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Review article

Gene and environment interaction: Is the differential susceptibility hypothesis relevant for obesity?

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ABSTRACT

The differential susceptibility model states that a given genetic variant is associated with an increased risk of pathology in negative environments but greater than average resilience in enriched ones. While this theory was first implemented in psychiatric-genetic research, it may also help us to unravel the complex ways that genes and environments interact to influence feeding behavior and obesity. We reviewed evidence on gene vs. environment interactions that influence obesity development, aiming to support the applicability of the differential susceptibility model for this condition, and propose that various environmental "layers" relevant for human development should be considered when bearing the differential susceptibility model in mind. Mother-child relationship, socioeconomic status and individual's response are important modifiers of BMI and food intake when interacting with gene variants, "for better and for worse". While only a few studies to date have investigated obesity outcomes using this approach, we propose that the differential susceptibility hypothesis is in fact highly applicable to the study of genetic and environmental influences on feeding behavior and obesity risk.

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1. Introduction

Changes in lifestyle overtime have led to an increased availability/consumption of energy-dense food, and to a decrease in physical activity, predisposing many more individuals to obesity and its complications. It is known that genetic heritage also contributes to obesity risk, and both linkage analysis and candidate gene association studies identified numerous genetic variants underlying body-weight regulation (Apalasamy and Mohamed, 2015; Locke et al., 2015). However, as is the case with other complex phenotypes, the total variance in BMI explained using these approaches is only in the 2–5% range. There are clear limitations when explaining obesity risk based on environment or genetics alone, and thus an urgent need to implement new strategies to unravel the complex mechanisms and pathways leading to pathological weight gain over time.

Different types of genetic variants, their frequency in the population, and the effect of the variant on phenotype can mediate the genetic effects on body weight. Variants include: a) single-nucleotide variations in which only one nucleotide is changed; b) copy number variations in which a stretch of DNA is repeated or deleted (often containing many genes); or c) small insertions and deletions of a few base pairs. Generally, the effect size of common obesity associated variants on body weight is modest (Van Der Klaauw and Farooqi, 2015).

Genome-wide Association Studies (GWAS) have made significant headway in identifying genetic variants underlying obesity (Cotsapas et al., 2009; Meyre et al., 2009; Jiao et al., 2011; Paternoster et al., 2011; Wang et al., 2011; Melka et al., 2012; Pei et al., 2014; Locke et al., 2015). However, most of these studies focused on body mass index as the main outcome, failing to take into consideration behavioral differences that can precede the development of obesity. A better understanding of individual behaviors, specially eating behavior, is very important to explain BMI variability and also BMI increases (Vainik et al., 2013). Therefore, not only metabolic variables but also behavioral variables should be the focus of studies involving genetic variants. We propose that a better understanding of individual behaviors is helpful in terms of identifying vulnerability and proposing interventions to prevent or reverse weight gain. Also, genes may work by modulating the way individuals respond to environmental variation, and these discrete and differential genes vs. environment interactions may not be readily captured in simple association studies.

Therefore, many studies are trying to elucidate how genes interact with environmental exposures to shape human health. The dominant paradigm in most of the gene X environment (GxE) work is based on the diathesis-stress hypothesis, in which some individuals are more vulnerable than others to the negative effects of environmental adversity (e.g., insensitive parenting, childhood maltreatment, poverty), saying nothing about different genetic predispositions for responsiveness to positive environmental experiences (Zuckerman, 1999; Cameron et al., 2005).

The differential susceptibility hypothesis (Belsky, 1997; Boyce and Ellis, 2005; Belsky and Hartman, 2014), firstly observed in psychiatric-genetic research (Belsky and Pluess, 2013), suggests an alternative approach to genetic association studies that may have particular utility for other common, complex diseases such as obesity. The differential susceptibility hypothesis proposes that, as a form of bet-hedging against an uncertain future, natural selection has maintained genes for both "conditional" (shaped by the environment) and "alternative" (fixed) health strategies (Rowe et al., 1997). In other words, individual variations in the magnitude of biological responses regulate openness or susceptibility to environmental influences, ranging from harmful to protective (Boyce and Ellis, 2005).

In recent years, evidence is clarifying that individuals vary both in relation to how much they are negatively affected by environmental adverse events (Caspi et al., 2002; Caspi et al., 2003) and how much they are positively influenced by the provision of resources and supports (Blair, 2002; Quas et al., 2004). Interestingly, it seems that the same characteristics that make individuals vulnerable to adversity could also make them more likely to benefit from environmental support (Boyce et al., 1995; Belsky, 1997; Boyce and Ellis, 2005; Belsky et al., 2007).

Belsky et al. (2009) suggests that individuals vary for genetic reasons in their susceptibility to context. According to Belsky's theory, vulnerability genes may function like developmental plasticity genes, resulting in certain individuals being more responsive than others to both positive (e.g healthy fetal environment, warm/sensitive care, high socioeconomic status) and negative (e.g. altered fetal environment, low maternal sensitivity, low socioeconomic status) environmental experiences, including the simple absence of contextual adversity (Belsky et al., 2009). There are two genes, the serotonin transporter gene (5-HTT) and the dopamine receptor gene (DRD4), that have been extensively studied as "vulnerability genes" predisposing carriers of particular alleles to psychiatric disorders in the face of adversity. However, recent evidence indicates that these genes might behave as "plasticity genes", making carriers of the putative risk alleles especially susceptible to environmental influences (Belsky and Hartman, 2014). Interestingly, these two genes known to have supported the differential susceptibility hypothesis have also been explored as potential genes associated to obesity (Fuemmeler et al., 2008). Many studies explore the relationship between overweight and the genetic variations in DRD2 and DRD4 receptors (Levitan et al., 2004a, 2004b; Levitan et al., 2006; Epstein and Temple et al., 2007; Kaplan et al., 2008; Levitan et al., 2010; Silveira et al., 2014). It is well established that dopamine system genes modulate experiential and behavioral responses to the environment on the one hand, while promoting phenotypic vulnerability to overeating and obesity on the other, though limited work to date has attempted to link these two effects. In addition, it is known that serotonin signaling modulates the reward value in humans (Seymour et al., 2012), expanding its classic role on mood regulation (Haddjeri et al., 1998) and emotional development (Pluess et al., 2011). These studies provide a basis to propose that dopamine and serotonin systems genes can promote overeating and obesity through the developmental plasticity effects.

According to this theory we can propose that individuals with genetic variants related to obesity could have a chance of not developing the disease if they could engage in an enriched/healthier environment. Therefore, combining the advance in genetic technology with theoretical hypotheses promotes the development of new studies handling both the genetic and environmental factors that contribute to obesity, promising to point to more effective interventions for prevention and treatment.

In this report we propose a brief review of the "plasticity genes" theory and the main genes involved (serotonin and dopamine systems' genes); and a more deep review and discussion regarding the