disease (MMD) is a rare cerebrovascular disease characterized by progressive stenosis of large intracranial arteries and a hazy network of basal collaterals called moyamoya vessels. A polymorphism (R4810K) in the *Ring Finger Protein 213 (RNF213)* gene, at chromosome 17q25.3, is the strongest genetic susceptibility factor for MMD in East Asian populations. MMD was regarded prevalent in childhood and in East Asian populations. However, the so-called MMD could represent only the tip of the iceberg. MMD is increasingly reported in adult patients and in Western populations. Moreover, the *RNF213* variant was recently reported to be associated with non-MMD disorders, such as intracranial atherosclerosis and systemic vasculopathy (e.g., peripheral pulmonary artery stenosis and renal artery stenosis). In this review, we summarize the spectrums of *RNF213* vasculopathy in terms of clinical and genetic phenotypes. Continuous efforts are required for pathophysiology-based diagnoses and treatment, which will benefit from collaboration between clinicians and researchers, and between stroke and vascular physicians.

Keywords Moyamoya disease · *RNF213* · Polymorphism · Vasculopathy

JEL Classification Moyamoya · Genetics · Biomarkers · Mechanisms

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Introduction

Moyamoya disease (MMD) is a rare cerebrovascular disease characterized by progressive stenosis of large intracranial arteries (including the distal internal carotid artery) and a hazy network of basal collaterals called moyamoya vessels. The etiology of MMD is unknown. As a result, criteria for the diagnosis of MMD are based on characteristic angiographic findings. Most research on angiographic features, diagnostic criteria, and treatment guidelines has been limited to pediatric MMD [1].

The prevalence of adult-onset MMD may be underestimated. Unlike in childhood-onset MMD, typical angiographic features might not be observed in the early phase of adult-onset MMD [2, 3]. One regional, all-inclusive data set of newly registered patients with MMD in Hokkaido, Japan, showed that the age of onset is rising and ischemic presentation is increasing [4]. The annual incidence of MMD has reportedly increased in Japan, China, Taiwan, and Korea [5]. Such changes in the epidemiology of MMD may be derived from the increasing number of adult patients diagnosed with MMD, rather than the actual changes in epidemiology or characteristics of MMD [5].

A polymorphism, R4810K (p.Arg4810Lys), in the *Ring Finger Protein 213* (*RNF213*) gene at chromosome 17q25.3 was identified as the strongest genetic susceptibility factor for MMD in East Asian populations, using genome-wide linkage and exome analysis [6, 7]. *RNF213* R4810K-related vasculopathy is not well characterized, except in MMD. However, *RNF213* variants may not be the only determinants of MMD. Very recent clinical studies showed that *RNF213* variants are associated not only with MMD but also with intracranial atherosclerosis [8] and systemic vascular diseases, such as peripheral pulmonary artery stenosis and renal artery stenosis [9, 10]. Moreover, not all the patients with MMD have this genetic variant.

Therefore, the so-called MMD may represent only the tip of the iceberg. These results call for the redefinition of MMD as a spectrum, considering the heterogeneity of innate angiogenetic capacity, genetic, and environmental factors. The purpose of this review is to summarize the spectrum of *RNF213* vasculopathy, in terms of clinical and genetic phenotypes. In addition, the clinical implications of the *RNF213* spectrum on the evaluation and management of MMD patients are discussed.

Search Strategy and Selection Criteria

Articles for inclusion in this review were identified using PubMed and ClinicalTrials.gov, with the search terms "moyamoya disease," "stroke," "*RNF213*," and "cerebrovascular disease," and were published in English, up until March 2019. We also considered other relevant articles and reviews. The final reference list was generated on the basis of originality and relevance to this topic. Because of space limitations, we were not able to discuss individual pathophysiologies of MMD in depth or with critical analyses.

Spectrums Related to MMD

Phenotypic variation of MMD and related *RNF213* vasculopathies may be caused by the complex interaction of the following factors (Fig. 1).

Age Spectrum

In children, ischemic symptoms, especially transient ischemic attack, are predominant, whereas adult patients present with intracranial hemorrhage more often than pediatric patients. In addition, moyamoya collaterals, which are the clinical hallmark of MMD, are more prominent in childhood MMD than in adult-onset MMD [3]. The differences in angiographic findings between childhood and adult MMD could be caused by either a more severe aberrant angiogenesis in childhood MMD or decreased angiogenetic capability in adult MMD. Aberrant angiogenesis and proliferative vasculopathy of MMD are prominent in childhood MMD. A long-term follow-up angiographic study showed that the age at diagnosis was the only independent predictor of contralateral progression [11]. The disease progresses angiographically until adolescence [12], and disease progression is relatively rare in adult MMD, especially in asymptomatic individuals. Conversely, angiogenesis is impaired with increasing age [13]. Aging causes rarefaction and insufficient collateral circulation in multiple tissues, resulting in more severe ischemic tissue injury, and vascular risk factors are associated with poor collaterals in preclinical and clinical studies [14]. Age-related angiogenetic capacity does not only affect the angiographic findings of MMD but also determines the mode of surgical treatment. Indirect revascularization techniques are generally preferable in childhood MMD, while direct bypass techniques are preferable in adult MMD patients [1, 15].

Genetic Spectrum

RNF213 Gene and Inheritance Pattern

The R4810K variant was identified in 95% of patients with familial MMD, 80% with sporadic MMD, and 1.8% of control individuals in a Japanese population [6]. *RNF213* encodes a relatively large protein with a dual AAA+ ATPase and E3 ligase activities [16]. In vitro and in vivo experiments revealed that *RNF213* is related to angiogenesis and vascular inflammation; however, the exact physiologic functions of *RNF213* remain unknown [16]. The R4810K variant is an Asian founder mutation and its prevalence is reported to be up to 2.5% in East Asians [16, 17], although it has not been reported in Western populations. Since the total number of carriers is estimated to be 15 million in Asian countries, the impact on cardiovascular health is extremely significant [18]. Homozygosity for R4810K predicted an earlier onset and a more severe form of MMD in both Japanese [19] and Korean [20] patients with MMD. Prevalence of homozygotes is reported as 7–8% of overall MMD patients. The penetrance rate of MMD in heterozygotes is as low as one per 150–300 [18], whereas the penetrance rate of MMD in homozygotes was calculated to be over 78% [19].

RNF213 Variant Homozygosity and Systemic Vasculopathy

The reason behind the specific site of vascular system involvement is one of the unanswered questions in MMD. Genetic and related changes in circulating factors confer pathophysiological effects on the systemic vessels, as well as major vessels of the circle of Willis. Site specificity and sparing of systemic vessels cannot be explained. There is a possibility that patients

Fig. 1 Spectrum of RNF213
vasculopathies. MMD,
moyamoya disease
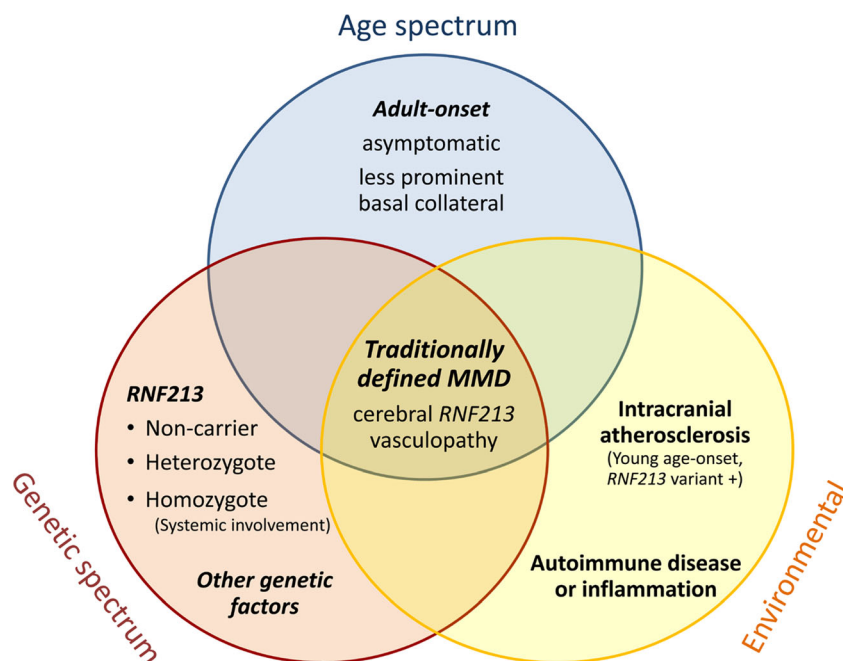
with *RNF213* variants might present with phenotypes other than MMD. *RNF213* vasculopathy could be a systemic disease, with MMD as a central nervous system subtype, especially in homozygous individuals.

Extracranial involvement of MMD has been described in case reports of coronary [21, 22], pulmonary [9], and renal artery stenosis in 7.9% of pediatric MMD patients [23], although genetic information was unavailable. Very recently, Fukushima and colleagues reported two cases of MMD and pulmonary artery stenosis, with homozygosity for R4810K variant [9]. One of them also had renal artery stenosis. It has been suggested that R4810K variant causes classical MMD when present in a heterozygous state, but the same variant results in MMD and systemic vascular diseases when present in the homozygous state, in a gene dosage-dependent manner [9]. We recently reported five index cases and their families harboring homozygous and heterozygous R4810K variants with various manifestations of vascular involvement [10]. Homozygous patients showed a very unique pattern of diffuse narrowing of the aorta and iliofemoral arteries, together with stenosis of renal, celiac, or peripheral pulmonary arteries, regardless of the presence or absence of MMD. Heterozygous patients were mostly asymptomatic or had isolated MMD. Therefore, R4810K is associated with a high penetrance of systemic vasculopathy in homozygous patients, and a low penetrance of MMD in heterozygous patients, suggestive of a gene-dosage effect.

It is possible that a significant proportion of homozygous patients are being treated without consideration of the particular *RNF213* variants present. R4810K-related vasculopathy might be important from a therapeutic view point. For example, stent insertion, which is an option for medically

intractable intracranial atherosclerotic stenosis, could be harmful for MMD patients. There have been several case series of stent insertion in MMD that showed occlusion by in-stent restenosis due to progressive intimal hyperplasia or serious adverse effects [24–27]. The same may be true for systemic vasculopathy related to *RNF213* variants. While arterial stenosis in fibromuscular dysplasia responds well to balloon angioplasty and atherosclerotic renal artery stenosis to stenting, balloon angioplasty or stenting in R4810K-related vasculopathy might result in immediate elastic recoil or progressive restenosis [10]. In this case, bypass surgery for renal artery stenosis could be considered for R4810K variant–related vascular stenosis, similar to that for MMD.

Genetic Factors Aside from the *RNF213* R4810K Variant

RNF213 R4810K is not a susceptibility variant for MMD in Western populations or South Asians. Several non-R4810K variants (rs148731719 and rs397514563) were recently found in Caucasian, and East and South Asian cases with MMD [7, 17, 28, 29]. In addition, clinical manifestations and possibly angiographic findings may differ between Western populations and East Asians [30]. The R4810K variant is reportedly related to ischemic-type MMD, whereas non-R4810K variants (especially A4399T) are associated with hemorrhagic-type MMD [28]. Further genetic studies in these populations are required.

Combinatorial interactions between *RNF213* variants and other gene variants must be considered. A recent case series of European familial MMD showed rare candidate variants of *RNF213* and *PALD1* within the same families, suggesting that variants in these two genes might act synergistically [31]. The

penetrance of MMD in carriers was incomplete, at around 25%, suggesting that additional genetic or environmental factors, other than these rare *RNF213* variants, are needed to develop MMD [31]. In addition, the interaction of *RNF213* variants with other genes or the environment may be the cause of the heterogeneity in the *RNF213* phenotype. Moreover, owing to the cell/tissue-specific expression pattern of non-coding RNAs and their remarkable stability in peripheral blood, a number of studies have highlighted the role of circulating non-coding RNAs in angiogenesis and atherogenesis [32]. A prospective study (ClinicalTrials.gov Identifier NCT02074111) is ongoing, to evaluate the levels of circulating microRNAs with respect to *RNF213* and caveolin-1 gene polymorphisms in MMD.

Environmental Spectrum

Environmental Factors

Beside genetic influence, additional insult may be required to induce MMD. First, from an epidemiological view point, the incidence rate of MMD is lower than that of carriers of *RNF213* variants. Second, recent in vivo experiments using genetically engineered *Rnf213* mice, such as *Rnf213*-deficient mice [33] or *Rnf213*-knock-in mice [34], addressed the mechanism underlying *RNF213* variation in the development of MMD pathology. However, the mice did not develop MMD under normal conditions. These negative results are consistent with the low penetrance rate of *RNF213* polymorphisms in patients with MMD, and may indicate the importance of environmental factors in addition to genetic factors [35]. Ito and colleagues subjected *Rnf213*-deficient mice to ischemic insult and found that post-ischemic angiogenesis was significantly enhanced in mice lacking *Rnf213*, after chronic hindlimb ischemia [36]. This suggests the potential role of defective *RNF213* in the development of abnormal vascular networks in chronic ischemia. Third, clinical data has also shown that environmental factors, such as an autoimmune response and infection/inflammation, may be associated with the angiographic features of MMD [35]. For example, autoimmune thyroid disease has been reported in different MMD populations (i.e., pediatric and adult-onset MMD, East Asians, and Western populations) and may be involved in MMD development [37–39]. *RNF213* may be a downstream mediator of the IFN-β signaling pathway in endothelial cells. Carriers of the R4810K may be susceptible to cerebral hypoxia because of insufficient angiogenesis, if inflammation and hypoxia occur simultaneously [40]. Pro-inflammatory cytokines activate *RNF213* transcription, and *RNF213* functions as a common downstream effector of the PI3 kinase-AKT pathway, in endothelial angiogenesis [41]. These in vitro experimental data suggest that although MMD is not an inflammatory disease, inflammation may play an important role in MMD

development, and that *RNF213* plays a unique role in endothelial cells with respect to gene expression in response to inflammatory signals from the environment. These clinical and preclinical observations may represent the "two-hit theory," which is apparent in a variety of disorders [35]. *RNF213* variation could lead to vascular fragility, which may increase the vulnerability of vessels to hemodynamic stress and secondary insults [35].

Intracranial Atherosclerosis and *RNF213* Variants

Both intracranial atherosclerosis and MMD are prevalent in Asians. Although several studies have described the role of *RNF213* in vascular development [6, 7], there is limited data on its role in atherosclerotic diseases, and no genetic factors specific to intracranial atherosclerosis have been reported. Patients with *RNF213* variation may be prone to atherosclerosis. Miyawaki et al. and Kamimura et al. tested for R4810K in patients with intracranial major artery stenosis without signs of MMD. The variant was present in 21.9–24.3% of patients with non-moyamoya intracranial stenosis [42–44]. Similarly, Matsuda et al. performed *RNF213* genotyping and vascular studies in 59 relatives of MMD patients. Six of 34 individuals with R4810K showed intracranial steno-occlusive lesions, whereas none of 25 individuals without the variant showed vascular lesions [45]. We recently tested whether *RNF213* is also a susceptibility gene for intracranial atherosclerosis in patients whose diagnosis had been confirmed by conventional angiography (absence of basal collaterals) and high-resolution magnetic resonance image (HR-MRI) (i.e., the presence of intracranial plaque and absence of MMD features) [8]. The results confirmed that R4810K was present in a quarter of patients with intracranial atherosclerosis, suggesting that *RNF213* is a susceptibility gene, not only for MMD but also for intracranial atherosclerosis in East Asians [8]. Among patients with intracranial atherosclerosis, R4810K carriers were younger, more often women, and more likely to have a family history of MMD and proximal anterior circulation stenosis than non-carriers [8, 44]. A recent large population study in Japan, evaluating R4810K in various stroke subtypes, confirmed that only large artery disease was associated with this variant. Patients with both R4810K and large artery disease showed lower age of stroke onset, female predominance, and anterior circulation distribution, compared with non-carriers [46].

In addition, other studies and ours showed that R4810K is associated with smaller sized intracranial arteries, suggesting impaired vasculogenesis [47, 48]. Hongo et al. measured the outer diameter of the middle cerebral artery (MCA) in a small cohort and showed that the outer diameter of the MCA was smaller in R4810K carriers [47]. Our HR-MRI study also showed that negative remodeling involves all the intracranial arteries measured not only the stenotic MCA segments but also the contralateral MCA, distal internal carotid artery, and

basilar artery in patients with this variant [48]. Hemodynamic studies have shown that, in the presence of intracranial atherosclerosis, the R4810K variant predisposes the smaller intracranial arteries to hemodynamic compromise [48].

Evaluation and Treatment in MMD Patients

The spectrums related to MMD may have clinical implications for diagnostic and therapeutic approaches in patients. In addition to the current paradigm of luminographic evaluation (cerebral angiography to identify moyamoya vessels) and bypass surgery to enhance collateral flow, the following diagnostic and therapeutic strategies should be considered, based on variations in *RNF213*-related vasculopathies.

Evaluation of MMD Patients and Their Families

Unlike in childhood MMD, genetic/molecular or dedicated imaging, rather than angiographic findings, could be particularly helpful in diagnosing MMD in adult patients with presumed MMD, in whom angiographic features of moyamoya vessels are not prominent. Many etiologies can cause intracranial arterial steno-occlusion in adults. For example, HR-MRI can show the characteristic features of MMD (a small vessel diameter, thin vessel wall, and diffuse concentric enhancement, which are consistent with pathogenesis and pathologic features) [49] and exclude other causes (e.g., plaque or dissection) [5, 49]. These features were observed not only with typical angiographic features of basal collaterals but also without them.

Systemic vascular evaluation of the pulmonary, renal, coronary, mesenteric, and aortoiliac arteries should be considered in family members of MMD patients when they present symptoms (i.e., shortness of breath, angina) or show signs of specific systemic vascular involvement (i.e., hypertension at a young age). Systemic evaluation should also be considered in R4810K homozygotes because of the high penetrance rate of systemic vascular involvement. In our institute, polyvascular CT angiography is being used to screen for systemic involvement, especially in R4810K homozygous MMD patients.

Practice guidelines for genetic testing and counseling in MMD patients and family members have not yet been established. Genetic testing in MMD should only occur in the context of genetic counseling and be supported by expertise in this area. A ≥ 3 generation family history should be obtained, that focuses not only on stroke or MMD but also systemic vascular involvement, such as peripheral pulmonary artery stenosis and renal artery stenosis. Patients should be informed that MMD is a familial disorder with low penetrance, and only one in 150–300 R4810K carriers will develop MMD. Genetic testing should be considered in East Asian patients with MMD and a family history of MMD, on both the paternal and maternal sides, who are potentially

homozygous for R4810K. Genetic testing might be considered in patients with systemic vasculopathy, who have a family history of MMD. On the contrary, genetic testing in asymptomatic adult MMD patients is not advisable. The benefits of genetic testing in non-East Asian populations are settled. In addition, blood tests for thyroid function and thyroid autoantibodies could be considered in patients with presumed MMD.
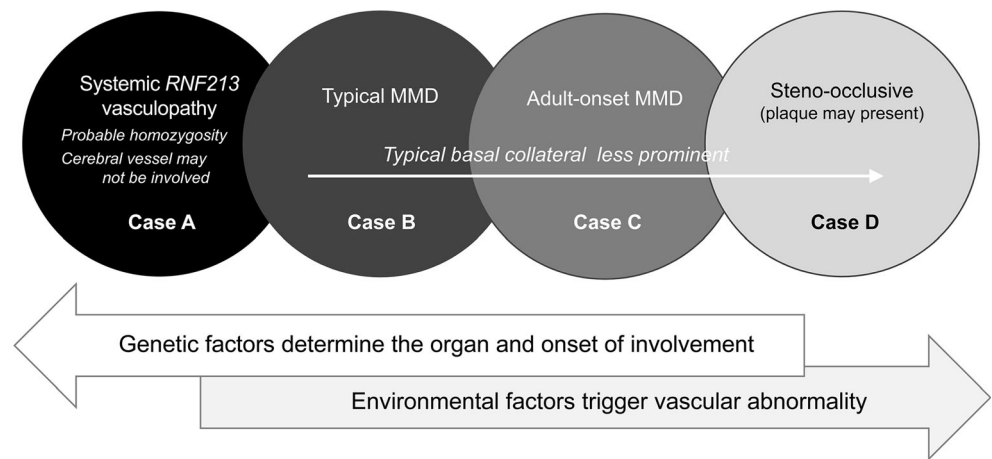
Treatment of Underlying Pathophysiology

At present, surgical re-vascularization is the mainstay of MMD treatment. However, surgical treatments pose a risk for perioperative ischemic complications and/or cerebral hyperperfusion syndrome [50]. With a better understanding of MMD pathophysiology, non-surgical approaches targeting MMD pathogenesis may become available to halt or slow disease progression [51]. Possible non-surgical approaches may include the application of certain trophic factors or chemicals that increase angiogenesis [52], anti-cancer drugs to decrease smooth muscle cell proliferation [53], retinoid to attenuate growth factor–stimulated smooth muscle cell migration and proliferation [54, 55], microRNA-based therapies to inhibit microRNAs related to MMD, [56, 57], and stem cell therapy to replace or restore function of endothelial or smooth muscle progenitor cells which are impaired in MMD [58–60]. However, none of these approaches has been tested in MMD patients.

In addition, strategies targeted at increasing caveolin-1 levels could be candidate therapies for MMD [61]. Caveolin-1, a scaffolding protein of the caveolae plasma membrane, is involved in the pathogenesis of cancers and vascular diseases [62]. Caveolin-1 overexpression enhances caveolae generation and accelerates capillary tube formation by nearly threefold, while caveolin-1 downregulation reduces capillary formation in vitro and in vivo, and is associated with pathological angiogenesis [62–64]. A decreased serum level of caveolin-1 has been reported to be a novel biomarker for MMD [65]. A recent HR-MRI study showed that serum levels of caveolin-1 were correlated with the degree of negative remodeling of major intracranial vessels in MMD patients [66].

Antiplatelet agents are widely used in patients with MMD. Although hemodynamic compromise is the major determinant of stroke in MMD patients, a multimodal MRI study showed that embolic phenomena played an important role in acute ischemic stroke in MMD patients [67]. Given the role of antiplatelet agents in microembolism, in patients with large intracranial stenosis, the short-term use of appropriate antithrombotic agents could be considered for MMD patients with recurrent embolic strokes. Cilostazol, a PDE3 inhibitor, has both antiplatelet and vasodilator action, activates bone marrow–derived endothelial progenitor cells, and inhibits smooth muscle cell proliferation [68, 69]. Statin treatment was reported to decrease matrix metalloprotease-9 levels, to

**Fig. 2** Four spectrums of RNF213 vasculopathy

Systemic *RNF213* vasculopathy
Probable homozygosity
Cerebral vessel may not be involved
Case A

Typical MMD
Case B

Typical basal collateral less prominent

Adult-onset MMD
Case C

Steno-occlusive (plaque may present)
Case D

Genetic factors determine the organ and onset of involvement

Environmental factors trigger vascular abnormality

inhibit neointima formation, and to increase circulating endothelial progenitor cells [70, 71].

The role of *RNF213* in controlling vascular risk factors is unknown. The R4810K variant might influence vascular risk factors, such as hypertension [72], and could also lead to vascular fragility, increasing vulnerability of vessels to

hemodynamic stress and secondary insults [35]. A long-term follow-up of angiographic-confirmed MMD patients showed that diabetes, an important vascular risk factor for intracranial atherosclerosis, was the only independent predictor of ischemic stroke recurrence in patients with MMD [73]. These features suggest that vascular risk factor control may be important in

Fig. 3 **a** A typical case of moyamoya disease (MMD). A 9-year-old female with a family history of MMD presented recurrent hemiparesis during hyperventilation and crying. Angiography shows occlusion of major intracranial vessels and prominent basal collateral circulations. **b** A 35-year-old heterozygote female with a healthy vascular risk factor profile presented with transient hemiparesis. Angiography showed no basal collaterals and high-resolution MRI showed eccentric enhancing plaque and negative remodeling, suggestive of RNF213-related premature atherosclerosis
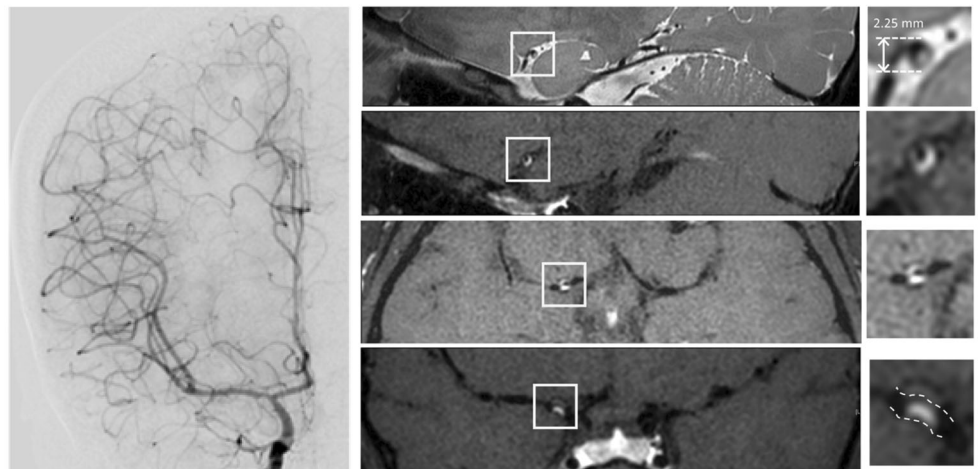
(A) Case B
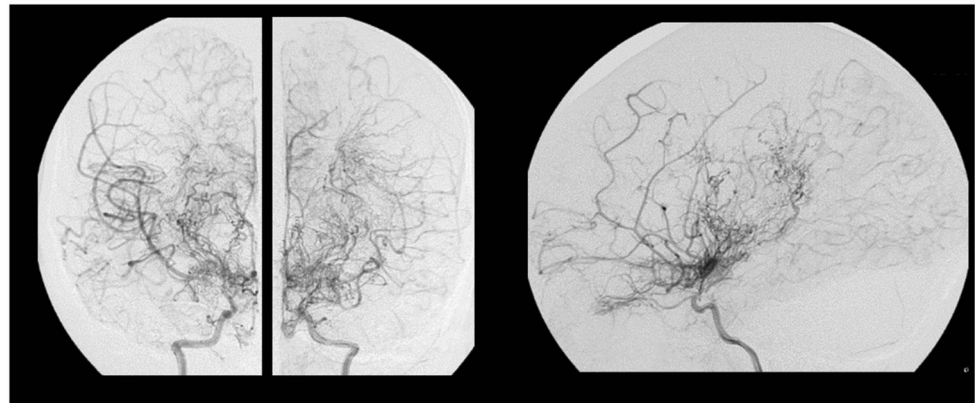
(B) Case D

Fig. 4 Genetic factors may determine differential features within a family with MMD. (A) A 64-year-old female heterozygote had history of stroke at her age of 50. Angiography showed bilateral carotid occlusion and less prominent moyamoya vessels. (B) The patient's 27-year-old homozygote son showed systemic involvement, including pulmonary, coronary, renal, and superior mesenteric artery. Computed tomography showed a small aorta. Cerebral involvement was not observed in this patient

(A) Case C

F/64

M/27

(B) Case A
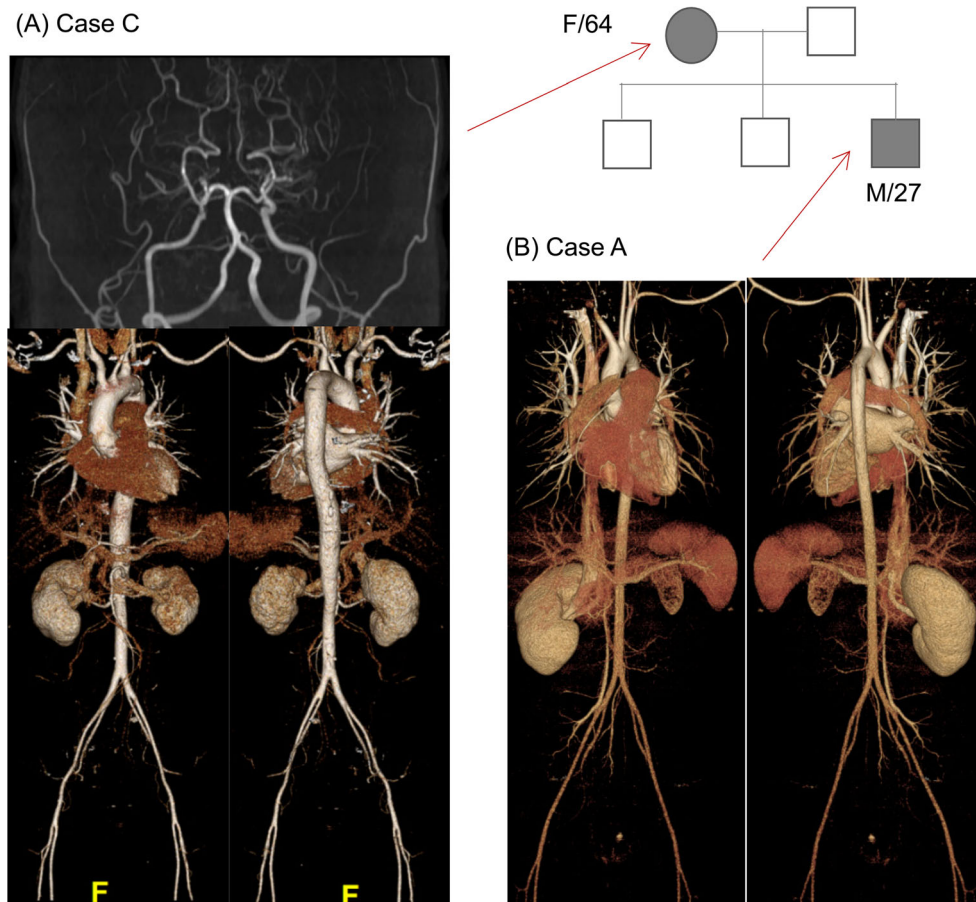
subjects with intracranial stenosis and *RNF213* variant carrier status.

Conclusions and Perspectives

Our literature review advocates that MMD requires redefinition, from childhood and cerebral vasculopathy to a broader spectrum vasculopathy affecting both cerebral and systemic vessel systems. Figure 2 shows four spectrums of RNF213 vasculopathy and their examples are provided in Figs. 3 and 4. Both genetic and environmental factors may play important roles in the development and phenotype of RNF213 vasculopathy, through complex mechanisms. Continuous efforts are required for pathophysiology-based diagnoses and treatments, which will benefit from collaboration between both stroke and vascular physicians, and the cooperation of all those involved, from the hospital bed through to the laboratory bench.

Compliance with Ethical Standards

Conflict of Interest   The authors declare that they have no conflict of interest.

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