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REVIEW

The genetics of childhood obesity and interaction with dietary macronutrients

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Abstract The genes contributing to childhood obesity are categorized into three different types based on distinct genetic and phenotypic characteristics. These types of childhood obesity are represented by rare monogenic forms of syndromic or non-syndromic childhood obesity, and common polygenic childhood obesity. In some cases, genetic susceptibility to these forms of childhood obesity may result from different variations of the same gene. Although the prevalence for rare monogenic forms of childhood obesity has not increased in recent times, the prevalence of common childhood obesity has increased in the United States and developing countries throughout the world during the past few decades. A number of recent genome-wide association studies and mouse model studies have established the identification of susceptibility genes contributing to common childhood obesity. Accumulating evidence suggests that this type of childhood obesity represents a complex metabolic disease resulting from an interaction with environmental factors, including dietary macronutrients. The objective of this article is to provide a review on the origins, mechanisms, and health consequences of obesity susceptibility genes and interaction with dietary macronutrients that predispose to childhood obesity. It is proposed that increased knowledge of these obesity susceptibility genes and interaction with dietary macronutrients will provide valuable insight for individual, family, and community preventative lifestyle intervention, and eventually targeted nutritional and medicinal therapies.

Keywords Childhood obesity · Energy balance · Mouse model · Refined carbohydrates · Saturated fat

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Introduction

Childhood obesity is a major health problem in the United States and developing countries throughout the world. The most recent National Health and Nutrition Examination Surveys (NHANES) indicate that childhood obesity in the United States has approximately doubled during the past three decades and adolescent obesity has more than tripled during the same period (Ogden et al. 2010, 2012). These studies also report that although the prevalence of childhood and adolescent obesity has not changed since 2007–2008, the prevalence of obesity among 2–5-year-olds (12.1 %), 6–11-year-olds (18.0 %), and 12–19-year-olds (18.4 %) remains at the highest recorded levels since establishment of the NHANES (Ogden et al. 2002). However, it should be noted that some epidemiological studies indicate that the prevalence of childhood obesity is continuing to increase in certain sex, age, ethnic, and socioeconomic status groups within the United States and that the current childhood obesity epidemic will contribute

to an increase in the number of obese adults (Serdula et al. 1993; Wang et al. 2012). It was reported that ~80 % of overweight children between 10 and 15 years of age become obese adults by 25 years of age and that overweight children before 8 years of age usually result in more severe adult obesity (Whitaker et al. 1997). With respect to the global prevalence of childhood obesity, it was estimated that 43 million preschool children (6.7 %) were overweight or obese in 2010 and projected to reach ~60 million preschool children (9.1 %) in 2020 (de Onis et al. 2010). A graph showing the increasing percentage of overweight children in different countries with the highest known prevalence of childhood obesity is provided (Fig. 1).

The childhood obesity epidemic is also anticipated to culminate in a large number of weight-associated complications affecting the neurological, cardiovascular, endocrine, musculoskeletal, renal, gastrointestinal, and pulmonary systems in addition to psychosocial problems (Fig. 2). These medical complications will further burden an already fragile national healthcare system as children progress through adulthood (Yach et al. 2006). It is projected that these complications will ultimately decrease the life expectancy of people in the United States by 2–5 years for the first time in modern history (Olshansky et al. 2005). To address and hopefully lessen the impact of this major health problem, experts from diverse fields of study are attempting to understand the etiology of childhood obesity. It is well accepted that the timing of this epidemic parallels an increased availability of calorie-dense foods and a more sedentary lifestyle in what is referred to as an "obesogenic environment" (Chaput et al. 2011). However, the cause of this epidemic is obscured because not all individuals become overweight or obese while living in the same environment. Therefore, variability among individuals is suspected to result from heritability of obesity susceptibility genes that interact with known and unknown components in the obesogenic environment to promote positive energy balance responsible for weight gain (Wardle et al. 2008b; Hofker and Wijmenga 2010).

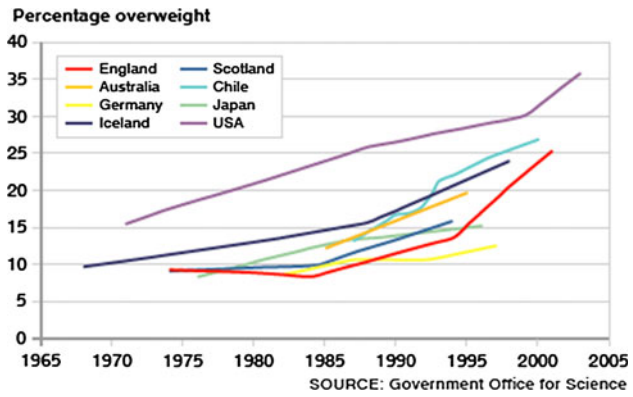

Fig. 1 The increasing percentage of overweight children in eight countries with the highest prevalence of childhood obesity

The objective of this article is to provide a review on the origins, mechanisms, and health consequences of obesity susceptibility genes and the interaction with dietary macronutrients that predispose to childhood obesity. It is proposed that increased knowledge of these obesity susceptibility genes and interaction with dietary macronutrients will provide valuable insight for individual, family, and community preventative lifestyle intervention and eventually targeted nutritional and medicinal therapies.

Definition of energy balance

The ultimate cause of weight gain is usually considered in terms of altered energy balance, the basic components of which include energy consumption, energy expenditure, and the storage of excess energy in the form of triacylglycerol within tissues, primarily adipose (Hill et al. 2012). For instance, when energy in the form of calories derived from food and drink exceeds energy expenditure involving the combination of resting metabolic rate, energy necessary for absorption and metabolism of dietary macronutrients, and energy expended during physical activity, a state of positive energy balance occurs characterized by the storage of this energy (~60 to 80 %) within adipose tissue. In contrast, when energy consumption is less than the energy expenditure, a state of negative energy balance occurs characterized by the mobilization of energy (~60 to 80 %) from adipose tissue. Therefore, any genetic or environmental factor that alters body weight must involve the basic components of energy balance over a period of time (Hill et al. 2003).

Heritability of body weight and interaction with environmental factors

It has been recognized for several decades that obesity is a heritable disorder. The Hereditary Abilities Study initiated in 1952 was a comprehensive study performed in the United States to investigate heritability of physical traits, including measures of adiposity (birth weight, body weight, and waist circumference) among monozygous and dizygous twins, which demonstrated that the greater part of variance for these traits was genetically determined (Clark 1956). These findings were consistent with other studies reported over 20 years later indicating a high heritability of body weight among monozygous and dizygous twins (Brook et al. 1975; Borjeson 1976; Feinleib et al. 1977). However, it became apparent that genetic susceptibility interacts with undefined environmental factors to increase adiposity and body weight, in what has formally become known as a "gene–environment interaction" and defined as

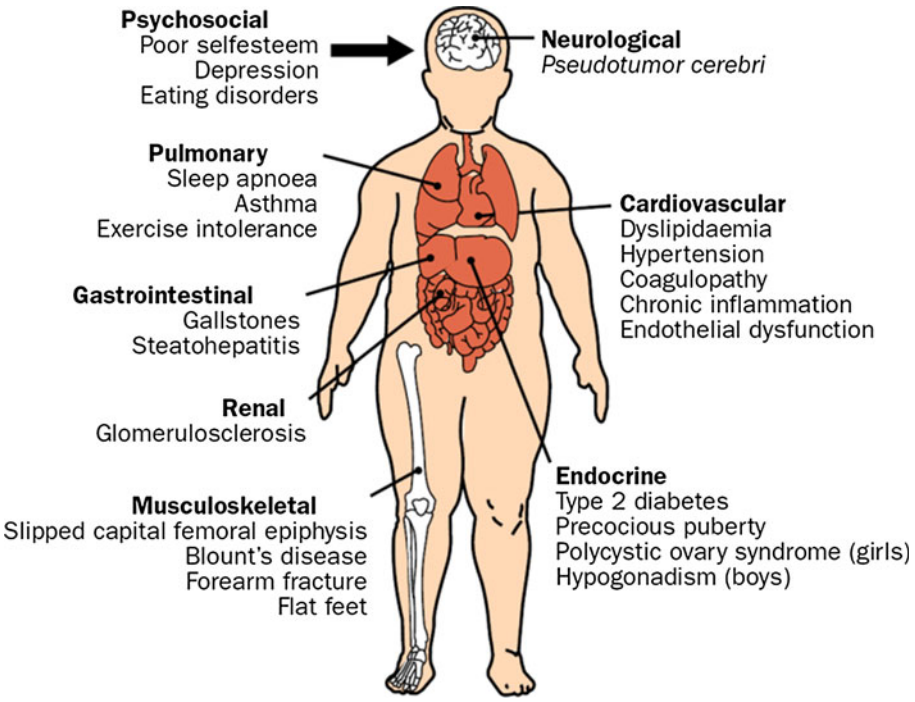

Fig. 2 The major complications associated with childhood obesity

"a response or adaptation to an environmental agent, a behavior, or a change in behavior conditional on the genotype of the individual" (Bouchard 2009). An early study clearly demonstrating a gene–environment interaction in relation to weight gain was performed using 12 monozygotic twins who consumed a 1,000 kcal/day surplus of calories for a period of 100 days while maintaining a sedentary lifestyle (Bouchard et al. 1990). The results from this study showed a significant within twin-pair resemblance in adaptation to the excess calories (3 times more variance in response between twin-pairs than within twin-pairs in relation to increased body weight) suggesting that genetic susceptibility influenced the amount of stored fat. A study designed to assess genetic and environmental influences using 114 monozygotic twins, 81 dizygotic twins, and 98 virtual twins (same age but unrelated siblings) indicated that genetic variation contributed ~65 % to heritability of body mass index (BMI) while undefined environmental factors contributed to the remaining balance (Segal and Allison 2002). The heritability of childhood obesity was more closely examined and confirmed in a study using 8,234 children, which demonstrated a fourfold increased risk of childhood obesity if one parent was obese and a 10-fold increased risk of childhood obesity if both parents were obese (Reilly et al. 2005). Another study using 672 twin pairs indicated that genetic variation contributed 84–88 % to heritability of body weight when measured at 5 months and 5 years of age (Dubois et al. 2007). Therefore, it has been estimated that obesity susceptibility genes contribute an estimated 40–70 % to variation in BMI within populations (Day and Loos 2011). It should also be emphasized that heritability estimates have been shown to increase from early childhood through adolescence due to genetic susceptibility genes interacting more strongly with environmental factors (Lajunen et al. 2009; Dubois et al. 2012).

Missing or hidden heritability of common diseases

The "common disease, common variant" hypothesis states that genetic risk for common diseases is due to alleles of high frequency (Pritchard 2001; Reich and Lander 2001). It was once believed that common variants of high frequency would explain common disease heritability, defined as the proportion of phenotypic variance in a population due to additive genetic factors. However, after identifying hundreds of different variants associated with common diseases, the variants in combination accounted for only a small proportion of the estimated disease heritability (Hindorff et al. 2009). For example, the estimated heritability for BMI within populations has been reported to be 40–70 %, yet only a few percent of the estimated heritability has been accounted for by the combined phenotypic effect size or penetrance of gene reference variants (Li et al. 2010; Speliotes et al. 2010). The identification of "missing heritability" is now an essential step for determining how allelic variants contribute to common diseases such as obesity and translating this genetic information into clinical practice (Maher 2008; McCarthy et al. 2008). The missing heritability of common diseases may be the result of differences in allelic architecture not detected using

genome-wide association studies (GWAS), in which case it may be more appropriately referred to as "hidden heritability" (Gibson 2010). Accumulating evidence now suggests that low-frequency alleles not detected by GWAS and also alleles with insufficient phenotypic effect size not detected by gene-linkage analysis represent "causal variants" responsible for hidden heritability of common diseases (Manolio et al. 2009). In other words, there is now evidence to suggest that partial linkage disequilibrium between reference variants and low-frequency causal variants with a minor allele frequency between 0.5 and 5.0 % and intermediate phenotypic effect sizes can fully account for hidden heritability of common diseases, where linkage disequilibrium is defined as a measure of the non-random association of alleles at two or more loci (Slatkin 2008). To date, several causal variants of intermediate effect size for common diseases have been found to exist in partial linkage disequilibrium ($r^2 < 0.5$) with reference variants (Zhu et al. 2012). This same study also provides evidence that the minor allele frequency for causal variants may range from $\sim$0.5 % (rare) to $\sim$5.0 % (low frequency), more than one causal variant may be in partial linkage disequilibrium with the reference variant, and that causal variants likely represent deleterious mutations that adversely affect encoded protein function and metabolism (Zhu et al. 2012).

Epigenetics and interaction with environmental factors

It should be noted that heritability of body weight and interaction with environmental factors may occur through a different mechanism. This mechanism is referred to as "epigenetics" and generally defined as the study of heritable changes which effect gene expression or function without modifying the DNA sequence (Bird 2007). Recent studies suggest that epigenetic adaptation through increased or decreased methylation of nucleotide bases (primarily cytosine) in addition to more generalized histone modification can alter the transcription of genes involved in regulating energy balance (Russo et al. 2010; Herrera et al. 2011). To date, the methylation status for a number of genes involved in metabolic or endocrine function has been identified that results from dietary changes during prenatal or early postnatal life and associated with childhood or adulthood adiposity (Tobi et al. 2009; Godfrey et al. 2011). However, it should be noted that the definitive role of epigenetic–environment interactions in relation to obesity remains controversial due to difficulties in discriminating the cause and effect for these DNA modifications (does epigenetic modification cause obesity or does obesity cause epigenetic modification) and the central importance of DNA sequence at particular loci (Martin et al. 2011; Youngson and Morris 2012). As a result, it is believed that meaningful clinical application of epigenetics in the prevention or treatment of obesity will remain a vision until further research is performed (Franks and Ling 2010).

Thrifty gene hypothesis

A presentation of gene–environment interactions should include the concept of "thrifty genes" first introduced and later modified by the American geneticist Neel (1962, 1999). In brief, the thrifty gene hypothesis states that certain groups of people with hunter-gatherer evolutionary lifestyles may have experienced repeated periods of feast and famine, which through adaptation, resulted in the natural selection of thrifty genes, thereby eventually predisposing these groups to chronic diseases of civilization such as obesity and diabetes. The thrifty genes encode proteins directly or indirectly involved in maintaining energy balance, such as the conversion of food calories into fat when food supplies are plentiful (feasting period). These genes were proposed to contain certain variants that were believed to enhance this conversion. The increased storage of fat was proposed to be used as an energy source when food calories become limited (fasting period). A key feature of the thrifty gene hypothesis is that selective advantage of these gene variants become a disadvantage (susceptibility to obesity and diabetes) for individuals living in an obesogenic environment. It must be emphasized that this particular feature suggests that thrifty genes represent gene variants present at a frequency greater than 1 % in a population due to natural selection, in contrast to gene variants present at lower frequency and responsible for rare monogenic forms of syndromic and non-syndromic obesity (Kagawa et al. 2002).

The thrifty gene hypothesis is consistent with higher frequency gene variants interacting with environmental factors to promote weight gain among certain populations. The most studied and documented population referenced in relation to thrifty genes includes the Pima Indians of Arizona. This population at one time had a subsistence lifestyle but is now predisposed to weight gain and diabetes as a result of a modern obesogenic lifestyle (Knowler et al. 1983, 1991). Moreover, a number of well-designed studies using both monozygotic and dizygotic twins have provided strong evidence demonstrating that children with obesity susceptibility genes living in an obesogenic environment (adopted family) are at increased risk of developing childhood obesity (Borjeson 1976; Silventoinen and Kaprio 2009; Silventoinen et al. 2010). These results are consistent with recent anthropological studies verifying that gene–environment interactions are responsible for marked differences among populations genetically susceptible to weight gain (Casazza et al. 2011).

It should be noted, however, that the thrifty gene hypothesis remains controversial due to suggestions that famines were neither long nor severe enough to select for thrifty genes and that no evidence exists for excessive weight gain between famines or during the feast periods (Prentice et al. 2008; Speakman 2008). In addition, it has been shown that the average daily energy expenditure is similar for modern hunter-gatherers and Westerners after controlling for body size, in contrast to previous assumptions that early hunter-gatherers had an increased daily energy expenditure (Pontzer et al. 2012). Other studies have also found no evidence for the natural selection of obesity and diabetes susceptibility genes identified using GWAS and that such genes are unlikely to exist in a stable polymorphic state (Southam et al. 2009; Baig et al. 2011). An alternative explanation that is gaining recognition for the current obesity epidemic involves a nonadaptive approach referred to as the "predation release" or "drifty hypothesis", which suggests that adiposity may result from random genetic mutations and drift that interact with environmental factors (Speakman 2008; Speakman and O'Rahilly 2012). Regardless of the evolutionary mechanism, it is clear that obesity susceptibility genes interact with known and unknown environmental factors that result in positive energy balance responsible for weight gain (Fig. 3).

The high-fat diet as a major component in the obesogenic environment

The obesogenic environment consists of a complex interplay of contributing factors that influence behavior thereby effecting dietary choice, physical activity, or metabolism responsible for maintaining energy balance (Patrick et al. 2004). A number of recent studies suggest that both sedentary behavior (viewing television, playing video games, doing cognitive work, and listening to music) and reduced overall physical activity along with shorter sleep duration promote the overconsumption of dietary macronutrients, particularly fats and refined carbohydrates (Stroebele and de Castro 2006; Graves et al. 2007; Temple et al. 2007; Chaput et al. 2008; Westerlund et al. 2009). The increased consumption of a high-fat diet, particularly a high-fat diet enriched with saturated fatty acids, has been found to be strongly associated with increased adiposity in overweight and obese children (Aeberli et al. 2006, 2008). Moreover, another recent study performed with 810 participants indicated a highly significant association of saturated fatty acid consumption (but not plant protein, carbohydrates, or other types of fat) at 6 months with body weight at 18 months of age (Lin et al. 2012). Consistent with these results, studies indicate that obesity susceptibility genes tend to preferentially interact with saturated fatty acids, but not monounsaturated fatty acids or polyunsaturated fatty acids, to promote weight gain (Razquin et al. 2010; Corella et al. 2011). For these reasons, it is widely accepted that high-fat diets, characterized by enhanced palatability and high energy density, may be primarily responsible for the current obesity epidemic. However, it should be noted that studies suggest that increased consumption of carbohydrates, particularly refined carbohydrates and sugar-sweetened beverages, during the past 30 years better parallels the increased prevalence of obesity (Gross et al. 2004; Malik et al. 2006, 2010).

The importance of gene–diet interactions believed responsible for chronic nutrition-related diseases, such as obesity and type 2 diabetes, has prompted the development of a relatively new scientific discipline referred to as "nutritional genetics" and "nutritional genomics" (Ordovas and Corella 2004). Although current childhood obesity intervention programs have traditionally focused only on generalized population guidelines, further investigation and insight into gene–diet interactions may serve an important role in both the prevention and treatment of childhood obesity (Papoutsakis and Dedoussis 2007; Hetherington and Cecil 2010). This will be possible by enhancing our knowledge surrounding the etiology and pathophysiology of childhood obesity and developing methods to prevent the onset and improve treatment of childhood obesity using targeted nutritional and medicinal therapies.

Childhood obesity susceptibility genes

During the course of a decade (1996–2005), an extensive amount of work was performed to identify candidate obesity susceptibility genes responsible for heritability of obesity phenotypes. The culmination of these studies resulted in the identification of 127 candidate obesity susceptibility genes (Rankinen et al. 2006). However, only a limited number ($\sim$25 %) of these candidate genes have been validated using independent studies. This small percentage of candidate obesity susceptibility genes in addition to many other genes recently identified using GWAS now comprise a comprehensive list of approximately 69 obesity susceptibility genes (34 genes from candidate studies and 35 genes from GWAS) that predispose to increased body weight, BMI, or body fat percentage (Hofker and Wijmenga 2010; Day and Loos 2011; Fernandez et al. 2012). There are three different types of childhood obesity (syndromic, non-syndromic, and common) based on distinct genetic and phenotypic characteristics that will be described in the following sections (Fig. 4).

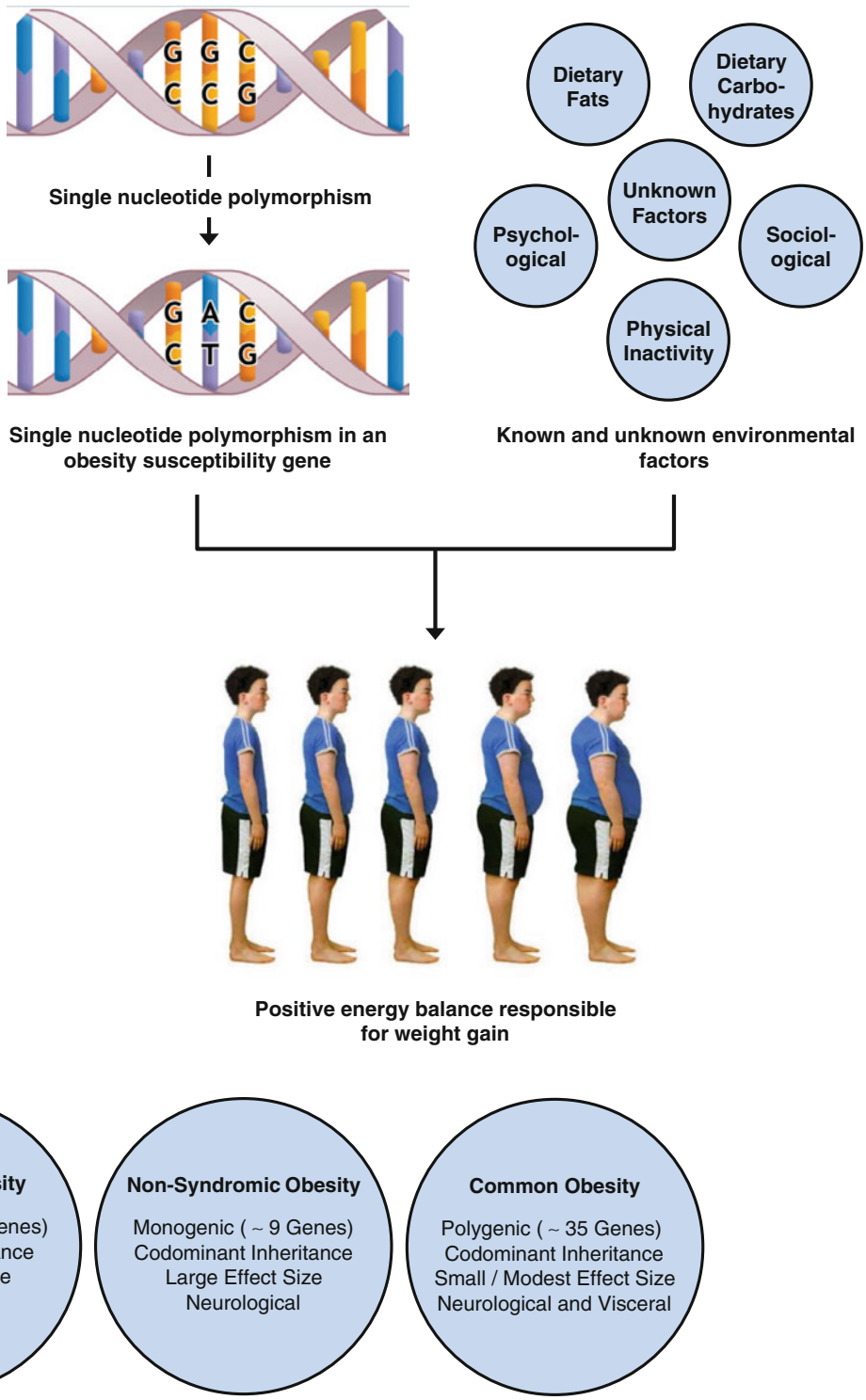

Fig. 3 The interaction of obesity susceptibility genes with single-nucleotide polymorphisms or variants with known and unknown environmental factors that predispose to weight gain

Fig. 4 The three different types of childhood obesity based on distinct genetic and phenotypic characteristics

Syndromic childhood obesity

The first type of childhood obesity is represented by approximately 30 unidentified susceptibility genes responsible for rare monogenic forms of syndromic obesity. The best-known examples of syndromic obesity are represented by Prader–Willi, Bardet–Biedl, Alstrom, Carpenter, Rubinstein–Taybi, and Cohen syndromes. In general, children with syndromic obesity have extreme adiposity, physical dysmorphology, and intellectual

disabilities, some with undefined neuroendocrine abnormalities. It is the latter abnormality believed responsible for adversely affecting function of the hypothalamus which serves as the brain appetite center regulating energy balance through food consumption and energy expenditure (Farooqi and O'Rahilly 2005; Mutch and Clement 2006; Goldstone and Beales 2008; Schaefer et al. 2010). As a result, children with syndromic obesity are usually characterized with severe hyperphagia and diminished satiety which promotes weight gain (Bray 1992; Sahoo et al. 2008; Marshall et al. 2011). These particular disorders are genetically complex and involve several overlapping and undefined loci believed responsible for the altered regulation of energy balance. With respect to a possible gene–diet interaction responsible for the best characterized form of syndromic obesity, in this case Prader–Willi syndrome, a recent study has indicated that a strict low-fat and modified carbohydrate diet (25 % protein, 20 % fat, and 55 % modified carbohydrate) can successfully prevent or at least reduce weight gain among patients with this disease (Schmidt et al. 2008). The reason being is that children with Prader–Willi syndrome have delayed gastric emptying due to ineffective stomach contractions. The therapeutic diet allows for increased and timely absorption of carbohydrates, otherwise somewhat inhibited by a high-fat diet, to prevent hypoglycemia and resultant food-craving behavior marked by hyperphagia. However, it should be noted that children with Prader–Willi syndrome receiving this therapeutic diet were of significantly decreased stature beginning at 2 years of age, suggesting that growth hormone may be a useful additional treatment for these patients. It is therefore suspected that this concern prompted authors from including children without Prader–Willi syndrome into the study.

Non-syndromic childhood obesity

The second type of childhood obesity is represented by approximately 8 susceptibility genes responsible for rare monogenic forms of non-syndromic obesity, defined by weight gain in the absence of other clinical symptoms (Choquet and Meyre 2010). The eight genes responsible for non-syndromic obesity include brain-derived neurotrophic factor (*BDNF*), leptin (*LEP*), leptin receptor (*LEPR*), melanocortin-4 receptor (*MC4R*), neurotrophic tyrosine kinase receptor type 2 (*NTRK2*), prohormone convertase 1 (*PCSK1*), proopiomelanocortin (*POMC*), and single-minded homolog 1 (*SIM1*). These 8 obesity susceptibility genes code for proteins which have a central role in the integration of peripheral and neuronal signals through the leptin/melanocortin pathway present in the hypothalamus and therefore also responsible for maintaining energy balance through food consumption and energy expenditure (Farooqi and O'Rahilly 2008). In the case of *LEP*, genetic mutations result in leptin deficiency, and administering leptin has been shown to have beneficial effects by restoring satiety and promoting weight loss (Farooqi et al. 2002). Mutations in these genes also cause severe hyperphagia and a lack of satiety that ultimately manifests in extreme forms of childhood obesity. To date, studies performed with patients possessing the best characterized form of non-syndromic obesity, in this case leptin deficiency, have shown that although restriction of a high-fat diet may partially or temporarily be successful, long-term weight management is difficult and usually unsuccessful (Erez et al. 2011).

Common childhood obesity

The third type of childhood obesity is represented by many undefined susceptibility genes believed responsible for contributing to common polygenic forms of childhood obesity (Zhao et al. 2011; Zhao and Grant 2011). These obesity susceptibility genes are associated with both common childhood and adult obesity, as shown in large population-based or case–control GWAS performed during the past several years (Meyre et al. 2009; den Hoed et al. 2010; Sandholt et al. 2010; Wu et al. 2010; Zhao et al. 2011) (Table 1). It is interesting to note that among the obesity susceptibility genes that have been identified using GWAS, different variants of the same gene (*FTO*, *MC4R*, and *BNDF*) may also be responsible for rare non-syndromic forms of childhood obesity. However, unlike the genes contributing to monogenic forms of childhood obesity characterized by large phenotypic effect sizes, genes contributing to common obesity have small to modest phenotypic effect sizes (~0.17 to 1.13 kg or 0.14–0.33 % body fat per risk allele) (Speliotes et al. 2010; Kilpelainen et al. 2011). That being the case, common obesity susceptibility genes function in an additive fashion and interact with environmental factors to promote positive energy balance resulting in substantial weight gain, consistent with common obesity being a complex genetic and metabolic disorder (Levin 2009; Sandholt et al. 2010). As indicated earlier, the prevalence of common childhood obesity has more than tripled during the past few decades and represents a major health problem as a result of numerous complications.

Gene–diet interactions predisposing to common childhood obesity

A list of 16 well-established obesity susceptibility genes associated with common childhood obesity within American, Chinese, and European populations identified using GWAS

Table 1 A list of 35 obesity susceptibility genes, reference SNPs, susceptible subjects, and phenotypes identified using GWAS adapted from Meyre et al. (2009), den Hoed et al. (2010), Sandholt et al. (2010), Wu et al. (2010), and Zhao et al. (2011)

Chromosome	Nearest gene	Reference SNP	Subjects	Phenotypes
1	*NEGR1*	rs2815752	Adults	Weight, obesity, BMI
1	*TNN13K*	rs1514175	Adults, children	BMI
1	*PTBP2*	rs1555543	Adults	BMI
1	*SEC16B*	rs543874	Adults, children	BMI
2	*TMEM18*	rs2867125	Adults, children	Weight, obesity, BMI
2	*RBJ*	rs713586	Adults, children	BMI
2	*FANCL*	rs887912	Adults	BMI
2	*LRP1B*	rs2890652	Adults	BMI
3	*CADM2*	rs13078807	Adults	BMI
3	*ETV5*	rs9816226	Adults	Weight, obesity, BMI
4	*GNPDA2*	rs10938397	Adults, children	Weight, obesity, BMI
4	*SLC39A8*	rs13107325	Adults	BMI
5	*FLJ35779*	rs2112347	Adults, children	BMI
5	*ZNF608*	rs4836133	Adults	BMI
6	*NUDT3*	rs206936	Adults	BMI
6	*TFAP2B*	rs987237	Adults	BMI
9	*LRRN6C*	rs10968576	Adults, children	BMI
10	*PTER*	rs10508503	Adults, children	BMI
11	*RPL27A*	rs4929949	Adults	BMI
11	*BDNF*	rs10767664	Adults, children	Weight, obesity, BMI
11	*MTCH2*	rs3817334	Adults	BMI
12	*FAIM2*	rs7138803	Adults, children	Weight, obesity, BMI
13	*MTIF3*	rs4771122	Adults	BMI
14	*PRKD1*	rs11847697	Adults	BMI
14	*NRXN3*	rs10150332	Adults, children	BMI
15	*MAP2K5*	rs2241423	Adults	BMI
16	*GPRC5B*	rs12444979	Adults	BMI
16	*SH2B1*	rs7359397	Adults	Weight, obesity, BMI
16	*MAF*	rs1424233	Adults, children	BMI
16	*FTO*	rs1558902	Adults, children	Weight, obesity, BMI
18	*MC4R*	rs571312	Adults, children	Weight, obesity, BMI
18	*NPC1*	rs1805081	Adults, children	BMI
19	*KCTD15*	rs299941	Adults	BMI
19	*QPCTL*	rs2287019	Adults, children	BMI
19	*TMEM160*	rs3810291	Adults	BMI

include brain-derived neurotrophic factor (*BNDF*), cardiac troponin I-interacting kinase (*TNNI3K*), Fas apoptotic inhibitory molecule 2 (*FAIM2*), homo sapiens hypothetical protein FLJ35779 (*FLJ35779*), fat-mass and obesity associated (*FTO*), glucosamine-6-phosphate deaminase 2 (*GNPDA2*), leucine-rich repeat neuronal 6C (*LRRN6C*), melanocortin-4 receptor (*MC4R*), musculoaponeurotic fibrosarcoma oncogene homolog (*MAF*), Niemann-Pick C1 (*NPC1*), neurexin-3-alpha (*NRXN3*), phosphotriesterase-related (*PTER*), glutaminyl-peptide cyclotransferase-like (*QPCTL*), Rab and DnaJ domain containing (*RBJ*), Saccharomyces cerevisiae 16 homolog B (*SEC16B*), and transmembrane protein 18 (*TMEM18*). Five of these obesity susceptibility genes (*FTO*, *MC4R*, *MAF*, *NPC1*, and *PTER*) were identified in the first or second case–control GWAS for early-onset (less than 6 years of age) and morbid-adult obesity (BMI $\geq$ 40 kg/m^2) (Hinney et al. 2007; Meyre et al. 2009). More recent meta-analysis of several case–control GWAS using $\sim$40,000 individuals has determined that three of these obesity susceptibility genes (*FTO*, *MC4R*, and *NPC1*) are also associated with body fat percentage which serves as an accurate measure for whole body adiposity (Kilpelainen et al. 2011; den Hoed et al. 2012). It has been hypothesized that individuals

possessing these obesity susceptibility genes associated with extreme (early-onset and morbid-adult) obesity and body fat percentage may either possess more than the average number and/or enhance phenotypic expression of other common obesity susceptibility genes (Meyre et al. 2009). The following sections will provide information describing what is now understood about obesity susceptibility genes interacting with either a high-fat diet or sugar-sweetened beverages to promote weight gain.

Obesity susceptibility genes that interact with dietary fats

The *FTO* gene is localized on chromosome 16q12.2 and encodes a Fe II- and 2-oxoglutarate-dependent dioxygenase that functions to catalyze demethylation of nucleotide bases (Gerken et al. 2007). The same study also indicated that the *Fto* gene in mice is expressed at high levels in the appetite center (arcurate nucleus) of the hypothalamus and regulated by periods of fasting/feeding. A direct *Fto* gene–diet interaction in relation to weight gain was first established in rats when fasting was shown to reduce the amounts of *Fto* mRNA and promote food consumption, while in contrast, feeding had the opposite result to increase amounts of *Fto* mRNA and decrease food consumption (Tung et al. 2010). These results provided the first indication that expression and functional amounts of the encoded FTO protein in the hypothalamus influenced appetite. The common *FTO* gene variant (rs9939609) was subsequently used in a population-based GWAS to identify this gene as the first to be associated with common childhood obesity (Frayling et al. 2007). Consistent with this result, a later case–control GWAS performed with lean and extremely obese German children indicated that this particular *FTO* gene variant was associated with common childhood obesity (Hinney et al. 2007). A number of other studies performed with both children and adults indicated that this *FTO* gene variant was associated with increased and preferential consumption of energy-dense macronutrients, particularly foods enriched with saturated fatty acids (Cecil et al. 2008; Timpson et al. 2008; Bauer et al. 2009). Studies have also provided evidence that weight gain among children and adults with this *FTO* gene variant results from an unusual eating behavior characterized by loss-of-control eating episodes for high-fat foods (Wardle et al. 2008a; den Hoed et al. 2009; Tanofsky-Kraff et al. 2009). Interestingly, the weight gain was found to be independent of alterations in energy expenditure typically associated with hypothalamic abnormalities and was unlike any other eating behavior previously reported in the general population (Speakman et al. 2008; Haupt et al. 2009; Jonassaint et al. 2011). At the same time, studies performed using two different *Fto* mouse models characterized by complete inactivation and a dominant point mutation of the *Fto* gene revealed a complex and contradictory phenotype compared to humans possessing the common *FTO* gene variant (Church et al. 2009; Fischer et al. 2009). In brief, these *Fto* mouse models were shown to be lean and protected from obesity despite being fed a basal or high-fat diet and having consumed increased amounts of these diets after adjustment for body weight. Consistent with the decreased relative amounts or function of the encoded FTO protein being associated with a lean phenotype for these mice, a subsequent study performed using a mouse model characterized by overexpression of the *Fto* gene marked by increased amounts of encoded FTO protein indicated a dose-dependent increase in adiposity, weight gain, and glucose intolerance resulting from increased food consumption when adjusted for body weight (Church et al. 2010). Therefore, the common *FTO* gene variant in the human population is a gain-of-function mutation that interacts with a high-fat diet to promote common childhood obesity through an unusual behavioral response characterized by an increased consumption of high-fat diets.

The *MC4R* gene is localized on chromosome 18q21.32 and encodes a complex plasma membrane protein that belongs to the seven transmembrane G protein-coupled receptor family that activates adenylate cyclase to produce cyclic adenosine monophosphate (cAMP) during signal transduction (Magenis et al. 1994; Yang et al. 2000). The first evidence indicating that the *MC4R* gene was associated with regulating energy balance resulted from mice possessing a targeted disruption of the *Mc4r* gene (Bultman et al. 1992; Huszar et al. 1997). These studies demonstrated that *Mc4r* heterozygous ($Mc4r^{+/-}$) mice were susceptible to intermediate weight gain compared to *Mc4r* normal ($Mc4r^{+/+}$) and Mc4r homozygous ($Mc4r^{-/-}$) mice, suggesting a codominant mode of inheritance for the phenotype. Moreover, in comparison with $Mc4r^{+/+}$ mice fed a high-fat diet, the $Mc4r^{-/-}$ mice were found to have hyperphagia and altered energy expenditure characterized by decreased diet-induced activity and thermogenesis (Butler et al. 2001; Weide et al. 2003). Consistent with these results, the $Mc4r^{-/-}$ mice developed hyperphagia when fed a high-fat diet, but not when fed a low-fat diet, providing evidence for a gene–diet interaction in relation to weight gain (Butler and Cone 2003; Sutton et al. 2006). An additional study performed using adenovirus to preferentially knockdown expression of the *Mc4r* gene in hypothalamus of rats revealed that a high-fat diet induces hyperphagia and weight gain (Garza et al. 2008). With respect to studies that have been performed investigating the *MC4R* gene in relation to weight gain in humans, a frameshift mutation in the *MC4R* gene provided the first compelling evidence that this gene was associated with extreme childhood obesity (Vaisse et al. 1998; Yeo et al.

1998). In support of these studies, additional studies found that individuals possessing *MC4R* gene variants were at increased risk of obesity and that binge eating was a major phenotype responsible for weight gain (Branson et al. 2003; Farooqi et al. 2003). These results were confirmed in a GWAS performed to identify chromosomal regions contributing to increased consumption of dietary components among 1,030 Hispanic children. This study found that *MC4R* gene variants have a key role in regulating body weight through both increased energy consumption and decreased energy expenditure (Cai et al. 2006; Cole et al. 2010). A more recent study suggests that individuals possessing *MC4R* gene variants consume increased amounts of food enriched with total and saturated fatty acids (Bauer et al. 2009). Therefore, similar to children with *FTO* gene variants, children possessing *MC4R* gene variants have an increased preference for calorie-dense foods enriched with fat, in addition to a decreased propensity for energy expenditure, both of which promote weight gain.

Finally, the *NPC1* gene is localized on chromosome 18q11.2 and encodes a complex multi-spanning transmembrane protein that possesses structural homology with members of the resistance-nodulation-division family of prokaryotic permeases (Carstea et al. 1997; Davies et al. 2000). Studies have demonstrated that the NPC1 protein has a central role in regulating the transport of lipoprotein-derived lipids, such as cholesterol and fatty acids, from late endosomes/lysosomes to other cellular compartments (Garver et al. 2002; Chen et al. 2005). Although the *NPC1* gene has been primarily investigated in relation to an autosomal-recessive lipid-storage disorder characterized by hepatosplenomegaly and neurological degeneration, four independent GWAS have now reported that a variant of the *NPC1* gene (rs1805081 encoding H215R) is associated with measures of common childhood obesity (BMI and body fat percentage) among European and Chinese populations (Meyre et al. 2009; Wu et al. 2010; Kilpelainen et al. 2011; den Hoed et al. 2012). In addition, a study performed using an *Npc1* mouse model indicated that *Npc1* heterozygous ($Npc1^{+/-}$) mice are predisposed to weight gain when fed a high-fat diet, but not when fed a low-fat diet, consistent with a gene–diet interaction responsible for promoting weight gain (Jelinek et al. 2009). These studies were confirmed using a different strain of mice that became obese and developed metabolic features associated with insulin resistance (Jelinek et al. 2010). Together, reanalysis of the combined data derived from both studies revealed that the *Npc1* gene interacts with both modifying genes and a high-fat diet to promote weight gain, features that are consistent with common and complex diseases such as obesity (Jelinek et al. 2011). However, unlike the *Fto* and *Mc4r* genes, these mouse studies clearly indicate that the *Npc1* gene does not promote weight gain through increased consumption of food or decreased energy expenditure, thereby excluding potential involvement of the hypothalamus. It is interesting to note that a number of earlier studies performed using both *NPC1* human fibroblasts and the *Npc1* mouse model provided information suggesting potential involvement of the NPC1 protein in regulating energy balance. For instance, *NPC1* heterozygous ($NPC1^{+/-}$) human fibroblasts have increased expression of caveolin-1, which serves as a protein marker for obesity and diabetes (Garver et al. 1997b; Catalán et al. 2008). These results were confirmed and extended using *Npc1* heterozygous ($Npc1^{+/-}$) mice, which compared to *Npc1* normal ($Npc1^{+/+}$) and *Npc1* homozyous ($Npc1^{-/-}$) mice, had livers with an increased expression of caveolin-1 and concentration of triacylglycerol, both of which serve as markers for obesity and diabetes (Garver et al. 1997a, 1999, 2007). More recent studies indicate that the *Npc1* gene is downregulated by dietary fatty acids, but not dietary cholesterol, through feedback inhibition of the sterol regulatory element-binding protein (SREBP) pathway (Jelinek et al. 2012). Therefore, additional studies must be performed to further characterize the *NPC1* gene in relation to common childhood obesity.

Obesity susceptibility genes that interact with dietary carbohydrates

It has been reported that three candidate obesity susceptibility genes, beta-2 adrenergic receptor (*ADRB2*), perilipin 1 (*PLIN1*), and peroxisome proliferator-activated receptor gamma (*PPARG*), which have not been found to be associated with either childhood or adult obesity using GWAS, interact with dietary carbohydrates to promote measures of obesity (Marti et al. 2002; Martinez et al. 2003; Smith et al. 2008). Moreover, a recent study performed using three different adult cohorts (Nurses' Health Study, Health Professionals Follow-up Study, and Women's Genome Health Study) indicated that six of 32 obesity susceptibility genes identified using GWAS interact with dietary carbohydrates (sugar-sweetened beverages including colas, fruit drinks/punches, and lemonades) to increase BMI when one or more servings are consumed per day (Qi et al. 2012). In this study, the obesity susceptibility genes found to interact with dietary carbohydrates to increase BMI included the *FAIM2*, *FLJ35779*, *FTO*, *LRRN6C*, *RBJ*, and *SEC16B* genes.

Preventative lifestyle intervention for common childhood obesity

The American Academy of Pediatrics proposed that prevention should be the first step in addressing the childhood

obesity epidemic (Krebs and Jacobson 2003). However, systematic review of the literature provides conflicting results as to effectiveness of preventative lifestyle interventions for childhood obesity. For instance, a recent systemic review with meta-analysis for 33 studies indicated significant immediate and post-treatment improvements in weight and cardio-metabolic outcomes for childhood obesity, but suggested that further research was needed to determine the optimal length, intensity, and long-term effectiveness of these interventions (Ho et al. 2012). Moreover, another recent systematic review based on 37 independent studies with 27,946 children (mostly 6–12 years of age) provides evidence that intensive school-based programs serve as the most promising type of preventative lifestyle intervention (Waters et al. 2011). However, this same systematic review and others provide evidence indicating that obesity prevention programs for older preschool children and adolescents (13–19 years of age) are less effective (Bond et al. 2009; Hesketh and Campbell 2010; Waters et al. 2011). Consistent with these later systematic reviews, a number of studies have reported that the cornerstone for preventative lifestyle intervention, namely modification of dietary and exercise habits, has been largely ineffective (Miller 1999; Birch and Ventura 2009). A recent meta-analysis of randomized controlled trials determined that school-based physical activity interventions did not improve BMI compared to pre-existing physical education activity, thereby suggesting that mandated increased physical activity does not have a significant effect on preventing childhood obesity (Harris et al. 2009). This result is consistent with a more recent non-intervention prospective study examining children between 7 and 10 years of age suggesting that physical inactivity is the result rather than the cause of childhood obesity (Metcalf et al. 2011). While many obesity interventions have focused only on behavioral change in relation to more appropriate eating and exercise habits, few interventions have taken into consideration the emerging role of obesity susceptibility genes and interaction with environmental factors. There is now a crucial need to understand the molecular basis responsible for childhood obesity to provide more effective preventative lifestyle intervention and clinical care. A decade ago John R. Speakman, a leading obesity expert, stated that "addressing the genetic side of this (gene–environment) interaction is potentially a far more tractable problem than addressing the environmental component by reengineering society, because the level at which interventions might ultimately be made is the individual rather than the society as a whole. There is a clear need, therefore, to understand the genetic basis of food intake, energy expenditure and hence, energy balance variations" (Speakman 2004). These recommendations have only recently gained momentum due to the limited success of conventional preventative lifestyle intervention methods in the face of our growing knowledge concerning gene–environment interactions and targeted intervention for genetically predisposed individuals, families, and communities (Khoury et al. 2005; Gluckman et al. 2011).

One way in which individual preventative lifestyle interventions could utilize genetic information is by providing individuals with personalized information to influence behavior. Many behavioral change strategies aim to increase the perception of risk in individuals to improve motivation. The genetic information would expand on the risk perception model to provide individualized risk information, as well as personalize the harms of the health condition. If individuals are aware that they have the possibility of becoming obese and developing chronic complications, they may be more likely to adhere to behavioral change intervention (McBride et al. 2002). It has been determined that the availability of genetic information results in better compliance and longer-term weight reduction when using personalized diet plans to treat patients with a history of failed weight reduction (Arkadianos et al. 2007). A more recent study demonstrated that genetic testing for the *FTO* gene variant serves as a useful preventative and clinical tool when combined with other information by providing an explanation for increased body weight (Meisel et al. 2011). On the other hand, there may be a problem in using this model, because if tested individuals are found not to have an obesity susceptibility gene variant the effect is a perception for decreased risk of obesity. This may actually defeat the original purpose for providing a technologically advanced intervention in that individuals may be less likely to change behaviors if they have a perceived decreased risk of obesity. In addition to personalizing medical information for patients, genetic information could also be used to stratify individuals based on increased risk. By doing this, individuals who have obesity susceptibility gene variants would be categorized as "high risk" and therefore provided more intensive preventative lifestyle intervention strategies than individuals categorized as "low risk". In this way, children who are genetically predisposed could be more closely monitored and potential preventative lifestyle interventions would become more cost-effective by targeting individuals at high risk (Johnson et al. 2005).

Unfortunately, although current individual preventative lifestyle interventions have only limited effectiveness, the benefits can be even less within a pediatric population. The reason is because most children have little control over their food choices and behaviors, and these choices impact weight status (Faith et al. 2004). A more logical place to intervene is at the family level. Family preventative lifestyle intervention strategies could have multiple positive effects as families not only control feeding practices of

children, but often share cultural, environmental, and genetic predisposition for diseases such as obesity (Johnson et al. 2005). Interventions that target susceptible families could benefit the children at high risk for obesity while also benefiting close family members. This benefit could occur through targeting group-focused health promotion strategies that aim to affect social norms, increase social support, and strengthen familial bonds (Teufel-Shone 2006). Finally, as more information is obtained concerning the unique distribution of specific obesity susceptibility gene variants among diverse populations, community preventative lifestyle intervention strategies can be applied to lessen the impact of childhood obesity. It must be noted that targeted individuals in the community who do not possess suspected obesity susceptibility gene variants will likewise benefit from such interventions, as environmental factors still have a role in the etiology of childhood obesity.

Nutritional and medicinal intervention for genetically predisposed children

The goal for successful nutritional and medicinal intervention of common childhood obesity depends on understanding the molecular basis or mechanism for how gene variants predispose to weight gain. For instance, the *FTO* and *MC4R* gene variants tend to increase preference for calorie-dense foods enriched with fat and decrease satiety. A nutritional or medicinal therapy may soon be identified that stimulate regions of the brain (arcurate nucleus of the hypothalamus) to promote satiety. Although only recently approved by the Food and Drug Administration (FDA), the medicinal therapies lorcaserin hydrochloride (Belviq) and the combination of phenteramine/topiramate (Qsymia) may prove useful in this regard. Similar therapies may also be developed that regulate tissue and whole body lipid metabolism (decrease lipogenesis or increase lipolysis within select lipid-storage tissues) as suspected for children with *NPC1* gene variations.

Conclusion and perspectives

The current epidemic of common childhood obesity represents a complex metabolic disease characterized by the interaction of obesity susceptibility gene variants with certain dietary macronutrients (saturated fatty acids or refined carbohydrates) and a sedentary lifestyle. The continued investigation of gene–diet interactions responsible for this health problem will be important for several reasons. First, diseases such as obesity and associated complications result from an undefined and complex interaction between susceptibility gene variants and various environmental components (Perusse and Bouchard 2000). The obesity susceptibility gene variants described in this article interact with the diet to either increase consumption of saturated fat and refined carbohydrates, decrease energy expenditure, or alter regulation of lipid metabolism to increase weight gain and adiposity (Bauer et al. 2009; Garver 2011). Second, the identification of gene–diet interactions should be at the forefront in attempts to understand the etiology and pathophysiology of nutrition-related diseases, particularly common childhood obesity (Levin 2009). Third, the interaction of specific gene variants with known dietary macronutrients will allow for more effective individual, family, and community preventative lifestyle intervention and eventually the development of targeted nutritional or medicinal therapies (Yang and Khoury 1997; Khoury et al. 2005). The overarching goal for investigating gene–diet interactions is to provide a plausible mechanism-based approach to personalized nutritional or medicinal therapy that will more effectively address the current epidemic of common childhood obesity.

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