Introduction

Is it nature or nurture, genes or environment, Grandma’s genes or Grandma’s homemade pork-and-beans? Just what is it that makes some people overweight, while others can seemingly eat forever without gaining a pound? (1). Obesity is defined as an abnormal increase in body fat (though not necessarily in body weight) (2). 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, heart disease and some type of cancers. The present article reviews role of genes that are identified in causing obesity.

Classification of obesity

The body mass index (BMI), also known as the Quetelet index, is used far more commonly than body fat percentage to define obesity. BMI is closely correlated with the degree of body fat in most settings. BMI = weight/height², where, weight is in kilograms and height is in meters (7). The most commonly used definitions, established by the World Health Organization (WHO) in 1997 and published in 2000, provided the values listed in the table 1 (8).

**Table 1. Classification of Obesity (8)**

<table>
<thead>
<tr>
<th>BMI</th>
<th>Classification</th>
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<tbody>
<tr>
<td>&lt; 18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>18.5–24.9</td>
<td>Normal weight</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>Overweight</td>
</tr>
<tr>
<td>30.0–34.9</td>
<td>Class I obesity</td>
</tr>
<tr>
<td>35.0–39.9</td>
<td>Class II obesity</td>
</tr>
<tr>
<td>≥ 40.0</td>
<td>Class III obesity</td>
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*BMI=Body Mass Index

Pathophysiology of obesity

A complex feedback control system consisting of a central processing unit which receives afferent signals and generates appropriate efferent stimuli in response controls food intake, satiety and
subsequently weight. Age and gender differences in food intake have been identified with an increase in adolescence, peaking in the second decade after which it declines (9). Gastric distension via activation of vagal afferents is a signal for satiety, with gastric contractions signalling for hunger. Nutrients, neural impulses and hormones themselves act as afferent signals in the regulation of energy intake and expenditure. Nutrient absorption, e.g. which of glucose initiates a sensation of satiety whereas a fall in glucose promotes hunger. This effect is itself mediated by different neurotransmitters, hormones and peptides (10).

Leptin is a peptide produced by adipocytes which has been closely correlated with fat mass, with secretion increasing as fat deposition increases (11). It acts to reduce food intake and is believed to increase sympathetic nervous system activity (12). This peptide has found use in a small number of individuals who have been shown to be deficient in the leptin gene. Another important peptide is Growth Hormone (GH) relin which is secreted by the stomach and duodenum and has been shown to stimulate GH secretion. It is an endogenous ligand for the GH receptor. GH relin increases food intake and its secretion is in turn suppressed by food intake (13, 14, 15). Serum concentrations increase in anticipation of a meal. Its secretion has been shown to increase after diet- and exercise-induced weight loss and is believed to be one of the reasons why lifestyle modification does not lead to permanent weight loss. Other peptides that have been shown to reduce food intake are cholecystokinin (CCK) (16), enterostatin (17) and polypeptide Y 3-36 (18). The list of peptides is ever on the increase and hormones themselves act as afferent signals in the regulation of energy intake and expenditure. There are certain genes that are linked to lipid and glucose metabolism and others have a role in adipose tissue development (23).

According to Josanne (2007), (20) the nucleus of the tractus solitarius in the hindbrain is the site where vagal and other neural input is integrated. The arcuate nucleus at the base of the hypothalamus receives signals from leptin and in turn increases both production and secretion of neuropeptide Y (NPY) and Agouti-related peptide (AgRP) thereby increasing food intake. On the other hand, cocaine-amphetamine-related transcript (CART) and pro opiomelanocortin (POMC) decrease food intake. The paraventricular nucleus of the hypothalamus is itself stimulated by peptides from arcuate nucleus and relays signals further. Destruction of the ventromedial hypothalamus has been shown to lead to increased food intake and subsequently obesity in animals treated experimentally. The lateral hypothalamic nucleus in turn exerts opposite effects such as decreased feeding and lowering body weight. Furthermore specific areas of the amygdala can affect feeding partially through the ventromedial hypothalamus (20).

Amongst the hormones that interact at the efferent end of the regulatory system, glucocorticoids are believed to play an important permissive role these effects possibly mediated via the sympathetic nervous system. For example, it has been noted that leptin deficiency does not result in obesity in the absence of glucocorticoids (21).

**Genetics of obesity**

In the past, people have often thought of obesity as a disease that is caused by too much food, too little exercise, and no self-control. Although this may be true in some cases, obesity is a multifactorial disease; environmental and genetic factors interact resulting in a disorder of energy balance. Genes are activated by a person’s environment, in other words “genetics loads the gun, but environment pulls the trigger” (22). Knowledge about the role genetics plays in bodyweight is still limited, but it is known that obesity has a polygenic cause; there is not one specific “obesity gene.” In fact, more than 250 genes have been found that relate to some cause of human obesity. These genes have been linked to variable biological functions that are related to fat store in adipocytes. Some have relation to food intake and others have to do with energy expenditure. There are certain genes that are linked to lipid and glucose metabolism and others have a role in adipose tissue development (23).

One of the earliest theories connecting genetics and obesity was proposed by James in 1962. His thrifty gene hypothesis aimed to explain the tendency of various ethnic groups towards obesity and diabetes (24). In essence, the theory proposes that our ancestors possessed a gene (or set of genes) that allowed them to increase rates of fat storage in times of prosper so that they could store energy during times of famine and therefore would not starve. Additionally, he proposed that...
this gene is still active in humans, conversely does not serve to advantage in current times because we rarely experience times of extreme famine (25). Instead, the thrifty gene continues to allow storing excess amounts of fat which, paired with a lower activity level, leads to obesity and other chronic diseases.

Obesity can be either monogenic or polygenic in inheritance. Five single gene defects have been identified;

**Agouti gene:** The protein binds to melanocortin-4 receptor in the hypothalamus thereby modulating food intake. Concentrations have been found to be higher in obese than non-obese men and correlate well with basal metabolic index (BMI) (26). A related gene which has been identified is the mahogany gene (27).

**Leptin gene:** Leptin is produced in fat cells, gut, and placenta, which signals the brain about the amount of stored fat (28, 29). Deficient mice have hyperphagia, insulin resistance and infertility. In humans leptin may act on the arcuate nucleus to decrease neuropeptide Y (NPY) production which usually stimulates food intake. Obesity due to leptin deficiency has been reported in two families, affected subjects responding well to leptin therapy (30, 31). In contrast the majority of obese subjects have a high level of circulating leptin level suggesting a level of leptin resistance (32).

**Leptin receptor gene:** Leptin receptor deficiency secondary to mutations in the leptin receptor gene has been reported in humans (33).

**Melanocortin-428** and **melanocortin-3 receptor gene defects** (35): Transgenic mice with mutations in these genes exhibit hyperphagia and severe obesity. Observations in these mice suggest that receptors for MSH normally inhibit food intake and fat accumulation.

Serotonin: Subtype receptor elimination in transgenic mice results in similar manifestations (36).

The heritability of weight, metabolic rate, thermic responses to food and spontaneous physical activity has been studied in families which included twins or adoptees. Twins separated at birth maintained the same characteristics regarding weight control despite different environmental backgrounds. Similarly studies in adopted children showed that regulation of weight and body composition was similar to that of biological parents and differed from that of the adoptive parents (37).

Numbers of variant genes associated with obesity have been reported (Table 2). Leptin is an adipocyte-derived hormone that is essential for normal body weight regulation. Its main physiological role may be to coordinate the metabolic, endocrine and behavioural responses to starvation. Leptin is taken up into the central nervous system (CNS) by a saturable transport mechanism and binds to the long form of the leptin receptor (Ob Rb), which is principally located in the arcuate nucleus of the hypothalamus (39). Within the arcuate nucleus, leptin is able to directly inhibit the expression of NPY and Agouti-related peptide (AGRP), peptides that increase food intake and decrease energy expenditure (40, 41). In contrast, expression of peptides that decrease food intake, such as cocaine and amphetamine regulated transcript (CART) and pro-opiomelanocortin (POMC) are increased (42).

Table 2. Selected genes with variants that have been associated with obesity (38)

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene name</th>
<th>Gene product’s role in energy balance</th>
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<tbody>
<tr>
<td>LEP</td>
<td>Leptin</td>
<td>Produced by fat cells</td>
</tr>
<tr>
<td>LEPR</td>
<td>Leptin receptor</td>
<td>When bound by leptin, inhibits appetite</td>
</tr>
<tr>
<td>INS</td>
<td>Insulin</td>
<td>Produced by pancreas</td>
</tr>
<tr>
<td>INSR</td>
<td>Insulin receptor</td>
<td>Induces uptake and storage of glucose</td>
</tr>
<tr>
<td>GHRL</td>
<td>Ghrelin</td>
<td>Produced by stomach</td>
</tr>
<tr>
<td>GHSR</td>
<td>Growth hormone secretagogue receptor</td>
<td>When bound by Ghrelin, stimulates appetite</td>
</tr>
<tr>
<td>MC4R</td>
<td>Melanocortin 4 receptor</td>
<td>When bound by alpha-melanocyte stimulating hormone, stimulates appetite</td>
</tr>
<tr>
<td>FTO</td>
<td>Fat mass- and obesity-associated gene</td>
<td>Promotes food intake</td>
</tr>
<tr>
<td>PPARG</td>
<td>Peroxisome proliferator-activated receptor gamma</td>
<td>Stimulates lipid uptake and development of fat tissue</td>
</tr>
<tr>
<td>ADIPOQ</td>
<td>Adipocyte-, C1q-, and collagen domain-containing</td>
<td>Produced by fat cells, adiponectin promotes energy expenditure</td>
</tr>
</tbody>
</table>

*C1q = complement component 1, q subcomponent, A chain*
Pathologies associated with obesity

In addition to mechanically affecting the body, i.e. by exacerbating osteoarthritis and back pain (43,44) because of extra weight placed on a skeleton, obesity is associated with higher incidence of several severe pathologies.

Diabetes mellitus: Accumulated data demonstrate the association between obesity, non insulin dependent diabetes mellitus—the most common primary form of diabetes—and impaired glucose tolerance (45). In obese individuals, the adipose tissue releases high amount of non esterified fatty acids, glycerol, pro-inflammatory cytokines, and hormones that are linked with the development of insulin resistance. Insulin resistance generates compensatory hyperinsulinemia, with over stimulation of pancreatic β-cells and reduction of insulin receptors (46).

Hypertension: Insulin in excess alters Na+ and Ca++ retention rates, in turn altering vascular reactivity and increase in cardiac output and peripheral resistance, which are the main components of blood pressure regulators. Epidemiological studies have demonstrated that between 65-75% of the risk for hypertension is accounted for by obesity (47, 48). Recently, endocrinological studies of adipose tissue revealed tight links between obesity and hypertension, likely consequent to the facts that the adipose tissue secretes bioactive molecules and immunomodulators (49,50). Out of these, leptin is endowed with significant pleiotropic actions on several organic systems (51,52). In chronic hyperlipidemia and in obesity, (53) saw the development of hypertension, and renal, vascular, and cardiac damage.

Dislipidemia: Obesity is the most common cause of Dislipidemia. Lipid over supply in a state of obesity, hyperinsulinemia, and/or insulin resistance results in increased non esterified fatty acid availability and, in turn, higher Triglycerides (TG) stores (54,55) in non adipose tissues, e.g. muscle, liver, pancreas. Fatty acid metabolites also accumulate and cause activation of signal transduction pathways that further induce inflammation and impair insulin secretion. Frequently, these fatty acid induced disorders are referred to as “lipotoxicity”. Thus evaluated TG level is often accompanied by a slight increase in total cholesterol and a marked drop in high density lipoprotein (HDL) cholesterol. Moreover low density lipoprotein (LDL) rich in TG partially metabolised by hepatic lipase, are converted into small LDL, with higher atherogenic potential (56,57). This may be due to a higher prevalence of hypertension and pro-inflammatory/prothrombotic states associated with adipose tissue accumulation.

Cardiac alterations: In general, obesity is an imperative determinant of cardiovascular diseases (CVD) (58,59) and increases the risk for heart failure, sudden cardiac death and angina or chest pain, and abnormal heart rhythm. All the heart failure is the most common cause of death in obese people; cardiomyopathy and sudden cardiac death also increase in healthy obese patients (60). In the Framingham heart study (61), the annual sudden cardiac death rate was nearly 40 times higher in obese people than in non obese population patients (60).

Metabolic Syndrome: Obesity is regarded as the major component of metabolic syndrome (62). This syndrome is characterized by co-occurrence of multiple metabolic disorders, namely overall and abdominal obesity, insulin resistance, hypertension, hyperglycemia, impaired glucose tolerance, and the combination of low HDL cholesterol and elevated TG level (63). The metabolic syndrome is also characterised by prothrombotic and proinflammatory states (64).

Lung diseases: Obesity is allied with an increased risk for chronic respiratory disorders, including chronic obstructive pulmonary disease, asthma, hypoventilation syndrome, and sleep apnea. In view of that, weight loss often leads to symptomatic improvement (65, 66). Respiratory disorders contribute to increased risk of hypertension, dysrhythmias, heart failure, stroke, myocardial infarction, and increased inflammation (67) hence, weight loss programs are mandatory in obese lung patients.

Cancer: In contrast with cardiovascular disease and diabetes, obesity is less often indicated as a risk factor for many cancers. Even so the international agency for research on cancer classified the evidence of a causal link as sufficient for cancers of breast, endometrial, colon, kidney, prostate, gall bladder and esophagus although the biological mechanisms that explain this link are not known for any of these cancers (68). The link between diet, obesity, and cancer is still not completely understood but the rising worldwide trend in obesity and cancer might be- at least in part- causal. Undeniably, overeating may be the largest avoidable cause of cancer in non smokers. While the putative cause of this obesity related cancer has been primarily ascribed to excess estrogen production by adipose tissue, inflammation due to adipocytokines secreted by
adipocytes, infiltrating macrophages or associated stromal cells might also play an important role (69). Higher adipocytokines (leptin, hepatocyte growth factor, adiponectin) levels can negatively affect cell proliferation, apoptosis, invasive growth, and angiogenesis. Obesity is associated with increased tumorigenesis that might explain the greater prevalence of neoplasia in obese individuals, who also have higher concentrations of inflammatory tumor growth factors (70).

**Neurological Disorders:** Psychological damage caused by overweight and obesity carries a large health burden (71). This disorder can range from lowered self esteem to frank clinical depression. Certainly, rates of anxiety and depression are 3 to 4 times higher among obese individual (72). Obesity significantly increases the risk of contracting Alzheimer’s disease. A strong correlation exist between BMI and high level of ß amyloid, i.e. the protein that accumulates in Alzheimer’s brain, destroying nerve cells and producing cognitive and behavioural problems. While the precise nature of association remains obscure, physiological changes, obesity may promote Alzheimer disease and dementia (73, 74). As an example, the FTO gene has a small but relevant effect on BMI and increases the risk for diabetes (75).

**Present to Future phase**

According to Nicole (2009), Research on the genetic components of obesity is extremely important. The more is known about the causes for this chronic disease the more efficiently it can be worked to prevent it. Although obesity has both genetic and environmental influences, it is believed that environment activates (or deactivates) certain genes. If these genes can be identified, then it will be able to avoid environmental influences which may cause them to be expressed. In the future when people are able to know for certain that they have a genetic predisposition for obesity, not only that it seems to run in their family, they will be able to have an individualized plan in order to maintain a healthy weight. Recognizing a genetic inclination is the first step in preventing a phenotypic expression of obesity. Genes are not our destiny. They may predispose for certain conditions or phenotypes, but in the case of obesity especially they are not the end-all-be-all. Obesity is a multi-factorial disease which is not caused by nature or nurture, but rather an interaction of the two. This means that even if it is in DNA to be obese there are ways to avoid it with the use of diet and exercise.

Many researchers and doctors alike are excited about the identification of obesity influencing genes because it will allow them to develop new medications and supplements to promote weight loss; however this is not the healthiest approach to take. Instead, health professionals should use the knowledge of a patient’s genetic predispositions in order to recommend effective dietary and lifestyle changes. Certain conditions or genes influence how an individual’s body will respond to the food that they consume, so in knowing a patient’s genetic makeup a health professional would be able to better advise them on what to avoid or what to focus on. The link between genetics and obesity should not be used as an excuse or as somewhere to put the blame, but rather as an opportunity for healthy approaches towards prevention as well as treatment (76).

**References**

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