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Genetic recipes for heart-healthy diets[1,2]

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Given the major impact of nutrients such as saturated fat and cholesterol on plasma lipoproteins, it is reasonable to suppose that interindividual variations in genes affecting lipoprotein metabolism and controlling intestinal nutrient absorption contribute to the large differences in lipoprotein response to dietary change that have been shown to exist among individuals (1, 2). Most specific gene variants found to date, however, have been studied primarily in relation to plasma concentrations of lipids and lipoproteins ("level" genes) rather than in relation to changes caused by diet or other sources of variation ("variability" genes) (3).

Several factors may contribute to the difficulty in identifying genes that influence the response to diet. Changes in dietary intake call into play many regulatory responses that can act to attenuate the effect of these changes on the organism's metabolic milieu, and thus, the effects of individual gene variants can be difficult to discern. Indeed, given the multiplicity of genes involved in key metabolic pathways, it may be that differences in groups of genes, rather than in individual genes, are required to generate major interindividual differences in responsiveness to diet. Furthermore, consider that functions have been identified for only a small portion of the DNA sequences in the human genome and that important regulatory variants may exist in the large portion of the genome that is considered to be noncoding.

An additional concern is that the measurements that are carried out to identify lipoprotein phenotypic variation may not be informative because these phenotypes are considerably downstream of gene products. For example, genetic influences on LDL-cholesterol concentrations represent a composite of effects on lipoprotein production, intravascular metabolism, plasma clearance, and composition—each of which may have multiple genetic influences. In this regard, recent studies have suggested that effects of isoforms of the apolipoprotein (apo) E gene on response to diet may be more evident from measurements of postprandial triacylglycerol (4) or LDL subclasses (5) than of LDL-cholesterol concentrations.

Note also that any given dietary manipulation chosen for study can result in overall changes in the diet with multiple metabolic effects that could be influenced by a diverse group of genes. For instance, with reduction in dietary saturated fat there may be increased intake of carbohydrate or unsaturated fat or decreased total energy intake and these dietary changes could influence lipoprotein concentrations through a variety of mechanisms involving many different genes. Another variable to be considered is the duration of the experimental diets because genetic influences on short-term metabolic responses may not be the same as those that operate over the long term.

A final potential confounding effect that applies to all efforts to identify genes responsible for specific human phenotypes is the influence of the genetic backgrounds of the individuals under study. For example, there may be modifying effects of specific genes or metabolic pathways that differ among ethnic or other population subgroups that are not relevant to other groups or to the general population.

Particularly in view of these potentially confounding factors, conclusions regarding the significance of genetic associations with dietary lipoprotein response will require confirmation in multiple population studies, and ideally, mechanistic information that can provide a meaningful basis for interpreting the findings. In recent years, numerous studies have reported associations of specific genetic polymorphisms with various diet-induced lipoprotein changes (6). In some cases, however, such as with the well-studied E*4* allele of the apo E gene, these associations have not been observed consistently (2, 5, 7–9). Moreover, most of these associations have been relatively weak, accounting for only a small portion of the variance in lipoprotein response. These results are consistent with the notion that any lipoprotein response reflects a composite of multiple genetic effects. Studies need to be carried out in populations that are of sufficient size to yield statistical power for identifying associations with genes, either singly or in combination, as well as gene dosage effects.

Rantala et al (10) used meta-analysis to overcome the limitations of individual studies, including their own, in assessing relations of variants of the apo B gene with the lipoprotein response to dietary fat and cholesterol. It is of interest that the studies used for the meta-analysis involved diets that varied widely in content and type of fatty acids as well as cholesterol. Although this approach therefore falls short of defining effects of apo B genotypes on response to specific nutrients, it can nevertheless lead to inferences regarding functional effects of apo B gene variants that are manifest by their influence on responsiveness to diet.

Previous studies have shown that the baseline LDL-cholesterol concentration is among the strongest predictors of response to reduction in saturated fat and cholesterol intake (2, 11). Therefore, there may be some congruence of level genes and variability genes in this laboratory measure. Of the 3 apo B variants

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reported by Rantala et al to be associated with responsiveness to diet of LDL cholesterol, 2 were associated with higher and 1 with lower ambient LDL concentrations. It will be necessary to determine the mechanisms underlying these discordant relations to adequately assess their biological and clinical significance.

Because many genes involved in lipoprotein metabolism act to ensure effective lipid transport under a range of dietary conditions, more extensive studies of their influence on dietary response should help to delineate their overall metabolic functions. This approach can also be of value in investigating the actions of other nutrient-related genes that may influence cardiovascular disease risk, such as those affecting carbohydrate, mineral, and homocysteine metabolism. Comprehensive analyses of these complex multigenic systems will likely require data from large populations and the use of computer-based mathematical modeling techniques to permit coherent interpretations of the results. With evolving technology for gene analysis and array-based assessment of dietary effects on gene expression, it may ultimately be possible to incorporate such genetic information in the development of dietary recommendations that are aimed at optimizing the health of individuals or population subgroups.

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