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The *APOE* gene and diets—food (and drink) for thought[1,2]

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Interest has increased in understanding the interaction between genes and nutrients in the development of atherosclerosis (1). Many studies have addressed the role of such interactions in the response of plasma lipid concentrations to variations in intakes of primarily fat and cholesterol. In the field of lipid and lipoprotein research, several candidate genes have attracted attention but the polymorphism at the apolipoprotein E gene (*APOE*) locus perhaps has the most extensive effects on lipoprotein metabolism in humans (2). This reflects the important functions of *APOE* in the lipolytic catabolism and receptor-mediated uptake of triacylglycerol-rich lipoproteins. The role of *APOE* has been extended to intracellular lipoprotein trafficking (3, 4). Over the years, a rich database has accumulated showing that variation at the *APOE* locus is associated with differences in risk of premature atherosclerosis and in the development of Alzheimer disease. In general, carriers of the *APOE***E4* (*E4*) allele have higher and carriers of the *APOE***E2* (*E2*) allele have lower LDL-cholesterol concentrations, and variation at the *APOE* locus accounts for ≈7% of the population variance in total and LDL-cholesterol concentrations (5). However, this pattern seems to some extent to be dependent on age. In elderly subjects and in children, there is less difference in LDL-cholesterol concentrations in carriers than in noncarriers of the *E4* allele (6, 7). Interestingly, in both of these age groups, the presence of the *E2* allele was associated with an antiatherogenic lipoprotein pattern. This pattern variation with age suggests that the effect of genetic variation in *APOE* on plasma lipids can be modified.

Currently, different and partially contradictory results were obtained in studies of the associations of *APOE* variation with plasma lipid responses to dietary variations. Although some studies found more pronounced dietary responsiveness in carriers of the *E4* allele, others reported no difference in response across *APOE* allele types to changes in dietary fat, cholesterol, or both (1, 2). An interesting and rather consistent finding, however, was the presence of an apparent sex effect. Thus, even in studies in which there was a response of plasma lipid concentrations, the *APOE* effect was generally seen in men but not in women (2, 8). In this issue of the Journal, 2 articles address gene-nutrient interactions at the *APOE* locus (9, 10).

Corella et al (9) investigated the plasma lipid response to alcohol across *APOE* genotypes in the Framingham Offspring Study population. It is interesting to note that this study also found a difference in the responses of men and women. In men, the expected pattern for LDL cholesterol, ie, higher concentrations in carriers of the *E4* allele than in carriers of the *E2* allele, was seen only among drinkers. Among nondrinkers, no significant difference in LDL-cholesterol concentrations across *APOE* genotypes was found, although there were substantially fewer nondrinkers than drinkers. In women, LDL cholesterol was significantly higher in carriers of the *E4* allele than in carriers of the *E2* allele among both drinkers and nondrinkers. The exact mechanisms involved remain to be clarified. Because associations between *APOE* allele types and plasma cholesterol responses were observed primarily in subjects susceptible to hypercholesterolemia, the results suggest that the metabolic stress of alcohol consumption might uncover underlying differences in cholesterol, triacylglycerol, or lipoprotein metabolism.

Although the *E4* allele is associated with increased cholesterol concentrations, the *E2* allele has been associated with lower cholesterol concentrations along with a slower clearance of triacylglycerol-rich lipoprotein remnants. Previous studies found a more pronounced triacylglycerol response in carriers of the *E2* allele when the dietary carbohydrate and fiber contents of the diet varied (2). The study by Erkkilä et al (10) provides further support for the association of carbohydrate and triacylglycerol metabolism with the *E2* allele. These authors evaluated plasma lipid responses to dietary fat and carbohydrate in men and women with coronary artery disease. Overall, carriers of the *E2* allele had lower LDL-cholesterol concentrations and a tendency to higher triacylglycerol concentrations relative to carriers of the *E3* and *E4* alleles. In addition, there was a positive association between dietary sucrose (6–7% of the total energy intake) and plasma triacylglycerol concentrations only in carriers of the *E2* allele. As in most other studies, however, it is important to note that the number of *E2* allele carriers was small (5% of all subjects) and in the present study they were mostly male. Thus, it is appropriate to exercise caution when interpreting the data.

Although it is difficult to speculate about the mechanisms behind these effects, one can envision several possibilities. First, *E2* allele carriers may have a compromised clearance system for triacylglycerol-rich lipoproteins. Thus, even a modestly increased VLDL production in response to sucrose could result in an increased plasma triacylglycerol concentration. Alternatively, in addition to affecting uptake of triacylglycerol-containing remnant particles, the *APOE* polymorphism may play a role in the intrahepatic synthesis and catabolism of triacylglycerol-rich

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lipoproteins (3, 4). Further work is needed to define whether variation at the *APOE* locus affects these pathways.

Although a growing number of studies address gene-nutrient interactions, in most studies this has been a secondary aim, usually analyzed a posteriori. It is important to keep in mind that multiple comparisons as well as low allele frequency could lead to spurious associations; therefore, these observations need verification. Because the *APOE* locus is an example of a polymorphism with important effects on plasma lipid patterns, the 2 studies in this issue of the Journal (9, 10) add fuel to the fire. However, our ability to confirm the presence of gene-nutrient interactions and to understand their metabolic basis will require larger and more detailed studies.

REFERENCES

1. Tall A, Welch C, Applebaum-Bowden D, Wassef M. Interaction of diet and genes in atherogenesis. Report of an NHLBI working group. Arterioscler Thromb Vasc Biol 1997;17:3326–31.
2. Ordovas JM, Schaefer EJ. Genes, variation of cholesterol and fat intake and serum lipids. Curr Opin Lipidol 1999;10:15–22.
3. Schwiegelshohn B, Presley JF, Gorecki M, et al. Effects of apoprotein E on intracellular metabolism of model triglyceride-rich particles are distinct from effects on cell particle uptake. J Biol Chem 1995;270:1761–9.
4. Mensenkamp AR, Jong MC, van Goo H, et al. Apolipoprotein E participates in the regulation of very low density lipoprotein-triglyceride secretion by the liver. J Biol Chem 1999;274:35711–8.
5. Wilson PWF, Schaefer EJ, Larson MG, Ordovas JM. Apolipoprotein E alleles and risk of coronary disease. A meta-analysis. Arterioscler Thromb Vasc Biol 1996;16:1250–5.
6. Pablos-Mendez A, Mayeux R, Ngai C, Shea S, Berglund L. Association of apoE polymorphism with plasma lipid levels in a multiethnic elderly population. Arterioscler Thromb Vasc Biol 1997;17:3534–41.
7. Isasi CR, Couch SC, Deckelbaum RJ, et al. The apolipoprotein ϵ2 allele is associated with an anti-atherogenic lipoprotein profile in children: The Columbia University Biomarkers Study. Pediatrics 2000;106:568–75.
8. Ordovas JM. The genetics of serum lipid responsiveness to dietary interventions. Proc Nutr Soc 1999;58:171–87.
9. Corella D, Tucker K, Lahoz C, et al. Alcohol drinking determines the effect of the *APOE* locus on LDL-cholesterol concentrations in men: the Framingham Offspring Study. Am J Clin Nutr 2001;73:736–45.
10. Erkkilä AT, Sarkkinen ES, Lindi V, Lehto S, Laakso M, Uusitupa MIJ. *APOE* polymorphism and the hypertriglyceridemic effect of dietary sucrose. Am J Clin Nutr 2001;73:746–52.