Annu. Rev. Nutr. 2006. 26:413–34
doi: 10.1146/annurev.nutr.26.061505.111218

First published online as a Review in Advance on April 18, 2006

GENETICS OF FOOD INTAKE AND EATING BEHAVIOR PHENOTYPES IN HUMANS

Tuomo Rankinen and Claude Bouchard
Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, Louisiana 70808-4124; email: RankinT@pbrc.edu, Bouchac@pbrc.edu

Key Words genotype, heritability, quantitative trait locus, single nucleotide polymorphism

■ **Abstract** This review summarizes the research advances of the past decade regarding the role of human genetic differences in energy and nutrient intake as well as in eating behavior phenotypes and selected eating disorders. The evidence for familial aggregation and heritability based on twin and nuclear family study designs is summarized. Genome-wide linkage scans and quantitative trait loci identified to date are discussed. DNA sequence variants in candidate genes are reviewed. Single genes associated with classical eating disorders are also incorporated. Epigenetic events will need to be incorporated in future studies designed to investigate the effects of DNA variants on dietary phenotypes. Understanding the relative contribution of global genetic variation and of DNA sequence variants in specific genes is important in the effort to influence dietary habits in a healthier direction.

CONTENTS

INTRODUCTION

This review summarizes the research advances of the past decade regarding the role of human genetic differences in energy and nutrient intake as well as in eating behavior phenotypes and selected eating disorders. This topic is particularly

important in the most affluent countries of the world, in which unhealthy nutritional habits and hyperphagia are thought to be very common. Indeed, in these countries, the profile of nutritionally related diseases has shifted from one driven by specific nutrient deficiencies to one dominated by excessive caloric intake, especially fat and sugar consumption. Understanding the relative contribution to this phenomenon of global genetic variation and of DNA sequence variants in specific genes is a key step in the effort to influence dietary habits in a more favorable direction.

The review is organized around two major sections. The first summarizes the evidence for familial aggregation and heritability based on twin and nuclear family study designs. The second part focuses on more direct evidence for genetic effects. Genome-wide linkage scans and quantitative trait loci (QTLs) identified to date are discussed. DNA sequence variants in candidate genes have begun to appear regularly in the literature and are reviewed herein. Single genes associated with classical eating disorders are also incorporated in the review.

The review covers only human studies. The phenotypes considered include daily energy intake, macronutrient intake (g/day or percentage of energy intake), and behavioral traits (restraint, disinhibition, and hunger) thought to underlie eating behavior. Moreover, data available on the genetics of anorexia nervosa, bulimia nervosa, and binge-eating disorder are also summarized. The review does not include food selection studies, the ability to taste specific substances, or indicators of aversion to specific foods.

GENETIC EPIDEMIOLOGY OF FOOD INTAKE PHENOTYPES

Considerable individual differences exist in caloric and nutrient intake on any given day and even when integrated over periods of days or weeks. However, as has been recognized for many years, within-subject variation in caloric and nutrient intake is just as large (2). The latter observation represents a major challenge in the efforts to undertake the dissection of the sources of variance in dietary intake, particularly when one wants to identify the potential contribution of human genetic differences to variation in food intake. Nonetheless, a good number of studies have been reported on this topic using not only classical genetic epidemiology designs but also a number of innovative approaches adapted to the unique nature of dietary intake behavior. These studies are reviewed herein for three families of dietary phenotypes.

Energy and Macronutrient Intake

FAMILY STUDIES A number of studies have used dietary recalls, food frequency questionnaires, three-day dietary food records, and other dietary assessment methods to investigate the resemblance among nuclear family members for daily caloric

intake and macronutrient consumption (60). Results from large studies, such as the Quebec Family Study (58), the San Antonio Family Heart Study (11, 55), the Stanislas Family Study (5, 76), and other family-based cohorts (37, 68) have revealed that there is evidence for familial aggregation of the individual differences observed in estimated age- and body mass–adjusted daily caloric intake as well as protein, carbohydrate, and lipid intake expressed in g/day, with little difference when reported as a percentage of energy intake. Correlations in the order of 0.2 to 0.3 are typically observed for spouses and sibling pairs, whereas slightly lower values are seen for parent-offspring dietary phenotypes. Heritability coefficients derived from a variety of quantitative procedures are generally low and rarely exceed 20% of the age- and sex-adjusted variance.

In the Ireland-Boston Diet-Heart Study launched in the late 1950s, men in the Boston area who still had a brother in Ireland were recruited (74). Dietary intake data were available on 293 men living in Boston and 357 of their siblings living in Ireland. Age- and country-adjusted sibling correlations reached 0.17 for daily caloric intake, 0.18 for fat intake in g/day but only 0.05 as percent of energy, 0.24 for protein intake in g/day and 0.08 as percent of energy, 0.13 for carbohydrate in g/day and 0.16 as percent of energy, and 0.09 for alcohol intake (68). These results are interesting because the siblings were all adults who were living apart. The sibling resemblance was consistently significant, with little difference in comparison with correlations reported for siblings living together in the nuclear family studies cited above.

Supportive evidence for the findings described above comes from two other studies with innovative designs. Food intake and preference were assessed during a home visit in 214 families that had 4- or 5-year-old same-sex twins (total of 428 twin children) and volunteered to participate (79). Among these families, 114 were classified as "lean families," with both parents having body mass index (BMI) values of less than 25. The remaining 100 families were defined as "obese families," with both parents exhibiting a BMI above 25. In practice, the mean BMI of the latter families was 29 for the fathers (reported) and 36 for the mothers (measured). Children from the obese families had a higher preference for fatty foods in a taste test, a lower preference for vegetables, and higher scores on a few indicators of response to food. In a recent study, 32 pairs of siblings aged 3 to 7 years consumed ad libitum lunches under two experimental conditions: one preceded by a low-energy preload drink and the other by a high-energy preload drink (30). Total energy intake across the two test situations exhibited a significant sibling correlation (0.49) when adjusted for age, sex, ethnicity, and BMI. Likewise, percentage of energy intake derived from lipids (0.53), carbohydrates (0.57), and proteins (0.66) adjusted in the same manner were characterized by significant familial aggregation.

TWIN STUDIES A large number of reports on energy and macronutrient intake in monozygotic (MZ) and dizygotic (DZ) twins using a variety of designs and analytical approaches have been published over the past 40 years. Although there

are negative reports, most studies suggest that evidence exists for a genetic effect on the number of calories consumed and on the preference for specific nutrients and food items. Only a small number of the published studies are highlighted here.

An examination of data from food frequency questionnaires obtained in 232 pairs of male MZ twins and 223 pairs of male DZ twins of the National Heart and Lung Institute Twin Study revealed significant genetic variance for total caloric intake as well as for fat and carbohydrate intake (28). A significant genetic effect was also seen for hot beverage consumption and for wine, beer, and other alcohol intake. However, when stratified on the basis of how frequently twins see each other, none of the dietary phenotypes showed consistent evidence for a genetic effect. These results were taken as evidence that there are environmental covariance differences among MZ and DZ twins that may have nontrivial effects on estimates of genetic variance in twin studies. However, another study based on 109 MZ and 86 DZ adult twin pairs could not replicate this finding using estimates of the frequency with which the twins get together and ratings of the similarities of their experiences during childhood and adolescence (15). Likewise, data from another large twin study did not support the hypothesis that the more frequent contacts among MZ brothers and sisters in comparison with DZ twins result in higher genetic effects for dietary phenotypes (75).

The latter study is of particular interest and is summarized here. Male and female twins were recruited through advertising that targeted retired persons and they completed a mailed version of the National Cancer Institute food frequency questionnaire (75). The final sample included all twins, 50 years of age and older, who responded to the dietary questionnaire and for whom zygosity information was available: 210 male MZ pairs, 725 female MZ pairs, 92 male DZ pairs, 376 female DZ pairs, and 245 opposite-sex DZ pairs. The data on 99 food items of the questionnaire were subjected to factor analysis, which yielded two common eating patterns: Factor 1 consisted of foods high in fat, salt, and sugar (less healthy pattern); factor 2 included vegetable, fruit, rice, yogurt, skim milk, and dark bread (healthy pattern). Information on use of food, consumption frequency, and serving size was available. Correlations for the latter traits, adjusted for age and sex, for factors 1 and 2 and for each of the five twin types are reproduced in Figure 1. Eating patterns scores were subjected to structural equation analysis and the results of the model-fitting procedures are depicted in Figure 2. Sex-specific models explained the data better for eating pattern 1 than for eating pattern 2. Overall, heritable factors account for about one third of the variance in whether a person consumes a specific food item and in the serving size and consumption frequency in both eating patterns. The common environmental influences are generally small; the specific environment component is the largest influence.

A study of 66 MZ and 51 DZ twin pairs reared apart provides support for the notion that the heritability of self-reported dietary characteristics is approximately one third of the phenotypic variance (47). Results of a model-fitting procedure revealed that the additive genetic estimate reached 40% for caloric intake per kg

body weight, 16% for protein, 35% for lipid, and 25% for carbohydrate intake. Meal and snack frequency generated genetic effects ranging from 30% to 33%, while consumption of a number of beverage types was characterized by additive genetic effects ranging from 20% to 46%. In a large epidemiological study based on the Finnish Twin Registry, data on breakfast eating frequency were collected by questionnaire on 2625 twin pairs and 2443 and 2220 of their mothers and fathers, respectively (48). The genetic effect was quite high, reaching at least 60% of the variance in frequency, with a substantial common environment effect as well. Approximately 19% of MZ pairs and 34% of DZ pairs were discordant for the frequency of breakfast eating. In an observational study conducted with 106 MZ and 94 like-sex DZ twin pairs, it was shown using four-day food diaries that the within-MZ pair resemblance was higher than was the DZ pair correlation for 12 of 13 nutrients examined, including total energy intake (42). However, the genetic variance was significant only for the intake of complex carbohydrates.

Consumption of 11 foods typical of the Swedish diet was examined in a sample of 98 MZ and 176 DZ twin pairs from the Swedish Twin Registry (41). There was weak evidence for a greater similarity in consumption among MZ twins than DZ twins for certain foods. In a study of MZ twins discordant for body weight, 23 overweight twins reported consuming currently and in the past more fatty foods than their normal-weight cotwins (66). Such results support the hypothesis that preference for fatty foods may be acquired independent of a genetic background favoring other types of foods.

One of the few experimental studies in this field was based on 36 MZ and 18 DZ adult twin pairs who spent two half-day sessions in a laboratory designed to investigate the magnitude of the genetic influences on total caloric intake as well as macronutrient consumption (31). Each twin person was served a buffet-style lunch (ad libitum) on each occasion and did not eat in the presence of his/her cotwin. The genetic variance for age- and sex-adjusted total caloric intake ranged from 24% to 33%. Although there was evidence of familial aggregation for macronutrient intake in this sample, genetic and common environmental effects could not be separated.

One of the most active laboratories in the study of food, nutrient, and beverage intake based mostly on seven-day food intake records using adult MZ and DZ twins has been that of J.M. de Castro (14, 15, 17–19, 21, 22, 24). In a recent review of his work (22), he summarized that heredity accounts for 42% of the variance in daily energy intake even after taking into account body size, 28% of the variance in meal size, and 34% in meal frequencies after adjustment for overall daily energy intake. Although in some of de Castro's early studies macronutrient intake was characterized by low heritability coefficients (8% for carbohydrate intake, 10% for fat intake, 7% for protein intake), higher genetic effects (from 35% to 63%) were reported in more recent work (15). Significant genetic influences were also reported by the same laboratory for daily intake of water and other beverages, particularly in males (14). A common finding is that the genetic effects are of a different magnitude between males and females for caloric and nutrient intake as well as

fluid consumption, and that there is a stronger common familial environmental effect in females (16). Assuming that we do not often eat unpalatable meals and that palatability has a large effect on intake, twin data indicated that the response of people in terms of total intake to the preferred level of palatability (in terms of caloric intake or meal size) is influenced by a genetic variance component (20).

SUMMARY FOR ENERGY AND MACRONUTRIENT INTAKE The main goal of this part of the review is to ascertain whether reliable evidence exists for the presence of a significant genetic component to human variation in estimates of energy intake and macronutrient intake or preference. Overall, family and twin studies indicate that there is a strong familial aggregation and that a genetic variance is present for all these eating behaviors. The magnitude of the genetic effects is heterogeneous among studies, but they typically range from about 20% to 40% of the age- and sex-adjusted variance. This is by no means a trivial genetic component. For instance, it is of about the same magnitude as that observed for a number of metabolic phenotypes, such as resting blood pressure and plasma triglyceride level.

It is, however, important to recognize that the genetic architecture of food intake phenotypes is complex and undoubtedly heterogeneous. This is suggested by a 1988 report (58) of the correlation patterns for various types of relatives by descent or adoption, which is summarized in Table 1. These correlations suggest that there is a common familial environmental effect for total energy intake adjusted for age, sex, and body weight or percentage of energy derived from the three major macronutrients. A strong spousal correlation is also indicated, which suggests assortative mating and possibly common familial environmental effects. The correlation patterns for relatives by descent indicate that the higher correlations

TABLE 1 Correlations for various pairs of relatives by descent or adoption for energy and macronutrient intake

Variable	Siblings by adoption (115)[a]	Foster parent–adopted child (314)	Spouses (339)	Parent–offspring (1212)	Siblings (361)	DZ twins (59)	MZ twins (59)
Energy intake (kcal/kg day)	0.21	0.29[b]	0.31[b]	0.26[b]	0.30[b]	0.58[b]	0.69[b]
Carbohydrate (% energy)	0.21[c]	0.08	0.50[b]	0.29[b]	0.37[b]	0.49[b]	0.70[b]
Fat (% energy)	0.04	0.18[b]	0.45[b]	0.31[b]	0.36[b]	0.59[b]	0.61[b]
Protein (% energy)	0.22[c]	0.22[b]	0.28[b]	0.27[b]	0.38[b]	0.55[b]	0.71[b]

[a]Number of pairs in parentheses.

[b]$p < 0.01$.

[c]$p < 0.05$.

DZ, dizygotic; MZ, monozygotic. From Reference (58).

in DZ twins as compared with regular siblings are the result of both genetic and common environmental effects. Finally, the correlations are highest in MZ twins, confirming that the genetic component for all four phenotypes is quite substantial.

This should not be a surprising observation, as a number of experimental and molecular genetic studies in animal models and in humans have revealed that several peripheral and central pathways, hormones, and receptors are involved in the regulation of caloric and macronutrient intake. In addition, human genetic studies have shown that genes encoding molecules participating in these pathways harbor considerable sequence variation, some of which have a dramatic impact on food intake.

Eating Behavior Traits

One of the most commonly used instruments to assess behavioral traits underlying eating behavior is the Three-Factor Eating Questionnaire (TFEQ) developed by Stunkard and Messick (72). The traits are labeled restraint, disinhibition, and hunger. In brief, restraint is defined as a cognitive avoidance of eating, disinhibition as a loss of restraint resulting in overeating, and hunger refers to the perceived need for food. Deficiencies in the original instrument have been identified, and revised questionnaire and factor structures have been proposed (73). Genetic studies of these traits are still rare but the results available thus far are of interest.

FAMILY STUDIES Using the TFEQ, 624 adults from 28 families participating in the Amish Family Diabetes Study were used to provide estimates of the heritability levels of the three eating behavior traits (70). The heritability coefficient for restraint reached 28%; for disinhibition, 40%; and for hunger, 23% ($p < 0.001$ for all). In the Quebec Family Study, the same eating behavior traits were evaluated with the same instrument (59). The heritability level was comparable for hunger, i.e., 28%, but the estimates were lower for disinhibition (18%) and restraint (6%). Overall, these studies suggest that there is a significant genetic component for hunger and disinhibition, but the data are equivocal for restraint.

TWIN STUDIES In a study based on 129 MZ and 81 DZ pairs from the Virginia Twin Registry, heritability levels of 45% for disinhibition and 8% for hunger were observed (57). On the other hand, restraint was not characterized by a significant genetic variance but rather by a substantial common environmental effect. In contrast, the restraint scale was characterized by a large genetic component (58%) in another twin study based on 39 MZ, 60 same-sex DZ, and 50 opposite-sex DZ pairs (23). In the latter, the heritability coefficients reached 24% for hunger whereas 40% of the variance in disinhibition was accounted for by shared familial environment. In a large study of 326 DZ and 456 MZ male twin pairs from the Swedish Young Male Twin Registry, which used a modification of the original questionnaire, the best model yielded heritability estimates of 59% for cognitive restraint, 60% for emotional eating, and 45% for uncontrolled eating (73).

SUMMARY FOR EATING BEHAVIOR TRAITS The studies summarized above have provided rather heterogeneous results. One firm conclusion can be drawn, and it has to do with the fact that no matter how the traits are defined and assessed, they are characterized by significant familial aggregation. Both family and twin studies suggest that there may be significant genetic components to these traits, but that the true magnitude of the genetic variance remains to be properly quantified.

Eating Disorders

A brief review of the genetic epidemiology of anorexia nervosa, bulimia nervosa, and binge-eating disorders is undertaken in this section. This is motivated by the fact that there are now a growing number of candidate gene studies and a few genome-wide scans that have been reported for these eating disorder phenotypes (44). Thus, it is important to assess the strength of the evidence for genetic contributions to these disorders since the cost of finding the genes and mutations is likely to be high.

ANOREXIA NERVOSA Anorexia nervosa is a severe, disabling condition. It is characterized by restricted eating, the pursuit of thinness, and the obsessive fear of being fat. The population prevalence of anorexia nervosa is about 1/1000 (45). Almost 90% of affected cases are adolescent girls.

Family Studies In a review of ten controlled family studies in which the frequency of affected relatives of affected probands was compared with the frequency of affected relatives of nonaffected probands, it was concluded that the frequency of anorexia nervosa in the relatives of a proband with the same disease was 2.69% compared with 0.18% in the relatives of healthy controls (39). This translates into a relative risk of 15.8, with 95% confidence intervals ranging from 5.66 to 44.02. Familial aggregation for the disease is quite high, and heritability estimates based on nuclear families reach about 70% (3, 39).

Twin Studies The vast majority of twin studies have observed a higher concordance rate for anorexia nervosa among pairs of MZ twins in comparison with DZ twins (10, 39, 44), although one large study did not (78). Heritability estimates based on twin data range from a low of about 35% to a high of about 85% (10, 39, 44). Although the evidence for an additive genetic effect is strong, there is little support for a role of shared environment.

BULIMIA NERVOSA Bulimia nervosa will affect 1% to 3% of women during their lifetime. The disorder is much less prevalent in males. Bulimia nervosa is quite rare before puberty (67).

Family Studies There is evidence for a significant familial aggregation for bulimia nervosa. In a study of 177 first-degree relatives of 47 probands with bulimia nervosa and of 190 relatives of 44 healthy control probands, 43% of sisters and 26%

of mothers with bulimia nervosa had a lifetime diagnosis of eating disorders. Rates among sisters and mothers of controls were only 5% (69). Some studies have suggested that anorexia nervosa and bulimia nervosa coaggregate in families, perhaps as a result of shared alleles or environment (71).

Twin Studies Twin studies of bulimia nervosa consistently support the hypothesis that there is a significant genetic component to the disorder. Pairs of MZ twins are more concordant than are pairs of DZ twins for the manifestation of bulimia nervosa. Heritability estimates range from a low of about 30% to a high of approximately 80% (8, 29, 67, 71, 77). In general, model-fitting procedures suggest that there is a strong additive genetic component (67).

BINGE EATING Binge eating is defined as eating an unusually large amount of food followed by inappropriate compensatory behaviors such as vomiting. Whether binge eating is a diagnostic entity distinct from other eating disorders remains a controversial issue. However, despite the concerns about the validity of the clinical phenotype, useful genetic information has accumulated on binge eating as defined above.

In a family-based study, a higher prevalence of binge eating was observed among subjects who reported having at least one first-degree relative with binge-eating disorders (60%) compared with binge eaters who did not have any affected first-degree relatives (5%) (35). However, most of the evidence comes from twin studies. In one study based on 1897 female twins, the reliability of binge-eating phenotypes assessed twice five years apart was judged to be low (8). The prevalence of lifetime history of binge eating was 23% at baseline and 19% at the second examination. Only 10% reported a positive history of binge eating at both examinations. The sample included 854 twin pairs and allowed for a model fitting on the full structural equation model and a number of restricted models. The predisposition to binge eating was best accounted for by additive genetic effects (about 50%) and specific environmental effects.

In a large study based on the Norwegian Twin Panel, binge-eating features over the preceding six months were assessed in 526 male MZ, 777 female MZ, 397 male DZ, 655 female DZ, and 979 opposite-sex DZ twin pairs (61). The heritability of binge eating reached 41%, with 95% confidence intervals ranging from 31% to 50%. Individual environmental effects accounted for the rest of the variance. Similar results were reported in a reanalysis of a large sample of the Virginia Twin Registry, with the heritability level attaining 49%, with confidence intervals from 38% to 61% (9). Several other studies have been published on this topic, and findings are generally consistent with the results summarized above.

SUMMARY FOR EATING DISORDERS While the debate continues on the true uniqueness of each of the three clinical disorders reviewed above, genetic epidemiology studies have accumulated in the past decade. It is evident that biological relatives of affected probands are at a much higher risk for these eating disorders than are

relatives of healthy controls. Twin studies have strongly suggested that additive genetic effects account for about half of the variance in any of these clinical phenotypes. Surprisingly, there is almost no support for the hypothesis that shared environmental factors play a role. Whether anorexia nervosa, bulimia, and binge eating are distinct clinical entities, and whether they are distinct from other compulsive behaviors, remains to be fully understood. Nonetheless, the evidence for a genetic contribution to these eating disorders as commonly defined is quite consistent. Thus, these data support the notion that it should be possible to identify the genes and mutations contributing to the observed familial risk for these eating disorders.

MOLECULAR GENETIC STUDIES

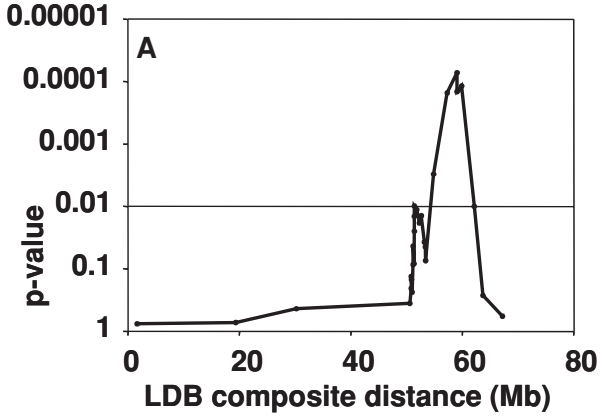
Genome-Wide Linkage Scans and Food Intake

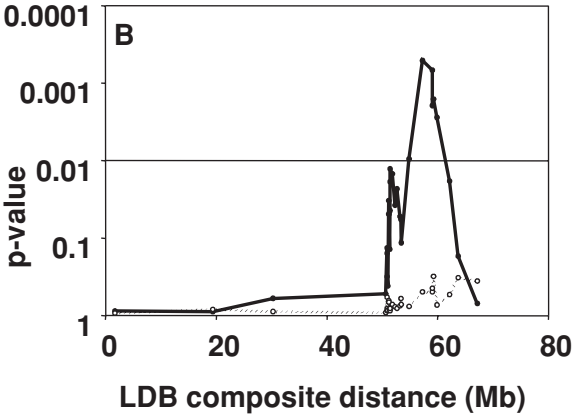
The majority of the nutritionally related genomic scans have dealt so far with "physiological" traits, such as nutrient absorption defects. However, genome scans on eating behavior–related phenotypes have been published recently. Steinle and coworkers reported a genome-wide linkage scan for three eating behavior traits in a cohort of 624 Old Order Amish subjects from 28 families (70). Five chromosomal regions with suggestive linkage were identified: 3p26 and 6p22 for restraint, 7p21 and 16q22 for disinhibition, and 3q13.3 for hunger (70).

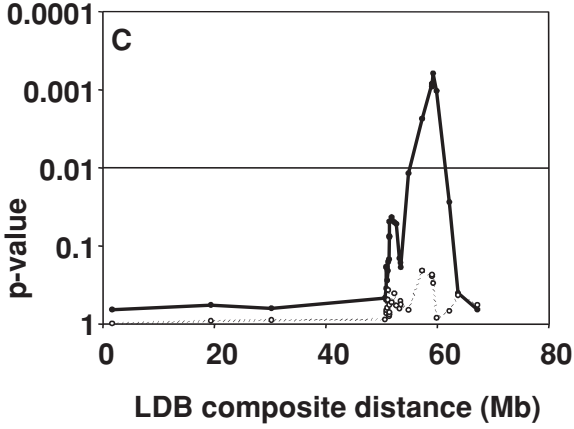
Promising linkage signals for disinhibition and susceptibility to hunger were detected on chromosome 15q24-q25 in the Quebec Family Study (6). The peak linkage coincided with a region containing a gene encoding neuromedin B (*NMB*). A C/A transversion in exon 2, which changes codon 73 from proline to threonine, showed suggestive associations with both eating-behavior phenotypes: The homozygotes for the threonine allele showed higher levels of disinhibition and susceptibility to hunger than did the proline allele carriers (6).

In the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study, an autosomal chromosome linkage scan was performed for energy and energy nutrient intakes in sedentary white and black families (12). Dietary intake traits were derived from a food-frequency questionnaire and were adjusted for age, sex, and body size. The strongest evidence for linkage was found in region 20q13.1 for total energy and carbohydrate, fat, and protein intakes. However, as depicted in Figure 3, after adjusting for total energy intake, the linkage evidence

Figure 3 Results of linkage analyses for total macronutrient intakes on chromosome 20 in the white families from the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study. Total energy (panel *A*), fat (panel *B*), and carbohydrate (panel *C*). In panels *B* and *C*, the solid lines represent daily nutrient intakes in grams, and the dotted lines represent nutrient intakes expressed as percentage of total energy intake. LDB, location database.







for macronutrient intakes disappeared, suggesting that the QTL influences total food or energy intake rather than specific macronutrients (12). The linkage region on chromosome 20 coincides with that previously reported in multiple studies for obesity and diabetes-related phenotypes (50, 51, 54).

In the San Antonio Family Heart Study (SAFHS), a genome-wide linkage scan for dietary intake phenotypes derived from food-frequency questionnaires was performed on 816 participants (11). A QTL for saturated fat intake was detected on chromosome 2p22 [logarithm of odds (LOD) = 2.62]. In addition, total energy, fat, protein, and monounsaturated fat intakes showed suggestive evidence of linkage with the same marker (LODs from 2.0 to 2.22). The QTL on 2p22 coincided with the linkage region previously observed for plasma leptin levels and fat mass in the SAFHS families. Adjustment for plasma leptin levels reduced considerably the linkage for saturated fat intake (LOD = 1.27), which suggests that the chromosome 2p22 region contributes to both saturated fat intake and body adiposity. A strong positional and functional candidate gene on the region is the *proopiomelanocortin* (*POMC*) gene. However, two single nucleotide polymorphisms (SNPs) in exon 3 of the *POMC* gene were not associated with saturated fat intake in the SAFHS subjects (11).

Lactose intolerance is a common autosomal recessive trait due to reduced activity of the lactase-phlorizin hydrolase enzyme [encoded by the *lactase* (*LCT*) gene] in the intestinal cells. The condition has a major effect on food intake because it limits the quality and quantity of dairy products the patients can consume. Although the decline in the enzyme activity has been well documented, mutation screenings of the coding and promoter regions of the *LCT* gene have failed to identify causal DNA sequence variations. However, in 2002, a Finnish group reported two mutations that were strongly associated with a lactose intolerance phenotype (26). First, a linkage with the *LCT* locus on chromosome 2q21 was confirmed with seven microsatellite markers, and the lactose intolerance locus was defined within a 3.4 Mb region. Fine mapping with additional polymorphic markers revealed a 200 kb region containing six markers, which showed significant linkage disequilibrium with the lactose intolerance trait. Haplotype analysis further restricted the critical region to a 47 kb interval. Mutation screening of the critical region revealed 43 SNPs and 9 insertion/deletion variants. Two of the SNPs showed complete cosegregation with the lactose intolerance trait: C/T and G/A transitions located approximately 14 kb ($C/T_{-13,910}$) and 22 kb ($G/A_{-22,018}$) upstream of the *LCT* locus, respectively (26). The $C/T_{-13,910}$ variant was completely associated with a biochemically verified lactase deficiency, and it was predicted to affect a binding site of transcription factor AP-2 (26). However, the functional properties of these two mutations remain to be confirmed in more direct in vitro experiments.

SUMMARY OF GENOMIC LINKAGE SCANS FOR FOOD-INTAKE PHENOTYPES Four genome-wide linkage scans pertaining to food intake and eating behavior phenotypes have been published to date. These studies have reported eight chromosomal

regions showing some evidence of linkage with relevant dietary traits. None of these regions have been fine mapped as of yet. Two positional candidate genes have been explored in more detail: One of them showed some associations with the target phenotype (*NMB* on chromosome 15q24-q25), whereas the other one (*POMC* on 2p22) provided no such evidence.

Genome-Wide Linkage Scans and Eating Disorders

Genome-wide linkage scans have also been used to identify QTLs for eating disorders. A genomic linkage scan was performed with 196 multiplex families ascertained through a proband with anorexia nervosa (25). A multipoint affected sib-pair linkage analysis performed in a subgroup characterized by extreme concordance for drive-for-thinness and/or obsessionality traits revealed three chromosomal regions with suggestive evidence of linkage: 1q31.3, 2p11.2, and 13q13 (25). In a subset of 37 families with at least two affected relatives with anorexia nervosa, a LOD score of 3.45 was reported on chromosome 1p36-p34 (40). A follow-up study of this region suggested that DNA sequence variation in the serotonin 1D (*HTR1D*) and delta opioid receptor (*OPRD1*) loci are associated with anorexia nervosa (4). In a cohort of 308 families identified through a proband with bulimia nervosa, a genomic scan using 360 microsatellite markers was executed (7). The strongest evidence of linkage (LOD = 2.92) in the entire sample was observed on chromosome 10p13-p14. The linkage analysis was repeated in a subgroup of families with at least two affected relatives reporting a symptom pattern that included self-induced vomiting. In this subset of families, the linkage evidence further increased on chromosome 10p13-p14, with a maximum LOD score reaching 3.39 (7).

SUMMARY OF GENOME-WIDE LINKAGE SCANS FOR EATING DISORDERS Five chromosomal regions have been reported to be linked with eating-disorder phenotypes. Two candidate genes (*HTR1D* and *OPRD1*) on chromosome 1p34-p36 have been investigated in some detail, and DNA sequence variations in both genes have been associated with anorexia nervosa.

Single-Gene Obesity Disorders Featuring Hyperphagia

The results from twin and family studies strongly suggest that genetic factors affect food and nutrient intake behavior in humans. The next logical questions are (*a*) which genes are involved, and (*b*) what are the changes in DNA sequence that contribute to the genetic effects? Some of the single-gene disorders associated with severe obesity are also characterized by drastic changes in eating behavior. Obese patients with mutations in *leptin* (*LEP*), *melanocortin 4 receptor* (*MC4R*), and *neurotrophic tyrosine kinase receptor type 2* (*NTRK2*) genes have been also diagnosed with severe hyperphagia.

In 1997, two severely obese children with leptin deficiency caused by frameshift mutations in the *LEP* gene were reported (56). These patients, together with a third,

unrelated obese child with the same *LEP* mutation, were later on treated with leptin (32, 34). Despite severe obesity, basal metabolic rate and total energy expenditure were normal before the treatment. However, food intake of the children was considerably increased; they ate the food quickly and reported feeling hungry shortly after each meal. Leptin therapy induced a drastic reduction in energy intake in all children (34). A four-year leptin therapy of a fourth obese and hyperphagic child homozygous for the same frameshift mutation confirmed these findings (38). In addition, three adults who were leptin-deficient due to a nonconservative missense mutation (Cys-to-Thr) in codon 105 of the *leptin* gene showed similar beneficial responses to 18 months of leptin replacement therapy (52).

More than 500 probands with severe early-onset obesity were screened for mutations in the *MC4R* gene (33). Twenty-nine of the probands had mutations, 23 being heterozygotes and 6 homozygotes. In addition to severe obesity, the mutation carriers had increased lean mass and linear growth and were hyperphagic. The severity of the symptoms correlated with the functional consequences of the mutations. Patients carrying mutations that resulted in inactive receptors exhibited more severe phenotypes than did patients with mutations causing only partial inactivation of the receptors (33).

The case of an eight-year-old male with severe early-onset obesity, hyperphagia, developmental delay, and other defects in higher neurological functions was described (80). Karyotypic abnormalities, as well as mutations in *leptin, leptin receptor, POMC*, and *MC4R* genes, and *PC1* deficiency were excluded. Sequencing of the exons encoding the ligand-binding and catalytic domains of the *NTRK2* gene revealed a heterozygous A-to-G de novo mutation in codon 722. The mutation resulted in a substitution of a highly conserved tyrosine residue by cysteine in the activation loop of the catalytic domain. Functional in vitro studies confirmed that the mutant *NTRK2* had markedly impaired ligand-induced phosphorylation (80).

SUMMARY OF THE SINGLE-GENE DISORDERS Mutations in three genes causing obesity have been also associated with hyperphagia. Leptin therapy has been shown to correct excessive food intake in patients with genetic hypoleptinemia.

Candidate Gene Association Studies for Food Intake Phenotypes

Genetic association studies for dietary intake phenotypes have focused on candidate genes related to neuropeptides, neurotransmitters, and their receptors and transporters. The association between energy and energy-nutrient intakes and DNA sequence variation in the *5-hydroxytryptamine (serotonin) receptor 2A (HRT2A)* gene was investigated in two groups of overweight and obese subjects from France (1). The A/A homozygotes of the -1438 G/A variant located in the promoter of the gene had about 10% (1 MJ/day) lower energy intake than the homozygotes for the common G allele (1). The same *HTR2A* variant was associated with

energy and fat intakes in children and adolescents from the Stanislas Family Study cohort. The A/A homozygotes reported about 8% (0.75 MJ/day) and 12.5% (11.4 g/day) lower energy and fat intakes, respectively, than did the G/G homozygotes (43).

The associations between food intake phenotypes and *dopamine transporter (SLC6A3)* and *dopamine D2 receptor (DRD2)* genotypes were investigated in a cohort of 88 Caucasian smokers (27). Neither *SLC6A3* nor *DRD2* markers showed significant main effects for energy and energy-nutrient intakes. However, significant genotype-by-food reinforcement interaction effects on energy intake were detected. Both gene markers were associated with total energy intake in a subgroup of subjects with high food reinforcement, but not among those with low reinforcement (27).

Agouti-related protein (AGRP) is a potent appetite modulator, and increased levels of AGRP have been reported to induce hyperphagia in mice. The associations between energy and energy-nutrient intakes and ethnic-specific DNA sequence variants of the *AGRP* locus were investigated in the HERITAGE Family Study (53). A G-to-A transition in the third exon of the *AGRP* gene induces a nonconservative alanine-to-threonine substitution in residue 67. This variant is found predominantly in Caucasians and is rare in African Americans. In whites, the Ala67Thr heterozygotes reported lower fat and higher carbohydrate intakes than did the Ala67Ala homozygotes, whereas total energy intake did not differ between the genotypes. In blacks, a C > T polymorphism located 38 nucleotides upstream of the *AGRP* start codon (−38C > T) was associated with protein intake but not with total energy or other energy nutrient intakes (53).

In the San Luis Valley Diabetes Study cohort, associations between *UCP2* and *UCP3* polymorphisms and dietary intake phenotypes were considered (13). A C/T variant in codon 210 of exon 5 and a C/T transition in the promoter region (−55 from the start codon) of the *UCP3* gene were associated with total energy and fat intakes. In a multivariant analysis, the two *UCP3* markers together with age and ethnicity explained about 12% and 10.7% of the variance in energy and fat intakes, respectively (13).

Promising linkages for eating disinhibition and susceptibility to hunger on chromosome 15q24-q25 were identified in the Quebec Family Study (6). The peak linkage was detected with markers flanking the gene encoding neuromedin B (*NMB*). Association analyses with a P73T mutation located in exon 2 of the *NMB* gene revealed statistically significant associations with disinhibition and susceptibility to hunger: The homozygotes for the less-frequent T allele showed higher values for both traits than did the heterozygotes and the P/P homozygotes. Energy nutrient intakes did not differ between the genotypes (6).

The genetic basis of eating disorders has also been investigated. Bergen and coworkers (4) followed up on their linkage findings for anorexia nervosa on chromosome 1p33-36 by investigating two positional and functional candidate genes, *HTR1D* and *OPRD1*. Resequencing both genes revealed several new sequence variants. Linkage analysis with the new markers increased the evidence of linkage

for restrictive anorexia nervosa in the region. Association studies in a case-control cohort and in families with anorexia nervosa probands provided support for the contribution of both *HTR1D* and *OPRD1* genes in the etiology of anorexia nervosa (4).

Candidate gene studies on eating disorders have mainly concentrated on genes involved in serotonergic and dopaminergic systems. However, as is often the case with complex multifactorial traits, the results have been inconclusive, with some studies reporting significant associations whereas others found no such evidence. For example, initial case-control studies reported strong associations between a promoter polymorphism (−1438A/G) in the *HTR2A* gene and anorexia nervosa, but subsequent studies have provided mixed results. A meta-analysis of nine studies supported the association of the −1438A allele with increased risk of anorexia nervosa, although the role of *HTR2A* was suggested to be modifying rather than directly causal (39, 49). Also, the *serotonin 2C receptor (HTR2C*) gene has been reported to be associated with susceptibility to anorexia nervosa (46). A nonconservative Cys23Ser mutation was more frequent in anorectic cases than in healthy controls. Furthermore, the Ser23 allele was associated with a lower minimum body mass index in anorexia nervosa cases, and it was transmitted more frequently from parents to affected cases than was the Cys23 allele (46).

Brain derived neurotrophic factor (BDNF) and its receptor *neurotrophic tyrosine kinase receptor type 2 (NTRK2)* have emerged recently as new candidate genes for eating disorders. A strong association between restricting anorexia nervosa, minimum BMI, and a Val66Met polymorphism in the *BDNF* gene was originally reported in a Spanish case-control study (62). Association of the Met66 allele with anorexia nervosa was subsequently replicated in a large case-control sample from five European countries (64) as well as in a large cohort of European families with anorexia nervosa proband (65). Furthermore, the same allele was found to be more frequent in bulimia nervosa patients than in healthy controls (64). Finally, DNA sequence variation in the *NTRK2* gene was reported to be associated with both binge-eating/purging anorexia nervosa and bulimia nervosa (63). Interestingly, a de novo mutation in the *NTRK2* gene was reported in a morbidly obese child who was also featured hyperphagic (80).

SUMMARY OF CANDIDATE GENE STUDIES FOR FOOD INTAKE PHENOTYPES The first wave of molecular genetic studies on food intake phenotypes have targeted candidate genes related to neurotransmitters, neuropeptides and their transporters, and receptors involved in the regulation of food intake. Some positive associations have been reported, but the findings are still inconclusive. Two studies have reported associations between *HTR2A* polymorphisms and energy intake in populations with no eating disorders, and there is some evidence that the gene may increase the predisposition to anorexia nervosa. Recent findings support the role of *BDNF* and its receptor *NTRK2* in the etiology of anorexia nervosa and bulimia nervosa, but additional studies are needed to confirm these reports.

SUMMARY AND PERSPECTIVES

The observations from twin and family studies clearly support the notion that genetic factors contribute to human variation in food intake and eating behavior phenotypes in humans. However, characterizing the molecular basis of the genetic components is a major challenge. Although genome-wide linkage scans and association studies with candidate gene markers have been published recently, the research on this area is still in its infancy. For example, none of the studies addressing the molecular genetics of food intake have been designed a priori to investigate these questions. Research programs with state-of-the-art phenotyping methods to minimize random variation in the primary traits as well as genetically informative study designs with sufficient sample sizes to provide optimal statistical power are needed to explore the molecular genetic basis of eating behavior in humans.

Although the genetic research of complex, multifactorial traits such as food intake is challenging, the observations from single-gene disorders are encouraging in the sense that they provide examples of how minor changes in the DNA sequence at key genes may have a major impact on food intake. For example, hyperphagia associated with genetic hypoleptinemia has been consistently reported in children and in adults. Furthermore, normalization of food intake with leptin therapy in these patients provides a good example of the clinical benefits of understanding the molecular basis of such disorders.

Another potential source of human variation in dietary intake, eating behavior traits, and eating disorders not captured by DNA sequence variation studies relates to epigenetic events. Epigenetic mechanisms can profoundly alter gene expression and in the process could potentially influence a variety of eating behaviors. There is already compelling evidence to the effect that nutritional factors can entrain DNA methylation and modifications in histone proteins. Such events are known to lead to the silencing of a gene, particularly when they occur in the promoter region of that gene. Cytosine residues (in CpG islands) methylation and histone (H3 and H4) methylation or acetylation occurring during early fetal life provide a mechanism for the programming of the developing organism beyond the blueprint specified in the genomic and mitochondrial DNA. However, it is important to recognize that these events are also taking place throughout life and may thus account for some of the phenotypic variation observed among adults in physiology and behavior. In this regard, the recent observation that the pattern of DNA methylation in MZ twins diverges more as they become older is of great interest (36). It reinforces the view of those who believe that considerable phenotypic differences can arise among people having the same genotype. Such phenotypic variations in physiology and behavior have been observed before among animals from inbred strains of rodents, but no satisfactory explanations have been provided thus far for them. Future progress in our understanding of the role of genetic factors in eating-behavior phenotypes requires that attention be paid not only to the role of DNA sequence variation but also to the potential influence of epigenetic events.

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

LITERATURE CITED

1. Aubert R, Betoulle D, Herbeth B, Siest G, Fumeron F. 2000. 5-HT2A receptor gene polymorphism is associated with food and alcohol intake in obese people. *Int. J. Obes. Relat. Metab. Disord*. 24:920–24
2. Beaton GH, Milner J, McGuire V, Feather TE, Little JA. 1983. Source of variance in 24-hour dietary recall data: implications for nutrition study design and interpretation. Carbohydrate sources, vitamins, and minerals. *Am. J. Clin. Nutr*. 37:986–95
3. Ben Dor DH, Laufer N, Apter A, Frisch A, Weizman A. 2002. Heritability, genetics and association findings in anorexia nervosa. *Isr. J. Psychiatry Relat. Sci*. 39:262–70
4. Bergen AW, van den Bree MB, Yeager M, Welch R, Ganjei JK, et al. 2003. Candidate genes for anorexia nervosa in the 1p33–36 linkage region: serotonin 1D and delta opioid receptor loci exhibit significant association to anorexia nervosa. *Mol. Psychiatry* 8:397–406
5. Billon S, Lluch A, Gueguen R, Berthier AM, Siest G, Herbeth B. 2002. Family resemblance in breakfast energy intake: the Stanislas Family Study. *Eur. J. Clin. Nutr*. 56:1011–19
6. Bouchard L, Drapeau V, Provencher V, Lemieux S, Chagnon Y, et al. 2004. Neuromedin beta: a strong candidate gene linking eating behaviors and susceptibility to obesity. *Am. J. Clin. Nutr.* 80:1478–86
7. Bulik CM, Devlin B, Bacanu SA, Thornton L, Klump KL, et al. 2003. Significant linkage on chromosome 10p in families with bulimia nervosa. *Am. J. Hum. Genet.* 72:200–7
8. Bulik CM, Sullivan PF, Kendler KS. 1998. Heritability of binge-eating and broadly defined bulimia nervosa. *Biol. Psychiatry* 44:1210–18
9. Bulik CM, Sullivan PF, Kendler KS. 2003. Genetic and environmental contributions to obesity and binge eating. *Int. J. Eat. Disord*. 33:293–98
10. Bulik CM, Sullivan PF, Wade TD, Kendler KS. 2000. Twin studies of eating disorders: a review. *Int. J. Eat. Disord*. 27:1–20
11. Cai G, Cole SA, Bastarrachea-Sosa RA, MacCluer JW, Blangero J, Comuzzie AG. 2004. Quantitative trait locus determining dietary macronutrient intakes is located on human chromosome 2p22. *Am. J. Clin. Nutr*. 80:1410–14
12. Collaku A, Rankinen T, Rice T, Leon AS, Rao D, et al. 2004. A genome-wide linkage scan for dietary energy and nutrient intakes: the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study. *Am. J. Clin. Nutr.* 79:881–86
13. Damcott CM, Feingold E, Moffett SP, Barmada MM, Marshall JA, et al. 2004. Genetic variation in uncoupling protein 3 is associated with dietary intake and body composition in females. *Metabolism* 53:458–64
14. de Castro JM. 1993. A twin study of genetic and environmental influences on the intake of fluids and beverages. *Physiol. Behav*. 54:677–87
15. de Castro JM. 1993. Independence of genetic influences on body size, daily intake, and meal patterns of humans. *Physiol. Behav*. 54:633–39
16. de Castro JM. 1998. Genes and environment have gender-independent influences on the eating and drinking of free-living humans. *Physiol. Behav*. 63:385–95
17. de Castro JM. 1999. Behavioral genetics of food intake regulation in free-living humans. *Nutrition* 15:550–54
18. de Castro JM. 1999. Heritability of hunger relationships with food intake in free-living humans. *Physiol. Behav*. 67:249–58
19. de Castro JM. 1999. Inheritance of pre-meal stomach content influences on food

intake in free living humans. *Physiol. Behav*. 66:223–32
20. de Castro JM. 2001. Heritability of diurnal changes in food intake in free-living humans. *Nutrition* 17:713–20
21. de Castro JM. 2002. Independence of heritable influences on the food intake of free-living humans. *Nutrition* 18:11–16
22. de Castro JM. 2004. When identical twins differ: an analysis of intrapair differences in the spontaneous eating behavior and attitudes of free-living monozygotic twins. *Physiol. Behav*. 82:733–39
23. de Castro JM, Lilenfeld LR. 2005. Influence of heredity on dietary restraint, disinhibition, and perceived hunger in humans. *Nutrition* 21:446–55
24. de Castro JM, Plunkett SS. 2001. How genes control real world intake: palatability–intake relationships. *Nutrition* 17:266–68
25. Devlin B, Bacanu SA, Klump KL, Bulik CM, Fichter MM, et al. 2002. Linkage analysis of anorexia nervosa incorporating behavioral covariates. *Hum. Mol. Genet.* 11:689–96
26. Enattah NS, Sahi T, Savilahti E, Terwilliger JD, Peltonen L, Jarvela I. 2002. Identification of a variant associated with adult-type hypolactasia. *Nat. Genet*. 30:233–37
27. Epstein LH, Wright SM, Paluch RA, Leddy JJ, Hawk LW Jr, et al. 2004. Relation between food reinforcement and dopamine genotypes and its effect on food intake in smokers. *Am. J. Clin. Nutr.* 80:82–88
28. Fabsitz RR, Garrison RJ, Feinleib M, Hjortland M. 1978. A twin analysis of dietary intake: evidence for a need to control for possible environmental differences in MZ and DZ twins. *Behav. Genet*. 8:15–25
29. Fairburn CG, Cowen PJ, Harrison PJ. 1999. Twin studies and the etiology of eating disorders. *Int. J. Eat. Disord*. 26:349–58
30. Faith MS, Keller KL, Johnson SL, Pietrobelli A, Matz PE, et al. 2004. Familial aggregation of energy intake in children. *Am. J. Clin. Nutr.* 79:844–50
31. Faith MS, Rha SS, Neale MC, Allison DB. 1999. Evidence for genetic influences on human energy intake: results from a twin study using measured observations. *Behav. Genet*. 29:145–54
32. Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, et al. 1999. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N. Engl. J. Med.* 341:879–84
33. Farooqi IS, Keogh JM, Yeo GSH, Lank EJ, Cheetham T, O'Rahilly S. 2003. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *N. Engl. J. Med*. 348:1085–95
34. Farooqi IS, Matarese G, Lord GM, Keogh JM, Lawrence E, et al. 2002. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J. Clin. Invest.* 110:1093–103
35. Fowler S, Bulik CM. 1997. Family environment and psychiatric history in women with binge eating disorder and obese controls. *Behav. Change* 14:106–12
36. Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, et al. 2005. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc. Natl. Acad. Sci. USA* 102:10604–9
37. Garn SM, Cole PE, Bailey SM. 1979. Living together as a factor in family-line resemblances. *Hum. Biol*. 51:565–87
38. Gibson WT, Farooqi IS, Moreau M, DePaoli AM, Lawrence E, et al. 2004. Congenital leptin deficiency due to homozygosity for the Delta133G mutation: report of another case and evaluation of response to four years of leptin therapy. *J. Clin. Endocrinol. Metab.* 89:4821–26
39. Gorwood P, Kipman A, Foulon C. 2003. The human genetics of anorexia nervosa. *Eur. J. Pharmacol*. 480:163–70
40. Grice DE, Halmi KA, Fichter MM, Strober M, Woodside DB, et al. 2002. Evidence for a susceptibility gene for anorexia nervosa on chromosome 1. *Am. J. Hum. Genet.* 70:787–92

41. Heitmann BL, Harris JR, Lissner L, Pedersen NL. 1999. Genetic effects on weight change and food intake in Swedish adult twins. *Am. J. Clin. Nutr*. 69:597–602
42. Heller RF, O'Connell DL, Roberts DC, Allen JR, Knapp JC, et al. 1988. Lifestyle factors in monozygotic and dizygotic twins. *Genet. Epidemiol.* 5:311–21
43. Herbeth B, Aubry E, Fumeron F, Aubert R, Cailotto F, et al. 2005. Polymorphism of the 5-HT2A receptor gene and food intakes in children and adolescents: the Stanislas Family Study. *Am. J. Clin. Nutr.* 82:467–70
44. Hinney A, Friedel S, Remschmidt H, Hebebrand J. 2004. Genetic risk factors in eating disorders. *Am. J. Pharmacogenomics* 4:209–23
45. Hoek HW. 1991. The incidence and prevalence of anorexia nervosa and bulimia nervosa in primary care. *Psychol. Med*. 21:455–60
46. Hu X, Giotakis O, Li T, Karwautz A, Treasure J, Collier DA. 2003. Association of the 5-HT2c gene with susceptibility and minimum body mass index in anorexia nervosa. *Neuroreport* 14:781–83
47. Hur YM, Bouchard TJ Jr, Eckert E. 1998. Genetic and environmental influences on self-reported diet: a reared-apart twin study. *Physiol. Behav*. 64:629–36
48. Keski-Rahkonen A, Viken RJ, Kaprio J, Rissanen A, Rose RJ. 2004. Genetic and environmental factors in breakfast eating patterns. *Behav. Genet*. 34:503–14
49. Kipman A, Bruins-Slot L, Boni C, Hanoun N, Ades J, et al. 2002. 5-HT(2A) gene promoter polymorphism as a modifying rather than a vulnerability factor in anorexia nervosa. *Eur. Psychiatry* 17:227–29
50. Klupa T, Malecki MT, Pezzolesi M, Ji L, Curtis S, et al. 2000. Further evidence for a susceptibility locus for type 2 diabetes on chromosome 20q13.1-q13.2. *Diabetes* 49:2212–16
51. Lee JH, Reed DR, Li WD, Xu W, Joo E-J, et al. 1999. Genome scan for human obesity and linkage to markers in 20q13. *Am. J. Hum. Genet.* 64:196–209
52. Licinio J, Caglayan S, Ozata M, Yildiz BO, de Miranda PB, et al. 2004. Phenotypic effects of leptin replacement on morbid obesity, diabetes mellitus, hypogonadism, and behavior in leptin-deficient adults. *Proc. Natl. Acad. Sci. USA* 101:4531–36
53. Loos RJ, Rankinen T, Rice T, Rao DC, Leon AS, et al. 2005. Two ethnic-specific polymorphisms in the human Agouti-related protein gene are associated with macronutrient intake. *Am. J. Clin. Nutr.* 82:1097–101
54. Luo TH, Zhao Y, Li G, Yuan WT, Zhao JJ, et al. 2001. A genome-wide search for type II diabetes susceptibility genes in Chinese Hans. *Diabetologia* 44:501–6
55. Mitchell BD, Rainwater DL, Hsueh WC, Kennedy AJ, Stern MP, MacCluer JW. 2003. Familial aggregation of nutrient intake and physical activity: results from the San Antonio Family Heart Study. *Ann. Epidemiol*. 13:128–35
56. Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, et al. 1997. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* 387:903–8
57. Neale BM, Mazzeo SE, Bulik CM. 2003. A twin study of dietary restraint, disinhibition and hunger: an examination of the eating inventory (three factor eating questionnaire). *Twin Res*. 6:471–78
58. Perusse L, Tremblay A, Leblanc C, Cloninger CR, Reich T, et al. 1988. Familial resemblance in energy intake: contribution of genetic and environmental factors. *Am. J. Clin. Nutr.* 47:629–35
59. Provencher V, Perusse L, Bouchard L, Drapeau V, Bouchard C, et al. 2005. Familial resemblance in eating behaviors in men and women from the Quebec Family Study. *Obes. Res.* 13:1624–29

60. Reed DR, Bachmanov AA, Beauchamp GK, Tordoff MG, Price RA. 1997. Heritable variation in food preferences and their contribution to obesity. *Behav. Genet*. 27:373–87
61. Reichborn-Kjennerud T, Bulik CM, Tambs K, Harris JR. 2004. Genetic and environmental influences on binge eating in the absence of compensatory behaviors: a population-based twin study. *Int. J. Eat. Disord*. 36:307–14
62. Ribases M, Gratacos M, Armengol L, de Cid R, Badia A, et al. 2003. Met66 in the brain-derived neurotrophic factor (BDNF) precursor is associated with anorexia nervosa restrictive type. *Mol. Psychiatry* 8:745–51
63. Ribases M, Gratacos M, Badia A, Jimenez L, Solano R, et al. 2005. Contribution of NTRK2 to the genetic susceptibility to anorexia nervosa, harm avoidance and minimum body mass index. *Mol. Psychiatry* 10:851–60
64. Ribases M, Gratacos M, Fernandez-Aranda F, Bellodi L, Boni C, et al. 2004. Association of BDNF with anorexia, bulimia and age of onset of weight loss in six European populations. *Hum. Mol. Genet.* 13:1205–12
65. Ribases M, Gratacos M, Fernandez-Aranda F, Bellodi L, Boni C, et al. 2005. Association of BDNF with restricting anorexia nervosa and minimum body mass index: a family-based association study of eight European populations. *Eur. J. Hum. Genet.* 13:428–34
66. Rissanen A, Hakala P, Lissner L, Mattlar CE, Koskenvuo M, Ronnemaa T. 2002. Acquired preference especially for dietary fat and obesity: a study of weight-discordant monozygotic twin pairs. *Int. J. Obes. Relat. Metab. Disord*. 26:973–77
67. Rowe R, Pickles A, Simonoff E, Bulik CM, Silberg JL. 2002. Bulimic symptoms in the Virginia Twin Study of Adolescent Behavioral Development: correlates, comorbidity, and genetics. *Biol. Psychiatry* 51:172–82
68. Sellers TA, Kushi LH, Potter JD. 1991. Can dietary intake patterns account for the familial aggregation of disease? Evidence from adult siblings living apart. *Genet. Epidemiol*. 8:105–12
69. Stein D, Lilenfeld LR, Plotnicov K, Pollice C, Rao R, et al. 1999. Familial aggregation of eating disorders: results from a controlled family study of bulimia nervosa. *Int. J. Eat. Disord.* 26:211–15
70. Steinle NI, Hsueh WC, Snitker S, Pollin TI, Sakul H, et al. 2002. Eating behavior in the Old Order Amish: heritability analysis and a genome-wide linkage analysis. *Am. J. Clin. Nutr.* 75:1098–106
71. Strober M, Freeman R, Lampert C, Diamond J, Kaye W. 2000. Controlled family study of anorexia nervosa and bulimia nervosa: evidence of shared liability and transmission of partial syndromes. *Am. J. Psychiatry* 157:393–401
72. Stunkard AJ, Messick S. 1985. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J. Psychosom. Res*. 29:71–83
73. Tholin S, Rasmussen F, Tynelius P, Karlsson J. 2005. Genetic and environmental influences on eating behavior: the Swedish Young Male Twins Study. *Am. J. Clin. Nutr*. 81:564–69
74. Trulson MF, Clancy RE, Jessop WJ, Childers RW, Stare FJ. 1964. Comparisons of siblings in Boston and Ireland. *J. Am. Diet. Assoc*. 45:225–29
75. van den Bree MB, Eaves LJ, Dwyer JT. 1999. Genetic and environmental influences on eating patterns of twins aged ≥50 y. *Am. J. Clin. Nutr*. 70:456–65
76. Vauthier JM, Lluch A, Lecomte E, Artur Y, Herbeth B. 1996. Family resemblance in energy and macronutrient intakes: the Stanislas Family Study. *Int. J. Epidemiol*. 25:1030–37
77. Wade T, Martin NG, Neale MC, Tiggemann M, Treloar SA, et al. 1999. The structure of genetic and environmental risk factors for three measures of disordered eating. *Psychol. Med.* 29:925–34

78. Walters EE, Kendler KS. 1995. Anorexia nervosa and anorexic-like syndromes in a population-based female twin sample. *Am. J. Psychiatry* 152:64–71
79. Wardle J, Guthrie C, Sanderson S, Birch L, Plomin R. 2001. Food and activity preferences in children of lean and obese parents. *Int. J. Obes. Relat. Metab. Disord*. 25:971–77
80. Yeo GS, Connie Hung CC, Rochford J, Keogh J, Gray J, et al. 2004. A de novo mutation affecting human TrkB associated with severe obesity and developmental delay. *Nat. Neurosci.* 7:1187–89

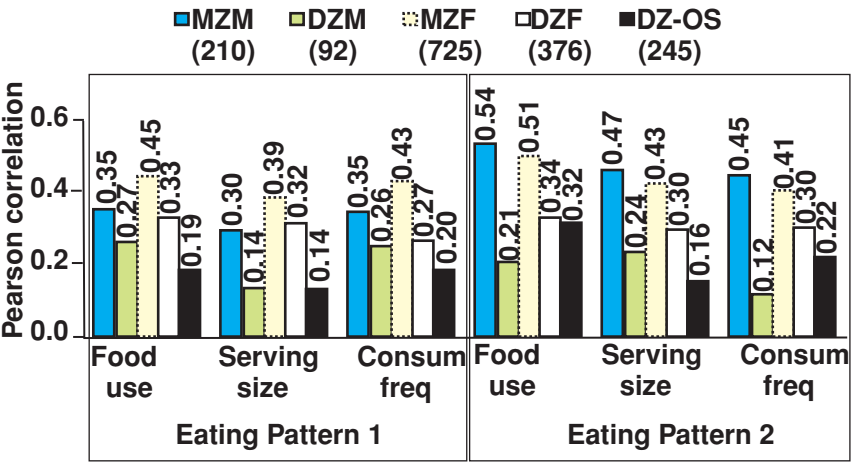


Figure 1 Correlation of eating patterns in monozygotic and dizygotic twins. Eating patterns were derived from a factor analysis of 99 food items obtained from a questionnaire. Eating pattern 1 consisted of foods high in fat, salt, and sugar. Eating pattern 2 included more vegetables, fruit, rice, yogurt, skim milk, and dark bread. Number of pairs is in parentheses. MZM, monozygotic male; DZM, dizygotic male; MZF, monozygotic female; DZF, dizygotic female; DZ-OS, dizygotic opposite-sex. From Reference 75.

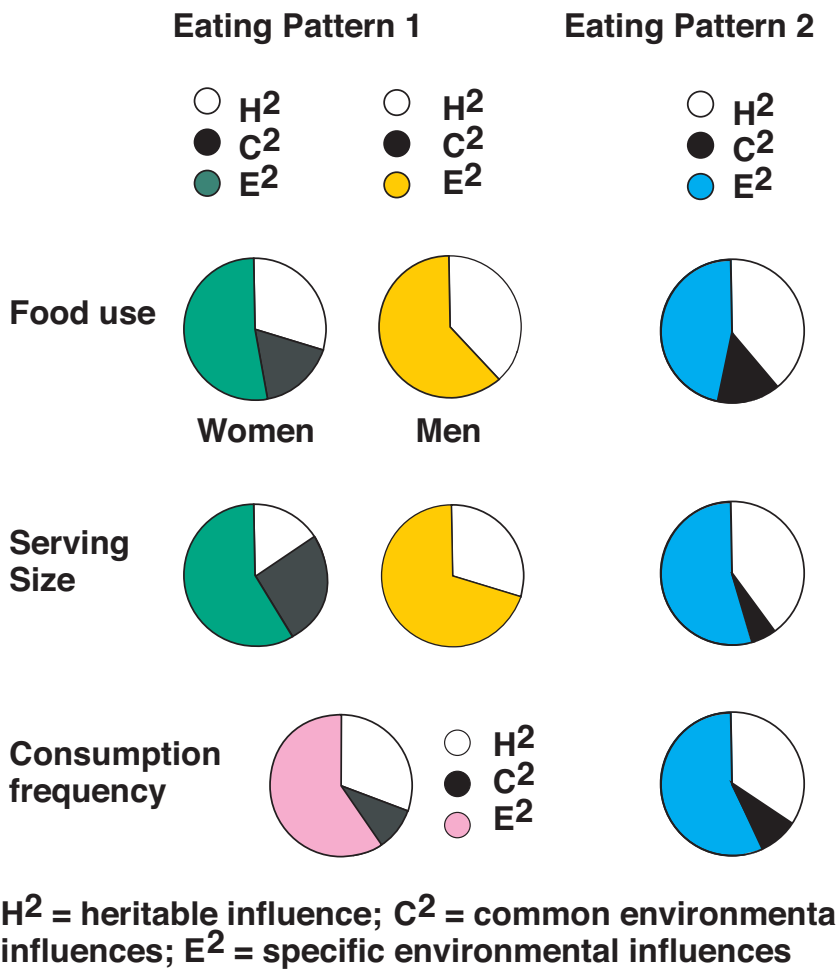


Figure 2 Overview of genetic and environmental influences on eating patterns as quantified from model-fitting procedures. Eating patterns were derived from a factor analysis of 99 food items obtained from a questionnaire. Eating pattern 1 consisted of foods high in fat, salt, and sugar. Eating pattern 2 included more vegetables, fruit, rice, yogurt, skim milk, and dark bread. (From Reference 75.)

Annual Review of Nutrition
Volume 25, 2005

CONTENTS