Association between moyamoya syndrome and the *RNF213* c.14576G>A variant in patients with neurofibromatosis Type 1

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OBJECTIVE In a minority of patients with neurofibromatosis Type 1 (NF-1), cerebral vasculopathy reminiscent of moyamoya disease develops. This phenomenon is called moyamoya syndrome (MMS), but there are no known risk factors for the prediction of MMS in NF-1 patients. Polymorphism of the *RNF213* gene has exhibited strong associations with familial and sporadic moyamoya disease and other cerebral vasculopathies. The aim of this study is to find whether the *RNF213* c.14576G>A variant is associated with MMS development in the NF-1 population or not.

METHODS The MMS group included 16 NF-1 patients with documented MMS. The control group consisted of 97 NF-1 patients without MMS. Genomic DNA samples were obtained from the saliva or blood of both groups, and the presence of the *RNF213* c.14576G>A variant was assessed by Sanger sequencing.

RESULTS In the MMS group, 3 patients had the *RNF213* c.14576G>A variant (18.7%), whereas no patients with this genetic variation were observed in the control group (0%). There was a meaningful association between the *RNF213* c.14576G>A variant and MMS development ($p = 0.0024$). The crude odds ratio was calculated as 50.57 (95% CI 1.57–1624.41). All 3 patients with MMS and the c.14576G>A variant were diagnosed with MMS at an early age and had bilateral involvement.

CONCLUSIONS The *RNF213* c.14576G>A variant is more common in NF-1 patients who develop MMS than in NF-1 patients without MMS. This variant might be a susceptibility gene for the NF-1–moyamoya connection.

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KEY WORDS moyamoya syndrome; neurofibromatosis Type 1; *RNF213*; polymorphism; vascular disorders

MOYAMOYA disease is a progressive steno-occlusive disease of intracranial vessels. This disease is idiopathic, and there is no established etiology. Occasionally, moyamoya-like phenomena, i.e., progressive steno-occlusive changes in the intracranial arteries with or without ischemic symptoms, develop in patients with other systemic diseases or conditions, and this situation is termed moyamoya syndrome (MMS).¹⁷ Neurofibromatosis Type 1 (NF-1) is one such disease. The incidence of cerebral vasculopathy in NF-1 patients has been reported to be 2%–6% in the published studies.^{2,4,15,16} Experi-

mental studies have elucidated the possible cellular/molecular mechanisms of the development of cerebral vasculopathy in NF-1 patients and focused on the disruption of the NF1-RAS-mTOR pathway in vascular endothelium.¹ However, there is no answer regarding the question of why only a small portion of NF-1 patients develop MMS while the majority do not.

The ring finger protein 213 (*RNF213*) gene variant c.14576G>A is strongly associated with familial and sporadic moyamoya disease.⁶ The homozygote AA variant is related to aggressive phenotypes of this disease with

ABBREVIATIONS IQR = interquartile range; MMS = moyamoya syndrome; MRA = MR angiography; NF-1 = neurofibromatosis Type 1.

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earlier onsets and cerebral infarctions.⁹ Interestingly, the *RNF213* c.14576G>A variant is also associated with non-moyamoya cerebrovascular disease.^{10,11} Therefore, it is possible that *RNF213* functions as a common susceptibility gene not only for moyamoya disease, in which the effect of the genetic variation is most powerful, but also for other vascular diseases.

We hypothesized that MMS develops in some susceptible individuals in NF-1 populations and that the *RNF213* c.14576G>A variant might be a susceptibility gene related to the NF-1–moyamoya connection. We compared the proportions of patients with the *RNF213* c.14576G>A variant in a group of NF-1 patients with MMS and a group of NF-1 patients with normal cerebral vasculatures to identify possible associations between this variant and MMS.

Methods

MMS Group

We searched for concomitant diagnoses of moyamoya disease or MMS with NF-1 in the electronic patient databases of the Seoul National University Children's Hospital and the Seoul National University Bundang Hospital. Twenty-six patients were identified in the databases. Among these 26 patients, 22 fulfilled the US National Institutes of Health (NIH) diagnostic criteria for NF-1 based on review of the medical records.³ The relevant information for the diagnosis of NF-1 was lacking or unavailable for 4 of the patients at the time of review. Three patients were lost to follow-up, and another 3 patients refused to participate in the study. Ultimately, 16 patients and/or their parents provided informed consent and the patients' saliva for DNA extraction. All of the patients underwent brain MR angiography (MRA), and 15 patients underwent cerebral angiography. Moyamoya-like vasculopathy was observed in all of the patients. Genetic testing had confirmed the presence of *NF1* gene mutation in 5 patients.

Control Group

For the control group (NF-1 patients without MMS), we collected DNA samples extracted for NF-1 genetic testing and stored in the Gene Bank of the Department of Laboratory Medicine, Seoul National University Children's Hospital. DNA samples from 110 NF-1 patients who met the NIH diagnostic criteria for NF-1 were retrieved. Mutation or deletion of the *NF1* gene was confirmed in all of the patients. DNA from an additional 5 NF-1 patients whose blood samples were stored in the Brain Bank of Seoul National University Children's Hospital were also used (all 5 of these patients met the NIH clinical criteria for NF-1).

Among the 115 NF-1 patients, 103 patients underwent brain MRI, and 19 of these patients also underwent brain MRA. There were no brain MRI or MRA data available for review in 12 cases, and we excluded these patients from the control group. Three patients had suspected cerebral vasculopathy on MRI/MRA. One of these 3 patients exhibited transient unilateral stenosis of the distal internal carotid artery, which was resolved on follow-up imaging. The second patient showed diffuse narrowing of a long segment of 1 middle cerebral artery without moyamoya collateral formation. The third patient exhibited narrowing of the entire length of 1 internal carotid artery from

the cervical segment to the bifurcation. These imaging features were not consistent with the definition of MMS, and these 3 patients were excluded from both the control and MMS groups. Among the remaining 100 patients, the qualities of the DNA samples were insufficient for this study in 3 patients. Therefore, 97 patients with diagnoses of NF-1 and the absence of cerebral vasculopathy were ultimately included in the control group. The study protocol was approved by the Institutional Review Boards of the Seoul National University Hospital and the Seoul National University Bundang Hospital.

RNF213 Gene Sequencing

DNA was extracted from saliva samples using the Ora-gene kit (DNA Genotek) according to the manufacturer's instructions. The saliva samples were stored at room temperature prior to DNA purification. DNA extraction was performed using a DNA extraction kit (Applied Biosystems), and DNA quantitation was conducted with a spectrophotometer. For the analysis of the *RNF213* c.14576G>A variant, the DNA was amplified by PCR using the appropriate primer sets (sense 5'-CTGATGCGTCAGCTCCATAG-3' and antisense 5'-TTCCTGCTTTGTGCAGTCAC-3').

The sequencing reactions were performed using the PCR products in reactions with the primers, and an ABI Big Dye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems). An ABI 3730XL DNA sequencer (Applied Biosystems) was used to resolve the products, and the data were analyzed with ABI sequencing analysis software (Applied Biosystems).

Statistical Analysis

We described the characteristics of 16 cases of MMS, and compared these cases to a control group for clinical characteristics and the frequencies of the *RNF213* c.14576G>A variant. We used chi-square or Fisher's exact tests for categorical variables and the Kruskal-Wallis test for continuous variables. To calculate the odds ratio (and 95% confidence interval) for MMS due to the presence of the *RNF213* c.14576G>A variant, a logistic regression model with Firth's bias correction was constructed. SAS 9.3 Software (SAS Institute Inc.) was used for both descriptive and inferential statistical analysis. Trial versions of NCSS, PASS, and GESS (NCSS LLC) were used for power analysis. All p values were two-sided, and statistical significance was assumed at $p < 0.05$.

Results

Characteristics of Each Group

In the MMS group ($n = 16$), the male-to-female ratio was 6:10. The median age at the time of MMS diagnosis was 5.5 years (interquartile range [IQR] 2.5–7.0 years). The clinical characteristics of the 16 patients are summarized in Table 1. Six patients had unilateral MMS involvement, and 10 patients had bilateral steno-occlusive disease. Fourteen patients had symptoms related to MMS and 7 of the patients experienced cerebral infarctions (5 lobar and 2 border-zone infarctions). The 14 patients received revascularization surgery (7 unilateral and 7 bilateral surgeries). Two patients were asymptomatic and were

TABLE 1. Clinical and genetic profiles of the 15 NF-1 patients with MMS

Patient No.	Sex	Age	RNF213 c.14576G>A	Optic Pathway Glioma	Surgery for Brain Tumors	History of CRT	Symptoms	Involvement of MMS	Infarction	Revascularization Surgery	Follow-Up (mos)*
1	F	21 mos	GA (heterozygous)	-	-	-	Involuntary movement	Bilateral	0	Bilateral	30
2	F	23 mos	GA (heterozygous)	-	-	-	Hemiparesis	Bilateral	Lobar	Bilateral	84
3	M	6 yrs	GA (heterozygous)	-	-	-	Motor TIA, HA, dizziness	Bilateral	Border zone	Bilateral	46
4	M	12 mos	Wild-type	-	-	-	Monoparesis	Unilateral	Lobar	Unilateral	6
5	F	17 mos	Wild-type	-	-	-	Hemiparesis, dysphasia	Bilateral	Lobar	Bilateral	201
6	F	3 yrs	Wild-type	+	-	-	None	Bilateral	0	None	29
7	M	3 yrs	Wild-type	-	-	-	Monoparesis	Bilateral	Lobar	Bilateral	176
8	F	5 yrs	Wild-type	-	-	-	HA	Unilateral	0	Unilateral	95
9	F	5 yrs	Wild-type	-	-	-	Motor TIA	Unilateral	0	Unilateral	107
10	F	6 yrs	Wild-type	-	-	-	Motor TIA, HA	Bilateral	Border zone	Bilateral	18
11	M	6 yrs	Wild-type	-	-	-	HA	Bilateral	0	Unilateral	29
12	M	6 yrs	Wild-type	-	-	-	Motor TIA, HA	Bilateral	0	Bilateral	95
13	F	8 yrs	Wild-type	-	-	-	Spastic diplegia	Bilateral	Lobar	Unilateral	69
14	F	11 yrs	Wild-type	-	+	-	None	Unilateral	0	None	55
15	M	12 yrs	Wild-type	-	-	-	Motor TIA, HA	Unilateral	0	Unilateral	42
16	F	24 yrs	Wild-type	-	-	-	Motor TIA	Unilateral	0	Unilateral	78

CRT = cranial radiation therapy; HA = headache; TIA = transient ischemic attack.

* The follow-up period was calculated from the initial documentation of MMS based on imaging studies.

followed-up with regular imaging studies (one had unilateral and the other bilateral involvement). One patient had an optic pathway glioma. One patient underwent surgery for a brain tumor (a low-grade glioma), and no patient was treated with cranial radiation therapy.

In the control group (n = 97), the male-to-female ratio was 45:52. The median age at the time of blood/DNA deposition was 7.0 years (IQR 3.0–16.0 years). Six patients had an optic pathway glioma. Five patients underwent surgery for brain tumors (2 anaplastic astrocytomas, 2 optic pathway glioma, and 1 malignant peripheral nerve sheath tumor). Three patients received cranial radiation therapy for brain tumors. The MMS group and the control group did not show significant statistical difference in the clinical characteristics listed in Table 2.

***RNF213* c.14576G>A Variant**

In the MMS group (n = 16), 3 patients had the *RNF213* c.14576G>A variant. All 3 of these patients were heterozygous for this variant (GA variant) (Fig. 1). The other 13 patients had wild-type *RNF213* genes. In the control group (n = 97), all of the patients had the wild-type *RNF213* gene (Table 3). The *RNF213* gene variant was more frequent in the MMS group (p = 0.0024 by Fisher's exact test). The crude odds ratio was calculated as 50.57 (95% CI 1.57–1624.41) and the association remained significant after the adjustment of other clinical characteristics (adjusted OR 37.26, 95% CI 1.12–1240.66). Post hoc analysis yielded a statistical power of 82.4%.

All 3 MMS patients with the c.14576G>A variant had bilateral arterial stenosis and/or occlusion. The patients were all symptomatic. One patient suffered from a lobar infarction and 1 patient had border-zone infarction before they were diagnosed with MMS. No tumors other than dermal neurofibromas were found in these patients (no brain or systemic tumors, including optic glioma). The average age at MMS diagnosis of these patients was 3.2 years, whereas the average age of the other 13 patients in the MMS group was 7.1 years. Although this difference was not statistically significant, it is possible that the c.14576G>A variant was related to the early development of MMS.

The 3 patients with cerebral vasculopathies other than MMS in the control group had the wild-type *RNF213* c.14576. Of the 12 patients excluded from the control group due to the absence of brain MRI, one had the *RNF213* GA genotype; however, we were unable to confirm whether this patient had asymptomatic MMS.

Discussion

Neurofibromatosis Type 1 is a genetic syndrome that affects the entire body and exhibits myriad phenotypes. Cerebral vasculopathy is a less common manifestation of this syndrome. Not all of the cerebral vasculopathies found in NF-1 are compatible with the definition of MMS, because NF-1 vasculopathy includes stenosis of long segments of arteries without collateral formation or aneurysmal dilation of vessels.^{2,19} Although there are extensive discrepancies between studies, approximately half of NF-1 patients with cerebral vasculopathy appear to harbor moyamoya-like vascular abnormalities (MMS).¹⁴

Neurofibromin acts as a cell-cycle regulator. The heterozygous loss of neurofibromin in NF-1 patients can elicit the abnormal proliferation of vascular endothelial cells and smooth muscle cells, which leads to aberrant vascular morphogenesis.¹ Knockdown of the *NF1* gene prompts proliferation of vascular endothelial cells in vitro and intimal hyperplasia of arteries after vascular injury in conditional knockout mouse models.^{1,21} A fundamental question, however, is: Why do the abnormal vascular responses develop predominantly in cerebral vasculatures and particularly in a minority of NF-1 patients? NF-1 is notorious for its poor genotype-phenotype correlations. With the exception of large deletions in 17q11 including the *NF1* gene, which have been correlated with severe phenotypes, there are few genetic or molecular markers with phenotypic connotations or prognostic implications in NF-1.¹³ Currently, no biological or clinical markers have been suggested to be indicative of MMS development in NF-1 patients. The absence of known risk factors presents an important problem in the clinical management of NF-1 patients. Although the incidence of MMS is not high in NF-1 populations, some patients develop cerebral infarctions prior to the diagnosis of MMS, as demonstrated in the present study and other studies.^{2,8} Currently, the management guidelines for NF-1 patients do not advocate routine brain MRI or MRA for screening examinations.²⁰ Therefore, the discovery of a risk factor for MMS could enable proactive screening and treatment for MMS in NF-1 patients and thus prevent cerebral infarction and neurological deficits.

The *RNF213* gene encodes the protein myosin. The function of myosin is actively being investigated but remains unclear.¹² The *RNF213* c.14576G>A variant is strongly associated with familial and sporadic moyamoya diseases.⁶ It is truly intriguing that this variant is also associated with cerebral steno-occlusive diseases other than

TABLE 2. Comparison of clinical characteristics for MMS group and control group*

Characteristic	MMS Group (n = 16)	Control Group (n = 97)	p Value
Male/female ratio	6:10	45:52	0.5078
Age in yrs, median† (interquartile range)	5.5 (2.5–7.0)	7.0 (3.0–16.0)	0.1502‡
Diagnosis of optic pathway glioma	1 (6.3%)	6 (6.2%)	1.0000§
Surgery for brain tumors	1 (6.3%)	5 (5.2%)	1.0000§
History of cranial irradiation	0 (0)	3 (3.1%)	1.0000§

* Values represent numbers of patients unless otherwise indicated.

† For the MMS group, median age at the time of MMS diagnosis; for the control group, median age at the time of blood/DNA deposition.

‡ The Kruskal-Wallis test was used for comparison.

§ The Fisher exact test was used for comparison.

FIG. 1. Sequencing results for the 3 patients with MMS showing that they had heterozygous c.14576G>A variants of the *RNF213* gene. (The patient numbers are from Table 1).

moyamoya disease.^{10,11} There is even evidence of an association of this genetic variant with systemic hypertension.⁷ Therefore, it is plausible that the *RNF213* gene may behave as a susceptibility gene for arterial steno-occlusive disease particularly in the cerebral vasculature.

We postulated that the coexistence of *NF1* gene haploinsufficiency and the *RNF213* c.14576G>A variant would increase the risk of MMS. We observed an association of the 2 genetic signatures in terms of the NF-1–moyamoya connection. The prevalence of *RNF213* c.14576G>A variant carriers in the East Asian population is reported to be 0.86%–2.72%.⁵ In the control group, we observed no patients with this genetic variant, which is compatible with the low prevalence of this variant. In contrast, the *RNF213* c.14576G>A variant was significantly better represented in the MMS group. This finding supports the notion that *RNF213* genotype, especially the c.14576G>A variant, might have a role as a phenotypic marker in NF-1 patients. However, the *RNF213* c.14576G>A variant was associated with only 18.7% of the patients with MMS in our study. The proportions are much higher in familial and sporadic

moyamoya disease.⁹ Therefore, there are likely other clinical or genetic factors that contribute to the development of MMS in patients with NF-1. Although we observed a significant correlation, the number of patients in the MMS group was too small to definitively confirm this connection. Because the prevalence of coexisting MMS and NF-1 is very low, a multi-institutional study with a larger number of MMS-affected patients is required to verify the results.

In this study, the 3 patients with the *RNF213* c.14576G>A variant and MMS exhibited earlier onsets of the condition and bilateral involvement. The homozygous c.14576G>A variant of *RNF213* is related to early onset and a severe phenotype (i.e., presentation with cerebral infarction) in moyamoya disease.⁹ It is not known whether the heterozygous genotype is related to more severe phenotypes than those observed in moyamoya disease patients without this variant. A high proportion of unilateral involvement is a characteristic of MMS, especially in the NF-1 background.^{8,14} Although limited by small numbers and lacking statistical significance, the earlier onset and bilateral involvement of the 3 patients are intriguing issues for further investigations.

The *RNF213* gene is known to have diverse polymorphisms other than the c.14576G>A variant. Miyatake et al.⁹ reported that there are no significant phenotypic differences between moyamoya disease patients with *RNF213* gene variants other than the c.14576G>A variant and patients without the variants. We did not analyze the whole *RNF213* gene and only concentrated on the specific disease-susceptible variant. In clinical practice, it is far more advantageous to examine genetic polymorphism in narrow windows than in the entire gene. However, a recent report detailed a novel *RNF213* variant, c.12554A>C, that was found in a family with heterogeneous cerebral vasculopathy, which supports the application of sequencing of the entire gene.¹⁸ More extensive genomic studies may reveal additional information regarding the NF-1–moyamoya connection.

Conclusions

In NF-1 patients with documented MMS, the *RNF213* c.14576G>A variant is highly represented. We propose that this *RNF213* variant might be a risk factor for development of MMS in NF-1 populations. However, this association is weaker than the robust contributions of the *RNF213* c.14576G>A variant to sporadic/familial moyamoya disease. Additional epidemiological and genomic research is required to fully illustrate the NF-1–moyamoya connection.

TABLE 3. Strength of statistical association between the *RNF213* c.14576G>A variant and development of moyamoya syndrome

Groups	Wild-Type	<i>RNF213</i> c.14576G>A Heterozygote	Crude OR (95% CI)	Adjusted OR* (95% CI)
Control group	97 (100%)	0 (0%)	Reference	Reference
MMS group	13 (81.3%)	3 (18.7%)	50.57 (1.57–1624.41)	37.26 (1.12–1240.66)

* Adjusted for age, sex, diagnosis of optic pathway glioma, surgery for brain tumor, and history of cranial irradiation using logistic regression with Firth's correction.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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