Advances in Social Science, Education and Humanities Research, volume 638
Proceedings of the 2021 International Conference on Public Art and Human Development (ICPAHD 2021)

A Review of the Genetic Effects on Appetite Regulation: An Obesity Perspective

Tianyu Wang

University of Western Ontario, 1151 Richmond Street, London, Ontario, Canada, N6A 3K7
Email: twang579@uwo.ca

ABSTRACT
Obesity is a worldwide epidemic. It is a medical condition in which abnormal or excessive fat has been accumulated to present health risks including diabetes, hypertension, heart disease and several cancers. Obesity is a multi-factorial health issue that is related to a combination of causes, such as behavior, genetics, and environment. It is important to explore the genetic factors and metabolic pathways in the precise treatment of obesity. Base on the summary of twin studies, this paper discussed the pathophysiological abnormalities that genetically affect obesity and the role of appetite regulation in addressing obesity. Obesity affects every major system of human body, so it is of great significance to understand its mechanism and carry out effective prevention and treatment.

Keywords: *Obesity, Appetite Control, Obesogenic, Gene, Behavioral Psychology*

1. INTRODUCTION

In the past few decades, obesity has become a global epidemic. Like other chronic diseases, obesity is now a major preventable cause of death worldwide, and the mortality rate of children and adults is increasing. There are many reasons for excessive fat deposition in obese people, but it is generally believed as a result of the imbalance of energy intake and consumption. To counter this view, by summarizing the key twin studies over the past two decades, the article will give a brief discussion of the relationship between appetite regulation and obesity genes. Moreover, the paper will examine the genetic effect on appetite regulation in terms of genetic basis, behavioral susceptibility hypothesis, and central nervous system circuits. Identifying variants in appetite through genetic basis are essential for understanding excessive weight gain. The findings might offer potential targets for obesity prevention efforts, but further research is needed to see if they can be implemented in human beings.

2. ANALYSIS OF GENETIC EFFECT ON HUMAN BODY WEIGHT

2.1. Genetic Basis of Human Body Weight

Studies on the main genetic effects of obesity have successfully identified some monogenic forms of obesity. For decades, the comparative research on the weight difference between identical twins and fraternal twins shows that even among those exposed to a similar environment, the susceptibility to obesity is quite different. Dozens of twin studies have confirmed that obesity has a strong genetic basis, and meta-analysis shows that human body weight is highly heritable (47-90%). [1] The emergence of genome-wide association studies (2007) began to identify some common genetic variations. Fat and obesity-related genes (FTO) are the most influential among all the common variants studied so far. It has been confirmed that adults with average height carrying two high-risk versions of FTO are about 3kg heavier than adults with lower versions of genes [1]. MC4R (encoding melanocortin four receptors) mutation accounts for about 5% of extreme early-onset obesity, and it is the most common genetic variation together with FTO mutation. Since 2006, genome-wide association studies have found 97 common variations closely related to the weight of adults and children. Table 1 shows the variant genes related to obesity. Weight has a strong genetic basis, and many studies have begun to identify some common variations involved in practice [2]. Stephen O'Rahilly, the professor of clinical biochemistry at University of Cambridge, emphasized three possible ways related to how genes affect weight: dividing nutrients into fat, total energy consumption, and energy intake [3]. It is essential to understand the mechanism of genes affecting body weight. If we can understand the

degree of genetic control of these different processes, we can explain why some are susceptible.

Gene symbol	Gene name	Gene product's role in energy balance
ADIPOQ	Adipocyte-, C1q-, and collagen domain-containing	Produced by fat cells, adiponectin promotes energy expenditure
FTO	Fat mass- and obesity-associated gene	Promotes food intake
LEP	Leptin	Produced by fat cells
LEPR	Leptin receptor	When bound by leptin, inhibits appetite
INSIG2	Insulin-induced gene 2	Regulation of cholesterol and fatty acid synthesis
MC4R	Melanocortin 4 receptor	When bound by alpha-melanocyte stimulating hormone, stimulates appetite
PCSK1	Proprotein convertase subtilisin/kexin type 1	Regulates insulin biosynthesis
PPARG	Peroxisome proliferator-activated receptor gamma	Stimulates lipid uptake and development of fat tissue

Figure 1 The variant gene associated with obesity [2]

2.2. Behavioral Susceptibility to Obesity

Appetite-regulating is related to brain circuits and psychological mechanisms. Psychological theories are classified into two categories: steady-state and incentive salience. In 1932, Walter Cannon first proposed the theory of homeostasis, he believed that humans had delicate mechanisms to maintain the internal environment stable despite environmental changes. [4] Although the homeostasis theory sounds consistent with our intuition of foods, it contradicts some behavioural phenomena. For example, the weight baseline and average BMI (Body Mass Index) have continued to increase over the past few decades. [5] If there was a stable target, the worldwide obesity rate would be a lot lower. Moreover, homeostasis theory only explains the body's energy needs, but not individual food preferences. The concept of incentive motivation divides dietary motivation into two components: liking and desiring. According to the behavioural susceptibility hypothesis, the obesity genes influence weight by affecting hunger and satiety. [6] Individuals are varied in food responsiveness and fullness. The desire of eating can be activated by the aroma, appearance, and taste of delectable food [7]. "Desiring" results from brain's analysis of sensory information which leads to emotional reactions. The responses may be affected by both nature and nurture. According to the idea, those who inherit a set of genes will exhibit increased food responsiveness and decreased satiety [6]. In the current "obesogenic" environment, which offers accessible high calories foods but limits opportunities for physical activity, individuals with these genes are more likely to overeat and gain excessive weight. Additionally, this approach contributes to the explanation of the seemingly contradictory phenomenon of genetics and environment determining weight. Some people inherited a set of genes that made them extremely food sensitive, and individuals with low satiety were more prone to overeat in the current environment than in the past.

2.3. The Appetite Pathway in the Brain, Leptin, and Pathology of Obesity

The term "obesity gene" refers to a protein encoded by the gene that is part of a system regulating appetite and energy balance. The defeat of the single gene may lead to the build-up of body fat and weight increase, either directly or indirectly [8]. The prominent one that has been identified is the gene coded for a hormone called leptin. The synthesis and secretion of leptin increase as the body fat level rises. Leptin binds to its receptor to form leptin-Rb, which triggers the production of the Proopiomelanocortin (POMC), a pituitary precursor, in hypothalamic neurons. The high expression of POMC raises the concentration of its breakdown product melanocyte-stimulating hormone (α-MSH), which subsequently binds to the MC4R, encodes the melanocortin 4 receptor, causing a physiological impact of appetite suppression [9]. By lowering the conjunction with leptin receptor inhibition of desire leads to decreased body fat content, reduced leptin synthesis, secretion, and reduced POMC expression in hypothalamic nerve cells. Due to an increase in MC4R unbound, decreased POMC

secretion leads to a decrease in α-MSH concentration, resulting in the physiological impact of increased appetite [9]. Through leptin-mediated appetite regulation, people's weight can be stabilized in a particular range under normal physiological conditions. When any of the above genes are mutated, and the feedback process is broken, people are easily addicted to foods, and more likely to be obese. Although obesity has often been attributed to an individual's imbalanced living habits, such as excessive calorie intake and insufficient exercise, genetic factors are equally important. Research into the genetic factors of obesity will ultimately contribute to the prevention and treatment of obesity.

3. DISCUSSION OF GENETICS BASIS AND EPIGENETICS OF OBESITY

A key study of twins in 1990 has found out that inherited factors play a bigger role in obesity than childhood environment. To evaluate the correlation between genetic and environmental effects on BMI, scientists have been studying twins to find out to what extent their appetite is genetically controlled and to what time they share a common genetic pathway [10]. Identical twins are gene clones of each other, and 50% of genes of non-identical twins are similar on average. Therefore, they are practically the same as any ordinary brothers and sisters in genetic correlation, but the key difference is that they share their environment to a very similar degree.[10] This study assumes the only difference between the two kinds of twins is that identical twins are more genetically similar than fraternal twins. It intuitively compares the similarities between twins with any specific characteristics of interest, such as BMI and eating habits. Statistics obtained from the twin model are called heritability. It is an index of the size of the genetic effect, emphasizing the traits of gene variation attributed to individual differences. Intra-group correlation is used as the basis for comparing the differences and similarities between identical and fraternal twins. The average correlation point of identical twins is 0.3 points higher than that of non-identical twins [10]. A quick way to estimate heritability is to double the difference between them. Therefore, the correlation model will show about 60% heritability of this trait.

The study focused on the appetite of children, not adults, for several reasons. First, children are less likely than adults to deliberately change their eating behavior when being observed, especially in weight research. Second, children diet less, which affects the relationship between their eating behavior and weight. Third, they don't have long-term obesity. Obesity itself will lead to biological abnormalities that affect appetite. If the observation starts early, the causal relationship between desire and weight can be sorted out. The first large-scale population-based twin study on appetite and weight was initiated by Professor Susan Carnell and Jane Wardell in 2008. [11] They measured anthropological data on 5,000 pairs of twins, including weight, height, and waist circumference, as well as two appetitive traits, including satiety responsiveness and food-cue responsiveness. This is the first time to discover the relationship between adiposity and appetite in a twin sample. Moreover, DNA and genome-wide correlation data indicate the relationship between appetite and the identified common genetic variation [11].

A questionnaire covering eight different eating behaviors of children, has been developed to measure these characteristics on a considerable population scale and the numbers needed to establish a reliable heritability estimate related to weight [12]. It is supposed to be related to weight, in which two scales measure food reactivity and satiety. Wardell in 2008 with Carnell looked to see how the aptitudes traits related to weight in the sample [12]. In order to explain the difference of BMI units, they divided the children into low normal or low healthy weight groups, high health rehabilitation groups, super rehabilitation groups, and clinical observation groups. The results show that there seems to be a linear relationship between weight and appetite characteristics. Obese children are only less sensitive to satiety than their peers. Children with lower average weight have a worse reaction to food than children with higher average weight. Likely, higher food responsiveness was directly related to raise of children's waist circumference.

The study also determined the heritability of these traits by comparing the similarities between identical twins and non-identical twins. The high similarity of identical twins in food responsiveness and satiety indicates that these two ability characteristics have a substantial genetic contribution [12]. It supports the view that genes help regulate appetite. By the age of 10, desire has a strong genetic basis, and the relationship between hunger and weight has been well established. The twins' early development study also had genotyping data. After analysing the association between satiety sensitivity and FTO genotype, children who carried two copies of the high-risk version were significantly less satiety sensitive than the other children. This relationship remained after adjustment of the children's BMI which indicated that some "obesity genes" are influencing satiety sensitivity independently of their body size.

4. CONCLUSION

Obesity has been included in one of the primary diseases that affect the quality of human life in the 21st century. By introducing the mechanism of obesity and the relationship between appetite and obesity genes, this paper concludes that genetic influences on body weight are substantial. Obesity genes could be influencing weight through their effects on appetites. Variants in appetite have a strong genetic basis and drive weight gain. Self-control alone is rarely enough to overcome the

powerful effects of genes. It is critical to assess how a healthy diet and exercise combined with a better understanding of how genes influence obesity can help turn the tide on this global epidemic.

REFERENCES

[1] Loos, R. J. F., & Bouchard, C. (2008). FTO: the first gene contributing to common forms of human obesity. Obesity reviews, 9(3), 246-250. https://doi.org/10.1111/j.1467-789X.2008.00481.x

[2] Office of Science (OS), Office of Genomics and Precision Public Health, 2013, Genes and obesity. https://www.cdc.gov/genomics/resources/diseases/obesity/obesedit.html

[3] O'rahilly, S., & Farooqi, I. S. (2008). Human obesity: a heritable neurobehavioral disorder that is highly sensitive to environmental conditions. Diabetes, 57(11), 2905-2910. https://doi.org/10.2337/db08-0210

[4] Cannon, W. B. (1932). The wisdom of the body. The American Journal of the Medical Sciences, 184(6), 864. https://doi.org/10.1097/00000441-193212000-00028

[5] Skinner, A. C., & Skelton, J. A. (2014). Prevalence and trends in obesity and severe obesity among children in the United States, 1999-2012. JAMA pediatrics, 168(6), 561-566. doi:10.1001/jamapediatrics.2014.21

[6] Llewellyn. (2018). Genetic susceptibility to the "obesogenic" environment: the role of eating behavior in obesity and an appetite for change. The American Journal of Clinical Nutrition, 108(3), 429–430. https://doi.org/10.1093/ajcn/nqy210

[7] Castellanos, E. H., Charboneau, E., Dietrich, M. S., Park, S., Bradley, B. P., Mogg, K., & Cowan, R. L. (2009). Obese adults have visual attention bias for food cue images: evidence for altered reward system function. International journal of obesity, 33(9), 1063-1073. https://doi.org/10.1038/ijo.2009.138

[8] Gong, D. W., Bi, S., Pratley, R. E., & Weintraub, B. D. (1996). Genomic structure and promoter analysis of the human obese gene (∗). Journal of Biological Chemistry, 271(8), 3971-3974. https://www.jbc.org/article/S0021-9258(17)36452-9/fulltext

[9] Kim, G. W., Lin, J. E., Valentino, M. A., Colon-Gonzalez, F., & Waldman, S. A. (2011). Regulation of appetite to treat obesity. Expert review of clinical pharmacology, 4(2), 243-259. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3111219/

[10] Stunkard, A. J., Harris, J. R., Pedersen, N. L., & McClearn, G. E. (1990). The body-mass index of twins who have been reared apart. New England journal of medicine, 322(21), 1483-1487. https://www.nejm.org/doi/full/10.1056/NEJM199005243222102

[11] Carnell, S.& Wardle, J. (2008). Appetite and adiposity in children: evidence for a behavioral susceptibility theory of obesity. The American Journal of Clinical Nutrition, 88(1), 22–29. https://doi.org/10.1093/ajcn/88.1.22

[12] Haworth, C. M. ., Carnell, S., Meaburn, E. L., Davis, O. S. ., Plomin, R., & Wardle, J. (2008). Increasing Heritability of BMI and Stronger Associations With the FTO Gene Over Childhood. Obesity (Silver Spring, Md.), 16(12), 2663–2668. https://doi.org/10.1038/oby.2008.434