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EDITORIAL

APOLIPOPROTEIN E AND CARDIOVASCULAR DISEASES

Since Utermann and colleagues first described the effect of apolipoprotein E (apoE) polymorphism on type III familial hyperlipoproteinemia in 1977, it has become clear that genetic variability of apoE not only is of key importance in lipid metabolism but also in cardiovascular disease (CVD), Alzheimer disease, cognitive function, and immunoregulation.

Polymorphism of apoE gene causes susceptibility to many diseases. Much attention has been paid to its role in atherosclerotic CVD and neurodegenerative disorders.[1,2] In general, the ε2 allele is consistently associated with lower levels of total plasma cholesterol, LDL cholesterol, and apoB; and elevated levels of triglyceride and apoE compared with the ε3 allele. Conversely, the ε4 allele is associated with higher levels of total and LDL cholesterol and apoB and lower levels of apoE. The apoE4 isoform has the highest fractional efficiency of cholesterol absorption from the gut and the highest binding affinity to the LDL receptor, leading to a larger down-regulation of the LDL receptor compared with the apoE2 or E3 isoform. However, this is likely only a partial contribution to the risk conveyed by apoE genetic variation, as apoE allele-specific properties are subject to various genetic and environmental influences. Thus, apoE has gender- and allele-dependent effect on overall lipoprotein metabolism, e.g., reverse cholesterol transport, platelet aggregation, immune function, and oxidative processes.[3] Further, the effect of the apoE gene on lipoproteins may differ with age. In elderly subjects, as well as in children, there is less difference in LDL cholesterol levels in individuals carrying the ε4 allele versus non-ε4 carriers.[4,5] Recently, the role of apoE has been extended also to intracellular lipoprotein trafficking, but there is limited information on whether these are influenced by genotype variations.[6,7]

As mentioned above, many studies have investigated the association of apoE genotype with CVD. In a recent meta-analysis, compared to E3/E3, the summary odds ratio for coronary disease was 0.80 (95% CI, 0.70-0.90) in ε2 carriers and 1.06 (95% CI, 0.99-1.13) in ε4 carriers. Based on these results, the authors conclude that compared to individuals with the E3/E3 genotype, ε2 carriers had 20% lower risk of CHD; and ε4 carriers, a slightly higher risk. Notably, subjects with E2/E2 genotype had about 30% lower LDL-C values than those with the E4/E4 genotype. In the current issue of the journal, Singh *et al.*[8] report on the relationship of apoE polymorphism with CHD in a northwest

Indian population of 193 angiographically diagnosed CHD patients and 150 healthy control subjects. The investigators found that carriers of the E3/E4 genotype had threefold higher risk of developing CHD (OR, 3.04; CI, 1.55-6.25; $P < 0.005$) and that this association remained significant after adjusting for age, sex, BMI, and lipid-lowering drugs. Although the authors found a significant association of the E3/E4 genotype with HDL-C and LDL-C, no associations were found with total cholesterol or triglyceride levels. Some limitations include the selection of control subjects based on ECG and the overall cross-sectional design. As the impact of genetic variability is likely to vary across populations, these types of studies are important and further studies to clarify the association of apoE genotype with CVD in various populations are warranted.

In conclusion, studies investigating the relation of apoE polymorphism to CHD risk in different ethnic groups are important and may provide important new insights into underlying mechanisms contributing to the etiology of CVD.

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