



Neurosurgical Forum
LETTERS TO THE EDITOR

***RNF213* variant and quasi-moyamoya disease**

TO THE EDITOR: I read the article written by Phi et al.⁸ with great interest (Phi JH, Choi JW, Seong MW, et al: Association between moyamoya syndrome and the *RNF213* c.14576G>A variant in patients with neurofibromatosis Type 1. *J Neurosurg Pediatr* 17:717–722, June 2016). The authors found the *RNF213* c.14576G>A variant in 3 (18.7%) of 16 patients with quasi-moyamoya disease associated with neurofibromatosis Type 1. This is a new discovery and is contrary to a previous report stating that this *RNF213* variant was not found in 9 patients with quasi-moyamoya.⁷ However, these *RNF213* variants have been found in 24%–26% of patients with atherosclerotic steno-occlusive changes of the intracranial cerebral arteries.^{1,6} The *RNF213* c.14576G>A variant is found in 95% of patients with familial moyamoya disease and 73% of patients with solitary moyamoya disease; it is found in 1.4% of normal Asian controls.^{3,5} These observations could be summarized as follows: the *RNF213* c.14576G>A variant is found not only in moyamoya disease, but also in quasi-moyamoya disease, at least in Asians. It is therefore strongly suggested that this *RNF213* variant is a sensitivity gene for the steno-occlusive changes of the intracranial arteries in spite of the presence or absence of any known associated diseases.

Moyamoya disease is named for the resemblance that basal brain vessels have to a hazy puff of cigarette smoke on cerebral angiograms.¹⁰ The development of moyamoya vessels is known to be variable. They are marked in some pediatric patients but are not well developed in other patients, especially adults. Of the 2 vascular structural changes (i.e., steno-occlusive changes of the intracranial cerebral arteries and moyamoya vessels), steno-occlusive changes are primary lesions of the disease, and moyamoya vessels represent compensatory (responsive) angiogeneses, and are thus developed mostly from normal structures.^{2,4} The term “moyamoya” has a negative meaning in the Japanese language: gloomy or unclear. This has given the impression, especially to Japanese patients, and even general physicians, that moyamoya disease is curious and strange. They misunderstand that the primary lesions are these abnormal (i.e., moyamoya) vessels and that they do not normally exist. This ignores the fact that the moyamoya vessels are composed primarily from preexisting

normal perforating arteries at the base of the brain, which are essentially normal.

In the diagnostic criteria proposed by the Research Committee on Spontaneous Occlusion of the Circle of Willis (moyamoya disease) in Japan, moyamoya disease is portrayed as a clinical entity without any known etiology.⁹ This definition does not coincide with the modern concept that diseases are caused by either genetic, environmental, or epigenetic factors or any combination thereof. Therefore, whenever the causative etiology is found, the diagnosis must be changed to quasi-moyamoya disease or moyamoya syndrome. If the *RNF213* c.14576G>A variant is accepted as a sensitivity gene for moyamoya disease and is found in quasi-moyamoya disease as discussed above, I would like to propose that the nomenclature be changed and updated. Specifically, the broad clinical entities with progressive steno-occlusive changes of the terminal portions of the internal carotid arteries would be defined under the former name, spontaneous occlusion of the circle of Willis, instead of moyamoya disease. In this definition, 1) the development of moyamoya vessels is not always necessary; 2) both unilateral or bilateral progressive steno-occlusive changes of the terminal portions of the internal carotid arteries are included; and 3) associated diseases, such as neurofibromatosis, atherosclerosis, and autoimmune diseases, do not constitute exclusion criteria. This new definition will enable deliberate consideration of the broad etiologies of this interesting, but not gloomy, disease predominantly observed in the Asian population.

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Disclosures

The author reports no conflict of interest.

Response

The concept of quasi-moyamoya disease, or moyamoya syndrome, carries important meanings.³ First, it is crucial to identify quasi-moyamoya disease in patients with diverse underlying diseases, such as neurofibromatosis Type 1, Down syndrome, or thyrotoxicosis, because the proportions of quasi-moyamoya disease associated with these conditions are usually small enough to be overlooked for months or years. Second, the presence of quasi-moyamoya disease can broaden the concept of moyamoya disease itself. The definition of moyamoya disease has been well established: 1) idiopathic, 2) bilateral, 3) spontaneous occlusion of the circle of Willis, and 4) development of moyamoya (collateral) vessels. These classic criteria of moyamoya disease have been challenged in many aspects. For example, unilateral moyamoya disease and steno-occlusive diseases without collateral vessel formation have been diagnostic troublemakers. However, a more serious question arises from the etiological aspect—i.e., the idiopathic origin of the disease.

As Dr. Komiyama exactly pointed out, the term “idiopathic” is contradictory to the modern concept that a disease is “caused” by some defect, some process, or some other specific thing. Especially in the genomic era, many genetic and epigenetic causes/associations are being discovered for syndromes hitherto known as idiopathic. Then, if we uncover a causative etiology of moyamoya disease, it ceases to be idiopathic and should be called quasi-moyamoya or moyamoya syndrome. Following the conjecture, quasi-moyamoya disease is not an aberrant form of disease but a broader category, including the strict definition of moyamoya disease. Therefore, Dr. Komiyama suggested that the definition of moyamoya disease be changed and updated. He proposed that the core feature of spontaneous occlusion of the circle of Willis be the most solid criterion, discarding other variable characteristics (idio-

pathic etiology, bilateral involvement, and the presence of collateral vessels). We believe that Dr. Komiyama marked the most essential nature of the elusive disease because all various quasi-moyamoya diseases and syndromes share the common characteristic, spontaneous occlusion of specific vessels in brain. We would like to add that the term moyamoya phenomenon can be substituted for moyamoya disease, because it becomes clear that classic moyamoya disease is not a homogeneous entity. Despite the strong associations of the RNF213 c.14576G>A variant with moyamoya disease in the Asian population, patients without this genetic variant display almost the same disease phenotype. Furthermore, the variant has not been found in patients with moyamoya disease who are of European descent.¹ Associations with mutations in other genes, such as ACTA2 and GUCY1A3, have also been reported in quasi-moyamoya disease.^{2,4} Therefore, it is highly likely that we are facing a common phenomenon, spontaneous occlusion of the circle of Willis, in many patients with different etiologies, rather than dealing with a single disease.

However, we still depend on the clinical criteria of idiopathic moyamoya disease because its proportion in all moyamoya phenomena is so high, especially in Asian populations, and the natural history and prognosis of idiopathic moyamoya disease are distinct from those of quasi-moyamoya diseases. Therefore, continuing investigation of etiologies and construction of a more sophisticated etiology-based classification system are required to address moyamoya phenomena. In the near future, we may diagnose a patient as having bilateral (or unilateral) moyamoya phenomenon (spontaneous occlusion of the circle of Willis) with collateral vessels, associated with a specific genetic/epigenetic variant.

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