

Gene-environment interactions and the genetic epidemiology of obesity: correlates for preventative medicine

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Abstract

As obesity rates continue to rise in the United States, and throughout the world, the role of genetics is playing an increasingly prominent role in understanding the underlying causes of this disease. Numerous studies have been undertaken to understand the role of genetics in obesity, and to identify those candidate genes which are associated with such. This has resulted in studies showing various degrees of association between obesity-related morphological characteristics, including increased body mass index, hip circumference and height/weight ratios, and genetic variants, particularly in the FTO and PFKP genes. The true value of these studies is not in their causal explanations for obesity, but rather in the importance of understanding the role of the gene-environment interaction, and the way in which such can be used to develop integrated public health prevention programs for obesity which are based upon lifestyle risk factors for such.

Keywords: obesity, genetic epidemiology, public health, gene-environment interaction, prevention

Introduction

Genetics is playing an increasing role in both public health and well as direct medical applications. Because of this increasing importance of genetics in public health, the role of genetics in addressing some of the most pressing public health concerns of our time is also increasing in importance. In the United States, and other developed countries, this means that genetic epidemiology will play an important part in understanding the underlying role that genetics play, in concert with environment and lifestyle choices, in the development of chronic diseases.

Chronic diseases currently represent the largest current threat to the health of Americans, with the three leading causes of death in the United States being heart disease, cancers and stroke.¹ These diseases all have genetic components, which when combined with environmental influences result in a high cost to society, both in terms of direct costs of treatment, as well as lives lost.² Obesity is the single risk factor that ties all three of these diseases together, and which itself has a genetic component³, which if understood could have a great impact on what has become an epidemic of obesity in the United States. Obesity is a major risk factor for other chronic diseases, with a relative risk of 1.9 for death by coronary heart disease (CHD), or similar to that of smoking, accounting for 35% of all deaths linked to CHD, and approximately 350,000 deaths in the United States each year.²

Epidemiology of obesity

Obesity is an increasing problem for the United States; as of 2008,

only Colorado had an incidence rate of obesity that was less than 20%, while 32 states have prevalence rates higher than 25%, and six states (Alabama, Mississippi, Oklahoma, South Carolina, Tennessee, and West Virginia) have obesity rates greater than 30% of their state's population.¹ The most dramatic increase in obesity between 1980 and 2015, has been among children; with prevalence rates for those aged 2-5 increasing from 5% to 12.4%; 6.5% to 17% for ages 6-11; and finally, a rise from 5% to 17.6% for those ages 12-19.¹ Given the understanding that many adult problems, particularly those which may contain a genetic basis,³ often have roots in childhood, this increasing trend among children represents a real threat to the future ability of public health agencies and healthcare entities to respond to obesity and its related diseases in an effective manner.²

Such is evidenced by the fact that those populations most likely to be obese are also those most likely to be socioeconomically disenfranchised, including ethnic and racial minorities, with the prevalence of obesity among African Americans at 35.7%, or 51% higher than Caucasians, and prevalence among Hispanics at 28.7%, or 21% greater than Caucasians.¹ This trend is particularly evident among pre-school aged children in this category, with an increase from 1998 to 2008 of 12.4% to 14.6% of low-income children being obese, with 21.2% of these being Native American, 18.5% Hispanic, and 11.8% African American.⁴ Furthermore, it is estimated that \$92.6 billion are spent each year diagnosing, treating and responding to the effects of obesity; of which approximately 50% is paid for by government health insurance programs such as Medicaid and Medicare which are responsible for providing healthcare to seniors and uninsured

Americans, including children under age 18.⁴ As such, the impact of obesity is seen to have a high cost both in terms of economics, as well as the resulting social costs in terms of morbidity and mortality.

Given the economic and social consequences associated with obesity, it is important to understand the role that genetics plays, in connection with environmental factors, in causing obesity, and its co-morbid conditions, such as hypertension, diabetes and CHD. Understanding the role of genetics is particularly important among children, whose risk factors are greatest for developing chronic disease later in life when obese during childhood. This article will review the role of genetics in obesity, particularly in reference to recent genome-wide association scans (GWAS) which have identified genes, such as the *FTO* gene, which are associated with obesity-related characteristics, such as increased body mass index (BMI), hip circumference, and height/weight ratio; and conclude with a discussion of the importance of genetics in understanding and controlling obesity from a population-based or public health perspective.

Genetic basis of obesity

Several studies have established an association between obesity characteristics and genetics; and while researchers caution that genetic evolution does not occur rapidly enough to account for what has become an obesity epidemic in the United States, and in many countries worldwide, there is compelling evidence that genes do play a role in concert with environmental factors in the development of obesity,⁵ and may be a genetic remnant allowing humans to store large energy reserves for use in times of famine.^{4,6}

While recent studies suggest that 40-70% of currently obese individuals may have an underlying genetic variant mediating their weight gain,^{4,6} it is important to understand that obesity as related to genetics is a complex interaction between environment, biological factors, behavioral factors, social mechanisms and the individual, with many individuals who carry a genetic variant that predisposes them to obesity maintaining a healthy height/weight ratio by controlling these factors through lifestyle choices.⁷ Indeed, Xiang et al.⁸ found that individuals with a genetic variant associated with characteristics of obesity were able to lose and maintain a healthy weight through diet and physical activity with equal success as a control group that did not have the genetic variant. Such suggests that while understanding the role of genetics is important in terms of developing public health intervention programs, that such must be matched with a clear understanding of the significance of the gene-environment interaction, as well as the role of developmental, behavioral and sociocultural factors, and that this must remain the key component of the development of obesity intervention programs in the public health sector.

Twin studies looking at the heritability of obesity have found obesity is one of the most commonly inherited phenotypic expressions of either mother/father or the twin sibling, with estimates of the heritability of increased BMI ranging from 0.5 to 0.7; 0.36 to 0.61 for increase hip circumference and height/weight ratio; and finally, from 0.45 to 0.6 for emotional and uncontrollable eating patterns.⁹⁻¹¹ However, Chung and Leibel¹⁴ as well as Wood⁶ point out that twin studies such as these, while suggesting a genetic association, fail to consider which or how many genes are available, or how these genes interact with environmental factors. This is an issue that is especially important when designing intervention programs that must understand the underlying socioeconomic and cultural factors that influence eating and physical activity.

The identification of genes associated with obesity is receiving increased attention as genetic methodologies, such as GWAS, become increasingly affordable. Several large-scale studies have been undertaken to identify those genes and loci within these genes which are associated with obesity. These studies have resulted in over 253 quantitative trait loci (QTL), or regions within specific chromosomes having a statistically significant association with a specific phenotype, associated with obesity through approximately 61 different GWAS.^{4,6} Of these 253 QTLs, there have been 127 genes with a positive association to obesity, of which 22 of these gene-associations have been supported in at least five different studies.¹² However, despite having been supported by other studies, to date the strength of these associations have not been able to make a strict causal relationship between the studied genes and obesity, but are mainly associative in nature.⁴ Many of these associations came from studies of the genetic susceptibility of type 2 diabetes mellitus (T2DM), which is commonly associated with obesity,⁴ thus underscoring the importance of understanding both the social and genetic causes of obesity as a comorbid condition of a wide range of chronic diseases.

One such GWAS of approximately 30,000 European adults first identified the Fat Mass and Obesity Associated (*FTO*) gene as a possible candidate gene for T2DM, but which was disregarded after controlling for BMI.¹³ *FTO* was subsequently found to be associated with obesity characteristics, including increased BMI and inappropriate height/weight ratios, independently of diabetes.⁷ A subsequent meta-analysis of 37 studies which included greater than 31,000 participants from approximately 10,000 families found an association between region 16q12.2 of the *FTO* gene and obesity characteristics, including increased BMI, increased hip circumference, and increased height/weight ratio.⁶ However, the authors cautioned that while an association was made, that it was a weak one, suggesting that even large-scale meta-analysis may not be powerful enough to correctly identify the actual risk associated with genetic variance and obesity, nor establish a causal relationship.

Given the potential power limitations of such meta-analysis as well as individual GWAS, the importance of gene-environment interactions becomes clear in understanding risk, and from a public health standpoint the development of intervention programs to reduce obesity. Given that the obesity epidemic has developed over the past several decades, genetic evolution cannot account for these changes.^{4,6}

Rather, Wood⁶ suggests that as environmental factors change making it easier to obtain food and less need to exert physical activity in the activities of daily living that the population at large will become increasingly obese as they take advantage of changes in their environment, and that those who were already overweight will become increasingly so through this mediation of environment and genetics. As such, as the availability of foods high in fats and processed carbohydrates supplants diets rich in fruits, vegetables and whole grains due to a variety of considerations, then those with a genetic predisposition to obesity will suffer the most from this gene-environment interaction.

Such is a particular risk for those who are socioeconomically disenfranchised, such as ethnic minorities, who have the highest rates of obesity¹, as their financial situation increases reliance on such food sources which are often less expensive,¹⁴ as well as individuals in the developing world where industrialization has resulted in an emerging trend of dietary and social customs similar to industrialized nations resulting in dramatically increasing rates of chronic diseases such

T2DM.¹⁵ Given that obesity is now becoming a global pandemic, the importance of understanding the role of gene-environment interactions become even more important.

Understanding this interaction between genetics and environment presents perhaps the greatest challenge to this area of genetic epidemiology, as understanding such will allow public health planners to truly implement obesity programs which are targeted at those most at risk, and therefore able to benefit most from such, thus reducing both the social and economic costs of such.

Current findings

Dong et al.¹⁶, represents a comprehensive review to identify genetic variants associated with obesity through GWAS methodologies to identify a gene-disease association. Previous studies had often been unsubstantiated as they failed to have significant population size, or went un-replicated; as such, the authors attempt to conduct a study which would be of sufficient population-size as to have statistical power, and which would further add to the evidence showing a connection between genetics and obesity.⁷ Given this, the authors hypothesized that by identifying those morphological characteristics most commonly associated with, and used in the diagnosis of, obesity, that they would then be able to conduct a GWAS to identify genetic variants associated with such.⁷ Those characteristics specifically associated with obesity, and for which the authors seek a gene-disease association, were increased BMI, hip circumference and height/weight ratios.⁷

In so doing, between 1995 and 2004, a population screening/cohort study design was utilized to conduct a GWAS of 4,741 Sardinians located in four towns of the Laneus Valley; 1,496 European-Americans from Tecumseh, Michigan; 839 Hispanic Americans and 1,101 African Americans from Maywood, Illinois.^{7,16} Participants were both male and female, with ages ranging from 14 to 102.⁷ Given that the focus of this gene-disease study was on identifying those morphological characteristics most associated with obesity and then identifying genes associated with these characteristics, the researchers gathered information on BMI, hip circumference and height/weight ratios for 9,584 (60%) of the participants; while genotyping was undertaken via blood samples for 7,946 (83%) using Affymetrix 10k and 500k chips.⁷ Population screening was initially undertaken in Sardinia, given that the populations is relatively isolated, and therefore it was possible to screen a large number of individuals for the genetic variants associated with obesity; later tests on a population of European-, African- and Hispanic-Americans were undertaken to verify these results in a more genetically variable group, given that previous studies have suggested that genetic variance may be linked to ethnicity.⁵

GWAS ultimately identified two single nucleotide polymorphisms (SNP) of the *FTO* (OMIM 610966) and Phosphofructokinase Platelet (*PFKP*) (OMIM 171840), genes.⁵ This included the rs9930506 variant of the *FTO* gene located on chromosome 16, allele A, at 16q12.2; and the rs66020204 variant of the *PFKP* gene located on chromosome 10, allele G, at 10p15.3-p15.2.⁷ While the authors did not give a suspected prevalence estimate of the two genetic variants, they did find that for variant rs9930506 of the *FTO* gene there was a strong association between BMI ($p = 8.6 \times 10^{-7}$), hip circumference ($p = 3.4 \times 10^{-8}$), and weight ($p = 9.1 \times 10^{-7}$); while there was also a strong association with the variant rs6606024 on the *PFKP* gene and BMI ($p = 4.9 \times 10^{-6}$), with no association between hip circumference and weight found for the *PFKP* gene.⁷

Given this, the authors concluded that in terms of a gene-disease association between the two genetic variants studied there is an increased risk of obesity as measured by BMI, hip circumference and weight in terms of appropriate height/weight comparisons. The authors also concluded that gene-environment interaction in terms of lifestyle choices, such as overeating and lack of physical exercise, are essential components to understanding the way in which genetic mediates the risk of developing obesity.⁷

Application to prevention and public health

Abdelmajed, et al.⁵ concluded that there was an association between variants in the *FTO* and the *PFKP* genes and obesity in terms of increased likelihood of having those morphological characteristics most commonly found in obese individuals. However, while the authors initially believed that by using a large and genetically diverse population—including 8,177 individuals from various ethnic backgrounds—that they could overcome the methodological issue of power related to the number of study participants, as well as identifying possible ethnic variants,⁵ other studies suggest that even large-scale meta-analysis including more than 31,000 subjects do not provide the statistical power needed to make a definitive disease-gene causal connection.^{4,6} Such calls into question the value of studies from the standpoint of application in public health interventions targeting obesity. Given preliminary evidence, there is a clear need to fully establish the linkage between obesity and genetic variance, particularly given that obesity is a co-morbid risk factor for many other chronic diseases, such as T2DM and CHD, each of which have their own genetic component.

However, while the strength of the association between obesity and those identified genetic variants of the *FTO* and *PFKP* genes remains to be proven through additional studies which replicate the authors findings and utilize large cohorts, the value of this and other similar studies,^{8,11,13} is found in their stressing the need to study the gene-environment interaction as the key to how obesity is mediated by genetic factors, as opposed to stating that there is a genetic causal relationship responsible for obesity.

Such is especially true when one considers that the upswing in obesity over the past several decades cannot have been caused by genetic changes, but rather by environmental factors working in concert with genetics.^{4,6} Recalling that while obesity is a problem among all demographics, but particularly among those population groups which are socioeconomically disenfranchised, including ethnic minorities who have prevalence rates 21% for Hispanics to 51% for African Americans higher than Caucasians, and children who have seen obesity rates climb 12.6% since 1980,¹ there is a clear need to understand those social, behavioral and economic factors that influence the risks for obesity within these groups, including genetic predisposition.

Such an approach, which can branch off of the current body of knowledge on the connection between genes such as *FTO* and *PFKP* and obesity, is well within the realm of epidemiology, combining the strengths of traditional epidemiological methods, with social/behavioural epidemiology and genetic epidemiology, to fully understand the way in which genetics interacts with environment to result in disease states, which appear in the case of obesity to be largely preventable.⁸

Conclusion and recommendations

The evidence associating genetic variants with obesity, particularly

in relation to gene-environment interaction, and lifestyle choices, is established. Given this, in terms of recommendations on the future of the study of gene-environment and gene-disease interaction in relation to obesity, two issues arise, first the need to undertake further research to understand the complex dichotomy between genetic variance and environment that results in obesity; and second, the need to develop guidelines on screening for research versus screening for public health and medical purposes.

First, given the evidence of an association between obesity and various genetic variants in the *FTO* and *PFKP* gene, additional research is needed to prove that there exists a causal relationship between obesity and genetic variants, that take into account issues related to ethnic variation, which Abdelmajed⁵ and Wood⁶ both cited as possible reasons for variance in the findings of the various in genetic/obesity studies. Furthermore, these studies must be designed in such a way as to take into account the various outside influences which have been shown to be associated with obesity, such as socioeconomic status.

Second, given the need to better understand the gene-environment interaction as a mediator of obesity, from a public health standpoint practitioners should be cautioned that it is not likely that a gene for which there is strict causal relationship to obesity will be discovered, and that the emphasis must remain on the need to promote healthy lifestyles, regardless of genetic risk, within the framework of continuing to understand and alter those social and other factors which also promote obesity, such as a lack of educational, employment and other opportunities within the larger environment.¹¹ This is especially true given that media coverage of the role of genetics as a causal factor for obesity, may create an unrealistic expectation among the general public that lifestyle modification in the face of genetic predisposition can do nothing to stop the onset of obesity, thus undermining the ability of public health agencies to advocate healthy lifestyle as the cornerstone of obesity and chronic disease prevention.

Such is underscored by the findings of Lappalainen et al.¹⁷, Xiang et al.⁸, Ng et al.¹⁴, and others, that among a Finnish cohort of those with the SNP variants associated with obesity that those with the variant were able to loose and maintain a healthy weight with equal success of those without the genetic variant when engaged in the same lifestyle modification program including diet and exercise. As such, in terms of screening for obesity-related genetic variants outside of the research setting, in which large-scale screening should continue to help better define the actual risk associated with obesity-related genetic variants, such should be limited to medically-relevant cases in which there is a demonstrated risk, and would not be advisable on a population-based scale. Such suggestions on screening are due to contradicting evidence as to the actual risk associated with the genetic variants,^{6,11,16} the limited evidence suggesting that identifying those individuals with the risk factor would improve health outcomes, as well as the cost associated with such.

In conclusion, while genetic epidemiology has the ability to significantly alter the face of public health by providing individualized counselling in terms of disease prevention, as well as large-scale health promotion to identified risk groups, practitioners and researchers must recall that genetic predisposition, and indeed gene-environment interaction, is not an absolute condition resulting in a disease state; but rather genetic predisposition, particularly in regard to obesity, appears to be overcome in many instances by adoption of healthy lifestyles choices, such as diet and exercise, and that the failure to do so can result in the onset of disease. This is the cardinal lesson of the studies

by Abdelmajed⁵, and others, or that the critical factor in understanding how to apply the association of genetic variance with disease state comes through understanding the gene-environment interaction, and then working to alter such.

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