REVIEW

The genetics of obesity and overweight

Onur Oral[1], Kerim Bakan[2] , Serdar Gur[2]

[1]Ege University, Faculty of Sports Sciences, Izmir, Turkey, [2]Istanbul Gelisim University, School of Physical Education and Sports, Turkey

ABSTRACT

The incidence of obesity, which is one of the most important health problems with the effect of the advancing world system, has increased dramatically in both adults and children in recent years. Obesity is usually caused by restricted movement and irregularity between energy intake/expenditure, and environmental conditions play a role in obesity, while studies reveal that genetic factors have an important effect as well as other factors that trigger obesity. Obesity paves the way for the formation of many metabolic diseases. Obesity, together with hypertension, insulin resistance, high triglyceride, and low HDL concentrations, is part of the metabolic syndrome. Although the amount of energy consumed by the consumed food is increased in many ways, it is thought that even if each activity is designed with the same intensity for similar individuals, differences in genetic factors create different results. Obesity not only increases the likelihood of risk factors for various diseases but also reduces the quality of life of individuals. This situation brings with it a lot of financial burdens. This review includes the examination of studies on the analysis of genetic factors of obesity, which is a global problem.

Keywords: Obesity, genetics, overweight

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INTRODUCTION

Obesity occurs when the energy taken is not expended at the same rate as it is taken. This may be correlated to the excess of the taken energy units, whereas it also might occur due to the lack of energy expenditure units and systems of our body. This ultimately results in the storage of triglycerides in adipose tissue.

Some of the undesired metabolic effects accompanied by obesity are increased risk of type 2 diabetes, cancer, fatty liver and related diseases, hormonal disorders, hypertension, cardiovascular disease (CVD), and increased mortality risk [1].

The occurrence and progression of obesity show differences with each individual. Age and gender are factors that affect this progress [2]. Comparing a man and a woman with identical BMIs, a man is likely to store less fat in his body [3].

Obesity might be accepted as it is related to a variety of factors. Besides the expenditure and storage of energy, many metabolic processes occur through the signals it sends to regulate the systems in the body. These signals affect the sympathetic and parasympathetic nervous systems, consequently the appetite and endocrine systems. The processes such as the storage and expenditure of energy are controlled through several homeostatic mechanisms. Studies show us that these mechanisms may be associated with genetic factors [4].

Obesity, according to its etiology, is categorized as monogenic obesity, syndromic obesity, and common/polygenic obesity. Monogenic obesity is a serious type of obesity however disorders in the development of the body are not seen. Syndromic obesity, on the other hand, brings along certain developmental problems such as organ-specific abnormalities, mental retardation, etc [4]. The effects of obesity can lead to many other problems and trigger the occurrence of Type 2 diabetes, cancer, hypertension, cardiovascular disease, and hormone disorders [1, 5, 6, 7].

OBESİTY AND PHYSİCAL ACTİVİTY

Physical activity can be defined as any movement performed by moving skeletal muscles in life and requiring energy expenditure. Physical activity also plays an active role in the fight against obesity, as it provides the individual with more energy expenditure than required in his/her vital activities, and helps the energy taken to provide the energy spent balance.

Obese individuals may also have genes such as the lepr (Leptin receptor) gene, which causes an increase in food intake with a central effect and turn decreases energy expenditure [8]. In addition, the POMC gene can cause ACTH deficiency and hypothyroidism, resulting in a slow metabolism and inability to obtain the desired efficiency from physical activities [9].

Physical activities increase their effectiveness in an intense exercise process, and the exercises can be at such a high intensity that they push the limits of the body, and different hormonal systems may come into play during the exercises at this level.

High-intensity exercise suppresses appetite in adults, and this is thought to be mediated by hormones that regulate appetite. The increase in IL-6 induced by high-intensity exercise has been associated with a decrease in appetite and is also active in suppressing appetite.

It has been reported that the reduction of ghrelin may be effective (The ghrelin receptor is GH secretor receptor type 1a (GHS-R1a), which is a G-protein-coupled receptor. This receptor is effective in the regulation of appetite and energy balance in the central nervous system but) is not functional in uptake [10]. Elevated ghrelin plasma levels during the following stress may play an active role in suppressing and countermeasures the outcome of stress, including stress-induced depression and anxiety [11, 12]. The acidic environment that occurs in high-intensity

exercises increases the stress in the body, and possible carcinogenic formations in the body can be prevented thanks to the hormones secreted by the body to suppress this stress. The secretion of ghrelin gormun is of great importance in this process. The effectiveness of this hormone also differs with genetic changes, so it is thought to be associated with physical activity and therefore obesity.

GENETİCS OF OBESİTY

Obesity has a significant genetic basis apart from malnutrition. Many successive studies related to the children who were born since the obesity epidemic, which started with the mechanization period after the industrial revolution replacing the workforce indicate that more than %70 of the reason for the inheritance of weight and the reason for weight gain within the population in contemporary Western environments are genetic differences [13]. In addition, the weight gain in the last 25 years is probably caused by the structural features of the food supply and the determinants of mobility in daily life and environmental conditions [14]. It should be noted, however, that genetic and environmental impacts are interdependent because the impact of environmental factors will vary depending on the individual genetic susceptibility, and vice versa [15].

Studies show that the hypothalamus is the only region in the central nervous system where hunger and satiety are evaluated. Hunger and satiety signals are transmitted in the hypothalamus by stimulating or inhibiting the receptors associated with these hormones. Obesity can also occur as a result of mutations in leptin and ghrelin hormones and/or receptors (mutations in the leptin-melanocortin pathway, leptin receptor gene mutations, POMC gene mutations, ghrelin receptor mutations, AgRP gene mutations, MC4R mutation, etc.). is growing [12].

Pre-pubertal individuals with leptin gene mutations have gonadotropin and thyrotropin deficiency throughout their adolescence. In addition, Leptin gene mutation was found to be highly associated with infection with T cell count and dysfunction. Leptin deficiency, which occurs spontaneously in some individuals during puberty, proves that it is due to a mutation in the leptin or leptin receptor gene. After leptin injection to individuals with leptin deficiency, a significant decrease in food intake was observed, and in addition, a positive effect was observed in the recovery of many dysfunctions, including immunity [9,16]. Eight genes(*LAMA5*, *SPP1*, *CAV3*, *RASGRF1*, *FAK*, *PDGFB*, *PDGFRa,* and *RAC2)* are supposed to be related to skeletal muscle development by suggesting that *FTO* stimulated differentiation of myoblasts (Figure 1) [17].

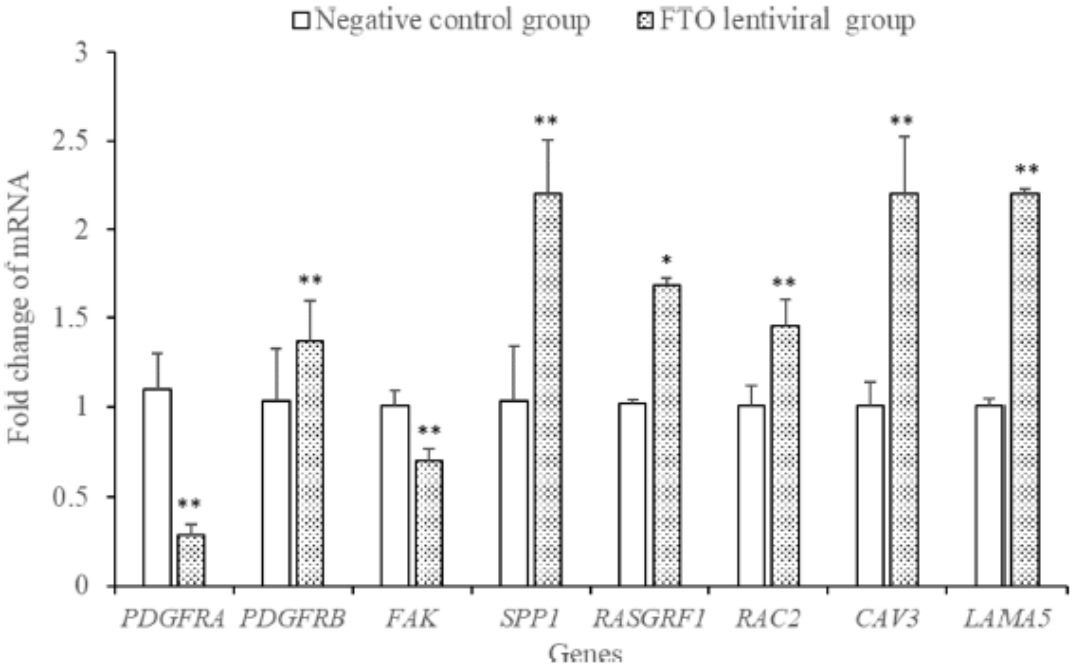

Figure 1. FTO transfected myoblasts significantly increased proliferation and showed that differentiation of myoblasts occurs through regulation in eight genes above (LAMA5, SPP1, CAV3, RASGRF1, FAK, PDGFB, PDGFRα, and RAC2), which are known to be directly or indirectly associated with the development of FTO-transfected skeletal muscle. (Validation of differentially expressed genes by qPCR (n = 3). * P <0.05, ** P <0.01 vs. control) [17]

MİTOCHONDRİAL FUNCTİON İN OBESİTY

Mitochondria is the origin of energy and thus metabolic activities in the body. Therefore, tending alterations, mitochondria are a potential key factor to affect metabolic disorders. The heritability of mitochondria comes from the mother. Considering this situation, maternal obesity is expected to have a significant impact, especially in embryogenesis, on the developing embryo [18]. The mitochondria were affected in various aspects such as mitochondrial DNA (mtDNA) content and biogenesis, generation of reactive oxygen species (ROS), and the increment of the potential of the mitochondrial membrane. Oxidative stress was the result of these aspects. Oxidative stress caused disorders in the development of embryos at early embryogenesis [19]. The effect of mitochondria supports the thesis that obesity can be maternal-based [20].

EPİGENETİCS

The term "epigenetics" refers to the DNA alterations that organize gene expressions, however, the nucleotide sequence is not affected [21]. The modifications in gene expressions, such as methylation and histone modifications, are suspected to affect the heritability of obesity [2]. There are two main methods for discovering the genes affecting

obesity. These epidemiologic methods are hypothesis-driven (candidate gene or biologic pathway) and hypothesis-free (genome-wide linkage and genome-wide association) [21].

Candidate gene single nucleotide polymorphism (SNP) analyses are a hypothesis-driven method. For this method, the reasons behind the genetic polymorphisms in the candidate gene need to be known. With this method, genetic variants that have an impact on various diseases such as obesity can be determined [21].

Genome-Wide Association Studies (GWAS) is another method and approximately 2000000 have been identified with this genetic variant. After the first GWAS for obesity traits was published in 2007, a cluster of common variants convincingly associated with BMI [22,23] has been identified in the first intron of the FTO locus. Many GWAS subsequently followed, and to date about 60 GWAS, more than 1,100 independent loci associated with a range of obesity traits have been identified [24].

With this method, it is possible to examine the relationship between these genetic variants and phenotypes [21]. There are two different paths to follow with this method: Genome-wide association scans (GWLS) and Genome-wide association studies (GWAS). With GWLS, chromosomal regions can be determined for different types of phenotypes. However, compared to GWLS, GWAS is considered to be a more effective way. Through GWAS, polygenic variants can be identified with satisfactory results. GWAS, which identifies genetic variants, is a successful path to follow in obesity studies [24]. The first GWAS was relatively small (n = ~5,000) and identified only the FTO locus [25,26]. The BMI-increasing allele of FTO is particularly common in populations of European descent (small allele frequency (MAF) 40-45%) and has a relatively large effect on BMI (0.35 kg m-2 per allele; equivalent to 1 kg)) for a person 1.7 m tall). Ten years and numerous GWAS later, the latest GWAS for BMI included approximately 800,000 individuals with MAFs as small as 1.6% and more than 750 loci identified with parallel effects (equivalent to 120) as low as 0.04 kg m2 per allele. g) for a person 1.7 m tall [27]. Combined, these genome-wide significant loci explained 6% of the variation in BMI45. It has established large-scale international collaborations such as the Genetic Research for Anthropometric Traits (GIANT) consortium [27,28].

GENETİC AND ENVİRONMENT RELATİON

Several studies conducted on people in Europe argued that there is a strong relationship between genetics and physical activity. The results indicated that the heritable effects of obesity are decreased as physical activity increases [29,30]. Especially FTO gene was determined to be affected in this situation [31]. Still, despite the studies, this significant link between genetics and physical activity seems to be valid mostly for the population of Chinese [32,33].

According to the data collected from studies, heritable effects on BMI can be

reduced when a person exercises on a medium or high level for a minimum of 30 minutes for a minimum of 5 days/times a week. Statistically, the rate of genetics' effect on BMI was %19 higher in people who are not physically active. Another result indicated that the effect of physical activity on the heritability of obesity was lower in women [34].

The twin study on the Chinese National Twin Registry (CNTR) in the years 2011 and 2013 was conducted. For this study, only twins of the same gender were considered and the number of subjects was 19,038. This research, it was aimed to determine the aspects affecting BMI and understand how physical activity changes the body mass index [34].

The results matched the known data. The twin study showed that genetic variants influencing obesity are in association with physical activity. The population of Vietnam-era twins that are male was examined and the results indicated BMI is more affected by genetic variants when an individual avoids physical activity [35]. A different study including the population of Denmark indicated that waist circumference and BMI are associated with physical activity through genetics [36].

1. *Upcoming Studies on Obesity Genetics*

GWAS (Genome-wide association studies) is commonly considered a successful and efficient method. However, no more than %2 of variations in BMI among individuals are explained, not even with the known loci. Even less data, not more than %1, is known with a variation of WHR among different people. It is a common idea as a result of many studies that genetics influence BMI at rates ranging from %40 to 70 [37]. Similarly, WHR is also affected by genetic components at a rate ranging from %30 to 60 [2]. Therefore, only a small proportion is explained and it is clear that the relationship between heritability and obesity offers more to discover. The impact of mutations, common alleles, and gene copy number variation is yet to be analyzed especially in terms of their relevance to epigenetics and the environment [38].

DISCUSSION

Several studies have been done on the attendance of twins, sisters, brothers, and nuclear families. These studies indicate that, when a person has a family member that is obese, he/she is at a greater risk of being obese. According to the information collected from the 1958 British Birth Cohort, an obese child whose mother and/or father are obese, he/she is tended to be obese as an adult [39].

Twin studies on monozygotic and dizygotic twins indicated a link between genetic relation level and tendency to obesity. While this rate is 0.68 in identical twins, it is 0.28 in dizygotic twins [30]. Another study shows us that adopted children have BMI similar to biological parents rather than adopting families and it is possible to state that rather than lifestyle, genetic weight is dominant over physical conditions [2,38].

Another study, the Ten-State Nutrition Study, also analyzed the relationship between relativeness and obesity in children and their parents. The results showed that the most

overweight child in the study is the one whose parents are both obese. Similarly, the thinnest child in the research was the one who had thin parents. Children with thin and obese parents showed an average degree of fatness [4].

Bouchard and fellows' research on twin pairs who are fed with extreme nutrition and low nutrition. It was seen that the relation between weight and nutrition intake varies due to genetics. The study argued that the genetic factors affecting weight gain are not simple and obesity may not be linked to one gene only [40].

Recent studies showed a possible connection between the body mass index (BMI) and genetic components. It is suggested that variations in the melanocortin 4 receptor (MC4R), neuropeptide Y receptor Y2 (Npy2R), fat mass and obesity-associated (FTO), and neuropeptide FF receptor 2 (NPFFR2) for adults [41] and the leptin receptor (LEPR) and protein kinase C (PRKCH) for children, may affect BMI [42].18 loci that were unknown before were found to be linked to BMI [43] and 14 loci were approved in another study which was done with 250.000 people and 2.8 million polymorphisms [44].

Common Type 2 obesity's genetic origin may be lying under the genes influencing insulin resistance through the dysfunction of 'normal' beta cells. However, GWAS (Genome-Wide Association Studies) indicate this situation may not be true. According to GWAS, an individual is likely to have Type 2 obesity with the heritable effects under the influence of pancreatic beta-cell functions [2].

Basal metabolism is a potential aspect that is affected by genetic variants. Yet, considering the studies conducted in the previous 15 years, the effect of pancreatic beta-cell dysfunction on the occurrence of Type 2 obesity is non-negligible [38].

CONCLUSION

While obesity increases the risk of many diseases, it also reduces the life quality of individuals. Although genetic susceptibility plays a major role in the development of obesity, the current obesity epidemic does not have a completely genetic basis. Over the past century, changes in living conditions with dietary and lifestyle basis have created a period where genetic factors might come to light. The war against obesity has been continued with the focus of many disciplines on this health issue and with the determination of strong relationships between genetic variants and obesity, the science of genetics has become a candidate to be one of the leading branches of science in solving this problem.

We think that to solve the direct and indirect damages of obesity to individuals and the world economy, genetic assistance should be obtained and preventive measures should be arranged accordingly. However, although the Genome-Wide Association has been successful in identifying obesity locusts, it only explains certain parts of variation between individuals. Therefore, it is critical that studies continue to identify additional genetic factors and that current studies become encouraging in this regard in the following periods. We also

believe that the department of Genetics will play a significant role in the future the struggle against obesity and consequently, when more molecular and physiological characterization of genes are formed, it will provide useful therapeutic responses for obesity interventions.

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Corresponding author: **Onur Oral,** E-mail: onur.oral@ege.edu.tr