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Significance of a Novel Apolipoprotein E Variant, ApoE Osaka/Kurashiki, in Lipoprotein Glomerulopathy

Lipoprotein glomerulopathy (LPG) is a unique kidney disease characterized by lipoprotein thrombi in the glomerulus¹⁾. Type III hyperlipoproteinemia with a high apolipoprotein E (apoE) level in serum is a distinctive feature in the lipoprotein profile²⁾. Approximately 100 cases of LPG have been reported in the world since we published the first case in the *American Journal of Kidney Diseases* in 1989³⁾, and the characteristics mentioned above are common to almost all LPG cases. Accordingly, it has been suspected that abnormal lipoproteins induced by apoE variants play a pivotal role in the formation of lipoprotein thrombi of LPG. Thirteen different apoE variants were detected in LPG cases since we discovered apoE Sendai (Arg145Pro) in 1997⁴⁾. These LPG-related apoE variants are mainly caused by point mutations of amino acid residues around the LDL-receptor binding domain, and constitute isoforms with apoE2 or E1 allele.

In this issue, cases of LPG with the same novel variant, apoE2 (Arg158Pro), are published independently, and the variants are called apoE Osaka and apoE Kurashiki, respectively^{5, 6)}. Patients in both reports were not relatives and the distance between their homes was 130 km, although they might have had remote ancestors in common.

ApoE is an arginine-rich protein and the substitution of cysteine for arginine at position 158 is recognized as a common apoE2 mutation causing familial type III hyperlipoproteinemia⁷⁾; however, the substitution of proline for arginine at the same position is not known so far. On the other hand, the substitution of proline for arginine was the first apoE mutation in LPG, called apoE Sendai (Arg145Pro)⁴⁾, which comprises the majority of apoE variants related to LPG. Moreover, apoE Chicago (Arg147Pro)⁸⁾ and apoE Guangzhou (Arg150Pro)⁹⁾ have been reported in the United States and China, respectively. Proline acts as a structural disrupter in the middle of the alpha helix, and is commonly found as the first residue of the alpha helix or in turns in an amino acid arrangement^{1, 4)}. Accordingly, proline is not in or around the LDL-receptor binding domain of apoE which forms a continuous alpha helix. Once the substitution of proline occurs in this area, however, apoE may seriously change its structure, aggregate lipoproteins and induce intra-glomerular lipoprotein thrombi of LPG.

It is of interest that the substitution of proline as-

sociated with LPG was found at position 158, where the common apoE2 mutant inducing familial type III hyperlipoproteinemia possesses cysteine. In this point, we recognize that both reports published in this issue^{5, 6)} are very valuable and propose that the novel variant be called apoE Osaka/Kurashiki.

In LPG, apoE variants having 3 amino acid deletions were reported independently as apoE Tokyo (del 141-143)¹⁰⁾ and apoE Maebashi (del 142-144)¹¹⁾. But both deletions were recognized to be the same because the amino acid arrangement was repeated between 141 and 146. Now, this variant is generally called apoE Tokyo/Maebashi and is found not only in Japan but also in China. The discovery of apoE Osaka/Kurashiki will widen the scope of the study of LPG.

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