Medical and Clinical Archives

Short Communication ISSN: 2515-1053

Gene-environment interaction: The causes of high obesity incidence

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Abstract

Urbanization has provided experimental settings for testing the interactive relationship between genetic background and changes in lifestyle and dietary patterns. The concept of gene-environment interaction was described by epidemic of obesity along with urbanization. Genome-wide association has identified several genes such as melanocortin-4 receptor that associates with environmental influences of obesity. Gene environment (GxE) interaction refers to modification by an environmental factor of the effect of a genetic variant on a phenotypic trait. GxE interactions can serve to modulate the adverse effects of a risk allele, or can exacerbate the genotype-phenotype relationship and increase risk.

Review

The recent epidemic of obesity along with the increasing spread of Western-type lifestyles worldwide is a good illustration of the concept of gene-environment interaction. Because the gene pool of a certain population has been relatively constant for many generations, it seems that dramatic changes in lifestyle and dietary habits have played a role in triggering the recent surge of excessive adiposity [1].

Urbanization and migration have provided good experimental settings for testing the interactive relationship between genetic background and changes in lifestyle and dietary patterns. Risk of obesity increases after migration from poor to affluent countries [2]; the adoption of a Western dietary pattern is believed to be the major cause of the obesity prevalent in immigrants [3]. In the United States, Asian American and Hispanic American adolescents are more than twice as likely to be obese as first-generation immigrants from their countries of origin [4].

Obesity is a multifactorial abnormality that has a genetic basis but requires environmental influences to manifest. Several genes such as FTO (fat mass and obesity associated) and MC4R (melanocortin-4 receptor) identified by genome-wide association (GWA) scans have been convincingly associated with obesity risk in various populations [5,6].

A gene environment (GxE) interaction refers to modification by an environmental factor of the effect of a genetic variant on a phenotypic trait [7]. Environmental factors can include climate, diet, dietary components such as saturated fatty acids, physical activity, sedentary behavior, alcohol, or sleep, among many others. Such GxE interactions can serve to modulate the adverse effects of a risk allele, or can exacerbate the genotype-phenotype relationship and increase risk [8].

Gene-environment (GxE) interactions describe a modifiable relationship between genetic variation and changes in phenotype [9,10]. To accomplish homeostasis, adjustments to molecular parameters must be enacted that correspond to the stimulatory challenge, which typically includes altered protein function or gene expression. This all amounts to continual changes to the phenotypes of the cell or organism and it is the timeliness and efficiency of these phenotypic adjustments that determine health and healthy aging. This process can be termed phenotypic flexibility, a phenomenon which is a central concept of the gene-environment interaction [11].

A report in 2011 cataloged 554 GxE interactions, 377 of which contained common traits and environmental factors, that reached statistical significance and were pertinent to nutrition, cardiovascular diseases, blood lipids and type-2 diabetes mined from 184 scientific reports [12]. Table (1) describes selected observational studies of gene-lifestyle interactions on obesity:

Reference	Gene (Variants)	Lifestyle factors	Major findings
Alonso, *et al.* [13]	UCP3 (-55C>T)	Physical activity	Carrying T-allele was associated with lower risk of obesity only in those with higher physical activity.
Ridderstrale, *et al.* [14]	PPARGC1A (GLy482Ser)	Physical activity	Elderly men carrying Ser-allele had increased risk of obesity.
Miyaki, *et al.* [15]	ADRB3 (Trp64Arg)	Total energy	Arg64-allele carriers were associated with greater obesity risk than Trp64Trp homozygotes, but only in the highest energy intake quartile.

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Key words: *obesity, gene-environment interaction, environmental factors, genetic predisposition, social networks*

Received: May 20, 2017; **Accepted:** June 09, 2017; **Published:** June 12, 2017

Song, *et al.* [16]	IL6R (Asp358Ala)	Total energy	Energy intake was significantly associated with WC in T-allele carriers, but not in GG homozygotes (p-interaction=0.03).
Marti, *et al.* [17]	PPARG (Pro12Ala)	Carbohydrate	Pro12Ala was associated with increased risk of obesity only in those with higher CHO intake (p-interaction=0.02).
Martinez, *et al.* [18]	ADRB2 (Gln27Glu)	Carbohydrate	Women with high CHO intake had greater risk of obesity than those with low CHO intake only in Gln27Glu heterozygotes.
Nieters, *et al.* [19]	11 genes (15 SNPs)	n-6 PUFAs	Substantial interaction between variants in PPARG2, TNFA, leptin (possibly APM1, HSL) and dietary n-6 FA intake in relation to obesity risk.
Robitaille, *et al.* [20]	PPARG (Pro12Ala)	Total fat, Saturated FAs	In women, Pro12Pro homozygotes were positively associated with total fat and SFA intake in relation to WC and BMI, but not in Ala-allele carriers.

According to Ellulu [21], obesity is caused by a complex interaction between the environment, genetic predisposition, and human behavior as the following:

1- Environmental factors are likely to be major contributors to the obesity epidemic. It is certain that obesity develops when there is a positive imbalance between energy intake and energy expenditure. Evidence supports the contribution of both excess energy intake and decreased energy expenditure in the obesity epidemic:

(1) Kant and Graubard [22] mentioned that the temporal trends in the increase of the quantity and energy density of foods consumed by adults parallel the increasing prevalence of obesity in the U.S. population. (2) Dietz and Gortmaker [23] demonstrated that the prevalence of obesity increased by 2% for each additional hour of television viewed. (3) There is also evidence that the relative availability and price of different food products affect food consumption [27]. (4) The built environment, such as quality of local parks, affects the level of physical activities in a community [25].

2- In addition to environmental factors, there is ***genetic predisposition*** to obesity. The single gene mutations are responsible for rare forms of monogenic obesity (leptin [LEP], leptin receptor [LEPR], melanocortin-4 receptor [MC4R], and pro-opiomelanocortin [POMC]) [26].

However, there is growing evidence that common genetic variants or single-nucleotide polymorphisms (SNP) may play an important role in the obesity epidemic. These SNPs have modest effects on an individual susceptibility to common forms of obesity, but due to their high frequency, they can have a large contribution to obesity on the population level [27]. Frayling, *et al.* [6] used a genome-wide association (GWA) study to identify a SNP located in the fat mass and an obesity-associated gene (FTO) that is associated with an increased risk of common obesity. FTO was initially identified in a GWA study to be associated with an increased risk of type 2 diabetes mediated through an effect BMI. In a GWA study of 38,759 patients, Frayling, *et al.* [6] found that a person who is homozygous for the risk allele (rs9939609 A allele) had a 1.67-fold increased odds of obesity when compared with those who do not have the risk allele.

3- Social networks have an important role in the obesity epidemic. Christakis and Fowler [28] explored the hypothesis that obesity may spread through social networks by evaluating an interconnected social network of more than 12,000 people from the Framingham Heart Study to examine the effects of weight gain among friends, siblings, and spouses. They found that a person's risk of becoming obese increased by 57% if a friend became obese, the risk of becoming obese increased by 40% and 37% if a person had a sibling or spouse who became obese, respectively.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the current presentation.

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