

Role of Genes in Obesity

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Citation: Mathew H, Saleem M (2018) Role of Genes in Obesity. *SCIOLOGENETIC SCIENCE* 2018;1:49-55

Accepted: October 16, 2018

Published: October 18, 2018

Abstract

Obesity is the outcome of an extreme difference between the energy intake and the energy expended, which leads to severe weight gain. The two main factors of obesity are environmental influences and genetics, but the extent of the genetic contribution to obesity continues to be unknown. Multiple studies using different tools have been used to support the significance of the genetic influence on obesity, such as twin and adoption studies, race/ethnicity, and mouse models. The use of mouse models has allowed for the greatest expansion of knowledge on the genetics behind obesity, and advancements continue to be made to this tool. There are many possibilities on how genetic variations could affect the development of obesity including eating behavior, metabolism and digestion, energy intake, and adiposity. The various tools that have been used in studies on obesity and the vast number of factors that are dictated by genes prove that the influence of genetics on obesity is substantial.

Keywords

Monogenic obesity, Polygenic obesity, Genetic and behavior, Gene mutation

Introduction

Obesity is commonly identified as the result of a difference between the amount of energy that is taken in and the amount of energy that is used, where substantially more energy is taken in than is being spent [1,2]. The prevalence of this disease is increasing at a high rate that it is considered an epidemic [2]. The estimated percentage of obesity in adults was 33% in 2010, and has been increasing over the past few years [2]. Additionally, obesity can lead to many other health complications such as diabetes and cardiovascular disease [3]. Due to these reasons, studies surrounding obesity have increased in order to expand treatment options and to find ways to detect the disease earlier on in life. Since past data has proved that environmental factors have a large influence on the prevalence of obesity, recent studies have turned to evaluating the influence of biology, more specifically, genetics, on the development of obesity. Certain studies have already identified almost 30 variants in genes that are involved in energy regulation that could lead to obesity [4]. These studies have since proved that life style choices are a huge contribution to obesity, but genetics is also a significant contribution to its development [2].

In this article, studies that provide evidence for the genetic contribution to obesity will be reviewed, and the effect genetics has on the various factors leading to obesity, such as eating behavior, metabolism and digestion, energy intake, and adiposity, will be analyzed. Understanding the way genetics contributes to obesity could lead to an improvement in treatments for obesity and aid health professionals in predicting a patient's vulnerability to the disease.

Categories of Genetic Etiology in Obesity

There are three forms of obesity that are identified based on the genetic etiology of obesity: Monogenic, syndromic, and polygenic obesity [2].

Monogenic obesity is caused by a single gene mutation [5]. As it will be explained later, monogenic obesity will cause the function of the hypothalamus or the leptin-melanocortin pathway to be lost [6]. For example, a mutation in the leptin



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receptor is a common result of monogenic obesity. Leptin is a hormone that is involved in the magnitude of food intake, thus a mutation in the leptin receptor will cause the hormone to not be able to carry out its function, leading to an increase in food consumption [3,7].

Syndromic obesity is described as obesity that is paired with a rare syndrome that can have characteristics such as delays in mental processing and internal organ irregularities [8]. A common example of a disorder that causes syndromic obesity is Prader-Willi syndrome, which is due the functional loss of chromosome 15, resulting in cognitive issues and a development of an appetite that is greater than average [8,9]. The loss of function in chromosome 15 could be caused by various genetic mistakes, the two main reasons being the complete deletion of the chromosome, and uniparental disomy [9].

Polygenic obesity is the result of small mutations of multiple genes [5,10]. Over 200 genetic mutations that are involved in various functions, such as digestion, multiplication of adipocytes, and metabolism, have been discovered to precede polygenic obesity [11]. A certain gene alone will not have a large effect on expressing the obesity characteristic, but the expression of a large group of genes related to obesity could have a significant effect on weight gain [10]. Additionally, the chance of developing obesity is increased when these genes that promote weight gain are paired with environmental influences that also promote obesity. The environmental factors combined with genetic variations can lead to adipose tissue agglomeration and insatiability, culminating in obesity [12]. Polygenic obesity is considered more common than the other two categories of obesity since it is based on the relationship between the environment and genetics [6].

Evidence of the Influence of Genetics on Obesity

Polymorphisms

Many studies have provided evidence of the significant contribution that genetics makes to the development of obesity in many different ways. A conclusion that was made through multiple studies is that between extreme cases of obesity and moderate cases of obesity, genetics plays a larger role in more extreme cases of obesity [13]. One study by Tang, et al. analyzed the strength of the association between certain genes and the development of obesity. This study found that certain forms of two of the genes, known as SH2B1 rs7498665 and FAIM rs7138803, that were analyzed resulted in a similar increased susceptibility to obesity in people [14]. This study proved that certain genes have an important role in the development of obesity since certain forms of those genes resulted in obesity in multiple people.

Twin and adoption studies

Twin and adoption studies are very important tools for providing evidence of the role of genetics. These forms of studies have provided evidence that about 40% to 70% of differences in the BMI (body mass index) is due to the contribution of genetics [3]. This demonstrates that the same polymorphism of a certain gene could be found being shared within families that have obesity.

Monozygotic twins share the same DNA while dizygotic twins share approximately 50% of their genes. A study by Naukkarinen, et al. showed that the correlation in BMI between two monozygotic twins that were exposed to different environments was about 0.79 [15]. This high correlation proves that the twins' genetics caused them to have very similar body weight regulation processes despite the fact that they had different environmental influences. Another study that supported the significant influence of genetics on obesity concluded through research that identical twins that have obese parents have a greater chance of becoming obese than identical twins of parents that are not obese [16].

Adoption studies have also been helpful in proving that those that were adopted shared a similar BMI as adults to their biological parents than they did to their



adopting parents [16]. Through the use of twin/adoption studies, the results proved that 25% to 40% of differences in adiposity between individuals is due to inheritance [16]. These studies show how much influence that genetics has on the regulation of body weight. Additionally, they suggest that genetic factors may have a stronger influence than environmental factors at times, since correlations in BMI between the adopted child and their biological parents are much stronger than that of the adopting parents and that child. It was also concluded that common environmental factors have an effect on BMI only during a portion of one's life, while genetic factors have a strong effect from childhood through adulthood [17].

Race and ethnicity

Using studies based on race and ethnicity to analyze genetic influence on obesity is not as popular since the genetic influence is harder to separate from the environmental influence, but studies have shown that the frequency of obesity in certain racial/ethnic populations are greater than in others. For example, studies performed in India show that there is a high frequency of genes that are associated with increased adipose tissue and poor metabolism [18].

The idea of a genotype that is referred to as a "thrifty genotype" is also studied based on race/ethnicity. This genotype allows for the buildup of adipose tissue, which would be beneficial for an environment that lacks food resources, but it would be harmful to an environment that may have many sources [16]. This genotype is more likely to be shared by racial and ethnic groups that have historically lived in environments with limited sources of food, and through natural selection and evolution, has developed to allow increased energy storage [19].

Mouse models

Mouse models have been a huge contribution to the study of genetics related to obesity. They are continued to be used and their advancements have allowed a better look into the genetics behind obesity in greater focus. Mouse models are advantageous tools due to their low cost and level of difficulty to use. Additionally, they provide researchers with strains of genes that are specifically defined, allowing them to be easily manipulated for more accurate evaluation, and environmental factors are easily controlled in order to understand the full effect of the genetic factors [20]. Mouse models were used to detect specific genes that had a large impact on the development of obesity, such as Wang, et al. who studied the relationship between the gene CYP2A6 and class I obesity [21]. Advancements have also allowed genetically engineered mice to be used to find many other genes that play a role in the obesity phenotype [22]. In the study by Kleinert, et al. certain mouse strains like the C57BL/6J strain is used to study diet-induced obesity in humans. The study also found strains like SWR/J that are not as vulnerable to obesity, which were used as models to study resistance to obesity [23]. Studies using mouse models also discovered that certain genes cannot work alone to develop the common obesity phenotype. Thus, it was concluded that monogenic obesity is considered rarer than polygenic obesity [22].

The mouse models were a step to understanding the impact of genes affecting the leptin-melanocortin pathway in humans. One such study by Couturier, et al. discovered that ablating the protein involved in the leptin receptor gene, OB-RGPR, causes the prevention of diet-induced obesity from forming [24]. Additionally, mouse models helped to give more insight into the mutations that caused syndromic obesity, such as the tub gene mutation. The tub gene mutation caused a gradual development of obesity that was also paired with retinal issues and the loss of hearing [25].

The Effect of Genetics of Different Factors Related to Obesity

Genetics in behavior

There are many aspects of behavior that genetics have some form of control over, such as the type of foods consumed, addiction, and the control of appetite.



One study showed that there is a genetic factor in whether or not one prefers certain foods. This was proved by using mouse models, where the preference for a certain food item was able to be bred into the test subjects [26]. The genes of humans' cause variations in taste as well, which cause differences in food preferences [26]. Thus, genes that promote a preference for sweet foods and foods that are high in carbohydrates are more likely to cause the development of obesity than genes that promote healthier food preferences.

It is found that through rewarding parts of the brain - obesity may develop due to addiction to food. Studies show that there exists a mutation of the gene, DRD2, that causes dopamine to not function properly which could lead to addictive behaviors, such as food binging [27]. This gene leads to an addiction to food, which will eventually result in weight gain/obesity. The DRD2 gene could additionally be paired with genes that control one's appetite. Variations in the genes that play a part in the leptin-melanocortin pathway can lead to increased appetite, thus leading to the development of obesity. One study that was performed on students found that genes that are linked to appetite control, such as the LEP-R and MC4R genes, have a high correlation between the expressing of those genotypes and the development of obesity [27,28].

Genetics in metabolism and digestion

The rate of metabolism and digestion is also a factor that is partly dictated by genes. The metabolic rate is defined as the rate at which energy is expended, thus resting metabolic rate refers to the energy that is released during the continuation of normal functioning of the body. The determination of the resting metabolic rate is partly based on genetics and there is relationship between this rate and weight gain [29]. Studies have also shown that the prevalence of metabolic disorders have increased throughout the years due to decreased natural selection since populations have advanced in terms of prosperity. These metabolic disorders can have an effect on the amount of adipose tissue that is produced, which leads to obesity [30]. Additionally, genes that are involved in the functioning of the liver showed variations in the main metabolic pathways, which could lead to the promotion of obesity. A study by Yang X, et al. evaluated nine genes that were hypothesized to cause obesity in the mouse models, and the result showed that eight of the genes lead to the development of obesity in the mice [31]. The function of the gut microbiota involved in digestion is partly based on genetics as well. Studies have shown that the gut microbiota of monozygotic twins are more similar than that of dizygotic twins, which supports the idea of genetics involved in this factor [32]. A study by Lu, et al. investigated the gene TLR4 and found that when this particular gene is expressed, it causes a metabolic syndrome and determines the function of gut microbiota [33].

Genetics in energy intake and release of energy

The total consumption of calories was found to have a genetic influence because when studies were done on monozygotic twins, the intake of calories was very similar to each other. The association between the monozygotic twins and the total amount of calories consumed was 0.80, which suggests a very strong relation [34]. Additionally, mutations in genes that function in metabolizing adipocytes leads to decreased activity, causing lipids to collect in adipose tissue [28]. Increased uptake of energy and decreased release of energy leads to a net positive amount of energy being taken in, which causes weight gain.

As mentioned earlier, leptin is a hormone that is involved in food consumption. This hormone is released in response to increased adiposity by decreasing appetite [35]. Mutations in the leptin receptor could cause the leptin hormone to not carry out its function, which causes energy intake to not decrease. Studies provide evidence that there are mutations occurring in the receptors of the leptin-melanocortin pathway, such as the mutation of melanocortin 4 receptor, which is predominantly found in obese individuals [36]. Mutations in parts of this important pathway is one of the main causes of the imbalance between energy intake and energy used. Due



to the influence that the melanocortin-4 receptor has on energy homeostasis, it is vulnerable to different practices that are being studied for the cure of obesity in individuals [37].

Genetics in adiposity

The proper functioning of fat cells, adipocytes, is a huge contributor to obesity, and variations in genes could affect the magnitude of the accumulation of adipose tissue in humans. One study found that a receptor that is key player in carrying out the function of the formation of adipose tissue, peroxisome proliferator-activated receptor, when mutated, has a positive correlation to the development of obesity [36,38]. There will be a rushing in the differentiation of pre-adipocytes to adipocytes, which leads to weight gain [19]. The function of the variation of this gene causes abdominal obesity, which is a huge promoter of cardiovascular disease.

A study by Lorenzo, et al. proved the role of genetics in adiposity when an ankyrin-B (AnkB) deficiency in adipose tissue leads to cell-autonomous adiposity [39]. The adipose tissue that lacks AnkB contains a buildup of lipid and spiked glucose absorption.

Discussion and Conclusion

The study of the various influences on obesity is very important because genetics was determined to be a greater contribution to the development of obesity than it was initially believed to be.

The tools being used to study the genetic contribution in obesity and researching the factors of obesity that are influenced by mutations in genes has provided a significant amount of evidence that genetics plays a large role in the development of obesity. Mouse models are the most advanced tools for identifying the genes that cause obesity if mutated, along with the magnitude of the influence of those genes. These models continue to be advanced in order to expand the research regarding genetic influence on obesity. Of the possible studies that can be used to study the genetic influences, mouse models are the most efficient in terms of cost and use. Environmental factors have a significant impact on obesity when paired with genetic mutations, but there is also monogenic obesity, which does not need to be paired with environmental factors in order to express the obesity phenotype. The various tools that have been used in studies on obesity and the vast number of factors that are dictated by genes are used to conclude that the influence of genetics on obesity is substantial. There are multiple solutions to treat and avoid the environmental factors of obesity, but the study of the genetic influence will allow advancements in the treatments and the prevention of genetically promoted obesity. For example, one treatment for the mutations in leptin receptors are being developed. A mutation in a certain gene that causes a leptin hormone deficiency is being treated with “recombinant-methionyl human leptin”, which allowed some weight loss [16].

Further research could be performed to find advancements in the treatment for genetically promoted obesity and ways to avoid its prevalence.

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