Review Article

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Genetics of Obesity

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Abstract

Obesity is defined as Body Mass Index (BMI) of more than 95th percentile for age and sex. It is on rise and affecting not only people in developed countries but also those in developing and modernizing countries. Obesogenic environment has resulted in major healthcare problem of obesity, but there is also substantial evidence for the heritability of obesity, and research in both rare and common forms of obesity has identified genes with significant roles in its etiology. However, many genes and variations do not fully explain the heritability of obesity, epigenetic markers may also be playing important role. Advances in genetic technology and application of clinical epidemiology will have a huge impact making the picture clearer. Though not exhaustive, this review will focus on our current knowledge and understanding of the role of genetic factors in obesity.

Keywords: Body Mass Index (BMI); Obesity.

Background

Obesity, defined as a condition characterized by '*excess body fat which creates increased risk for morbidity and/or premature mortality*', is becoming one of the foremost public health challenges.

Worldwide, 2.8 million people die each year as a result of being overweight (including obesity)and an estimated 35.8 million (2.3%) of global DALYs are caused by overweight or obesity [1]. They lead to adverse metabolic effects on blood pressure, cholesterol, triglyceridesand insulin resistance. Risks of coronary heart disease, ischaemic stroke and type 2 diabetes mellitusincrease steadily with increasing body mass index (BMI), a measure of weight relative to height. Raised BMI also increases the risk of cancer of the breast, colon/rectum, endometrium, kidney, oesophagus (adenocarcinoma) and pancreas. Mortality rates increase with increasing degrees of overweight, as measured by BMI. To achieve optimal health, the median BMI for adult populationsshould be in the range of 21 to 23 kg/m2, while the goal for individuals should be to maintain a BMI inthe range 18.5 to 24.9 kg/m2. There is increased risk of co-morbidities for BMIs in the range of 25.0 to29.9 kg/m2, and moderate to severe risk of co-morbidities for a BMI greater than 30 kg/m2 [2].

"This insidious, creeping pandemic of obesity is now engulfing the entire world. It's as big a threat as global warming and bird flu." This warning came from Paul Zimmet during his opening address at the 10th International Congress on Obesity in Sydney in 2006 [3]. The UK Foresight report described obesity as a "complex web of societal and biological factors that have, in recent decades, exposed our inherent vulnerability to weight gain." The obesity still regarded as a culmination of Obesogenic environment. Even some social groups do not consider Obesity as a disease.

Obesity is also associated with an insidious, creeping increase in hitherto uncommon diseases such as non-alcoholic fatty liver disease and polycystic ovaries syndrome. A cluster of cardio metabolic risk factors has been described in association with obesity. These factors, both individually and collectively, enhance the risk of

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several of above mentioned diseases.

Recent advances in our understanding of the role of adipocyte as a regulator of metabolic functions have resulted in a comprehensive delineation of molecular pathways in several cases of obesity. Adipocyte are involved in pathophysiology of inflammation and energy homeostasis. Adipocytes secrete proteins collectively called adenosines which control and regulate a wide array of physiological processes including feeding behavior, energy homeostasis, insulin sensitivity and action, lipid and glucose metabolism, as well as vascular tone and endothelial function. Most of these effects are mediated through paracrine, anticrime, and endocrinal pathways.

Many genes have been incriminated for Obesity.The recent isolation of fat mass and obesity-associated (FTO) gene and its association with obesity is of considerable interest. Although the exact biologic process linking FTO and obesity is undefined, it is obvious that FTO variants mediate obesity by increasing energy input.

Amongst the most worrying problems is a steep rise in the prevalence of obesity among children which makes them much more prone to chronic diseases as they grow older, thereby curtailing both the longevity as well as quality of life?

This simple and easy-to measure parameter (waist/height ratio) is not dependent on ethnicity nor does it require sophisticated instrumentation.

Because obesity is associated with diverse chronic diseases, it became difficult to pinpoint where our adipose tissue, a friendly part of body, went wrong [4]. Following hypothesis were proposed:

1. 'Thrifty Genotype' which suggested that populations varied genetically and defined thrifty genes as those characteristic of individuals 'exceptionally efficient in the intake and/or utilization of food' [5].
2. 'Thrifty Phenotype' hypothesis focused on life-course plasticity and proposed that low birth weight babies responded to their low level of nutritional intake in early life through alterations in growth and metabolism. Also known as Barker hypothesis, the metabolism of mother get imprinted on the baby who continue to behave similarly despite change in the environment later in life. They are thus predisposed to obesity and metabolic syndrome [6].
3. 'Drifty Genotype' hypothesis proposed that genetic drift may have allowed substantial genetic variability to accumulate without being able to impact on phenotype before the modern 'obesogenic' environment [7].

Genetics of Obesity

There were only few genes linked to obesity at the turn of this millennium which increased to eight monogenic and 4 polygenic genes by 2008 [8]. It has been argued that there is a continuum between Monogenic and polygenic obesity. Four genes (*MC4R, PCSK1, POMC and BDNF*) have been involved in both these conditions.

It is also argued that genetic influences are more pronounced in people with severe and early onset obesity. This is the group also which faces most complications of obesity. The genes involved in obesity can be broadly categorized as follows:

1. Non-syndromic which are not part of any syndrome.
   a. Monogenic due to mutations in *LEP, LEPR, POMC, MC4R, PC1, NPY and SIM1.*
   b. Polygenic due to *ADRB1, ADRB2, ADRB3, UCP1, 2 and 3.*
2. Syndromic: Obesity as part of certain syndrome
   a. Pleiotropic syndromes where one gene mutations can have wide range of symptoms and clinical features
   b. Contiguous gene deletions or chromosomal re-arrangement.

Methods of studying genes for obesity: Till recently Genome Wide Association Studies (GWAS) led to discovery of of highly relevant candidate genes. The SH2B1 gene identified by GWAS is associated with Mendelian form of obesity and its inactivation leads to hyperphagia, lepin resistance and obesity [9]. On the other hand *FTO* gene is a major contributor for polygenic obesity.

Food Intake Regulation by Central Nervous System

It has been shown that CNS plays an important role in food intake by human. Defects in differentiation of paraventricular nucleus and in the leptin/ melanocortin pathways have been shown to lead to obesity in human with hyperphagia as a common feature [10].

The obesity predisposing SNP variant near *MC4R* region was associated with increased feeling of hunger, and intake of fat and decreased satiety [11].

Story of *FTO* Gene

Though the *FTO* gene has been cloned in mice in

1999, it was only in 2007, using GWAS, a UK research team led by Dr Andrew Hattersley of Peninsula Medical School in Exeter discovered a gene variant that showed strong link with body mass index (BMI) [12]. The gene harbouring the variant was named as fat mass and obesity-associated (FTO). At that time it was a gene of unknown function in an unknown pathway. More than 400 articles have been published since then increasing our understanding of the mechanisms linking this gene to the pathophysiology of obesity. Studies have confirmed the association between FTO and obesity-related phenotypes in populationstudies worldwide [13]. Recently, it has been revealed that FTO and obesity association might be due to linkage disequilibrium between FTO intronic variations and other genes [14].

The study of FTO demonstrates how genetic approaches can lead to functional output and contributes to our understanding of physiology of obesity.

Advantages of Studying Genetics of Obesity

Above story illustrates how a gene can be unifying our integrative approaches to study many non-communicable diseases and also our understanding of pathophysiology of common conditions. Some of the other advantages are:

1. Illuminating new pathways involved in energy balance
2. Help in exploring causality in Epidemiological studies
3. Useful in understanding past human history [5,15]
4. Genes interaction with environment to modify phenotype. Recent literature provides firm evidence that genetic susceptibility to obesity can be blunted in part through physical activity [16].
5. Response to therapy (Pharmacogenomics).and prediction for obesity development still hold grounds [17].

Few common Genes involved in Obesity

Some common and known genes and syndromes have been summarized in Table 1.

Table 1: Common genes in Obesity [18]

Non syndromic	Syndromic
Mutations in leptin and its receptor *LEP* and *LEPR*	Bardet-Biedl syndrome with polydactyly (BBS1- BBS11)
Mutations in pro-opiomelanocortin (*POMC*) gene	Albright's hereditary osteodystrophy syndrome
Melanocortin 4 receptor gene (*MC4R*) mutations	Borjeson, Forssman, Lehmann syndrome
Proprotein convertase 1 (*PC1*) gene mutations	Cohen syndrome
Neuropeptide Y (*NPY*) gene mutations	Alstrom syndrome
Mutations in Ghrelin receptor gene	Ulnar- mammary syndrome
Mutations in genes related to taste	Simpson GolabiBehmel, Type 2
Beta adrenoceptor gene and factors (*ADRB1, ADRB2, ADRB3*)	Wilson- Turner
Beta 1 and 3 adrenoceptor gene mutations	Mehmo syndrome
Mutations in uncoupling proteins (*UCPs*) gene	Prader-Willi
Peroxisome Proliferator activated Receptor G mutations (*PPARG2* for example)	WAGR syndrome

Closer look at studies shows heritability of obesity is a relatively high for non-syndromic obesity which ranges from 40- 70 % in different studies. Genome wide association studies (GWAS) have changed the pace of detection of variants.

It is also becoming clear, in both rare and common forms of obesity, that epigenetic influences, defined as any heritable influence on genes that occurs without a change in the DNA sequence, are also becoming important. Failures of imprinting of genes are known to cause extreme forms of Obesity. Prader Willi syndrome represent the imprinting effects. Comprehensive review on Epigenetics for Obesity are available [19].

Recently with Next Generation Sequencing (NGS) and exome sequencing, genomic scans have identified strong links between obesity and certain regions of genome. The picture is emerging and with better tools it will be becoming clearer in the near future.

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