J Turgut Ozal Med Cent
DOI: 10.5455/jtomc.2017.03.032 2017; 24(4):531-4

Review Article

Is obesity genetic disease?

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Abstract

Obesity is a complex disease that has unfavorable impacts for all ethnic populations in worldwide. Genetics, environment and lifestyle are among aetiological factors of this disease. Genetic contribution associated with this disease is generally classified into 2 types: monogenic syndromes that display severe obesity, and the polygenic model of common obesity. Single-gene mutations can cause severe obesity resulting from alteration in central and peripheral appetite control mechanisms. Candidate gene and genome-wide association studies have led to the identification of nine loci associated with Mendelian forms of obesity and 58 loci contributing to polygenic obesity. These loci explain a small fraction of the heritability for obesity and many genes remain to be identified. The interaction of several polymorphisms and epigenetic modifications open a new research field for common obesity. As a result, still remains to be a mystery.

Keywords: Genetic; Obesity; Body Mass Index; Gene.

Obesity became pandemic all over the world in the 21st century. In the short period from 1980 to 2013, the count of obesity increased by 2.1 billion from 857 million While the rate of increase has decreased recently, the upward trend continues (1). These growth rates have begun to create significant economic burdens due to reduced productivity in the western countries and increased medical costs (2). Because of the chronic clinical consequences of obesity (for example diabetes metillus, cardiovascular disorders), obesity is now considered to be a chronic disease and considered to be one of the major causes of mortality (3). An epidemiological study conducted between 2011 and 2012 found that 60% of adults and 30% of young people were obese (4). Over the past 40 years, obesity rates have risen all over the world, and the rate of increase in America has tripled. Obesity was found in 17% of pre-school children (5).

Syndromic and nonsyndromic obesity

Obesity is mainly divided into two categories as syndromic Obesity is mainly divided into two categories as syndromic and nonsyndromic obesity in medical genetics. Syndromic obesity is defined as an inherited group of obesity, usually accompanied by dysmorphic features and congenital anomalies. These include classical examples such as Prader-Willi syndrome and Bardet-Biedl syndrome. Many family studies conducted through linkage analysis on the common forms of obesity in childhood have identified a number of loci that may be associated with the disease. This approach has been particularly helpful in elucidating the genetic background of syndromes such as Prader-Willi, Alstrom and Bardet-Biedl leading to obesity (6). Nonsyndromic obesity is a polygenic and monogenic background in the etiology and often includes the group in which the only determinant phenotype is obesity (7).

As a result of twin and family studies, it has been shown that 40-80% genetic factors contribute to BMI (Body Mass Index) differences among individuals (8). This is defined as the 'Common Disease Common Variation (CD-CV)' of the disease. According to this hypothesis, multiple common variants (some of which vary in minor allele frequency from 5% to 50%) together contribute to the development of obesity risk (9).

Meta-analysis and GWAS studies related to obesity

Meta-analysis and GWAS studies on obesity in animal models have provided important data related to the genetic causes of obesity. In these studies, some genes, especially leptin and its receptor genes, have appeared on the foreground (10). These results are predominantly related to the hormonal and neural mechanisms involved in appetite control and modulation of adipocytes, and their associated genes, in connection with the hypothalamus. Leptin and leptin receptor genes (LEP and LEPR) involved in the hypothalamic leptin-melanocortin pathway (POMC-ADCY3, PCSK1, MC4R, BDNF) have been identified in the literature as obese-related candidate genes in the later

Received: 23.03.2017 **Accepted:** 23.08.2017
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period (11). In children with severe obesity, the NTRK2B and SIM1 genes and loci associated with these genes have been reported (12). It was also found that mutations in these genes lead to autosomal dominant obesity. However, the first gene identified after Genome-wide association studies (GWAS) was the MC4R gene (13).

Over the past 9 years, studies on GWAS have identified about 100 loci associated with obesity. The INSIG2 gene locus was the first locus to be detected in this direction (14). Although this locus has been shown to be associated with obesity in European and African races, this association has not been identified in other people (15). Similar studies have reported the locus of the FTO (fat mass- and obesity-associated gene) gene (16). This locus is supported by subsequent reports, which are strongly associated with obesity, especially in children (17).

Through meta-analysis, efforts have been made to identify loci related to obesity. Here, 32 loci were reported by the GIANT (Genetic Investigation of Anthropometric Traits) consortium as a result of the meta-analysis involving a large number of patients associated with obesity (18). Among these, BDNF, FTO, GNPDA2, MC4R, NRXN3, QPCTL, SEC16B, TMEM18 and TNNI3K are the most common (19). As a result of these studies, it was observed that four of them were coherent with obesity. Studies on adults have shown that some loci are similar to loci determined in children. However, this only accounts for 1-2% of the loci determined in children (20).

Recently, four new loci have been identified in GWAS studies on obese children, including LEPR, PRKCH, PACS1 and RMST genes (1500 children and 5400 controls) (21). These results are more diverse than the mild forms of obesity and carry important data that can be used to create obesity subgroups in the future.

In addition, data supporting the monogenic forms of obesity as well as the polyphenic form of obesity have been obtained in GWAS studies. For example, it has been determined that SNPs and deletions in SH2B1 gene may be associated with the Mendelian form of obesity (22). In mouse studies with SH2B1 genetic silencing, hyperphagia, leptin resistance and obesity were observed (23). However, recently it has been reported that eight genes in the paraventricular nucleus and leptin-melanocortin pathway may cause monogenic obesity with hyperphagia (24).

Relationship of eating habits with genetics

Three polymorphisms associated with polygenic obesity due to food intake and eating behavior have been reported several times in the literature. These are SNPs such as rs17782313 located near the MC4R gene and rs1421085 and rs9939609 in the FTO gene (25). It has also been found that FTO variants that cause obesity tendency are also associated with excessive eating in adults and children (26).

SNPs close to the MC4R gene were found to affect appetite and satiety (27). In a recent GWAS study, Bauer et al. (28) reported new genes (KCTD15, MTCH2, NEGR1) associated with dietary intake and the preference for abundant energy foods.

Increasing evidence suggests that interactions between eating habits and genetic material also determine the susceptibility to obesity. In one study have shown that over-fat food habits increase the effect of the FTO gene on obesity (29). The association between apolipoprotein A-II (APOA2) – 265 T> C substitution and high-fat meals has been reported in independent studies on five different populations (30).

Mendelian randomization approach and obesity

The concept of genetic epidemiology is used today to elucidate genetic factors underlying common diseases and complex features. This epidemiological approach is also called Mendelian randomization (31). This approach has been successfully applied to obesity after identification of FTO variants associated with polygenic obesity (32). Frayling and colleagues conducted a successful Mendelian randomization study based on BMI based on the association between obesity and type II diabetes. When a similar approach was performed on 12 previously identified variants associated with obesity, genetic variants predisposing to obesity were also found to increase the risk of developing type II diabetes (32, 33).

Obesity and epigenetics

Epigenetic-wide association studies (EWAS) have helped to reveal obesity-related epigraphic loci through obesity epigenetic maps (34). With analyses involving 45 thousand CpG regions and subsequent cohort studies, Dick et al. (35) showed that increases in methylation of HIF3A (hypoxia inducible factor 3, alpha subunit) were associated with obesity. In another study, Feinberg and colleagues (36) analyzed 4 million CpG regions in 74 individuals and eventually identified 4 loci with variable methylation near genes, known to play a role in the regulation of diabetes and weight gain.

In contrast, a study involving 353 CpG regions found that obesity accelerated hepatic epigenetic senescence (known as DNA age) (19, 37). This reveals the role of obesity in liver fatigue and its associated comorbidity. Studies aiming to determine the epigenetic markers associated with obesity continue at an accelerated pace (37).

Gender differences and obesity

Men and women show significant differences in terms of obesity. For better diagnosis and treatment approaches in both sexes, it is important to identify the factors underlying observed gender differences. Traditionally, these gender differences have been significantly associated with differences in male and female gonadal secretions affecting many aspects of metabolism and similar diseases. In a study by Link and colleagues, the effects of gonadal hormones and sex chromosomes on lipid metabolism were examined and found to be related to obesity (38).

CONCLUSION

TThe heritability of obesity is reported to be 40-80%. Rare but serious syndromic obesity can now be identified early in life. Possible targets for obesity-related drug therapy are being investigated and tested at the moment and offer promise for the future. The most common GWAS links to obesity were detected in the FTO gene (on 16p11.2). The effect of FTO gene mutations on obesity can be reduced by person-specific physical exercises and diet. In addition, two gene polymorphisms downstream of MC4R (BDNF1 and SIM1) were found to be associated with obesity (39). In conclusion, obesity is a multifactorial disease that involves genetics. As with this article, many experimental and clinical studies support this view. Genetic studies on obesity have begun to give hope to the person-specific diagnosis and treatment of obesity

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