Annu. Rev. Nutr. 2005. 25:341–90
doi: 10.1146/annurev.nutr.25.050304.092656

SINGLE NUCLEOTIDE POLYMORPHISMS THAT INFLUENCE LIPID METABOLISM: Interaction with Dietary Factors

Dolores Corella[1,2] and Jose M. Ordovas[1]

[1]Nutrition and Genomics Laboratory, Jean Mayer–U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts 02111, and the [2]Genetic and Molecular Epidemiology Unit, School of Medicine, University of Valencia, Valencia 46010 Spain; email: dolores.corella@uv.es, jose.ordovas@tufts.edu

Key Words cholesterol, genes, nutrition, prevention, cardiovascular

■ **Abstract** Cardiovascular disease (CVD) risk is the result of complex interactions between genetic and environmental factors. During the past few decades, much attention has focused on plasma lipoproteins as CVD risk factors. The current evidence supports the concept that gene-environment interactions modulate plasma lipid concentrations and potentially CVD risk. The findings from studies examining gene-diet interactions and lipid metabolism have been highly promising. Several loci (i.e., APOA1, APOA4, APOE, and LIPC) are providing proof-of-concept for the potential application of genetics in the context of personalized nutritional recommendations for CVD prevention. However, the incorporation of these findings to the clinical environment is not ready for prime time. There is a compelling need for replication using a higher level of scientific evidence. Moreover, we need to evolve from the simple scenarios examined nowadays (i.e., one single dietary component, single nucleotide polymorphism, and risk factor) to more realistic situations involving interactions between multiple genes, dietary components, and risk factors. In summary, there is need for both large population studies and well-standardized intervention studies.

CONTENTS

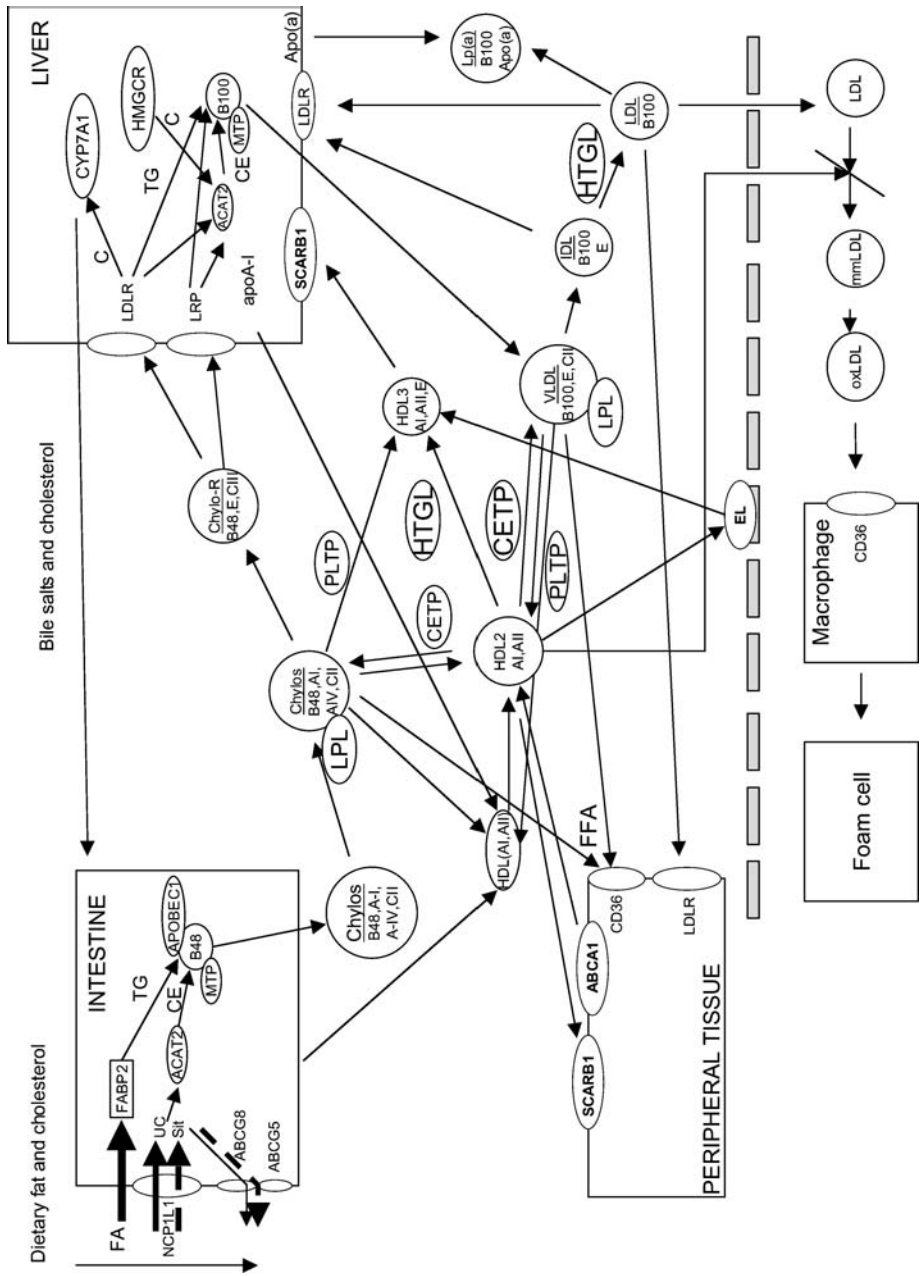
INTRODUCTION 342
Metabolism of Lipoproteins Carrying Exogenous Lipids 344
Endogenous Lipoprotein Metabolism 345
Reverse Cholesterol Transport 345
CANDIDATE GENES FOR LIPID METABOLISM 346
REGULATION OF LIPID METABOLISM: GENES VERSUS ENVIRONMENT . . 348
GENE-DIET INTERACTIONS 348
Interindividual Variability 348
Measurement of Gene-Diet Interaction 350

Methodological Issues in Assessing Gene-Diet Interaction 351
Misclassification of Dietary Exposures 352
Misclassification of Genetic Data 352
Sample Size Considerations 352
Nutrigenetics and Nutrigenomics 353
LESSONS FROM MONOGENIC DISORDERS 353
COMMON GENETIC VARIANTS AND THEIR INTERACTION WITH DIETARY FACTORS 355
Biological Interactions Versus Statistical Interactions 355
Gene-Diet Interactions Modulating Plasma Lipoprotein Concentrations 358
FUTURE OPPORTUNITIES FOR PERSONALIZED NUTRITION: WHAT NEEDS TO BE DONE? 382
SUMMARY AND CONCLUSIONS 383

INTRODUCTION

Lipoprotein metabolism comprises complex biological pathways. Their homeostasis is achieved by the coordinated action of a large number of nuclear factors, binding proteins, apolipoproteins, enzymes, and receptors (Figure 1). These pathways are also intertwined with energy metabolism and are subjected to hormonal controls that are essential for adjustment to environmental and internal conditions. Lipoprotein metabolism is commonly subdivided into three components: the exogenous pathway, the endogenous pathway, and the reverse cholesterol transport.

Figure 1 Human lipoprotein metabolism. Abbreviations: AI, apolipoprotein A-I; AII, apolipoprotein A-II; AIV, apolipoprotein A-IV; AV, apolipoprotein A-V; ABCA1, ATP-binding cassette, subfamily A, member 1; ABCG5, ATP-binding cassette, subfamily G, member 5; ABCG8, ATP-binding cassette, subfamily G, member 8; ACAT2, cytosolic acetoacetyl-CoA thiolase; apo, apolipoprotein; APOBEC1, apolipoprotein B mRNA editing enzyme; B48, apolipoprotein B-48; B100, apolipoprotein B-100; CII, apolipoprotein C-II; CIII, apolipoprotein C-III; CD36, CD36 antigen; CE, cholesteryl esters; CETP, cholesteryl ester transfer protein; chylos, chylomicron; chylo-R, chylomicron remnants; CYP7A1, cholesterol-7-alpha-hydroxylase; E, apolipoprotein E; FA, fatty acid; FABP2, intestinal fatty acid–binding protein; FFA, free fatty acid; HDL, high-density lipoprotein; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HTGL, hepatic triglyceride lipase; IDL, intermediate density lipoproteins; LDL, low-density lipoprotein; LDLR, LDL receptor; Lp(a), lipoprotein a; LPL, lipoprotein lipase; mmLDL, minimally modified LDL; MTP, microsomal triglyceride transfer protein; NPC1L1, Niemann-Pick C1-like 1; oxLDL, oxidized LDL; PLTP, phospholipid transfer protein; SCARB1, scavenger receptor type I B; Sit, sitosterol; TG, triglycerides; UC, unesterified cholesterol; VLDL, very-low-density lipoprotein.



Metabolism of Lipoproteins Carrying Exogenous Lipids

Most of our knowledge about the relation between plasma lipid concentrations and cardiovascular disease (CVD) risk comes from studies in the fasting state. However, humans are almost continuously in the postprandial state. The increased awareness of the atherogenic properties of postprandial triglyceride-rich lipoproteins (TRLs) and the dramatic interindividual variability in the postprandial lipoprotein response have stimulated research to gain more in-depth knowledge about the genetic and nongenetic factors modulating absorption, transport, and catabolism of dietary lipids (46, 50, 81). Dietary fats represent 30%–40% of the energy intake in the Western world, mostly in the form of triacylglycerols (TAGs) (~100 g per day). Under normal circumstances, the digestive system is very efficient in both digesting and absorbing the TAGs. Several enzymes contribute to the degradation, with most of the activity being driven by pancreatic lipase in the duodenum. Following its absorption into the enterocyte, fatty acids are transported intracellularly by the intestinal fatty acid–binding protein (IFBP). Then the resynthesis of TAGs for assembly of chylomicrons (CMs) occurs predominantly in the *sn*2-monoacylglycerol pathway and (in a lesser amount) in the glycerol-3-phosphate pathway. TAG synthesis occurs primarily in the smooth endoplasmic reticulum (SER) (76).

Cholesterol is another major dietary lipid absorbed in the enterocyte. Its homeostasis is maintained by a delicate equilibrium between dietary cholesterol absorption, de novo synthesis, and fecal excretion (46). The process of intestinal cholesterol absorption from foods has been difficult to understand, and only very recently, specific sterol carriers have been identified and characterized, such as the Niemann-Pick C1-like 1 (NPC1L1) (1, 29). In addition, other proteins, such as the scavenger receptor type I B (SCARB1) (61) and the ABC transporters (ABCG5 and ABCG8) (87), have been implicated in cholesterol absorption.

Both dietary TAG and cholesterol are secreted into the bloodstream as part of CM particles (101). The apolipoproteins associated with nascent CMs are apoB48, apoA-I, apoA-IV, apoC-II, and apoC-III. CM synthesis requires apoB48, which is translated from an apoB100 mRNA that is post-transcriptionally edited to end protein synthesis at codon 2153. This involves enzymatic deamination through the action of apoB mRNA editing enzyme (APOBEC1) (33). Microsomal triglyceride transfer protein (MTP) plays an important role in this process by binding to apoB and determining the complete synthesis and lipidation of nascent apoB when enough lipids are available (49). CMs are secreted into lymph vessels and then enter the blood circulation. Once the intestinal lipoproteins are in contact with other plasma lipoproteins [i.e., high-density lipoproteins (HDLs)], there is rapid transfer of proteins and lipid subfractions in order to facilitate their metabolic fate, which occurs in two main steps. First, the TAGs of CMs are hydrolyzed by lipoprotein lipase (LPL) in extrahepatic tissues to form CM remnants. CM remnants are removed from the plasma by hepatic receptors that bind to the apoE present in the particle (101).

Endogenous Lipoprotein Metabolism

The liver is the central organ for endogenous lipoprotein metabolism, beginning with the synthesis of very-low-density lipoproteins (VLDLs). As early as 1976, Havel & Kane (40) provided the basis for our understanding of VLDL assembly and secretion by proposing a mechanism involving the fusion of newly synthesized apoB with a droplet of TAG produced in the SER compartment. Most of the TAG utilized for the assembly of VLDL in the secretory apparatus of the hepatocyte is mobilized by lipolysis of the cytosolic TAG pool, followed by re-esterification. The lipases involved include arylacetamide deacetylase and/or TAG hydrolase. Some of the re-esterified products of lipolysis gain access to an apoB-rich VLDL precursor to form mature VLDL. Some, however, are returned to the cytosolic pool in a process that is stimulated by insulin and inhibited by MTP. Phospholipids also contribute to VLDL TAG in a process that involves ADP-ribosylation factor-1 (ARF-1)-mediated activation of phospholipase D. Phospholipases may prime membrane transport steps required for second-step fusion and/or channel phospholipids into a pathway for VLDL triglyceride production. VLDL production is controlled primarily at the level of presecretory degradation. Recently, it was discovered that the LDL receptor modulates VLDL production through its interactions with nascent VLDL in the secretory pathway (36). VLDL particles are precursors of intermediate-density lipoproteins and finally of LDL particles. LDL is known to be heterogeneous, comprising a number of distinct subpopulations defined on the basis of a number of characteristics, including particle density, size, charge, and chemical composition (60).

Reverse Cholesterol Transport

The classical HDL-dependent protective mechanism involves promoting efflux of excess cholesterol from cells in the arterial wall and returning it to the liver for excretion into the bile, a process known as reverse cholesterol transport. HDL is synthesized by both the liver and the intestine. Its precursor form is discoidal in shape and matures in circulation as it picks up unesterified cholesterol, and probably phospholipids, from cell membranes by a mechanism mediated by the ATP-binding cassette, subfamily A, member 1 (ABCA1) transporter. Unesterified cholesterol is esterified to cholesteryl ester within the HDL particle by the enzyme lecithin-cholesterol acyltransferase (LCAT) and the small HDL3 particle becomes a larger HDL2 particle. HDL cholesteryl ester can be taken up selectively by the liver or by organs synthesizing steroid hormones, such as the adrenals, through the action of the scavenger receptor class B type I (SCARB1). Cholesteryl ester can also be selectively transferred to apoB-containing lipoproteins in exchange for TAG through the action of cholesteryl ester transfer protein (CETP). Conversely, phospholipid transfer protein (PLTP) mediates transfer of phospholipids from apoB-containing lipoproteins to HDL. The TAG received by HDL2 is hydrolyzed by hepatic lipase and the particle is converted

back to HDL3, completing the HDL cycle in plasma. Other members of the family of triglyceride lipase genes also influence the metabolism of HDL (3, 4, 22).

CANDIDATE GENES FOR LIPID METABOLISM

Genetic variability has been identified in humans for all the known lipid-related genes, and some of those variants have been studied for the past two decades, resulting in a plethora of reports and associations with abnormal lipid metabolism and plasma lipoprotein profiles. A detailed description of the biological role of each of the products from those candidate genes is beyond the scope of this review; they have been the focus of other publications (13, 69, 82). Some of the most important known genes involved in lipoprotein metabolism are ABCA1; ATP-binding cassette, subfamily G, member 5 (ABCG5); ATP-binding cassette, subfamily G, member 8 (ABCG8); acetylcholesterol acyltransferase 1 (ACAT1); cytosolic acetoacetyl-CoA thiolase (ACAT2); APOA1; APOA2; APOA4; APOA5; APOB; APOBEC1; APOCI; APOC2; APOC3; APOC4; APOE; APOH; APOJ; APOL1–APOL6; putative low-density lipoprotein (LDL) receptor adaptor protein (ARH); CD36 antigen (CD36); CCAAT/enhancer-binding protein-alpha (CEBPA); CETP; cubilin (CUBN); cholesterol-7-alpha-hydroxylase (CYP7A1); estrogen receptor 1 (ERS1); intestinal fatty acid binding protein (FABP2); 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR); LCAT; hepatic lipase (LIPC); hormone-sensitive lipase (LIPE); endothelial lipase (LIPG); lipoprotein a (LPA); LDL receptor (LDLR); lipoprotein lipase (LPL); low-density lipoprotein receptor-related protein 1 (LRP1); LRP2; LRP5; liver X receptor-alpha (LXRA); MTP; NPC1L1; low-density lipoprotein, oxidized, receptor 1 (OLR1); perilipin (PLIN); phospholipid transfer protein (PLTP); paroxonase 1 and 2 (PON1 and PON2); peroxisome-proliferator activator receptor-alpha (PPARA); PPAR-delta (PPARD); PPAR-gamma (PPARG); SCARB1; retinoid X receptor-alpha (RXRA); SREBP cleavage-activating protein (SCAP); sterol regulatory element–binding protein 1 (SREBP1); upstream stimulatory factor protein 1 (USF1), and VLDL receptor (VLDLR). This list is not, by any means, closed. In fact, its ranks are being continuously populated with new candidate genes emerging from the active research ongoing in this area. When it comes to the associations of genetic variants at these loci with plasma lipid levels in the general population, the genes with findings that are more consistent are the APOE in terms of associations with total cholesterol and LDL-C concentrations (38, 86), CETP with HDL-C levels (80), and the LPL and APOA5 loci with TAG levels (47, 91, 118). Most other loci have shown significant associations with different plasma lipids; however, for many of them there is lack of replication, producing doubts about their significance as global genetic markers. Moreover, most of them have to be tested in the context of gene-environment interactions.

There is still some confusion concerning the nomenclature of the identified gene variants (mutations or polymorphisms). To prevent this confusion some authors

(2) recommend using the terms "sequence variant" or "allelic variant" for any genomic change regardless of their frequency of phenotypic effects. However, in large epidemiological studies, the term "polymorphism" is still used as it was originally defined (a locus in which the least common allele occurs with a frequency of at least 1%). Thus, polymorphisms can be caused by mutations ranging from a single nucleotide base change to variations in several hundred bases, such as large deletions and/or insertions. The simpler and most common type of polymorphism, known as single nucleotide polymorphism (SNP), results from a single base mutation replacing one base for another. SNPs are estimated to represent about 90% of all human DNA polymorphisms. SNPs occur with a very high frequency, with estimates ranging from about 1 in 1000 bases to 1 in 100–300. Overall, it has been estimated that the human genome contains about ten million SNPs (18). Not long ago, the number of identified polymorphisms in candidate genes for lipid metabolism was small and there were dozens of studies focusing on a very limited number of specific genetic variants in different populations. This provided the opportunity to check the replication of the observed associations and potentially to increase the level of evidence, as in the case of the association between the *APOE* polymorphism and plasma LDL-C (86).

Currently, the vast number of SNPs available for candidate genes adds a level of complexity to the data interpretation as more investigators may focus their association studies on different SNP sets even for a single locus. In this regard, Humphries et al. (48) have strongly recommended making a distinction between functional SNPs (i.e., those altering an amino sequence or a transcription factor-binding element) and nonfunctional SNPs to avoid the use of nonfunctional genetic variants in association studies. They suggested that before SNPs are included in an epidemiological study, their functionality should be supported by good in vitro data. However, as these in vitro data may be difficult to obtain, some researchers have proposed the use of bioinformatic tools to infer functionality (100). One of the problems with the results obtained from association studies using apparently nonfunctional SNPs (that in some cases act as markers of the unknown functional variant) is their different degree of linkage disequilibrium with the true functional SNP among different populations (78). Thus, a nonfunctional variant may have a different impact in association studies depending on the linkage disequilibrium with the functional polymorphism and thus would contribute to the lack of replication of these studies in different populations. Lack of replication is the most excruciating problem in the hundreds of published reports of gene-lipid associations involving lipid metabolism (51). However, an important cause of variability is the potential influence of environmental factors. Moreover, taking into account the classical definition of phenotype (observable physical or biochemical characteristics of an organism, determined by both genetic makeup and environmental influences), an important reason to explain the controversial findings from studies involving genotype-phenotype association is that the majority of initial studies analyzing the association between SPNs and lipid traits did not consider the potential gene-environment interactions.

REGULATION OF LIPID METABOLISM: GENES VERSUS ENVIRONMENT

The homeostasis of lipid metabolism is the result of interactions between multiple genes and environmental (nongenetic) factors. Although currently there are no precise estimates about the specific contribution of genetic and environmental factors (tobacco smoking, alcohol consumption, dietary intake, physical activity, etc.) to dyslipidemia, it is thought that there are very few cases in which alterations of lipid metabolism are induced by genetic variation that will develop regardless of environmental factors. Even in those cases, environmental factors may affect the age of onset and severity of the disease (8). Overall, gene-environment interaction refers to the differential phenotypic effects of different environments on individuals with the same genotype or to the differential effects of the same environment on individuals with different genotypes (88). Genetic variation and the different individuals' responses to environmental factors present an opportunity and a challenge to cardiovascular prevention. On the other hand, some researchers prefer to use the concept of "context-dependent" genetic effect that involves gene-gene interactions (epistasis) as well as gene-environment interactions (56). Whether as a specific term, or integrated in the context-dependent concept, the study of gene-environment interactions will largely contribute to deciphering the underlying mechanisms for lipid-related disorders and to facilitating cardiovascular disease prevention. Along these lines, from a public health perspective, nutrition is the most important environmental factor interacting with our genes to increase or decrease the likelihood of developing lipid disorders.

The interactions involving dietary factors are called gene-diet interactions. Although the presence of a genetic component determining the differences in interindividual dietary response to specific nutritional recommendations and dietary interventions has been proposed for several decades (44), it has not been until recent years that researchers began to explore its molecular basis. In the next sections, a detailed description of the fundamentals and the main recent examples of gene-diet interactions involving lipid metabolism is provided.

GENE-DIET INTERACTIONS

Interindividual Variability

It is well known that the effect of dietary changes on plasma lipid concentrations differs significantly between individuals (53, 58). Some individuals (hyporesponders) appear to be relatively insensitive to dietary intervention, whereas others (hyperresponders) have enhanced sensitivity (57). In assessing the impact of these different interindividual responses to the same diet, Schaefer et al. (106) reported the effects of National Cholesterol Education Program (NCEP) Step 2 diets on plasma lipoprotein profiles in 72 men and 48 women. Compared with the baseline

diet (an average American diet), consumption of an NCEP Step 2 diet was associated with significant decreases in LDL-C and HDL-C in both men and women. However, a large variability in lipid response to the diet was observed, with changes in LDL cholesterol ranging from +3% to −55% in men and from +13% to −39% in women. On average, such diets do achieve significant reductions of LDL-C concentrations; however, the magnitude of change varies substantially among individuals, with many showing either little change or even increases in LDL-C. From these data, it is clear that what is good at the population level is not necessarily good at the individual level. Moreover, low-fat diets can also result in reduced plasma HDL and/or increased TAG concentrations (58) that may be particularly harmful for some subjects. For example, it has been shown that individuals with a predominance of small, dense LDL particles (subclass pattern B), a phenotype that is associated with an increased risk of coronary heart disease, benefit more from a low-fat diet (59, 60) than do those with the subclass pattern A (larger LDL). Indeed, the latter group exhibited a more atherogenic pattern B subclass after consuming a low-fat diet. Currently there is still substantial controversy about what is the best diet to prevent heart diseases: the traditionally recommended low-fat diet, the Mediterranean diet based on a relatively high contribution of monounsaturated fatty acids (MUFAs), or even the emerging low-carbohydrate diet (20). However, although the general dietary recommendations have partially addressed the problem of special populations (i.e., children, pregnant women, elderly subjects), a key factor that has not been taken into account is the individual variation concerning such general recommendations. In this regard, increasing numbers of intervention studies are focusing on the interindividual differences in response to diet rather than showing the mean effect. The results of these studies show repeatedly the aforementioned dramatic variability in responses to diets designed to change plasma lipid profile. Moreover, increasing evidence supports that this variability in response is an intrinsic characteristic of the individual rather than the result of different dietary compliance with the experimental protocols. One of these studies, recently published by Jacobs et al. (52), demonstrates that individual TAG responses to a high-fat or to a low-fat diet are vastly different. Whereas some subjects have distinctly lower plasma TAG concentrations after consuming a high-fat diet, others had clearly lower TAG concentrations after consuming a low-fat diet. The authors suggest that many patients with hypertriglyceridemia are not treated optimally if general advice for either a low-fat or a high-fat diet is given; they conclude that the most beneficial alternative is to fit a dietary recommendation to each patient individually based on the patient's response to a low-fat or a high-fat diet (52). Therefore, studying the reasons for this variation in response to diet will allow us to better identify individuals who can benefit from a particular dietary intervention. Obviously, this is not an easy task. Parks et al. (90) proposed the use of an algorithm (discriminant function analysis) to predict which patients would experience significant elevations in plasma TAG after consuming a very low-fat, high-carbohydrate diet. Although three variables (baseline body mass index, fasting TAG, and insulin concentrations) accurately classified 90% of those

who would experience an elevation in TAG ≥ 10% ($P < 0.05$) and 67% of those who experienced no change in the Parks et al. study (90), the predictive algorithm was not useful in subsequent studies (52).

Currently, considerable support exists for the notion that the interindividual variability in response to dietary modification is determined by genetic factors, especially for lipid and lipoprotein phenotypes (65). Indirect evidence supporting this hypothesis comes from the general observation that the phenotypic response to diet is determined partly by the baseline value of the phenotype that is itself affected by genetic factors (5, 58). However, taking into account the complexity of lipid metabolism, the main problem is how to uncover and elucidate the many potential gene-diet interactions.

Measurement of Gene-Diet Interaction

The nature versus nurture controversy in lipid metabolism is being replaced by systematic evaluation of nature-nurture interaction. Methods used in genetics and epidemiology to study gene-environment interaction continue to evolve, and both unmeasured genotype approach (genetic epidemiology) and measured genotype approach (molecular epidemiology) have been used to detect gene-environment interactions in humans. The unmeasured genotype approach is based on statistical analysis of the distribution of phenotypes in individuals and families and does not rely on any direct measure of DNA variation (30). The purpose of such studies is to provide clues to the importance of genetic factors embodied in the concept of heritability and measured by analysis of variance or correlation. No specific genes are measured at this stage. Heritability is defined as the proportion of phenotypic variance attributable to genetic variance. A value of 1.0 indicates that all of the population variation is attributable to genetic variation. A value of 0.0 indicates that genes do not contribute at all to phenotypic individual differences. The quantity (1.0 minus heritability) gives the environmental contribution to the trait, and it is the proportion of phenotypic variance attributable to environmental variance or the extent to which individual differences in the environment contribute to individual differences in behavior. Several twin and family studies have analyzed the genetic and environmental influence on lipid traits (42).

With advances in molecular genetics, the study of gene-environment interactions is now performed at the gene level. With this approach, genetic variation in one or in various candidate genes is investigated to discern the role of these candidate genes in determining gene-diet interactions. Direct measurement of DNA variants (i.e., SNPs) is needed to give precision and meaning to the genetic effects in gene-diet interactions. The concept of gene-diet interactions can be used in several different ways (37, 105). For example, statistical interaction exists if the degree or direction of the effect of one dietary factor (e.g., dietary fat) differs according to values of a second factor (gene variants). In recent years, an epidemiologic framework for evaluating gene-diet interaction has been proposed (9). In a simple gene-diet interaction model, in which both the susceptibility genotype

at a single locus and the dietary exposure are considered dichotomous, one can construct an extended 2-by-2 table incorporating genetic and environment factors in studying disease etiology (e.g., hypercholesterolemia). The interaction of these two factors can be measured as a departure from a multiplicative model of disease risk (12, 105). Using such an approach, it is relatively easy to find parsimonious models by keeping statistical interactions to a minimum. However, in the study of lipid metabolism, rather than dichotomous traits, it is common to predict continuous variables such as plasma cholesterol concentrations as well as to analyze continuous variables to measure dietary intake. Then, in addition to a logistic regression model, covariance regression models with interaction terms are needed (12). Hierarchical multilevel interaction models then can be fitted, and the presence of a gene-diet interaction is identified by the detection of a statistically significant interaction term between the dietary exposure and the corresponding genetic variable. However, from a strict point of view it is not clear what ultimately constitutes interaction or synergy on the biological level; any statistical approach is inherently arbitrary and model-dependent (37).

Methodological Issues in Assessing Gene-Diet Interaction

Gene-diet interactions in epidemiological studies are currently detected based on the statistical significance of the interaction terms. Taking into account that a statistically significant association does not imply causality, special attention to bias is required. This issue is crucial and determines the study design as well as adequate control of misspecification. In terms of study design, intervention studies—mainly randomized controlled trials—offer the highest level of evidence (62). In intervention studies, as opposed to observational studies, the study conditions are controlled directly by the investigators, including the amount of food or nutrient administered as well as the time period. This control minimizes the possibility of bias and increases the level of causality. However, in observational studies (i.e., cohort, case-control, cross-sectional), the researcher does not provide food to study participants and obtains information about the type and amount of food consumed by dietary questionnaires, a method that increases the likelihood of confounding and decreases the level of evidence provided. However, some authors have pointed out the importance of Mendelian randomization (the random assortment of genes from parents to offspring that occurs during gamete formation and conception) in increasing the level of evidence provided by observational studies in which genetic polymorphisms are determined and dietary intake is estimated (28). Mendelian randomization can increase the level of evidence of observational studies because it results in population distributions of genetic variants that are generally independent of environmental factors that typically confound epidemiological associations between putative risk factors and disease. In some circumstances, this can provide a study design akin to randomized comparisons. In fact, Tobin et al. (114) have suggested that the approach should be termed "Mendelian deconfounding."

Misclassification of Dietary Exposures

Precise measurement of an individual's exposure to dietary factors is often difficult because of the individual's poor recall or ignorance of previous exposures, the complex pattern of nutrient intake, and the lack of good biological indicators of exposure levels for many nutrients. Therefore, in the study of gene-diet interaction, the consequences of a dietary mismeasurement can lead to bias in the estimation associated with interaction effects and possible loss of precision and power in the estimation of interactions. Nondifferential misclassification usually leads to biases of interaction toward the null value, and differential misclassification may produce biased interactions in either direction (increasing or decreasing risk). Therefore, high-quality dietary information in epidemiological studies is a key factor for establishing causality. More information about validity of the specific dietary instruments (i.e., diet records, 24-hour recalls, food-frequency questionnaires) can be found in Reference (83). In addition, another important question to be raised relates to which type of dietary information is more relevant in gene-diet interaction studies. Should we be using nutrients, foods, or dietary patterns? There is not a unique response, and it depends on the aims of the study and on the specific hypothesis that is under investigation. Each one of these approaches has advantages and methodological limitations (83).

Misclassification of Genetic Data

When measuring individuals' genotypes at the DNA level, misclassification can occur as the result of several factors. One of them is error in the laboratory determination. With the application of high-throughput methods, a number of which are under development, quality control procedures in the laboratory are particularly important. A misclassification of the genotype (i.e., a data set containing less than 95% reproducibility) can bias the measure of the association and largely affect gene-nutrient interactions. Quality control measures include internal validation, blinding, duplicates, test failure rate, inspection of whether genotype frequencies conform to Hardy-Weinberg equilibrium, and blinding of data entry (64). Another factor that may contribute to misclassification of genetic data is linkage disequilibrium. In addition to these factors, in the last few years it has been proposed that individual SNPs are not the best approach to measure the individual's genotype; the simultaneous analysis of different genetic variants (haplotypic approach) has been suggested as more appropriate (102). Moreover, Neale et al. (78) propose a shift toward a gene-based approach in which all genetic variants in the intragenic and regulatory regions of a candidate gene are considered jointly.

Sample Size Considerations

One of the most frequent errors in epidemiological studies aimed at investigating gene-diet interactions in lipid metabolism is the lack of statistical power (Type II error). In an epidemiological study of a given sample size, the power to detect

statistical interactions is less than the power to detect main effects, and the variance of the interaction estimate also will be greater than the variance of the main effects estimate under a no-interaction model. More information about sample size and power calculation needed to detect gene-environment interaction for categorical and continuous variables can be found in Reference (35).

Nutrigenetics and Nutrigenomics

In the field of gene-diet interactions, two different concepts have emerged: nutrigenetics and nutrigenomics. Nutrigenetics examines the effect of genetic variation (mainly SNPs) on the interaction between diet and specific phenotypes. This includes the identification of gene variants associated with differential responses to nutrients. The goal of nutrigenetics is to generate recommendations regarding the risks and benefits to the individual of specific dietary components. It has been also termed "personalized nutrition." Nutrigenomics focuses on the effect of nutrients on the genome, proteome, and metabolome. Nutrigenomics involves the characterization of gene products and the physiological function and interactions of these products, promoting an increased understanding of how nutrition influences metabolic pathways and homeostatic control (77, 119). Several approaches are available for analyzing the effects of dietary factors, including differential gene expression, as well as proteomic methods to determine changes in protein levels and protein modifications (116). The role of genes implicated in lipid metabolism may be further studied by developing transgenic and gene-targeted animals treated with different diets, as well as by using other gene expression strategies. The combination of these technologies will contribute to the study of the function and nutritional regulation of different lipid metabolism–related genes as well as to the identification of new targets for therapeutic approaches (77).

LESSONS FROM MONOGENIC DISORDERS

Monogenic disorders are highly penetrant; however, even for these diseases there is evidence of dietary modulation having significant effects over the expression of the mutation and the disease risk associated with the genetic defect. The classical example involves familial hypercholesterolemia (FH). FH is a codominant inherited disorder of lipid metabolism characterized by very high concentrations of LDL-C, tendon xanthomas, *arcus lipoides corneae*, and increased risk of premature coronary heart disease (7). The clinical phenotype is more severe for homozygotes than for heterozygotes. Fortunately, homozygotes are rare ($\sim$1 per million) and the term FH is usually applied to the more common heterozygous condition (1 per 500 individuals in most countries). It has been known since the 1970s that the FH phenotype results from mutations in the LDLR gene, resulting in defective uptake of plasma LDL and dramatic elevation in plasma LDL-C levels (14). To date, more than 800 mutations have been reported to cause FH (http://www.ucl.ac.uk/fh; http://www.umd.necker.fr). Despite its mostly monogenic basis, the phenotypic

expression in FH subjects varies dramatically (117). One obvious explanation is that this variability may be due to the severity of the specific mutation within the LDLR gene. Mutations have been categorized into five different classes. The so-called null-alleles result in failure to produce any protein, whereas other mutations lead to impairments in binding capacity, in post-translational processing, or in recycling (31).

The effects of mutation type on lipoprotein levels and on the risk for CVD have been studied extensively, with controversial results (10). However, the clinical presentation differs substantially even among individuals who share an identical LDLR mutation (120). Therefore, additional factors are presumed to influence the course of FH and lead to the dramatic variation in clinical manifestations. In a recent work, Bertolini et al. (11) investigated the presence of modifying genes affecting lipoprotein metabolism as a possible explanation of these differences. They found a significant modulation of common polymorphisms on clinical phenotypes of FH such as (*a*) plasma LDL-C (APOE, MTP, and APOB); (*b*) plasma HDL-C (LIPC, FABP-2, and LPL); (*c*) plasma TAG (APOE and APOA4), and (*d*) coronary artery disease (CAD) (FABP-2). In addition, Bertolini et al. (11) also suggested an important contribution of dietary factors to the variability in the FH phenotypes. There is indirect and direct evidence that diet modifies the effect of the genetic variation on FH phenotypes. This evidence comes from observational studies in the United States (123), Europe (108), and Asia (96, 109). In the United States, Williams et al. (123) screened 1134 individuals from 18 pedigrees in large families from Utah. In four pedigrees with FH, male heterozygotes had a mean serum cholesterol level of 352 mg/dL, myocardial infarction at an average age of 42 years, and coronary death at an average age of 45 years. However, the four ancestral males born before 1880 who were the known founders of the LDLR mutations for each of the pedigrees survived to ages 62, 68, 72, and 81 years. This suggests that some healthy lifestyle factors protected these men against the expression of a mutation that has led to coronary disease by age 45 years in all of their heterozygous great-grandsons. Specifically, the previous generations of these families consumed diets that were lower in total fat—particularly saturated fat—than the diets of their contemporary descendants. These findings were corroborated in the Netherlands (108) in a large Dutch pedigree. Similar observations, using a different approach, were made in Asian populations (95, 109).

Direct evidence that diet modulates the effect of LDLR mutations in FH patients came from experimental studies involving dietary modifications. However, in a systematic review that included published and unpublished randomized controlled trials from 1978 to 2000 in which a cholesterol-lowering diet in children and adults with FH was compared to other forms of dietary treatment or to no dietary intervention, Poustie et al. (98) concluded that there is a lack of adequate data to demonstrate that dietary intervention modulates clinical phenotypes. Nevertheless, scores of individual studies show significant differences (41). One of the main limitations of the systematic review by Poustie et al. (98) is the limited number of included studies owing to the strict inclusion criteria. Although

pharmacological treatment with statins is currently the most potent intervention to reduce LDL-C concentrations in FH patients (21, 122), consensus panels from several Western countries recommend a healthy diet to decrease LDL-C concentrations and reduce CAD risk in these patients. In addition, it has been reported that a healthy diet can increase the LDL-C-lowering efficacy of hypocholesterolemic drugs (21). Moreover, it has been recommended that prevention of CAD in FH patients should be initiated in childhood. However, because treatment with statins has several limitations in patients younger than age 18 in most countries, a dietary approach is most important in the treatment of children with FH. An NCEP-ATPIII diet, supplemented with plant stanols/sterols (121), has a very appropriate nutrient composition, and according the current dietary guidelines can be recommended for all FH subjects, including children over age 2 (21). This dietary intervention to lower LDL-C concentrations is a good example of how diet can help to modify a genetically determined trait and it provides a strong basis to propose that other gene-dietary interactions can be detected in subjects whose genetic disease predisposition is due to common genetic SNPs in genes related to lipid metabolism.

COMMON GENETIC VARIANTS AND THEIR INTERACTION WITH DIETARY FACTORS

The evidence for gene-diet interactions between common SNPs at candidate genes and dietary factors in the field of lipid metabolism is continuously increasing. This evidence is presented below, following a discussion about the significance of statistical interactions and biological interactions.

Biological Interactions Versus Statistical Interactions

As pointed out for monogenic diseases, diet can play a pivotal role in the expression of the final phenotype. Understanding these simpler monogenic-nutrient interactions should help us to gain further insight into the more complex interactions for common genetic variants involved on the phenotypic expression of common lipid disorders. However, it should be noted that the term "gene-diet interactions" could be used in different ways (105): as biological interaction and as statistical interaction. The term "biological interaction" is commonly applied in monogenic diseases and is currently used in some dietary interventions in clinical practice to prevent the disease. For example, in subjects with mutations in the phenylketonuria gene, dietary restriction of the harmful nutrient (phenylalanine) has been successfully implemented in clinical practice for many years (19). Therefore, biological interaction exists when two or more factors influence a phenotype at the same time, and it does not necessarily entail statistical interaction (113). Apart from biological interactions, the primary interest of researchers nowadays has focused on statistical interactions. A statistical interaction exists if the degree or direction of the effect of one factor (e.g., an SNP) differs according to values of a second factor (e.g., a nutrient). Accordingly, the vast majority of reports examining gene-diet

interactions involving common genetic variants and plasma lipid variables focus on statistically significant interactions (10, 12). However, biological interaction needs to be taken into consideration when designing preventive and therapeutic dietary interventions to modify specific phenotypes in genetically susceptible individuals. To illustrate the differences between statistical and biological interactions, two examples in the framework of the Framingham Study are presented. A classical example of gene-diet statistical interaction is the one found between the –75G/A polymorphism of the APOA1 gene and polyunsaturated fatty acid (PUFA) intake in the Framingham Study (85). In women, a statistically significant gene-diet interaction ($P < 0.05$) was found between PUFA intake (<4% of energy from fat, 4%–8%, and >8%) and the APOA1 SNP in determining plasma HDL-C concentrations (Figure 2). This interaction shows that PUFA intake modulates the effect of the –75A/G SNP on HDL-C concentrations. Thus, in carriers of the A allele, higher PUFA intakes were associated with higher HDL-C, whereas the opposite effect was observed in G/G homozygotes.

On the other hand, an example of a biologically significant but statistically insignificant interaction was found between the CETP TaqIB polymorphism and

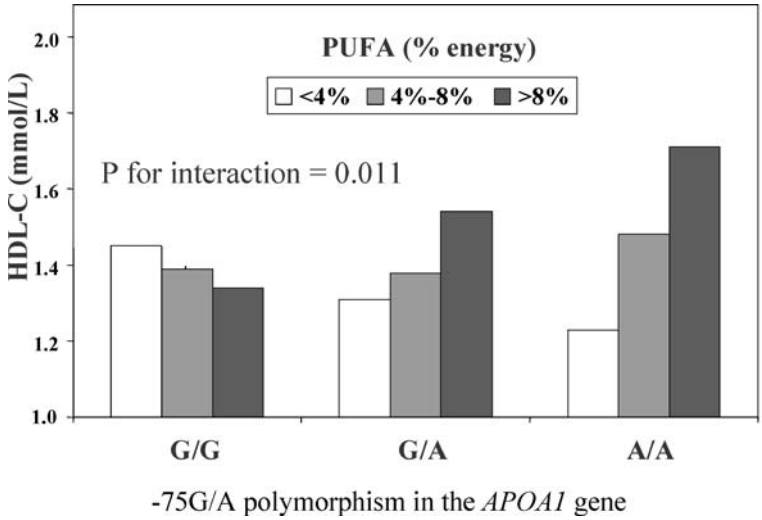


Figure 2 Statistical interaction between the –75G/A polymorphism in the APOA1 gene promoter and polyunsaturated fatty acid (PUFA) intake (<4%, 4%–8% and >8% of energy) in determining plasma HDL-C concentrations in women participating in the Framingham Study. Means of HDL-C were adjusted by age, body mass index, alcohol consumption, tobacco smoking, energy, and saturated fat and monounsaturated fat consumption. The reported P value was obtained for the interaction term between APOA1 genotype and PUFA in the multivariate lineal regression model including the covariates.

alcohol consumption in determining plasma HDL-C concentrations (D. Corella & J.M. Ordovas, unpublished data). We genotyped a population-based sample of 1411 men and 1505 women from the Framingham Study. B1B1 individuals had lower HDL-C concentrations compared with B1B2 and B2B2 individuals ($P < 0.001$) (82). Three categories of alcohol intake were considered according to reported daily intake: no alcohol intake, moderate intake, and high intake. No statistically significant interaction between the CETP-TaqIB genotype and alcohol intake was found. However, as observed in Figure 3, a biologically significant gene-diet interaction was observed. Thus, B1B1 subjects could have higher HDL-C concentrations when consuming alcohol than B2 carriers who do not consume alcohol. Taking into account that low HDL-C concentrations are considered a

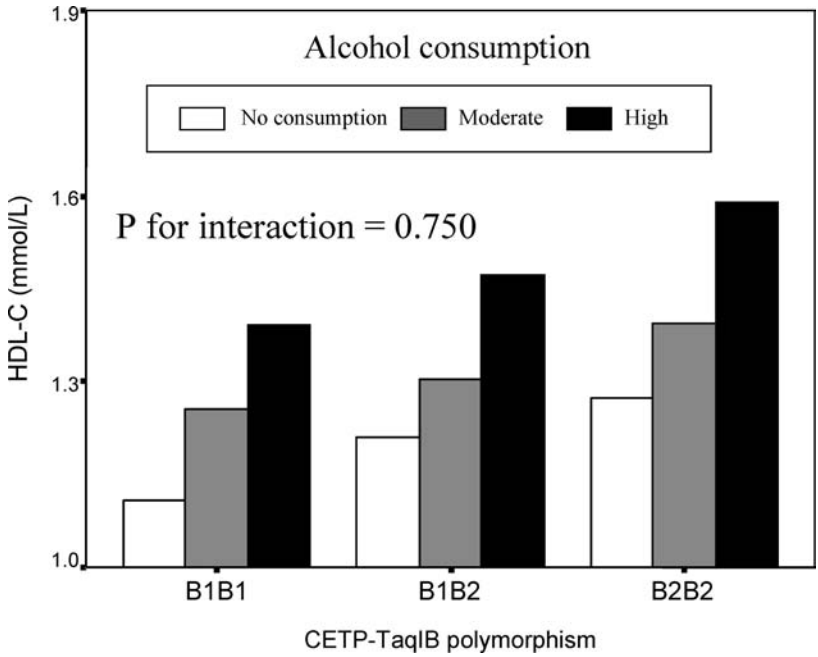


Figure 3 Biological interaction between the TaqIB polymorphism in the cholesteryl ester transfer protein (CETP) gene and alcohol intake in determining plasma high-density lipoprotein cholesterol (HDL-C) concentrations the Framingham Study. Three groups of alcohol intake were defined according to the reported amount of alcohol consumed per day: no consumption (alcohol consumption = 0 g/day), moderate (<26.4 g alcohol/day for men, <13.2 g/day for women), and high consumption (>26.4 g alcohol/day for men, >13.2 g alcohol/day for women). Means of HDL-C were adjusted by gender age, body mass index, tobacco smoking, and energy intake. The reported P value was obtained for the interaction term between the CETP genotype and alcohol intake in the multivariate lineal regression model including the covariates.

cardiovascular risk factor, dietary interventions aimed at increasing HDL-C in genetically susceptible B1B1 individuals could be a preventive measure. Our results clearly show that alcohol consumption can increase HDL-C concentrations in B1B1 individuals in a dose-dependent manner.

Gene-Diet Interactions Modulating Plasma Lipoprotein Concentrations

We summarize below the current evidence for gene-diet interactions in the field of lipid metabolism using as outcomes plasma lipid concentrations but also disease phenotypes such as obesity, cardiovascular diseases, and diabetes. Among dietary factors, total fat, specific fatty acids, carbohydrates, total energy intake, and alcohol intake are discussed. The evidence from observational as well as intervention studies is presented. Moreover, differences between studies in the fasting state as well as in the postprandial state are considered.

RESULTS FROM INTERVENTION STUDIES Intervention studies in which subjects receive a controlled dietary intake provide the best approach to ascertain true dietary intake under highly controlled conditions. However, these well-controlled feeding studies have several important logistic limitations, including the small number of participants and the brief duration of the interventions. Hundreds of intervention studies have examined gene-diet interactions on different parameters of lipid metabolism. However, the level of replication among studies that analyze the same genetic variation tends to be low. Potential reasons for the lack of replication are the different characteristics of study subjects, length of intervention, sample size limitation, and heterogeneity in the design. In a systematic review of literature published from 1966 to 2002, Masson et al. (72) identified 17 reviews on gene-diet interactions and 74 relevant articles that included dietary intervention studies in which measurements were taken of the lipid and lipoprotein response to diet in different genotype groups. They analyzed the published articles according to seven groups of genetic loci: APOA1, APOC3, and APOA4 cluster; APOB; APOE; enzymes (LPL, LIPC, and CYPA7); LDLR; other genes, including CETP, FABP; and neuropeptide Y. At each locus, one or more polymorphisms were included and the mainly short-term response to a defined dietary intervention [i.e., high-fat diet versus a low-fat diet, high saturated fatty acid (SFA) versus high PUFA, high MUFA versus low MUFA, etc.] was examined. After a comparative analysis of the individual findings, Masson et al. (72) concluded that there is evidence to suggest that variations in *APOA1*, *APOA4*, *APOB*, and *APOE* contribute to the heterogeneity in the lipid response to dietary intervention. However, the effects of the reported gene-diet interactions are not consistently seen and are sometimes conflicting. For example, for the *APOE* locus, 46 studies were analyzed. Of those, significantly different LDL-C responses to changes in the fat content of the diet by *APOE* genotype were reported in 11 studies. Table 1 includes a summary of this

TABLE 1 Summary of studies examining gene-diet interactions modulating fasting plasma lipid responses in intervention trials*

Gene/polymorphism	Population	Dietary factors examined	Conclusions	Reference
Apolipoprotein A-I (APOA1)				
APOA1 (−75G/A)	Systematic review	Various interventions	Thirteen reports have been published. Five found that the presence of the A allele was associated with greater LDL-C responses to changes in dietary fat.	(72)
Apolipoprotein A-IV (APOA4)				
APOA4 Gln360His	Systematic review	Various interventions	In general, *Gln/Gln* subjects show significantly greater total and LDL-C responses and *Gln/His* subjects show greater HDL-cholesterol responses to changes in dietary fat, cholesterol, or both. One study found no significant differences in LDL-C responses between genotypes. However, dense LDL decreased more in subjects carrying the *His* allele when PUFAs replaced SFAs in the diet. In the same study, there was a significant difference in HDL-C responses between genotype groups such that concentrations decreased in *Gln/Gln* subjects and increased in *Gln/His* subjects.	(72)
APOA4 Thr347Ser	Systematic review	Various interventions	The Ser allele was associated with increased total and LDL-cholesterol responsiveness when subjects switched from a high-SFA diet to the NCEP Step I diet. When the same subjects	(72)

(*Continued*)

TABLE 1 (*Continued*)

Gene/polymorphism	Population	Dietary factors examined	Conclusions	Reference
			changed from the NCEP Step I diet to a high-MUFA diet, subjects with the *Thr/Thr* genotype had a 1% decrease in total cholesterol concentrations, whereas subjects with the *Ser* allele had a 5% increase in total cholesterol concentrations. When the Thr347Ser and the apoA-I–75 (*G/A*) genotypes were combined, carriers of the *A* and *Ser* alleles showed greater LDL-C responses to changes in dietary fat. However, a study in FH subjects investigating both the Gln360His and Thr347Ser polymorphisms found no gene-diet or haplotype-diet interactions.	
APOA4 (Gln360His, Thr347Ser), CETP (TaqIB), SCARB1 (Exon 8), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR, VNTR) and APOE (E2/E3/E4)	41 males and 71 females (mean BMI 23, mean age 33 years)	Plant stanol ester consumption	No significant differences between the polymorphisms and dietary responsiveness to plant stanol ester consumption could be found, which indicates that it is unlikely that one of the single polymorphisms analyzed in this study is a major factor in explaining the variation in serum LDL cholesterol responses.	(97)

APOA4 (Thr347Ser), APOB (−516C > T), APOC3 (3175C > G), APOE (E2/E3/E4), CETP (TaqIB), FABP (Ala54Thr), LIPC (−480C > T), LPL (Asn291Ser)	The intervention study (RIVAGE) in Marseille. 300 patients randomized into two groups over periods of 3 and 12 months. Data obtained in about 100 patients after three months of dietary change.	Mediterranean or low-fat types versus standard Western type	The preliminary findings show interactions for APOE and LDL-cholesterol and TAG, APOA4 and LDL-C, MTP and LDL-C, and FABP2 and TAG.	(120)
Apolipoprotein B (APOB)				
APOB (XbaI)	Systematic review	Various interventions	Based on meta-analyses (see Reference 98a), X−X+ subjects had greater LDL-C responses that did X+X+ subjects.	(72)
APOB (EcoRI)	Systematic review	Various interventions	Based on meta-analyses (see Reference 98a), R−R− subjects had greater LDL-C and total cholesterol responses that did R+R+ subjects.	(72)
APOB (MspI)	Systematic review	Various interventions	Based on meta-analyses (see Reference 98a), M+M+ subjects had greater LDL-C and triglyceride responses that did M+M− subjects.	(72)
APOB (Ins/Del signal peptide)	Systematic review	Various interventions	Ten intervention studies found no significant effects of this polymorphism on dietary responsiveness, whereas two studies reported significantly greater responsiveness in I/I subjects.	(72)
APOB (Ins/Del signal peptide)	231 unrelated subjects (146 women/ 85 men). BMI > 25	25% reduction in energy intake during 2.5 months	Del allele associated with higher baseline LDL-C levels but also with increased response to dietary intervention.	(55)

(*Continued*)

TABLE 1 (*Continued*)

Gene/polymorphism	Population	Dietary factors examined	Conclusions	Reference
Apolipoprotein C-III (APOC3)				
APOC3 (SstI, C1100T)	Systematic review	Various interventions	Variation at the apo C-III *Sst*I site influenced dietary responsiveness such that after the subjects changed from a low-fat diet to a high-MUFA diet, LDL-cholesterol concentrations increased in *S1/S1* subjects but decreased in *S1/S2* subjects. When the effect of this polymorphism with the APOA1–75G/A polymorphism was studied, it was found that total and LDL-cholesterol concentrations decreased most in subjects with the G/G-S1/S2 polymorphism and increased most in subjects with the G/A-S1/S1 polymorphism. The C1100T polymorphic site has not been associated with the magnitude of the lipid response.	(72)
APOC3 (SstI)	59 volunteers (18 smokers: 8 with the S1S1 genotype, 10 with the S2 allele; 41 nonsmokers: 29 with the S1S1 genotype, 12 with the S1S2 genotype)	Three different diets: a diet enriched in saturated fatty acids (SFA) (38% fat, 20% SFA) followed by a randomized, crossover period during which they ate a diet enriched in carbohydrates	S1S1 smokers were not influenced by any of the diets, but the atherogenic ratio decreased in S2 carriers when they changed from the diet rich in SFA to a diet rich in olive oil or carbohydrates. No significant difference was observed when the S2 nonsmokers changed from one diet to another, but there was a decrease in the LDL-C/HDL-C ratio when S1S1 subjects changed from the saturated diet to either of the other diets.	(92)

		(NCEP-1) (30% fat, 10% SFA, 55% carbohydrates) and a diet enriched in MUFA (8% fat, 22% MUFA).		
Apolipoprotein E (APOE)				
APOE (E2/E3/E4)		Various interventions	46 interventions involving altering the dietary fat content of the diet. Significantly different total and LDL-C responses between genotype groups were reported in 8 and 11 studies, respectively, with E4 subjects showing the greatest responses. However, subjects with the E2 allele had greatest responses to other diet interventions (i.e., wheat and oat bran, fiber)	(72)
APOE (E2/E3/E4)	65 normal males, mean age 37.5 years, BMI 29.2, recruited in the Quebec City area. Ethnic origin not indicated, most probably white.	High CHO versus high MUFA. Ad libitum, parallel design. Intervention lasting 6–7 weeks. Food was provided to the participants.	Variability in response to a high-CHO diet is primarily determined by APOE genotype, whereas the response to a high-MUFA is determined by waist circumference.	(27)
APOE (E2/E3/E4)	White women, mean age 60 (50–65 years), BMI approximately 32.4	10-week dietary intervention (Amer. Heart Assoc. Step I). Only advice was provided.	In response to the dietary advice to follow an AHA Step I diet, those with the E4 allele benefited the most, while the lipid profile could worsen in those without the E4 allele.	(79)

(*Continued*)

TABLE 1 (*Continued*)

Gene/polymorphism	Population	Dietary factors examined	Conclusions	Reference
APOE (E2/E3/E4)	104 patients with hyperlipidemia. Mean age about 54, BMI around 22.5. Presumably Japanese. Approximately 50% male.	Response to dietary therapy (not specified)	Plasma TC and TG levels were significantly lowered by the dietary treatment in patients with 3/3, 2/3, and 3/4 genotypes; but 2/4 subjects did not respond to the diet.	(112)
APOE (E2/E3/E4)	205 women (ages 49–65 years)	Double-blind, placebo-controlled trial of 43.5 mg red clover–derived isoflavones/d.	Interactions between apoE genotype and treatment tended to be significant for changes in total and LDL cholesterol ($P = 0.06$ and $P = 0.05$), and differences between treatments were significant in E2/E3 women.	(6)
APOE (E2/E3/E4)	84 healthy subjects	3 dietary periods, each lasting 4 weeks. The first was an SFA-enriched diet (38% fat, 20% SFA), which was followed by a carbohydrate (CHO)-rich diet (30% fat, <10% SFA, 55% carbohydrate) or a monounsaturated	LDL size was significantly higher in APOE3/4 subjects compared with APOE3/3 and APOE2/3 subjects in the basal state. LDL size was smaller after the CHO diet than after the MUFA or SFA diets. After the CHO diet, a significant increase in LDL size was noted with respect to the MUFA diet in APOE3/4 subjects, whereas a significant decrease was observed in the APOE3/3 individuals. Therefore, a diet high in MUFA increases LDL particle size compared with a CHO diet, and this effect is dependent of APOE genotypes.	(75)

		fatty acid (MUFA) olive oil–rich diet (38% fat, 22% MUFA) following a randomized crossover design.		
Cholesteryl ester transfer protein (CETP)				
CETP (Taq1B)	Systematic review	Various interventions	B1B1 subjects showed greater total and LDL-cholesterol responses to changes in the type of dietary fat than did subjects who were homozygous or heterozygous for the B2 allele in 1 of 3 studies.	(72)
CETP (I405V)	Subjects with moderate primary hypercholes-terolemia (ages 20–60; 50 women, 10 men)	Margarine (20 g/d) without PSE (placebo) or with PSE (2.8 g/d = 1.68 g/d phytosterols) for four weeks each period, in a crossover, double-blind study	Percent reductions in TC with consumption of PSE for the II, IV, and VV phenotypes were 7.2, 4.2, and not significant, respectively, whereas for LDL-C significant reductions occurred only for II (9.5%). However, the CETP concentration diminished only in the II phenotype.	(68)
CETP (I405V and Taq1B) and APOE (E2/E3/E4)	60 subjects with moderate primary hypercholes-terolemia (ages 20–60; 50 women; 10 men)	Margarine (20 g/d) without PSE (placebo) or with PSE for four weeks each period, in a crossover, double-blind study	In relation to the I405V CETP polymorphism, the % reductions in TC with consumption of PSE for the II, IV, and VV phenotypes were 7.2, 4.2, and not significant, respectively.	(68)

(*Continued*)

TABLE 1 (*Continued*)

Gene/polymorphism	Population	Dietary factors examined	Conclusions	Reference
Cholesterol 7-alpha-hydroxylase (CYP7A1)				
CYP7A1 (A278-C)	Systematic review	Various interventions	This SNP was not associated with dietary responsiveness in one study.	(72)
CYP7A1 (A278-C)	496 normolipidemic subjects (meta-analysis including 26 previously published dietary trials)	Increased intake in dietary cholesterol (742 mg/d), cafestol (57 mg/d), saturated fat [change of 8–9 energy percent/d (en%/d)] and trans fat (change of 10–11 en%/d) in 496 normolipidemic subjects	After adjustment for the apolipoprotein E genotype effect, AA subjects consuming a cholesterol-rich diet had a smaller increase in plasma HDL cholesterol than did CC subjects (0.00 ± 0.02 versus 0.17 ± 0.04 mmol/L; $P < 0.001$). Upon intake of cafestol, AA subjects had a smaller increase in plasma total cholesterol than did CC subjects (0.69 ± 0.10 versus 1.01 ± 0.10 mmol/L; $P = 0.028$). No effects of the polymorphism were found in the saturated and trans fat interventions. In conclusion, the CYP7A1 polymorphism has a small but significant effect on the increase in plasma HDL cholesterol and plasma total cholesterol after an increased intake of dietary cholesterol and cafestol.	(43)
Intestinal fatty acid–binding protein (FABP2)				
FABP2 A54T	Systematic review	Various interventions	One study showed that T54/T54 subjects had greater total and LDL cholesterol responses to a soluble-fiber diet than did the other two genotypes, and the heterozygotes had a significantly greater total cholesterol response to soluble fiber than did the A54/A54 homozygotes.	(72)

Low-density lipoprotein receptor (LDLR)				
LDLR (HincII, PvuII)	Systematic review	Various interventions	A significant interaction between diet and variation in the LDL receptor gene was shown in two studies. After wheat- or oat-bran supplementation, the total and LDL cholesterol reductions were significantly different among the HincII genotype groups, with 2/2 subjects showing the greatest reduction and 1/1 subjects showing the smallest reduction. In terms of the PvuII site, subjects lacking the cutting site were found to have greater HDL responses to low-fat diets.	(72)
Hepatic lipase (LIPC)				
LIPC (NlaIII, MspI)	Systematic review	Various interventions	These SNPs were not associated with the response to diet.	(72)
Endothelial lipase (EL)				
LIPG (Thr111Ile)	83 sedentary, healthy men and women ages 50–75	Subjects were weight-maintained on an Amer. Heart Assoc. Step 1 Diet and then studied before and after aerobic exercise training	The LIPG genotype was associated with interindividual variability in HDL-C and its subfractions and their response to exercise training.	(39)

(*Continued*)

TABLE 1 (*Continued*)

Gene/polymorphism	Population	Dietary factors examined	Conclusions	Reference
Lipoprotein lipase (LPL)				
LPL (HindIII, S447X, N291S)	Systematic review	Various interventions	The H-allele at the HindIII SNP was associated with greater cholesterol and TG responses. Subjects with the S447X polymorphism showed significantly greater decreases in LDL-C levels than did S/S subjects when PUFA replaced SFA in the diet. Subjects heterozygous for the N291S SNP showed greater responses in TG than did N/N subjects. No significant interactions were noted for the PvuII and the T-93G SNPs.	(72)
Paraoxonase 1 (PON1)				
PON1 (G192Arg)	37 healthy, nonsmoking women	A controlled, crossover dietary intervention of two 5-week periods was conducted. The two study diets were either low or high in vegetables, and thus in natural antioxidants, with some differences in fatty acid contents.	The reduction of PON1 activity due to the high-vegetable diet was greatest among the women with the PON1(192Arg) allele and PON1(55Leu/Leu) genotype.	(99)

Peroxisome proliferator-activated receptor gamma (PPARG)				
PPARG (Pro12Ala)	76 men and 74 women (age 49, BMI 26.5 kg/m^2	Subjects were randomly assigned to consume either fish oil supplements or placebo capsules containing olive oil for three months.	Carriers of the Ala12 allele presented a greater decrease in TG concentration in response to n-3 fatty acid supplementation than did subjects with the Pro12Pro genotype when the total dietary fat intake was below 37 E% or the intake of saturated fatty acids was below 10 E%.	(63)
Scavenger receptor class B, member 1 (SCARB1)				
SCARBI [exon 1 (G–>A)]	97 healthy volunteers with exon 1 polymorphism	Both groups consumed 3 diets (SFA-rich, CHO-rich, MUFA-rich diets) lasting 4 weeks each according to a randomized crossover design.	Carriers of the minor allele, 1/2, are more susceptible to the presence of SFA in the diet because of a greater increase in LDL cholesterol.	(94)

*Abbreviations: BMI, body mass index; CHO, carbohydrate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; PSE, plant sterol esters; SFA, saturated fatty acid; SNP, single nucleotide polymorphism.

systematic review as well as an enumeration of more recent reports (after 2002) (6, 27, 39, 43, 55, 63, 68, 72, 75, 79, 92, 94, 97, 99, 112, 120) examining gene-diet interactions in the fasting state. In addition to the above-mentioned reasons contributing to the lack of replication of these types of studies, it should be noted that the composition of the dietary intervention greatly varies between studies. It would be appropriate to standardize a minimum set of variables when considering the design of future intervention studies in order to fix certain conditions (e.g., patients characteristics, medications, and composition and length of the dietary treatment and sample size) and to allow better comparison among studies and even potentially to carry out meta analyses, something that it is impossible under the current experimental conditions.

RESULTS FROM OBSERVATIONAL STUDIES In observational studies, large numbers of subjects can be studied and long-term dietary habits can be estimated. However, the level of evidence of the results obtained from these studies traditionally has been considered to be lower than that of experimental studies. This level can be increased by taking into consideration the principle of Mendelian randomization that was discussed in the "Methodological Issues Assessing Gene-Diet Interaction" section above. Table 2 summarizes the findings of a number of observational studies involving gene-diet interactions on lipid metabolism in the fasting state (15–17, 23–25, 32, 34, 45, 66, 73, 84, 85, 89, 95, 103, 104, 110, 111, 115). In general, as pointed out for the intervention studies, replication of results is still very low. However, taking into account that larger sample sizes are required in observational studies as compared with intervention studies, one factor that has limited replication is the lack of published studies analyzing the same SNPs and dietary factors. In addition, these findings need an increased interface with nutrigenomic studies to acquire mechanistic knowledge for the reported statistical interactions.

GENE-DIET INTERACTIONS IN THE POSTPRANDIAL STATE Humans are typically in a nonfasting state. Postprandial lipemia, characterized by a rise in TRLs after eating, is a dynamic, nonsteady-state condition (49). Over 25 years ago, Zilversmit (125) proposed that atherogenesis was a postprandial phenomenon as postprandial lipoproteins and their remnants could deposit into the arterial wall and accumulate in atheromatous plaques. Several studies have investigated the potential interaction between some polymorphisms in candidate genes and diet on postprandial lipids. Table 3 summarizes the findings of these studies involving *APOA1, APOA5, APOC3*, *APOE*, *LPL*, *NPY*, and *SCARB1* gene variants (26, 54, 67, 70, 71, 74, 93, 102, 107, 125). In postprandial studies, subjects usually receive a fat-loading test meal in which composition varies depending on the nutrient(s) to be tested. After the test meal, blood samples are taken again to measure postprandial lipids. Meal absorption is a complex phenomenon, and because postprandial hyperlipidemia

TABLE 2 Summary of studies analyzing gene-diet interactions with plasma lipid outcomes in observational studies

Gene/polymorphism	Population	Dietary factors examined	Conclusions	Reference
Apolipoprotein A-I (APOA1)				
APOA1 (−75G/A)	755 men and 822 women from the Framingham Offspring Study	Semiquantitative FFQ	In women carriers of the A allele, higher PUFA intakes were associated with higher HDL-C concentrations, whereas the opposite effect was observed in G/G women.	(85)
Apolipoprotein A-IV (APOA4)				
APOA4 [G360H; 347(Thr→Ser)]	758 randomly selected subjects (mean age 36.7) from two Spanish regions differing in latitude and fat intake: Aragon and Comunidad Valenciana	Ecological data (3 household budget surveys, Natl. Inst. Statistics)	The magnitude of the effects associated with the APOA4 alleles was higher in subjects from Aragon compared with the Comunidad Valenciana, suggesting a possible influence of the higher fat intake in Aragon. In the combined association analysis, subjects with the 360Gln/347Ser pseudohaplotype had the highest LDL-C concentrations, supporting the antagonistic effect between the 360His and the 347Ser alleles on this trait.	(34)
APOA4 (G360H)	222 men and 236 from rural and urban Costa Rica	FFQ	Lifestyles associated with an urban environment, such as increased saturated fat intake, elicit a more adverse plasma lipoprotein profile among Costa Rican carriers of the APOA4-360H allele than in APOA41 homozygotes. Therefore, under the conditions studied, persons with the APOA4-360H allele may be more susceptible to CHD.	(17)

(*Continued*)

TABLE 2 (*Continued*)

Gene/polymorphism	Population	Dietary factors examined	Conclusions	Reference
Apolipoprotein C-III (APOC3)				
APOC3 (T-455C, T-625del & C3238G 3′ UTR)	336 randomly selected residents from Costa Rica	FFQ	Compared to a SAT-rich diet is associated with a beneficial lipoprotein profile only among homozygotes of the APOC3 promoter 455T-625T polymorphism.	(15)
Apolipoprotein E (APOE)				
APOE (E2/E3/E4)	132 free-living subjects participating in the EPIC study	FFQ	Elevated plasma cholesterol levels associated with high SAT fat intake can be expected, particularly in those individuals who combine a risky dietary behavior with the presence of the E4 allele.	(65)
APOE (E2/E3/E4)	420 randomly selected free-living Costa Ricans	FFQ	The APOE2 allele could modulate the effect of habitual saturated fat on VLDL-C and HDLC in a population with an average habitual total fat intake of less that 30%.	(16)
APOE (E2/E3/E4)	284 men and 130 women with CAD (mean age 61 years), participants in the EUROASPIRE Study	Four-day food record	CAD patients with the E2 allele will likely have a greater TG response to high dietary sucrose intakes than will patients with the E3 or E4 alleles.	(32)

APOE (E2/E3/E4)	Population control for a case-control Alzheimer's study, >60 years of age. 46 E4+ (30.4% male) and 171 E4− subjects (48.5% male). Ethnicity not indicated.	Dietary recall over two age periods (20–39 and 40–59 years)	The proportion of subjects with the E4 allele was higher in the lowest tertile of fat intake compared with subjects in the highest tertile, suggesting that older persons with the E4 allele who survived free of disease may be protected by a lifelong lower dietary fat intake.	(95)
APOE (E2/E3/E4)	396 men and 513 women aged 18 to 66 years from a Mediterranean Spanish population	Ecological data (three household budget surveys, National Institute of Statistics)	In women, an interaction between alcohol consumption and APOE in determining LDL-C concentrations was found. LDL-C concentrations in female drinkers with the E2 variant were significantly lower than in nondrinkers with the E2 variant. Likewise, in female drinkers with the E4 variant, LDL-C concentrations were significantly lower than in nondrinkers with E4. Moreover, in female drinkers, LDL-C concentrations did not differ between carriers of the E4 and the E3 variants, and in nondrinkers, LDL-C concentrations did not differ between carriers of the E2 and the E3 variants. We also found a statistically significant interaction effect between the APOE polymorphism and physical activity in determining HDL-C concentrations in men.	(23)
APOE (E2/E3/E4)	1014 men and 1133 women from the Framingham Offspring Study	FFQ	In men, the effects of alcohol intake on LDL cholesterol were modulated in part by variability at the APOE locus. Alcohol-related increases in LDL-C concentrations are noted for APOE4 males, whereas the opposite effect is seen in APOE2 males.	(25)

(*Continued*)

TABLE 2 (*Continued*)

Gene/polymorphism	Population	Dietary factors examined	Conclusions	Reference
APOE (E2/E3/E4) and CYP-7A1 (−204A→C)	131 males for whom dietary composition markedly changed and total cholesterol decreased (from 6.21 +/− 1.31 mmol/L in 1988 to 5.43 +/− 1.06 mmol/L in 1996) over an eight-year follow-up study	Changes in food intake according to food questionnaire during an 8-year period	APOE genotype influenced plasma total and LDL cholesterol, with carriers of the E4 having the highest and E2 carriers the lowest levels, this reached borderline significance for cholesterol in 1988 and strongly affected the 1996 levels of LDL-C. However, APOE did not influence the change in these measures over time. In contrast, the CYP-7A1 −204A→C polymorphism did not affect lipid measures per se but was strongly associated with a decrease in plasma total cholesterol over the eight-year time period.	(45)
Cholesteryl ester transfer protein (CETP)				
CETP (TaqIB and −629C > A)	1300 Chinese, 364 Malay and 282 Asian Indian men, and in 1558 Chinese, 397 Malay, and 306 Asian Indian women	FFQ	Dietary cholesterol showed a significant interaction with the TaqIB polymorphism in determining HDL-C concentrations in Indians and Malays, but not in Chinese.	(111)
Liver fatty acid–binding protein (FABP1)				
FABP1 T94A	623 French-Canadian men	FFQ	T94/T94 exhibit higher apoB levels, whereas carriers of the A94 allele seem to be protected against high apoB levels when consuming a high-fat and high-saturated-fat diet.	(104)

Hepatic lipase (LIPC)				
LIPC (−514C/T)	1020 men and 1110 women participating in the Framingham Offspring Study. Mostly from white ethnicity	Semiquantitative FFQ	Dietary fat intake modifies the effect of the −514(C/T) polymorphism on HDL-C concentrations and subclasses. TT subjects may have an impaired adaptation to higher animal fat diets that could result in higher CVD risk.	(84)
LIPC (−514C/T)	Singaporean men and women (1324 Chinese, 471 Malay, and 375 Asian Indian)	FFQ	There were differences in the association of −514C > T polymorphism with plasma lipids according to dietary intake and ethnic background. Specifically, the TT genotype is associated with a more atherogenic lipid profile when subjects consume diets with a fat content >30%.	(110)
Endothelial lipase (EL)				
LIPG (Thr111Ile)	281 white women and 216 white men, ages 17 to 76 years (mean age ∼39 years), from the Quebec Family Study. BMI ranging from 16.8 to 64.9 (mean ∼29.0).	Three-day dietary record	A gender-specific gene-diet interaction among women suggests that the T111I missense mutation may confer protection against the lowering effect of a high dietary PUFA intake on plasma apoA-I and HDL3-C levels.	(89)

(*Continued*)

TABLE 2 (*Continued*)

Gene/polymorphism	Population	Dietary factors examined	Conclusions	Reference
Lipoprotein lipase (LPL)				
LPL-HindIII, LPL-S447X, and APOC3-SstI APOE (E2/E3/E4)	Spanish population (n = 1029)	Ecological data (three household budget surveys, National Institute of Statistics)	There was a significant interaction between APOE and LPL variants and HDL-C levels in both genders ($P < 0.05$). The increases in HDL-C observed for the rare alleles were higher in epsilon4 than in epsilon3 subjects, and absent in epsilon2 individuals. This effect was modulated by smoking (interaction HindIII-APOE-smoking, $P = 0.019$), indicating that smoking abolished the increase in HDL-C levels observed in epsilon4/H(−) subjects.	(24)
Paraoxonase 1 (PON1)				
PON1-192	654 males, ages 25 to 74, randomly selected from the REGICOR Study	72-hour recall questionnaire	The beneficial effect of increasing oleic acid intake on HDL and PON1 activity at population level is especially observed in subjects carrying the R allele of the PON1-192 polymorphism.	(115)

Peroxisome proliferator-activated receptor alpha (PPARα)				
PPARα-L162V	Men with (n = 281) and without (n = 351) the metabolic syndrome	FFQ	The frequency of the V162 allele was higher in subjects with simultaneous abdominal obesity, hypertriglyceridemia, and low HDL-C levels. Carriers of the V162 were characterized by higher plasma apolipoprotein B and TG levels. In a model including the PPARalpha-L162V polymorphism, fat or saturated fat, the interaction term between the polymorphism and fat intake, and covariates (smoking habits and energy and alcohol intake), the interaction explained a significant percentage of the variance observed in waist circumference.	(103)
Peroxisome proliferator-activated receptor gamma (PPARG)				
PPARG (Pro12Ala)	Subjects (n = 2141) were controls selected for three case-control studies nested within the Nurses' Health Study	Semiquantitative FFQ	Among Pro/Pro individuals, those in the highest quintile of total fat intake had higher BMI compared with those in the lowest quintile, whereas among 12Ala variant allele carriers, no significant trend was observed between dietary fat intake and BMI. In contrast, intake of MUFA was not associated with BMI among homozygous wild-type women but was inversely associated with BMI among 12Ala variant allele carriers. The relationship between dietary fat intake and plasma lipids also differed according to PPARG genotype.	(73)

*Abbreviations: BMI, body mass index; CAD, coronary artery disease; CHD, coronary heart disease; CHO, carbohydrate; FFQ, food frequency questionnaire; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; PSE, plant sterol esters; SFA, saturated fatty acid; SNP, single nucleotide polymorphism; TG, triglyceride.

TABLE 3 Summary of studies analyzing gene-diet interactions with plasma lipid outcomes in postprandial studies

Gene/polymorphism	Population	Phenotypes	Dietary factors examined	Conclusions	Reference
Apolipoprotein A-I (APOA1)					
APOA1 (−75G/A)	28 G/G and 23 G/A healthy males, homozygotes for the apo E3 allele	Postprandial lipids	Fat loading test	A greater postprandial response in large TRLs was observed in G/A than in G/G subjects.	(70)
Apolipoprotein A-V (APOA5)					
APOA5 (−1131T > C)	Healthy, nonobese subjects [n = 158; mean (± SEM) age: 33.8 ± 1.2 year; body mass index (in kg/m^2): 23.3 ± 0.3]	Measurements included fasting and postprandial lipid concentrations, lipid peroxidation, C-reactive protein concentrations, and DNA damage.	Fat loading test	After consumption of a mixed meal, carriers of the C allele had significantly greater increases in total chylomicron and VLDL TAG than did subjects with the TT genotype. Moreover, carriers of the C allele had higher dense LDL, serum C-reactive protein, and urinary 8-epi-prostaglandin F(2alpha) concentrations and more lymphocyte DNA damage.	(54)
APOA5 (S19W, −1131T > C; −12238T > C)	Healthy young men (n = 774) who had undergone both an OFTT and an OGTT. Participants in the EARSII Study.	Fasting and postprandial lipids and insulin	OFTT and OGTT	Results strongly support the role of APOA5 in determining plasma TG levels.	(71)

Apolipoprotein C-III (APOC3)					
(apo) CIII C3238G, C-482T, and T-455C	122 viscerally obese men (abdominal visceral AT area $\geq 130\ cm^2$)	Lipoproteins and response to a 75 g OGTT	OGTT	S1/S2 heterozygotes (n = 24) were characterized by increased fasting plasma TG concentrations compared with S1/S1 homozygotes. No association was found between the response to the OGTT and any of the apoC-III gene variants (SstI, T-455C, or C-482T) examined.	(26)
Apo CIII T2854G	Healthy and normolipidemic Korean men (n = 262)	Postprandial lipids	Fat loading test	The data show that the APOAC3 T2854G polymorphism is associated with elevated postprandial TAG concentrations in the study population of Korean men.	(124)
Apolipoprotein E (APOE)					
APOE (−219G/T)	51 healthy white APOE3/3 subjects. Average age ~23, BMI ~24.5	Postprandial lipids	Oral fat loading test	The −219G/T polymorphism influences postprandial lipid metabolism, prolonging postprandial lipemia in subjects with the TT genotype.	(74)
APOE (E2/E3/E4)	16 FCH parents (52 ± 9 years old), 16 offspring (22 ± 5 years) and 12 healthy controls. Ethnic origin not indicated, but probably white	Postprandial lipids	Oral fat loading test	The six-hour postprandial TG values were correlated with fasting TG and were associated with the APOE4 allele.	(102)

(*Continued*)

TABLE 3 (*Continued*)

Gene/polymorphism	Population	Phenotypes	Dietary factors examined	Conclusions	Reference
Neuropeptide Y (NPY)					
NPY (Leu7Pro)	Seven middle-aged obese subjects with Leu7Pro genotype were matched with seven subjects with Leu7Leu genotype for gender, age, apolipoprotein E phenotype, and BMI	Postprandial lipemia, postheparin plasma LPL and HL	Oral eight-hour fat tolerance test	This study suggests compositional differences in lipoprotein particles might exist between the genotype groups that affect postprandial lipid metabolism.	(107)
Lipoprotein lipase (LPL)					
LPL HindIII (H1/H2) and Serine 447-Stop (S447X)	51 healthy male volunteers	Postprandial lipid levels	Fat loading test	Data revealed that subjects that are homozygous for the H2 allele (H2H2) showed a higher postprandial response for small TRL, RP, large TRL-RP, large TRL-B48, and small TRL-B48 levels. Furthermore, in the	(67)

				case of the S447X polymorphism, 447Ter carriers had a lower postprandial response for small TRL-RP, large TRL-B48, and small TRL-RP. Subjects with the LPL H2S447 genotype had higher plasmaTAG, larger TRL-TAG, larger TRL-RP, smaller TRL-RP, and larger TRL-B48 ($P < 0.037$) than did H1X447 subjects.	
Scavenger receptor class B, member 1 (SCARB1)					
SCARBI [exon 1 (G→A)]	47 normolipidemic volunteers who were homozygous for the E3 allele at the APOE gene	Postprandial lipid levels	Fat loading test	Postprandial responses for TAGs and RP in small TAG-rich lipoproteins were higher in 1/1 individuals than in 1/2 individuals.	(93)

*Abbreviations: BMI, body mass index; FCH, familial combined hyperlipidemia; HL, hepatic lipase; LPL, lipoprotein lipase; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; RP, retinyl palmitate; PSE, plant sterol esters; SFA, saturated fatty acid; SNP, single nucleotide polymorphism; OFTT, oral fat tolerance test; OGTT, oral glucose tolerance test; TAG, triacylglycerols; TG, triglyceride; TRL-RP, dial triglyceride-rich lipoproteins-retinyl palmitate; VLDL, very-low-density lipoprotein.

and hyperglycemia are simultaneously present in the postabsorptive phase, particularly in diabetics and in subjects with impaired glucose tolerance, the distinct role of these two factors is a matter of debate (26). Consistency is still very low and, similar to the conclusions reached above for the other experimental approaches, replication is a major need for postprandial studies, where the number of subjects and the complexity of the designs may add even more bias than that of other experimental approaches.

FUTURE OPPORTUNITIES FOR PERSONALIZED NUTRITION: WHAT NEEDS TO BE DONE?

Although the current evidence from both experimental and observational nutrigenetics studies is not strong enough to start making specific personalized nutritional recommendations based on genetic information, we have many examples of common SNPs that modulate the individual response to diet as proof of concept of how gene-diet interactions can influence lipid metabolism. It is critical that these preliminary studies go through further replication in nutrigenetic designs. Overall, the evidence from intervention trials showing gene-diet interactions in lipid metabolism is weak. Many of the trials were short term, of poor experimental design for the stated purpose, and conducted on small sample sizes. To assess the modulation by specific SNPs of the effects of dietary interventions on lipid metabolism, there is a need for well-designed, adequately powered, randomized controlled studies, or studies that are of equivalent level, of greater duration, and in which careful consideration is given to which patients to include. Emphasis should be placed on carrying out appropriate studies to increase consistency. Moreover, nutrigenomic research should also investigate the potential mechanisms involved in the gene-diet interactions reported by nutrigenetic studies. In a few years, both nutrigenetics and nutrigenomics will increase the level of evidence of some of the observed interactions, and personalized nutrition will be both possible and potentially successful (119). One of the first applications of personalized nutrition seems to be centered in dislipidemic patients who require special intervention with dietary treatment. It is known that these individuals will display dramatic heterogeneity in response to the currently recommended therapeutic diets and that the recommendations will need to be adjusted individually. This process could be more efficient if the recommendations are carried out based on genetic and molecular knowledge. Moreover, compliance with dietary advice may increase when it is supported with information based on nutritional genomics and when the patient feels that the advice is personalized. However, a number of important changes in the provision of health care are needed in order to achieve the potential benefits associated with this concept, including a teamwork approach, with greater integration among physicians, dieticians, and genetic counselors. After more experience is gained from patients and/or individuals at high risk, these approaches could be applied toward primary prevention.

SUMMARY AND CONCLUSIONS

In summary, the current evidence supports the concept that gene-diet interactions modulate plasma lipid concentrations and, potentially, cardiovascular risk. However, the application of these findings to the clinical environment is not ready for prime time. Current and future findings need to be replicated using experimental approaches providing the highest level of scientific evidence. Moreover, most of the past and current studies are being conducted using the simplest scenarios, i.e., one single dietary component, one single SNP, and one single risk factor. We have to evolve toward more realistic situations involving interactions of multiple genes, dietary components, and risk factors. This will require large genetic epidemiological studies and intervention studies involving groups of individuals selected for specific genotype combinations and phenotypic characteristics. Another current major gap relates to the inaccuracies of the dietary instruments used in epidemiological studies and the databases used to translate foods into nutrients. These areas need further development to achieve more precision and consistency from nutrigenomic studies.

ACKNOWLEDGMENTS

The authors' study is supported by grants from the American Heart Association (0335432T), USDA/FAS/ICD/RSED/SCRP, and NIH/NHLBI (HL54776); contracts 53-K06-5-10 and 58-1950-9-001 from the U.S. Department of Agriculture Research Service; and grants G03/140 and PI02-1096 from the Instituto de Salud Carlos III, Spain.

The *Annual Review of Nutrition* is online at http://nutr.annualreviews.org

LITERATURE CITED

1. Altmann SW, Davis HR Jr, Zhu LJ, Yao X, Hoos LM, et al. 2004. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. *Science* 303:1201–4
2. Antonarakis SE, Nomenclature Working Group. 1998. Recommendations for a nomenclature system for human gene mutations. *Hum. Mutat.* 11:1–3
3. Assmann G, Gotto AM Jr. 2004. HDL cholesterol and protective factors in atherosclerosis. *Circulation* 109 (23 Suppl. 1): III8–14
4. Assmann G, Nofer JR. 2003. Atheroprotective effects of high-density lipoproteins. *Annu. Rev. Med.* 54:321–41
5. Asztalos B, Lefevre M, Wong L, Foster TA, Tulley R, et al. 2000. Differential response to low-fat diet between low and normal HDL-cholesterol subjects. *J. Lipid Res.* 41:321–28
6. Atkinson C, Oosthuizen W, Scollen S, Loktionov A, Day NE, Bingham SA. 2004. Modest protective effects of isoflavones from a red clover–derived dietary supplement on cardiovascular disease risk factors in perimenopausal women, and evidence of an interaction with ApoE genotype in 49–65-year-old women. *J. Nutr.* 134:1759–64
7. Austin MA, Hutter CM, Zimmern RL, Humphries SE. 2004. Familial hypercholesterolemia and coronary heart

disease: a HuGE association review. *Am. J. Epidemiol.* 160:421–29
8. Austin MA, Hutter CM, Zimmern RL, Humphries SE. 2004. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *Am. J. Epidemiol.* 160:407–20
9. Beaty TH, Khoury MJ. 2000. Interface of genetics and epidemiology. *Epidemiol. Rev.* 22:120–25
10. Bertolini S, Cantafora A, Averna M, Cortese C, Motti C, et al. 2000. Clinical expression of familial hypercholesterolemia in clusters of mutations of the LDL receptor gene that cause a receptor-defective or receptor-negative phenotype. *Arterioscler. Thromb. Vasc. Biol.* 20:E41–52
11. Bertolini S, Pisciotta L, Di Scala L, Langheim S, Bellocchio A, et al. 2004. Genetic polymorphisms affecting the phenotypic expression of familial hypercholesterolemia. *Atherosclerosis* 174:57–65
12. Botto LD, Khoury MJ. 2001. Commentary: facing the challenge of gene-environment interaction: the two-by-four table and beyond. *Am. J. Epidemiol.* 153: 1016–20
13. Breslow JL. 2000. Genetics of lipoprotein abnormalities associated with coronary artery disease susceptibility. *Annu. Rev. Genet.* 34:233–54
14. Brown MS, Goldstein JL. 1976. Analysis of a mutant strain of human fibroblasts with a defect in the internalization of receptor-bound low density lipoprotein. *Cell* 9:663–74
15. Brown S, Ordovas JM, Campos H. 2003. Interaction between the APOC3 gene promoter polymorphisms, saturated fat intake and plasma lipoproteins. *Atherosclerosis* 170:307–13
16. Campos H, D'Agostino M, Ordovas JM. 2001. Gene-diet interactions and plasma lipoproteins: role of apolipoprotein E and habitual saturated fat intake. *Genet. Epidemiol.* 20:117–28
17. Campos H, Lopez-Miranda J, Rodriguez C, Albajar M, Schaefer EJ, Ordovas JM. 1997. Urbanization elicits a more atherogenic lipoprotein profile in carriers of the apolipoprotein A-IV-2 allele than in A-IV-1 homozygotes. *Arterioscler. Thromb. Vasc. Biol.* 17:1074–81
18. Cargill M, Altshuler D, Ireland J, Sklar P, Ardlie K, et al. 1999. Characterization of single-nucleotide polymorphisms in coding regions of human genes. *Nat. Genet.* 22:231–38
19. Cederbaum S. 2002. Phenylketonuria: an update. *Curr. Opin. Pediatr.* 14:702–6
20. Chahoud G, Aude YW, Mehta JL. 2004. Dietary recommendations in the prevention and treatment of coronary heart disease: Do we have the ideal diet yet? *Am. J. Cardiol.* 94:1260–67
21. Civeira F, Intl. Panel Manag. Familial Hypercholesterolemia. 2004. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis* 173:55–68
22. Connelly MA, Williams DL. 2004. Scavenger receptor BI: a scavenger receptor with a mission to transport high density lipoprotein lipids. *Curr. Opin. Lipidol.* 15: 287–95
23. Corella D, Guillen M, Saiz C, Portoles O, Sabater A, et al. 2001. Environmental factors modulate the effect of the APOE genetic polymorphism on plasma lipid concentrations: ecogenetic studies in a Mediterranean Spanish population. *Metabolism* 50:936–44
24. Corella D, Guillen M, Saiz C, Portoles O, Sabater A, et al. 2002. Associations of LPL and APOC3 gene polymorphisms on plasma lipids in a Mediterranean population: interaction with tobacco smoking and the APOE locus. *J. Lipid Res.* 43:416–27
25. Corella D, Tucker K, Lahoz C, Coltell O, Cupples LA, et al. 2001. Alcohol drinking determines the effect of the APOE locus on LDL-cholesterol concentrations

in men: the Framingham Offspring Study. *Am. J. Clin. Nutr.* 73:736–45
26. Couillard C, Vohl MC, Engert JC, Lemieux I, Houde A, et al. 2003. Effect of apoC-III gene polymorphisms on the lipoprotein-lipid profile of viscerally obese men. *J. Lipid Res.* 44:986–93
27. Couture P, Archer WR, Lamarche B, Landry N, Deriaz O, et al. 2003. Influences of apolipoprotein E polymorphism on the response of plasma lipids to the ad libitum consumption of a high-carbohydrate diet compared with a high-monounsaturated fatty acid diet. *Metabolism* 52:1454–59
28. Davey Smith G, Ebrahim S. 2003. Mendelian randomization: Can genetic epidemiology contribute to understanding environmental determinants of disease? *Int. J. Epidemiol.* 32:1–22
29. Davis HR Jr, Zhu LJ, Hoos LM, Tetzloff G, Maguire M, et al. 2004. Niemann-Pick C1 Like 1 (NPC1L1) is the intestinal phytosterol and cholesterol transporter and a key modulator of whole-body cholesterol homeostasis. *J. Biol. Chem.* 279:33586–92
30. de Andrade M, Amos CI, Thiel TJ. 1999. Methods to estimate genetic components of variance for quantitative traits in family studies. *Genet. Epidemiol.* 17:64–76
31. Dedoussis GV, Schmidt H, Genschel J. 2004. LDL-receptor mutations in Europe. *Hum. Mutat.* 24:443–59
32. Erkkila AT, Sarkkinen ES, Lindi V, Lehto S, Laakso M, Uusitupa MI. 2001. APOE polymorphism and the hypertriglyceridemic effect of dietary sucrose. *Am. J. Clin. Nutr.* 73:746–52
33. Fujino T, Navaratnam N, Scott J. 1998. Human apolipoprotein B RNA editing deaminase gene (APOBEC1). *Genomics* 47:266–75
34. Ganan A, Corella D, Guillen M, Ordovas JM, Pocovi M. 2004. Frequencies of apolipoprotein A4 gene polymorphisms and association with serum lipid concentrations in two healthy Spanish populations. *Hum. Biol.* 76:253–66
35. Garcia-Closas M, Lubin JH. 1999. Power and sample size calculations in case-control studies of gene-environment interactions: comments on different approaches. *Am. J. Epidemiol.* 149:689–92
36. Gibbons GF, Wiggins D, Brown AM, Hebbachi AM. 2004. Synthesis and function of hepatic very-low-density lipoprotein. *Biochem. Soc. Trans.* 32(Pt. 1):59–64
37. Greenland S. 1993. Basic problems in interaction assessment. *Environ. Health Perspect.* 101(Suppl. 4):59–66
38. Hagberg JM, Wilund KR, Ferrell RE. 2000. APO E gene and gene-environment effects on plasma lipoprotein-lipid levels. *Physiol. Genomics* 4:101–8
39. Halverstadt A, Phares DA, Ferrell RE, Wilund KR, Goldberg AP, Hagberg JM. 2003. High-density lipoprotein-cholesterol, its subfractions, and responses to exercise training are dependent on endothelial lipase genotype. *Metabolism* 52:1505–11
40. Havel RJ, Kane JP. 1975. Quantification of triglyceride transport in blood plasma: a critical analysis. *Fed. Proc.* 34:2250–57
41. Hegele RA. 2002. Environmental modulation of atherosclerosis end points in familial hypercholesterolemia. *Atherosclerosis* 2(Suppl.):5–7
42. Heller DA, de Faire U, Pedersen NL, Dahlen G, McClearn GE. 1993. Genetic and environmental influences on serum lipid levels in twins. *N. Engl. J. Med.* 328:1150–56
43. Hofman MK, Weggemans RM, Zock PL, Schouten EG, Katan MB, Princen HM. 2004. CYP7A1 A-278C polymorphism affects the response of plasma lipids after dietary cholesterol or cafestol interventions in humans. *J. Nutr.* 134:2200–4
44. Holtzman NA. 1988. Genetic variation in nutritional requirements and susceptibility to disease: policy implications. *Am. J. Clin. Nutr.* 48:1510–16
45. Hubacek JA, Pitha J, Skodova Z, Poledne R, Lanska V, et al. 2003. Polymorphisms

in CYP-7A1, not APOE, influence the change in plasma lipids in response to population dietary change in an 8-year follow-up; results from the Czech MONICA study. *Clin. Biochem.* 36:263–67

46. Huff MW. 2003. Dietary cholesterol, cholesterol absorption, postprandial lipemia and atherosclerosis. *Can. J. Clin. Pharmacol.* 10(Suppl. A):26–32
47. Humphries SE, Montgomery HE, Talmud PJ. 2001. Predisposing genes, high-risk environments and coronary artery disease: LPL and fibrinogen as examples. *World Rev. Nutr. Diet.* 89:61–67
48. Humphries SE, Ridker PM, Talmud PJ. 2004. Genetic testing for cardiovascular disease susceptibility: a useful clinical management tool or possible misinformation? *Arterioscler. Thromb. Vasc. Biol.* 24:628–36
49. Hussain MM, Shi J, Dreizen P. 2003. Microsomal triglyceride transfer protein and its role in apoB-lipoprotein assembly. *J. Lipid Res.* 44:22–32
50. Hyson D, Rutledge JC, Berglund L. 2003. Postprandial lipemia and cardiovascular disease. *Curr. Atheroscler. Rep.* 5:437–44
51. Ioannidis JP, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG. 2001. Replication validity of genetic association studies. *Nat. Genet.* 29:306–9
52. Jacobs B, De Angelis-Schierbaum G, Egert S, Assmann G, Kratz M. 2004. Individual serum triglyceride responses to high-fat and low-fat diets differ in men with modest and severe hypertriglyceridemia. *J. Nutr.* 134:1400–5
53. Jacobs DR Jr, Anderson JT, Hannan P, Keys A, Blackburn H. 1983. Variability in individual serum cholesterol response to change in diet. *Arteriosclerosis* 3:349–56
54. Jang Y, Kim JY, Kim OY, Lee JE, Cho H, et al. 2004. The 1131T→C polymorphism in the apolipoprotein A5 gene is associated with postprandial hypertriacylglycerolemia; elevated small, dense LDL concentrations; and oxidative stress in nonobese Korean men. *Am. J. Clin. Nutr.* 80:832–40
55. Jemaa R, Mebazaa A, Fumeron F. 2004. Apolipoprotein B signal peptide polymorphism and plasma LDL-cholesterol response to low-calorie diet. *Int. J. Obes. Relat. Metab. Disord.* 28:902–5
56. Kardia SL. 2000. Context-dependent genetic effects in hypertension. *Curr. Hypertens. Rep.* 2:32–38
57. Katan MB, Beynen AC, De Vries JH, Nobels A. 1986. Existence of consistent hypo- and hyperresponders to dietary cholesterol in man. *Am. J. Epidemiol.* 123: 221–34
58. Katan MB, Grundy SM, Willett WC. 1997. Should a low-fat, high-carbohydrate diet be recommended for everyone? Beyond low-fat diets. *N. Engl. J. Med.* 337: 563–66
59. Krauss RM. 2001. Atherogenic lipoprotein phenotype and diet-gene interactions. *J. Nutr.* 131:340–43S
60. Krauss RM. 2001. Dietary and genetic effects on low-density lipoprotein heterogeneity. *Annu. Rev. Nutr.* 21:283–95
61. Krieger M. 2001. Scavenger receptor class B type I is a multiligand HDL receptor that influences diverse physiologic systems. *J. Clin. Invest.* 108:793–97
62. LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. 1997. Discrepancies between meta-analyses and subsequent large, randomized, controlled trials. *N. Engl. J. Med.* 337:536–42
63. Lindi V, Schwab U, Louheranta A, Laakso M, Vessby B, et al. 2003. Impact of the Pro12Ala polymorphism of the PPAR-gamma2 gene on serum triacylglycerol response to n-3 fatty acid supplementation. *Mol. Genet. Metab.* 79:52–60
64. Little J, Bradley L, Bray MS, Clyne M, Dorman J, et al. 2002. Reporting, appraising, and integrating data on genotype prevalence and gene-disease associations. *Am. J. Epidemiol.* 156:300–10
65. Loktionov A. 2003. Common gene polymorphisms and nutrition: emerging

links with pathogenesis of multifactorial chronic diseases. *J. Nutr. Biochem.* 14: 426–51

66. Loktionov A, Scollen S, McKeown N, Bingham SA. 2000. Gene-nutrient interactions: dietary behaviour associated with high coronary heart disease risk particularly affects serum LDL cholesterol in apolipoprotein E epsilon4-carrying free-living individuals. *Br. J. Nutr.* 84:885–90
67. Lopez-Miranda J, Cruz G, Gomez P, Marin C, Paz E, et al. 2004. The influence of lipoprotein lipase gene variation on postprandial lipoprotein metabolism. *J. Clin. Endocrinol. Metabolism* 89:4721–28
68. Lottenberg AM, Nunes VS, Nakandakare ER, Neves M, Bernik M, et al. 2003. The human cholesteryl ester transfer protein I405V polymorphism is associated with plasma cholesterol concentration and its reduction by dietary phytosterol esters. *J. Nutr.* 133:1800–5
69. Lusis AJ, Mar R, Pajukanta P. 2004. Genetics of atherosclerosis. *Annu. Rev. Genomics Hum. Genet.* 5:189–218
70. Marin C, Lopez-Miranda J, Gomez P, Paz E, Perez-Martinez P, et al. 2002. Effects of the human apolipoprotein A-I promoter G-A mutation on postprandial lipoprotein metabolism. *Am. J. Clin. Nutr.* 76:319–25
71. Martin S, Nicaud V, Humphries SE, Talmud PJ, EARS Group. 2003. Contribution of APOA5 gene variants to plasma triglyceride determination and to the response to both fat and glucose tolerance challenges. *Biochim. Biophys. Acta* 1637:217–25
72. Masson LF, McNeill G, Avenell A. 2003. Genetic variation and the lipid response to dietary intervention: a systematic review. *Am. J. Clin. Nutr.* 77:1098–111
73. Memisoglu A, Hu FB, Hankinson SE, Liu S, Meigs JB, et al. 2003. Prospective study of the association between the proline to alanine codon 12 polymorphism in the PPARgamma gene and type 2 diabetes. *Diabetes Care* 26:2915–17
74. Moreno JA, Lopez-Miranda J, Marin C, Gomez P, Perez-Martinez P, et al. 2003. The influence of the apolipoprotein E gene promoter (−219G/T) polymorphism on postprandial lipoprotein metabolism in young normolipemic males. *J. Lipid Res.* 44:2059–64
75. Moreno JA, Perez-Jimenez F, Marin C, Gomez P, Perez-Martinez P, et al. 2004. The effect of dietary fat on LDL size is influenced by apolipoprotein E genotype in healthy subjects. *J. Nutr.* 134:2517–22
76. Mu H, Hoy CE. 2004. The digestion of dietary triacylglycerols. *Prog. Lipid Res.* 43:105–33
77. Muller M, Kersten S. 2003. Nutrigenomics: goals and strategies. *Nat. Rev. Genet.* 4:315–22
78. Neale BM, Sham PC. 2004. The future of association studies: gene-based analysis and replication. *Am. J. Hum. Genet.* 75: 353–62
79. Nicklas BJ, Ferrell RE, Bunyard LB, Berman DM, Dennis KE, Goldberg AP. 2002. Effects of apolipoprotein E genotype on dietary-induced changes in high-density lipoprotein cholesterol in obese postmenopausal women. *Metabolism* 51:853–58
80. Ordovas JM. 2000. Genetic polymorphisms and activity of cholesterol ester transfer protein (CETP): Should we be measuring them? *Clin. Chem. Lab. Med.* 38:945–49
81. Ordovas JM. 2001. Genetics, postprandial lipemia and obesity. *Nutr. Metab. Cardiovasc. Dis.* 11:118–33
82. Ordovas JM. 2002. HDL genetics: candidate genes, genome wide scans and gene-environment interactions. *Cardiovasc. Drugs Ther.* 16:273–81
83. Ordovas JM, Corella D. 2004. Nutritional genomics. *Annu. Rev. Genomics Hum. Genet.* 5:71–118
84. Ordovas JM, Corella D, Demissie S, Cupples LA, Couture P, et al. 2002. Dietary fat intake determines the effect of a common polymorphism in the hepatic lipase

gene promoter on high-density lipoprotein metabolism: evidence of a strong dose effect in this gene-nutrient interaction in the Framingham Study. *Circulation* 106:2315–21

85. Ordovas JM, Corella D, Cupples LA, Demissie S, Kelleher A, et al. 2002. Polyunsaturated fatty acids modulate the effects of the APOA1 G-A polymorphism on HDL-cholesterol concentrations in a sex-specific manner: the Framingham Study. *Am. J. Clin. Nutr.* 75:38–46
86. Ordovas JM, Mooser V. 2002. The APOE locus and the pharmacogenetics of lipid response. *Curr. Opin. Lipidol.* 13:113–17
87. Ordovas JM, Tai ES. 2002. The babel of the ABCs: novel transporters involved in the regulation of sterol absorption and excretion. *Nutr. Rev.* 60:30–33
88. Ottman R. 1990. An epidemiological approach to gene-environment interaction. *Genet. Epidemiol.* 7:177–85
89. Paradis ME, Couture P, Bosse Y, Despres JP, Perusse L, et al. 2003. The T111I mutation in the EL gene modulates the impact of dietary fat on the HDL profile in women. *J. Lipid Res.* 44:1902–8
90. Parks EJ, Rutledge JC, Davis PA, Hyson DA, Schneeman BO, Kappagoda CT. 2001. Predictors of plasma triglyceride elevation in patients participating in a coronary atherosclerosis treatment program. *J. Cardiopulm. Rehabil.* 21:73–79
91. Pennacchio LA, Rubin EM. 2003. Apolipoprotein A5, a newly identified gene that affects plasma triglyceride levels in humans and mice. *Arterioscler. Thromb. Vasc. Biol.* 23:529–34
92. Perez-Martinez P, Gomez P, Paz E, Marin C, Gavilan Moral E, et al. 2001. Interaction between smoking and the SstI polymorphism of the apo C-III gene determines plasma lipid response to diet. *Nutr. Metab. Cardiovasc. Dis.* 11:237–43
93. Perez-Martinez P, Lopez-Miranda J, Ordovas JM, Bellido C, Marin C, et al. 2004. Postprandial lipemia is modified by the presence of the polymorphism present in the exon 1 variant at the SR-BI gene locus. *J. Mol. Endocrinol.* 32:237–45
94. Perez-Martinez P, Ordovas JM, Lopez-Miranda J, Gomez P, Marin C, et al. 2003. Polymorphism exon 1 variant at the locus of the scavenger receptor class B type I gene: influence on plasma LDL cholesterol in healthy subjects during the consumption of diets with different fat contents. *Am. J. Clin. Nutr.* 77:809–13
95. Petot GJ, Traore F, Debanne SM, Lerner AJ, Smyth KA, Friedland RP. 2003. Interactions of apolipoprotein E genotype and dietary fat intake of healthy older persons during mid-adult life. *Metabolism* 52:279–81
96. Pimstone SN, Sun XM, du Souich C, Frohlich JJ, Hayden MR, Soutar AK. 1998. Phenotypic variation in heterozygous familial hypercholesterolemia: a comparison of Chinese patients with the same or similar mutations in the LDL receptor gene in China or Canada. *Arterioscler. Thromb. Vasc. Biol.* 18:309–15
97. Plat J, Mensink RP. 2002. Relationship of genetic variation in genes encoding apolipoprotein A-IV, scavenger receptor BI, HMG-CoA reductase, CETP and apolipoprotein E with cholesterol metabolism and the response to plant stanol ester consumption. *Eur. J. Clin. Invest.* 32:242–50
98. Poustie VJ, Rutherford P. 2001. Dietary treatment for familial hypercholesterolaemia. *Cochrane Database Syst. Rev.* 2:CD001918

98a. Rantala M, Rantala TT, Savolainen MJ, Friedlander Y, Kesaniemi YA. 2000. Apolipoprotein B gene polymorphisms and serum lipids: meta-analysis of the role of genetic variation in responsiveness to diet. *Am. J. Clin. Nutr.* 71(3):713–24

99. Rantala M, Silaste ML, Tuominen A, Kaikkonen J, Salonen JT, et al. 2002. Dietary modifications and gene polymorphisms alter serum paraoxonase activity in healthy women. *J. Nutr.* 132:3012–17
100. Rebbeck TR, Spitz M, Wu X. 2004.

Assessing the function of genetic variants in candidate gene association studies. *Nat. Rev. Genet.* 5:589–97

101. Redgrave TG. 2004. Chylomicron metabolism. *Biochem. Soc. Trans.* 32(Pt. 1):79–82
102. Reiber I, Mezo I, Kalina A, Palos G, Romics L, Csaszar A. 2003. Postprandial triglyceride levels in familial combined hyperlipidemia. The role of apolipoprotein E and lipoprotein lipase polymorphisms. *J. Nutr. Biochem.* 14:394–400
103. Robitaille J, Brouillette C, Houde A, Lemieux S, Perusse L, et al. 2004. Association between the PPARα-L162V polymorphism and components of the metabolic syndrome. *J. Hum. Genet.* 49: 482–89
104. Robitaille J, Brouillette C, Lemieux S, Perusse L, Gaudet D, Vohl MC. 2004. Plasma concentrations of apolipoprotein B are modulated by a gene-diet interaction effect between the LFABP T94A polymorphism and dietary fat intake in French-Canadian men. *Mol. Genet. Metab.* 82:296–303
105. Rothman KJ, Greenland S, Walker AM. 1980. Concepts of interaction. *Am. J. Epidemiol.* 112:467–70
106. Schaefer EJ, Lamon-Fava S, Ausman LM, Ordovas JM, Clevidence BA, et al. 1997. Individual variability in lipoprotein cholesterol response to National Cholesterol Education Program Step 2 diets. *Am. J. Clin. Nutr.* 65:823–30
107. Schwab US, Agren JJ, Valve R, Hallikainen MA, Sarkkinen ES, et al. 2002. The impact of the leucine 7 to proline 7 polymorphism of the neuropeptide Y gene on postprandial lipemia and on the response of serum total and lipoprotein lipids to a reduced fat diet. *Eur. J. Clin. Nutr.* 56:149–56
108. Sijbrands EJ, Westendorp RG, Defesche JC, de Meier PH, Smelt AH, Kastelein JJ. 2001. Mortality over two centuries in large pedigree with familial hypercholesterolaemia: family tree mortality study. *BMJ* 322:1019–23
109. Sun XM, Patel DD, Webb JC, Knight BL, Fan LM, et al. 1994. Familial hypercholesterolemia in China. Identification of mutations in the LDL-receptor gene that result in a receptor-negative phenotype. *Arterioscler. Thromb.* 14:85–94
110. Tai ES, Corella D, Deurenberg-Yap M, Cutter J, Chew SK, et al. 2003. Dietary fat interacts with the $-514C > T$ polymorphism in the hepatic lipase gene promoter on plasma lipid profiles in a multiethnic Asian population: the 1998 Singapore National Health Survey. *J. Nutr.* 133:3399–408
111. Tai ES, Ordovas JM, Corella D, Deurenberg-Yap M, Chan E, et al. 2003. The TaqIB and $-629C > A$ polymorphisms at the cholesteryl ester transfer protein locus: associations with lipid levels in a multiethnic population. The 1998 Singapore National Health Survey. *Clin. Genet.* 63:19–30
112. Tamasawa N, Murakami H, Yamato K, Matsui J, Tanabe J, Suda T. 2003. Influence of apolipoprotein E genotype on the response to caloric restriction in type 2 diabetic patients with hyperlipidaemia. *Diabetes Obes. Metab.* 5:345–48
113. Tiret L. 2002. Gene-environment interaction: a central concept in multifactorial diseases. *Proc. Nutr. Soc.* 61:457–63
114. Tobin MD, Minelli C, Burton PR, Thompson JR. 2004. Development of Mendelian randomization: from hypothesis test to "Mendelian deconfounding". *Int. J. Epidemiol.* 33:26–29
115. Tomas M, Senti M, Elosua R, Vila J, Sala J, et al. 2001. Interaction between the Gln-Arg 192 variants of the paraoxonase gene and oleic acid intake as a determinant of high-density lipoprotein cholesterol and paraoxonase activity. *Eur. J. Pharmacol.* 432:121–28
116. Trayhurn P. 2003. Nutritional genomics—"Nutrigenomics". *Br. J. Nutr.* 89:1–2
117. Umans-Eckenhausen MA, Defesche JC,

Sijbrands EJ, Scheerder RL, Kastelein JJ. 2001. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. *Lancet* 357:165–68

118. van Dijk KW, Rensen PC, Voshol PJ, Havekes LM. 2004. The role and mode of action of apolipoproteins CIII and AV: synergistic actors in triglyceride metabolism? *Curr. Opin. Lipidol.* 15:239–46
119. van Ommen B, Stierum R. 2002. Nutrigenomics: exploiting systems biology in the nutrition and health arena. *Curr. Opin. Biotechnol.* 13:517–21
120. Vincent S, Planells R, Defoort C, Bernard MC, Gerber M, et al. 2002. Genetic polymorphisms and lipoprotein responses to diets. *Proc. Nutr. Soc.* 61:427–34
121. Vuorio AF, Gylling H, Turtola H, Kontula K, Ketonen P, Miettinen TA. 2000. Stanol ester margarine alone and with simvastatin lowers serum cholesterol in families with familial hypercholesterolemia caused by the FH-North Karelia mutation. *Arterioscler. Thromb. Vasc. Biol.* 20:500–6
122. Wiegman A, Hutten BA, de Groot E, Rodenburg J, Bakker HD, et al. 2004. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 292:331–37
123. Williams RR, Hasstedt SJ, Wilson DE, Ash KO, Yanowitz FF. 1986. Evidence that men with familial hypercholesterolemia can avoid early coronary death. An analysis of 77 gene carriers in four Utah pedigrees. *JAMA* 255:219–24
124. Woo SK, Kang HS. 2003. The apolipoprotein CIII T2854G variants are associated with postprandial triacylglycerol concentrations in normolipidemic Korean men. *J. Hum. Genet.* 48:551–55
125. Zilversmit DB. 1979. Atherogenesis: a postprandial phenomenon. *Circulation* 60:473–85

Annual Review of Nutrition
Volume 25, 2005

CONTENTS

DIETARY FIBER: HOW DID WE GET WHERE WE ARE?, *Martin Eastwood and David Kritchevsky* 1

DEFECTIVE GLUCOSE HOMEOSTASIS DURING INFECTION, *Owen P. McGuinness* 9

HUMAN MILK GLYCANS PROTECT INFANTS AGAINST ENTERIC PATHOGENS, *David S. Newburg, Guillermo M. Ruiz-Palacios, and Ardythe L. Morrow* 37

NUTRITIONAL CONTROL OF GENE EXPRESSION: HOW MAMMALIAN CELLS RESPOND TO AMINO ACID LIMITATION, *M.S. Kilberg, Y.-X. Pan, H. Chen, and V. Leung-Pineda* 59

MECHANISMS OF DIGESTION AND ABSORPTION OF DIETARY VITAMIN A, *Earl H. Harrison* 87

REGULATION OF VITAMIN C TRANSPORT, *John X. Wilson* 105

THE VITAMIN K-DEPENDENT CARBOXYLASE, *Kathleen L. Berkner* 127

VITAMIN E, OXIDATIVE STRESS, AND INFLAMMATION, *U. Singh, S. Devaraj, and Ishwarlal Jialal* 151

UPTAKE, LOCALIZATION, AND NONCARBOXYLASE ROLES OF BIOTIN, *Janos Zempleni* 175

REGULATION OF PHOSPHORUS HOMEOSTASIS BY THE TYPE IIa Na/PHOSPHATE COTRANSPORTER, *Harriet S. Tenenhouse* 197

SELENOPROTEIN P: AN EXTRACELLULAR PROTEIN WITH UNIQUE PHYSICAL CHARACTERISTICS AND A ROLE IN SELENIUM HOMEOSTASIS, *Raymond F. Burk and Kristina E. Hill* 215

ENERGY INTAKE, MEAL FREQUENCY, AND HEALTH: A NEUROBIOLOGICAL PERSPECTIVE, *Mark P. Mattson* 237

REDOX REGULATION BY INTRINSIC SPECIES AND EXTRINSIC NUTRIENTS IN NORMAL AND CANCER CELLS, *Archana Jaiswal McEligot, Sun Yang, and Frank L. Meyskens, Jr.* 261

REGULATION OF GENE TRANSCRIPTION BY BOTANICALS: NOVEL REGULATORY MECHANISMS, *Neil F. Shay and William J. Banz* 297

POLYUNSATURATED FATTY ACID REGULATION OF GENES OF LIPID METABOLISM, *Harini Sampath and James M. Ntambi* 317

SINGLE NUCLEOTIDE POLYMORPHISMS THAT INFLUENCE LIPID METABOLISM: INTERACTION WITH DIETARY FACTORS, *Dolores Corella and Jose M. Ordovas* 341

THE INSULIN RESISTANCE SYNDROME: DEFINITION AND DIETARY APPROACHES TO TREATMENT, *Gerald M. Reaven* 391

DEVELOPMENTAL DETERMINANTS OF BLOOD PRESSURE IN ADULTS, *Linda Adair and Darren Dahly* 407

PEDIATRIC OBESITY AND INSULIN RESISTANCE: CHRONIC DISEASE RISK AND IMPLICATIONS FOR TREATMENT AND PREVENTION BEYOND BODY WEIGHT MODIFICATION, *M.L. Cruz, G.Q. Shaibi, M.J. Weigensberg, D. Spruijt-Metz, G.D.C. Ball, and M.I. Goran* 435

ANNUAL LIPID CYCLES IN HIBERNATORS: INTEGRATION OF PHYSIOLOGY AND BEHAVIOR, *John Dark* 469

DROSOPHILA NUTRIGENOMICS CAN PROVIDE CLUES TO HUMAN GENE–NUTRIENT INTERACTIONS, *Douglas M. Ruden, Maria De Luca, Mark D. Garfinkel, Kerry L. Bynum, and Xiangyi Lu* 499

THE COW AS A MODEL TO STUDY FOOD INTAKE REGULATION, *Michael S. Allen, Barry J. Bradford, and Kevin J. Harvatine* 523

THE ROLE OF ESSENTIAL FATTY ACIDS IN DEVELOPMENT, *William C. Heird and Alexandre Lapillonne* 549

INDEXES

Subject Index 573

Cumulative Index of Contributing Authors, Volumes 21–25 605

Cumulative Index of Chapter Titles, Volumes 21–25 608

ERRATA

An online log of corrections to *Annual Review of Nutrition* chapters may be found at http://nutr.annualreviews.org/