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EDITORIAL COMMENT

What Can Be Seen From "Intracranial-Vascular"–Susceptibility Genetic Factor in "Cardiovascular-Susceptible" Familial Hypercholesterolemia*

A New Clue

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Familial hypercholesterolemia (FH) is 1 of the most common genetic diseases, with a genetic defect in LDL-receptor function.[1] Highly elevated serum LDL-C levels from birth are the cause of premature coronary artery disease (CAD) in these patients. Early diagnosis is essential to prevent their early deaths, but FH has been still underdiagnosed and undertreated in many countries, also in east Asia, despite efforts to raise awareness up to the present.

It has been a kind of mystery why elevated LDL-C in FH clearly accelerates atherosclerosis in coronary arteries but not in intracranial arteries. Without appropriate intensive therapies, patients with homozygous FH, a severe form of FH with 2 pathogenic variants, frequently die young of cardiovascular disease[2] but rarely of intracranial artery disease,[3] with some exceptional cases. Also, in a large cohort of individuals with genetically verified heterozygous FH, the risks of cerebrovascular disease and ischemic stroke were not increased.[4]

Many LDL-lowering clinical trials have shown a clear risk reduction in cardiovascular disease but less reduction in cerebrovascular disease. Acceleration of atherosclerosis with LDL-C seems not the same in coronary arteries as in intracranial arteries, and the underlying mechanisms at the molecular level are not well elucidated.

DISCOVERY OF RNF213 GENE IN MOYAMOYA DISEASE

Moyamoya disease is a rare cause of stroke, and RNF213 is the major susceptibility gene in people from east Asia.[5] It is characterized by progressive stenosis of the terminal portion of the internal carotid arteries and compensatory capillary collateral arteries. The Arg4810Lys variant of the RNF213 gene is strongly associated with moyamoya disease, but its penetrance rate is <1%. By contrast, the Arg4810Lys variant had been reported to have an important role in the development of intracranial major artery stenosis/occlusion (ICASO).[6]

THE RNF213 GENE VARIANT INCREASED ICASO IN FH IN A DIFFERENT MANNER THAN IN CAD

In this issue of *JACC: Asia*, Noda et al[7] report that FH patients show an increased prevalence and severity of ICASO associated with the Arg4810Lys variant. FH may be a kind of naturally occurring accelerated atherosclerosis model in which affected individuals have elevated LDL-C from birth. It is intriguing that CAD-associated indices in FH, like tendon xanthomas, pathogenic LDLR gene variants,[8] or "severe FH" with double mutations in LDLR and PCSK9 genes,[9] were not associated with ICASO in FH. The Arg4810-Lys variant in RNF213 gene in FH was not associated with CAD in this study. This RNF213 gene variant

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seems basically a cerebrovascular-susceptive genetic factor.

The authors speculate that the Arg4810Lys variant in the RNF213 gene may downregulate PECAM-1, an important shear stress sensor, and may cause inflammatory changes and mitotic abnormalities in endothelial cells. The underlying mechanisms in the differences between coronary arteries and intracranial arteries should be elucidated in future studies.

Only exceptional cases of FH show symptomatic intracranial artery disease in young individuals, but this study could reveal a genetic background for these cases. This study may reveal 1 clinical clue to this mystery and may enable the development of new strategies for intracranial artery disease.

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