

Role of Ring Finger Protein 213 in Moyamoya Disease

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Abstract

Objective: The aim of this study was to help people comprehensively understand the research advances related to ring finger protein 213 (*RNF213*) in moyamoya disease (MMD) and to understand the disease at the molecular level to provide a new perspective of the diagnosis of the disease.

Data Sources: This review was based on data in articles published between 2005 and 2015 that were retrieved from the PubMed database. The search terms included *RNF213*, MMD, intracranial major artery stenosis /occlusion (ICASO), genotype, phenotype, mutant and variants, and the combinations of these terms.

Study Selection: Articles related to MMD and *RNF213* were selected for review, and we also reviewed publications related to ICASO.

Results: *RNF213* is not only associated with MMD but also associated with intracranial major artery stenosis. In addition, *RNF213* variants exhibit apparent ethnic diversity; specifically, the c.14576G>A variant is mainly detected in Korean, Chinese, and Japanese populations, particularly the latter population. The genotypes of *RNF213* correlate with the phenotypes of MMD; for example, the homozygous c.14576G>A variant is associated with early-onset, severe symptoms, and an unfavorable prognosis. Furthermore, the *RNF213* c.14576G>A variant should be considered during the diagnosis of MMD because no patients with quasi-MMD have been reported to carry the *RNF213* c.14576G>A variant whereas 66 of 78 patients with definite MMD have been found to carry this variant.

Conclusions: The growing literature demonstrates that MMD is primarily caused by the synergy of genetic and environmental factors, and unknown genetic modifiers might play roles in the etiology of MMD. Further research should be conducted to clarify the pathogenic mechanism of MMD.

Key words: Moyamoya Disease; Research Progress; Ring Finger Protein 213; Variant

INTRODUCTION

Moyamoya disease (MMD) is an infrequent disease that is characterized by progressive occlusive or stenotic lesions at the distal portions of internal carotid arteries and an aberrant vascular network at the base of the brain that resembles “puffs of smoke” on angiography.^[1,2] MMD has captured increasing and intensive attention from neurosurgeons because it has been deemed to be a major cause of stroke in adults and particularly in children^[3-5] despite its relative low incidence. Although a large number of studies have been conducted, the actual etiology and pathogenesis remain extremely unclear. However, in recent years, ring finger protein 213 (*RNF213*) was identified as a susceptibility gene among East Asian populations,^[1,6] which resulted in a shift of people’s attention to the relevant genetic factors. *RNF213* encodes a 596,000 protein that includes an alpha-2-macroglobulin, an AAA-type ATPase and ring finger domains from its amino to

carboxyl termini.^[7] Kamada *et al.*^[11] stated that the *RNF213* c.14576G>A variant is detected in 95% of familial MMD cases and 79% of sporadic patients. Nevertheless, a portion of MMD patients do not carry the c.14576G>A variant and this portion is higher in western countries. It is generally accepted that MMD is caused by genetic and environmental factors. It is disappointing that we have been unable to determine whether MMD is caused by a synergy of genetic

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Received: 15-06-2016 **Edited by:** Li-Shao Guo
How to cite this article: Ma YG, Zhang Q, Yu LB, Zhao JZ. Role of Ring Finger Protein 213 in Moyamoya Disease. Chin Med J 2016;129:2497-501.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.191824

and environmental factors or some other unknown causes. Further research should be directed toward illuminating the cause of MMD and identifying a more effective therapeutic strategy. The aim of this literature review is to help people comprehensively understand the research advances related to *RNF213* in MMD patients.

FEASIBLE PATHOGENIC MECHANISM OF MOYAMOYA DISEASE RELATED TO RING FINGER PROTEIN 213

Because the *RNF213* c.14576G>A variant is detected in 95% of familial MMD cases and 79% of sporadic patients,^[1] an increasing number of researchers have focused on mimicking MMD in mice via knock-in and knock-out technologies. However, Sonobe *et al.*^[8] did not discover any modification of angiogenesis after they generated mice lacking *RNF213*. Soon after, this same team generated mice with the R4859K mutation of *RNF213* and obtained results similar to those of the earlier study.^[9] To determine whether ischemia can result in cerebrovascular abnormalities in knockout mice, these authors redesigned their experiment and once again found no changes.^[10] Consequently, numerous researchers have insisted that MMD is primarily triggered by both genetic and environmental factors despite the ambiguous causes. Previous studies of environmental factors and the development of the MMD have emphasized the latent role of varicella zoster virus infection.^[11,12] A study of MMD and inflammatory signals suggested that *RNF213* is associated with the immune response.^[13] In addition, two groups have recently demonstrated that interferon, which is invariably induced by inflammatory and immune responses, can stimulate the expression of *RNF213*.^[13,14] Based on the two studies mentioned above, we have adequate reason to believe that the MMD is not triggered by a single genetic factor but rather is triggered by both environmental and genetic factors. Another examination conducted by Sato-Maeda *et al.*^[15] indicated that the *RNF213* gene is also expressed during transient middle cerebral artery occlusion, particularly in neurons, and this result provided new insight into the role of *RNF213* in neuroprotection. This result also partially elucidates why MMD patients are prone to ischemic lesions. This subject is introduced in the next section.

Several studies have reported that *RNF213* c.14576G>A variant carriers have reduced angiogenesis abilities, which contrast sharply with the pathologic characteristics of MMD. However, one study suggested that transient middle cerebral artery occlusion can activate the expression of *RNF213*.^[15] These findings indicate the possible occurrence of a vicious cycle in which the expression of *RNF213* aggravates ischemia, and ischemia induces the expression of *RNF213*. Further research is certainly indispensable to confirming this hypothesis. Hitomi *et al.*^[16] induced pluripotent stem cells (iPSCs) using the fibroblasts of MMD patients and healthy controls in an effort to detect the associated angiogenic activities and discovered that the proliferation abilities of the cells from the patients and carriers were reduced compared with those of the cells from the controls.

Therefore, how the *RNF213* c.14576G>A variant gives rise to reduced angiogenesis has become an important question. From our perspective, this reduced angiogenesis ability might be caused by a mitotic abnormality, the pattern described by Hitomi *et al.*^[17] or through the regulation of the expression of matrix metalloproteinase 1.^[13] Although we know of the critical connection between *RNF213* and angiogenesis abnormalities, we do not possess sufficient evidence to interpret how reduced angiogenesis results in an aberrant vascular network at the base of the brain.

RING FINGER PROTEIN 213 AND INTRACRANIAL MAJOR ARTERY STENOSIS/OCCCLUSION

RNF213 has also been reported to be associated with intracranial major artery stenosis. Miyawaki *et al.*^[2] studied patients with non-MMD intracranial major artery stenosis/occlusion (ICASO) and found that 9 of 41 patients (21.9%) carried the c.14576G>A variant. To confirm their previous research, the following year, this group conducted a 2-center-based case-control study in a larger population. Consistent with the results of the previous study, the c.14576G>A variant was found to be present in 20/84 patients in a non-MMD ICASO group, which indicated that the c.14576G>A variant is significantly associated with non-MMD ICASO.^[18] Bang *et al.*^[19] analyzed 352 consecutive patients with relevant intracranial arterial stenosis and discovered that 176 of the 352 patients with intracranial arterial stenosis carried the c.14429G>A variant, which is also termed c.14576G>A. In addition, the mutation genotypes of the *RNF213* gene in an MMD population from Taiwan (China) revealed that half of the carriers of the c.14576G>A variant had intracranial arterial stenosis.^[20] Liu *et al.*^[6] generated *RNF213*-knockdown zebrafish and discovered irregular wall formations in major arteries and abnormally sprouting vessels. Interestingly, some other vascular diseases, such as premature coronary artery disease and stroke, aortic coarctation, thoracic aortic aneurysm, and stenosis of other arteries, have also been reported to be associated with *RNF213* variants.^[21] In addition, two patients with co-occurring pulmonary hypertension and MMD were reported to have homozygous p.R4810K mutations in *RNF213*.^[22] Interestingly, diabetes and blood pressure have also been found to be associated with *RNF213*; the ablation of *RNF213* blocks the development of diabetes in mice, and the *RNF213* c.14576G>A variant increases the risk of hypertension.^[23,24] Although the specific mechanisms remain unknown, we predict that *RNF213* variants are indeed correlated with angiocardopathy and cerebrovascular diseases. Based on the above research, we draw the following conclusions: (1) *RNF213* is associated with non-MMD ICASO and other cerebrovascular diseases, and (2) *RNF213* is not associated with non-MMD ICASO; however, MMD has been misclassified as ICASO due to the late onset and the absence of one or two of the diagnostic criteria. These conclusions suggest that *RNF213* genotype should be included in the diagnostic criteria for MMD because the treatment strategies for MMD and ICASO are completely different. If

MMD is treated with strategies designed for ICASO, the actual result may be the opposite of the intended result.

RING FINGER PROTEIN 213 VARIANTS EXHIBIT APPARENT ETHNIC DIVERSITY

There is no doubt that *RNF213* is a strong susceptibility gene for MMD among East Asian people. However, *RNF213* mutations exhibit obvious racial diversity. Liu *et al.*^[6] reported that the minor allele frequencies of p.R4810K are 1.4%, 1.3%, and 1.0% among the general populations of Japan, Korea, and China, respectively, but this does not explain the relatively lower frequency of MMD among the Chinese. However, a subsequent large-scale screening for p.R4810K among East and Southeast Asians demonstrated that this contradiction was attributable to selection bias and suggested that carriers of the c.14576G>A (p.R4810K) variant are indeed less frequent among the Chinese than the Japanese and Korean populations. Moreover, the c.14576G>A variant was detected in only 4 of 11 locations in China and was not detected in Southeast Asia,^[25] which indicates that environment factors might play a role in MMD. An investigation of the frequency of the *RNF213* c.14576G>A variant in two Korean populations revealed that the estimated frequencies of the variant allele were 1.13% and 1.32% in cord blood samples and adult samples, respectively,^[26] which again confirms that the frequencies of the variant allele in Japan and Korea are higher than the frequency in China and that *RNF213* variants exhibit ethnic diversity. Given that there is no large-scale research on the association between *RNF213* and MMD in the Chinese Han population, Wu *et al.*^[27] analyzed 170 MMD cases and 507 controls and discovered that the c.14576G>A variant is related to MMD and that the frequencies of this variant allele are much lower among the Chinese Han population than the populations of Japan and Korea. These authors identified eight other non-R4810K variants. Among these variants, the A4399T polymorphism was deemed to be associated with MMD.^[27] Intriguingly, this group stated that male Chinese patients are more likely to be adversely affected than females (1.3:1), which contrasts with the opposite pattern in Japan (1:18).^[28] In addition, the incidence of MMD in East Asian is much higher than that in European countries,^[29-31] which could be partly be due to the ethnic diversity of *RNF213* mutations. One study reported that no p.R4859K carriers were detected among 400 Caucasian controls and five Caucasian MMD patients.^[1] Moreover, Cecchi *et al.*^[21] also reported that the c.14576G>A variant was identified in 9/16 MMD patients of Asian descent and in 0 of 94 patients of non-Asian descent. In conclusion, we believe that *RNF213* exhibits strong and obvious ethnic diversity. The c.14576G>A variant is mainly detected in Japanese, Korean, and Chinese populations. However, the frequency in the latter population is much lower than those of the former two populations. In addition, the rare *RNF213* variants mainly exist in China and other non-Asian countries; however, a recent study argued that the Japanese also carry some rare variants.^[32]

RING FINGER PROTEIN 213 GENOTYPES CORRELATE WITH MOYAMOYA DISEASE PHENOTYPES

There are numerous differences in the clinical manifestations of MMD between young children and adults. The former primarily presents with ischemia whereas the latter presents with intracranial hemorrhage.^[33,34] In addition, a portion of patients with MMD have severe symptoms and early-onset whereas some patients present with slight headache or are asymptomatic. Although a clear understanding of the pathogenesis of MMD has not yet been achieved, the heterogeneity of *RNF213*, which has significant associations with MMD,^[1] provides a clue that indicates that the clinical manifestations of MMD may be associated with genetic background. Although two Turkish siblings who were homozygous for the c.14576G>A *RNF213* variant exhibited distinct clinical features and Inoue *et al.* also reported a family case of MMD that involved different phenotypes among family members with the heterozygous c.14576G>A variant,^[35,36] these authors have been unable to demonstrate that there is no relation between the *RNF213* genotypes and phenotypes. A study conducted by Miyatake *et al.*^[37] discovered that patients who were homozygous for the c.14576G>A variant of *RNF213* presented with earlier onsets and more serious symptoms than MMD patients who carried were heterozygous for the c.14576G>A variant. In addition, Miyatake *et al.*^[38] reported sibling cases of MMD in which the homozygous c.14576G>A variant manifested with an early-onset and severe clinical manifestation whereas the heterozygous c.14576G>A variant manifested with a relatively late onset and mild symptoms. In accordance with the above results, a recent study also confirmed that the homozygous c.14576G>A variant is associated with early-onset, severe symptoms, and an unfavorable prognosis.^[39] In addition, according to this report, the *RNF213* c.14576G>A variant mainly causes MMD that presents with ischemia whereas the p.A4399T variant is primarily associated with hemorrhaging in MMD.^[20,27] Importantly, Kobayashi *et al.*^[14] reported that *RNF213* R4810K carriers have lower angiogenic capacities and are prone to cerebral hypoxia insults. It has been reported that Chinese heterozygous carriers of the p. R4810K variant are younger at diagnosis, have more familial cases, more ischemic cases, and more frequently exhibit involvement of the posterior cerebral artery.^[40] Further research with large-scale populations should be performed to prove the conclusions of these authors. Overall, strong evidence demonstrates that various genotypes can lead to distinct phenotypes of MMD. This finding motivates us to reacquaint ourselves with the roles played by genetics in the mechanism of MMD and to routinely detect the genotypes of MMD patients to identify those who likely to experience early-onsets, severe symptoms, and bad prognoses because early diagnoses and interventions could prevent malignant outcomes of MMD.

RING FINGER PROTEIN 213, MOYAMOYA SYNDROME, AND THE UNILATERAL MOYAMOYA PHENOMENON

The guidelines for the diagnosis of MMD created in 1997 clarify the diagnostic criteria for MMD as follows: (1) stenosis or occlusion of the distal internal carotid artery, (2) an aberrant vascular network, and (3) bilateral lesions.^[41] The absence of any of these criteria excluded a patient from the spectrum of MMD. For example, unilateral lesions can only be called unilateral moyamoya phenomena and not MMD. Furthermore, if a patient meets all three of the above criteria and has other relevant basic diseases, such as hyperthyroidism, Turner syndrome, meningitis, Behcet disease, idiopathic pachymeningitis, and neurofibromatosis Type 1, the patient should be given a diagnosis of moyamoya syndrome or quasi-MMD but not MMD.^[4,42-44] Given that the *sRNF213* c.14576G>A variant has been identified as a susceptibility gene for MMD,^[1,2] Miyawaki *et al.*^[45] analyzed the genotypes of nine patients with quasi-MMD to clarify whether moyamoya syndrome, which characteristics similar to those of MMD, exhibits an identical etiology or genetic background. These authors discovered that none of the patients with quasi-MMD had the *RNF213* c.14576G>A variant whereas 66 of 78 patients with definite MMD had the variant. These findings indicate that MMD and quasi-MMD may be two completely separate diseases. Although these conditions have similar imaging manifestation, their pathogeneses might be totally different because the latter is more similar to the complications of other associated basic diseases, whereas the former is mainly associated with the genetic background. In addition, some individuals argue that the unilateral moyamoya phenomenon, especially combined with the *RNF213* c.14576G>A variant, should be classified as MMD.^[46] Mineharu *et al.*^[47] also reported on a patient with the c.14576G>A variant who exhibited rapidly progressing unilateral MMD. All of the above findings hint that the *RNF213* c.14576G>A variant should be considered in the diagnosis of MMD.

CONCLUSIONS

The growing literature demonstrates that the MMD is mainly caused by the synergy of genetic and environmental factors. We believe that an unknown genetic modifier might play a role in the etiology of MMD. Far-reaching research should be conducted to clarify the pathogenic mechanism of MMD. In addition, from our perspective, genotype should be considered in the diagnosis of MMD to enable the application of therapy through the relevant effective surgery as soon as possible and to prevent misdiagnoses. Certainly, we all anticipate an easier but effective therapeutic strategy to cure this disease as predicted by some authors.

Financial support and sponsorship

This study was supported by the grants from the National Science and Technology Supporting Plan (the “11th Five-Year Plan”) (No. 2006BAI01A13) and the National Natural Science Foundation of China (No. 81371292).

Conflicts of interest

There are no conflicts of interest.

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