Special Article

Gene-environment interaction and obesity

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The epidemic of obesity has become a major public health problem. Common-form obesity is underpinned by both environmental and genetic factors. Epidemiological studies have documented that increased intakes of energy and reduced consumption of high-fiber foods, as well as sedentary lifestyle, were among the major driving forces for the epidemic of obesity. Recent genome-wide association studies have identified several genes convincingly related to obesity risk, including the fat mass and obesity associated gene and the melanocortin-4 receptor gene. Testing gene-environment interaction is a relatively new field. This article reviews recent advances in identifying the genetic and environmental risk factors (lifestyle and diet) for obesity. The evidence for gene-environment interaction, especially from observational studies and randomized intervention trials, is examined specifically. Knowledge about the interplay between genetic and environmental components may facilitate the choice of more effective and specific measures for obesity prevention based on the personalized genetic make-up.

INTRODUCTION

The prevalence of obesity has been increasing at an alarming rate worldwide during past decades.[1] Accordingly, the World Health Organization has described obesity as a "global epidemic". In the United States, it is estimated that >60% of adults are either obese or overweight. The number of children and adolescents who are considered overweight (i.e., ≥95th percentile) or at risk for overweight (i.e., ≥85th percentile) has increased similarly.[2] Obesity is usually associated with many metabolic abnormalities including dyslipidemia, insulin resistance and hyperglycemia, and increased risk of coronary heart disease, type 2 diabetes, asthma, sleep apnea, hypertension, certain cancers, and all-cause mortality.[3,4]

Classic genetic analyses performed in families, adoptees, and twins have clearly shown there is a genetic contribution to obesity.[5–7] A popular conception regarding the genetic makeup of complex diseases, including obesity, is the "common disease/common variant" (CD/CV) hypothesis.[8] According to this theory, common disorders are governed by common genetic variants that do not conform to Mendelian patterns of inheritance in their effects. The recent advance in genome-wide association (GWA) mapping holds tremendous potential for contributing to the identification of human obesity genes and provides deeper insight into the genetic effects on obesity development. Several genes such as *FTO* (fat mass and obesity associated) and *MC4R* (melanocortin-4 receptor) identified by GWA scans have been convincingly associated with obesity risk in various populations.[9–13] Of note, the phenotypic variance accounted for by an individual genetic variant is essentially minor. These findings indicate that large-scale population sets are needed to identify the small genetic effects, particularly for the variants with low frequency. Thus, it is not surprising that replication of genetic association may fail in some small samples or in subjects exposed to other environmental factors.

Obesity is a multifactorial abnormality that has a genetic basis but requires environmental influences to manifest. Numerous epidemiological studies and clinical trials have examined the roles of lifestyle (e.g., physical

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inactivity) and dietary factors (e.g., fat, carbohydrates, protein, and minerals) in obesity prevention and weight control. In the past decade, the body of studies on gene-environment interactions has also grown rapidly. This review summarizes recent advances in identifying the genetic and environmental factors (with a focus on lifestyle and diet) related to obesity, and examines the published empirical evidence for gene-environment interactions associated with obesity risk.

FROM LINKAGE SCAN TO GENOME-WIDE ASSOCIATION MAPPING

Familial aggregation is a prominent characteristic of monogenic-form obesity but is less evident for common-form obesity.[14] An appreciation of the genetic contribution to common-form obesity is a relatively recent development. The fraction of the population variation explained by genetic factors (heritability) has been considered in a large number of twin, adoption, and family studies. In general, ~40–60% of the variation in obesity-related phenotypes, such as body mass index (BMI), sum of skinfold thickness, fat mass, and leptin levels, has been estimated to be heritable.[15] The past decade witnessed tremendous efforts to find the specific loci or genes for obesity, primarily through the combination of linkage scan and candidate gene-based association studies. Linkage analysis is performed to identify the disease loci by examining the cosegregation of genetic markers distributed evenly throughout the genome with the disease within families. As summarized in the latest version of the Human Obesity Gene Map, there are 253 quantitative-trait loci (QTLs) identified in 61 genome-wide scans, and 52 genomic regions contain QTLs supported by two or more studies.[16] While linkage analysis is massively successful in identifying mutations underlying the rare Mendelian disorders, it does have shortcomings and the identification of variants for common-form obesity has met with limited and uneven success through this approach.

The candidate-gene association analyses focus on loci identified functionally (experimental evidence) or positionally (linkage evidence).[17] To date, 127 different candidate genes have been associated with obesity-related phenotypes.[14,16] Of note, the vast majority of the candidates are selected because of their known or hypothesized role in the development of obesity such as adipogenesis, lipid turnover, insulin signaling, mitochondrion and energy expenditure, and adipokine secretion.[18] Few genes are chosen from areas containing pure linkage signals. An example of linkage mapping-based success is the recent identification of *PCSK1* (prohormone convertase 1/3) gene variants conferring obesity risk. In this study, Benzinou et al.[19] sequenced the candidate gene *PCSK1* located in a 5.6-Mb interval on chromosome 5q linked with obesity-associated traits and found 19 common SNPs. In a total of 13,659 individuals of European ancestry, variants rs6232 and rs6234-rs6235 pair were consistently associated with obesity in adults and children ($P = 7.27 \times 10^{-8}$ and $P = 2.31 \times 10^{-12}$, respectively). Significant associations of biologically relevant genes such as *PPARG* (peroxisome proliferators-activated receptor gamma), *UCP1* (uncoupling protein 1), *UCP2*, *UCP3*, *ADRB2* (beta-adrenergic receptor 2), *ADRB3*, and *PLIN* (perilipin) have been observed in at least five human studies. Most genetic associations, however, are difficult to replicate. Several factors may account for the low reproducibility in associations: inadequate sample sizes for modest effect, inadequate capture of the genetic variation, varying criteria for selection of candidates, and genuine heterogeneity in genetic effects. It was estimated that 20 to 30% of genetic associations were real and had modest effects, while false-positive associations were abundant in the literature.[20] Large-scale meta-analysis may lessen the influence of both false-positive and false-negative findings and facilitate the derivation of more reliable associations.[21,22]

Most candidate-gene association studies focus on only a limited number of single nucleotide polymorphisms (SNPs). The narrow scope in surveying for the variation in the whole genome substantially hampers the success of the candidate-gene approach. Identification of susceptibility genes for obesity on the whole-genome scale has been enhanced by recent advances in genotyping technology along with the HapMap initiative, which has increased collection of variation information in the human genome. In the first GWA study on obesity, Herbert et al.[23] genotyped 116,204 SNPs among 694 individuals from the Framingham Heart Study offspring cohort. A common SNP, rs7566605 (G > C; MAF = 20%) near the insulin-induced gene 2 (*INSIG2*), was significantly associated with childhood and adulthood obesity risk. The CC genotype was related to 22% increased risk of obesity. However, several later studies generated highly mixed results.[24,25] In 2007, the Welcome Trust Case-Control Consortium (WTCCC) reported that the common variant rs9939609 (T > A; MAF = 30%) was significantly associated with obesity risk. In the replication samples of 38,759 European participants, the AA genotype was related to 1 kg/m^2 higher BMI, 2.3 kg higher body weight, and 67% increased risk of obesity compared to the TT genotype.[10] This finding was replicated in most additional studies, although the data are not entirely consistent ,especially in some ethnic groups.[11,26–28] In a recent analysis combining several GWA scans, Loos et al.[29] found significant associations between SNP rs17782313, which is mapped 188kb downstream of a biological candidate gene *MC4R* for monogenic obesity, and fat mass

and obesity risk: the per-minor allele increase in BMI was 0.49 kg/m^2. This study demonstrates that the different forms of variants (rare vs. common) in some genes may cause either monogenic or common-form obesity that shares the same phathophysiological changes.

LIFESTYLE AND DIETARY RISK FACTORS FOR OBESITY

Weight gain and obesity in free-living populations result from a long-term positive energy balance, i.e., the amount of energy consumed is greater than the amount of energy spent. A wealth of evidence points to many dietary and lifestyle factors that can directly or indirectly tip the balance of energy input and output. The contributions of environmental factors to obesity have been the focus of many research initiatives. Recently, Papas et al.[30] performed a meta-analysis on the relationship between obesity and the built environment, which largely determines the availability and convenience of options for physical activity and food acquisition. The authors found statistically significant relationships between some aspects of the built environment and risk of obesity in 17 of 20 studies.

Increasing energy intake is a major contributor to the current obesity epidemic. The past several decades have witnessed a marked increase in the total amount of energy intake, especially in populations with rising rates of obesity. For example, data from the National Health and Nutrition Examination Survey (NHANES) showed that energy intake increased from an average of 2450 kcal/day in 1971–1974 to 2618 kcal/day in 1999–2000, an increase of 168 kcal/day or 7%, among men in the United States. The upward shift was greater among women, increasing by 335 kcal/day or 22%.[31] Because of the high energy density of fat and the enhanced palatability of high-fat foods, it was widely believed that high intakes of dietary fat contributed to the greater weight gain.[32] However, epidemiological studies and clinical trials have generated data that is quite mixed and there are diverse opinions about whether or not the percentage of dietary fat plays an important role in the rising prevalence of obesity.[33] In the last half century, there has been a sudden upsurge in consumption of carbohydrates (CHOs) as the major component of the diet, and carbohydrates are now being eaten in a more refined form.[34] Few epidemiological studies have directly assessed the relationship between CHOs and obesity, while some evidence from short-term intervention trials indicate that CHO restriction may moderately promote weight loss.[35] The proportion of CHO in the diet tends to vary reciprocally with fat.[36] Therefore, it is difficult to segregate the impact of the total amount of CHO in the diet from total fat. Many studies have shown that diets rich in whole grains and fiber were inversely related to BMI and weight gain,[37,38] which is likely due to the incomplete digestion and absorption and increased satiety caused by delayed gastric emptying and subsequent gastric distention. In addition, other foods/nutrients such as nuts, fruits and vegetables, dairy products, coffee, and calcium were also associated with body fatness in some but not all studies.[39–42] The inconsistency in these observations is partly due to the complexity of confounding by other sociodemographic and lifestyle variables.

The adverse effect of unhealthy dietary habit (e.g., more consumption of refined CHOs; reduced intake of fiber, vegetables, and fruit; and overeating) on obesity can be exacerbated by the lack of physical activity that results from the popularization of television and computers and the increasing use of labor-saving transportation devices. Some large studies have shown that the risk of significant weight gain is greater in individuals who were sedentary than in those who were more active. For example, Williamson et al.,[43] investigating the effects of self-reported recreational physical activity (low, medium, high) on 10-year weight change in 3515 men and 5810 women, found that the relative risks for gaining >13 kg in individuals whose activity level was low compared with those in the high-activity level were 2.3 in men and 7.1 in women. Similarly, in a study of 12,699 adult Finns, Russanen et al.,[44] found that people who rarely engaged in leisure-time physical activity were 1.6 (men) and 1.9 (women) times as likely to gain 5 kg in 5 years as those who frequently engaged in such activity. Schoeller[45] reviewed cross-sectional data from double-labeled water studies and longitudinal studies: The data similarly indicate that the prevalence of overweight, BMI, or body fat increases along with decreasing physical activity. The role of sedentary behavior as a contributor to the obesity epidemic has also been evaluated in children and adolescents. Although television-watching and physical inactivity have been related to obesity,[46] the increase in adiposity may be due to snacking that occurs during TV viewing.

GENE-ENVIRONMENT INTERACTION: PHENOMENA AND TESTING

The recent epidemic of obesity along with the increasing spread of Western-type lifestyles worldwide is a good illustration of the concept of gene-environment interaction. Because the gene pool of a certain population has been relatively constant for many generations, it seems that dramatic changes in lifestyle and dietary habits have played a role in triggering the recent surge of excessive adiposity. The question is why are humans living in a modern social environment so susceptible to obesity? A widely held hypothesis is that the evolutionary process generates this genetic predisposition.[47] The first exposi-

tion of this idea was by Neel,[48] who suggested that obesity and diabetes stemmed from natural selection of our ancient ancestors favoring a "thrifty" genotype that enabled highly efficient storage of fat during periods of food deficiency. Famine has been a common feature of human history, stretching back to the earliest part of the Paleolithic period 50,000 years ago.[49,50] Compared with lean individuals, those who had more body fat more likely carried certain genetic information that favored more efficient storage of energy; they were, therefore, more likely to survive periods of famine. In addition, lean people were more likely to succumb to various conditions such as infectious disease. Thus, the ability to conserve calories by storing more fat offers a genetic advantage for selection of this genotype during periods of food scarcity. When individuals are faced with higher caloric loads in a modern context, however, carrying the thrifty genotype becomes a risk factor for obesity and related metabolic disorders. This may well be the case for genes such as *PPARG*, *FTO*, and *MC4R* that are linked with obesity and diabetes.[10,29,51]

Urbanization and migration have provided good experimental settings for testing the interactive relationship between genetic background and changes in lifestyle and dietary patterns. Risk of obesity increases after migration from poor to affluent countries.[52] The adoption of a Western dietary pattern is believed to be the major cause of the obesity prevalent in immigrants.[53] The children of immigrants may fare even worse. In the United States, Asian American and Hispanic American adolescents are more than twice as likely to be obese as first-generation immigrants from their countries of origin.[54]

These observations support a model in which susceptibility to obesity is determined largely by genetic factors, but the environment prompts phenotypic expression. The concept that "nurture" operates on an underlying pool of genes that contribute to obesity susceptibility has important implications for our approach to the prevention and treatment of obesity. The causal web of obesity is complex, and it is a significant challenge to uncover the intricate pattern of interlinking threads. Recent advances in genetic mapping for complex diseases make it feasible to systematically evaluate nature-nurture interactions at the molecular level. Conceptually, gene-environment interaction occurs when the effect of one factor on a person's health is conditional on the other. In recent years, an epidemiologic framework for evaluating gene-environment interaction has been proposed.[55] Statistically significant interaction can be detected in different ways. The most common approach is to test departure from the multiplicative model of interaction, i.e., to test whether the relative risk for joint exposure is statistically significantly greater or smaller than what would be expected by multiplying the relative risk for environmental exposure alone and for the genetic susceptibility alone. Alternatively, the interactions of the genotype and environmental factors can be measured as a departure from an additive model of disease risk.[56] The appropriate scale of interaction testing that may reflect biological interaction has been a controversial topic, as some argue that the assessment of interaction on an additive scale is more indicative of the underlying causal mechanism.

OBSERVATIONAL EVIDENCE

When information on both environmental exposures (lifestyle and dietary intake) and genotyping is collected, the gene-environment interactions can be tested by the observational studies. Cross-sectional and retrospective case-control designs are most often used for studying gene-environment interactions in relation to continuous differences in obesity-related traits and dichotomous obesity status. A case-only design has also been employed for examining multiplicative gene-environment interactions, assuming the environment factors and genotypes are independent.[57] As a limitation, a case-only study cannot detect the main effects of exposure variables. Although such studies are relatively easy to conduct, they are susceptible to the influence of selection, recall (e.g., diet and lifestyle), and survival bias. Prospective cohort studies collect information on environmental exposure before the occurrence of disease and hold an advantage in minimizing these biases.[58] Most studies focus on "candidate genes", especially those related to appetite control, food intake, energy balance, and adipose metabolism (Table 1). Among environmental factors, physical inactivity, total energy intake, and consumption of various dietary fats (total fat, saturated fat acid [SFA], polyunsaturated fat acid [PUFA]) and CHOs (including fibers) have attracted a great deal of attention. Gene-environment interactions can be assessed at single SNP and haplotype (the combination of SNPs) levels. Due to statistical and computational difficulty, the test on gene-environment interaction has not yet been practical on a whole-genome scale.

Several studies specifically examined the interactions between energy intake and genes involved in the regulation of energy balance and adipose tissue metabolism. Miyaki et al.[59] found that high energy intake interacted with the Trp64Arg polymorphism of *ADRB3* gene and led to a significant increase in risk of obesity. In a recent study of 285 healthy Japanese men, Song et al.[60] found that a missense variant in the *IL6R* (interleukin 6 receptor) gene, Asp358Ala (T > G substitution) interacted significantly with dietary energy intake levels in relation to the risk of abdominal obesity (P for interaction = 0.03). There was significant association between waist circumference and dietary energy intake in individuals with the

Table 1 **Selected observational studies of gene-lifestyle interactions on obesity.**

Reference	Subjects*	Gene (variants)	Lifestyle factors	Major findings
Meirhaeghe et al. (1999)[68]	1152	ADRB2 (Gln27Glu)	Physical activity	Men carrying Gln27Gln genotype had increased risk of adiposity only with no physical activity. No interaction was observed in women
Luan et al. (2001)[64]	592	*PPARG* (Pro12Ala)	Total fat, P:S ratio	BMI was higher among Ala allele carriers only when the P:S ratio was low, and the opposite was seen when P:S ratio was high (*p*-interaction = 0.0039)
Corbalan et al. (2002)[69]	252 F	ADRB2 (Gln27Glu)	Physical activity	In women who were more active, Glu-allele carriers had higher BMI than non-carriers.
Marti et al. (2002)[67]	313	*PPARG* (Pro12Ala)	CHO	Pro12Ala was associated with increased risk of obesity only in those with higher CHO intake (*p*-interaction = 0.02)
Martinez et al. (2003)[66]	313	*ADRB2* (Gln27Glu)	CHO	Women with high CHO intake had greater risk of obesity than those with low CHO intake only in Gln27Glu heterozygotes (*p*-interaction = 0.058)
Nieters et al. (2002)[62]	306	11 genes (15 SNPs)	n-6 PUFA	Substantial interaction between variants in PPARG2, TNFA, leptin (possibly APM1, HSL) and dietary n-6 FA intake in relation to obesity risk
Robitaille et al. (2003)[65]	313 M/407 F	*PPARG* (Pro12Ala)	Total fat, SFA	In women, Pro12Pro homozygotes were positively associated with total fat and SFA intake in relation to WC and BMI, but not in Ala-allele carriers
Memisoglu et al. (2003)[63]	2142 F	*PPARG* (Pro12Ala)	Total fat, fatty acids, P:S ratio	BMI was positively related to total fat only in Pro12Pro homozygotes (*p*-interaction = 0.0003); BMI was negatively related to MUFA only in Ala-allele carriers (*p*-interaction = 0.003)
Robitaille et al. (2004)[61]	632 M	*PPARA* (Leu162Val)	Total fat, SFA	Total fat and saturated fat intake were positively related to WC only in Leu162Leu homozygotes (*p*-interaction = 0.01 and 0.008, respectively)
Alonso et al. (2005)[72]	300	UCP3 (-55C > T)	Physical activity	Carrying T-allele was associated with lower risk of obesity only in those with higher physical activity
Berentzen et al. (2005)[73]	1285	UCP2 (ID), UCP3 (-55C > T)	Physical activity	No interaction in relation to 10-year weight change
Miyaki et al. (2005)[59]	295 M	*ADRB3* (Trp64Arg)	Total energy	Arg64-allele carriers were associated with greater obesity risk than Trp64Trp homozygotes, but only in the highest energy intake quartile
Moran et al. (2005)[70]	1016	ACE (I/D)	Physical activity	Carrying D-allele was associated with increased fat thickness; this association was strongest in women with no extra exercise
Ridderstrale et al. (2006)[71]	902 M/899 F	PPARGC1A (GLy482Ser)	Physical activity	Elderly men carrying Ser-allele had increased risk of obesity
Song et al. (2007)[60]	285 M	*IL6R* (Asp358Ala)	Total energy	Energy intake was significantly associated with WC in T-allele carriers, but not in GG homozygotes (*p*-interaction = 0.03)
Andeasen et al. (2008)[28]	17,162	FTO (rs9939609)	Physical activity	Physically inactive AA homozygotes had an increase in BMI compared with TT homozygotes (*p*-interaction = 0.007)

* If not indicated, the studies include both male (M) and female (F).
Abbreviations: BMI, body mass index; CHO, carbohydrates; MUFA, monounsaturated fatty acid; P:S ratio, ratio of polyunsaturated fat to saturated fat; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; WC, waist circumstance.

TT + GT genotypes ($P = 0.048$), but not in subjects with the GG genotype. Because of their high energy intensity, dietary fats have been a focus of attention relative to their interactions with genetic components in determining obesity risk. In a cross-sectional study of 632 men, Robitaille et al.[61] found that intake of total fat and SFA was significantly associated with waist circumference in individuals carrying the *PPARA* Leu162/Leu162 genotype, but not in those with the Val162 allele (*P*-interaction = 0.01 between fat intake and waist circumference: *P*-interaction = 0.008 between SFA intake and waist circumference). In a case-control study of 154

obese subjects (BMI > 35 kg/m^2) and 154 age- and sex-matched normal-weight controls, Nieters et al.[62] reported possible interactions between dietary fatty acids and genes including *LEP* (-2548 G/A; $P = 0.045$ for linoleic acid), *TNF* (-307G/A; $P = 0.142$ for linoleic acid; $P = 0.095$ for arachidonic acid), and *PPARG2* (Pro12Ala; $P = 0.166$ for linoleic acid; $P = 0.080$ for arachidonic acid). In the Nurses' Health Study, it was found that women in the highest quintile of total fat intake had significantly higher mean BMI than those in the lowest quintile (27.3 vs. 25.4 kg/m^2; $P < 0.0001$) if they carried the *PPARG* Pro/Pro genotype. No significant trend was observed between dietary fat intake and BMI among women carrying the 12Ala variant (P-interaction = 0.003).[63] Dietary fat-*PPARG* interactions were also observed in other studies.[64,65]

A few studies tested the interaction between genetic variants and intake of CHOs (Table 1). In a case-control study with 154 obese subjects (BMI > 30 kg/m^2) and 154 lean controls (BMI < 25 kg/m^2) (~80% women), Martinez et al.[66] found that, in women carrying the *ADRB2* Gln27Glu genotype, higher intake of CHO (>49% of energy) was associated with 2.56 times greater obesity risk than in those with lower intake. Among women with the wild-type homozygotes, CHO intake was associated with reduced obesity risk, although the association was not statistically significant. The test for interaction was only marginally significant ($P = 0.058$). Similarly, a higher CHO/fat ratio (>1.77) was significantly associated with 3.21 times higher obesity risk only in women carrying the Gln27Glu genotype. In the same study sample, a significant interaction ($P = 0.02$) was also observed between CHO intake and the Pro12Ala polymorphism of the *PPARG* gene in relation to BMI. Individuals with the Pro12Ala genotype had higher BMI than those with the Pro12Pro genotype (35.1 vs. 32.4 kg/m^2) when their CHO intake was above the median (49% of energy). The opposite association (31.5 vs. 33.4 kg/m^2) was observed in those who had lower CHO intakes.[67]

In addition to the dietary components, several studies have documented potential interaction between physical activity and genetic variants (Table 1). Meirhaeghe et al.[68] found a significant interaction between the Gln27Glu polymorphism and physical activity in relation to body weight ($P = 0.009$), BMI ($P = 0.007$), and waist ($P = 0.03$) and hip ($P = 0.01$) circumference in men. The Gln homozygotes had significantly higher adiposity measures than the Glu-allele carriers only in men who did not engage in physical activity; the gene-physical activity interaction was not observed in women. Another study,[69] however, reported a significant interaction between this genetic variant and physical activity in women. Among those who were physically active, Glu-allele carriers had higher BMI than non-carriers. In a cross-sectional study with 1016 teen-aged Greeks, Moran et al.[70] reported that carrying the D allele in the *AGE* gene was associated with increased adipose tissue thickness. This association was strongest in women who participated in no extra exercise and accounted for 6.5% of the phenotypic variance in adipose tissue thickness. In a population-based study of 899 women and 902 men aged 30 and 75 years, Ridderstrale et al.[71] reported that carrying Gly482Ser of the *PPARGC1A* gene was associated with increased risk of obesity only in elderly men (age $\geq$ 50) with low physical activity. Some other studies suggested that the genetic variants in *UCP2* and *UCP3* genes might also modulate the effects of physical activity on obesity risk.[72,73] Recently, Andreasen et al.[28] reported a significant interaction between the *FTO* gene variant rs9939609 and physical activity in relation to obesity risk in a Danish population. Significant differences in BMI between the AA and TT genotypes were observed only among physically inactive subjects. The results suggest that higher physical activity may attenuate the adverse effects of the *FTO* variant on obesity.

GENETIC MODIFICATION ON DIET/LIFESTYLE INTERVENTION AND WEIGHT LOSS AND MAINTENANCE

Although observational studies are relatively easy to conduct, the results obtained from them are at most suggestive, as various sources of bias (selection, survival, and recall bias) may lead to spurious results and statistical significance does not necessarily imply causality. More reliable evidence for interactions between the genetic components and diet/lifestyle factors can be derived from randomized clinical trials. In contrast to observational studies, the study conditions in randomized clinical trials are controlled directly by the investigators, including the specifically defined dietary intakes and physical activity. This control minimizes the possibility of bias and increases the level of causality. In principle, the best-powered design is to examine the intervention of monitored changes in diet/lifestyle among subjects with predetermined genotypes, matched for potential confounders. However, this is not an efficient approach considering the increasingly expanding list of susceptibility genes to be tested. In fact, most studies genotype candidate genes in existing trials testing the effects of various diet/lifestyle interventions on weight changes and maintenance (Table 2).

Many studies have examined the modification effects of the key genes regulating energy balance on weight loss intervention. Shiwaku et al.[74] investigated 76 healthy perimenopausal Japanese women (age 54.7 years; BMI 21–33 kg/m^2) in a behavioral weight-loss program with a 10% low-calorie diet (LCD) and exercise (over 7000 steps/day) regimen. The intervention induced a signifi-

Table 2 **Selected intervention studies of gene-lifestyle interactions on weight change.**

Reference	Subjects*	Gene (Variants)	Intervention	Major findings
Yoshida et al. (1995)[75]	88 F	*ADRB3* (Trp64Arg)	LCD + exercise, 3 mo	Arg64-allele carriers lost less weight than Trp64Trp homozygotes ($P < 0.05$)
Fumeron et al. (1996)[81]	163	*UCP1 (Bcl*I A > G [3826]), *ADRB3* (Trp64Arg)	LCD, 2.5 mo	*UCP1* G-allele carriers lost less weight ($P < 0.05$) than AA homozygotes
Sakane et al. (1997)[76]	61 F	*ADRB3* (Trp64Arg)	LCD + exercise, 3 mo	Arg64-allele carriers had smaller decreases in weight and WHR than Trp64Trp homozygotes
Kogure et al. (1998)[82]	113 F	*UCP1* (-3826 A > G), *ADRB3* (Trp64Arg)	LCD + exercise, 3 mo	*UCP1 GG* homozygotes lost less weight than A-allele carriers ($P < 0.05$); *ADRB3* Arg64-allele carriers lost less weight than Trp64Trp homozygotes; Those carrying both variants had less weight loss than those carrying either genotype alone.
Mammes et al. (1998)[84]	38 M/79 F	*LEP* (8 SNPs)	LCD, 2.5 mo	In women, the SNP -2549C allele was associated with lower BMI loss ($P = 0.05$) after intervention
Mammes et al. (2001)[85]	114 F/65 M	*LEPR* (T343C)	LCD, 2.5 mo	Women carrying C- allele lost more weight than TT homozygotes ($P = 0.006$)
Xinli et al. (2001)[83]	31 M/16 F	*ADRB3* (Trp64Arg)	Low cholesterol and SFA based on NCEPA step1 diet, 3 mo	Increases in weight and BMI were lower in children with Trp64Trp homozygotes than in the Arg64-carriers and the control group ($P < 0.05$)
Rawson et al. (2002)[77]	34 F	*ADRB3* (Trp64Arg)	AHA step2 diet (1200 kcal/d), 13.5 $\pm$ 2.6 mo	No interaction in relation to body composition and total daily energy expenditure
Shiwaku et al. (2003)[74]	76 F	*ADRB3* (Trp64Arg)	LCD + exercise, 3 mo	Arg64-allele carriers lost less weight than Trp64Trp homozygotes ($P = 0.035$)
Aberle et al. (2005)[86]	606 M	*APOA5* (-1131T > C)	Low fat, 3 mo	C-allele carriers lost more weight than TT homozygotes ($P = 0.002$)
Corella et al. (2005)[87]	9 M/39 F	*PLIN* (11482G > A)	LCD, 1 y	GG homozygotes lost more weight than A-allele carriers ($P = 0.02$)
Shin et al. (2005)[79]	296 F	*UCP1* (A3826G, A1766G, Ala64Thr)	VLCD, 1 mo	The common haplotype [GAG] was associated with less reduction of WHR ($P = 0.006$) and body fat mass ($P = 0.05$) than in non-carriers
Cha et al. (2006)[78]	214 F	*UCP3* (6 SNPs)	VLCD, 1 mo	The common haplotype [CGTACC] was associated with an increased reduction in body weight ($P = 0.016$) and BMI ($P = 0.039$); Int3-47G > A G-carriers lost more weight than AA homozygotes ($P = 0.02$)
De Luis et al. (2006)[88]	14 M/55 F	*FABP2* (Ala54Thr)	LCD + exercise, 3 mo	Thr-allele carriers had greater decrease in fat mass than Ala54Ala homozygotes ($P < 0.05$)
Goyenechea et al. (2006)[89]	22 M/55 F	*IL6* (-174G > C), *PPARG* (Pro12Ala)	LCD, 2.5 mo	*IL6* C-allele carriers had less weight regain after 1-y weight-loss program ($P = 0.049$); carriers of both variants maintained the weight loss better ($P = 0.043$) than non-carriers
Santoro et al. (2007)[90]	107 M/77 F	*MC3R* (C17A, G241A)	LCD + exercise, 2 mo	Wild-type homozygotes lost more weight than rare-allele carriers ($P = 0.03$) after 12 mo
Yoon et al. (2007)[80]	301 F	*UCP2* (4 SNPs), *UCP3* (10 SNPs)	VLCD, 1 mo	UCP2 -866G > A and the major haplotype [GGCdelCGTACC] had a significant reduction in fat mass ($P = 0.002$ and 0.004)

* If not indicated, the studies include both male (M) and female (F).
Abbreviations: BMI, body mass index; LCD, low-calorie diet; VLCD, very-low-calorie diet; WHR, waist-to-hip ratio.

cant difference in weight loss (−0.74 vs. −0.01 kg) between women with the wild-type genotype and those with a Trp64Arg variant in the *ADRB3* gene.[74] Similarly, several other studies also showed that carriers of *ADRB3* 64Arg allele might lose less weight than the Trp64Trp homozygotes in response to the LCD intervention.[75,76] However, in another weight-loss intervention study (American Heart Association step2 diet) of 34 obese (BMI $\geq$ 27 kg/

m^2), postmenopausal, Caucasian women (19 carriers and 15 non-carriers for the Trp64Arg variant), no effect of the Trp64Arg variant was found on weight loss, body composition (BMI, percent body fat, fat-free mass, fat mass), and energy expenditure.[77] Korean researchers conducted a 1-month weight control program with a very-low-calorie diet (VLCD; 700 kcal/day) in 453 overweight Korean female subjects (BMI > 25 kg/m^2). In a series of analyses among women who finished the intervention ($n = 214$, 296, and 301), SNPs/haplotypes in the uncoupling protein gene family (*UCP1*, *2*, and *3*) were significantly associated with an increased reduction in body weight, body fat mass, and waist-to-hip ratio.[78–80] The modification of variants in the *UCP* gene family on weight change in response to LCD intervention was also observed in other studies.[81,82]

Similar genetic modification effects on dietary intervention were also observed in children. Xinli et al.[83] examined the effect of the Trp64Arp polymorphism in *ADRB3* on obesity after 3 months of dietary intervention (a diet low in cholesterol and SFA, based on the step1 diet of the National Cholesterol Education Program of America) in 47 obese Chinese children. The increases in weight and BMI were significantly lower in obese children without the variant than in the control group. Changes in weight and BMI in obese children with the variant were similar to the results in the controls.

Some other genetic variants were also found to modulate the effects of dietary intervention on weight loss. Mammes et al.[84,85] examined the variants in *LEP* and *LEPR* genes in modifying the response to LCD intervention. In one analysis including 117 obese patients (79 women and 38 men; mean age 42 years; mean BMI 33.2 kg/m^2) who were prescribed a LCD with a 25% reduction in their spontaneous energy intake for 2.5 months, a SNP -2549C > A (MAF = 0.44) near to 5′ region of *LEP* gene was significantly related to lower BMI loss ($P = 0.05$).[84] In their later study of an expanded sample of 179 patients (114 women and 65 men; BMI ≥ 27 kg/m^2), they found that women carrying the C allele of Ser (T) 343 Ser (C) variant of *LEPR* gene lost more weight in response to LCD than the non-carriers ($P = 0.006$).[85] In another study, 606 hyperlipemic and overweight men were instructed to reduce their daily intake of fat to a maximum of 45–50 g. Patient compliance was supervised by means of a nutritional diary that was reviewed at follow-up visits at 6 weeks and 3 months. The reduction of BMI was significantly higher in carriers of the C allele of the -1131T > C polymorphism in *APOA5* (apolipoprotein A5) gene compared with the non-carriers ($P = 0.0021$).[86] The common variants in genes such as *PLIN*, *IL6*, *PPARG*, *FABP2* (fatty acid binding protein 2), and *MC3R* (melanocortin-3 receptor) were also found to modulate the intervention (LCD or LCD and exercise) on weight loss (Table 2).[87–90]

CONCLUSION

Recent changes in the availability and cost of palatable energy-dense food and the reduction in physical activity during work and recreation on the background of evolutionarily engraved response patterns (genetic predisposition) have undoubtedly contributed to the current obesity epidemic. Evidence from association studies and intervention trials continues to mount, indicating that genetic components may modify lifestyle effects on the development of obesity. However, these findings are at most preliminary. Various sources of bias may lead to spurious interactions in observational studies, especially cross-sectional and retrospective studies. A randomized clinical trial is an excellent model for testing gene-lifestyle interactions. However, since most interventions combine changes in diet, weight loss, and physical activity, it is difficult to tease out the interactive effect attributable to any specific component. In addition, most intervention trials are small and short-term, thus limiting the statistical power and the ability to identify moderate interactions and long-term genetic effects. Therefore, a large-scale, prospective study with detailed information for lifestyle and dietary intake would be an ideal model for identifying gene-environment interactions.

DNA sequencing alone does not provide enough information to determine the molecular pathways of an organism in healthy and diseased states. This understanding has helped spawn numerous multidisciplinary approaches to the study of complexity in human health. Increasing research effort is now invested in post-genomic science, particularly in the related disciplines of transcriptomics, proteomics, and metabolomics. One such effort is the field of nutrigenomics,[91,92] a new form of nutrition science targeting the detection of multilayer interactions among food/nutrients and genes, proteins, and metabolites. There is a strong demand for technological solutions that will help to integrate the various "omics" information with our traditional knowledge of nutrition.

Population-wide prevention and treatment efforts aimed at reducing obesity are usually costly and difficult to conduct. Therefore, efforts to prevent obesity at the public health level can be focused on identification and counseling of susceptible individuals. This situation emphasizes the need for greater understanding of the ways in which interactions between diet/lifestyle and genes may help distinguish who will and who will not respond to dietary interventions. Such knowledge will provide a strong scientific rationale for tailoring diet/lifestyle interventions from a one-size-fits-all approach to

a personalized approach. Attempts to integrate the emerging knowledge into personalized health practices are still in the very early stages.

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