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Synergistic Interaction of Thyroid Autoantibodies and Ring Finger Protein 213 Variant in Moyamoya Disease

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Abstract

Recently, thyroid autoantibodies were found to be associated with moyamoya disease (MMD). The ring finger protein 213 (*RNF213*) p.R4810K variant represents the most important susceptibility genotype of this disease, but its relationship with thyroid autoantibodies remains to be elucidated. Thus, in this study, we aimed to evaluate the clinical relevance of thyroid autoantibodies in each *RNF213* genotype in patients with MMD. Included in this study were patients with MMD without a thyroid disease history and in euthyroid status; they were then classified into the mutated or nonmutated based on the *RNF213* p.R4810K genotype and positive or negative based on thyroid autoantibody (thyroperoxidase and thyroglobulin) levels. Clinical data of each group were thereafter evaluated. Among the 209 patients, the mutated *RNF213* p.R4810K variant and positive thyroid autoantibodies were detected in 155 and 41 patients, respectively. Positive thyroid autoantibodies were found to be more common in the nonmutated patients than in the mutated patients (31.5% vs. 15.5%; P = 0.011). In the mutated patients, as compared to autoantibody-negative patients, autoantibody-positive patients were determined to be more likely to have advanced disease with posterior cerebral artery involvement (54.2% vs. 29.0%; P = 0.017), white matter infarction (58.3% vs. 37.6%; P = 0.046), and a higher modified Rankin Scale at last visit (16.7% vs. 3.1%; P = 0.021). These results suggest that thyroid autoantibodies can act as an immunity inducer in patients with MMD lacking the susceptibility gene *RNF213* p.R4810K variant. Moreover, the simultaneous presence of thyroid autoantibodies and the variant seems to aggravate the disease, which indicates synergy between thyroid autoantibodies and the variant.

Keywords: moyamoya disease, *RNF213*, thyroid autoimmunity, anti-thyroid autoantibodies, thyroid disease

Introduction

Moyamoya disease (MMD) is a rare cerebrovascular disease often characterized by the progressive occlusion of the intracranial carotid artery that sometimes occur in patients with Graves' disease.[1,2] Its clinical presentation can vary from children to adults or from asymptomatic to ischemic or hemorrhagic stroke; stenoocclusive changes were also noted to occur in posterior cerebral artery (PCA) in advanced stages of MMD. The concomitant occurrence of MMD and Graves' disease was first reported in 1991; afterward, patients with concomitant MMD and Graves' disease were diagnosed with "quasi-moyamoya disease," which means moyamoya-like vascular lesions caused by underlying disease, rather than the true MMD, for a long time.[3] However, afterward, many studies have shown that thyroid autoantibodies (ThyAbs) were more frequently detected in patients with MMD as compared to the normal population in both children and adults, even if the patients were in euthyroid status.[4-8] In a recent study, higher prevalence and incidence of MMD were observed in patients with Graves' disease (0.045% and 5.94 patients per 100,000 person-years) as compared to the general population (0.005% and 1.13 patients per 100,000 person-years).[2] Considering these reports, it is difficult to prove the causal relationship between thyroid disease and MMD; thus, patients with MMD

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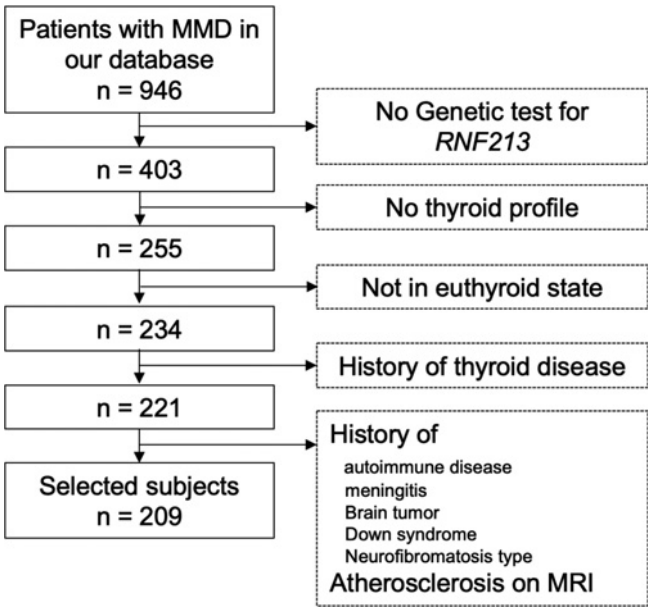

Fig. 1 Selection criteria of the patients included in this study.
Abbreviations: MMD, moyamoya disease; *RNF213*, ring finger protein 213; MRI, magnetic resonance imaging

and hyperthyroidism are now diagnosed as true MMD as per the revised diagnostic criteria in 2021.

In 2011, the ring finger protein 213 (*RNF213*) has been identified as the strongest susceptibility gene for MMD in the East Asian population.[9-11] The founder variant *RNF213* p.R4810K was detected in around 80% of Japanese patients with MMD; also, it is known to be a risk factor of ischemic stroke due to large artery atherosclerosis in the general population without MMD (odds ratio of 3.58). The exact function of this gene remains to be elucidated, but its related function may include the inflammatory system and immune function,[12] the endothelial blood-brain barrier function, vascular remodeling and angiogenesis after ischemic insults, and systemic blood pressure.[13] Although many studies have proved the relationship between *RNF213* p.R4810K and the disease onset, surgical effect of revascularization or disease progression during follow-up,[4,5,11] this variant alone cannot explain why patients with the same single variant exhibit a wide range of clinical characteristics. Moreover, some patients lack this variant but still end developing MMD. Therefore, nongenetic factors are suspected to induce MMD or contribute to the variation of clinical characteristics.[6]

Autoimmune aberrance, especially thyroid disease, has been increasingly implicated as a nongenetic factor for MMD pathogenesis. ThyAbs is known to cause systemic inflammation and induce extra-thyroid diseases such as cardiovascular disease[7] and aggravate the severity of acute ischemic stroke of patients in euthyroid status.[8] Some studies in China and Italy suggested ThyAbs may increase the risk of ischemic stroke[14] and aggressive presentation[15] in MMD as well. It is possible that ThyAbs alone, without hyper- or hypothyroidism, can induce vascular lesions of MMD. Also, because *RNF213* has been strongly related to immune function,[15] there may be possible interaction between ThyAbs and *RNF213* p.R4810K variant. However, to date, the relationship between ThyAbs and *RNF213* p.R 4810K variant in euthyroid patients with MMD has never been reported.

Thus, in this study, we aimed to evaluate the distribution and clinical relevance of ThyAbs (thyroperoxidase [TPO] and thyroglobulin [Tg]) in each genotype of the *RNF 213* p.R4810K variant and elucidate its clinical significance.

Materials and Methods

Patient selection

This study was approved by the local institute (G2016-009) and conducted as the study registered with the University Hospital Medical Information Network Clinical Trials Registry (unique identifier: UMIN000035257). The data of patients with MMD obtained from our institute database (1968-2021) were screened using the protocol shown in Fig. 1. In our institute, genetic studies were started on patients with MMD in 2012,[4] and since 2016, thyroid function tests and autoantibody levels have been routinely evaluated in most patients to assess MMD pathogenesis. All patients were confirmed to have MMD using conventional magnetic resonance imaging (MRI) and/or catheter angiography as per the diagnostic guidelines.[3] Patients were included in this study based on the following inclusion criteria: (1) *RNF213* genotypes and ThyAbs (TPOAb and TgAb) were tested, and (2) euthyroid status (normal levels of thyroid-stimulating hormone [TSH], free T3, and free T4) at the initial visit was confirmed. Meanwhile, we excluded patients with a history of thyroid disease regardless of the current usage of thyroid medication, autoimmune disease, meningitis, brain tumor, Down syndrome, and neurofibromatosis type I and those with imaging features suggesting atherosclerotic origin.

By retrospectively reviewing our database, the following medical history parameters at onset were collected: sex, age at onset, laterality, family history, first presentation (intracranial hemorrhage, cerebral infarction, frequent [more than once in a month] transient ischemic attacks [TIAs], rare TIAs, headache, others, and asymptomatic), initial magnetic resonance angiography stage of the worst side,[3] lesions observed at the initial MRI (white matter hyperintensities, white matter lesions, cortical infarction, and hemorrhage), posterior cerebral artery (PCA) involvement, stroke events during follow-up, and final modified Rankin Scale (mRS) at the final visit during the follow-up period. Patients diagnosed at or under the age of 15 years were regarded as patients with childhood-onset MMD.

As a routine follow-up, we recommended that patients

Table 1 The relationship between *RNF213* genotype and thyroid autoantibodies in all patients

Thyroid Autoantibodies	*RNF213* genotype		P-value
	G/G (n = 54)	G/A or A/A (n = 155)	
TPOAb (+)	10 (18.5%)	10 (6.5%)	*0.013
TgAb (+)	12 (22.2%)	20 (12.9%)	0.081
ThyAbs (+)	17 (31.5%)	24 (15.5%)	*0.011

Abbreviations: *RNF213*, ring finger protein 213; TPOAb, anti-thyroperoxidase antibodies; TgAb, anti-thyroglobulin antibodies; ThyAbs, thyroid autoantibodies (TPOAb positive or TgAb positive)
Values were shown in number (percentage).
*P < 0.05 (one-sided Fisher's exact test comparing the number of patients with positive antibodies between nonmutated (G/G) and mutated (G/A or A/A) group).

have an annual visit and MRI scan at our department, even when they do not exhibit any symptoms.

Genetic test for the *RNF213* p.R4810K variant

Blood samples were collected from each patient, and DNA was extracted (Genomix 2.4 Biologica) by the depository (H.U. Frontier, Tokyo, Japan). Polymerase chain reaction (PCR) primers (forward: CTCGCAGCCAGTCCAAAGT; reverse: ATGTTTTTGGGGTTCAAGCA) were designed for *RNF213* c.14429G>A (NM_001256071.2), and PCR amplification was performed in a PTC100 programmable thermal controller (Bio-Rad Laboratories, CA, USA). The reaction mixture (10 μL) consisted of deoxynucleoside triphosphates (0.25 mM), 1× PS GXL buffer (TaKaRa, Shiga, Japan), forward and reverse primers (0.5 μM), 0.1 μL prime-Star GXL (TaKaRa), and DNA template (10 ng). The amplification program involved an initial denaturation at 98°C (10 s), followed by 35 cycles of 98°C for 10 s, 55°C for 15 s, 68°C for 30 s, and a final extension step at 68°C for 6 min. The PCR products were purified and sequenced using a BigDye Terminator v1.1 Cycle Sequencing Kit and an Applied Biosystems 3130xl Genetic Analyzer (Thermo Fisher Scientific, MA, USA) by another depository (Genome Laboratory, Tokyo Medical, and Dental University). Based on the observed *RNF213* p.R4810K genotype, patients were classified into the mutated (G/A or A/A) and nonmutated (G/G) groups.

Thyroid function and autoantibody test

Blood samples from patients were analyzed for TPOAb, TgAb, TSH, free T3, and free T4 using commercial radioimmunoassay kits (chemiluminescence immunoassay method, ARCHITECT Abbott Japan, Tokyo, Japan). The normal ranges were as follows: TPOAb, 0-5.6 IU/mL; TgAb, 0-4.1 IU/mL; TSH, 0.5-5.0 μLU/mL; free T3, 2.3-4.3 pg/mL; and free T4, 0.9-1.7 ng/dL. ThyAbs (+) and ThyAbs (−) were defined as positive (for TPOAb and/or TgAb) and negative (for both TPOAb and TgAb), respectively.

Statistical analysis

First, we compared the frequency of ThyAbs (+) between the nonmutated and mutated groups. Because we did not have the original data of healthy controls, we used the reported values of ThyAbs (+) in healthy controls from a previous study[16] in order to compare the frequency of ThyAbs (+) in patients with MMD for each sex. We have also compared each clinical factor between ThyAbs (+) patients and ThyAbs (−) patients with and without the *RNF213* variant. As a subanalysis, each comparison was performed in adult patients alone. Comparisons between groups were performed using one-sided Fisher's exact test and Mann-Whitney U test. Data were considered statistically significant at P < 0.05.

Results

Prevalence of *RNF213* and ThyAbs

Of the 946 patients with MMD in our database, 209 were selected and analyzed (Fig. 1; follow-up period 91.5 [94.0] months on average [standard deviation]). Among these 209 patients (0-75 years of age at onset, 42 childhood-onset, 145 females), the *RNF213* p.R4810K variant was detected in 155 patients (152/209 [72.7%] G/A and 3/209 [1.4%] A/A), while a total of 41 patients showed ThyAbs (+) (20/209 [9.6%] TPOAb and 32/209 [15.3%] TgAb). Furthermore, the nonmutated group had significantly more patients with ThyAbs (+) than the mutated group (Table 1 and Fig. 2). The difference remained significant when adult patients alone were analyzed (P = 0.039 for TPOAb, P = 0.035 for TgAb, and P = 0.011 for ThyAbs). All three patients with homozygote (A/A) variant lacked TPOAb and TgAb.

Compared to the reported prevalence of ThyAbs (+) in the healthy Japanese population[16] (TPOAb, 7.2% and TgAb, 12.8%), in our analysis, the prevalence of ThyAbs (+) was relatively higher in patients with MMD (all patients, TPOAb, 9.6% and TgAb, 15.3%). Although the prevalence rate of ThyAbs (+) in patients with the *RNF213* p.R4810K variant was not significantly different as compared to the reported values of healthy controls (Table 1), patients without the *RNF213* p.R4810K variant had a significantly higher prevalence of ThyAbs, especially in the females (Table 2).

RNF213, ThyAbs, and clinical presentation

In the mutated group, patients with ThyAbs (+) were more frequently found to have advanced vascular lesion with PCA involvement, white matter infarction on initial MRI, and a high final mRS of 3-6 (Table 3 and Fig. 1). Similar results were observed in the adult-only subanalysis, which demonstrated the high prevalence of PCA involvement (Supplementary Table S1, 11/18 [61.1%] vs. 27/106 (25.5%); P = 0.004) and low prevalence of nonhemorrhagic, nonischemic onset (others and asymptomatic, 1/18 [5.6%] vs. 32/106 [30.2%]; P = 0.021). Two of the three homozy-

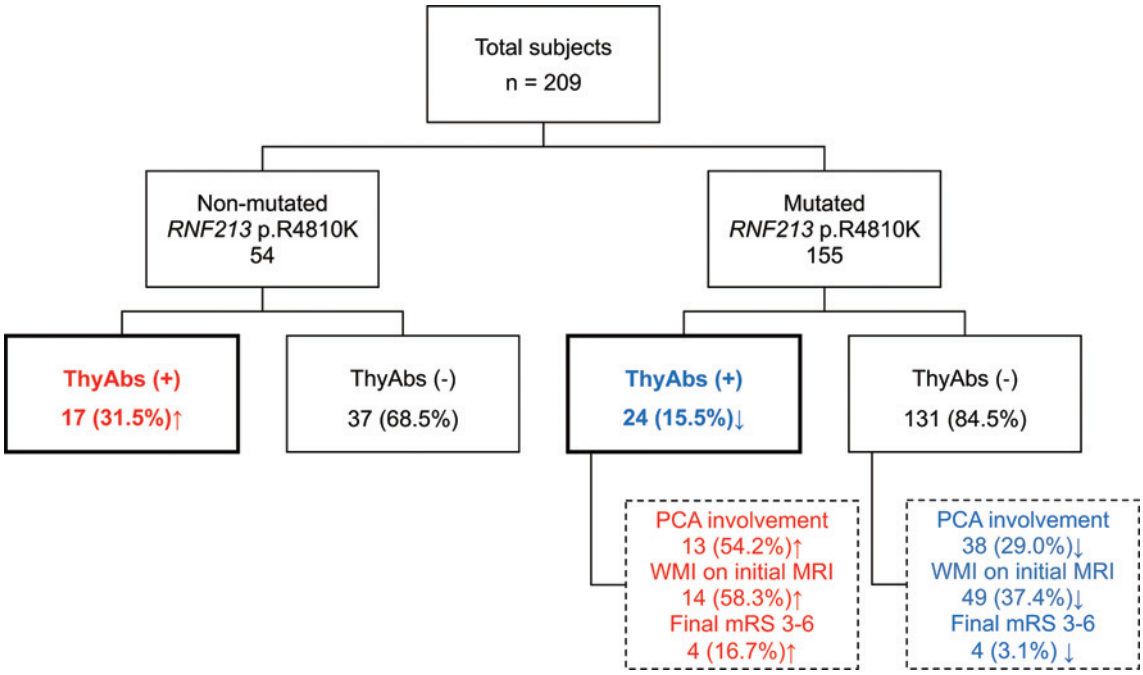

Fig. 2 Summary of the results of this study.
Abbreviations: *RNF213*, ring finger protein 213; ThyAbs, thyroid autoantibodies (TPOAb positive or TgAb positive); PCA, posterior cerebral artery; WMI, white matter infarction; MRI, magnetic resonance imaging; mRS, modified Rankin Scale

Table 2 *RNF213* genotype and thyroid autoantibodies in MMD patients and reported healthy controls

Thyroid Autoantibodies	MMD Patients *RNF213* Genotype						Reported Healthy Controls†		
	G/G (n = 54)			G/A or A/A (n = 155)					
	All	Female	Male	All	Female	Male	All	Female	Male
TPOAb (+)	10 (18.5%)**	8 (21.1%)*	2 (12.5%)	10 (6.5%)	10 (8.6%)	0 (0%)	68 (6.8%)	49 (9.4%)	19 (3.9%)
TgAb (+)	12 (22.2%)*	9 (23.7%)	3 (18.8%)	20 (12.9%)	17 (14.5%)	3 (7.9%)	114 (11.3%)	86 (16.5%)	28 (5.7%)
ThyAbs (+)	17 (31.5%)**	14 (36.8%)**	3 (18.8%)	24 (15.5%)	21 (18.0%)	3 (7.9%)	129 (12.8%)	93 (17.9%)	36 (7.4%)

P < 0.05* and <0.01** (one-tailed Fisher's exact test) compared to the reported values in the healthy controls from reference 18† (Takeda K et al. Endocrine journal 2009).
Abbreviation: *RNF213*, ring finger protein 213

gous (A/A) patients were found to have PCA involvement, but all of them had good final mRS of 0 or 1.

As all the patients (and adult-only subanalysis) were analyzed regardless of the genotypes, patients with ThyAbs (+) were found to have fewer bilateral lesions at initial presentation as compared to patients with ThyAbs (−) (32/41 [78.0%] vs. 153/168 [91.1%]; P = 0.006, Supplementary Table S2). In adult-only subanalysis, PCA involvement was more common in patients with ThyAbs (+), though not statistically significant (12/32 [37.5%] vs. 117/135 [21.5%]; P = 0.051).

When further categorizing ThyAbs to TPOAb and TgAb, patients with TPOAb (+) in the mutated group had fewer bilateral lesions as compared to patients with TPOAb (−) (Supplementary Table S3). On the other hand, patients in the mutated group with TgAb (+) had more frequent PCA involvement, white matter infarction, cortical infarction, and high final mRS as compared to patients with TgAb (−) (Supplementary Table S4).

Discussion

As per the findings of this study, we can conclude the following: (1) patients without the *RNF213* p.R4810K variant were more likely to have ThyAbs as compared to patients with the *RNF213* p.R4810K variant and the general population. (2) Patients with the *RNF213* p.R4810K variant and ThyAbs (+) were more likely to have advanced vascu-

Table 3 Relationship between clinical presentation, *RNF213* p.R4810K genotype, and thyroid autoantibodies (ThyAbs) in all patients

Total n = 209	G/G (n = 54)			G/A or A/A (n = 155)		
	ThyAbs (+)	ThyAbs (–)	P-value	ThyAbs (+)	ThyAbs (–)	P-value
Number of patients	17 (31.5)	37 (68.5)		24 (15.5)	131 (84.5)	
Female	14 (82.4)	24 (64.9)	0.162	21 (87.5)	96 (73.3)	0.105
Age at onset (average, range)	36.2 (0-59)	37.8 (0-75)	0.756	28.7 (2-59)	32.7 (2-73)	0.674
Childhood onset (≤15 years old)	3 (17.6)	8 (21.6)	0.522	6 (25.0)	25 (19.1)	0.337
Bilateral lesion	12 (70.6)	31 (83.8)	0.222	20 (83.3)	122 (93.1)	0.112
Family history of MMD	2 (11.8)	4 (10.8)	0.623	8 (33.3)	28 (21.4)	0.202
Clinical symptom at onset						
Cerebral hemorrhage	0 (0)	5 (13.5)	0.138	2 (8.3)	18 (13.7)	0.366
Cerebral infarction	3 (17.6)	5 (13.5)	0.491	5 (20.8)	21 (16.0)	0.373
Frequent TIAs	0 (0)	5 (13.5)	0.138	1 (4.1)	4 (3.1)	0.574
Rare TIAs	2 (11.8)	6 (16.2)	0.509	10 (41.7)	44 (33.6)	0.294
Headache	4 (23.5)	5 (23.5)	0.293	4 (16.7)	13 (9.9)	0.256
Others/asymptomatic	8 (52.9)	11 (23.8)	0.175	2 (8.3)	31 (23.7)	0.071
MRA stage ≥3	12 (70.6)	31 (83.8)	0.222	21 (87.5)	115 (87.8)	0.595
PCA involvement	1 (5.9)	3 (8.1)	0.627	13 (54.2)	38 (29.0)	*0.017
WMI on MRI	7 (41.2)	14 (37.8)	0.523	14 (58.3)	49 (37.4)	*0.046
WMH on MRI	7 (41.2)	22 (59.5)	0.169	12 (50.0)	69 (52.7)	0.492
Cortical infarction on MRI	3 (17.6)	6 (16.2)	0.590	8 (33.3)	23 (17.6)	0.072
Hemorrhagic lesion on MRI	0 (0)	6 (16.2)	0.090	6 (25.0)	29 (22.1)	0.469
Stroke events during follow-up	2 (11.8)	5 (23.5)	0.616	6 (25.0)	21 (16.0)	0.215
Final mRS ≥3	0 (0)	3 (8.1)	0.313	4 (16.7)	4 (3.1)	*0.021

Abbreviations: *RNF213*, ring finger protein 213; TIA, transient ischemic attack; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; PCA, posterior cerebral artery; WMH, white matter hyperintensities; WMI, white matter infarction; mRS, modified Rankin Scale. Values were shown in number (percentage). P-value was calculated using one-sided Fisher's exact test and Mann-Whitney U test, appropriately, *P < 0.05.

lar lesion with PCA involvement, white matter infarction on initial MRI, and a high final mRS. (3) Patients with ThyAbs were less likely to present with bilateral lesions. The rate of detection of the *RNF213* variant in patients with MMD was 74.2% (155/209), which was higher than that of the normal population (1.9%), as calculated from the Human Genetic Variation Database (https://www.hgvd.genome.med.kyoto-u.ac.jp/) and is consistent with rates previously reported in Japan.[17]

Prevalence of thyroid autoantibodies and *RNF213* p.R4810K variant

Although many studies have shown higher ThyAbs (+) in patients with MMD,[14,15,18-20] our study is the first to show the relationship between ThyAbs and the *RNF213* p.R4810K variant. We do not have the data on the *RNF213* genotype and ThyAbs in healthy controls; however, the reported value of the *RNF213* p.R4810K variant in the normal population is within 1-2%; hence, most healthy individuals lack the *RNF213* p.R4810K variant, and we believe that MMD patients without the *RNF213* p.R4810K variant had a higher prevalence of ThyAbs than the non-MMD healthy population without the *RNF213* p.R4810K variant. These results suggest that ThyAbs induce the onset of MMD in patients lacking the *RNF213* p.R4810K variant, as *RNF213* p.R4810K variant induces MMD regardless of the presence of ThyAbs.

Pathogenesis of thyroid autoantibodies and interaction with *RNF213* p.R4810K variant

In patients with *RNF213* p.R4810K variant, ThyAbs may exacerbate MMD pathogenesis and could result in a higher frequency of PCA involvement and white matter infarction upon initial MRI, higher final mRS, and lower frequency of nonischemic and nonhemorrhagic onset as compared to patients without ThyAbs. PCA involvement in MMD indicates a more advanced stage and thus an indicator of poor outcome.[21] Generally, PCA involvement is more common in patients with the p.R4810K variant,[22] and the prevalence of PCA involvement in MMD at initial diagnosis was reported to be 18.1-36.2% and 21.2-43.4% in pediatric and adult patients, respectively.[21,23,24] Our patients with the p.R4810K

variant and ThyAbs (+) showed a high incidence of PCA involvement (54.2%) as compared to these reports. Hence, ThyAbs may have synergistic interaction with the *RNF213* p.R4810K variant that exacerbates MMD pathogenesis.

Looking at the difference between TPOAb and TgAb, TPOAb was unrelated to PCA involvement nor final mRS (Supplementary Table S3), and only TgAb was related to them (Supplementary Table 4). As the number of patients with TPOAb (+) or TgAb (+) is smaller than ThyAbs (+), it is difficult to conclude which of the three, namely, ThyAbs, TPOAb, and TgAb, more strongly affect MMD pathogenesis. Thus, this warrants prospective analysis in the future.

Regardless of the *RNF213* genotype, our patients with ThyAbs were less likely to present with a bilateral lesion; on the other hand, although insignificant, adult patients with ThyAbs tended to have PCA involvement compared to those without ThyAbs. In a previous study, a higher prevalence of autoimmune thyroid disease was determined in patients with unilateral MMD than in those with bilateral MMD,[25] so the result was partly consistent with our findings. We could not explain why adult patients with ThyAbs tended to have unilateral disease, which is a sign of early disease, as well as PCA involvement, which is an indicator of advanced disease. Perhaps, pathogenesis of ThyAbs on angioarchitecture may be different from the way *RNF213* p.R4810K variant affects angioarchitecture.[22] It is also possible that having a small number of participants has affected our results. Basic experiments using ThyAbs are required to further understand the effect of ThyAbs on the cerebral arteries. Nevertheless, PCA involvement in adult patients with ThyAbs plus p.R4810K variant (11/18 [61.1%]) is high as compared to the prevalence in all adult-onset patients with thyroid autoantibodies; thus, it can be concluded that the synergistic interaction between ThyAbs and p.R4810K might be actually present.

Limitations

This study has its limitations. First, this was a single-center study with a small sample size and retrospective clinical data. Second, as the number of patients was limited, it is difficult to perform reliable multivariate analysis to evaluate the effect of age on ThyAbs. Third, because we do not have the data on *RNF213* and thyroid autoantibodies in the same healthy controls, we cannot prove that association between thyroid autoantibodies and the *RNF213* p.R4810K variant did not exist in healthy controls and was unique in MMD. Fourth, as the prevalence of the *RNF213* p.R4810K variant differs from country to country, the generalizability of our results on a broader context may be limited. Because the number of homozygous patients (A/A) was small, we could not determine the difference between heterozygous and homozygous patients. Finally, *RNF213* variants other than p.R4810K were not evaluated. Nevertheless, this study revealed a possible synergic interaction between the *RNF213* p.R4810K variant and ThyAbs in patients with MMD.

Supplementary Material

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Ethical Considerations

This study was approved by the ethics board of the scientific research department of Tokyo Medical and Dental University Hospital (G2016-009). Written informed consent was obtained from the participants. For children under the age of 18 years, written informed consent was obtained from their parent/legal guardian/next of kin to participate in this study.

Authorship Statement

Thiparpa Thamamongood contributed to the conception and design, acquisition and interpretation of data, drafting of the article, and statistical analysis. Shoko Hara contributed to the conception, design, acquisition, and interpretation of data. Hiroyuki Akagawa contributed to the conception, design, acquisition, and interpretation of data. Motoki Inaji contributed to the acquisition of data. Yoji Tanaka contributed to the acquisition of data. Tadashi Nariai contributed to the conception, design, acquisition, and interpretation of data. Taketoshi Maehara contributed to the acquisition of data. All authors have contributed to the critical revision of this article, reviewed the submitted version of manuscript, and approved the final version of the manuscript.

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Conflicts of Interest Disclosure

The authors have no conflicts of interest to declare.

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