—Review—

RNF213-Related Vasculopathy: Various Systemic Vascular Diseases Involving *RNF213* Gene Mutations: Review

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Moyamoya disease (MMD) is a cerebrovascular disorder that is predominantly observed in women of East Asian descent, and is characterized by progressive stenosis of the internal carotid artery, beginning in early childhood, and a distinctive network of collateral vessels known as "moyamoya vessels" in the basal ganglia. Additionally, a prevalent genetic variant found in most MMD cases is the p.R4810K polymorphism of *RNF213* on chromosome 17q25.3. Recent studies have revealed that *RNF213* mutations are associated not only with MMD, but also with other systemic vascular disorders, including intracranial atherosclerosis and systemic vascular abnormalities such as pulmonary artery stenosis and coronary artery diseases. Therefore, the concept of "*RNF213*-related vasculopathy" has been proposed. This review focuses on polymorphisms in the *RNF213* gene and describes a wide range of clinical and genetic phenotypes associated with *RNF213*-related vasculopathy. The *RNF213* gene has been suggested to play an important role in the pathogenesis of vascular diseases and developing new therapies. Therefore, further research and knowledge sharing through collaboration between clinicians and researchers are required. (J Nippon Med Sch 2024; 91: 140–145)

Key words: internal carotid artery, *RNF213*, *moyamoya disease*, *vasculopathy*

Introduction

Moyamoya disease (MMD) is characterized by cerebral ischemia resulting from the stenosis or occlusion of the terminal portion of the bilateral internal carotid artery and the formation of a network of small abnormal vessels in the basal ganglia that serve as collateral blood vessels[1]. MMD is typically diagnosed based on distinctive MRI, MRA, and angiographic findings[2]. The annual incidence of MMD is low in Europe and the United States but high in East Asia, with recent increases in Japan, Korea[3], and China[2]. Since MMD often occurs within families, genetic mutations are considered to play a role[2,4]. Herein, we discuss the detection of *RNF213* and its association with systemic vascular diseases[2,5]. We also provide an overview of current research[6,7] and summarize the functions of the *RNF213* protein and its role in "*RNF213*-related vasculopathy," particularly clinical phenotypes, with the goal of contributing to research in multiple fields.

Creation of the "*RNF213*-Related Vasculopathy" Concept

After the discovery that chromosome 17q25.3 is involved in moyamoya disease[8], the R4810K polymorphism (p.Arg 4810Lys) in the ring finger protein 213 (*RNF213*, mysterin) gene on chromosome 17q25.3 was identified as a

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Table 1 Systemic vascular lesions reported to be associated with RNF213

Organ	Vessels	Disease
Brain	Carotid artery	Moyamoya disease
		Atherosclerotic intracranial carotid stenosis
		Cerebral aneurysm
Lung	Pulmonary artery	Pulmonary arterial hypertension
		Pulmonary artery stenosis
Abdominal	Renal artery	Renal artery stenosis
Heart	Coronary artery	Coronary artery occlusive disease

susceptibility gene for MMD in East Asian populations using genome-wide linkage and exome analysis[2,9]. The p.R4810K polymorphism (*RNF213* c.14576G>A, rs 112735431), the founder of moyamoya disease in Asia, including Japan, is a missense mutation that changes the 4,810th amino acid residue of *RNF213* (arginine) to lysine[2,9–11]. *RNF213* or its polymorphism is found in approximately 80% of Japanese[1,11] patients with moyamoya disease, 80-90% of Korean patients, and 20-30% of Chinese patients, but it is not prevalent in Western countries[12–14]. R4810K is more prevalent among Japanese individuals, while A4399T is more frequent in individuals of Chinese descent[15]. Reports from Korea suggest that 4950G > A (rs371441113) is the most common variant[3]. Thus, *RNF*213-related vasculopathy includes a range of genetic polymorphisms. However, the precise details of these variants remain unclear. The R4810K polymorphism is absent in Caucasians in the general population but is present in 1.5% of carriers in Japan and Korea and 0.5% in China, suggesting that it is a variant specific to East Asia[4,16]. In addition to the p.R4810K polymorphism, several missense mutations, including p.P4007R and p.T4589P, have been identified in Chinese families with moyamoya disease[12,15,17,18]. In contrast, a rare variant of *RNF213*, which accumulates in the C-terminal region of the RING finger domain (amino acid numbers: 3997-4093), has been reported in Caucasian individuals with MMD[11,19]. Therefore, *RNF213* is a disease susceptibility polymorphism shared across racial groups, although exhibiting variations in its mutations[12,18,20].

This polymorphism has been associated with intracranial arterial stenosis, occlusion, and atherothrombotic stroke in East Asia, even in cases that did not meet the diagnostic criteria for MMD[7,11,21–23]. Recently, the *RNF213* polymorphism has been shown to be associated with both intracranial arteries and arteries throughout the body, including the cervical[21,24], coronary[25], pulmonary[26–28], abdominal visceral[29], and peripheral arteries, and has been reported to be associated with vascular diseases throughout the body, resulting in *RNF213*-related vasculopathy, which may be the most significant risk factor for vascular diseases[5,12,30,31] (**Table 1**). Most lesions are stenotic and have vascular origins. However, they are also associated with aneurysms[7,32]. Based on this, Okazaki et al.[21] proposed "RNF213-related vasculopathy" as a new disease spectrum in 2019. More recently, moyamoya disease and intracranial carotid stenosis, as well as lesions of the coronary arteries, pulmonary arteries, and abdominal aorta have been identified as "*RNF213*-related vasculopathy"[21,33,34]. Analysis of these systemic cardiovascular diseases based on the prevalence of *RNF213* variants may lead to a more detailed classification of cardiovascular diseases and the elucidation of their underlying pathophysiologies. In this article, we review the functions of *RNF213* encoded by the *RNF213* gene and discuss the relationship between *RNF213* polymorphisms and diseases in various vascular regions. It has been proposed that integrating *RNF213*-related vasculopathy into fields such as clinical medicine and genetic diagnostics will help advance research.

RNF213 Gene (Mysterin) Function

Moyamoya disease leads to progressive arterial stenosis and occlusion of limited intracranial vessels bilaterally, resulting in cerebral ischemia and infarction in pediatric patients, and hemorrhage due to the disruption of collateral channels in adult patients[1,8,35]. The lesions exhibit an abnormal proliferation of vascular smooth muscle cells and infiltration of the vascular intima, resulting in intimal thickening and lumen narrowing[36,37]. The *RNF213* gene comprises 5,256 amino acids and is located on the long arm of chromosome 17[2]. Molecular cloning led to the discovery, naming, and functional analysis of mysterin (MMD-associated AAA+ and RNF protein), also

known as *RNF213* and ALO17[38]. Encoding a giant protein with a molecular mass of 591 kDa, *RNF213* contains a core sequence with a RING finger domain, characteristic of E3 ubiquitin ligase, and AAA ATPase domain[19,38]. E3 ubiquitin ligase ubiquitinates substrate proteins to facilitate their degradation by the proteasome, and AAA ATPase is involved in this process[38,39]. Zebrafish phenotypes expressing mysterin suppressors were analyzed, and intracellular binding proteins were sought to identify mysterin substrates and functions. Many early developmental abnormalities have been detected, and mysterin-stabilizing factors were successfully identified[39]. Mysterin is also found in intracellular lipid droplets and is believed to stabilize them by excluding adipose triglyceride lipase (ATGL), inhibiting lipolysis[40]. No functional difference was detected between wild-type mysterin and the East Asian p.R4810K mutant[38].

RNF213 is thought to help regulate vascular endothelial function and angiogenesis, as *RNF213* knockout zebrafish show defects in eye and brain vessel formation[39,41]. In contrast, the *RNF213* gene is believed to induce vascular abnormalities in collaboration with environmental factors, such as infection and autoimmunity, or with other genes, as *RNF213* knockout mouse models develop normally without exhibiting the intracranial vascular phenotype characteristic of moyamoya disease[5,42].

The clinical effects of this rare *RNF213* variant have also been reported[29]. Patients without p.R4810K had an earlier age of onset (7.1±3.7 vs. 4.4±0.9 years), often beginning in infancy, and a higher percentage of infarcts (24.0 vs. 7.6%) and lower percentage of transient ischemic attacks (36.0 vs. 71.7%) than those with the heterozygous variant. Eight rare mutations other than p.R4810K were isolated from 25 patients without p.R4810K mutations. Three of the four pediatric-onset patients had variants other than p.R4810K, with more severe functional effects[29]. Similarly, Ishigami et al.[43] reported more bilateral lesions ($p = 0.008$) and progressive condition (Suzuki grade ≥ 4; $p = 0.017$) in the heterozygous (GA) group. Multivariate logistic regression analysis showed that younger age at diagnosis ($p < 0.001$; odds ratio [OR], 0.936; 95% CI, 0.914-0.959) and GA ($p = 0.017$; OR, 3.326; 95% CI, 1.237-8.941) were significantly associated with bilateral lesions. Patients with MMD and *RNF213* heterozygous mutations are at risk of contralateral cerebral infarction if one side of the brain is symptomatic. Torazawa et al.[44] reported that 72% of patients were GA for p.Arg4810 Lys and 28% were wild-type (GG). The GG and p.Ala 4399Thr hemispheres had more bleeding events ($p = 0.028$), and GG was more likely to cause de novo bleeding in the asymptomatic hemisphere than GA (adjusted hazard ratio [aHR], 5.36). This indicates that GG with p. Arg4810Lys is a risk factor for de novo bleeding in asymptomatic hemispheres with MMD.

RNF213 Variants and Head and Neck Vascular Disease

RNF213 p.Arg4810Lys variant is associated with ischemic stroke, particularly large artery stroke. In moyamoya disease, p.Arg4810Lys is a risk factor for ischemic stroke in general[21]. Intracranial atherosclerosis and moyamoya disease are prevalent in Asian populations. Limited data are available regarding the role of *RNF213* in atherosclerotic diseases, and no genetic factors specific to intracranial atherosclerosis have been reported. In East Asia, including Japan, cerebral infarction attributed to atherothrombotic intracranial artery stenosis is more frequent than in Western populations. While this regional difference was initially thought to be influenced by environmental factors including diet, the higher incidence of cerebral infarction due to intracranial atherosclerosis among East Asians in the U.S. suggests a possible genetic contribution. Similar findings have been reported in Korean and Chinese populations, suggesting a role for *RNF213* p.R 4810K polymorphism in the increased prevalence of intracranial arterial stenosis across East Asia[45].

Miyawaki et al.[11], Uemura et al.[46], and Murai et al.[7] examined the presence of the R4810K mutation in patients with intracranial aortic stenosis without signs of MMD. This variant was detected in 21.9-24.3% of patients with non-MMD intracranial stenosis[11,47]. Among the patients with intracranial atherosclerosis, R4810K carriers tended to be younger, more frequently female, and had a higher likelihood of a family history of proximal anterior circulation stenosis than noncarriers[47]. Ischemic stroke patients with the p.R4810K were recently found to have smaller vasculature in the middle cerebral artery and reduced diameters in the common carotid, cervical internal carotid, and cervical vertebral arteries[48].

The influence of *RNF213* polymorphisms extends beyond stenotic lesions in head and neck vessels. In a study involving a small number of Korean patients, p.R 4810K was associated with intracranial artery dissection[49]. Additionally, in a study of French Canadian participants, the *RNF213* genetic end polymorphism (rs6565666) was linked to intracranial aneurysms[32]. While some reports from Japan have refuted the connection between cerebral aneurysms and *RNF213*[11], others have identified an association between *RNF213* and saccular aneurysms of the

internal carotid artery[7]. Given that moyamoya disease primarily affects the terminal portion of the internal carotid artery, this suggests a potential vascular specificity for the action of this mutation[50]. In summary, *RNF213* polymorphisms have been implicated in various vascular diseases of the head and neck region. This should be considered when evaluating and managing cerebrovascular disorders.

RNF213 Gene and Coronary Artery Disease

In a recent case-control study involving Japanese participants[6], patients with coronary artery disease had significantly more minor variant alleles than controls (2.04 vs. 0.98%; OR, 2.11; p = 0.017). After adjustment for risk factors, the association remained significant (OR, 2.90; 95% CI: 1.37-6.61; p = 0.005). In a replication study, the association remained significant after adjusting for age and sex (OR, 4.99; 95% CI: 1.16-21.53; p = 0.031), but not after further adjustments for risk factors (OR, 3.82; 95% CI: 0.87-16.77; p = 0.076)[6]. However, a subsequent genome-wide association analysis of 168,000 individuals demonstrated an association between p.R4810K and coronary disease. This association was identified alongside PCSK9, APOB, HHIPL1, and LDLR (OR, 1.61; 95% CI: 1.46-1.78; P = 2.3 × 10-21)[25]. Subsequent reports have been sporadic[24].

RNF213 and Pulmonary Artery Disease

Peripheral pulmonary artery stenosis and pulmonary arterial hypertension (PAH) are associated with *RNF213*-related lung vasculopathy. In a Japanese case of moyamoya disease, homozygous variants of *RNF213*p.R 4810K were reported to cause severe pulmonary hypertension, indicating their roles as related genes[51]. p.R4810K heterozygosity was detected in 9.2% of patients with idiopathic PAH without obvious pathological mutations in known causative genes such as BMPR2[28]. Interestingly, these patients did not present with intracranial vascular lesions[28].

Hiraide et al.[52] reported that 7.9% of *RNF213* carriers responded poorly to treatment with pulmonary vasodilators and exhibited a poorer life expectancy than BMPR2 mutation-positive patients. Two of five patients with peripheral pulmonary artery stenosis (PPAS) and homozygous for the RNF213 p.Arg4810Lys variant did not have moyamoya disease[27]. PPAS was found in three of 306 (0.98%) patients with MMD/quasi-MMD who were RNF 213 wild-type, heterozygous, and homozygous for MMD/quasi-MMD[26]. The association between PPAS and the homozygous polymorphism c. 14576G > A was statistically significant (p = 0.0018) in patients with MMD/quasi-MMD. The embryology of these systemic vessels has also been discussed[53]. The neural crest is a transient structure present in early embryogenesis and is involved in the development of the internal carotid, coronary, and some pulmonary arteries. Within the cranium, smooth muscles of the vertebrobasilar arterial system in the posterior circulation, which are not neural crest-derived, are derived from the smooth muscles of the petrous to the terminal part of the ICA vessel wall to the periphery. Therefore, RNF-related vascular diseases may be associated with the neural crest[30].

Conclusion and Future Perspective

In this report, we outline the relationship between *RNF 213*, a disease susceptibility gene for moyamoya disease, and systemic diseases. The emerging concept of *RNF213*-related vasculopathy is gaining acceptance due to increased disease recognition and advances in genetic analysis. The p.R4810K polymorphism can lead to various disease phenotypes depending on other genetic and environmental factors. Therefore, elucidating the function of mysterin and developing disease prevention and treatment methods based on this understanding is highly desirable. Moyamoya disease presents as cerebral infarction in children, and the incidence of intracranial hemorrhage increases with progression into adulthood. Recently, surgical revascularization has been effective in preventing recurrent intracranial hemorrhage; however, its relationship with RNF213 remains unclear. This requires further research.

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