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Disruptions in Energy Balance: Does Nature overcome Nurture?

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Abstract

Fat accumulation, in general, is the result of a breakdown in the homeostatic regulation of energy balance. Although, the specific factors influencing the disruption of energy balance and why these factors affect individuals differently are not completely understood, numerous studies have identified multiple contributors. Environmental components influence food acquisition, eating, and lifestyle habits. However, the variability in obesity-related outcomes observed among individuals placed in similar controlled environments support the notion that genetic components also wield some control. Multiple genetic regions have been associated with measures related to energy balance; however, the replication of these genetic contributors to energy intake and energy expenditure in humans is relatively small perhaps because of the heterogeneity of human populations. Genetic tools such as genetic admixture account for individual's genetic background in gene association studies, reducing the confounding effect of population stratification, and promise to be a relevant tool on the identification of genetic contributions to energy balance, particularly among individuals of diverse racial/ethnic backgrounds. Although it has been recognized that genes are expressed according to environmental influences, the search toward the understanding of nature and nurture in obesity will require the detailed study of the effect of genes under diverse physiologic and behavioral environments. It is evident that more research is needed to elucidate the methodological and statistical issues that underlie the interactions between genes and environments in obesity and its related comorbidities.

Keywords

genes; environment; admixture; energy balance; gene-environment interactions

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Introduction

Overweight and obesity are the result of a disruption in energy balance. The prevalence of overweight and obesity in the United States is alarming. It has been estimated that approximately 30% of the US adult population have a body mass index (BMI = kg/m²) greater than 30 [1], a cut off used to classify adults as obese. Studies evaluating samples from the Union Army veterans have documented an increase in the percentage of individuals with a BMI of at least 30 since the beginning of the 20th century [2], supporting that the concerning increases in body size has been a gradual problem for an extended period of time. Perhaps the most remarkable public health concern is the increased trend of overweight and obesity among children and adolescents. Data from the National Health and Nutrition Examination Survey (NHANES) has demonstrated that children as young as thirteen years of age exceed the waist circumference cutoff value for obesity-related disease risk in adults. A dramatic increase in adverse metabolic outcomes, particularly insulin resistance and adverse lipid profiles [3], parallels the increase in overweight and obesity in children. The understanding of the factors contributing to the etiology of obesity and its comorbidities is imperative.

The disproportional prevalence of obesity-related metabolic risks in children of diverse ethnic backgrounds has been an area of concern and investigation. The prevalence of being overweight and becoming overweight at any age during adolescence is approximately twice as high among African and Hispanic Americans when compared to European American children [4]. New incidence of type 2 diabetes among children and adolescents ranges from 8 – 45% depending upon geographic location with African American (AA) and Hispanic American (HA) children at higher risk of developing the condition [5]. It is believed that inherent ethnic differences in metabolism and fat accumulation in combination with the obesogenic environment may put different populations at greater risk for disease.

It is generally accepted that fat accumulation is a result of a breakdown in the homeostatic regulation of energy balance. However, neither the specific factors influencing the disruption of energy balance nor why these factors affect individuals differently are completely understood. Scientific data has demonstrated that the accumulation of body fat is a complex process. In humans, social, dietary, physical activity, and other environmental factors have been considered as possible causes for the obesity epidemic. However, a wide collection of scientific literature supports the contributions of genes to various aspects related to obesity and fat accumulation. The overall consensus of the scientific community is that excessive body fat is the end of a cascade of interactions among environmental, behavioral and genetic factors. At a time when the life expectancy of individuals is increasing, the detrimental consequences that body fat accumulation will have in health outcomes becomes a concern to scientists, epidemiologists, health professionals and policy makers. It is evident that the understanding of the interactions between nature and nurture is an area in need of research as the scientific community continues to investigate the etiology of this complex disease.

Environmental Components to Energy Balance

Our inability to accurately define “environment” presents the greatest challenge of studying the influence of “nurture” in the development of obesity and its comorbidities. The term environment encompasses a wide variety of components, which include (but are not limited to) variations in family structure, socio-economic status (SES), area of residence, community dynamics, occupation, health status, and individual experiences. These components influence contexts of food acquisition, eating, and lifestyle habits, playing a role in the development of obesity [6]. Environmental components encompass direct and indirect influences in a person’s past or present experiences and have the potential to affect the balance between energy intake and expenditure.

The contributions of environmental factors to obesity have been the focus of numerous research initiatives. For example, Papas and colleagues performed a meta-analysis of studies attempting to link the environment to obesity and found statistically significant relationships between factors that scientists defined as “environment” and the risk for the development of obesity in 17 out of 20 studies [7]. An interesting aspect of the meta-analysis was that in all these studies, the environment was defined in different terms, including food consumption patterns, physical activity and economic factors. Because the disruption of energy balance that leads to obesity is greatly influenced by energy intake, eating practices and behaviors have been a big focus of the exploration of environmental factors in obesity. It has been suggested that most eating behaviors are defined within the family context, and eating in the absence of hunger, a behavior defined as “environmental” perhaps because of the way it reflects social, cultural and individual responsiveness to portion size, has been documented to promote excessive energy intake among young children [8]. In addition, adaptation of new patterns of dieting that reflect changes in dietary composition and increases in caloric intake have been proposed as determinants of overweight and obesity among children, as exemplified by the increased weight gain experience by children who have recently migrated to the US.

Sedentary behaviors have also been evaluated as environmental contributors to the obesity epidemic in children and adolescents and have been a matter of interesting controversy. For example, several studies have reported that the increase in the amount of time spent viewing television (with reports suggesting that children and adolescents watch an estimated 3 hours of television per day) have displaced physical activity and, consequently, increase BMI in the youth [9–11]. However, others have suggested that alternative to television viewing it is the snacking that occurs during television viewing that may be a more plausible cause for increased obesity [5]. This observation is supported by those believing that snacking has increased total daily energy and fat intake during the last decade and that, consequently, has contributed greatly to the recent obesity epidemic [12]. However, while some longitudinal studies have shown that snacking has a significant correlation with increases in body weight [13], other studies have concluded that the consumption of snacks does not seem to influence weight change among children and adolescents [13]. Such conflicting findings demonstrate the need to further explore the complexity of behavioral aspects evaluated as environment and the extent to which these aspects may differ among individuals.

Other environmental factors besides physical activity and food intake have been explored as plausible contributors to the obesity epidemic. In a review of the literature, Keith and colleagues documented that other ‘non-traditional’ factors such as ambient temperature, amount of hours of sleeping at night, and increasing gravida age are contributors to the obesity epidemic [14]. It has recently been shown that maternal characteristics and behaviors can influence prenatal development of food choices [15]. Mennella and Beauchamp [16] have demonstrated that food preferences in children are related to early exposure to foods in utero and in mother’s milk, a remarkable finding that reflects that appropriate environmental control at early stages might result in an early intervention. Nevertheless, because it is the interaction of the individual with the environment that actually influences obesity-related outcomes, additional research is necessary to understand the mechanisms to which this interaction occurs, particularly among individuals of diverse racial/ethnic backgrounds who might have different cultural and behavioral practices that might differentially impact obesity.

It is evident that avoidance of obesogenic environmental factors is an effective way to prevent the disruption in energy balance that leads individuals to become overweight and obese. It has been observed that changes in dietary habits and caloric restriction are effective in reducing body weight to a healthier standard, but the ability to maintain weight loss over time is limited in most people. The radical decrease in physical activity accompanying the increase in obesity suggests that physical activity might be the major environmental determinant driving the

obesity epidemic [17]. However, the variability in obesity-related outcomes and body composition that is observed among individuals placed under similar restricted environments such as dietary and exercise regimens support the notion that non-environmental components exert a control in aspects of energy balance and support genetic contributions. Data documenting racial/ethnic differences in obesity and its comorbidities have suggested that, independent of social and financial aspects, genetic background contributes to racial and ethnic differences in obesity and metabolic risk factors [18–20]. As we study, evaluate and measure environmental factors as relevant components associated with obesity, it is pertinent to be aware of the interaction of environmental factors with individual genetic susceptibility.

Genetic influences in obesity-related traits

The evaluation of environmental factors does not seem to explain the totality of the variation at the population level that accounts for individual differences in body fat accumulation. In humans, this is particularly evident when comparing individuals of diverse ethnic/racial backgrounds. For example, differences in body fat has been documented between AA and EA women after exposing them to comparable dietary interventions to achieve similar BMI [21], and studies have indicated that the differences in obesity-related traits between AA and EA adult and adolescent women remain even after accounting for the effect of socioeconomic status (SES) and education [22;23]. The observations of differences among individuals above and beyond environmental factors support the contributions of genes.

Ideally, the identification of genetic influences starts by the identification of regions across the genome that are statistically associated with a trait of interest, followed by the identification of genes within those regions, the confirmation of those genes as contributors to the phenotype and the identification of mechanisms of action for which those genes influence the phenotype. Consequently, different approaches including genome wide linkage, genome-wide association, and candidate gene analysis have been used to identify the contributions of DNA variation in measures related to energy intake, energy expenditure and fat accumulation. According to the 2005 update of the obesity gene map, approximately 408 regions have been identified within the mouse genome as harboring a quantitative trait loci (QTL) that influences body weight and/or adiposity and 253 have been reported for the human genome [24], distributed across every human autosomal chromosome. However, although 135 candidate genes have been associated with obesity, only 22 different genes have been able to be replicated in at least 5 studies, showing the difficulties of studying and understanding the genetic determinants to complex traits that result from the contributions and interactions of multiple genes and environmental factors.

Animal models have provided meaningful information toward the genetics of energy balance, from the identification of sections of DNA and candidate regions to the proposal of mechanisms and metabolic pathways that may account for observed obesity related phenotypes. Since the remarkable identification of leptin [25], numerous investigators have documented genes, proteins and putative mechanisms influencing processes related to both energy intake and energy expenditure, particularly in the brain. For example, the arcuate nucleus of the hypothalamus has been identified by several researchers as being an important mediator of feeding behaviors. Bouret and Simerly [26] noted that, in mice, metabolic circuits from the arcuate nucleus of the hypothalamus develop after birth and genetic expression of the leptin gene appears to play a crucial role in regulating food intake and adiposity. Fox noted that nutritional and hormonal influences could alter vagal development by modulating gene expression, gene products, or sensitivity of tissues to gene products, and that manipulation of vagal development that increases vagal sensory innervation of the small intestines is associated with enhanced satiation, increased sensitivity to the satiating effects of cholecystikinin (CCK), and reduced meal size [27]. Moran and Bi [28] observed that lack of expression of the CCK1

receptor for the gut hormone CCK results in hyperphagia and obesity of Otsuka Long-Evans Tokushima Fatty (OLETF) rats and that exercise, as an environmental factor, can alter the expression of CCK, supporting a gene-environment interaction that can have an impact on the full expression of obesity in these rats. Animal genetics have perhaps contributed the most to the development of hypotheses toward the identification of genetic influences in aspects of energy balance in humans and to the consideration of biological mechanisms that may contribute to energy intake, energy expenditure and fat accumulation.

The 22 candidate genes that have been replicated in at least 5 human studies are shown in Table 1. The most replicated of these genes have been involved in adipogenesis (PPARG), mitochondrion and energy expenditure (UCP1, UCP2, UCP3), or lipolysis (ADRB2, ADRB3), have been identified as adipokines (LEP, LEPR, ADIPOQ), have been involved in hormonal or neuronal pathways (NR3C1, HTR2C) or participate in signal transduction (GNB3). PPARG has received particular attention because of its identification as a key component of fat cell function responsible for the implementation of adipogenesis. Uncoupling proteins as mitochondrial membrane transporters involved in the release of stored energy as heat, play an influential role in energy expenditure. The process of lipolysis is modulated by stimulatory factors involving catecholamines as well as hormonal and neuronal pathways which has lead to associations with adrenoreceptors, glucocorticoid metabolism and signal transduction. In addition, the adipokines, which affect metabolic functioning of fat cells and impact other tissues throughout the body, have been documented to mediate fat metabolism and obesity. The identification of the function of these candidate genes as they relate to obesity and its related phenotypes promises to provide mechanistic explanations toward the physiological role of genes in aspects of energy balance.

Regardless of the advances in mouse genetic models and its translation into human research, the story of genetic influences in aspects of energy balance is far from been finalized, and the understanding of genetics of obesity and its comorbidities continues to be an area of need for evaluation, inquiry and discovery. The large number of genes and loci that have been identified to date without the identification of “the obesity gene” exemplifies the complexity of gene mapping for susceptibility to obesity and the need of understanding that, as a complex trait, obesity is the product of the action of multiple genes. In humans, the inability to replicate genetic association findings represents a matter of particular concern for researchers in the field, raising issues of validity of the phenotypic measurements, heterogeneity of samples, and control of Type I error rates. Although false positive associations are abundant in the literature, it has been proposed that 20% to 30% of genetic associations contributing to the risk of obesity in humans are real and have modest contributing effects to phenotypic variation [24]. Development of new analytical approaches and methodology to address the interactive nature underlying genetic influences in energy balance are needed, particularly at an actual time of abundant genotypic capabilities.

Genetic admixture

Unlike animal models where the environmental factors can be easily controlled, humans coexist within a multiplicity of environments that mediate their genetic makeup. This heterogeneity represents perhaps the most remarkable challenge in the search for genetic influences in men and women. As phenotypic differences in measurements associated with energy balance are observed among human populations, approaches have been developed that explore the variability in genetic background that occur from the intermixing of individuals in today's world while capitalizing in the environmental similarity shared by individuals self-classified as members of one group. Genetic admixture is an approach that assesses the ancestral genetic component of individual's genetic makeup.

The majority of the populations of the New World have been originated through the intermixing of long-separated “parental” populations that mated during the historical period of colonization. During the rediscovery of America, individuals of European descent arrived to territories occupied by American Indians, introducing Africans mainly from the West Coast of Africa. The intermixing of these long-separated “parental” populations created new admixed groups that under historical, geographical and cultural interactions formed the basis for what today we refer to as racial and ethnic groups. This intermixing also allowed the sharing and shuffling of genetic information, particularly of those DNA sequences that appear in greater frequency within individuals whose direct ancestral lineage descends from one parental population (e.g. European) when compared to others descending from different parental lineage (e.g. Africans or American Indians). Thousands of Ancestry Informative Markers (AIMs), have been identified across the human genome, and their utility for assessing ancestry has been quantified by subtracting the frequency of the marker in one parental population to the frequency of the marker on another parental population [29–31].

The identification of AIMs have served to narrow down DNA regions that influence disease-related phenotypes in admixed populations, an approach known as admixed mapping, under the premises that if higher disease prevalence in the admixed group responds to the presence of particular AIMs inherited from one parental population, those individuals having more risk alleles would be expected to have a higher likelihood of developing disease. Admixture mapping has been used to identify genes for cardiovascular disease risk [32], asthma [33], and prostate cancer [34] in African Americans, and genes for blood pressure [35], breast cancer [36], and lupus [37] in Hispanic Americans. In addition, the information of these AIMs is translated into a quantitative value that represents an estimate of the degree of the individual’s ancestral background, known as an estimate of genetic admixture.

There are other applications of genetic admixture methodology, particularly to the field of obesity and its related conditions. For example, estimates of genetic admixture have been associated with body composition parameters on different individuals and to outcomes related to insulin in response to glucose [19]. Research has demonstrated that the use of estimates of genetic admixture as covariates in genetic association studies reduces Type I error rates in the genetic association analyses and provides a genomic control for the effect of population stratification. The work of Divers and colleagues [38] demonstrates that adjustment for admixture in genetic association studies reduces Type 1 error rates. Figure 1 represents an adaptation of this work where data of three genes contributing significantly to a phenotype were simulated and a test for phenotype-genotype association was conducted in the presence and absence of admixture as a covariate. The inclusion of admixture in the model reduces the false positive rate and the association of these three genes with the phenotype can only be recovered without Type I errors when admixture measured without error is included in the model [38]. Some researchers have supported the use of estimates of genetic admixture to account for the genetic variation that accompanies racial/ethnic categorization. Figure 2 shows how the genetic background of individuals classified as part of one ethnic group (e.g. Hispanics) can differ according to their location and historical background, demonstrating the utility of genetic admixture in the control of population stratification. As the exploration of genetic influences underlying energy balance in humans continues to advance, the utility of genetic admixture as a tool to scientifically assess the heterogeneity that accompanies the study of human populations appears promising.

The interaction of gene and environment

As obesity prevalence increases in the population, researchers confront the need to investigate how genetic makeup interacts with environments that provide unlimited supply of affordable, energy-dense foods, and behaviors of limited energy expenditure. It is evident that the greatest

difficulty in the exploration of the interaction of nature vs nurture relies on disentangling the multiplicity of environmental exposures and genetic makeup that contribute to a disruption in energy balance.

There are several challenges when facing the exploration of the relationship between genes and environment. The first one is the definition of what entails environment when evaluating a particular trait and the development of an appropriate measurement that assess its contributions to phenotypic variability. A good example of this challenge is the evaluation of physical activity as an environmental factor contributing to obesity. It is well documented that engaging in physical activity under conditions of restricted and/or constant energy intake result in negative energy balance to reduce body weight, or energy equilibrium to keep weight constant. However, to what extent is engaging in physical activity an environmental measure? It is generally accepted that the decision of engaging in physical activity responds to a variety of factors, including accessibility to environmental settings where to engage in activity and the behavioral commitment to participate in exercise. Franks et al [39] showed that after adjusting for age, sex, ethnicity, study date, season and weight, familiar resemblance in physical activity energy expenditure in a sample of children was explained predominantly by shared environmental factors and not by genetic variability. However, a year later a QTL on chromosome 18 was identified for physical activity in a sample of children [40]. The discrepancy in these results might easily be explained by differences in the outcome used to define “physical activity”. In our laboratory, we have observed that multiple measures to assess physical activity (i.e., questionnaires, accelerometers, and treadmill tests) are not necessarily correlated in a multiethnic sample of children, providing support to the idea that these measures might represent different underlying constructs (unpublished data). A similar situation occurs when evaluating food intake as a measure of energy intake. Although individual choices exert an environmental dominant role, other factors such as taste differences, satiety, and physiological or behavioral response to stressors are controlled by genetic factors. It seems obvious that detailed exploration of the measures used to define environment is required to appropriately address the interrelationships between nature and nurture.

Another aspect to take into account when exploring the interactions between genes and environment is that although individual's genetic makeup remains constant throughout the lifespan, environmental effects accumulate progressively across a timeframe. Therefore, measuring an obesity-related outcome at one particular time represents the point of a continuum and, unless environmental exposure is obtained retrospectively, there would be no information of the external factors that progressively contributed to the outcome measured. The vast majority of investigators understand that obesity is a complex multifactorial condition; however, at the time of phenotypic assessment, it is often viewed from a one-dimensional perspective (i.e. body weight).

It is generally recognized that genes are expressed according to environmental influences. Exposing individuals to the same environment does not necessarily translate into identical outcomes. On the other hand, environmental variability can elicit a wide range of individual outcomes even in the presence of genetic similarity or homogeneity. With such variability in environmental exposures, it is difficult to identify which environmental factors should be measured in a population, and how to statistically account for their contributions to outcome variation. Clearly the disruption of energy balance that translates into obesity responds to nature, nurture and their interaction. Although recent literature has explored the interactions between gene and environment in aspects of energy balance, energy expenditure and obesity-related outcomes, it is evident that more research is needed to explore the methodological and statistical issues that underlie such interaction.

Conclusions

The search toward the understanding of nature and nurture in obesity continues to be a challenge as genes and environments interact to elicit a variety of effects in different physiologic and behavioral environments. The most remarkable reason for this centers on the complexity of obesity itself: a complex trait where many influences act create an outcome that represents the end of a cumulative process. Scientific research is beginning to explore approaches where the multifactorial nature of obesity is considered in experimental designs, including the inclusion of individual's genetic ancestral background, socio economic aspects, cultural factors and behavioral practices [41]. These approaches are believed to provide better insights into the etiology of obesity and disruptions of energy balance as an epidemiological risk, and are hopeful in the development of intervention strategies to attack the obesity epidemic. However, the control of energy balance that will prevent obesity and its comorbidities comes down to the individual level, where each person needs to take responsibility for their caloric intake and expenditure, taking into account their uniqueness of genetic background and environmental exposures to designate preventive approaches at the individual level.

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Figure 1. Role of Genetic Admixture in Reducing Type I error rates

The three circled dots represent the three simulated genes influencing the trait and all values above the horizontal line that are not the three influential genes represent false positive in a phenotype-genotype association. (A) represents an association without controlling for admixture, (B) represents an association controlling for a true value of admixture and (C) an association controlling for a value of admixture with an error (noise level) of 0.2.

Figure 2.
Distribution of genetic admixture estimates of two samples of Hispanic children from Mexico (A; n= 41) and from Alabama (B; n= 30)

Table 1

Candidate genes associated with obesity-related phenotypes that have been replicated in at least 5 studies. (*Modified from Rankinen et al, 2006*)

Gene	Name	Location	# of Studies Replicated
ACE	Angiotension Converting Enzyme	17q24.1	5
ADIPOO	Adiponectin	3q27	11
ADRB2	Adrenonegic Receptor - β	5q31-q32	20
ADRB3	Adrenonegic Receptor - β	8p12-p11.2	29
DRD	Dopamine Receptor D2	11q23.2	5
GNB3	G-protein-3 - β	12p13.31	14
HTR2C	5 HT Receptor	Xq24	10
IL6	Interleukin-6	7p21	6
INS	Insulin	11p15.5	7
LDLR	Low Density Lipoprotein Receptor	19p13.2	5
LEP	Leptin	7q31.3	11
LEPR	Leptin Receptor	1q31	16
LIPE	Hormone Sensitive Lipase	19q13.2	5
MC4R	Melanocortin - 4 Receptor	18q22	8
NR3C1	Glucocorticoid Receptor	5q31	10
PLIN	Perilipin	15q26	5
PPARG	Peroxisome proliferative Activated Receptor- γ	3p25	30
TNF	Tumor Necrosis Factor	6p21.3	9
UCP1	Uncoupling Protein 1	4q28-q31	10
UCP2	Uncoupling Protein 2	11q13.3	11
UCP3	Uncoupling Protein 3	11q13	12
VDR	Vitamin D Receptor	12q13.11	5