Gene-diet interactions in obesity\textsuperscript{1–4}

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ABSTRACT A considerable amount of research on the genetics of obesity has been reported in the past few years. Despite evidence that genetic factors play a significant role in the etiology of this nutritional disease and the increasing number of obesity genes identified, relatively little is known about the role of genes in the response of obesity phenotypes to alterations in energy balance or diet composition. This is especially true for dietary fat, which is known to be associated with obesity at the population level. The aim of this review was to summarize the evidence currently available about the role of gene-nutrient interactions in human obesity. Evidence from both genetic epidemiology and molecular epidemiology studies suggests that genetic factors are involved in determining the susceptibility to gaining or losing fat in response to diet or the risk of developing some of the comorbidities generally observed in obese individuals. Recent evidence suggests that quantitative trait loci identified from animal models of diet-induced obesity could influence body fat in humans. Despite the limited number of studies, the evidence on gene-diet interactions in obesity is convincing. More research is needed to identify the genes responsible for these interaction effects, and the use of animal models of diet-induced obesity represents a promising approach. Finally, data on children are needed to allow assessment of the tracking of nutrient intake between childhood and adulthood. In addition, gene-diet interactions in children need to be investigated to determine whether the genes involved are the same as those found in adults. \textit{Am J Clin Nutr} 2000;72(suppl):1285S–90S.

KEY WORDS Genetics, diet, obesity, children, review

INTRODUCTION Risk factors for several of the major chronic diseases, such as cardiovascular disease, hypertension, diabetes, obesity, and cancer, are often observed during childhood. Therefore, preventive measures adopted early in life may help reduce the prevalence of these diseases in adulthood. Diet is undoubtedly such a risk factor that could benefit from early intervention. This was a central argument for the American Heart Association and the National Cholesterol Education Program in recommending that children adopt nutritional habits that limit the intake of fat to 30% of energy and the intake of cholesterol to ≤ 300 mg/d. At the population level, these policies assume that all individuals respond similarly to dietary modifications and benefit more or less equally from dietary recommendations aimed at reducing risk of disease. However, it is well documented that there are considerable interindividual differences in the response of plasma lipid concentrations to alterations in the amount of fat and cholesterol in the diet.

Some individuals appear to be relatively insensitive (low responders) to dietary intervention, whereas others (high responders) are quite sensitive (1, 2). Furthermore, what is good at the population level is not necessarily good at the individual level. 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 (3) than those with the subclass pattern A. Indeed, the latter group exhibit the more atherogenic pattern B subclass after consuming a low-fat diet (4). Although most of the evidence regarding the variability in the response to diet has been obtained in adults, there is evidence that the heterogeneity in the response can also be observed in children (5).

There is strong evidence that this variability in the response to diet is partly determined by genetic factors, especially for lipid and lipoprotein phenotypes. Indirect evidence in favor of this hypothesis comes from the fact that the phenotypic response to diet is determined partly by the baseline value of the phenotype that is itself affected by genetic factors. For example, baseline serum cholesterol concentrations are correlated with the response to dietary cholesterol (2) and it is known that ≈ 50% of the population variance in fasting serum cholesterol is genetically determined. The same is true for the response of plasma lipoproteins to changes in dietary lipids. A study of the response of plasma lipids to changes in dietary lipid intake in 125 children aged 4–10 y showed that baseline plasma lipid concentrations were the strongest independent predictor of changes in plasma lipids after 3 mo of intervention (6). Variability in the response to dietary cholesterol or dietary fat was also observed in a variety of animal species, and hypo- and hyperresponsive animal strains can be obtained through selective breeding. These

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ROLE OF DIETARY FAT IN OBESITY

The role of dietary fat in the etiology of obesity was addressed in several studies but remains controversial (10–15). It is generally accepted that high-fat diets induce an overconsumption of energy, which can lead to the development of obesity. One controversial question is whether or not a high-fat diet by itself, ie, independent of total energy intake, is a risk factor for obesity. The epidemiologic evidence linking consumption of high-fat diets to obesity should be considered suggestive rather than definitive (11). One of the major arguments against the role of dietary fat in the development of obesity comes from population data showing an increase in the prevalence of obesity in most industrialized countries despite a reduction in the proportion of energy intake derived from fat. However, the counterargument is that the reduction in the proportion of energy from fat has been relatively small, ≈3–5%, and would not necessarily be associated with a reduction in body weight (15). On the other hand, between-population (ecologic) studies have shown that the prevalence of overweight and obesity tends to be higher in countries with high fat intakes, an observation that supports the hypothesis of a role of dietary fat in the development of obesity.

Data from cross-sectional studies have reported significant positive correlations, ranging from 0.20 to 0.40, between energy-adjusted fat intake and various measures of obesity, although some studies found no such association (11). A positive relation between the percentage of energy derived from fat and obesity was also observed in children. In our own data from the Quebec Family Study, we reported a positive association between dietary fat intake and total body fat (16) and body mass index (BMI; in kg/m²) (17). The epidemiologic studies are difficult to interpret because the key variables, dietary fat and obesity, cannot be measured directly in large cohorts and are subject to bias (12). Finally, the results of prospective studies of dietary fat and weight changes have been inconsistent (12, 13).

A review of the results from 28 clinical trials on the effects of a reduction in the amount of energy from fat in the diet showed that a reduction of 10% in the percentage of energy derived from fat was associated with a reduction in weight of 16 g/d (15). The comparison of BMIs between subjects consuming high-fat and low-fat diets is another approach that has been used to study the relation between dietary fat and obesity. Data from the Leeds High Fat Study (18) showed that there were 19 times more obese subjects (BMI > 30) among individuals consuming a high-fat diet (>45% of energy as fat) than among those consuming a low-fat diet (<35% of energy as fat). In addition, these studies showed that, for a given amount of energy from fat (18) or a given percentage point reduction in the percentage of energy from fat (15), there was marked heterogeneity in the response of body mass. This heterogeneity is compatible with the notion that there are individual differences in the susceptibility to dietary fat and suggests that gene-dietary fat interactions may play a role.

RELEVANCE OF GENOTYPE-ENVIRONMENT INTERACTION EFFECTS IN OBESITY

Genotype-environment interactions arise when the response of a phenotype (eg, fat mass) to environmental changes (eg, dietary intervention) is modulated by the genotype of the individual. There are 2 different levels on which genotype-environment interaction effects could be relevant for obesity. First, they could be involved in determining the susceptibility to gain fat in response to environmental risk factors such as a high-fat diet or a low physical activity level. Second, genotype-environment interaction effects could also be involved in the susceptibility of obese individuals to develop comorbidities associated with obesity (eg, diabetes, hyperlipidemia, hypertension, and coronary heart disease) or in response to treatment. Definition of these interaction effects for phenotypes related to obesity is therefore important because it will eventually allow the identification of individuals at risk of obesity, the development of complications associated with obesity, and the identification of those likely to be resistant to dietary interventions and hence requiring, perhaps, more drastic or better-adjusted dietary prescription.

EVIDENCE FROM GENETIC EPIDEMIOLOGY

Methods from both genetic epidemiology (unmeasured genotype approach) and from molecular epidemiology (measured genotype approach) have been used to detect genotype-environment interaction effects 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. The measured genotype approach uses genetic variation in random genetic markers or in candidate genes and attempts to evaluate the effect of variation at the DNA level on the quantitative phenotype under study. Three methods can be used to detect genotype-environment interaction effects when no genotype data are available.

The first method consists of an investigation of the relations between genetic predisposition, associated risk factors, and disease in an epidemiologic framework (19). The genetic susceptibility may be either polygenic (a familial predisposition) or due to a Mendelian gene (an individual affected by a genetic disease). The risk factor represents one of the many risk factors associated with the disease and may itself be influenced by genetic and environmental agents. Five different models describing the relations between the disease, the risk factor, and genetic predisposition were proposed (19). These models are summarized in Figure 1. Model A posits that the genotype does not cause the disease directly but increases the expression of the risk factor. In model B, the genotype exacerbates the effect of the risk factor on the disease. Model C is the reverse of model B; the risk factor exacerbates the effect of the genotype and only the latter is required for disease expression. In model D, both the genotype and the risk factor are required to raise the risk level, whereas in model E the genotype and the risk factor each influence the risk of disease individually.
FIGURE 1. Five hypothetical models describing the relations between genetic susceptibility to disease and risk factors for disease in an epidemiologic framework. Adapted from reference 19.

Some of these models provide examples of gene-diet interactions. Phenylketonuria is the classic case fitting model A. On the basis of this model, the accumulation of the amino acid phenylalanine from dietary origin in the blood causes mental retardation because individuals affected by this inherited disease lack the enzyme responsible for the degradation of phenylalanine into tyrosine. An example of gene-nutrient interactions based on model D is the relation between glucose-6-phosphate 1-dehydrogenase (G6PD) deficiency, fava bean consumption, and hemolytic anemia. Only individuals with a G6PD deficiency and consuming fava beans develop a severe form of hemolytic anemia. These are 2 examples in which a genetic susceptibility evidenced in the presence of a dietary challenge is due to genetic defects that have been identified at the molecular level. Two studies in which the genetic susceptibility was polygenic rather then monogenic provided evidence of nutrient-gene interaction effects on obesity (20) and plasma lipids (6) and illustrate the paradigm outlined in model B. In one study, dietary fat intake and weight gain over a 6-y follow-up period were investigated in 361 women, taking into account the family history of obesity (20). Overweight women (BMI > 25) with at least one obese parent were considered to have a familial predisposition. After control for total energy intake, smoking habits, physical activity, and menopausal status, a high dietary fat intake (average of ≈40% of energy from fat) was associated with a significant increase in BMI, but only in the women with the familial predisposition. Moreover, fat intake was found to be a predictor of the development of obesity only in women with a familial predisposition (20). In a study by Dixon et al (6), the response of plasma lipids to dietary modifications elicited by means of a nutrition education program was investigated in 125 children aged 4–10 y with elevated LDL-cholesterol concentrations at baseline. Significant reductions in plasma total and LDL-cholesterol concentrations were found, but only in children with little evidence of a family history of coronary heart disease (CAD) as assessed by the occurrence of a myocardial infarction or hypercholesterolemia in none or not more than one first or one second-degree relative. After adjustment for age, sex, and BMI, a significant interaction between changes in the amount of cholesterol in the diet and family history of CAD was observed for the changes in plasma total and LDL-cholesterol concentrations. Interestingly, neither apo E phenotype nor lipoprotein(a) concentrations, either independently or interactively with changes in dietary lipids, were found to influence changes in plasma lipids (6). These results suggest that children with a positive family history of CAD are more resistant to dietary intervention aimed at reducing lipid concentrations.

The second method that can be used to detect genotype-environment interaction effects based on the unmeasured genotype approach consists of incorporating genotype-environment interaction effects in the statistical genetic models used to assess the contribution of genetic and environmental factors. An example of such a model is the major gene model, which is characterized by the segregation of a single locus that has a large effect on the phenotype. Under this model, which can be tested by complex segregation analysis, the phenotype is assumed to be influenced by the independent and additive contributions from a major gene effect, a multifactorial background due to polygenes, and a unique environmental component (residual). Ignoring existing genotype-environment interaction effects was shown to reduce the power to detect major gene effects (21, 22). Three segregation analysis studies of obesity have provided evidence for a single gene with sex-specific effects, age-specific effects, or both. In the Quebec Family Study, we reported that the BMI was influenced by a single gene with sex- and age-specific effects (21), whereas a similar type of major gene effect was reported in French families for a measure of height-adjusted weight (23). In Mexican American families, Comuzzie et al (24) reported a major gene with sex-specific effects for body fat mass measured by bioelectrical impedance. These findings suggest the existence of a putative gene that affects body mass or body fat, the effects of which are dependent on the sex and the age of the individual, which represents a special case of genotype-environment interaction effect.

We proposed that another method to test for the presence of a genotype-environment interaction effect in humans was to challenge several genotypes in a similar manner by submitting both members of monozygotic twin pairs to a standardized treatment (environment) and then compare the within- and between-pair variances of the response to the treatment (25). The finding of a significantly higher variance in the response between pairs than within pairs suggested that the changes induced by the treatment are more heterogeneous in genetically dissimilar individuals, which translates into a higher intrapair resemblance in the response. Using this method, we performed a series of studies to investigate the role of the genotype in determining the response to changes in energy balance by submitting both members of male monozygotic twin pairs either to positive energy balance induced by short-term and long-term overfeeding (26, 27) or to negative energy balance induced by exercise training in the presence of constant energy intake conditions (28, 29). The results of the long-term overfeeding (27) and negative energy balance (29) experiments are reviewed here.

The long-term overfeeding study

In this experiment, 12 pairs of healthy, male, monozygotic twins with no familial history of obesity, hyperlipidemia, or diabetes were submitted to a 4.2 MJ (1000 kcal) energy surplus 6 d/wk for 100 d (27). The excess energy intake over the entire experiment reached 353 MJ (84000 kcal). Significant increases in body weight and fat mass were observed after the period of overfeeding. The mean body mass gain was 8.1 kg, but there were considerable interindividual differences in the adaptation to excess energy, with a 3-fold difference between the lowest and highest gains. However, as indicated in Figure 2 (left panel), this heterogeneity in the response was not randomly distributed across genotypes. For instance, there was ≥3 times (F ratio = 3.4) more variance in the response between pairs than within pairs for the changes in body
Body weight (kg) 60 ± 8
total variability in responsiveness.

FIGURE 2. Intrpair resemblance for changes in body weight after long-term alterations in energy balance in monozygotic twins. Left panel: Twelve pairs of monozygotic twins were subjected to a 353-MJ (84 000-kcal) surplus over 100 d. Right panel: Seven pairs of monozygotic twins were subjected to an energy deficit of 244 MJ (58 000 kcal) over 93 d caused by exercise. Adapted from references 27 and 29.

The negative energy balance study

Seven pairs of young, adult, male identical twins completed a negative energy balance protocol during which they exercised on cycle ergometers twice a day, 9 of 10 d, over a period of 93 d while maintaining constant daily energy and macronutrient intakes (29). The mean total energy deficit above the estimated energy cost of body weight maintenance, caused by exercise, reached ∼244 MJ (58 000 kcal). The mean loss in body weight was 5.0 kg (range: 1.0–8.0 kg). Intrapair resemblance was observed for the changes in body weight (Figure 2, right panel), fat mass, percentage fat, and subcutaneous fat (Table 1). Even though there were large individual differences in response to the negative energy balance protocol, subjects with the same genotype were more alike in response than were subjects with different genotypes, particularly for changes in subcutaneous fat, fat mass, and visceral fat, with F ratios > 10 (Table 1).

The results of these intervention studies in monozygotic twins indicate that there are considerable differences in the way individuals respond to chronic alterations in energy balance conditions. Within-pair similarity observed in the response to the standardized energy surplus or the energy deficit suggests that the genotype plays a significant role in determining this biological variability in responsiveness.

EVIDENCE FROM MOLECULAR EPIDEMIOLOGY

With advances in molecular genetics, the study of gene-nutrient interactions is now performed at the gene level. With this approach, genetic variation in various candidate genes is investigated for their role in determining the response to diet. Three methods can be used to provide evidence for genotype-environment interaction effects in humans when candidate genes are available. The first is to compare the influence of a gene on a given phenotype between populations of different ethnic and cultural backgrounds. An example of this approach is provided by the study of Hallman et al (30), who showed that the effect of apo E polymorphism on total cholesterol concentrations varied among populations with different amounts of fat in their diet. The cholesterol-raising effect of the e4 allele, for example, was found to be highest in populations consuming high-fat diets (eg, Tyrolea and Finland) and lowest in populations consuming low-fat diets (eg, Japan and Sudan). The second method involves a comparison of the effect of a gene on a phenotype of interest between subgroups of individuals within the same population, but categorized on the basis of variables that can potentially affect the phenotype, eg, the amount of fat in the diet. An example of this approach is in the results of Zee et al (31), who reported an association between a polymorphism in the LDL receptor gene and hypertension, but only in overweight or obese subjects. No example of gene-nutrient interaction effects based on this method has been reported thus far for obesity. In the third method, the response to diet is investigated among individuals with different genotypes at a given candidate gene or marker locus. This is the approach that is most often used to identify the genes responsible for gene-nutrient interactions, especially for lipid phenotypes for which several polymorphisms in various apolipoprotein genes are documented (see reference 8 for a review).

TABLE 1

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1 Adapted from references 27 and 29.
2 ± SD.
3 The changes observed in all phenotypes after overfeeding and negative energy balance were significant: 4 P < 0.05, 5 P < 0.01.
4 Subcutaneous fat is the sum of 10 skinfold-thickness measures.
Few candidate genes have been investigated for their role in the response of obesity phenotypes to changes in diet. Lipoprotein lipase is the enzyme responsible for the hydrolysis of triacylglycerol-rich lipoproteins and plays an important role in the regulation of plasma lipoprotein composition and concentrations and in the partitioning of exogenous triacylglycerol between adipose tissue for storage and skeletal muscle for oxidation. Moreover, it was shown recently that transgenic mice that overexpress lipoprotein lipase in the skeletal muscle were protected against diet-induced obesity only (32). The lipoprotein lipase gene located on chromosome 8p22 could therefore be considered a strong candidate for gene-environment interactions in obesity. Using data from our intervention studies in monozygotic twins, we found that a BamHI restriction length fragment polymorphism in the lipoprotein lipase gene was associated with the response to overfeeding (33). Changes in body weight and percentage body fat in response to overfeeding were more important in carriers of the BamHI restriction site (9.1 kg weight and 7.9% body fat) compared with noncarriers (7 kg weight and 5.6%). Similarly, a lipoprotein lipase HindIII polymorphism located in intron 8 of the gene was found to modulate the relation between visceral fat and plasma triacylglycerol (34). Other data suggest that the apo A-II MspI polymorphism is associated with lower HDL₃-cholesterol concentrations, but only in men with high amounts of abdominal visceral fat or with evidence of an insulin-resistance state (35).

EVIDENCE FROM ANIMAL MODELS

Animal models of diet-induced obesity could be of benefit in understanding the role of gene-environment interactions in obesity. One benefit is the possibility of controlling rigorously the diet and other relevant environmental factors affecting obesity and the possibility of performing selective breeding studies. In a comparison of the response of 9 mouse strains to a high-fat diet, West et al (36) found a range in adiposity gain of ~6-fold between the sensitive AKR/J strain and the resistant SWR/J strain. Examination of the segregation of this trait in the progeny of crosses between the sensitive and the resistant strains showed a polygenic pattern of inheritance with a minimum of 3 loci determining the response to dietary lipids (37). Using the quantitative-trait-loci (QTL) mapping method, West et al (37, 38) identified 3 dietary obese (Dob1 QTL), These loci—Dob1, Dob2, and Dob3—were located on mouse chromosomes 4, 9, and 15, respectively. On the basis of the synteny between the mouse and human genomes, these QTL map to human chromosomes 1p36-1p35 and 9p13 for Dob1, 3p21 for Dob2, and 8q23-q24 for Dob3. Other QTL from the same cross were reported, but only in abstract forms.

These positional candidate genes in rodents can be used to test for linkage with body fat phenotypes in humans. Using data from the Quebec Family Study, we tested for linkage between markers syntenic to Dob1 on human chromosome 1 and various obesity phenotypes. The phenotypes investigated included BMI, subcutaneous fat assessed by the sum of 6 skinfold-thickness measures, and percentage body fat and fat mass derived from underwater weighing (39). These obesity phenotypes were adjusted for age and sex and were tested for linkage with the sibpair linkage method. Significant evidence of linkage was observed between BMI, subcutaneous fat, percentage body fat, fat mass, and the markers D1S193 and D1S200, whereas the marker D1S255 was found to be linked only to subcutaneous fat and percentage body fat.

SUMMARY AND RECOMMENDATIONS FOR FUTURE STUDIES

Despite the limited number of studies, the data reviewed in this article suggest that genetic factors play an important role in determining the response of body mass and body fat stores to chronic alterations in energy balance. Considering the epidemiologic evidence suggesting an association between dietary fat intake and the development of obesity, more studies are needed to understand the role of the genotype in the response of body composition to changes in dietary fat intake. The most recent obesity gene map indicates that there are >100 genes or marker loci that have the potential to influence obesity (40). Efforts are needed to identify among these genes those responsible for modulating the response to diet. For this purpose, QTL identified from animal models probably represent the most promising approach. Candidate genes or genomic regions identified in these animal models can be tested in humans by using association or linkage studies with obesity phenotypes or, more interestingly, with the response of these phenotypes to dietary interventions.

A major concern is the lack of data on children. Although we assume that the response to diet in children is characterized by a degree of variability similar to that observed in young adults, studies are needed to investigate this issue specifically in children. It is possible that the effect of some genes on the response may differ between adults and children. Another issue that requires investigation concerns the tracking of dietary intake, especially fat intake. No data are available to determine whether consumption of a high-fat diet early in life increases the risk of exhibiting the same pattern of nutrient intake during adulthood. It is important to understand the tracking of key nutrients before developing new dietary recommendations for children. An understanding of the tracking pattern will also be useful in the study of the role of genetic factors in dietary responsiveness.

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