The impact of a person’s genetics versus one’s environment on weight remains one of the most heavily debated topics in obesity medicine. The modernization of our society has, no doubt, contributed to high rates of obesity by promoting an environment with decreased physical activity and increased calorie consumption.

Do Genetics Play a Role in Obesity?

Throughout the last 30 years, studies have shown the undeniable impact of genetics on obesity. Twin studies have shown that identical twins adopted by different families had a very high connection in body weight despite growing up in two separate environments. Contradicting research has shown the greater impact of genetics over environmental factors on obesity, suggesting genetics contribute to 40 – 70 percent of obesity. Recent science has also discovered more than 50 genes strongly associated with obesity. So, while changes in the environment have greatly increased the rates of obesity throughout the last 30 years, the presence or absence of genetic factors protect us from or predispose us to the disease of obesity.

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What Does Your Brain Have to do with Controlling Body Weight?

In order to better understand the role of genetics on body weight, let’s discover how body weight is regulated. Body weight is primarily regulated by two different areas in the brain:

- The arcuate nucleus, a collection of neurons (nerve cells) that contains a substance called neuropeptide Y (NPY) which can cause weight gain
- The neuron system that causes weight-loss (POMC system)

Everyone has a different “baseline balance” between these two opposing systems, which explains why some people are constantly hungry and others have to be reminded to eat. The “baseline balance” of these two systems is continuously changed through a process. Activation of the NPY (weight gain) system increases appetite and slows down metabolism, while activation of the POMC (weight-loss) system reduces appetite and increases metabolism.

These brain systems are continuously activated by hormone signals transmitted from the rest of the body – including the stomach, small and large intestines, pancreas and fat cells that are ultimately regulated by both genetic and environmental factors. While we often feel that we primarily control our body weight with “willpower,” in reality, our body weight is heavily influenced by genetic and environmental factors which impact “hormone power.”
Gene Mutations that Cause Obesity

Given the large influence of genetics on body weight, let’s take a closer look at the role of genes. Mutations in more than 50 genes have been strongly associated with obesity, most with mild effects. Most of these gene mutations have been shown to deactivate the “weight-loss system” within the brain. This results in overpowering levels of hunger and cravings which eventually lead to increased food intake and weight gain.

Most people affected by obesity have multiple genes that predispose them to excess weight. The most common gene associated with obesity is the FTO (fat mass and obesity associated) gene, which is present in up to 43 percent of the population and significantly increases the risk of developing obesity.

This gene has been associated with increased appetite, energy intake, fat intake, reduced satiety and control over eating. Also, this gene doesn’t decrease one’s desire to perform physical activity. In fact, high physical activity reduces the risk of obesity by 40 percent in individuals with the FTO susceptibility gene. While testing for the FTO gene can be performed, it is not practically helpful because interventions are the same for individuals with and without the FTO gene.

In rare cases, a single gene mutation can cause severe obesity. These mutations develop in childhood, usually before the age of two. Leptin Deficiency and POMC Deficiency are extremely rare, but MC4R deficiency is found in up to five percent of children affected by obesity. Children with MC4R deficiency tend to be very tall for their age and develop obesity before the age of five that continues through adulthood. All of these mutations result in children feeling extremely hungry, leading to severe overeating and extreme increases in body weight that worsens through adulthood.

What are the Different Genetic Mutations, and Can Testing Be Performed?

Currently, genetic testing can be performed for Leptin Deficiency, POMC Deficiency and MC4R mutations. Some clinicians suggest testing for these genetic conditions in children who develop severe obesity at a young age since these conditions cause obesity soon after birth. Also, if obesity is associated with intellectual disabilities or delayed developmental milestones, these children might be evaluated by a geneticist.

Below is a chart to help give you a better idea of genetic mutations, prevalence and the onset of obesity.

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<th>Genetic Mutation</th>
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<th>Clinical Presentation</th>
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| Melanocortin-4 Receptor (MC4R) Deficiency | 1-6%       | • Early onset obesity from birth onwards  
• Increased linear growth by age 5 (but not necessarily taller as an adult) |
| Leptin Deficiency                    | Extremely rare | • Early onset severe obesity from birth onwards  
• Constant hunger  
• Delayed or no puberty  
• Infertility |
| POMC Deficiency                      | Extremely rare | • Early onset severe obesity from birth onwards  
• Constant hunger  
• Adrenal Insufficiency sometimes associated  
• Red hair and pale skin |
| Fat Mass and Obesity (FTO) Gene      | 30-40%     | • Common presentation in adults with increased hunger and cravings |
Another area of study in obesity is epigenetics. Epigenetics is the study of changes in organisms caused by modification of gene expression rather than the alteration of the genetic code itself. Environmental exposures during critical times of development can cause permanent changes in offspring. When a mother is carrying a child in utero, what happens to mom during that pregnancy can have a lifelong impact on her child’s metabolism.

If a mother gains more than 45 pounds during pregnancy, there is a more than 40 percent risk of that child having obesity by the age of 9-14. Children born to mothers with gestational diabetes have also been found to have higher rates of excess weight or obesity and insulin resistance by their adolescent years. There is now focus on helping patients attain healthy bodyweight prior to becoming pregnant, as well as maintaining healthy amounts of weight gain during pregnancy to help reduce the future risk of obesity in children.

So What Can You Do?

Although the role of genetic testing in addressing excess weight continues to be an area of active research, there are a few things you can do:

- Children with severe obesity before the age of two should be considered for genetic testing.
- What happens during pregnancy can have a lifelong impact on offspring, so maintaining a healthy weight before and during pregnancy is key.

Knowing your family history can help you understand your risk for obesity and obesity-related conditions such as diabetes and heart disease. Your family history can reflect the impact of your shared genetics and environment amongst family members.

If you have a family history of obesity, are you predestined to develop obesity? No! While multiple genes can increase levels of hunger and cravings, following a consistent approach that incorporates solid nutritional, physical activity and behavioral components can reduce and reverse obesity. If high levels of hunger and cravings are preventing you from achieving a healthy body weight, then consider seeing an obesity medicine specialist and using one of the nine FDA-approved medications for weight management – most of which help control hunger.

Regarding the highly debated question: “Is it Nature versus Nurture that causes obesity?” the true answer is that both Nature and Nurture determine and affect one’s bodyweight.

About the Author:
Dr. Sicat, MD, FACE attended Williams College and medical school at the Medical College of Virginia at Virginia Commonwealth University (MCV_VCU,) and remained there to complete his Internal Medicine residency in 2002. Dr. Sicat is board certified in bariatric medicine by the American Board of Obesity Medicine (ABOM) as well as the American Board of Bariatric Medicine (ABBM). He is also board certified in Internal Medicine (2002) and Endocrinology, Diabetes and Metabolism (2004).