Genetic Predictors of Plasma Lipid Response to Diet Intervention

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Introduction
The merger of the fields of Nutrition and Genetics is providing the tools to answer relevant biologic questions. Among them, we should emphasize the elucidation of the molecular basis underlying the dramatic interindividual variability in response to diet interventions. Intense research has focused in recent years on the interaction between several genetic loci and the individual variability in response to dietary interventions. These studies have been the subject of recent reviews focusing on candidate gene loci including apolipoprotein (APO) A1, APOA4, APOB, APOC, APOE, LPL, and CETP, and have been shown to explain a significant, but still rather small, proportion of the interindividual variability in dietary response. Other genes code for products that play a relevant role in lipoprotein metabolism and are prime candidates for future studies (ie, CYP7). Future progress in this complex area will come from experiments carried out using animal models and from carefully controlled dietary protocols in humans.

Genetic Determinants of Low-Density Lipoprotein Cholesterol Response to Dietary Intervention
The role of plasma LDLC in predicting coronary heart disease (CHD) risk is well established. Dietary fat and cholesterol are two major factors determining LDLC concentrations. However, LDLC responses to diet intervention vary dramatically in both human subjects and animal models. It is believed that part of this variability is genetically controlled; however, information about the specific genetic contribution and the genes involved is still scarce.

A major difficulty in defining the genetic component involved in this variability comes from the complexity of carrying out well-controlled, large dietary intervention in families. Therefore, information will have to be derived for the most part using relevant animal models. In this regard, Rainwater et al. [4] have recently explored the genetic component of cholesterolemic responses to dietary cholesterol and fat in 575 pedigreed baboons. Three traits were examined in these animals: 1) LDLC concentrations (baseline) while consuming a diet low in fat and cholesterol (LDLCB); 2) The change in LDLC concentration (versus baseline) after consuming a diet high in saturated fat diet (LDLCRF); and 3) The change after consuming a diet high in both cholesterol and saturated fat (LDLCRC). Two of these traits were strongly heritable, \( h^2 = 0.59 \) for LDLCB and \( h^2 = 0.59 \) for LDLCRC, whereas the LDLCRF was only weakly heritable \( h^2 = 0.14 \). Moreover, LDLCB and LDLCRC showed a significant genetic correlation \( D_C = 0.54 \). This is a strong indication that one or more genes exert pleiotropic effects on the LDLC concentrations when animals were consuming a low-fat, low-cholesterol diet, as well as the LDLC response to a high-fat, high-cholesterol diet. Segregation analysis demonstrated the presence of a major locus accounting for most of the genetic variation in \( D_C = 0.54 \). This is a strong indication that one or more genes exert pleiotropic effects on the LDLC concentrations when animals were consuming a low-fat, low-cholesterol diet, as well as the LDLC response to a high-fat, high-cholesterol diet. Segregation analysis demonstrated the presence of a major locus accounting for most of the genetic variation in LDLCRC, whereas this same locus had minor effects over LDLCB or LDLCRF. Moreover, these analyses revealed the presence of a major locus, different from the previous, that influenced LDLCRC. Linkage analysis demonstrated that none of the loci were linked to the LDL receptor (LDLR) gene, a likely candidate for LDLR.

This information, especially in an animal model phylogenetically close to humans, will be highly valuable in understanding the information gathered in humans using candidate genes.
Apolipoprotein E (APOE)
The APOE gene has been the locus most intensively examined in terms of its potential as a determinant of the individual variability in LDL response to diet interventions. Previous findings related to this locus have been extensively reviewed [1-3] and only those findings that were not previously considered will be presented here. Despite the large number of studies examining the relationship between APOE genetic variability and LDL response to diet intervention, the magnitude and significance of the reported associations remain controversial and this locus continues to be the subject of intense research. Along these lines, Blauw-before et al. [5] have examined the effect of the APOE genotype on the LDL response to a long-term (1-year) low cholesterol diet on 36 type 1 diabetes mellitus subjects. The E4 allele was present in 11 of them and their dietary response was compared with that of those that were E4-. Both groups reduced their cholesterol intake in the same magnitude; however, those in the APOE4 group had a significantly higher decrease in LDL than those in the E3 group. Therefore, in this group of subjects with Diabetes, the effect of the APOE4 allele was similar to those reported by other investigators in healthy subjects.

Intestinal Fatty Acid Binding Protein (IFABP)
The fatty acid binding protein-2 gene (FABP2) codes for the intestinal fatty acid binding protein (IFABP). The IFABP is a member of a family of small (14-15 kD) intracellular lipid binding proteins. Besides the IFABP, this family also includes the heart, epidermal, brain, and liver FABPs, testicular, myelin, adipocyte, and ileal lipid binding proteins (LBP), and cellular retinol and retinoic acid-binding proteins [6]. The gene located in 4q28-q31 [7] has the conserved 4 exons and 3 introns characteristic of this family of genes [7,8]. IFABP plays important roles in several steps of fat absorption and transport: 1) uptake and trafficking of saturated and unsaturated long-chain fatty acids; 2) targeting free fatty acids (FFA) toward different metabolic pathways; 3) protecting the cytosol from the cytotoxic effects of FFA and 4) modulating enzyme activity involved in lipid metabolism [9,10]. Besides FFA, the IFABP may bind other ligands, such as phenolic antioxidants. The IFABP is abundant in the enterocyte and represents 2% to 3% of an enterocyte's cytoplasmic mass [11]. There has been found that the expression of IFABP mRNA is under dietary control [12]. Additional support for the importance of FABPs comes from evolutionary data. FABPs, which have conserved sequences, have been found in animal species as diverse as humans, cows, pigs, rats, rabbits, fish, chickens, worms, sharks, frogs, and insects. The human IFABP has 82% amino acid sequence identity to the rat IFABP. The FABPs also share a similar structural motif. Sacchettini et al. [13] found that the FABPs each have ten anti-parallel B-strands, which form two orthogonal B-sheets. There are two short α-helices that are connected to the first two B-strands. This structure has been characterized as a B-clam because it resembles a clamshell. It is hypothesized that fatty acids enter the FABP by passing a portal that includes three structures; the portal is comprised of one the α-helices, and two sharp turns between B-strands, which includes residues 54-55 and 73-74 [13,14]. A mutation in the IFABP at any of these amino acid residues that surround the portal may alter fatty acid entry into the protein. This may result in abnormal binding of fatty acids, which then may influence lipid profiles and consequently disease risk.

In 1995, Baier et al. [15] reported a new G>A mutation, which results in an amino acid substitution in IFABP at residue 54, alanine (ala) 54 (wild-type) Æthreonine (thr, mutant-type). This polymorphism is very common, with thr54 allelic frequency of approximately 29% in most populations. To date, the alan54thr mutation in the IFABP is the only functional mutation found in humans in a member of the cytoplasmic fatty acid binding protein family [16]. This amino acid substitution was found associated with elevated fasting insulin levels, insulin resistance, and increased fatty acid binding in Pima Indians [15]. Associations of this polymorphism with several biochemical and anthropometric variables have been subsequently carried out in Japanese, Mexican-American, Native Americans and Caucasian populations. In general, the presence of the thr54 allele has been associated in some, but not all [17-21], studies with higher fasting insulin concentrations [15,22], and insulin resistance. On the other hand, a study of Keewatin Inuit found the thr54 allele to be associated with lower 2-hour glucose concentrations [21]. It is well known that Inuits have large dietary intakes of omega-3 fatty acids from fish. This finding in Inuits suggests that differences in the type of fatty acid consumed interacts with the functional differences in the gene products to produce phenotypic differences [21]. Several studies have utilized the euglycemic, hyperinsulinemic clamp for determining insulin resistance. Using this approach, the FABP2 mutation was associated with a lower mean insulin-stimulated glucose uptake rate in Pima Indians. However, no significant findings were noted in subjects with Familial Combined Hyperlipidemia (FCHL) [23] and in overweight, Finnish subjects [24]. In a separate study, Stern et al. [25] found that the FABP was not significantly linked to the major gene for the age of onset for noninsulin-dependent diabetes mellitus (NIDDM) [25].

Several studies have found an association between the presence of the thr54 mutation and higher mean fat oxidation rate [15,23] and greater fasting plasma triglyceride (TG) [17,26]. However, Vidgren et al. [27] examined a small group of Finnish subjects after an overnight fast and found no differences in the proportion of long-chain fatty acids (LCFA) in serum lipids among the three genotypes. Only one study has been reported examining the potential role of this gene as a determinant of interindividual variability in LDL response to diet intervention. Hegele et al. [28] found that the alan54thr mutation was associated with variation in the response of plasma lipo-