Current Connections Between Genetics and Obesity

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The increasing prevalence of obesity in developed countries, especially the United States, has become an extremely important public health issue and has also prompted much research to be done. Obesity is defined as an excess of body weight due to an abnormal accumulation of fat. Typically, people classified as obese are 15-20% heavier than average. In order to assess body weight researchers and clinicians use the body mass index (BMI). BMI is simply an individual's weight (in kilograms) divided by their height (in meters) squared. A BMI between 25 and 29.9 classifies an individual as overweight and a value above 30 classifies them as obese. The World Health Organization (WHO) estimates that there are more one billion overweight adults in the world, with one-third of them meeting the definition of being clinically obese (Stein, 2008). In 2002, obesity-related healthcare costs in the United States totaled $92.6 billion, and the costs have only gone up since then (Stein, 2008). These costs are mainly stemming from treatment of chronic diseases that obesity contributes to, such as cardiovascular disease, type II diabetes, and cancer.

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 multi-factorial 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" (Kelly, 2006). Knowledge about the role genetics plays in bodyweight is still limited, but we do know that obesity has a polygenetic 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 adiposities. 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" (Al Rubeaan, 2008). The most powerful research tools in studies of human obesity are the use of transgenic animals, twin studies, and quantitative trait loci (QTL).

One of the earliest theories connecting genetics and obesity was proposed by James V. Neel in 1962. His thrifty gene hypothesis aimed to explain the tendency of various ethnic groups towards obesity and diabetes. 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 prosperity so that they could store energy during times of famine and therefore would not starve. Neel proposed that this gene is still active in humans, however does not serve to our advantage in current times because we rarely experience times of extreme famine (Harsch, 2006). Instead, the thrifty gene continues to allow us to store excess amounts of fat which, paired with a lower activity level, leads to obesity and other chronic diseases.

Using transgenic animals has led researchers to come to many powerful conclusions regarding the relationship between genetics and obesity. Previously, researchers discovered that selective breeding was able to produce differences in food intake between different mice. These conclusions led scientists to probe further into what exactly was causing the marked differences, hence the beginning of transgenic studies. The first successful transgenic mouse was generated and used in a research study in 1982 (Kelly, 2006). Since this time, a number of studies have shown that mutations in certain genes can cause obesity in mice.

Transgenic mice have classically been used in studies of the ob gene, which was given its name after it was discovered in an obese mouse. Ob/ob mice (offspring that received the ob gene from both parents) ate two to three times more than the control group and were substantially

heavier, even when put on a controlled diet. The ob gene controls the production of leptin, a hormone that plays a role in appetite and metabolism. An ob/ob mouse is leptin-deficient and therefore does not experience the same feelings of satiety or satisfaction from food. Although studies on the ob gene and leptin were very conclusive in mice, the same effects were not proven in humans. On the other end of the spectrum, in 1999, Gregory Barsh from Stanford University discovered the Mahogany gene (mg) in mice. A mutation in the mahogany gene allowed the mice to eat high-calorie, high-fat diets and still remain thin. Mice with a normal mahogany gene gained significant amounts of weight with both high- and low-fat diets. After Barsh's study, continued research on the mahogany gene has shown that it is present in a region of the hypothalamus which is associated with body weight regulation (Kelly, 2006).

Many recent transgenic studies have focused on the role of the agouti gene. The agouti protein binds to the melanocortin-4 receptors (MCR-4) in the skin as well as in the brain. Binding to MCR-4 receptors in the hypothalamic nuclei affects feeding behavior; the blockage of MCR-4 causes elevated levels of neuropeptide Y which is predicted to cause over-eating and obesity. Dominant mutations in the agouti gene in mice cause obesity and mild hyperphagia as well as many symptoms involved with metabolic syndrome such as excess insulin in the blood, peripheral insulin resistance, impaired glucose tolerance, and an increased susceptibility to cancer (Michaud et al., 1997). Metabolic syndrome is a collection of disorders and/or diseases that increase a person's risk for diabetes as well as cardiovascular disease.

After finding promising results in mice, researchers moved onto humans. The agouti gene in humans, also referred to as murine agouti or aP2-agouti, is normally expressed in adipose tissue and may regulate fatty acid metabolism by acting directly on adipose tissue. When transgenic mice were generated that expressed the aP2-agouti they were not obese nor were they

diabetic, but after seven days of insulin injections they were significantly heavier than insulin-treated, non-transgenic mice. Also, it was observed that the agouti gene caused an influx of free calcium into the cells but no change in the efflux (Xiaocun et al., 2004). Numerous cell processes are performed via calcium signaling therefore it was hypothesized calcium levels in the peripheral tissues may play a role in agouti-induced obesity. "Free calcium in the cells appears to play an important role in the metabolic derangements associated with obesity, hypertension, and insulin resistance. Factors important in obesity, such as insulin and the agouti protein—normally expressed in human adipocytes—have been shown to trigger an increase in the influx of free calcium" (Parikh et al., 2003). Obese persons have a higher amount of free calcium in their cells than do non-obese persons. On the other hand, there have been numerous studies looking at the effects of dietary calcium intake on body weight which conclude that it actually causes one to lose weight. What is the explanation for this seemingly paradoxical relationship between free calcium and dietary calcium? One hypothesis is that a diet high in calcium works to lower amounts parathyroid hormone (PTH) and 1,25-dihydroxy vitamin D in the blood. PTH works to increase levels of calcium in the blood, so a lower quantity of it would obviously lead to lower levels of free calcium (Parikh et al., 2003).

Dr. Randy Jirtle and Dr. Robert Waterland designed another experiment to look at the role of the agouti gene. They hypothesized that our body types may be heavily influenced by what our mothers eat before and during pregnancy. The study involved two pregnant mice, both of which had a piece of DNA inserted in front of the agouti gene. This piece of DNA, or a transposon, affects how the agouti gene next to it is expressed. One of the pregnant mice was fed supplements containing methyl groups, which bind to the inserted transposon, and the second mouse was fed regular food. Once the methyl groups in the first mouse bind to the transposon,

proteins approaching the agouti gene are unable to bind to it and produce new proteins. Since this blockage does not occur in the second mouse, the new protein is still able to be produced in and causes its offspring to overeat and have yellow fur (Jirtle et al., 2008). This study shows the importance not only of the agouti gene but also of how a mother's diet affects its offspring; something as simple as consuming methyl groups in a supplement can block the agouti protein and therefore produce normal size offspring. Research on the agouti gene is still in process and will hopefully uncover more conclusive evidence on how this gene works in humans to produce the obesity phenotype.

In conclusion, agouti protein in the central nervous system (CNS) antagonizes melanocortin receptors which results in obesity, hyperphagia, and hyperinsulinemia. In the peripheral tissues, agouti expression that is paired with insulin treatment results in significant weight gain. Also, the agouti protein raises the amount of free calcium in the blood which has been observed as a marker of obesity.

Twin studies are the easiest and most reliable way to trace genetic obesity in humans. Research on identical twins has shown genetic influences on food intake, attitude, appetite, physical activity, and food preferences. The studies are performed either by comparing pairs of twins or by observing twins that have lived separately. For example, twins separated at birth and adopted by different families. Although twin studies do not identify a particular gene responsible for a given trait, they give researchers primary conclusions as to which aspects of obesity are influenced by genetics. This can, in turn, lead to further research possibly using transgenic studies or QTL.

A study in 1992 recorded the dietary intake of identical twins living separately for one week (Kelly, 2008). Approximately 65% of total calorie consumption and 70%-80% of

beverage consumption was the same. The fact that the twins made such similar choices regarding their diets shows that there may be a genetic component that leads us to enjoy or desire certain foods. Another study of 4,000 twin pairs in Finland found a 62% rate of heritability for physical activity (Kelly, 2008). Heritability is defined as "an indication of the proportion of variation within a population that is due to genetics" (Al Rubeaan, 2008). The two previous studies show that the similar body types and weight gain patterns of twins may be heavily influenced by genetic predispositions for both dietary intake and the level of physical activity.

A Canadian study at Laval University in 1990 had 12 pairs of twins (all thin, young men) spend 120 days in a separated section of a dormitory. They were all fed 1,000 calories more than what they needed to maintain their original body weight. The weight gain results were very different across the twin pairs; one pair gained only 9.5 pounds while another gained 29 pounds. Furthermore, some gained more weight in the abdominal area while others gained more in the buttocks and thighs. Most importantly, each brother gained an almost identical amount of weight as his twin. The researchers came to the conclusion that "genetic factors are involved in adaptations to overfeeding, variations in weight gain, fat distribution, tendency to store energy as fat or lean tissue and the various determinants of how energy is metabolized" (Stein, 2008).

Stunkard, et al. performed a study which compared the BMI of twins who lived together and of twins that lived separately. In total, there were over 600 pairs of twins included in this study. Researchers found that the correlation coefficients of BMI values of twins reared apart were 0.70 for men and 0.66 for women. These coefficients are only slightly lower than those of twins who were raised together showing that it is the genetic factors, not environmental, that influence our BMI (Stunkard et al., 1990).

Studies are also often done on people that have been adopted to see whether their phenotype is more similar to their biological or adopted parents. Adoption studies are a simple way to trump the argument that obesity is only affected by the environment in which one lives; if this were true then the subjects would be more similar to their adopted parents that they had lived with their entire lives, instead of their biological parents who they were rarely around. Although this research is not able to identify particular genes, it is extremely useful in showing how traits are passed on and does prove that nature, or genetics, plays an important role in obesity. A study in 1986 examined this relationship by observing 540 Danish adoptees (Stunkard et al., 1986). This group had a range of body types, from thin to morbidly obese. There was a strong relationship between the weight class of the subjects and their biological parents, but no such relationship with their adopted parents. Not only obesity was found to be heritable, but body mass and type as well. Body mass is the quantitative measurement of how much a given individual weighs, while body type refers to fat distribution patterns and where the individual tends to gain weight. There are two main body types which define where a person is most likely to gain weight; android and gynoid refer to someone who is more likely to gain weight in the abdominal area or the hips and buttocks, respectively.

A more precise way to identify genes responsible for obesity is using quantitative trait loci (QTL). QTL maps generations in order to trace and locate various genotypes and relate them to phenotypes. This is the first step in identifying a multitude of genes that influence complex traits, unlike the transgenic studies which only manipulate one gene at a time. The major genes that have been identified using QTL are ob (which influences the hormone leptin), fat mass and obesity-associated gene (FTO), proopiomelanocortin (POMC), melanocortin-4 receptor (MC4-R), and peroxisome proliferators-activated receptor (PPAR-y 1 and 2). The first

four genes listed have roles in controlling appetite (ob also influences energy expenditure) and PPAR-y 1 and 2 are involved with adipocyte differentiation as well as insulin levels (Kelly, 2006).

The FTO gene is located on chromosome 16 and produces a protein that appears to be related to the system of appetite as well as satiety. A gene can be further broken down into a pair of alleles, which can vary and therefore produce different genotypes and phenotypes. A human study identified the rsA allele of the FTO gene, which is hypothesized to be positively correlated with weight gain. Individuals who carry two of the alleles were heavier than individuals who carried one, and both groups were heavier than the general population. An increase in the rsA allele is connected with an increased BMI which begins in youth and continues to increase throughout adulthood. The allele also has effects on body fat distribution, insulin sensitivity, and energy intake versus expenditure (Al Rubeaan, 2008).

Genetic forms of obesity can also be caused by chromosomal diseases such as Prader-Willi syndrome (PWS) and Bardet-Biedl syndrome (BBS). PWS is caused by an absence of segment 11-13 on chromosome 15 and is characterized by mental retardation, decreased muscle tone, and an insatiable appetite which leads to massive obesity. It is estimated that obesity occurs in 90% of cases and constitutes the major cause of death among affected patients (Davies et al., 2008). BBS is an autosomal recessive disorder that is characterized by early-onset severe abdominal obesity, slight mental retardation, abnormal retinal development, and limbs which are too short or formed incorrectly. Furthermore, studies have shown that BBS can express the hormonal and metabolic changes that are characteristic of metabolic syndrome. BBS is a pleiotropic genetic disorder, meaning that it affects one gene which influences a number of different phenotypes (Jordan, 2008; Davies et al., 2008). Although both of these syndromes have

more serious symptoms than obesity, the genes that they affect have been shown to predispose one for being overweight.

Further research on the genetic components of obesity is extremely important; the more we know about the causes for this chronic disease the more efficiently we can work to prevent it. Although obesity has both genetic and environmental influences, it is believed that our environment activates (or deactivates) certain genes. If we can identify what these genes are, then we 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 predisposition is the first step in preventing a phenotypic expression of obesity.

Genes are not our destiny. They may predispose us 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; it is not caused by nature or nurture, but rather an interaction of the two. This means that even if it is in your 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. It is exciting for some people to think that in the future we may be able to eat whatever we want while not exercising and reverse the damage done by taking a prescription, but dietary intake and lack of physical activity affect many things besides how a person looks. Even if one was to take a medication to prevent them from gaining weight they could still suffer from many deleterious health effects stemming from their diet such as diabetes or cardiovascular disease. 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.

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