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Letter to the Editor

RNF213 Polymorphism in Intracranial Artery Dissection

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Dear Sir:

Cervicocerebral artery dissections (CADs) account for approximately 20% of strokes in young individuals.[1] CADs are associated with trauma or neck rotation, but such history is absent in many patients. One postulated cause of CAD is an underlying arteriopathy,[1] possibly associated with genetic predisposition. There appears to be an ethnic difference in the location of CAD; in non-Asians, intracranial dissections (IC-CADs) account for <10% of all CADs,[2] whereas in Asians, IC-CAD is more common than extracranial artery dissections (EC-CADs).[3,4] Genetic variation may explain these differences.

The ring finger protein 213 (*RNF213*) gene, in the 17q25-ter region, is one of the genes shown to be associated with the ethnic difference in the location of cerebral vascular diseases. *RNF213* was initially identified as a susceptibility gene for moyamoya disease,[5] but *RNF213* variants are also associated with non-moyamoya vascular diseases.[6] Although there are some exceptions,[7] this genetic variant is mostly associated with intracranial arterial diseases, such as intracranial atherosclerosis. Thus, we hypothesized that *RNF213* polymorphisms may be associated with IC-CAD, and assessed this gene in IC-CAD patients compared with age-sex matched normal subjects, as well as with EC-CAD patients.

We prospectively and consecutively enrolled patients diagnosed with IC-CAD or proximal internal carotid artery (ICA) dissection, as confirmed by appropriate imaging techniques, and who were admitted to Asan Medical Center from March 2014 to February 2017. Magnetic resonance angiography (MRA) or computed tomographic angiography (CTA) was initially used for diagnosis. Duplex sonography, high-resolution magnetic resonance imaging, or digital subtraction angiography (DSA) was also performed when needed. Imaging diagnosis of CAD was made when there were: double lumen (a false lumen or an intimal flap), an intramural hematoma, a nonatherosclerotic tapered, flame-shaped stenosis/occlusion or pearl-and-string sign, or a dissecting aneurysm at a non-branching site.[3] Age- and sex-matched controls, who visited due to a non-stroke diagnosis, such as tension-type headache and peripheral vestibulopathy, were enrolled from an outpatient clinic.

To assess *RNF213* polymorphisms, genomic DNA was extracted from peripheral blood using a Puregene Blood Kit (Qiagen, Hilden, Germany). To identify the major single nucleotide polymorphisms of *RNF213* in East Asian patients[8] (i.e., p.D4013N, p.P4608S, p.R4810K, p.R4853K, p.D4836N, and p.E4950D), three exons (exons 44, 60, and 62) and the appropriate exon–intron boundaries of *RNF213* were amplified by polymerase chain reaction and directly sequenced using an ABI3130*xl* Genetic Analyzer (Applied Biosystems, Foster City, CA, USA), according to manufacturer instructions. The results were compared with established human *RNF213* sequences (GenBank accession no. NM_001256071.1).

All statistical analyses were performed using SPSS version 21.0 software (IBM Co., Armonk, NY, USA). Categorical variables were compared using the chi-square test or Fisher's exact test, and continuous variables were compared using a Mann-Whitney U test. A *P*-value <0.05 was considered statistically significant. This study was approved by the local Institutional Review Board, and informed consent was obtained from all participants.

We enrolled 24 patients with IC-CAD (21 middle cerebral artery, two intracranial ICA, and one posterior cerebral artery).

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Table 1. Baseline characteristics and prevalence of the *RNF213* variant

Characteristic	Control (n=24)	Subjects (n=24)	*P*
Demographics			
Age (yr)	42.9±8.4	41.8±10.2	0.657*
Male sex	7 (29.2)	8 (33.3)	1.000
Medical history			
Hypertension	1 (4.2)	8 (25.0)	0.063
Diabetes mellitus	0 (0)	3 (9.4)	0.252
Hyperlipidemia	4 (16.7)	6 (25.0)	0.724
Smoking	4 (16.7)	6 (25.0)	0.724
Coronary artery disease	0 (0)	0 (0)	NC
Family history of moyamoya disease	0 (0)	1 (4.2)	1.000
RNF213 variant	1 (4.2)	8 (33.3)	0.023

Values are presented as mean±standard deviation or number (%). Fisher's exact test.
RNF213, ring finger protein 213; NC, not calculated.
*Mann-Whitney U test were used.

Eleven had ischemic stroke, seven had transient ischemic attack, and three had headache. Three patients were asymptomatic and were admitted to evaluate the cause of intracranial artery stenosis. Of the 24 patients, only two patients had a history of head or neck trauma, including excessive neck rotation. The diagnostic imaging techniques used were MRA (n=21), CTA (n=3), DSA (n=13), and high-resolution MRA (HRMRA; n=21). Twenty-four age- and sex-matched subjects and eight extracranial ICA dissection patients were used as controls. For the eight patients with EC-CAD, a history of trauma was obtained in two patients, and the diagnostic imaging techniques used were MRA (n=7), CTA (n=2), DSA (n=6), HRMRA (n=3), and duplex sonography (n=3).

Baseline characteristics were similar between IC-CAD patients and controls, although dissection patients tended to have hypertension more often. Of the 24 patients with IC-CAD, eight (33.3%) had an *RNF213* variant. Among various single nucleotide polymorphisms of *RNF213* gene, only the heterozygote of the p.R4810K (c.14576G>A) variant was found in our patients, the prevalence of which was significantly higher (*P*=0.023) in IC-CAD patients than in controls (Table 1). When adjusted for hypertension and *RNF213* polymorphism, both hypertension (adjusted odds ratio [OR], 10.185; 95% confidence interval [CI], 1.066 to 97.305; *P*=0.04) and the presence of the *RNF213* variant (adjusted OR, 14.247; 95% CI, 1.563 to 129.841; *P*=0.018) were independently associated with IC-CAD. However, none of the eight extracranial ICA dissection patients had *RNF213* variants. One IC-CAD patient with the *RNF213* variant had a family history of moyamoya disease.

We found that one-third of IC-CAD patients had the *RNF213* variant, suggesting that this variant may be associated with IC-CAD. As none of the EC-CAD patients had this genetic variant, *RNF213* alleles may not be causally associated with the dissection pathology per se, but may increase the vulnerability of the intracranial artery for developing dissection. Interestingly, among the patients with IC-CAD, one had a family history of moyamoya disease. It has been suggested that *RNF213* polymorphism is a non-specific marker that increases vulnerability for intracranial arterial disease, and secondary insults or other genetic factors may determine the ultimate phenotype in these patients.[6] As *RNF213* variants are more prevalent in East Asians than in Caucasians,[5] this genetic difference may explain the higher risk of intracranial arterial diseases, including IC-CAD, in Asia.[9] Our study is limited due to the small number of enrolled patients. Further studies are needed to confirm our preliminary findings.

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