Review Article

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The current review of adolescent obesity: the role of genetic factors

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Abstract: Obesity, a complex, multi-factor and heterogeneous condition, is thought to result from the interaction of environmental and genetic factors. Considering the result of adolescence obesity in adulthood, the role of genetic factors comes to the fore. Recently, many genome-wide association studies (GWAS) have been conducted and many *loci* associated with adiposity have been identified. In adolescents, the strongest association with obesity has been found in single nucleotide polymorphisms (SNP) in the *FTO* gene. Besides *FTO*, GWAS showed consistent effects between variants in *MC4R, TMEM18, TNNI3K, SEC16B, GNPDA2*, *POMC* and obesity. However, these variants may not have similar effects for all ethnic groups. Although recently genetic factors are considered to contribute to obesity, relatively little is known about the specific *loci* related to obesity and the mechanisms by which they cause obesity.

Keywords: adiposity; adolescent; *FTO*; genetic; obesity; polymorphism.

Introduction

There is no currently internationally accepted definition of childhood and adolescent obesity [1]. However, the World Health Organization (WHO) defines overweight and obesity as "*abnormal or excessive fat accumulation that presents a risk to health*" [2, 3]. In the literature, "childhood obesity" can be used instead of both childhood and adolescent obesity [3].

The direct measurement methods are expensive and not accessible, so in the evaluation of the body fat amount, the body mass index (BMI, kg/m^2) calculation is generally used in the clinic. BMI is accepted as a standard measurement method for two-year-olds and older. Thanks to the BMI, body fat amount and adiposity are estimated in a healthy adolescent population. However, BMI value may cause false predictions in short adolescents with high muscle mass [4, 5]. In addition to BMI, waist circumference and waist-hip ratio are used to evaluate abdominal obesity, and skinfold thickness is used as an indicator of adiposity [6–8].

There is a common formulation of BMI for the classification of obesity in adults. However, it is hard to develop a common index in children and adolescents due to physiological changes occurring with growth and development [9]. For this reason, the World Health Organization has developed some methods depending on age. WHO issued "Standard Growth Curves" for ages 0–5 in 2006 and "Growth Reference Values" for children and adolescents aged between 5 and 19 in 2007 [10]. Although these standards are employed worldwide, it is emphasized that countries should work on their standards due to the significant differences in late childhood [11].

The Centers for Disease Control and Prevention (CDC) defines slightly overweight and obese according to the percentiles determined for age and gender by WHO. Overweight is defined as BMI ≥85 percentile and <95 percentile while obesity is defined as BMI 95 percentile and above [12]. The classification made by the CDC expert committee for adolescents and children is given in Table 1 [13]. The Disease Control and Prevention Center recommends WHO's standard growth curves for infants and young children under two years, and the CDC/National Health Statistics Center growth references for children 2 years and older [13].

In recent years, the prevalence of obesity in children and adolescents has increased significantly in developed and developing countries and has become a global public health issue. According to the current data of the CDC, the obesity rate in children and adolescents aged 2–19 has

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Table 1: Body weight classification in adolescents.

Body weight category	Percentile range
Underweight	<5 percentile
Normal or healthy weight	≥5 percentile and <85 percentile
Overweight	≥85 percentile and <95 percentile
Obese	≥95 percentile

reached 18.5%, affecting a total of 13.7 million children and adolescents [14].

According to the nutrition research conducted with 43 million children living in 144 different countries by the WHO, the rate of slightly overweight and obese in preschool children increased from 4.2% in 1990 to 6.7% in 2010 [15]. Considering the prevalence of obesity in adolescents, it increased from 10.6% in 1988–1994 to 20.6% in 2013–2014 [16]. About 5.9% of children and adolescents aged 2–19 have been reported to be seriously obese (BMI 95 percentile 120% or BMI ≥35 kg/m^2) [17].

To evaluate the BMI changes over the years and the BMI trends in the coming years, 19.2 million people from 200 different countries were investigated. The study covering the years 1975–2014 revealed that the probability of achieving the global obesity target would be almost zero if trends continue after 2000. In 2025, the global prevalence of obesity is expected to reach 18% in men and exceed 21% in women, and the serious obesity rate is expected to exceed 6% in men and 9% in women. However, it is anticipated that the prevalence of low-weight individuals will continue in poor regions of the world, especially in South Asia [18]. The prevalence of obesity in adolescents in Turkey is reported to be 2–15% [19]. According to the Turkey Nutrition and Health Survey, the obesity prevalence age of 6–18 has been reported to be 8.2% (9.1% male, female 7.3%) [20]. Alper et al. [21] investigated the obesity prevalence trends in children and adolescents in Turkey and reported that it increased 11.6 times between 2011–2015 and 1990–1995 and rose from 0.6 to 7.3%.

Three types of obesity can be considered based upon genetic and phenotypic traits: monogenic syndromic obesity, monogenic nonsyndromic obesity and polygenic/common obesity. The activity of a single gene (Mendelian/monogenic) or more than one gene (polygenic/common) may be reflected in a trait [22]. Nonsyndromic early-onset severe obesity is generally monogenic, while other forms of obesity are polygenic and take place because of the cumulative action of multiple susceptibility genes [23].

Since obesity and obesity-related noncommunicable diseases decrease the quality of life of adolescents, the increase in adolescent obesity rates should be seriously taken into account [24]. Therefore, it is important to understand the etiology of obesity, which is becoming a major public health problem day by day. Considering the limited genetic data on obesity during adolescence, this review attempts to explain the role and mechanisms of underlying genetic factors in adolescent obesity.

Adolescent obesity and genetic factors

The prevalence of obesity and obesity-related disease has risen rapidly in recent years and has become a major public health problem in many populations [25]. Although adolescent obesity is explained as an energy balance disruption caused by increased energy intake and/or decreased energy expenditure, childhood obesity has an exceedingly complex etiology. It is a pathological condition resulting from the interaction of many factors. These factors are mainly environmental, genetic, behavioral and ecological (family, school, etc.) [18].

The changes in the lifestyle of individuals in recent years have also seriously affected the epidemic of obesity. Some researchers note that lifestyle changes are the result of a change called “social globalization”. With this change, individuals’ access to foods with high energy content has become easier, and a sedentary lifestyle has started to become widespread [26]. However, populations sharing the same obesogenic environment have both obese and normal-weight individuals with different rates of obesity. This can be explained by the fact that some individuals are more sensitive to gaining weight than others when exposed to the same obesogenic environment. This difference is considered due to the individual genetic profile [22].

The polygenic/common obesity seen in many cases arises from the combination of environmental factors with many gene variants of minor effect, while genes have a major effect in monogenic obesity [27, 28]. It is reported that at least 5–7% of nonsyndromic early-onset obesity is monogenic. Monogenic obesity is explained by before age 5 years and the BMI is over three standard deviations above normal [27]. The leptin–melanocortin system, located in the hypothalamus, is one of the most significant pathways responsible for controlling body weight and food intake. Most nonsyndromic forms of obesity result from mutations in the genes which affect the leptin–melanocortin pathway [27, 29]. While the mutations in *LEP*, *LEPR*, *POMC*, *PCSK1* and *TUB* genes are autosomal

recessive, autosomal dominant mutations have been identified in *BDNF, NTRK2, SIM1, MC4R, SH2B1, MRAP2* and *LRP2* genes [27]. These mutations are caused by defects in proteins that act in the hypothalamus to control food intake and energy expenditure. Children with these types of defects can develop severe hyperphagia, which leads to rapid body weight gain in the first year of life. It is to be acknowledged that the most common monogenic form of obesity is because of the mutations in *MC4R* gene in humans. [30].

There are some suggestions in the literature that early body weight-related problems may continue in adulthood [31]. Childhood obesity importantly increases the prevalence of adult obesity and is related to a lot of comorbidities [32]. In an American cohort study conducted to determine the effects of adolescent obesity, adolescents were followed periodically in four waves at certain intervals (first Wave: 1994–1995, 20,745 individuals aged 11–20 years, average age 15.9 years; second Wave, 1996, 14,738 individuals aged 12–21, average age 16.5 years; third Wave, 2001–2002, 15,197 individuals aged 18–27, average age 22.3 years; and fourth Wave, 2007–2009, 15,701 individuals aged 23–32, average age is 28.9 years. At the last stage, the study was completed with 8,834 individuals). Obese adolescents have a higher tendency to become seriously obese in adulthood compared to normal body weight/slightly overweight adolescents. Therefore, obesity in the adolescent period is significantly associated with severe obesity in adulthood [31]. According to the predictions made in a systematic review and meta-analysis study based on BMI, it was stated that approximately 55% of obese children would continue to be obese in the adolescent period and approximately 80% of obese adolescents would still be obese during adulthood. It was also highlighted that obese children and adolescents were five times more likely to become obese in adulthood than nonobese children [33].

In a study on the role of genetic factors in obesity etiology, it was concluded that in twins who were raised together or separately, genetic factors constitute 30–70% of the change in BMI among individuals [34]. The compliance rates between monozygotic twins for fat mass are reported as ~80 and ~40% for dizygotic twins [34]. Pigeyre et al. (2016) indicated the heritability degree of BMI (interindividual variation rate that can be attributed to genetic factors) as 40–70%, while in a study conducted in 1997, the variation rate inherited factors responsible for adiposity was reported to be 30–50% [35, 36]. In a study with monozygotic and dizygotic twins in China, genetics has been shown to play an increasingly important role in explaining body weight, height and BMI variation, especially in boys, from early childhood to late adolescence [37]. In a systematic review that examined the effects of genetics and the environment in twins and adopted children, it was indicated that genetic factors may have a much stronger effect on BMI trends than environmental factors up to the age of 18 [38].

Thrifty genotype hypothesis

The Thrifty Genotype Hypothesis was first developed by the American geneticist James V. Neel, and it was revised later. This hypothesis, which emerged concerning gene-environment interactions, includes the concept of "thrifty genes". Although Neel reported that these genes increase susceptibility to type 2 diabetes in certain groups of people, this hypothesis often sheds light on studies related to obesity [39, 40]. According to this hypothesis, indigenous people with a hunter-gatherer lifestyle did not always achieve sufficient food, and they had famine periods from time to time. As a result of repeated recurrence of feeding and fasting periods, adaptation occurred in these individuals and resulted in the natural selection of thrifty genes. Thus, by storing excess energy in the form of fat when they reached the food, they continued to survive by using this stored fat during famine periods. Therefore, individuals having thrifty genes will more likely to survive times of food shortage than the others. However, the fact that individuals have these thrifty genes that seem to be advantageous can turn into a disadvantage when they are chronically exposed to the "obesogenic environment" characterized by a high-fat diet and a sedentary lifestyle. This may lead to increased susceptibility especially to obesity and diabetes in individuals [39–41].

The most researched and documented population of thrifty genes is Arizona Pima Indians. While the life and nutrition style of this population consisted of only enough food for themselves, an increase in body weight and diabetes rates are observed as a result of a modern obesogenic lifestyle they have today [42, 43]. Type 2 diabetes mellitus is a common disease among Pima Indians and is strongly associated with obesity. Continuous supply of food to individuals who develop thrifty genes can lead to obesity, insulin resistance and diabetes in these individuals [42].

There is no shared agreement in the scientific literature about the thrifty genotype hypothesis. However, regardless of its evolutionary mechanism, it is accepted by many researchers that genes that increase susceptibility to obesity are associated with positive energy balance, which leads to an increase in body weight by interacting with known and unknown environmental factors [41]. Since the human population is genetically diverse and heterogeneous with

more than 7.7 million single-nucleotide polymorphisms (SNP), identifying potential gene–diet interactions related to various diseases in humans, including obesity, is further complicated by gene–gene interactions [3]. Gene–diet interactions need to be well understood to develop personalized dietary recommendations. In a systematic review examining diet and SNPs interactions, it has been reported that there is no consistent evidence for total energy, carbohydrate, and fat intake with SNPs [44]. Further clinical studies are needed to understand the mechanisms underlying genetic variables and how they can interact with lifestyle and the environment.

Genome-wide association studies (GWAS)

The main purpose of human genetics is to identify genetic risk factors for rare Mendelian diseases such as cystic fibrosis as well as common diseases such as type 2 diabetes. Many different technologies, study designs and analytical tools are available to identify genetic risk factors [45]. It has long been known that the risk of complex disorders such as cardiovascular diseases, type 2 diabetes or cancer is greatly influenced by the individual's genetic history, but risk-bearing genetic structures are not exactly known [46].

With recently conducted genome-wide association studies (GWAS), it is aimed to determine the genetic risk factors for diseases common in populations, to measure and analyze DNA sequence changes in the human genome [47]. Before the commencement of the GWAS, reference genome sequences were obtained through the Human Genome Project (1990–2003), one of the two major projects. Although it was assumed that genetic information related to diseases could be obtained easily in the first years of this project, GWAS studies conducted in recent years have offered a different perspective [48].

The primary purpose of GWAS is to use genetic risk factors to make predictions about who is at risk, to develop new prevention and treatment strategies, and to define the biological basis of disease susceptibility [49]. Advocates of GWAS studies argue that such studies will identify many variants that contribute to common diseases, but the size of the data sets obtained will present significant analysis and interpretation problems. Other researchers continue to question the necessity and usefulness of this still expensive approach [50].

The first GWA was conducted on age-related macular degeneration, and the *Complement Factor H* gene was identified as the major risk factor. This study played an important role in understanding the biological basis of genetic effects and developing new pharmacological treatments [51]. Genome-wide association studies in the literature are regularly followed, updated and published. According to the most recent publication, as of September 2018, this database contains 5,687 GWAS, which includes 71,673 variant-trait relationships from 3,567 publications [52]. While these GWAS shed light on understanding disease susceptibility (through the identification of disease-causing genes and mechanisms), they have also led to new developments in clinical care developments (e.g. setting new drug targets and disease markers) and in personalized medicine (e.g. optimization of the sample, risk prediction and genotype-based treatments) [53].

Recently, GWAS have identified a large number of (more than 700) *loci* associated with adiposity [54]. The vast majority of these *loci* are defined for BMI (92% of *loci*) and waist/hip ratio, which is adiposity-related markers [55]. Yengo et al. (2018) determined 941 near-independent genome-wide significant SNPs at 536 polygenic *loci* for BMI [56]. On the other hand, a more recent GWAS on 362,499 individuals from UK Biobank identified 98 independent *loci*, 29 of which have not previously been associated with anthropometric traits [57]. These *loci* have been guiding in defining the role of genetic factors in the pathophysiology of human obesity [55]. Hundreds of genes were examined in studies on candidate gene approaches before 2007, but few of these genes were confirmed as genetic risk factors for obesity. Four reports in 2007 (1-GWAS for anthropometric features, 2-GWAS for early-onset severe obesity, 3-GWAS for type 2 diabetes, 4-fat mass and obesity-related gene-fat mass and obesity-associated gene study) explained that SNPs in the first intron of the fat mass and obesity-related gene *FTO* were associated with obesity-related parameters [58–61].

Genome-wide association studies in adolescent obesity

There are some studies examining birth weight, BMI, widespread obesity and severe early obesity in children, although most GWAS are performed in adults. In GWAS, in which BMI and widespread obesity are examined in children, many identical *loci* have been identified with GWAS in adults. Although it has some genetic similarities with early-onset severe obesity and birth weight BMI and widespread obesity, it is largely guided by its unique *loci* [62]. In children and adolescents, consistent effects have been demonstrated for variants in *MC4R* as well as *FTO*. In a study in which GWAS in children were analyzed, whether 25 SNPs are associated with pediatric BMI in European-Americans in 13 previously reported BMI locations (*NEGR1, SEC16B, TMEM18, INSIG2, SFRS10/ETV5/DGKG, GNPDA2,*

Table 2: Single-nucleotide polymorphisms associated with obesity in adolescents.

Sample characteristics	Major variables studied	BMI, kg/m^2	Main findings	Author/ year
1,423 overweight/obese, 607 with normal body weight Chinese individuals, between 11 and 14 years old	*PP13439-TMEM212* (rs6794092), *ROPN1L* (rs2967951), *CDH12 (*rs268972), *MFAP3-GALNT10* (rs2033195), *MFAP3-GALNT10* (rs815611), *FTO* (rs62048402 and rs9939609), *FER1L4* (rs6088887)	Individuals with normal body weight: 18.2–20.4 Individuals overweight/obese: 24.1–27.5	*Polymorphisms in the *FTO* (rs62048402 and rs9939609) have a nominal effect on BMI/obesity. *rs268972, rs2033195, rs9939609 and rs6088887 have cumulative effects on the risk of obesity/overweight	Meng et al., 2014
European-American adolescent cohort, In the European study; 2,404 boys (mean age 16.2 years), 2,671 girls (mean age 16.4 years), In the American study; 1,803 boys (mean age 14.6 years), 2,011 girls (mean age 14.8 years)	34 SNPs related to BMI and the relationship of these SNPs with each other were examined; *ADCY9* (rs2444217), *BDNF* (rs10767664), *CADM2 (*rs13078807), *ETV5* (rs7647305), *FAIM2 (*rs7138803), *FANCL* (rs887912), *FLJ3577* (rs2112347), *FTO* (rs9939609), *GNPDA2* (rs10938397), *GPRC5B* (rs12444979), *KCTD15* (rs29941), *LMX1B* (rs867559), *LRP1B* (rs2890652), *LRRN6C* (rs10968576), *LZTR2* (rs543874), *MAP2K5* (rs2241423), *MC4R* (rs571312), *MTCH2* (rs3817334), *MTIF3* (rs4771122), *NCR3_BAT2* (rs1077393), *NEGR1* (rs2568958), *NRXN3* (rs10146997), *NUDT3* (rs206936), *POMC* (rs713586), *PRKD1* (rs11847697), *PTBP2* (rs1555543), *QPCTL* (rs2287019), *RPL27A* (rs4929949), *SH2B1* (rs4788102), *SLC39A8* (rs13107325), *TFAP2B* (rs987237), *TMEM18* (rs6548238), *TNNI3K* (rs1514175), *ZC3H4* (rs3810291)	In the European study; Boys: 23.26 Girls: 22.84 In the American study; Boys: 21.68 Girls: 22.02	*The interaction between *PRKD1-FTO* genes was found significant. *This study suggests possible epistatic effects on BMI in the adolescent period. This suggests potential interactions between genes in biological pathways that are important in obesity.	Young et al., 2016
The study group included 487 obese children and adolescents (mean age 14.38 years); the control group included 442 healthy individuals in (mean age 26.07 years)	15 SNPs associated with obesity at early age; *FTO* (rs1121980), *FTO* (rs9939973), *FTO* (rs7193144), *FTO* (rs9940128), *C20orf75* (rs6076920), *SNP_A19679675* (rs41492957), *FTO* (rs8050136), *TSHR* (rs3783950), *BC041448* (rs2969001), *FTO* (rs9939609), rs619819, rs2172478, *PCSK2* (rs16998603), *HLA-DQA2* (rs9276431), *none* (rs10008032)	The study group: 33.4 The control group: 18.3	Variants in the *FTO* gene have been reported to contribute strongly to early-onset obesity. Among the 15 SNPs studied, the positive findings of *FTO* SNPs represent.	Frayling et al., 2007
1,252 children (mean age 9.7 years) and 790 adolescents (mean age 15.5 years) Individuals were randomly selected from two different countries (Denmark and Estonia).	17 SNPs, which are thought to increase susceptibility to obesity, were studied. rs2815752, rs10913469, rs2605100, rs6548238, rs7647305, rs10938397, rs987237, rs545854, rs1488830, rs925946, rs10838738, rs7138803, rs10146997, rs8055138, rs1121980, rs17782313 and rs11084753 (*NEGR*, *SEC16B*, *LYPLAL1*, *TMEM18*, *ETV5*, *GNPDA2*, *TFAP2B*, *MSRA*, *BDNF*, *MTCH2*, *BCDIN3D*, *NRXN3*, *SH2B1*, *FTO*, *MC4R*, and *KCTD15 loci*, respectively)	Children; Boys: 17.1±2.2 Girls: 17.1±2.6 Adolescents; Boys: 20.5±2.5 Girls: 20.5±2.7	Nine of the variants studied were associated with BMI ($p<0.05$), while the strongest relationship was found between the variant close to the *TMEM18* gene and BMI ($p=8.5 \times 10^{-11}$).	den Hoed et al., 2010

Table 2: (continued)

Sample characteristics	Major variables studied	BMI, kg/m^2	Main findings	Author/ year
598 Caucasian adolescents aged between 12 and 18 years	*PAX5* (rs16933812), *MRPS22* (rs7638110), *MC4R* (rs17773430), *MTCH2* (rs7120548), *FTO* (rs9930333), *GPRC5B* (rs4780831), *MTIF3* (rs1885989), *NRXN3* (rs10483942), *LRP1B* (rs1476250), *SEC16B* (rs10159282), *SLC39A8* (rs2165265), *ZNF608* (rs4421098), *NEGR1* (rs2630397), *RPL27A* (rs7925000), *CADM2* (rs17292179), *ETV5/DGKG* (rs17295554)	ND	**PAX5* ($p=9.3 \times 10^{-9}$) was associated with total body fat, while *MRPS22* ($p=4.6 \times 10^{-8}$), *MC4R* ($p=5.8 \times 10^{-6}$), *FTO* (1.9×10^{-4}) and *MTCH2* (1.9×10^{-4}) were found to be related to BMI. **PAX5, MRPS22* and *FTO* were also associated with higher blood pressure.	Melka et al., 2012
773 (395 boys, 378 girls) mexican children and adolescent individuals aged 5–15 years	*NEGR1* (rs34305371), *SEC16B-RASAL2* (rs10913469), *TMEM18* (rs65482389), *TMEM18* (rs7561317), *IL-1beta* (rs1143643), *ADIPOQ* (rs6444174), *GNPDA2* (rs16857402), *TNF-α* (rs1800750), *IL-6* (rs1524107), *IL-6* (rs2069845), *LEP* (rs2167270), *MTCH2* (rs10838738), *LGR4-LIN7C-BDNF* (rs925946), *BCDIN3D-FAIM2* (rs7138803), *FTO* (rs62033400), *MC4R* (rs11872992), *MC4R* (rs17782313), *KCTD15* (rs29942)	Obese individuals: 24.98 (22.5–21.6) Nonobese individuals: 17.3 (15.7–19.7)	Polymorphisms in the *TMEM18* gene (rs6548238; rs7561317) were associated with obesity (p=0.008).	Jimenez-Osorio et al., 2018
29,880 European adolescence and young adults between ages 16–25 years	*FTO* (rs9940128), *TMEM18* (rs12463617), *MC4R* (rs7234864), *TNNI3K* (rs12142020), *SEC16B* (rs591120), *GNPDA2* (rs13130484), *POMC* (rs1561288), *PRKD1* (rs11847697), *CADM2* (rs13078807), *SH2B1* (rs7359397)	Individuals with extreme values for BMI are excluded.	*This study identified seven independent *loci* near *FTO, TMEM18, MC4R, TNNI3K, SEC16B, GNPDA2* and *POMC*. *Four *loci* (*near PRKD1, TNNI3K, SEC16B,* and *CADM2*) had larger effects, and one locus (near *SH2B1*) had a smaller effect on BMI during adolescence and young adulthood compared with older adults.	Graff et al., 2013

ND, no data.

MTCH2, BDNF, FAIM2, SH2B1, FTO, MC4R and *KCTD15*) were examined. The relationship between BMI and 15 different variants, with the strongest association in the *FTO* gene, has been reported [63]. In another study, the effect of GWAS *loci* of all type 2 diabetes in Chinese children on pediatric BMI was evaluated. Researchers have argued that the *HHEX-IDE* gene is associated with an increase in BMI. This gene has been emphasized since the increase in BMI in childhood affects the risk of type 2 diabetes in older ages. Besides, variants occurring in *FAIM2, NPC1, FTO, MC4R, BDNF* and *GNPDA2* genes have been reported to be associated with BMI variation in Chinese children [64]. Some SNPs, especially *FTO* (rs1558902) *MC4R* (rs571312), *TMEM18* (rs2867125), *GNPDA2* (rs10938397), *BDNF* (rs10767664) and *FAIM2* (rs7138803), are associated with BMI, obesity and body weight for both adults and children. On the other hand, different variants of the same genes (*FTO*, *MC4R* and *BNDF*) have been reported in both widespread obesity and nonsyndromic obesity in children [41].

Obesity risk allele carriers are thought to have a greater rate of change in BMI increase during adolescence and early adulthood, and as the age increases some variables may

Table 3: Potential candidate genes and variants related to obesity in both adolescents and adults.

Variants' names	Potential candidate genes (BMI-associated loci)	Risk alleles	Effect estimates		p-Values		Author
Children and adults			**Per allele change in BMI β (s.e.m.)**				Speliotes et al., 2010
rs1558902	*FTO*	A	0.39 (0.02)		4.8×10^{-120}		
rs2867125	*TMEM18*	C	0.31 (0.03)		2.77×10^{-49}		
rs571312	*MC4R*	A	0.23 (0.03)		6.43×10^{-42}		
rs10938397	*GNPDA2*	G	0.18 (0.02)		3.78×10^{-31}		
rs10767664	*BDNF*	A	0.19 (0.03)		4.69×10^{-26}		
rs2815752	*NEGR1*	A	0.13 (0.02)		1.61×10^{-22}		
rs7359397	*SH2B1*	T	0.15 (0.02)		1.88×10^{-20}		
rs9816226	*ETV5*	T	0.14 (0.03)		1.69×10^{-18}		
rs3817334	*MTCH2*	T	0.06 (0.02)		1.59×10^{-12}		
rs29941	*KCTD15*	G	0.06 (0.02)		3.01×10^{-9}		
rs713586	*RBJ*	C	0.14 (0.02)		6.17×10^{-22}		
rs12444979	*GPRC5B*	C	0.17 (0.03)		2.91×10^{-21}		
rs2241423	*MAP2K5*	G	0.13 (0.02)		1.19×10^{-18}		
rs2287019	*QPCTL*	C	0.15 (0.03)		1.88×10^{-16}		
rs1514175	*TNNI3K*	A	0.07 (0.02)		8.16×10^{-14}		
rs13107325	*SLC39A8*	T	0.19 (0.04)		1.50×10^{-13}		
rs2112347	*FLJ35779*	T	0.10 (0.02)		2.17×10^{-13}		
rs10968576	*LRRN6C*	G	0.11 (0.02)		2.65×10^{-13}		
rs3810291	*TMEM160*	A	0.09 (0.02)		1.64×10^{-12}		
rs887912	*FANCL*	T	0.10 (0.02)		1.79×10^{-12}		
rs13078807	*CADM2*	G	0.10 (0.02)		3.94×10^{-11}		
rs11847697	*PRKD1*	T	0.17 (0.05)		5.76×10^{-11}		
rs2890652	*LRP1B*	C	0.09 (0.03)		1.35×10^{-10}		
rs1555543	*PTBP2*	C	0.06 (0.02)		3.68×10^{-10}		
rs4771122	*MTIF3*	G	0.09 (0.03)		9.48×10^{-10}		
rs4836133	*ZNF608*	A	0.07 (0.02)		1.97×10^{-9}		
rs4929949	*RPL27A*	C	0.06 (0.02)		2.80×10^{-9}		
rs206936	*NUDT3*	G	0.06 (0.02)		3.02×10^{-8}		
Children			**Effect allele frequency**				Graff et al., 2017
rs9939609	*FTO*	A/T	0.3952		0.0000000005377		
rs571312	*MC4R*	A/C	0.2188		0.0000425		
rs543874	*SEC16B, LZTR2*	G/A	0.2058		0.0000001724		
rs6548238	*TMEM18*	C/T	0.8429		0.000002315		
rs987237	*TFAP2B*	G/A	0.1925		0.0001747		
rs3817334	*MTCH2*	T/C	0.3795		0.0008378		
			Childhood[a]	**Adults[a]**	**Childhood**	**Adults**	Scherag et al., 2010
rs10926984	*SDCCAG8*	T	1.12 (0.94;1.33)	1.19 (1.03;1.39)	0.20	0.03	
rs12145833	*SDCCAG8*	T	1.15 (0.96;1.37)	1.18 (1.02;1.35)	0.12	0.03	
rs2783963	*SDCCAG8*	C	1.10 (0.92;1.32)	1.18 (1.01;1.35)	0.28	0.03	
rs11127485	*TMEM18*	T	1.35 (1.14;1.61)	1.45 (1.25;1.67)	5.87×10^{-4}	3.48×10^{-7}	
rs17150703	*TNKS/MSRA*	A	1.06 (0.86;1.30)	1.00 (0.85;1.18)	0.59	0.99	
rs13278851	*TNKS/MSRA*	A	1.05 (0.86;1.29)	0.98 (0.83;1.15)	0.61	0.77	
rs516175	*TNKS/MSRA*	T	1.12 (0.93;1.35)	0.97 (0.82;1.13)	0.25	0.66	
rs1558902	*FTO*	A	1.35 (1.19;1.52)	1.45 (1.31;1.60)	1.78×10^{-6}	2.12×10^{-13}	
rs9935401	*FTO*	A	1.35 (1.20;1.53)	1.35 (1.22;1.49)	1.70×10^{-6}	4.58×10^{-9}	
rs17700144	*MC4R*	A	1.44 (1.25;1.66)	1.14 (1.01;1.28)	6.85×10^{-7}	0.03	

Table 3: (continued)

Variants' names	Potential candidate genes (BMI-associated loci)	Risk alleles	Effect estimates		p-Values		Author
			Childhood[b]	Adults[b]	Childhood	Adults	Meyre
rs1421085	*FTO*	C	0.112 (0.073, 0.151)	0.080 (0.040, 0.119)	1.9×10^{-8}	7.5×10^{-5}	et al., 2009
rs17782313	*MC4R*	C	0.097 (0.047, 0.146)	0.074 (0.029, 0.119)	1.3×10^{-4}	1.3×10^{-3}	
rs1805081	*NPC1*	A	−0.087 (−0.156, −0.019)	−0.062 (−0.119, −0.005)	1.3×10^{-2}	3.4×10^{-2}	
rs1424233	*MAF*	A	0.091 (0.053, 0.13)	0.030 (−0.009, 0.069)	3.2×10^{-6}	1.3×10^{-1}	
rs10508503	*PTER*	C	0.144 (−0.15, 0.438)	0.017 (−0.048, 0.082)	3.4×10^{-1}	6.1×10^{-1}	
rs4712652	*PRL*	A	0.031 (−0.023, 0.084)	−0.078 (−0.146, −0.010)	2.6×10^{-1}	2.4×10^{-2}	
			Childhood	**Adults**	**Childhood**	**Adults**	León-Mim-
rs2241766	*ADIPOQ*	G	0.05 (0.16)	0.14 (0.18)	0.757	0.420	ila
rs1800849	*UCP3*	T	0.03 (0.061)	−0.01 (0.07)	0.597	0.855	et al., 2013
rs9939609	*FTO*	A	0.08 (0.05)	0.05 (0.06)	0.125	0.392	
rs6548238	*TMEM18*	C	0.09 (0.07)	0.25 (0.09)	0.149	0.005	
rs7566605	*INSIG2*	G	0.03 (0.05)	0.15 (0.06)	0.475	0.007	
rs7138803	*FAIM2/ BCDIN3*	A	0.33 (0.13)	0.51 (0.15)	0.008	0.001	
rs10938397	*GNPDA2*	G	0.09 (0.04)	0.08 (0.05)	0.021	0.106	
rs17782313	*MC4R*	C	20.04 (0.07)	−0.04 (0.09)	0.607	0.690	
Adolescents			ND				Zhao
rs1558902	*FTO*	A				1.42×10^{-8}	et al.,
rs571312	*MC4R*	A				0.00101	2011
rs1514175	*TNNI3K*	A				0.0105	
rs543874	*SEC16B*	G				0.00378	
rs2867125	*TMEM18*	T				2.03×10^{-4}	
rs10938397	*GNPDA2*	G				0.00970	
rs10767664	*BDNF*	T				0.0296	
rs10150332	*NRXN3*	C				$7{,}97 \times 10^{-4}$	
rs2287019	*QPCTL*	T				0.0153	

BMI, body mass index; ND, no data. [a]Odds ratio for effect allele of (95% CI). [b]Per allele change in BMI (95% CI).

have stronger predictive effects during adolescence and young adulthood due to increasing environmental effects, which may mask genetic effects. As the age and number of exposure to environmental effects will increase as you get older, studies conducted in the early stages can give clearer results [65, 66]. Additionally, it is suggested that adolescent and early adulthood is a high-risk period in terms of body weight gain [67]. In a study on this subject, a positive correlation was found between the variants in/near *FTO, MC4R, MTCH2, TFAP2B, SEC16B* and *TMEM18* and the change in BMI during adolescence and young adulthood [65]. Similarly, changes in BMI from childhood to adulthood and *FTO* and *MC4R* (two variants defining susceptibility in BMI in the early period) were investigated, and changes in BMI during adolescence and early adulthood were reported to offer stronger evidence than in late adulthood [66].

In a GWA study conducted in 2013, seven independent *loci* ($p<5.0 \times 10^{-8}$) were identified in adolescent and early adulthood individuals; *FTO* ($p=3.72 \times 10^{-23}$), *TMEM18* ($p=3.24 \times 10^{-17}$), *MC4R* ($p=4.41 \times 10^{-17}$), *TNNI3K* ($p=4.32 \times 10^{-11}$), *SEC16B* ($p=6.24 \times 10^{-9}$), *GNPDA2* ($p=1.11 \times 10^{-8}$) and *POMC* ($p=4.94 \times 10^{-8}$) [67]. Besides, the genetic effect of BMI *loci* changes in a complex way over time. Therefore, it is important to investigate *loci* that affect obesity risk throughout life [68]. Table 2 summarizes the studies on obesity and genetics in adolescents. Similar to adult studies, the strongest relationship with obesity in adolescents was found in SNPs in the *FTO* gene. The dominant SNPs may differ when ethnic groups change [60, 69–72]. Potential candidate genes and variants related to obesity in both adolescents and adults are shown in Table 3 [68, 73–77]. Even though similar genes are associated with BMI, *loci* may vary according to

ethnicity and age groups. As the genetic data expand in the literature studies, it has been shown that, in addition to basically known genes, new *loci* may also be associated with obesity. On the other hand, the majority of BMI-associated *loci* are shared between adolescents/childhood and adult cohorts, but the index SNPs may slightly vary. The overlapped obesity susceptibility *loci* show a consistent direction of effects on BMI. Given the current knowledge evidencing the involvement of BMI-related *loci* in the regulation of energy balance through the central nervous system, one may postulate that similar mechanisms may be in play in early childhood obesity. Graff et al. (2017) investigated the obesity susceptibility variants in a cohort study. They found that SNPs in/near *FTO, MC4R, MTCH2, TFAP2B*, *SEC16B* and *TMEM18* were significantly associated ($p<0.0015\approx0.05/34$) with BMI change in European Americans, while there are no significant SNPs after Bonferroni correction in African Americans and Hispanic Americans [68]. In a GWA study among European children, four new *loci* associated with severe early-onset obesity were shown (rs564343 in phosphofurin acidic cluster sorting protein 1; *PACS1*, rs11109072 in rhabdomyosarcoma 2 associated transcript; *RMST*, rs1957894 in protein kinase C eta; *PRKCH* and rs11208659 in *LEPR*). The *loci* in the *PACS1, RMST* and *PRKCH* genes were studied in Chinese children, and only the rs564343 in *PACS1* gene was found to be associated with a severe risk of obesity [78]. In a review investigating the differences in the effect and Asians, but less important among those of African descent. However, in Asian children, this relationship has been found to be either the same or stronger than European children [79].

Genome-wide association studies have made significant progress in identifying SNPs associated with BMI in children and adolescents. It was shown that BMI is highly heritable, especially in populations with higher average BMI, in countries with a higher gross domestic product, and families of lower socioeconomic status [80]. Known SNPs explain ~6% of the variance of BMI, despite >50% evidence of inheritance from twin and family studies. This phenomenon is known as "missing heritability" [56, 81]. In a study using a novel method, genome-wide complex trait analysis, it was found that this analysis explains a significant proportion of the genetic impact defined as "missing heritability" [81]. However, to better understand the effects of genetic factors in childhood obesity, there is a need for large-scale studies considering age stratification in different ethnic groups.

Conclusion

Adolescent obesity has become a major public health problem in both developed and developing countries today. Although the etiology of obesity involves many factors, the interaction of genetic factors with the environment has been one of the most striking issues recently. Comorbid diseases associated with obesity affect adolescents both physically and mentally. Therefore, studies are being conducted to attempt to develop new methods for the prevention and treatment of obesity. Although there are significant improvements regarding the factors that cause obesity, there is not yet sufficient data on the etiology, genetics and other factors influencing obesity. Genetic factors that play a role in the etiology of obesity and the interaction of these factors with biological, environmental, and ecological factors may shed light on new developments in obesity treatment. Understanding the mechanisms that explain obesity will be a significant step in the development of new therapeutic approaches. Although the *FTO* locus has been the most associated with obesity among the *loci* identified so far, this locus can explain a very small part of the interindividual variations. Therefore, to identify related *loci* in adolescent obesity, there is a need for large-scale research on a community basis, which includes different ethnic groups due to the different variants among the populations as well as the important role of age stratification in future genetic studies, like GWAS, should be considered.

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