Developing Novel Therapeutic Strategies Against Ring Finger Protein 213 Vasculopathy: Is It an Achievable Goal?

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Intracranial atherosclerosis (ICAS) represents the most important cause of stroke in the world, and its global burden as a cause of stroke is likely to increase further.[1] ICAS is a progressive disease characterized by the eccentric accumulation of lipids and cellular and fibrous elements in the large arteries, leading to changes ranging from slight wall thickening and nonstenosing plaques to hemodynamically significant luminal narrowing.[2] ICAS accounts for 5% to 10% of stroke in non-Hispanic whites, 15% to 30% in non-Hispanic blacks or African Americans, and up to 30% to 50% in Asians. The global burden of ICAS as cause of stroke is likely to increase further, giving the aging of the world population and rising prevalence of vascular risks.[3]

Ring finger protein 213 (*RNF213*), a gene located in chromosome 17q, encodes a protein with 5256 amino acids, containing a C3HC4-type RING finger domain and an AAA domain, which are involved in mediating protein-protein interactions and ATPase activity, respectively.[4] This gene is a susceptibility gene for Moyamoya disease, a vascular disorder of intracranial arteries.[4] Recently, several studies indicated the *RNF213* variant had significant association with ICAS.[5,6]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Choi et al[7] report on the association of *RNF213* p.Arg4810Lys variant (c.14429G>A, *rs112735431*) with plaque characteristics, vascular remodeling, and hemodynamics in patients with ICAS stroke in South Korea. Among 690 patients with intracranial stenosis selected from 2012 to 2017, 144 were confirmed as having ICAS by high-resolution magnetic resonance imaging. The study found that almost 30% of cases were *RNF213* variant carrier, and outer vessel diameters of the intracranial arteries in carrier were significantly smaller than in noncarrier. Through multivariate testing, the authors indicated that the association between the outer vessel diameter and the genetic variant remains significant after adjusting for demographic characteristics (age, sex, height, and body mass index), whereas the characteristics of plaques had no significant difference between 2 groups. A further multiple regression analysis showed that *RNF213* variant was independently associated with a smaller diameter of the stenotic segment. The researchers also reported on the correlation of fractional flow ratio with the degree of stenosis and outer vessel diameter of stenotic segments. However, only the outer vessel diameter of stenotic segments contributed to the fractional flow ratio after adjusting other factors.

The results presented by Choi et al[7] are consistent with recently published studies of another variant in this same protein, *RNF213* c.14576G>A (*rs112735431*), which was identified as a possible genetic risk factor associated with ICAS.[5] Approximately 22% of patients with non–Moyamoya disease ICAS possess this *RNF213* variant in East Asia.[5,8] A recent study from Japan demonstrated that the outer diameter of the stenotic/normal side middle cerebral artery was smaller in this variant carrier group than in the variant noncarrier group.[9] Another study in China also observed a shrunken outer diameter, concentric thickening vessel wall, and collateral vessel structures on the stenotic part in *RNF213* variant carriers among patients with intracranial major artery stenosis.[10] In addition, brain arterial diameter is a risk factor for vascular events, and brain arterial wall thickening is inherently associated with aging.[11,12]

What is the clinical significance of these findings? To provide precision medicine, we require both refined diagnostics and targeted therapeutics. Atherosclerosis is a slow, complex, multifocal arterial disease affecting medium and large arteries; and it involves interactions of multiple environmental and genetic factors. Environmental factors, such as dietary habits, play a significant role in development of atherosclerosis, whereas genetic factors represent a consequential determinant of atherosclerotic disease risk.[13]

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This interesting work from Choi et al[7] enhances our understanding of the impact of *RNF213* variant on intracranial artery diameter and brain blood flow.

The next challenge is how to translate this information into an improved therapeutic approach to decrease ICAS-related events. The first step is variant assessment. It is necessary to determine which atherosclerotic disease phenotype is associated with this *RNF213* variant, and which type of variation may lead to clinically relevant consequences, because different types of variants in the same gene may be associated with distinct phenotypes or inheritance patterns.[14] Further genome-wide association studies in multiple populations are needed to confirm the correlation between genotype and phenotype. Then, this variant may be of use as a specific biomarker for patients with the corresponding atherosclerotic disease phenotype. Furthermore, this genetic biomarker might be used as a predictor of outcomes as well as the current radiological and hemodynamic markers for diagnosis, classification, and treatment of related ICAS disease.

Disclosures

Dr Gutierrez reports National Institute on Aging 5R01AG057709. Dr Liu has no disclosures to report.

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