Genetic interactions with diet influence the risk of cardiovascular disease

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ABSTRACT

Single-nucleotide polymorphisms are an integral component of the evolutionary process that over millennia have resulted from the interaction between the environment and the human genome. Recently, recent changes in diet have upset this interaction with respect to the nutritional environment, but nutritional science is beginning to better understand the interaction between genes and diet, with the resulting potential to influence cardiovascular disease risk by dietary modification. Single-nucleotide polymorphisms in several genes have been linked to differential effects in terms of lipid metabolism; however, even a simple model of benefit and risk is difficult to interpret in terms of dietary advice to carriers of the various alleles because of conflicting interactions between different genes. The n=3 family of polyunsaturated fatty acids is underrepresented in our modern diet; much of the benefit of polyunsaturated fatty acids found in studies of various polymorphisms seems to be linked to increased n=3 polyunsaturated fatty acid intake. The nascent science of nutrigenomics faces many challenges; more and better research is needed to clarify the picture, rebut scepticism, and revitalize the discussion concerning genetic polymorphism and its interaction with diet. Am J Clin Nutr 2006;83(suppl):443S–6S.

KEY WORDS Cardiovascular disease, cardiovascular risk, polymorphism,apolipoprotein, apolipoprotein A-I, APOA1, apolipoprotein A-V, APOA5, HDL cholesterol, triacylglycerol, polyunsaturated fatty acids

INTRODUCTION

Over the years, many epidemiologic and interventional studies have allowed us to characterize the factors associated with increased risk of cardiovascular disease (CVD), and we now have well-established scientific guidelines and risk assessor models that allow us to identify who is at risk, why, and what can be done to minimize that risk (Figure 1). Of course, not all CVD risk factors are modifiable. Age, sex, and family history, by which we usually mean genotype, cannot be modified, whereas smoking, alcohol intake, physical activity, and diet and the intermediate risk factors of hypertension, blood lipid profile, glucose intolerance, and overweight or obesity can be modified by lifestyle or pharmaceutical intervention (2). The goal of cardiovascular risk modification is to increase life expectancy and to maintain health and well-being for as long as possible into old age by avoiding the negative outcomes of coronary artery disease, stroke, and peripheral vascular disease.

One of the areas in which our understanding of the development and progression of CVD is currently expanding rapidly is how genetic variation interacts with the environment, and specifically dietary intake, to influence overall CVD risk. The interaction between genes and environment is an integral component of evolution, and this includes the cross-talk between a subset of genes and diet that has resulted in adaptations for specific nutrients. However, the typical diet has changed dramatically over the past 200 y or so—too quickly to be accompanied by a commensurate evolutionary adaptation—and this imbalance has resulted in associations between certain genetic polymorphisms and diet and increased CVD risk.

With adequate information on the interaction between specific genetic polymorphisms and diet and CVD risk, it may be possible to provide individuals with dietary guidance tailored according to their genotype. This article discusses some of the genetic polymorphisms known to affect CVD risk factors and how their phenotypic manifestations may be modified by dietary intake.

EFFECT OF APOLIPOPROTEIN A-I GENETIC POLYMORPHISM AND POLYUNSATURATED FATTY ACID INTAKE ON HDL CHOLESTEROL

Apolipoprotein (apo) A-I is a key component of HDL. HDL is produced by the liver and intestine and is responsible for the transport of cholesterol from peripheral tissues back to the liver for metabolism through a series of complex interactions with other lipoproteins, enzymes, transfer proteins, and receptors (3). Both apo A-I and HDL-associated cholesterol have been identified as protective factors for CVD (4, 5).

The gene coding for apo A-I, APOA1, which is found on the long arm of chromosome 11, is highly polymorphic, and a specific single-nucleotide polymorphism in its promoter region known as APOA1 −75G→A) (6, 7) has been extensively studied in relation to apo A-I and HDL-cholesterol concentrations, with conflicting results (8–23). A meta-analysis involving some of these studies concluded that the rarer A allele may be associated with mildly increased (=0.05 mg/dL) apo A-I concentrations (6). Could these inconsistencies between studies be the result of...
interactions with dietary factors that modulate the effect of this genetic polymorphism?

One way in which diet may influence APOA1 gene expression is through dietary intake of the essential fatty acids, the n−3 and n−6 polyunsaturated fatty acids (PUFAs), which are also referred to as omega-3 and omega-6 fatty acids. Animal studies have shown that PUFA intake can modulate the gene expression of several enzymes involved in lipid and carbohydrate metabolism (24). In a study involving 50 men and women fed diets rich in saturated fat, monounsaturated fat, or PUFA, reductions in LDL cholesterol associated with the PUFA diet compared with the saturated fat diet were more marked in women who were carriers of the rarer A allele than in women who were homozygous for the G allele, but no such effect was evident in men (25).

In another study involving 755 men and 822 women from the Framingham Offspring Study, a significant interaction in terms of HDL-cholesterol concentration was observed between APOA1 genotype and PUFA intake (Figure 2; 26). In that study, the subjects were divided into low (<4% of energy), medium (4–8% of energy), and high (>8% of energy) PUFA intake groups. In women who were carriers of the A allele, HDL-cholesterol concentrations increased significantly with increasing PUFA intake. The opposite effect was seen in women who were homozygous for the G allele (HDL-cholesterol concentrations decreased as PUFA intake increased). In men, PUFA intake had no significant effect on either HDL cholesterol or apo A-I concentrations.

This meant that when PUFA intake provided <4% of energy, women who were homozygous for the G allele had 14% higher HDL-cholesterol concentrations than did carriers of the A allele, and when PUFA intake provided >8% of energy, HDL-cholesterol concentrations in carriers of the A allele were 13% higher than those of G/G subjects (26). This raises the possibility of providing individualized nutritional advice on the basis of genotype: women who are carriers of the A allele should increase their intake of PUFAs to increase HDL-cholesterol concentrations and reduce CVD risk, whereas G/G women should receive the opposite advice.

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GENE POLYMORPHISM

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor supergene family that plays a central role in (among other things) fatty acid oxidation and extracellular lipid metabolism (27–29). PPARs bind to fatty acids and fatty acid metabolites and regulate the expression of genes involved in their transport and metabolism. About 300 genes are known to be activated by members of the PPAR family.

The gene for PPAR-α has a polymorphism at codon 162 (the PPARA Leu162Val polymorphism) that has been associated with alterations in total cholesterol, LDL-associate cholesterol, and apo B concentrations (30–32). In an analysis involving 1128 men and 1244 women in the Framingham Offspring Study, the presence of the less common V162 allele was associated with significantly higher serum concentrations of total cholesterol, LDL-cholesterol, apo B, and apo C-III than in carriers of the L162 allele in men, even after adjustment for age, BMI, cigarette smoking, and use of β-blockers, or diuretics. In women, the same trend was seen, but it was less pronounced (32).
Is there any interaction between this polymorphism and PUFA intake? Another investigation of 2106 men and women from the Framingham Offspring Study showed that for persons with the common \( L162 \) allele, increased intake of PUFAs had little effect on fasting triacylglycerol concentrations. In those with the less common \( V162 \) allele, however, fasting triacylglycerol concentrations fell markedly with increasing PUFA intake (33).

Thus, PUFA intake interacts with 2 polymorphisms (\( APOA1 \) −75G−A and \( PPARA \) Leu162Val), and these interactions influence CVD risk in different directions through their effects on 2 different CVD risk factors (HDL cholesterol and triacylglycerol). This complicates any attempts to provide dietary advice based on genotype. For example, in subjects who are homozygous for both \( APOA1 \) −75G and \( PPARA \) Leu162, increasing PUFA intake decreases HDL-cholesterol concentrations but does not affect triacylglycerol concentrations; thus, the net effect is an increase in CVD risk and the dietary advice is to consume less PUFAs. Persons who are carriers of the \( APOA1 \) −75T allele and who are homozygous for \( PPARA \) V162 should be recommended to increase their PUFA intake. For other genotype combinations, however, the evidence may be insufficient to recommend either increased or decreased intake of PUFAs.

So, with our current knowledge, if the model is expanded to include 3 genes (ie, \( APOA1 \), \( PPARA \), and \( APOA5 \)) but to still only consider 1 dietary component and 2 risk factors, it is no longer possible to provide dietary recommendations on the basis of genotype, even in what is still a very simple situation. Clearly, further research is needed to better understand the more realistic scenario in which interactions occur among multiple genes as well as with dietary and other environmental factors.

**DIFFERENTIAL EFFECTS OF n−6 AND n−3 POLYUNSATURATED FATTY ACIDS**

So far, PUFAs have been considered as a single factor. What happens when these interactions are analyzed in terms of the n−6 and n−3 PUFAs? The n−3 PUFAs are found in large amounts in marine fish, whereas cooking oils, spreads, and hidden fats are the main dietary sources of the n−6 series. The 2 PUFA families interact metabolically in a system that has evolved over many millions of years and that is geared to a preferred ratio of n−6 to n−3 PUFAs. For various reasons, it is believed that the ratio has become unbalanced in today’s diet in favor of the n−6 family.

A significant interaction has also been described for the \( PPARA \) Leu162Val polymorphism and n−6 PUFA intake. In persons with the less common \( V162 \) allele, increased n−6 PUFA intake is associated with a marked reduction in triacylglycerol concentration, whereas this association is not observed in \( L162 \) carriers (33). Conversely, when n−3 PUFA intakes are taken into consideration, both \( L162 \) and \( V162 \) carriers experience beneficial decreases in triacylglycerol concentrations as the intake of n−3 PUFAs becomes higher.

**DIFFERENTIAL EFFECTS OF n−6 AND n−3 POLYUNSATURATED FATTY ACIDS ON 5-LIPOXYGENASE**

The interaction between genotype and dietary PUFA intake is not limited to lipid metabolism. 5-Lipoxygenase is a pivotal enzyme in the production of leukotrienes from arachidonic acid. A recent publication by Dwyer et al (33) investigated the relationship between a polymorphism in the 5-lipoxygenase promoter region and carotid intima-media thickness in 470 healthy, middle-aged women and men from the Los Angeles Atherosclerosis Study (33).

In that study, variant 5-lipoxygenase genotypes (lacking the common allele) were found in 6.0% of the cohort (33). Carotid intima-media thickness was significantly higher among carriers of 2 variant alleles when adjusted for age, sex, height, and racial or ethnic group. A positive association was apparent among carriers of 2 variant alleles between arachidonic acid intake and carotid intima-media thickness, but not among carriers of the common allele. This association was blunted by increased dietary intake of n−3 PUFAs.

Thus, here is yet another case of PUFA intake interacting with a genetic polymorphism for an enzyme implicated in the CVD process. The evidence is certainly growing for a role in genetic testing to allow the development of individualized nutritional advice with the aim of reducing CVD risk.

**THE CONSUMER FACTOR**

Science forms the basis for this discussion of nutrigenomics. But how does the consumer perceive this? According to the results of a survey of 1000 Americans by Cogent Research in 2003 (34), 62% of respondents reported they have heard nothing about nutrigenomics. Only 7% responded that they have heard “a fair amount” or “a lot” about the subject. Of those interviewed, >70% responded that they were interested or extremely interested in the concepts of nutrigenomics for disease prevention, overall wellness, and mental alertness. If specific products did arise from nutrigenomics, those interviewed responded they would be most interested in an in-depth wellness assessment, but there was also strong interest in vitamins, fortified foods, and natural foods.

The results of the survey also highlight the pivotal influence of physicians in health and wellness. At the moment, consumers still prefer testing, even for nutritional benefits, at their doctor’s office or in the privacy of their homes and consider possible venues such as fitness centers and health food stores with reluctance. Much the same pattern is seen concerning who respondents said they would trust to deliver a nutrigenomics recommendation, ie, their doctor, a medical or other association, and a dietitian or nutritionist headed the list of influential information sources.

**CONCLUSIONS**

Clearly, nutrigenomics faces challenges. Although the evidence base is growing, consistent data are lacking, which hampers the ability to make specific recommendations. This can be addressed with population studies of appropriate experimental design, clinical trials of adequate size and quality, and product-specific trials in subjects selected for specific genetic variants. As progress continues to be made in developing the scientific evidence base for nutrigenomics, attention must also be paid to addressing some of the other issues surrounding the field, such as acceptance by the public and establishing appropriate, credible sources to disseminate information.

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REFERENCES


