JCN Open Access LETTER TO THE EDITOR

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2020;16(2):330-332 / https://doi.org/10.3988/jcn.2020.16.2.330

No Association of *RNF213* Polymorphism with Reversible Cerebral Vasoconstriction Syndrome

Joomee Song[a]
Yeon Hee Cho[b]
Mi Jeong Oh[b]
Soohyun Cho[a]
Oh Young Bang[a]
Mi Ji Lee[a]
Chin-Sang Chung[a]

[a]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[b]Samsung Biomedical Research Institute, Seoul, Korea

Received September 10, 2019
Revised November 20, 2019
Accepted November 21, 2019

Correspondence
Mi Ji Lee, MD, PhD
Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06531, Korea
Tel +82-2-3410-3599
Fax +82-2-3410-1430
E-mail mijilee.md@gmail.com

Chin-Sang Chung, MD, PhD
Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06531, Korea
Tel +82-2-3410-3596
Fax +82-2-3410-0052
E-mail cspaul@naver.com

Dear Editor,

Asian cohorts of reversible cerebral vasoconstriction syndrome (RCVS) have unique characteristics such as large proportions with idiopathic RCVS and pure cephalalgic presentation, and a lower prevalence of hemorrhagic strokes.[1-3] It can be hypothesized that genetic factors contribute to the risk of developing idiopathic RCVS such that the clinical manifestations will differ between ethnic groups. However, genetics studies have rarely addressed this issue.

The Ring Finger Protein 213 gene (*RNF213*) is a susceptibility gene of moyamoya disease, whose polymorphism is highly prevalent in East Asians.[4] Moreover, *RNF213* variants are also related to intracranial artery stenosis and dissection, which are more common in Asians than in Caucasians.[5,6] Based on these findings, we hypothesized that *RNF213* is a susceptibility gene for intracranial arteriopathy that predisposes Asians to idiopathic RCVS.

We prospectively screened patients who presented with thunderclap headache from November 2016 to January 2018. The required number of included patients was calculated to detect an *RNF213* mutation in 30% of RCVS patients assuming a RCVS prevalence of 57% in the patients who have thunderclap headache[7] with 80% power, with an overall significance criterion of 5%. Patients with subarachnoid hemorrhage due to aneurysmal rupture were excluded. Causes of thunderclap headache were classified using our previously described protocol.[3] RCVS was diagnosed based on the third edition beta version of the International Classification of Headache Disorders (ICHD-3 beta).[8] RCVS was categorized into definite (angiogram-proven) and probable (angiogram-negative). This study was approved by Samsung Medical Center Institutional Review Board (2016-09-122).

Fifty eligible patients who gave informed consents were included in this study. The mean age of the 50 subjects was 47.8 years (range 20−62 years) and they were predominantly female (*n*=33, 66.0%). The 50 patients included 34 (68.0%) with RCVS and 6 (12.0%) with other secondary causes: 4 with intracranial arterial dissection, 1 with meningitis, and 1 with cervicogenic headache. The remaining 10 (20.0%) patients were classified as having primary thunderclap headache. The demographics and characteristics of patients with RCVS vs. those with non-RCVS etiology are summarized in Table 1. Most (94.1%) of the RCVS patients were idiopathic. The demographics and vascular risk factors did not differ between patients with RCVS and those with non-RCVS etiology. Two (5.9%) patients with RCVS had accompanying neurological complications.

The patients underwent blood sampling for the genome analysis. The c.14429G>A mutation of *RNF213* (GenBank accession number NM_001256071.1) was tested,[4] which revealed that neither the patients with RCVS nor those with other causes of thunderclap headache carried the c.14429G>A (p.Arg4810Lys) mutation of *RNF213*.

Our data suggest that *RNF213* is unrelated to the development of RCVS, and hence that RCVS and moyamoya disease have different genetic backgrounds despite overlap in their pathophysiology such as in endothelial dysfunction.[4,9]

Table 1. Demographics and characteristics of the study patients

	RCVS (*n*=34)	Non-RCVS (*n*=16)	*p*
Age, years	49.9 [27–62]	43.1 [20–59]	0.06
Sex, male	10 (29.4)	7 (43.7)	0.31
Hyperlipidemia	5 (14.7)	2 (12.5)	1.00
Diabetes mellitus	2 (5.9)	1 (6.2)	1.00
Hypertension	2 (5.9)	1 (6.2)	1.00
Ischemic stroke	1 (2.9)	0 (0)	1.00
Intracerebral hemorrhage	1 (2.9)	0 (0)	1.00
Ischemic heart disease	0 (0)	0 (0)	-
Arrhythmia	1 (2.9)	0 (0)	1.00
Diagnosis			
RCVS	34 (100.0)		
Intracranial arterial dissection		4 (25.0)	
Primary thunderclap headache		10 (62.5)	
Other*		2 (12.5)	
Associated neurological symptoms	3 (8.8)	6 (37.4)	
Neurological complications			
Cerebral infarction	0 (0)	0 (0)	
Cortical SAH	1 (2.9)	0 (0)	
PRES	0 (0)	0 (0)	
Seizure	1 (2.9)	0 (0)	
RCVS etiology			
Idiopathic	32 (94.1)		
Postpartum	0 (0)		
Medication	2 (5.9)		

Data are median [interquartile range] or *n* (%) values.
*Other includes meningitis and cervicogenic headache.
PRES: posterior reversible encephalopathy syndrome, RCVS: reversible cerebral vasoconstriction syndrome, SAH: subarachnoid hemorrhage.

The different complication rates between Asian and Western cohorts may be attributable to differences in study settings and social factors, such as the headache-clinic-based (Korea and Taiwan) vs. stroke-center-based (United States) recruitment of patients.[1-3] The easy accessibility to university hospitals under the Korean National Health Insurance program might lead to a larger proportion of patients consulting headache specialists and being diagnosed with RCVS before they develop neurological deficits. In addition, illicit drug use is relatively rare in Korea, while it is reported as a major cause of RCVS in Western patients.[1,3,10] Genetic factors other than *RNF213* may additionally contribute the development of idiopathic RCVS.

Author Contributions

Conceptualization: Mi Ji Lee. Formal analysis: Yeon Hee Cho, Mi Jeong Oh. Investigation: Mi Ji Lee, Soohyun Cho, Chin-Sang Chung. Methodology: Yeon Hee Cho, Mi Jeong Oh. Writing—original draft: Joomee Song, Mi Ji Lee, Yeon Hee Cho, Chin-Sang Chung. Writing—review & editing: Mi Ji Lee, Chin-Sang Chung.

ORCID iDs

Joomee Song https://orcid.org/0000-0001-7590-6825
Yeon Hee Cho https://orcid.org/0000-0001-9363-7374
Mi Jeong Oh https://orcid.org/0000-0003-1411-7384
Soohyun Cho https://orcid.org/0000-0002-3900-3204
Oh Young Bang https://orcid.org/0000-0002-7962-8751
Mi Ji Lee https://orcid.org/0000-0003-1364-1969
Chin-Sang Chung https://orcid.org/0000-0002-0049-558X

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Acknowledgements

None.

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