Letter to the Editor

RNF213 Genetic Variant and the Arterial Circle of Willis

Dear Editor,

Comments on "Genetic Analysis of Ring Finger Protein 213 (RNF213) c.14576G>A in Intracranial Atherosclerosis of the Anterior and Posterior\ Circulations"

I have read with great interest the article "*Genetic analysis of ring finger protein 213 (RNF213) c.14576G>A in intracranial atherosclerosis of the anterior and posterior circulations*"[1] by Shinya et al published in the *Journal of Stroke and Cerebrovascular Disease*. They reported the high prevalence (23.3%, 10 of 43 patients) of the RNF213 genetic variant c.14576G>A in the intracranial atherosclerosis in the anterior circulation, but not in the posterior circulation (0%, 0 of 61 patients). This difference of the prevalence of the RNF213 variant was discussed embryologically by the fact that these 2 circulations are different because the arterial media in the anterior circulation are of neural crest origin, but those in the posterior circulation are of mesodermal origin, quoting my paper[2] in 2003. Original embryological work on the distribution of cephalic neural crest cells to cerebral arteries was done by Etchevers et al[3] in 2001.

The definition of the anterior circulation is worth thinking about. Shinya et al[1] defined the anterior circulation as the territory of the internal carotid artery and anterior and middle cerebral arteries, whereas the posterior circulation was defined as the basilar artery and intracranial vertebral artery. They excluded the posterior cerebral artery because they did not find an atherosclerotic lesion in this artery in their series. Embryologically, neural crest cells are distributed to the territory of the primitive internal carotid artery, which is divided into the cranial and caudal divisions at the origin of the posterior communicating artery.[4] The cranial division includes the distal internal carotid artery, anterior and middle cerebral arteries, and anterior choroidal artery (embryological old artery), and the caudal division includes the posterior communicating artery, the P1 portion of posterior cerebral artery, and the distal basilar artery as well as the diencephalic and mesencephalic arteries.[5] In early embryogenesis, the telencephalic branch of the primitive anterior choroidal artery is transferred to the caudal division of the primitive internal carotid artery, consequently becoming the P2-4 portions of the posterior cerebral artery. This phenomenon is called *distal annexation*. Thus, the neural crest cells are distributed to the distal internal carotid artery, anterior and middle cerebral arteries as well as the posterior communicating artery, posterior cerebral artery, and distal basilar artery, in other words, to the arterial circle of Willis and its branches.

Although the embryological border between the primitive internal carotid system and vertebro-basilar system was reported at the junction of the primitive trigeminal artery to basilar artery between the superior cerebellar artery and anterior inferior cerebellar artery,[5] this border must be located at basilar artery between the origins of the posterior cerebral artery (P1) and superior cerebellar artery because the cerebellum is embryologically a dorsal outgrowth of the isthmus and the first rhombomere,[6] which are supplied by the vertebro-basilar system. In fact, the media of superior cerebellar artery are of the mesodermal origin.[3] In this context, the conclusion of Shinya et al[1] could mean that the RNF213 genetic variant is exclusively found in patients with intracranial atherosclerosis in the territory of the primitive internal carotid artery, in other words, the circle of Willis and its branches.

Moyamoya disease is also called the spontaneous occlusion of the circle of Willis,[7] but now "moyamoya" is predominantly used because of the resemblance of moyamoya vessels in catheter angiography to the appearance of the cigarette puff, which is expressed in Japanese as "moyamoya."[8] The RNF213 variant is found in more than 70% of patients with this disease.[1,9,10] It is reasonable to use "the spontaneous occlusion of the circle of Willis" instead of "moyamoya disease" because the primary lesion occurs in the main arteries of the circle of Willis, not the well-developed secondary collaterals, ie, moyamoya vessels. Shinya et al[1] suggested a strong relationship between the primary vascular lesions in intracranial atherosclerosis and moyamoya disease in the territory of the circle of Willis of neural crest origin and RNF213 genetic variants. Because a disease of the neural crest origin is called neurocristopathy,[11] spontaneous occlusion of the circle of Willis is a vascular form of cephalic neurocristopathy.[12] The RNF213 genetic variant is probably the susceptibility gene not only for spontaneous occlusion of the arterial circle of Willis,[9,10] but for stenoocclusive diseases of the circle of Willis due to a variety of etiologies at least including atherosclerosis[1] and quasi-moyamoya disease,[13] which can be regarded as cephalic neurocristopathies.

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