Original Article

Smaller outer diameter of atherosclerotic middle cerebral artery associated with RNF213 c.14576G>A Variant (rs112735431)

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Abstract

Background: Intracranial atherosclerosis (ICAS) involves diverse histologies and several remodeling patterns. Ring finger protein 213 (RNF213) c.14576G>A variant (rs112735431), recently reported to be associated with ICAS, may be linked with negative remodeling (outer diameter – reducing morphological alteration) of intracranial arteries. This study investigated the outer diameter of atherosclerotic middle cerebral artery (MCA).

Methods: Patients with unilateral atherosclerotic MCA stenosis/occlusion were enrolled in this single-hospital-based case-control study at The University of Tokyo Hospital. The patients were divided into two groups by the presence of RNF213 c.14576G>A (variant group and wild-type group) and the outer diameter of the MCA was measured with high-resolution magnetic resonance imaging.

Results: Twenty-eight patients with the wild type and 19 patients with the variant type were included. The outer diameter of the stenotic side MCA was smaller in the variant group than in the wild-type group ($P = 8.3 \times 10^{-6}$). The outer diameter of the normal side MCA was also smaller in the variant group than in the wild-type group ($P = 5.2 \times 10^{-3}$). The ratio of stenotic side to normal side was also smaller in the variant group than in the wild-type group ($P = 1.5 \times 10^{-5}$).

Conclusions: This study indicates that RNF213 c.14576G>A is associated with negative remodeling of ICAS.

Key Words: Atherosclerosis, remodeling, genetics, intracranial artery stenosis, magnetic resonance imaging (MRI), RNF213

INTRODUCTION

Intracranial atherosclerosis (ICAS) is one of the main causes of ischemic stroke.[16] The degree of intracranial artery stenosis is an important predictor of ischemic stroke in patients with ICAS, so evaluation of ICAS has mainly been based on assessment of the intraluminal status of atherosclerotic arteries.[17] However, the morphological

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characteristics of the arterial wall of the stenotic lesion of ICAS have recently received much attention.\(^\text{[45]}\)

Classification of arterial remodeling patterns is one of the widely used evaluation methods for arterial wall morphological characteristics. Progress in imaging technology such as high-resolution magnetic resonance imaging (MRI) has enabled the visualization of arterial morphological changes in ICAS,\(^\text{[12,49]}\) and as reported in\(^\text{[23,24]}\) (GenBank accession number, NM_020914.4),\(^\text{[5,41,44,46]}\)\(^\text{[2,14,21,22]}\) exon 61, which includes the c.14576G>A variant; a gene located in chromosome 3, based on the National Center for Biotechnology Information Reference sequence NP_065965.4). This RNF213\(^\text{[37]}\) ring finger protein 213 was originally identified as a susceptibility gene variant of moyamoya disease (MMD), which is characterized by the progressive stenosis of the terminal portions of the bilateral internal carotid arteries.\(^\text{[2,14,21,22]}\) Recently, negative remodeling has been reported to characterize the features of the arterial wall in MMD patients, which is defined as outer diameter-reducing morphological alteration of the arteries occurring with the progress of luminal stenosis.\(^\text{[13,19,29]}\)

In the present study, we hypothesized that RNF213 c.14576G>A, the genetic variant associated with ICAS, is also associated with negative remodeling of ICAS. To prove this hypothesis, we analyzed the outer diameter of the intracranial arteries of ICAS patients divided into two groups according to the presence of RNF213 c.14576G>A.

**MATERIALS AND METHODS**

**Patient population**

This study prospectively enrolled patients with unilateral atherosclerotic middle cerebral artery (MCA) stenosis/occlusion who visited The University of Tokyo Hospital, Tokyo, Japan between April 2013 and December 2015. The criteria for inclusion were: (1) unilateral MCA (M1 portion) >50% stenosis/occlusion on magnetic resonance angiography (MRA); and (2) one or more risk factors of atherosclerosis including hypertension, diabetes mellitus, dyslipidemia, and history of cigarette smoking. Patients with non-atherosclerotic vasculopathy, such as dissection, vasculitis, or MMD, and evidence of cardioembolism were excluded. We also evaluated for the presence of symptoms. Symptomatic patients were defined as having both of MRI finding of cerebral ischemia in the distribution of the stenotic MCA and consistent focal neurological deficit.

**MRI studies**

MRI/MRA was performed in all patients. MRA was used to evaluate stenosis. Degree of luminal stenosis was classified into 5 intracranial artery stenosis (IAS) grades, according to a previously reported study, as: normal, no evidence of stenosis (grade 0); mild stenosis, <50% stenosis (grade 1); moderate stenosis, >50% stenosis (grade 2); severe stenosis, partial occlusion, no distal flow signal (grade 3); and occlusion, no distal flow signal (grade 4).\(^\text{[37]}\) The outer diameter of M1 portion of MCA was measured at the greatest minor axis on axial fast imaging employing steady-state acquisition (FIESTA) MRI using a 3T-MRI scanner (Signa, HDxt 3T; GE Healthcare, Milwaukee, WI) and a 12-channel phased array head neck spine coil. Three-dimensional time-of-flight MRA was performed with the following parameters: repetition time (TR)/echo time (TE) = 26/2.9 ms, field of view (FOV) = 20 cm, thickness/intervals = 0.4/0.2 mm, matrix = 512 × 512, and number of excitations (NEX) = 1. Then, FIESTA MRI was obtained using the following parameters: TR/TE = 4.81/1.86 ms, FOV = 20 cm, slice thickness/intervals = 0.4/0.2 mm, matrix = 512 × 512, and NEX = 1. The voxel size was 0.4 × 0.4 × 0.2 mm\(^3\) for both MRA and FIESTA.

**Identification of RNF213 c.14576G>A variant (rs112735431)**

Peripheral blood samples were obtained from all enrolled patients. Genomic DNA was obtained from the peripheral blood leukocytes at SRL, Inc. (Tachikawa, Tokyo, Japan) using a DNA extraction kit (Talent Srl, Trieste, Italy). Screening for the RNF213 c.14576G>A was performed by direct Sanger sequencing in all cases. RNF213 exon 61, which includes the c.14576G>A variant of RNF213 (GenBank accession number, NM_020914.4), was amplified by polymerase chain reaction (PCR). The primers 5’-CTGCAATCACGAGAATGACACTG and 5’TGACGAGACGCTTTCAGAG were used for amplification and sequencing, as reported previously.\(^\text{[21]}\) PCR was performed in a total of 20 μL reaction mixture containing 50 ng of genomic DNA, 10 μL of 2× PCR
buffer, 4 μL of 2 mM deoxynucleotide triphosphate, 1 μL of each forward and reverse primers (20 μM), and 0.4 μL of 1 U/μL KOD FX Neo (TOYOBO Co., Ltd., Osaka, Japan). Initial denaturation was performed at 94°C for 2 minutes, followed by 35 cycles of amplification consisting of denaturation at 98°C for 10 s, annealing at 60°C for 30 s, and extension at 68°C for 30 s. The PCR products were treated with QIAquick Gel Extraction Kit (Qiagen N.V., Venlo, Netherlands) after agarose gel electrophoresis. Direct sequencing was performed at FASMAC Co., Ltd. (Atsugi, Kanagawa, Japan) using an ABI Genetic Analyzer 3130XL or ABI DNA Analyzer 3730xL (Applied Biosystems, Foster City, CA). Cycle sequencing was carried out using the BigDye Terminator v3.1 cycle sequencing kit (Applied Biosystems). Sequence chromatographs were analyzed with a Sequence Scanner version 1.0 (Applied Biosystems). All investigators involved in genotyping were unaware of the phenotypic information. All analyses of the sequenced data were performed at the Department of Neurosurgery, The University of Tokyo.

### Statistical analysis

The Pearson Chi-square test was used to compare the clinical characteristics between the wild type group (patients with RNF213 c.14576G>A wild type, GG) and variant group (patients with RNF213 c.14576G>A variant both heterozygote and homozygote, AG and AA). The Mann–Whitney U test was used to compare non-normally distributed continuous variables, such as age and diameter of the intracranial arteries between the two groups. All analyses were performed using JMP Pro version 11.0.0 (SAS Institute, Inc., Cary, NC). P value less than 0.05 was considered to be statistically significant.

### Ethical considerations

This study was approved by the Human Genome, Gene Analysis Research Ethics Committee of the Faculty of Medicine, The University of Tokyo (approval number: 3516; approval date: September 12, 2011). Written informed consents were obtained from all participants in this study.

### RESULTS

#### Clinical characteristics

Table 1 shows the clinical characteristics of the patients including 28 patients with the wild type and 19 patients with the variant type. The distribution of IAS grade, mean age, number of women, and number of symptomatic patients were similar in the wild-type and variant groups. Patients with diabetes mellitus were significantly more common in the wild-type group than in the variant group (P = 0.030). The numbers of patients with hypertension, dyslipidemia, ischemic heart disease, arteriosclerosis obliterans, and history of cigarette smoking were not significantly different.

#### Outer diameter

Figure 1 represents examples of measurement of the outer diameter in both groups. Table 2 shows the

| Characteristics | Wild Type (G/G) | Variant (A/G + A/A) | P |
|-----------------|-----------------|---------------------|---|
| Number of patients | 28              | 19                  |    |
| Genotype        |                 |                     |    |
| GG              | 28              | 0                   |    |
| GA              | 0               | 18                  |    |
| AA              | 0               | 1                   |    |
| IAS grade, n (%)|                 |                     |    |
| 2               | 11 (39.3)       | 8 (42.1)            |    |
| 3               | 5 (17.9)        | 5 (26.3)            |    |
| 4               | 12 (42.8)       | 6 (31.6)            | 0.80|
| Age, mean±SD (range), y | 62.1±12.9 (41-83) | 61.2±11.3 (38-77) | 0.64|
| Female, n (%)   | 12 (42.8)       | 11 (57.8)           | 0.31|
| Symptomatic, n (%) | 7 (25.0)       | 4 (23.4)            | 0.75|
| Underlying diseases |                |                     |    |
| Hypertension    | 12 (42.8)       | 10 (52.6)           | 0.50|
| Diabetes        | 6 (21.4)        | 0 (0.0)             | 0.030|
| Dyslipidemia    | 5 (17.8)        | 6 (31.5)            | 0.27|
| Ischemic heart diseases | 4 (14.2) | 3 (15.7) | 0.88|
| Arteriosclerosis obliterans | 0 (0.0) | 1 (5.2) | 0.21|
| Smoking         | 6 (21.4)        | 6 (31.5)            | 0.43|
| Alcohol         | 5 (18.5)        | 5 (26.3)            | 0.48|

IAS: Indicates intracranial artery stenosis. RNF213: Ring finger protein 213. SD: Standard deviation
c.14576G>A might affect either the protein stability of RNF213 or its presence in the cell membrane, which might lead to negative remodeling. In this study, we aimed to investigate the influence of RNF213 c.14576G>A on ICAS, with the presence of RNF213 variant on ICAS being identified as a negative remodeling factor. The present study identified C.14576G>A as a genetic factor in the structure of intracranial artery. The present study investigated only ICAS patients classified by the presence of RNF213 c.14576G>A, hence further study should compare the character-matched groups of healthy individuals classified by the presence of RNF213 c.14576G>A to confirm the influence of RNF213 c.14576G>A on the normal intracranial artery.

RNF213 encodes a protein with 5256 amino acids harboring a RING (really interesting new gene) finger motif and an AAA (adenosine triphosphatase associated motif and an AAA (adenosine triphosphatase associated domain) motif, indicating E3 ubiquitin ligase activity and energy-dependent unfoldase. RNF213 mRNA is ubiquitously expressed in various human tissues, but is especially highly expressed in immune tissues, such as lymphocytes, monocytes, eosinophils, and neutrophils. The study by Streib et al. hypothesized that RNF213 is highly expressed in immune tissues, and our results indicate that RNF213 c.14576G>A is associated with negative arterial remodeling in ICAS.

The histology of positive remodeling of atherosclerotic arteries in ICAS as well as other systemic arteries is known to involve lipid-rich plaque burden, intraplaque hemorrhage, fibrin cap, and infiltration of inflammatory cells. However, the histological characteristics of negative remodeling is less well known, and few detailed histological findings have been reported. Negative remodeling of the coronary artery has been observed to involve shrinkage of the arterial wall resulting in stenotic lumen instead of intraluminal plaque deposition. Assuming that negative remodeling ICAS undergoes similar histological changes, RNF213 c.14576G>A might manifest as the morphological shrinkage of the arterial wall in ICAS. However, detailed histological findings of wall shrinkage in negative remodeling atherosclerosis have not been elucidated even in the coronary artery. To investigate the detailed effects of the RNF213 c.14576G>A on ICAS, more histological observations of negative remodeling in ICAS are required.

The smaller outer diameter on the normal side in the variant group indicates that the RNF213 c.14576G>A affects the outer diameter of normal intracranial arteries. Consequently, the present study identified RNF213 c.14576G>A as a genetic factor in the structure of normal intracranial artery. This important result suggests that the RNF213 c.14576G>A may affect either the morphogenesis or the morphological change of the intracranial artery. The present study investigated only ICAS patients classified by the presence of RNF213 c.14576G>A, hence further study should compare the character-matched groups of healthy individuals classified by the presence of RNF213 c.14576G>A to confirm the influence of RNF213 c.14576G>A on the normal intracranial artery.
Knockdown of RNF213 in zebrafish caused irregular wall formation in trunk arteries and abnormal sprouting vessels, indicating the potential function of RNF213 in the development of intracranial angiogenesis. On the other hand, transgenically generated RNF213-deficient mice and RNF213-knock-in mice expressing a missense mutation in mouse RNF213 p. R4828K on exon 61, corresponding to human RNF213 p. R4859K, grow normally, with no significant differences in MRA findings or the anatomy of the circle of Willis compared with wild-type littermates. These findings indicate that other secondary insults such as environmental factors besides RNF213 deficiency are necessary for the onset of intracranial major artery stenosis and intracranial arterial remodeling. In vitro studies of induced pluripotent stem cell-derived vascular endothelial cells from patients with MMD and carriers of RNF213 c.14576G>A variant showed lower angiogenic activities in the tube formation assay than in carriers of the wild-type variant, indicating the potential function of RNF213 in endothelial cells. Recently, the signaling pathways for the regulation of RNF213, such as interferon-beta signaling, and the relationship of RNF213 with the known molecular pathways for vascular remodeling, such as non-canonical Wnt signaling, have gradually been identified. However, the precise molecular mechanism by which the RNF213 c.14576G>A causes human intracranial arterial remodeling is not completely understood, and further molecular biological functional analysis of RNF213 is required.

Remodeling patterns are associated with the risk of ischemic stroke, and so influence the therapeutic choice of ICAS. Conventionally, evaluation of the severity of luminal stenosis has mainly focused on the intracranial artery, and transluminal angioplasty has been considered as an effective therapeutic choice to improve ICAS and subsequent ischemic stroke. The Stenting vs. Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial evaluated the effectiveness of intraluminal angioplasty, but failed to prove the efficacy of intracranial artery stenting, as the rate of periprocedural stroke after percutaneous transluminal angioplasty and stenting was higher than the estimated probability. One important possible reason is that the SAMMPRIS trial included patients selected on the basis of angiographical arterial stenosis but the wall characteristics such as outer diameter and eccentricity were not evaluated. Therefore, patients with negative remodeling of stenotic M1 might have suffered damage to the arteries through excess inflation of the balloon and stent. Indeed, in previous studies with coronary intervention, it has shown that remodeling pattern of coronary artery has relationship with the incidence of adverse cardiac events including post-interventional dissection. Evaluation of wall morphology with high-resolution MRI may provide information about the optimum stent size and inflation pressure, and the present study suggests that preoperative investigation of the RNF213 c.14576G>A may also improve the effectiveness of intracranial artery stenting.

The present study has some limitations. Only the outer diameter was measured on MRI as the morphological feature of ICAS and wall structure itself was not investigated. Wall imaging could observe more detailed influence of the RNF213 c.14576G>A on the morphological characteristics of ICAS. In addition, to evaluate the effect of RNF213 c.14576G>A on the normal intracranial artery, character-matched groups classified by the presence of RNF213 c.14576G>A of healthy individuals, not only of atherosclerotic patients, must be compared.

**CONCLUSION**

This study indicates that RNF213 c.14576G>A is associated with negative remodeling of ICAS.
Identification of the RNF213 c.14576G>A may lead to optimum treatment of ICAS.

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Conflicts of interest
There are no conflicts of interest.

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