

The Role of Genes in the Current Obesity Epidemic

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Abstract

Introduction: Obesity is a global pandemic and a major health concern. Obesity is a common but complex, multifactorial disorder with high heritability, where as much as 80% of the variance in the body mass index (BMI) is attributable to genetic factors. **Materials and Methods:** Literature on the contributing factors of the current obesity epidemic, and genetic basis of human obesity, were reviewed. **Results:** The current increasing prevalence of obesity is a relatively recent global event driven by our modern lifestyle and dietary habits. Common obesity is the result of subtle interaction between numerous related genetic variants and environmental factors. The role of the obesity genes in this current epidemic is passive, but its impact is highly significant, because individuals with these genes may be predisposed to severe or even morbid obesity when exposed to the modern “obesogenic” environment. **Conclusions:** The human weight regulation mechanism evolved and becomes efficient in preventing weight loss, but is relatively ineffective in preventing excessive weight gain. The modern “obesogenic” environment encourages a sedentary lifestyle and provides easy access to processed food, which leads to a reduction of energy expenditure and increased caloric intake. We have inadvertently created a biology-environment mismatch, as the human weight regulation is unable to evolve fast enough to keep pace with the environmental change. This resulted in maladaptation of an otherwise sound and metabolically efficient physiological mechanism, with serious metabolic consequences.

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Introduction

Obesity is a global pandemic and a major health concern because of the consequent morbidity and premature mortality; obesity predisposes to serious morbidities such as type 2 diabetes, hypertension and coronary heart disease. Industrialisation and modernisation is rightly blamed for the increasing obesity prevalence all over the world, as it created an “obesogenic” environment with caloric abundance and ubiquitous automation which encouraged sedentary lifestyles,^{1,2} resulting in energy intake and expenditure imbalance and favours the net deposition of calories as fat. Although this trend of increasing body girth is very much driven by the “obesogenic” environment, it is facilitated by the individual’s genetic susceptibility to excessive weight gain.³

Obesity is a common but complex, multifactorial disorder with high heritability. While it is well established that obesity runs in families, the familial clustering is not just due to a common lifestyle and shared environment. Studies

in twins, adoptees and families indicate that as much as 80% of the variance in the body mass index (BMI) is attributable to genetic factors. Relative risk of obesity among siblings was estimated to be 3 to 7,⁴ the concordance rate of obesity is higher between monozygotic twins than dizygotic twins,⁵⁻⁷ and adoptees’ weight is often closer to their biological parents than their adoptive parents.⁸ These and several other comprehensive studies incorporating twins, adoptees and family data have estimated the heritability of BMI or body fat to be 25% to 40%.⁸⁻¹¹ These studies supported the role of genes in the pathogenesis of human obesity.

However, obesity has a wide phenotypic variability, ranging from the mildly overweight to the morbidly obese, as well as the spectrum of early (childhood) to late (adult) onset. The relative contribution of the environment and genetic susceptibility towards the pathogenesis of obesity varied between different obese individuals, even within the same family, and may contribute to this phenotypic

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variability. The environment and a sedentary lifestyle may be the dominant contributing factor in the development of late onset obesity in an adult, while genetic factors may exert a greater influence in a young child who developed early onset obesity in the “obesogenic” environment, and such notion is supported by the knowledge that the heritability of early-onset obesity may be considerably higher than that of adult-onset obesity.⁸ This heterogeneity may even extend to the individual’s response to weight losing measures. In individuals where environmental factors are predominant, they may find it easier to lose weight compared to individuals whose genetic factors predominate.

While family, twins and adoption studies as well as numerous linkage and association studies have provided considerable evidence which supported the genetic basis for human obesity, the current increasing prevalence of obesity is a relatively recent global event which occurred only in the last few decades. It is inconceivable that genetic mutations or major shifts in allelic frequencies of obesity-related genes are responsible for this surge, given the stable gene pool of the world’s population in this short period of time.^{12,13} However, though the role of the obesity genes in this current epidemic is passive, its impact is highly significant, because individuals with these genes may be predisposed to severe or even morbid obesity when exposed to the modern “obesogenic” environment. Historically, mankind has faced prolonged periods of starvation and hardship, and was constantly required to gather or hunt for food. The ability to conserve energy in the form of adipose tissue would therefore confer a significant survival advantage, where the human body is enriched with genes which favour the storage of energy, and diminished energy expenditure (thrifty gene hypothesis), and therefore more likely to survive natural selection over the centuries.^{2,14} The human weight regulation mechanism evolved and became efficient in preventing weight loss, but relatively ineffective in preventing excessive weight gain.

The modern “obesogenic” environment of industrialised countries developed over the past few decades in our bid to reduce work and improve efficiency and quality of life. The population becomes increasingly sedentary and reliant on machines and automation. Coupled with easy access to processed food, this led to a reduction of energy expenditure and increased caloric intake. While human ingenuity has succeeded in creating an environment of work efficiency and plenty, it has also inadvertently created a biology-environment mismatch, as the human weight regulation is unable to evolve fast enough to keep pace with the environmental change. This resulted in maladaptation of an otherwise sound and metabolically efficient physiological mechanism, with serious metabolic consequences. Consequently, the proportion of overweight people has

risen steadily over the years. In particular, there is a pronounced increase in morbid obesity which cannot be explained by a mere shift in population mean.¹² The hypothesis is that the “obesogenic” environment has caused a subgroup of the population, who are genetically susceptible to severe weight gain, to become excessively obese.¹⁵ These individuals may possess the ‘thrifty genes’ (obesity genes) which would otherwise be protective against starvation (and therefore confer selection advantage historically). However, in the present day ‘obesogenic’ environment, high-risk groups such as the Pima Indians, Pacific Islanders, Afro-Americans and Hispanic-Americans might develop severe obesity.¹⁶

Obesity gene research has advanced rapidly over the past 2 decades, which has provided revelation of the molecular mechanism of energy homeostasis in the process. Traditional methods employed to uncover these obesity genes include genome-wide scans which studied unrelated obese individuals, linkage studies which examined related pairs or families with obesity, and association studies which investigated the association between obesity and polymorphic variants of candidate genes predicted to affect weight regulation. Unlike other multifactorial disorders, these approaches have not been as promising for common obesity, because the obese phenotype is very heterogeneous, even within the same family. There is variable contribution from genetic, environmental and behavioural influences which differ for every obese individual, confounding efforts to analyse this condition. While several syndromic forms of human obesity such as the Prader-Willi syndrome and Bardet-Biedl syndrome have been genetically mapped and causative genes identified, their exact roles in the pathogenesis of obesity and the underlying molecular mechanisms have not been isolated yet.¹⁷

The search for genetic factors predisposing to common obesity is challenging and progress has been slow, as it is likely that each individual genetic variant exerts subtle effect on body weight and thus proving its association with increased adiposity can be difficult. It is still unclear if the genetics of common obesity conform to the “common variant-common disease model”, where common polymorphisms in multiple loci contribute collectively to the risk of obesity, or the “rare variants-common disease model” where multiple rare alleles collectively exert an effect.¹⁸ The availability of advanced computers and technologies such as high density single nucleotide polymorphism (SNP) microarrays and high throughput sequencing machines have made it possible to analyse combinations of multiple SNPs or haplotypes in candidate genes related to weight regulation, and hopefully we will be wiser about the genetic architecture of common obesity in the very near future. A novel but converse approach to

identify genes affecting weight regulation is to study individuals who are thin and have difficulty gaining weight (obesity resistance), such as children with a failure to thrive and without identifiable disorders.^{18,19} Just like obesity, leanness is heritable,²⁰ and it is therefore conceivable that studies of the reverse phenotype can complement the efforts to uncover the obesity genes.

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