

Genotype-specific weight loss treatment advice: how close are we?

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Abstract: Obesity, whose prevalence is continually rising, is one of the world's greatest health care burdens. This multifactorial condition is associated with many obesity-related conditions, such as type 2 diabetes, dyslipidemia, and cardiovascular disease. Weight loss is a significant challenge facing those wishing to reduce their disease risk. Of course, like obesity itself, weight loss is a complex phenomenon dependent on many environmental and genetic influences, and thus individual responses to weight loss interventions are incredibly variable. Currently, there are 3 major interventions used to reduce weight: diet, exercise, and pharmacotherapy. The findings from studies examining gene–diet (nutrigenetic), gene–exercise (actigenetic), and gene–pharmaceutical (pharmacogenetic) interactions, although not clinically applicable at this time, are gaining awareness. This review article summarizes the current evidence to support the contribution of DNA sequence variation in genes related to energy balance (expenditure and intake) in the response to weight loss intervention. There is no doubt that replication using more rigorous study designs that include the study of interactions between multiple genes and interventions is required to move towards the development of genotype-specific weight loss treatment strategies.

Key words: obesity, gene-environment interaction, weight loss, exercise, diet, pharmacogenetics, nutrigenetics.

Résumé : L'accroissement de la prévalence de l'obésité représente un des problèmes de santé majeurs à travers le monde. On associe cet état qui dépend de nombreux facteurs à des problèmes de santé dont le diabète de type 2, la dyslipidémie et la maladie cardiovasculaire. Perdre du poids constitue tout un défi pour ces personnes qui désirent réduire le risque de problème de santé. Tout comme l'obésité, la perte de poids dépend de nombreux facteurs environnementaux et héréditaires conditionnés par les traits personnels ; les réponses individuelles à la problématique de la perte de poids sont immensément variables. À l'heure actuelle, il y a trois principaux types d'intervention en matière de perte de poids : la diète, l'exercice physique et la pharmacothérapie. Les observations rapportées dans les études nutriginétiques (diète-gène), actiginétiques (activité physique-gène) et pharmacogénétiques (médicament-gène) présentent beaucoup d'intérêt quoiqu'elles ne soient pas applicables pour le moment. Cet article-synthèse présente le bilan des études scientifiques portant sur la variation de la séquence des gènes dans l'ADN en relation avec l'équilibre énergétique (dépense et apport) observée au cours des programmes de perte de poids. Il est impératif de faire d'autres études comportant de meilleurs schémas expérimentaux qui analyseront les interactions entre les multiples gènes et les programmes de perte de poids afin d'en arriver à développer des programmes de perte de poids présentant des stratégies qui soient ajustées aux génotypes.

Mots-clés : obésité, interaction généticoenvironnementale, perte de poids, activité physique, diète, pharmacogénétiques, nutriginétiques.

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Introduction

According to the Centers for Disease Control and Prevention, obesity is estimated to cost US consumers over \$100

billion dollars per year in health care costs and money spent on weight loss products and services. In Canada the burden is about \$4.3 billion (Katzmarzyk and Janssen 2004). This figure only includes direct costs and is much higher when workplace absenteeism and money spent on weight loss are included. There is no doubt that both genetic and environmental factors are jointly responsible for the obesity epidemic that has generated a North American health care crisis. Given this fact, it is hypothesized that we do not inherit a disease state per se but, rather, we inherit a set of susceptibility genes that interact with environmental factors and therefore result in an increased risk of certain conditions (Cooper 2003; Loos and Bouchard 2003). The term for differing response to environmental exposure is gene–environment interaction (GEI). A GEI implies a change in the direction

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or magnitude of the effect of a genetic variant when the environment changes. This has also been described as *context dependency* or the conditional nature of the interrelationship between genes and environments (Kardia 2000).

As with susceptibility to disease, response to weight loss intervention is multifactorial. Twin studies have demonstrated that there is considerably more variability in change in body composition between pairs of monozygous (i.e., identical) twins exposed to conditions of diet restriction, overfeeding, or exercise-induced negative energy balance than within identical twin pairs (Bouchard et al. 1990; Bouchard et al. 1994; Hainer et al. 2000). These studies strongly suggest that predisposition to lose or gain body fat in response to standardized energy balance paradigms is influenced by genetics. The most recent publication of the human obesity gene map has shown more than 258 putative quantitative trait loci (QTLs) on all 21 autosomal chromosomes as well as the X chromosome. Overall, >600 genes, markers, and chromosomal regions have been associated with or linked to human obesity phenotypes (Rankinen et al. 2006).

The current management of obesity is primarily to reduce energy intake and increase energy expenditure, although many people are resistant to weight loss or rapidly regain lost weight after cessation of treatment. Identifying individuals responsive to lifestyle modification to control body mass would be extremely advantageous.

Although GEIs are commonly reported to result in increased or decreased susceptibility to obesity or its comorbidities, work in both animal models and humans indicates that individual genotypic variations alter not only susceptibility to disease but nutrient metabolism and response to exercise as well. The effectiveness of weight loss interventions is widely variable. Studies using identical twin pairs have shown that there was 12.8 times more variability in weight loss response to diet between than within twin pairs (Hainer et al. 2000). Similarly, in an exercise-based study of negative energy balance in twin pairs there were large individual differences in response, but subjects with the same genotype were more alike in their response than subjects with different genotypes, particularly for body fat and abdominal visceral fat changes (Bouchard et al. 1994). Furthermore, identical dietary conditions have shown significant between-individual differences, with weight loss ranging from 4.8 kg to 13.5 kg (Hellstrom et al. 1997) and large interindividual variability in the reduction in basal metabolic rate during food restriction, with coefficients of variation ranging from 25% to 65% (Dulloo and Jacquet 1998). Our genetic uniqueness accounts for the considerable heterogeneity in weight loss response, and thus the focus of this review will be the effect of obesity treatment “conditional on”, or in the context of, genetic make-up. This includes the study of *pharmacogenetics*, or the role of genotype on drug metabolism and outcome, *nutrigenetics*, the field of study combining nutrition and genetics, and *actigenetics*, the study of gene-exercise interactions or the notion that individuals respond differently when exposed to the same exercise environment.

A full genome scan is the only unbiased strategy for identifying genes related to weight loss in response to treatment intervention. The cost and complexity of performing such studies has resulted in only 1 relevant genome scan, the

HERITAGE Family Cohort Study (Chagnon et al. 2001). This study, which included 364 sibling pairs from 99 Caucasian families, was conducted for body-composition phenotypes in response to exercise training. Evidence of significant linkage was observed for changes in fat-free mass with the calcium-binding protein A1 (S100A) and the insulin-like growth factor I genes. Suggestive evidence was also found for the linkage of changes in fat mass and percentage fat with chromosomal regions 1q31 and 18q21–q23, in percentage fat with the uncoupling protein 2 and 3 genes, and in body mass index (BMI) with 5q14–q21.

Thus, the majority of data described in this review were generated from small-scale candidate gene association studies, and we recognize that common criticisms related to lack of replication and statistical thoroughness (adjustment for multiple comparisons) do apply.

The purpose of this article is to provide a synthesis of the current evidence, through a literature review, on the role of nutrigenetic, actigenetic, or pharmacogenetic effects on weight loss, weight maintenance, or weight gain. It was not the authors' intention, however, to conduct a systematic review because of time and resource limitations. The most plausible candidate genes accounting for the body composition changes in response to dietary or exercise interventions are those encoding proteins that are key regulators of energy balance pathways, such as those implicated in controlling the efficiency of caloric expenditure or those involved in feeding and fat deposition. Relevant studies of variants in candidate genes related to energy balance, lipid metabolism, and body fat regulation were identified mainly through (i) electronic searches in MEDLINE (1966 to July 2006, Ovid interface) and PubMed (1990 to July 2006, NCBI interface) limited to human studies and the English language and (ii) searches of the reference lists of all included articles to ensure that all relevant material was obtained.

Nutrigenetics

Leptin (LEP) and its receptor

Leptin links fat mass (size of energy stores) to food intake and energy expenditure through a negative feedback loop that is under hypothalamic control (Magni 2003; Gale et al. 2004). Leptin was initially touted as a major suppressor of appetite because of the findings that total deficiency of leptin or its receptor leads to hyperphagia and obesity in mice and humans (Campfield et al. 1995; Montague et al. 1997) and that exogenous administration decreases body mass, body fat, and food intake and increases energy expenditure in animals and some humans (Pellemounter et al. 1995; Halaas et al. 1995). However, as body fat determines the circulating leptin concentration, obese individuals generally have increased levels (Haffner et al. 1996; Considine et al. 1996; Adami et al. 1998), prompting the hypothesis that leptin resistance, rather than deficiency, may play an important role in the development of obesity in humans. Only 1 group has explored the relation between the leptin gene and response to a weight loss intervention. These authors found a C-2549A LEP promoter single nucleotide polymorphism (SNP) to be associated with differing BMI response to a low-calorie diet in obese women (Mammes et al. 1998). The A allele of the promoter SNP was associated with a

lower BMI reduction than that seen in C/C homozygotes. This polymorphism does not modify or create a documented regulatory site, hence it may be located in a yet unknown regulatory site, or it may be in linkage disequilibrium (see Appendix) with a mutation, creating a regulatory site in part of the gene not explored yet.

Leptin acts through the leptin receptor (LEPR), which is expressed in the nervous system and peripheral tissues such as adipose tissue, skeletal muscles, pancreatic β -cells, and liver. Genetic mutations in the LEPR have been found to cause early-onset morbid obesity with related phenotypes in animals (Chua et al. 1996a; Chua et al. 1996b) and humans (Clement et al. 1996). Linkage and association studies have shown this gene to be a plausible candidate for the obesity phenotype (Chagnon et al. 1999; Chagnon et al. 2000). With regard to the effects of polymorphisms in the LEPR in relation to weight loss response, Mammes et al. (2001) identified that overweight women carrying the C allele of the Ser³⁴³Ser (T/C) polymorphism in exon 9 lost more weight in response to a low-calorie diet than noncarriers and that this persisted after adjustment for baseline BMI. These results indicate that variations at the LEPR locus, associated with common obesity phenotypes, may be a part of the polygenic influences on the response to nutritional environment.

Serotonin receptor

The serotonin (5-hydroxytryptamine (HT)) system plays a role in the control of food intake and body mass gain (Wurtman and Wurtman 1984; Sargent et al. 1997; Halford et al. 1998). Indeed, previously marketed appetite suppressants such as *d*-fenfluramine have targeted receptors in this system to inhibit the reuptake of 5-HT into nerve terminals (Garattini et al. 1986). Of the 14 serotonin receptor subtypes described (Boess and Martin 1994; Martin and Humphrey 1994), the 5-HT_{2C} receptor in particular has been implicated, since knockout of this receptor in mice can result in obesity and increased feeding (Tecott et al. 1995). Thus the relation between SNPs in the 5-HT_{2C} receptor and weight loss has been explored. A Cys²³Ser substitution in the 5-HT_{2C} receptor subtype was found to be present at higher frequency in teenage girls reporting rapid weight loss as a result of reduced food intake (Westberg et al. 2002). While it has been suggested that the Ser²³ allele is associated with higher receptor expression (Sodhi et al. 1999) and altered eating behaviour (Holmes et al. 1998; Quedsted et al. 1999), the functional role of this SNP has not been established.

Uncoupling protein-1 (UCP1)

The UCPs are a family of carrier proteins located in the inner mitochondrial membrane and thought to play a role in the regulation of energy metabolism by uncoupling respiration from phosphorylation, leading to the generation of heat instead of ATP and thus increasing energy expenditure. In humans, UCP1 is considered a key moderator of the thermogenic function of brown adipose tissue (BAT) (Nedergaard et al. 2001). The thermogenic activity of BAT depends on its quantity, its UCP1 content, and the extent of stimulation by the sympathetic nervous system (Nedergaard et al. 1999). An A to G transition in the 5'UTR (untranslated region) of the UCP1 gene (A-3826G) has been shown to be related to weight change in response to alterations in energy intake.

Although this SNP was not associated with weight gain in the monozygous twin pairs from the Quebec overfeeding study (Ukkola et al. 2001c), Fumeron et al. (1996) did find the UCP1 genotype to be associated with weight loss in a group of 163 overweight individuals exposed to a low-calorie diet for 10 weeks. This group found that the G/G homozygotes lost less weight than the heterozygotes, who in turn lost less than A/A homozygotes. While the G allele of this UCP1 promoter polymorphism is strongly associated with lower UCP1 mRNA abundance in intraperitoneal adipose tissue of obese study subjects, it is likely only a marker for expressional differences and not the causative mutation (Esterbauer et al. 1998). In the context of dietary thermogenesis, G/G allele carriers have a significantly lower thermogenic capacity in response to fat intake (Nagai et al. 2003). The association of this G/G genotype with lower UCP1 mRNA expression and impaired UCP1-linked thermogenesis suggests that this SNP may adversely affect the regulation of body mass. Identification of the specific functional UCP1 gene mutation(s) will be essential to quantify the actual contribution of gene structure to its expression level and to evaluate its possible role in dietary response.

Apolipoprotein A5 (APOA5)

This member of the apolipoprotein family, which plays a role in triglyceride (TG) metabolism, accelerates lipoprotein catabolism by enhancing the clearance of very low density lipoprotein from plasma and activating lipoprotein lipase (Fruchart-Najib et al. 2004). A -1131 T/C polymorphism was found to be associated with reduction in BMI in response to short-term dietary restriction in hyperlipaemic, overweight men (Aberle et al. 2005). Carriers of the C allele, which is believed to impair ribosomal translation efficiency (Martin et al. 2003), lost significantly more weight than T/T homozygotes.

Perilipin (PLIN)

Perilipins are phosphorylated proteins in adipocytes that are localized at the surface of the lipid droplet (Greenberg et al. 1993; Blanchette-Mackie et al. 1995). These proteins have been shown to be essential in the regulation of TG deposition and mobilization (Souza et al. 1998; Brasaemle et al. 2000; Mottagui-Tabar et al. 2003), and variations at the PLIN locus are associated with obesity (Qi et al. 2004). A gene-diet interaction was found between the PLIN 11482G>A intronic polymorphism and weight loss in patients undergoing 1 year dietary treatment. The dietary intervention resulted in significant decreases in body mass in GG patients. Conversely, carriers of the minor A allele did not show significant changes in body mass. While the molecular mechanism for this finding remains unknown, this gene-diet interaction was consistently observed at 3, 6, and 12 months, even after adjustment for differences in body mass at baseline and for other potential confounders (Corella et al. 2005). Thus, it is unlikely that this finding is a chance occurrence, and consequently the PLIN locus may predict outcome of body mass regulation strategies based on low-energy diets.

Adipsin

Although generally thought of as a storage depot for fat,

adipose tissue also functions in an endocrine manner, secreting a large number of proteins, including adiponectin (Ahima and Flier 2000). This protein, also called complement factor D, is a component of the alternative pathway of complement activation important in the natural defense against infectious agents (Muller-Eberhard 1988). Adiponectin/complement factor D is present in high amounts in adipose tissue and may play a role in the regulation of systemic energy balance (Choy et al. 1992). In humans, the concentrations of adiponectin tend to be elevated in the obese state or in increased adiposity (Napolitano et al. 1994). Genes encoding proteins that are regulators of energy balance are likely involved in the modulation of the response to environmental pressures causing weight gain. Hence, the role of a restriction fragment length polymorphism (RFLP) adiponectin Hinc II in the metabolic and body composition changes in response to overfeeding was studied in the context of the Quebec overfeeding study (Ukkola et al. 2003). The absence of the adiponectin Hinc II RFLP, whose functional significance and exact site are yet unknown, induced greater increases in body mass and fat mass (abdominal, total, and subcutaneous) in response to the caloric surplus.

Glucocorticoid receptor (GRL)

The GRL is a ligand-activated transcription factor that, in the hormone-bound state, modulates the expression of glucocorticoid-responsive genes by binding to a specific glucocorticoid response element DNA sequence. This gene thus plays an important role in the metabolism of adipose tissue and in the regulation of abdominal fat distribution (Bjorntorp 1996).

An intronic C to G variation creating a Bcl I restriction site 646 nucleotides downstream of exon 2 has been associated with an elevated BMI and a greater amount of visceral fat (Buemann et al. 1997; Rosmond et al. 2000). A study was recently completed that explored the possible genetic contributors to weight loss maintenance over 1 year following a 6-week dietary weight loss intervention (Modifast, Novartis Nutrition). Interestingly, using the 3-factor eating questionnaire, which measures cognitive dietary restraint, disinhibition of dietary restraint, and emotional eating, as well as hunger, Vogels et al. (2005) found that carriers of the GRL G/G genotype had significant decreases over time in their disinhibition of dietary restraint or emotional eating scores and significantly fewer feelings of hunger during weight loss. While this may have resulted in decreased food intake, the G/G genotype was a strong independent predictor of successful weight maintenance (i.e., 5-fold greater chance of success).

Similarly, this GRL Bcl I RFLP polymorphism was strongly associated with the change in body mass in response to overfeeding in monozygous twins, accounting for about 4% of the change (Ukkola et al. 2001a). The GRL C/C carriers ($n = 12$) experienced greater increases in body mass and abdominal visceral fat than heterozygous carriers ($n = 12$). It was speculated that individuals carrying both C alleles could be sensitized to glucocorticoids caused either by increased peripheral sensitivity or by diminished feedback inhibition through glucocorticoid receptors in the central nervous system. Taken together these results suggest that those with the C/C genotype are more prone to issues of weight regulation, whereas G/G carriers have a greater

ability to maintain weight loss. Given that this SNP is found in an intronic region, its effects are likely caused by another variant with which it is in linkage disequilibrium.

Acyl CoA synthetase 5 (ACSL5)

The acyl CoA synthetase (ACSL) genes catalyze the production of fatty acyl-CoAs for synthesis or degradative pathways. The ACSL5 isoform maps to 10q25.1-2, an obesity locus identified in independent populations (van der Kallen et al. 2000; Dong et al. 2003). Since the ability to maintain or increase fatty acid transport capacity may be a determining factor in the success of a weight reduction program (Blaak et al. 2001) and ACSL5 has been shown to increase with food deprivation in rats (Nicklas et al. 2001), it was hypothesized that ACSL5 genotype may influence the rate of weight loss in response to energy restriction in women. A common C to T change (rs2419621) in the 5'UTR region of the gene *ACSL5* was found to be associated with positive diet response in obese women (Adamo et al. 2007). Furthermore, carriers of the variant allele (T) were also found to have greater skeletal muscle ACSL5 gene expression. From these results it was speculated that rs2419621 ACSL5 SNP acts as a *cis*-acting regulatory variant affecting ACSL5 expression levels or is in linkage disequilibrium with the causative regulatory variant. Follow-up work has identified that the T allele creates a consensus E-box motif sequence (CANNTG) recognized by the muscle-specific myogenic regulatory factors (Adamo et al., personal communication). Given that the ACSL enzymes are responsible for activating free fatty acids, thereby permitting them to undergo further processing through storage or oxidation, and skeletal muscle has very little capacity for storage, the presence of the variant T allele may influence the rate of weight loss by increasing ACSL5 levels and promoting the fatty acid β -oxidation pathway.

Actigenetics

Adrenergic receptors (ADR β_2)

The ADR β_2 , a major lipolytic adrenergic receptor isoform in human fat cells, is known to be downregulated in subcutaneous adipose of obese subjects (Schiffelers et al. 2001). Several coding SNPs that result in significantly changed receptor function have been described (Green et al. 1993; Green et al. 1994; Green et al. 1995). Specifically, the Gln²⁷Glu polymorphism was markedly associated with obesity, and homozygotes for Glu²⁷ had excessive fat mass and fat cells that were approximately 50% larger than those of controls (Large et al. 1997). In a large representative sample of the French population, Meirhaeghe et al. (1999) explored the relation between the Gln²⁷Glu polymorphism and anthropometric response to physical activity. The risk of obesity associated with the Gln²⁷Gln genotype was significantly increased in men who did not regularly participate in physical activity, while the risk was not significant in active men. This study was the first to identify that physical activity may counterbalance the effect of a genetic predisposition to increased body mass, fat mass, and obesity.

CYP19

This gene encodes aromatase, an enzyme that converts

androstenedione and testosterone to estrone and estradiol, respectively. Genetic variability in this gene can affect estrogen and androgen concentration (Tworoger et al. 2004a), both of which are involved in body fat regulation and therefore could be important modifiers of exercise on fat loss (Bjorntorp 1996; Marin et al. 1996; Hautanen 2000; De 2000).

CYP19 contains a tetranucleotide repeat polymorphism (TTTA)_n in intron 4, the most common repeats being the 7, 8, and 11 repeats (Haiman et al. 2000). Women carrying the 8-repeat (8r) allele have been shown to have higher estrone and estradiol concentrations compared with women with no 8r alleles (Haiman et al. 2000; Tworoger et al. 2004a). The role of this gene polymorphism in body composition change was examined in postmenopausal women randomly assigned to undergo either a 1-year aerobic exercise intervention (moderate exercise 45 min/d, 5 d/week) or stretching control (60 min stretching and relaxation class 1d/week), all of whom were asked to maintain their regular eating habits (Tworoger et al. 2004b). The 11r allele was associated with differing intervention effect. Among exercisers, those with 2 vs. no 11r alleles had a significantly larger reduction in BMI, total fat, and percentage body fat. The heterozygotes showed an intermediate response. The CYP19 tetranucleotide repeat occurs around the exon border and therefore may affect tissue/physiological condition-specific splicing. Therefore, it has been suggested that the CYP19 11r allele effect may be confined to fat tissue, or it may be involved in the regulation of aromatase only under conditions of fat loss (Tworoger et al. 2004b). Moreover, since aromatase activity is 6 to 30 times higher in fat taken from the upper thigh, buttocks, and flank than the abdomen (Killinger et al. 1987; Killinger et al. 1990), it is possible that the effect of the CYP19 polymorphisms on fat loss may differ across body fat zones, accounting for the difference in total body fat measures but not subcutaneous vs. intra-abdominal fat.

Catechol-O-methyl-transferase (COMT)

The product of the COMT gene converts catechol estrogens such as 2-hydroxyestradiol into less active metabolites. A valine/methionine substitution (Val^{108/158}Met) results in a protein 2- to 3-fold less active in vitro (Lotta et al. 1995; Dawling et al. 2001). The Met allele is associated with increasing concentrations of 2- and 16- α -hydroxyestrone, suggesting that it is also less active in vivo (Tworoger et al. 2004a). The role of the Val^{108/158}Met polymorphism in body composition response to the exercise intervention was evaluated as described above for CYP19 (Tworoger et al. 2004b). Among exercisers, those carrying the Met/Met vs. Val/Val genotype had a smaller decrease in percentage body fat and a smaller, albeit not significant, decrease in BMI and total fat. Heterozygotes in the exercise intervention group were intermediate between the homozygote genotypes.

It has been previously reported that women who are homozygous for the Met allele have increased urinary 2- and 16- α -hydroxyestrone concentrations (Tworoger et al. 2004a). In combination with in vitro results (Lotta et al. 1995; Dawling et al. 2001), the current data suggest that the Met allele leads to a variant protein that is less active at metabolizing hydroxyestrogens (catechol estrogens) to methox-

estrogens (*O*-methylated catechols). COMT activity may be important in fat regulation because 2-methylestradiol (less active metabolite of 2-hydroxyestradiol) inhibits preadipocyte proliferation and differentiation in vitro (Pico et al. 1998; Anderson et al. 2001).

Epistasis between CYP19 and COMT

Exercisers who had the COMT Val/Val genotype and had at least 1 copy of the CYP19 11r allele had significantly greater percentage and total fat loss and a larger reduction in BMI than exercisers without this combination of genotype/allele (Tworoger et al. 2004b). This suggests that having multiple “positive” genotypes can act synergistically and that future studies should consider multiple genes in a pathway.

Nutrigenetics and (or) actigenetics

Peroxisome proliferator activated receptor γ_2 (PPAR γ_2)

The PPARs are ligand-dependent nuclear transcription factors. The γ_2 isoform is primarily expressed in adipose tissue, where it modulates the expression of target genes involved in adipocyte differentiation. The most widely studied SNP in this gene is a Pro to Ala substitution at codon 12 of PPAR γ_2 -specific exon B. Studies have demonstrated that the Ala variant is associated with reduced transcriptional activity (Deeb et al. 1998; Masugi et al. 2000), as well as reduced binding affinity to the cognate promoter element (Deeb et al. 1998).

In a recently completed study comparing extreme tails in the distribution of weight loss among highly compliant obese women undergoing strict dietary intervention (Optifast 900, Novartis), the PPAR γ_2 Ala¹² allele was shown to be significantly more frequent in diet-resistant individuals even after correction for baseline mass and BMI (Adamo et al. 2007). Although in disagreement with the findings of Lindi et al. (2001), the association between the Ala allele and resistance to diet-induced weight loss corroborates the findings of Nicklas and colleagues, who found that postmenopausal women carrying the Ala allele experienced a reduction in the amount of resting energy derived from fat after a 6-month hypocaloric diet (Nicklas et al. 2001). Furthermore, the Ala allele was found to be the best predictor of weight regain in this weight loss population, supporting the fact that reduced fat oxidation is predictive of long-term weight gain and regain (Nicklas et al. 2001).

It is interesting to note that diet and exercise have opposing effects on weight loss in Ala carriers. Carriers appear to be more resistant to diet-induced weight loss but show enhanced weight loss brought on by a standard exercise training intervention (Ostergard et al. 2005). In response to an exercise program, offspring of T2D patients carrying the Ala¹² polymorphism had a more pronounced weight loss compared with carriers of the Pro allele, suggesting that the PPAR γ genotype effect is dependent on the intervention used to bring about weight loss (Ostergard et al. 2005).

Adrenergic receptors

The adrenergic system plays a key role in regulating energy balance through stimulating both thermogenesis and lipid metabolism in adipose tissue. Knockout mouse studies

have conclusively shown that the beta-adrenergic receptors are necessary for diet-induced thermogenesis and that this efferent pathway plays a critical role in the body's defense against diet-induced obesity (Bachman et al. 2002). Although variants in the adrenergic receptor genes have been studied extensively for their association with body composition, fewer studies have looked at them in the context of response to treatment intervention. The β_3 -adrenergic receptor (ADR β_3), located mainly in adipose tissue, mediates lipolysis in response to catecholamines (Schiffelers et al. 2001). The Trp⁶⁴Arg ADR β_3 gene polymorphism alters the conformation of the first intracellular loop and the movement of the receptor to the cell surface (Walston et al. 1995; Clement et al. 1995), resulting in decreased receptor sensitivity (Hoffstedt et al. 1999). This SNP reduces thermogenesis in brown adipocytes and has been linked to lower lipolytic activity and lipid accumulation in white adipocytes (Arner and Hoffstedt 1999; Umekawa et al. 1999). Obese Japanese women who carried this particular SNP lost less weight than their Trp⁶⁴Trp counterparts (Yoshida et al. 1995) during a combined low-calorie diet and exercise intervention. Similarly, healthy perimenopausal (Shiwaku et al. 2003) women as well as women with type 2 diabetes (Sakane et al. 1997) who carried the Arg⁶⁴ allele were shown to have smaller decreases in body mass and waist-to-hip ratio after a 12-week weight-loss program (low calorie diet and exercise regime) compared with noncarriers, even though food intake, exercise, and serum thyroid hormone levels were similar in both groups. These studies reported that carriers of the Arg allele had a lower metabolic rate and hypothesized that their relative resistance to weight loss might be due to this unfortunate circumstance. On the other hand, others have not confirmed this relation with weight loss specifically (Fumeron et al. 1996; Tchernof et al. 2000; Kim et al. 2003) but have reported that carriers of the Arg⁶⁴ variant have an impaired capacity to lose visceral fat in response to a 3-month weight reduction period (Tchernof et al. 2000; Kim et al. 2003), in keeping with the lower ADR β_3 -induced lipolysis noted in Arg⁶⁴ carriers (Umekawa et al. 1999).

The relation between the β_2 -adrenergic receptor (ADR β_2) variants (Arg¹⁶Gly and Gln²⁷Glu) and successful weight loss was studied in overweight men undergoing a 24-month weight loss program consisting of a low-calorie diet (1600 kcal/d) and daily aerobic exercise training (>1 h/d). Individuals were categorized as weight loss resistant (failed to lose weight during intervention), maintenance of weight loss ($\geq 10\%$ reduction in weight at 6 months and maintenance for an additional 18 months), rebound weight gain (defined as significant weight loss at 6 months but subsequent regain during the following 18 months), and finally slow weight loss (no weight loss at 6 months but success by 24 months; Masuo et al. 2005b). The Gly¹⁶ variant was found to be significantly more frequent in the weight loss resistant, rebound weight gain, and slow weight loss groups than the weight loss maintenance group. The weight loss resistant and slow weight loss groups had higher frequencies of the Glu²⁷ allele compared with a combined group including weight loss maintenance and rebound weight gain (Masuo et al. 2005b). While there was a mean loss in fat mass in Glu²⁷ carriers from entry to 6 and 24 months it was significantly lower than that seen in the Gln homozygotes.

Since exercise may also counterbalance a genetic predisposition to obesity, a Spanish group tested the hypothesis of a potential different metabolic response among ADR β_2 Gln²⁷Gln versus Glu²⁷Glu obese women tested for peak oxygen consumption on a treadmill (Macho-Azcarate et al. 2003). In this study, 10 obese women with the Gln²⁷Gln genotype were compared with 9 matched obese women bearing the Glu²⁷Glu genotype. There was a significantly lower fat oxidation in the Glu²⁷Glu obese women during the recovery than in Gln²⁷Gln obese individuals. These data suggest that exercise would not be equally beneficial for the 2 ADR β_2 polymorphism homozygous groups, since both lipolysis and fat oxidation promoted by a peak oxygen consumption test appeared to be blunted in the obese group carrying both Glu alleles. Therefore this ADR β_2 SNP not only modifies the response to dietary intervention but may also alter the response to exercise as a weight-lowering strategy (Macho-Azcarate et al. 2002).

The Quebec overfeeding study, which involved a group of 12 pairs of male monozygotic twins who ate a 4.2 MJ/d energy surplus, 6 d a week for over 100 days (Ukkola et al. 2003), found the β_2 Gln²⁷Glu SNP to be associated with differing gains in body mass. In response to the overfeeding paradigm the Gln²⁷Gln genotype showed the strongest association with the gains in body mass and subcutaneous fat (Ukkola et al. 2001b), accounting for about 7%. However, a study performed in Japan found that over a 5-year period, nonobese male carriers of the Glu²⁷ allele actually saw a greater increase in BMI, waist-to-hip ratio, and total fat mass (Masuo et al. 2005a) than Gln²⁷ homozygotes. While this was not an "overfeeding" paradigm but, rather, a longitudinal observational study, the Gln²⁷Gln genotype was related to lower weight gain over time. Hence these findings are inconsistent with those reported by Ukkola et al. (2001b) and Masuo et al. (2005a, 2005b).

The Gly¹⁶Arg and Gln²⁷Glu are in strong linkage disequilibrium. Functional studies have shown that these amino-terminus SNPs alter cellular trafficking of the receptor protein, resulting in variation in agonist-promoted receptor downregulation (Green et al. 1994). Thus, if Glu carriers are more resistant to downregulation, and β receptors normally stimulate lipolysis, the finding that Gln/Gln individuals are more prone to weight gain makes theoretical sense but does not explain why carriers of the Glu allele were found to be more resistant to weight-loss intervention (Masuo et al. 2005b). Although the Gln²⁷Glu specific results appear conflicting, genetic variation at the ADR β_2 locus could be 1 of the factors responsible for interindividual response to positive or negative energy balance

Epistasis between UCP1 and ADR β_3

Two groups have examined the possible synergistic effect of the A-3826G UCP1 and the Trp⁶⁴Arg ADR β_3 variants on body mass changes. Kogure et al. (1998) investigated these SNPs in relation to response to a 3-month combined low-calorie diet and exercise-weight loss treatment in obese Japanese women. Obese women with the UCP1 GG homozygote genotype lost less weight than A carriers, but the weight loss was even less pronounced in those with both G alleles in UCP1 and the Trp⁶⁴Arg polymorphism in the ADR β_3 gene. Those carrying this combination lost less

weight than either those with the $ADR\beta_3$ gene polymorphism alone (including Arg homo or heterozygotes) or UCPI GG homozygotes alone. Similarly, Fogelholm et al. (1998) examined the synergist effect of this UCPI SNP and the previously reported $ADR\beta_3$ variant on body mass changes in obese, clinically healthy, premenopausal women. Subjects with both mutations had a lower weight reduction during the 12-week very low calorie diet than the controls. During the 40-week maintenance phase, weight in subjects with both mutations increased significantly but remained unchanged in the others. In summary these studies indicate that the effects of the GG genotype of the UCPI SNP, in combination with the ^{64}Arg allele of $ADR\beta_3$, are additive and result in poorer weight loss response to intervention.

Pharmacogenetics

LEPR

A second LEPR polymorphism found to be associated with a weight loss phenotype is the 3'UTR pentanucleotide CTTTA insertion/deletion (I/D). The STOP-NIDDM study, which was a longitudinal, double-blind, placebo-controlled trial randomly assigned individuals from 8 countries, the majority of whom were overweight or obese, to treatment with placebo or acarbose to improve glucose homeostasis (Chiasson et al. 1998). All participants were also provided with counseling on weight-reducing or weight-maintaining diet and advised to adopt a regular exercise routine. Over the 3-year follow-up, carriers of the I allele in both the acarbose and placebo groups improved their body composition to a greater extent than D/D homozygotes (Zacharova et al. 2005); however, carriers in the acarbose group saw more significant improvement in weight and BMI. Assuming both genotypes were equally likely to have followed the dietary and exercise advice, the association of this polymorphism with greater weight loss in the long-term suggests that it may modulate the response to diet and (or) exercise. The mechanism through which the LEPR SNPs might act to modify weight loss response is unknown.

Serotonin receptor

As previously discussed in the nutrigenetics section, the serotonin pathway has a role to play in control of body weight. A second polymorphism in the 5-HT_{2C} subtype specifically in the promoter region (-759C/T), associated with obesity and weight gain in response to antipsychotic (neuroleptic) drugs (Reynolds et al. 2002), was studied in obese women participating in a randomized trial of psychological treatments for weight loss. Among these women, heterozygotes (C/T) lost less weight during the trial than did homozygotes (CC or TT) and weighed more 6 and 12 months later (Pooley et al. 2004), suggesting that this polymorphism may be a risk factor for obesity and, through heterosis (see Appendix), influences weight loss. The occurrence of heterosis for the C-759T polymorphism would imply that there must be sex differences in some aspects of appetite and weight regulation, since 5-HT_{2C} is located on chromosome X (Milatovich et al. 1992).

Phenylethanolamine N-methyltransferase (PNMT)

The PNMT gene product mediates the conversion of nor-

epinephrine(NE) to epinephrine and is a rate-limiting enzyme in the catecholamine biosynthesis pathway. As epinephrine is involved in regulating lipolysis, this enzyme may participate in body mass regulation. In humans, the agent sibutramine, whose primary and secondary metabolites are pharmacologically active, is thought to induce the natural processes leading to enhancement of satiety and thermogenesis by inhibiting serotonin (5-HT) and noradrenaline (NE) reuptake (Lean 1997). The putative role of epinephrine in sibutramine-related weight loss justifies PNMT as a candidate gene in pharmacogenetic response. Thus, the response to the weight loss agent sibutramine was explored in obese women carrying a G-148A variant in the promoter region of the PNMT gene. In the population of women participating there was a significant genotype-dependent variation in the effective weight loss. Compared with heterozygotes (G/A), the presence of the homozygote genotype of the PNMT variant (A/A or G/G) was associated with a statistically significant weight loss during the first 3 months of treatment, which remained following 6 months of sibutramine treatment (Peters et al. 2003), suggesting molecular heterosis.

G-protein β_3 subunit gene (GN β_3)

As mentioned earlier, the weight loss agent sibutramine is a centrally acting NE and serotonin reuptake inhibitor (Lean 1997; Wirth and Krause 2001). Since these neurotransmitters (NE and serotonin) activate G protein-coupled receptors, variants in this family of genes are potential candidate genes for pharmacogenetics exploration. A polymorphism in the GN β_3 subunit, C825T, located in exon 10 is associated with alternative splicing of the gene resulting in expression of a truncated yet functionally active variant form of the protein (Siffert et al. 1998). The association between the GN β_3 C825T variant and weight loss outcome was tested in obese patients enrolled in a randomized, placebo-controlled clinical trial (Hauner et al. 2003). Depending on randomization, patients underwent a 54-week structured weight loss program with or without 15 mg of sibutramine. Carriers of the T allele in the placebo group experienced a significantly greater weight loss than CC homozygotes. However, it was reported that in the sibutramine-treated group, individuals with the CC genotype benefited to a greater extent from the adjunct pharmacological therapy. Thus Hauner et al. conclude that the C825T polymorphism identifies obese individuals who will benefit most from sibutramine treatment (Hauner et al. 2003). This finding was surprising considering that the "T" allele is associated with enhanced intracellular signaling through activation of G protein-coupled receptors, including the G protein β_3 subunit. Generally, pharmacological studies have illustrated that carriers of the 825T allele show greater response to drug treatment aimed at G protein-coupled receptors (Baumgart et al. 1999; Zill et al. 2000). The reasons for this discrepancy are not known, but it has been suggested that those with the CC genotype may defend their body weight more aggressively and thus require adjunct treatment to lose weight. While additional studies are certainly warranted to confirm these results, this variant has potential to identify those individuals who will respond to nonpharmacological treatment and those who need an extra push.

Norepinephrine transporter protein 1 (NET1) and glutamate receptor, ionotropic *N*-methyl-D-aspartate subunit1 (GRIN1)

The norepinephrine transporter (NET) mediates reuptake of released catecholamines, thus playing a role in the limitation of signaling strength in the central and peripheral nervous systems. This protein is the pharmacological target of a highly selective neuronal NE reuptake inhibitor GW320659, and serotonin, norepinephrine, and dopamine reuptake inhibitors have been shown to decrease food intake and induce weight loss in obese patients (Lean 1997; Glazer 2001). A recent 24 week randomized, double-blind, placebo-controlled, parallel group study evaluated GW320659 as a treatment for obesity (GlaxoSmithKline study OBS20001) (Spraggs et al. 2005). This study found that common polymorphisms in the pharmacological target NET1 and in GRIN1, another candidate gene in the pathway hypothesized to be involved in the neuronal pathway of appetite suppression, correlated with weight loss response (Spraggs et al. 2005). Recursive partitioning analysis identified 3 genetic markers (2 in NET1 T66C and G1287A and 1 in GRIN1 G-38A) that have a substantial effect on weight loss response to the reuptake inhibitor in obese subjects. Other than dose level, these 3 genetic polymorphisms were the strongest determinants of GW320659 response. The functional significance of the NET1 and the GRIN1 polymorphisms, which do not result in amino acid substitutions, has not yet been established. The NET1 SNPs may be in linkage disequilibrium with functional SNPs not explored in this study, and the GRIN1 A-38G SNP, located in the 5'-flanking region of the gene, might influence receptor expression and *N*-methyl-D-aspartate neurotransmission, resulting in enhanced weight loss.

Conclusion

The significance of GEIs in the realm of exercise and nutrition is by no means a new concept. As a matter of fact, discussion of such ideas can be traced back to the writings of Hippocrates, dated as early as 400 BC. Since then we have gained considerable insight regarding the contribution of genetic make-up to almost every aspect of human health, both in function and dysfunction. However, researchers are only beginning to correlate DNA variants with individual responses to medical treatments, identify particular subgroups of patients, and develop treatment interventions customized for those populations. While the pharmaceutical field has made considerable in-roads vis-à-vis the exploration of genetic contributors to treatment response, the complexity of nutrient interactions, variation in dietary practices, and the infinite combinations and (or) permutations of exercise regimes, genotype-specific diet, and exercise, recommendations remain a somewhat futuristic prospect.

In spite of available information on both genetic and environmental contributors to response to treatment intervention, there are relatively few examples of robust, replicated gene-environment interactions in the literature. The main reason is that many individual studies have been designed to examine the main effects of the intervention itself on weight loss and do not have adequate power to examine interactions with genetic variants and consequently may lead to high lev-

els of false-positive findings. Unfortunately, the cost associated with performing large-scale, well-controlled diet or exercise intervention trials frequently prohibits the concomitant collection and analyses of sample sizes large enough to identify strong gene-environment interactions. Thus the results summarized in this review are from small studies, showing moderate to weak association, and until replicated with consistent results must be interpreted with caution.

Nevertheless several examples have been provided as to how lifestyle intervention and genetic factors interact to produce differing body composition response (see Table 1). For instance, nutrigenetics is likely an important contributor to interindividual response to dietary intervention, as illustrated by common variants in LEP, LEPR, ADR β_3 , UCP1, GRL, Adipsin, PPAR γ_2 , ACSL5, APOA5, and PLIN modifying treatment-related weight loss. The data previously described indicate that actigenetics is also a key factor in body fat regulation, and, in particular, polymorphisms in ADR β_2 , PPAR γ_2 , CYP19, and COMT may modify the effect of moderate-intensity exercise on fat loss in women. The pharmacogenetic data reinforce the view that variations in epinephrine metabolism may contribute significantly to the efficacy of sibutramine and other related weight loss agents, and such variations may be linked to GN β_3 , PNMT, NET1, and GRIN1 genotype. Furthermore, the observation that heterozygosity at the 5-HT $_{2C}$ - 759C/T locus may impair the ability of obese women to lose a clinically meaningful amount of weight over a 6-12 month period (Pooley et al. 2004) indicates the potential value of pharmacogenetic testing for 5-HT $_{2C}$ polymorphisms when evaluating antiobesity drugs that act directly or indirectly upon the receptor.

The aforementioned studies had significant design limitations. The credibility of underpowered genetic association studies has been questioned, and it is possible that the results may not be consistent upon replication (Lohmueller et al. 2003). A meta-analysis of 379 studies exploring 36 genetic associations with diseases or phenotypes found considerable inconsistency in results, the effect identified in the initial study being stronger than in subsequent studies (Ioannidis et al. 2001). Few studies discussed have explored epistatic interactions that have an important role in phenotypic variability and are believed to be of paramount importance in the pathogenesis of most common human diseases. The effect at 1 locus can increase (synergistic epistasis) or decrease (antagonistic epistasis) the effect at another locus. However, the genetic dissection of such phenomena remains challenging. Improved understanding of the relation between the polymorphisms independently involved in a given complex of disorders is critical for improving the ability of genotypic information to predict the phenotype. Thus, if several polymorphisms in a gene contribute to altered function, measuring a subset of known variants will result in misclassification and so will increase the sample size that is required to detect interactions (Deitz et al. 2004). To complicate matters, if the functional gene variant is unknown and researchers are trying to detect genetic association through linkage disequilibrium (see Appendix), there will likely be substantial misclassification of the genetic variable, leading to dilution of the relative risk for the interaction (Hunter 2005). Furthermore, another phenomenon, known as epigenetics, has a significant impact on genetic

Table 1. Summary of studies examining nutrigenetic, actigenetic, or pharmacogenetic effects on weight loss response.

Gene/polymorphism	Population	Intervention	Conclusions	Loci
Nutrigenetics				
Leptin (LEP) C-2549A promoter	N = 79 OB women	Low-calorie diet (25% reduction in energy intake)	The C variant of the LEP promoter SNP was associated with a greater change in BMI in response to a weight loss intervention (-1.85 vs. -1.2 kg/m ² ; <i>p</i> = 0.05) (Mammes et al. 1998).	7q31.3
Leptin receptor (LEPR) Ser ³⁴³ Ser (T/C)	N = 116 OW French women	Low-calorie diet (25% reduction in energy intake)	Overweight women carrying the C allele in exon 9 polymorphism lost more weight in response to a low-calorie diet than noncarriers (Mammes et al. 2001)	1p31
Serotonin receptor 2C (5HT _{2C}) Cys ⁷² Ser	N = 148 teenage girls (57 showing weight loss vs. 91 with weight maintenance)	Weight loss over time in teenage years	The Ser substitution was found to be higher in teenage girls reporting weight loss vs. not reporting weight loss (Westberg et al. 2002).	Xq24
Uncoupling proteins (UCP1) A-3826G 5'UTR	N = 163 OW individuals	10-week low-calorie diet	G/G genotype was associated with resistance to low-calorie diet (Fumeron et al. 1996; Kogure et al. 1998).	4q31
APOA5 T-1131C 5'UTR	N = 606 hyperlipemic OW men	Short-term, monitored fat restriction diet	Individuals who carried at least 1 C allele lost significantly more weight than T homozygotes (13.4% vs. 0.4%) (Aberle et al. 2005).	11q23
Perilipin (PLIN) G11482A intronic	N = 48 OB patients	2-week very low energy diet; 603 kcal/d followed by 1200 kcal/d for 1 year.	The GG genotype was found to be predictive of weight loss response to dietary restriction (-6.6 kg; 0.37 kg and -0.09 kg for G/A and A/A, respectively) (Corella et al. 2005).	15q26
Adipsin Hinc II RFLP	N = 12 twin pairs	100 days of overfeeding	Absence of HincII RFLP induced greater weight gain in response to caloric intake (9.3 vs. 7.3 kg; <i>p</i> < 0.05) (Ukkola et al. 2001b).	19p13.3
Glucocorticoid receptor (GRL) C/G intron 2	N = 120 OB individuals. N = 12 twin pairs	6 week very low calorie diet + 1 year follow-up. 100 d of over-feeding	G/G genotype predictor of successful weight maintenance (Vogels et al. 2005). C/C carriers experienced greater increases in body mass (16.3% vs. 11.2%; <i>p</i> = 0.01) and abdominal visceral fat (103% vs. 58%; <i>p</i> = 0.04) than heterozygous carriers (Ukkola et al. 2001b)	5q31
Acyl CoA synthetase 5 (ACSL5) rs2419621C/T 5'UTR	N = 141 OB women	Caloric restriction: Optifast meal replacement	The T variant was found to be associated with greater response to dietary intervention in obese women (odds ratio = 3.45, confidence interval 1.61–7.69) (Adamo et al. 2007).	10q25.1–2
Actigenetics				
β ₂ -adrenergic receptor (ADRB ₂) Gln ²⁷ Glu	N = 8 OB Glu ²⁷ Glu female carriers, N = 7 OB Gln ²⁷ Gln female carriers	Exercise intervention	β ₂ polymorphism was found to alter the response to exercise as a weight-lowering strategy (Macho-Azcarate et al. 2003)	5q32–q34
Cytochrome P450 (CYP19) TTTA _n intronic	N = 173 postmenopausal OW/OB women	1 year exercise intervention: 225 min/week of moderate intensity exercise	Carrying 2 intron 4 repeat alleles vs. none was associated with greater change in body composition in response to the intervention (-1.0 vs. 0.0 kg/m ² ; <i>p</i> = 0.007) (Tworoger et al. 2004b).	15q21.1
Catechol-O-methyltransferase (COMT) Val ^{108/158} Met	N = 173 postmenopausal OW/OB women	1 year exercise intervention: 225 min/week of moderate intensity exercise	Met/Met substitution resulted in less change in body composition in response to an exercise training program (-0.7% vs. -1.9%; <i>p</i> = 0.05) (Tworoger et al. 2004b).	22q11.2
Nutrigenetics and (or) actigenetics				
PPAR _γ 2 Pro ¹² Ala exonB	N = 70 OW/OB postmenopausal women. N = 141 OB women. N = 29 offspring of type 2 diabetics	6-month hypocaloric diet. Caloric restriction: Optifast meal replacement. 10 week standardized exercise training program	Follow-up weight regain greater in Ala carriers (5.4 vs. 2.8 kg, <i>p</i> < 0.01) (Nicklas et al. 2001). The Ala allele was associated with resistance to diet-induced weight loss in obese women (OR = 3.48, CI = 1.41–8.56) (Adamo et al. 2007). Ala carriers displayed greater training-induced weight change (Ostergard et al. 2005)	3p25

Table 1 (continued).

Gene/polymorphism	Population	Intervention	Conclusions	Loci
β_3 -adrenergic receptor (ADRB ₃) Trp ⁶⁴ Arg	N = 88 OB Japanese women. N = 61 OB Japanese women with type 2 diabetes. N = 76 perimenopausal women (BMI ≥ 21). N = 24 OB women	3 month diet and exercise intervention. 12-week diet and exercise intervention. 3 month diet and exercise intervention. Medically supervised 1200 kcal/d diet	The Arg ⁶⁴ allele predicted difficulty in losing weight (5.2 vs. 5.5 vs. 8.3 kg for Arg/Arg, Arg/Trp, Trp/Trp, respectively) (Yoshida et al. 1995). Carriers of the Arg ⁶⁴ showed resistance to weight loss compared with noncarriers (5.8 vs. 8.3%) (Sakane et al. 1997). Carriers of Arg allele did not show significant change in body composition variables compared with Trp homozygotes (Shiwaku et al. 2003). Carriers of Arg allele lost 43% less visceral adipose than noncarriers (Tchernof et al. 2000)	5q32-q34
β_2 -adrenergic receptor (ADRB ₂) Gln ²⁷ Glu Arg ¹⁶ Gly	N = 154 OB Japanese men. N = 12 twin pairs	24-month low calorie diet (1600 kcal/d) and 1 h daily aerobic exercise. 100 d of over-feeding	Glu ²⁷ was associated with resistance to weight loss and slow weight loss. Gly ¹⁶ was associated with resistance to weight loss and rebound weight gain (Masuo et al. 2005a). Carriers of Gln ²⁷ Gln SNP experienced a greater weight gain response (17% vs. 11%, $p < 0.001$) (Ukkola et al. 2001b).	5q32-q34
Uncoupling proteins UCPI A-3826G 5'UTR	N = 113 OB Japanese women	3-month low cal diet + exercise intervention	G/G carriers were more resistant to weight change in response to alterations in energy intake (-4.3 (G/G) vs. -7.7 (G/A) vs. -7.4 kg (A/A), $p < 0.001$) (Fumeron et al. 1996; Kogure et al. 1998).	4q31
Pharmacogenetics				
Leptin receptor (LEPR) CTTTA ins/del	N = 770 OW/OB participants from STOP-NIDDM study	Acarbose vs. placebo treatment	In the total population, carriers of Ins allele in 3'UTR lost significantly more weight than Del/Del (0.4 vs. 0.2 kg, $p = 0.016$) and had a greater change in BMI (-0.4 vs. -0.1 kg/m ² , $p = 0.009$) (Zacharova et al. 2005). The change in BMI was greater in the I carriers in the acarbose group vs. placebo (-0.6 vs. -0.2 kg/m ²)	1p31
Serotonin receptor 2C (5HT2C) C-759T promoter	N = 95 OB women	Psychological treatment for weight loss	Heterozygote C/T carriers lost less weight than CC or TT homozygotes (6.8 vs. 9.7 kg; $p = 0.047$) (Pooley et al. 2004).	Xq24
Phenylethanolamine N-methyltransferase (PNMT) G-148A promoter	N = 149 OB women	Sibutramine treatment	A/A and G/G genotypes were highly predictive of significant weight loss during a multifactorial weight loss intervention (3 mo: 3.4% vs. 1.4%, $p = 0.003$; 6mo: 8.2% vs. 4.8%, $p = 0.018$) (Peters et al. 2003).	17q21-q22
G protein β_3 subunit gene (GN β_3) C825T exon 10	N = 111 OB subjects	54 weeks sibutramine and adjunct lifestyle therapy vs. placebo and adjunct lifestyle therapy	CC genotype carriers were more responsive to sibutramine treatment (Hauner et al. 2003).	12p13
Norepinephrine transporter (NET1) T66C G1287A	N = 191 OB subjects	Treatment with NE/dopamine reuptake inhibitor (GW320659)	The CC genotype and AA genotypes were associated with increased weight loss following treatment (-7.8 vs. -2.5, $p = 0.0045$) (Spraggs et al. 2005).	16q12.2
NMDA receptor (GRIN1) A-38G 5'UTR	N = 191 OB subjects	Treatment with NE and dopamine reuptake inhibitor (GW320659)	The AA genotype was associated with increased weight loss following treatment (Spraggs et al. 2005).	9q34.3

Note: BMI, body mass index; NE, norepinephrine; OB, obese; SNP, single nucleotide polymorphism; OW, overweight. To be consistent with the text, relevant overfeeding data are also included in the table.

expression. This class of potentially heritable change in DNA is not associated with alterations in the primary nucleotide sequence or copy number but, rather, is modulated by 2 major mechanisms: methylations of cytosine–guanine dinucleotides and covalent modifications of DNA-bound histones, notably acetylations and methylations (Martin 2005). Cytosine methylations at regions of gene promoters rich in CpG islands are generally associated with the silencing of genes, whereas histone acetylations are generally associated with the activation of genes. Global and locus-specific differences in DNA methylation and histone acetylation have been reported in identical twins of various ages showing that whereas young identical twin pairs are essentially indistinguishable in their epigenetic markings, older identical twin pairs show substantial variations (Fraga et al. 2005). The reported epigenetic shifts associated with aging could have arisen through endogenous, stochastic epigenetic events in the cell, independent of environmental perturbations, but could also have resulted from such environmental perturbations. Epigenetic modifications of energy balance gene structure through nutritional and physiological stress provide mechanisms for inducing obesity that are independent of new mutations to the genome. It has been suggested that methionine supplementation can induce hypermethylation of DNA in specific genomic regions (Waterland 2006). So far, this mechanism has barely been studied in the case of obesity.

As genetic testing becomes more economical and we gain a deeper understanding of knowledge generated from the Human Genome Project, more comprehensive gene variant studies will be made possible. The development and utilization of highly parallel genome-wide methodologies for genotyping, epigenetic profiling, mapping of DNA binding sites, and sequencing will inevitably revolutionize scientific discovery (Fan et al. 2006). These high-throughput assays are sensitive, accurate, and rapid and should enable whole-genome association studies to identify multiple polymorphisms that each weakly predicts risk of disease or response to treatment. Copy number variations (CNV) also have considerable potential to influence gene expression, phenotypic variation, and adaptation by disrupting genes and altering gene dosage (Buckland 2003; McCarroll et al. 2006; Nguyen et al. 2006). CNV assessment should become standard practice in the design of studies exploring the genetic basis of phenotypic variation, including susceptibility to disease and response to treatment (Redon et al. 2006). The combination of all these potential risk variants into a risk score will more effectively predict disease and (or) response. In this way, genetic-based treatment recommendations creep ever closer.

We may discover that some individuals require more stringent and stronger treatment intervention than others according to their genetic predisposition. This is, however, a double-edged sword, as knowing that one is less likely to respond to a treatment intervention may result in feelings of futility, and individuals may surrender, believing they are bound by genetics and doomed to failure. Further insight regarding the interaction between genetics and environmental factors will ultimately lead to the discovery of pathways involved in disease pathogenesis and response to treatment interventions. Such knowledge will have a profound impact on

the way disorders are diagnosed, treated, and prevented and will bring about revolutionary changes in clinical and public health practice.

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Appendix A. Definitions.

SNP: single nucleotide polymorphisms. These are DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered. These variations account for about 90% of polymorphisms and represent a natural genetic variability at high density in the human genome.

5'UTR: 5' untranslated region. It is the region at the 5' end (upstream) of a mature gene transcript (preceding the initiation codon) that is not translated into a protein. This region is known to contain regulator regions that control or guide gene transcription.

3'UTR: 3' untranslated region. It is the region at the 3'

end (downstream) of a mature gene transcript that is not translated into a protein. The 3' UTR may contain sequences that regulate translation efficiency, mRNA stability, and polyadenylation signals.

Epigenetic: something that affects a cell, organ, or individual without directly affecting its DNA. An epigenetic change may indirectly influence the expression of the genome without a change in the sequence of the DNA through DNA methylation or chromatin remodeling, for example.

Epistasis: interaction between nonallelic genes, such that one gene masks or interferes with the effect of the other gene.

Exon: coding region of a gene

Haplotype: A set of closely linked genetic markers present on a single chromosome that tend to be inherited together (not easily separable by recombination). Some haplotypes may be in linkage disequilibrium.

Intron: noncoding region of a gene

Linkage disequilibrium (LD): linkage disequilibrium is the condition in which the haplotype frequencies in a population deviate from the values they would have if the alleles at each locus were combined at random.

Molecular heterosis: when individuals heterozygous for a specific genetic polymorphism show a significantly greater effect (positive heterosis) or lesser effect (negative heterosis) for a quantitative or dichotomous trait than subjects homozygous for either allele.

Recursive partitioning: the division of sets into groups of higher and lower response as a function of their descriptors.

QTL: quantitative trait loci. This is a region of DNA that is associated with a particular phenotypic trait like skin colour, weight, lipid level, etc.