

Genetics of Obesity in Asia

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Introduction

The obesity epidemic is recognized globally as a significant public health concern. The World Health Organization estimates that approximately 2-3 billion people will be overweight and over 700 million will be obese by 2015.¹ Earlier identified as a problem confined in developed countries, many developing countries have recently shown a significant rise of obesity cases.² It is a major cause of disability and premature deaths in both developed and developing countries from obesity-related diseases such as cardiovascular disease, strokes and complications of diabetes.

Epidemiology of Obesity in Asia

The prevalence rates of obesity are reported to be very high in North America and Europe with much lower rates in Asia.³ However, it has been recently demonstrated that the number of obese individuals in most Asian countries has increased dramatically.² Yoon et al in 2006 reported survey figures from 1993-2001 demonstrating that Thailand had the highest rate of obesity in Asia at 6.8% among adults being obese followed by Singapore at 6%; China, Taiwan and Malaysia had prevalence figures between 4 and 4.4% of obese adults.⁴ Hong Kong had 3.8% of obese adults followed by the Philippines at 3.3%, Korea at 3.2% and Japan at 3.0%. India had the lowest percentage of obese adults at 2.2%.⁴

Genetics and Obesity

Although socioeconomic and lifestyle changes are major contributing factors in the development of obesity, it has been proven in many studies that genetics also play a significant role. Obesity is regarded as a multifactorial condition wherein susceptibility is determined by the interplay of genetics and environmental factors.⁵ It is generally regarded as a complex genetic disorder. Like many other common chronic conditions such as hypertension, diabetes and cancer, obesity usually has an onset in adulthood, demonstrates familial aggregation and

does not show Mendelian patterns of inheritance⁶. Discovering genetic risk factors for complex disorders such as obesity can pave the way for the development of molecular-based susceptibility testing for prediction of disease (presymptomatic testing)⁶.

The contribution of genetic factors to obesity has been well established through twin and family studies. Studying sets of twins, who are reared together or apart allows one to determine whether a condition has a strong genetic influence over the environment and vice versa. The heritability of fat mass seen in twin studies was 40-70% while a concordance rate of 0.7-0.9 between monozygotic twins compared to 0.35-0.45 among dizygotic twins has been observed.⁸ These studies have proven that heritable factors are responsible for as much as 45 -80 % of variations observed in body mass index among individuals and risk of obesity while heritability of obesity in families have been reported between 20 and 50%.^{5,7}

In the three billion base pairs of the human genome, variations exist on the average, every 500 to 1000 base pairs. These stable, heritable variations in the genome are called polymorphisms and are present in greater than 1% of the population. Some of these genetic polymorphisms are functionally significant and can have effects on the gene product. They can be used for disease association studies and can act as markers for disease susceptibility.⁹ One of the most widely studied variations are called single nucleotide polymorphisms (SNPs) where a nucleotide base is replaced by another nucleotide base.

Methods of Identifying Genes Associated with Obesity

A number of research tools are now available to study these variations in the genome that may confer an increased susceptibility to obesity among individuals in different populations. These genetic approaches commonly used to identify the genes related to obesity include candidate gene and genome-wide association studies. Candidate gene studies find an association between variants in an individual's genome within or very

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near candidate genes and a disease of interest such as obesity. There is *a priori* knowledge of the biological function of the candidate gene to be tested because of its involvement in regulating the development of the disease being evaluated.⁵ Genome-wide association studies on the other hand, involves scanning many markers randomly throughout the genome to find genetic variations associated with a disease. However, there is no *a priori* hypothesis about any particular gene or genes of interest, and its greatest advantage is the discovery of novel genes along biologic pathways with no apparent relation to the pathophysiology of obesity. Genetic studies have repeatedly demonstrated that some genes are associated at a higher frequency among the obese than in the non-obese individuals suggesting that a considerable proportion of weight variation may be due to genetic factors.

It is reported that there are approximately 127 genes associated with obesity from candidate gene association studies.⁵ These genes chosen for their role in various metabolic processes have been replicated in many studies worldwide. The genes that have been identified so far are involved in a variety of biological processes that include regulating food intake or how food is efficiently or inefficiently metabolized in the body and subsequently stored as fat. The association of variations found in a number of these genes and risk for obesity will be described in some studies done among different Asian populations.

Studies on Genetics of Obesity amongst Asians

The evaluation of genetic susceptibility loci for obesity has been extensively carried out in the Chinese population. Shi J et al validated five loci from previous genome-wide association studies, obesity-related phenotypes in adult Chinese women. These include *FTO*, *MC4R*, *BAT2*, *SEC16B*, and *SH2B1*. The *FTO* gene is the fat mass and obesity associated gene and is also known as alpha-ketoglutarate-dependent dioxygenase enzyme. It is widely expressed in different tissues with the highest concentration in the hypothalamus and pancreatic cells. The *MC4R*, on the other hand, is the gene that encodes the melanocortin 4 receptor. Both *FTO* and *MC4R* genes have been consistently reported in different populations to be associated with obesity.¹⁰ *MC4R* has been recognized to play a significant role regulation of food intake and energy homeostasis.⁵ *BAT 2* is the human leukocyte antigen B (HLA)-associated transcript 2, a gene highly expressed in the hypothalamus. The other candidate genes were *SEC16* homolog B (*Saccharomyces cerevisiae*) (*SEC16B*) and *SH2B* adaptor protein 1 (*SH2B1*). It has been suggested through observations that neuronal *SH2B1* protein regulates energy balance and glucose homeostasis, possibly by enhancing hypothalamic leptin signalling.¹⁰ However, the mechanism linking the *BAT2* and *SEC16B* genes to obesity is still unknown. The calculated odds ratios for obesity in these different genes ranged from 1.46 (95% confidence

interval (CI): 1.12, 1.92) for *BAT2* to 2.16 (95% CI: 1.39, 3.37) for *MC4R*.¹⁰ Interestingly, the authors further examined a genetic risk score, calculated by summing the number of risk-increasing alleles that each woman carried at these 5 loci, and they found a significant association with the prevalence of obesity. Women carrying 5 or more risk alleles had a 3.13-fold (95% CI: 2.06, 4.77) higher prevalence of obesity than women carrying 1 or no risk.¹⁰

Another population-based study involving a cohort of 3,210 Chinese Hans conducted by Qi et al, investigated the prohormone convertase (*PCSK1*) gene and predisposition to obesity and type 2 diabetes. This gene encodes an enzyme that converts inactive prohormones such as proinsulin, proglucagon and proopiomelanocortin into biologically active peptide hormones.¹¹ Mutations in this *PCSK1* lead to impaired glucose tolerance and common variants in this gene have been reported to be associated with obesity among Europeans. The authors sought to replicate these previous studies to determine if the same variants of the *PCSK1* gene might predispose to obesity among the Chinese. They were only able to demonstrate modest evidence for association of the *PCSK1* variant rs6234 with BMI and overweight in men only and not among women and concluded that it may not be an important contributor to obesity in the Chinese population.¹¹

Because several independent studies have reported strong associations of variations in the fat mass and obesity-associated (*FTO*) gene with obesity among Europeans, Chang Y-C et al in 2008 did replication studies on the role of these *FTO* gene variants in obesity and type 2 diabetes in the Chinese population. They genotyped 19 single nucleotide polymorphisms of the *FTO* gene and analyzed its association with obesity in 638 cases and 1610 controls. They were able to confirm an association of *FTO* genetic polymorphisms with obesity and BMI in the Chinese population with an effect size on obesity risk and BMI comparable with previously reported risk among the Europeans.¹²

A similar study on *FTO* variants and association with obesity was done among the Chinese and Malay population in Singapore. Tan J et al investigated the association between 9 previously reported *FTO* SNPs with obesity, type 2 diabetes and related traits in participants of the 1998 Singapore National Health Survey which included 2,919 Chinese, 785 Malays, and 594 Asian Indians as well as 2,996 Malays recruited from another study. The investigators found that variants at the *FTO* gene are associated with obesity in ethnic Chinese and Malays living in Singapore.¹³

Likewise, a study on the variations of the *FTO* gene and its association with severe obesity has been conducted among the Japanese by Hotta K et al in 2008. They investigated 15 SNPs on the *FTO* gene using 927 cases of adults with

obesity and 1,527 normal-weight controls. A significant association in intron 1 SNP rs1558902 with severe obesity was found among the Japanese with an odds ratio (OR) adjusted for age and gender of 1.41 [95% confidential interval (CI) = 1.22–1.62; *p* value of 0.0000041].¹⁴

Genome-wide association studies have shown that variations in the insulin-induced gene 2 (*INSIG2*) are associated with obesity; such association has been seen in Caucasian populations.¹⁵ *INSIG2* is a ubiquitously expressed gene known to be downregulated by insulin in the liver, involved in fatty acid synthesis and an intermediate in the feedback control of cholesterol synthesis.¹⁵ Hotta K and his colleagues investigated the relationship of the *INSIG2* gene SNP rs7566605 and obesity among the Japanese from a total of 908 severely obese cases and 1,495 controls. The results of this study showed that the rs7566605 SNP of the *INSIG2* gene was significantly associated with obesity with an odds ratio of 1.61 [95% confidential interval (CI) = 1.24–2.09] adjusted for gender and age and may therefore influence the risk of severe obesity in the Japanese population.¹⁶

Cha S. et al (2009) similarly examined the effect of the rs7566605 polymorphism near the *INSIG2* gene on both obesity- and cholesterol-related traits among 2,364 Koreans. However, they failed to demonstrate any association of the rs7566605 polymorphism with cholesterol- and obesity-related phenotypes, although there was a suggestion of the possible involvement of *INSIG2* with the plasma level of the total cholesterol in women included in this study.¹⁷

In a study done among Filipinos from Cebu by Marvelle A. et al in 2008, the researchers found a significant association between the *FTO* gene and susceptibility to obesity.¹⁸ This conclusion was drawn from data gathered from 1,886 adult Filipino women from the Cebu Longitudinal Health and Nutrition Survey (CLHNS) cohort. The researchers investigated the association of obesity related traits and 19 SNPs previously identified in 10 genes namely *ADRB2*, *ADRB3*, *FTO*, *GNB3*, *INSIG2*, *LEPR*, *PPARG*, *TNF*, *UCP2*, and *UCP3* that had been previously reported to be associated with an obesity-related quantitative trait. The other candidate genes included in this study, apart from those previously described in the other studies above, are the *ADRB2* and *ADRB3* genes, which are adrenergic beta 2 and beta 3 receptors with the latter being involved in the regulation of lipolysis and thermogenesis.⁵ *GNB3* codes for guanine-nucleotide-binding protein (G protein) and together with *ADRB2* and *ADRB3* are genes which are part of the catecholaminergic pathway. *LEPR* codes for the leptin receptor and is a member of the class 1 cytokine receptor family and thought to be involved in the regulation of body weight. *PPAR-G*, *PPARG*, the peroxisome proliferator-activated receptor gamma, is a nuclear receptor which regulates fatty acid storage as well as

glucose metabolism. The uncoupling proteins *UCP2* and *UCP3* function to uncouple ATP production from mitochondrial respiration with an end result of affecting the efficiency of energy metabolism.¹⁹ This candidate gene study done in a cohort of Filipinos was able to show the association of the A allele of *FTO* variant rs9939609 with BMI and waist circumference. They also demonstrated evidence of association with the homozygous T allele of *ADRB3* rs4994 with BMI, waist circumference and percent body fat; however, only the rs4994 SNP reached statistical significance, not observed in previous studies. The authors concluded that a SNP within the first intron of *FTO* was associated with BMI among this cohort of Filipino women from Cebu and as also seen in other population groups, the gene maybe important in susceptibility to obesity.¹⁸

Conclusions

Knowing the genes related to obesity have far reaching effects individually and globally. Genetic information can be used to predict an individual's predisposition to the development of obesity and its complications. It also allows for the discovery of novel and personalized treatment strategies to be applied to different population groups being cognizant of the fact that inter-ethnic differences exist. The genetic and genomic studies being done among Asian populations will contribute greatly to the wealth of information on genetic predisposition to obesity. These unique and innovative genomic approaches and discoveries may lead to a better understanding of molecular pathways that give rise to obesity and can pave the way to better management and control of obesity, not only in Asia but throughout the world.

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