Implications of Gene–Behavior Interactions: Prevention and Intervention for Obesity

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A vast body of research exists to demonstrate that obesity is a complex disorder with a strong genetic basis and a multifactorial etiology. Yet despite the overwhelming evidence that genes play an important role in the development of obesity, many people argue that the increasing prevalence of obesity is simply due to an abundance of palatable food and a dearth of opportunities for physical exercise. While activity and eating behaviors contribute substantially to the development of obesity, considering these to be the only etiologic factors is directly contradictory to what is now known about how eating and energy balance are regulated. Our understanding of the molecular processes controlling eating behavior, in particular, has accelerated exponentially in the last 10 years, and this is one area in which obesity genetics has made great progress. Our challenge is to understand more fully how genetic variation may interact with behavioral factors to influence the regulation of body weight and adiposity. Although exercise and diet strategies are used routinely for obesity treatment, there is a huge variability in how individuals respond to these interventions. There is also a substantial amount of evidence that such responses may also be regulated by genes. Understanding gene–response relationships is the key to developing more efficacious intervention and prevention programs for obesity.

Obesity has presented one of the greatest public health challenges in the last decade, as obesity prevalence among all age groups continues to rise, and efficacious strategies for intervention and/or prevention of this disease have proven elusive. Among the greatest public health concerns today is the rapid rise in obesity in the pediatric population, which now exceeds 18% in children (6–11 years) and 17% in adolescents (12–19 years), while obesity among young adults (20–39 years) approaches 30% (1). Extreme obesity (body mass index, BMI ≥ 40 kg/m^2) among adolescents and young adults has also risen dramatically, particularly among minority populations, ranging from 5% in non-Hispanic whites to almost 12% of non-Hispanic blacks in this age group (2). Obesity established in adolescence strongly predicts obesity for the remainder of adult life, and the consequences are potentially devastating, characterized by a lifelong burden of comorbid conditions and depression. The public health consequences of such early-onset chronic disease are substantial, adding to an already overburdened public health system. Importantly, current options for treating obesity in both children and adults have had limited success, and the need for new insight into factors leading to early onset obesity and its concomitant comorbidities is great.

Between 24% and 38% of adult Americans and more than half of all obese individuals reported that they were trying to lose weight according to the latest National Health Interview Survey (3). An estimated $33 billion is spent yearly on unsuccessful efforts to lose weight, illustrating the fact that obesity is both difficult to alleviate and, even today, not well understood (4). Because obesity has a multifactorial etiology, the strategies and methods for its treatment are equally numerous and varied. Obesity treatments currently available include dietary, pharmacological, behavioral, and surgical approaches. How individuals respond to each of these types of interventions may be critically influenced by genetic variation and gene–environment interaction.

INTERVENTIONS CURRENTLY AVAILABLE FOR THE TREATMENT OF OBESITY

Behavioral interventions for obesity typically focus on behavior modification and reassessment, including encouraging healthy eating practices, lower caloric and fat intake, regular meal patterns, increased fruit, vegetable, and grain consumption, physical activity, and social support (5,6). While short-term treatment efficacy of weight control via the use of behavior modification has dramatically improved over the past 20 years, long-term success has been elusive, particularly in the clinically severe obese (7). A recent review of all clinical weight loss trials lasting 12 months or longer concluded that only reduced-energy diets in combination with exercise and/or pharmacological agents produced moderate weight loss that persisted as long as 6 months (8). Interventions that included weight loss advice/information or exercise alone produced the least weight loss, and all interventions demonstrated a tendency for weight regain after 6 months (8). Behavioral weight-loss methods used in almost all weight loss interventions, such as self-monitoring, goal setting, stimulus control, reinforcement,

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and cognitive change, appear to improve the long-term efficacy of most studies and to slow weight regain (9–11).

In terms of medical treatments, usually reserved for the moderate to severely obese, bariatric surgery and two primary anti-obesity drugs, sibutramine and orlistat, are widely used at present. Weight loss following bariatric surgery has been reported in the range of 60–70% of excess weight (difference between preoperative and ideal body weight) at 2 years, and may remain as high as 50% at 10 years (12). Nevertheless, 10–15% of patients undergoing this procedure will fail to lose weight or will have weight regain (13), with some patients regaining all or most of the lost weight within 3–5 years following surgery (14). Both sibutramine and orlistat have been found to produce modest but significant weight loss in clinical trials, although attrition rates were high for both types of trials (33% in orlistat studies and 48% in sibutramine studies) (15). In a clinical study of the long-term effects of sibutramine, response to the drug treatment ranged from a weight gain of 2.3 kg to a weight *loss* of almost 13 kg (16). Similar variation in weight loss following drug treatment has been reported in other studies (17–20). Thus, even for presumably "durable" treatments such as bariatric surgery and also for shorter-term pharmacological treatment, there is a strong physiologic drive opposing weight loss and promoting obesity in some individuals.

Based on a review of the literature, no single intervention strategy emerges as the ideal treatment for all individuals. A wide variability in response to weight loss treatment is a common theme among weight loss intervention studies, suggesting that many interventions may be efficacious for select individuals but result in little or no change in others. A major limitation of many weight loss studies is that they only report mean group weight changes and often only in those individuals completing the intervention. Few studies include analyses designed to dissect the factors that predict response vs. nonresponse to the intervention.

Why is weight loss so difficult to achieve, and why is weight regain virtually inevitable following termination of an intervention? Central to the design of most obesity intervention strategies is the assumption that obesity results from a simple imbalance between energy intake and energy expenditure. Thus, most intervention programs for weight management focus on decreasing energy intake through various alterations in diet or eating behavior and/or promoting energy expenditure in the form of physical activity and exercise. It is assumed that the act of eating is entirely volitional and is driven by a deliberate decision to ingest food, based on cognition, conscious feelings of hunger, or emotions that trigger eating. While certainly one must eat to become obese, and physical activity can counterbalance the effects of excessive food intake, we now know that a complex, highly regulated, and redundant neural system exists that regulates feeding behavior and energy homeostasis.

THE PHYSIOLOGY OF BODY WEIGHT REGULATION

At the core of the regulatory mechanisms controlling energy balance are the leptin and melanocortin pathways, and the discovery of these pathways has been heralded as breakthroughs in obesity research. Leptin is expressed almost exclusively within adipocytes and serves as a signal of stored adipose to the brain (21). Numerous studies have shown that leptin levels correlate with the amount of stored body fat in both humans and animals and that infusion of leptin decreases feeding and increases metabolic rate in rodents (22–28). As leptin levels rise and fall concurrently with changes in body fat stores (e.g., consequent to a weight loss intervention), concomitant changes in satiety signaling and energy metabolism take place as the body strives to maintain energetic homeostasis (29). Leptin does not appear to serve simply as an "energy sensor" but has also been shown to influence both glucose and lipid metabolism, fetal development, sexual maturation, reproductive function, insulin signaling, and immune response, revealing adipose as an active endocrine organ with global systemic effects (30–35).

The melanocortin system, including agouti-related protein (AGRP), proopiomelanocortin (POMC), melanocortin receptors (MC3R, MC4R), melanocortin concentrating hormone (MCH), neuropeptide Y (NPY), and other components, is at least one pathway with which the leptin signaling system interacts to regulate fat storage and utilization (36–38). In addition to its action on eating behavior and basal metabolism, defects in melanocortin signaling are associated with lowered energy expenditure due to fat oxidation, providing a mechanism by which obese individuals can accumulate more fat for a given amount of food (39–41).

In addition to the complex pathways controlling eating behaviors and metabolic rate, tremendous advances have been made in our understanding of the factors involved in adipocyte formation. Obese individuals have both larger and a greater number of adipocytes than their lean counterparts, and the development of morbid obesity requires both hypertrophy and hyperplasia of adipocytes, which can continue throughout life (42). There is little evidence that weight loss induces necrosis or apoptosis in adipocytes, except in extreme cases, such as starvation, malignancy, and/or streptozotocin-induced diabetes (43,44). Thus, once acquired, it is likely that adipocytes remain intact in their capacity to accumulate stored lipid, contributing to weight gain following a weight loss intervention.

The leptin and melanocortin pathways represent the core components of what we now know is an amalgamation of complex, highly redundant pathways regulating energy balance, which have been elegantly described in several recent reviews (45–50). Through the action of these systems, which include both central (e.g., brain) and peripheral (e.g., gut, skeletal muscle, adipose) components, the body robustly defends its lower limit for weight and adiposity with little inhibition of the upper limit (51). The powerful mechanisms that exist to promote eating behavior, to attenuate energy expenditure, to reinforce food-associated pleasure, and to foster the accumulation and maintenance of adipose tissue depots constitute the basis of why so many weight loss interventions fail.

THE GENETIC UNDERPINNINGS OF OBESITY

Obesity can result from defects in any part of these complex feedback systems for the regulation of body weight. In fact, DNA sequence defects in *LEP, LEPR, POMC, PC1*, and *MC4R* have all been shown to produce early onset morbid obesity, hyperphagia, hyperinsulinemia, and hyperglycemia in humans (52–61). Adults with leptin or leptin receptor deficiencies also have impaired reproductive function and hypogonadism. Of all genetic defects identified to date in extreme forms of human obesity, the most compelling are found within the *MC4R* gene. Of the numerous studies that have reported mutations within *MC4R*, many have been shown to produce alterations in binding affinity or receptor activation, and most are associated with extreme obesity and overeating resulting from haploinsufficiency of the receptor protein (57–61). In addition, it is estimated that up to 3–5% of severe obesity may be accounted for by these common variants in the *MC4R* gene (62).

In terms of genetic contributions to more common forms of obesity, studies of families, adoptees, and twins estimate the heritability (the amount of population variability in a trait that can be accounted for by variation in genes) of body mass, percent body fat, and fat patterning to range from 0.37 to 0.78 (63–67). Thus, substantial evidence exists that both extreme and prevalent forms of obesity are influenced in large part by genetic variation. Intervention studies in monozygotic twins in which subjects were over- or underfed for extended periods have revealed a high concordance among twin pairs for both weight gain and weight loss, providing evidence that response to treatment also has a substantial genetic component (68).

Considerable evidence indicates that the processing of "energy in" and "energy out" can be influenced by the quality, quantity, and even timing of nutritional intake and physical activity. A congressionally mandated study, commissioned from the Institute of Medicine to evaluate strategies for the prevention and intervention of childhood obesity, concluded that,

> Although 'energy intake = energy expenditure' looks like a fairly basic equation, in reality it is extraordinarily complex when considering the multitude of genetic, biological, psychological, sociocultural, and environmental factors that affect both sides of the equation and the interrelationships between these factors (69).

Yet, despite advances in our increasing understanding of the genetic basis of obesity and the physiological forces that control eating and energy balance, these components are largely ignored in almost all intervention and prevention programs designed to reduce body weight and obesity.

The good news is that the efforts to incorporate genetic and/or gene–environment information into obesity intervention and prevention do not have to begin *de novo*. There are already large and growing bodies of literature in the fields of gene–nutrition, gene–exercise, and gene–drug interactions and obesity genetics that can be used to guide the identification of the appropriate markers. The Human Obesity Gene Map was created in 1994 as a catalog of all genes (i) linked or associated with human obesity, (ii) resulting in human obesity through Mendelian or single gene mutation, and/or (iii) producing obesity in animal models. A total of 189 genes related to obesity have been identified in this database through 2005. Of the many genes putatively associated with the development of obesity, 22 genes have been supported by five or more studies and 12 have been supported by 10 or more studies (70). These genes fall into five major categories: (i) thriftiness (beta-adrenergic receptors 2 and 3 [*ADRB2; ADRB3*], uncoupling proteins 1, 2, and 3 [*UCP1, UCP2, UCP3*]; (ii) hyperphagia (dopamine D2 receptor [*DRD2*], 5-hydroxytryptamine (serotonin) receptor 2C [*HTR2C*], *LEP, LEPR, MC4R,* nuclear receptor subfamily 3, group C, member 1 [*NR3C1*]; (iii) low lipid oxidation (angiotensin-converting enzyme [*ACE*], adiponectin [*ADIPOQ*], guanine nucleotide binding protein, beta-3 subunit [*GNB3*], hormone sensitive lipase [*LIPE*], low density lipoprotein receptor [*LDLR*]; (iv) adipogenesis (peroxisome proliferator-activated receptor gamma [*PPARG*], vitamin D receptor [*VDR*], resistin [*RETN*], interleukin-6 [*IL6*], tumor necrosis factor alpha [*TNF*]); and (v) low physical activity [*DRD2, MC4R*] (71). The best substantiated gene associations for obesity are in plausible functional pathways, and thus, these genes provide a logical place to begin in identifying gene–environment interactions that may mediate response to treatment.

Genes in the pathways controlling energy balance and adipocyte formation described earlier may also influence response to weight loss interventions. Preliminary studies of weight loss response suggest that they do. Mammes *et al.* reported that a G>A transition at position −2549 in the promoter region of the *LEP* gene is associated with common forms of obesity and that carriers of the −2549A allele have higher baseline leptin levels and lower weight loss following a low calorie diet (72,73). Carriers of the C allele of a variant in the *LEPR* gene (Ser[T]343Ser[C]) lost more weight in response to a low calorie diet than the noncarriers ($P = 0.006$) (74). In another study of the Lys656Asn variant within *LEPR*, homozygotes for the Lys656 allele experienced significant decreases in weight, BMI, fat mass, waist circumference, systolic blood pressure, and leptin levels compared to carriers of the Asn656 allele (75). Several studies have investigated the effect of a common polymorphism in the *PPARG* gene, Pro12Ala, for response to obesity and diabetes interventions. Lindi *et al.* reported that Ala12 carriers gained significantly more weight over a 10-year period of follow-up in a longitudinal study, while Ala12Ala homozygotes had lower fasting plasma insulin both at baseline and after 10 years, despite significant weight gain (76). Consistent with these findings, in a separate study Ala12 carriers undergoing a 6-month hypocaloric diet lost a similar amount of weight compared to Pro12 homozygotes yet gained significantly more weight following completion of the intervention (77). These studies serve to illustrate that genetic variation can have significant impact on both weight loss and weight maintenance following an obesity intervention. Additional genes that have been significantly associated with weight loss following an intervention (e.g., lifestyle, pharmacological, dietary, and exercise) are summarized in **Table 1**.

Table 1 Genes significantly associated with weight loss phenotypes in intervention studies

Gene	Variant	Intervention	Significant outcome	Population studied
ACSL5	rs2419621	Meal replacement	Diet response	Obese Canadian women (86)
ADRB3	Trp64Arg	12-week low calorie diet	Resistance to weight loss	Japanese obese women (87–89)
IL-6	–174G>C	Laparoscopic adjustable gastric band	Weight loss	White obese males and females (90)
IL-6	–174G>C	10-week low energy diet	Weight maintenance after weight loss	Spanish adult males and females (91)
LEP	–2549G>A	25% reduced caloric diet	Weight loss	French white male and female adults (72)
LEPR	Ser343Ser	25% reduced caloric diet	Weight loss	French white male and female adults (74)
LEPR	Lys656Asn	Mediterranean hypocaloric diet and exercise	Weight loss	Spanish males and females (75)
MC3R	Thr6Lys	Reduced calorie diet	Weight loss	Obese Italian male and female children (92)
PLIN	11482G>A	1-year low energy diet	Weight loss	Adult males and females (93)
PPARG	Pro12Ala	10-year weight tracking	Weight gain, fasting insulin	Finnish male and female adults (76)
PPARG	Pro12Ala	Low calorie diet	Weight gain	Postmenopausal women (77)
PPARG	Pro12Ala	Meal replacement	Diet resistance	Obese Canadian women (86)
UCP2	Ala55Val	Laparoscopic adjustable gastric band	Weight loss	Severely obese bariatric surgery patients (94)
UCP3	CGTACC haplotype of-55C/T, Int2-143G/C, Tyr99Tyr, Int3-47G/A, Int4-498C/T, and Tyr210Tyr	Very low energy diet	Weight loss	Korean overweight females (95)

GENE–ENVIRONMENT INTERACTION IN OBESITY

In terms of response in obesity-related comorbidities, the *GNB3* gene is well studied in terms of interaction and can serve as an example for how such gene–environment interaction may be applied to obesity interventions and/or treatments. The *GNB3* gene has been proposed as a candidate gene for both essential hypertension and obesity. Grove *et al.* reported a significant interaction between the C825T variant within *GNB3* and both obesity and physical activity in predicting hypertension in African-American adult males and females (78). Homozygotes for the T825 allele who were also obese and inactive had significantly increased risk for hypertension (OR = 2.71, 95% CI = 1.19–6.17, $P < 0.02$). Though obesity and inactivity are established risk factors for hypertension, individuals who were C825/C825 homozygotes experienced no increase in risk for hypertension with increasing levels of obesity and inactivity, suggesting that among this population, the C825 allele confers a protective effect for hypertension, even in the presence of inactivity and obesity (78). Because the T825 allele appears to interact with obesity and physical inactivity in exacerbating risk for hypertension, this type of study is important not only for identifying individuals at increased risk for disease but also for ascertaining individuals most likely to respond to exercise and diet interventions. Consistent with the previous study, Danoviz and colleagues reported that the C825T genotype was predictive of systolic blood pressure only in individuals with increased BMI ($P = 0.02$), with the presence of the T allele significantly associated with a 1.5-fold (95% CI 1.04–2.26) increased risk of hypertension (79). Hauner *et al.* recently investigated the role of the C825T polymorphism within the *GNB3* gene in weight loss response following a reduced calorie diet combined with sibutramine treatment and found that CC homozygotes lost significantly more weight when taking sibutramine compared to placebo, while carriers of the 825T lost comparable amounts of weight in either group (20). These findings are consistent with the observations made in previous studies that C825 homozygotes would be unlikely to reduce blood pressure in response to diet and exercise therapy but may benefit from the addition of pharmacotherapy. Contrary to the studies listed earlier, polymorphisms of the *GNB3* gene were not associated with long-term (3 years) weight loss, resolution of comorbidities, or the development of complications in severely obese patients undergoing laparoscopic gastric banding (80). The above example demonstrates that gene effects on obesity-related comorbidities (e.g., blood pressure) (i) are often not detectable in the absence of obesity, (ii) may be dependent on the severity of the obesity, and (iii) may have differential effects depending on the type of treatment/intervention.

In identifying genes that may influence response to interventions, extensive studies of gene–exercise and gene–diet interaction are well described in the literature. In 2000, Bouchard and colleagues began to document the reports of genetic variation associated with exercise and physical activity in the form of the "The human gene map for performance and health-related fitness phenotypes" (81). Each year, this group updates the list of gene variants identified through association or linkage studies as being related to physical activity,

including a comprehensive summary of genes related to exercise performance, response to exercise, and health-related fitness. As of the most current version of the performance gene map, more than 700 papers have been published documenting the interaction between physical exercise, genes, and these physiologic outcomes (82). Of these, 22 autosomal genes are associated with change in or interaction with body composition or body mass and exercise or physical activity.

Nutritional genomics is a mature and growing field of research, which includes (i) nutrigenomics: the study of interaction of dietary components with the genome and the resulting proteonomic and metabolomic changes and (ii) nutrigenetics: understanding the gene-based differences in response to dietary components (83). Nutrition scientists are keenly aware that nutritional intake can alter the expression of genes and that genetic variation can have a significant effect on metabolic response to food and the ability of dietary factors to provide protective effects against disease (84). Markers for gene–diet interactions can include both gene expression assays/microarrays and genetic sequence variants. Studies of gene–diet interaction are a logical source of information from which to derive plausible markers for gene-based interventions.

CHALLENGES IN UTILIZING GENETIC INFORMATION TO ENHANCE OBESITY TREATMENT

How can we use our increasing knowledge of the specific physiologic and genetic factors underlying obesity to improve intervention and prevention strategies for weight loss/weight maintenance in individuals of all ages? The challenges for incorporating genetic and gene–environment information into obesity treatment and prevention are many. First, established and replicable biomarkers must be identified that strongly predict treatment outcomes. The identification of biomarkers that influence obesity and weight loss will require prospective intervention-by-genotype studies and a focus on response phenotypes; response in this instance should be defined very broadly to include both weight loss as well as responses in risk factors for obesity-related comorbidities (e.g., blood pressure, plasma lipids). Second, practical, accurate, and affordable methods for characterizing the biomarkers must be available. These biomarker measurement methods cannot be restricted to individuals undergoing medical treatment but should also be available to practitioners and interventionists who can most readily use this information. Third, measurement of the biomarkers must be acceptable in the population at large. Individuals need to be as comfortable with genetic information as they are with having any other screening measure (e.g., cholesterol) performed. Fourth, the use of genetic information to "personalize" and enhance obesity interventions requires that such information be used responsibly, and the potential for misuse of the genetic information must be negligible.

Currently, every baby born in the United States is screened for the presence of phenylketonuria (PKU), an autosomal recessive disease in which the enzyme required for converting phenylalanine to tyrosine, phenylalanine hydroxylase, is defective. Undetected, the condition can result in severe mental retardation and early mortality. The screening tests used to detect PKU (the Guthrie inhibition assay or the McCamon–Robins fluorometric test) are both highly accurate and easily performed using blood spots (85). The development of PKU is a classic gene–nutrition interaction, and when the diet is altered to eliminate phenylalanine, normal development occurs. Is there a PKU "counterpart" for obesity? It is unlikely that a single gene mutation exists that is predictive of diet or exercise response. Yet, given the progress to date in identifying gene–exercise/gene–diet interactions that influence weight loss, it is possible that multiple genotypes will collectively provide substantial predictive power to determine the most efficacious intervention/prevention strategy for a given individual.

The studies performed to date investigating the role of genetic variation in response to obesity interventions have established a foundation of research supporting the incorporation of genetic markers in the design of intervention strategies. Prospective studies in which individuals are selected by genotype and undergo controlled interventions are urgently needed to identify/verify predictive markers of response to obesity interventions. Obesity candidate genes also need to be rigorously examined as markers for identifying individuals at risk for the development of obesity across the life span to develop more efficacious prevention strategies. Robust statistical analysis techniques designed to take into account multiple genetic variants and environments are also critically needed. Given the progress made to date, there is promise of a "personalized" genetic approach to obesity intervention and prevention.

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