Review Article

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A Review of Genes Associated with Obesity Susceptibility: Findings from Association Studies

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Abstract:

Obesity is described as the accumulation of excess body fat. Several health issues are caused by excess fat, including cancer, type 2 diabetes, and cardiovascular disease. Additionally, obesity rates among schoolchildren and young adults are rising globally, putting young people at risk of chronic diseases. Genetics, epigenetic modification, epigenomics, and environmental factors influence inheritance patterns significantly. This systematic study aimed to classify and investigate the polymorphisms of novel candidate obesity genes. Several genes have been suggested, includingat mass and obesity-associated gene (*FTO*), leptin gene (*LEP*), leptin receptor gene (*LEPR*), peroxisome proliferator-activated receptor gamma gene (*PPARG*), melanocortin 4 receptor (*MC4R*), insulin-induced gene 2 (*INSIG2*), proprotein convertase subtilisin/kexin type 1 (*PCSK1*), adrenoceptor beta 2 (*ADRB2*), and uncoupling protein 2 (*UCP2*). The study's literature review identified genes in scientific papers published in databases such as Web of Science, PubMed, Google Scholar, Embase, and others over the past three decades. There is evidence that genetic variations contribute to childhood obesity, adolescent obesity, and young adult obesity. Identifying functional differences and further defining the implicated molecularly and physiologically involved genes andpathways in efficient therapeutic approaches in fighting. Technological advances have recently demonstrated that genetic changes and mutations can be used as biological markers, risk indicators, and therapeutic targets.

Keywords: genetics, predictive markers, obesity, polymorphism

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Introduction

Obesity results from a chronic surplus in energy consumption compared with expenditure on energy, which causes excessive triglycerides to be stashed in adipocytes[1]. Undesired obesity metabolism can contribute to an increased threat of type 2 diabetes, multiple forms of cancer, a fatty liver, hormonal distortions, high blood pressure, cardiovascular disease (CVD), and higher mortality (Figure 1)[2]. The body mass index (BMI) is used as a primary indicator of obesity. The World Health Organization (WHO) defines an obese individual as having a BMI of 30 to 40 kg/m. Obesity has been linked to an increased

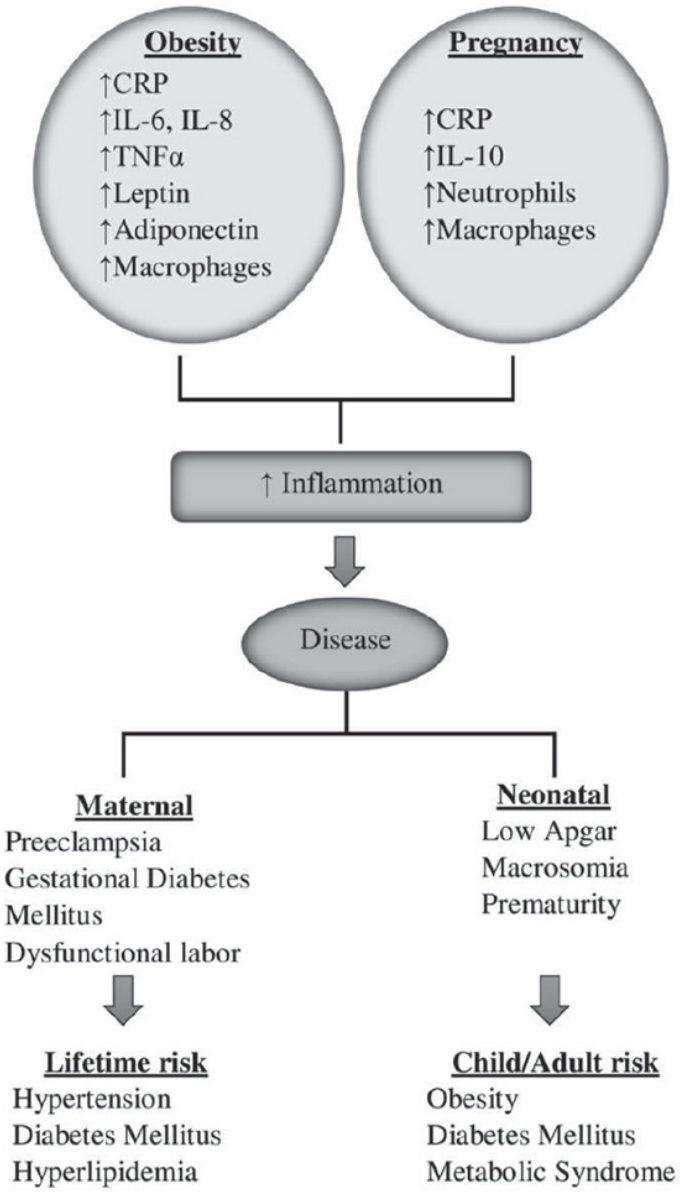

Figure 1 Significant complications of obesity

risk of polycystic ovary syndrome (PCOS), infertility, and pregnancy-related issues such as miscarriage, cesarean section, stillbirth, and birth abnormalities in children (Figure 2)[3]. It is estimated that more than seven hundred million people globally will become obese by 2015[4]. Changes to more sedentary lifestyles and improving socio-economic development, will increase epidemiology further.

Another significant factor is that in school children and young adults worldwide, obesity prevalence rates are increasing, predisposing young people to chronic diseases. Across the world and in developed and developing nations, women are more likely to be overweight and obese than men. Obesity is now known as an outbreak, genetic predisposition is also required, as shown by 40 to 70% of heritability estimates. During the twentieth century, research demonstrated that obesity-related traits have a hereditary component[5]. A single gene mutation, mainly in the leptin-melanocortin pathway, encodes proteins tightly linked to the control of energy intake and expenditure Genes that might qualify as candidate genes for such processes are chosen based on their perceived function or role in the biochemical processes of the particular genotype, for example, the structural allele for a secreting protein[6].

Genetic aspects of obesity

Obesity is generally divided into subgroups based on suspected etiological conditions, such as monogenic obesity (very severe obesity in the absence of developing retardation), a high proportion of CVD is associated with obesity (mental retardation, dysmorphic features, and developmental malformations and polygenic obesity (which also affects the general population). There are about 20 gene disorders resulting in an autosomal form of obesity, the first of which was identified in 1997. Notably, the mutations affect the leptin/melanocortin pathway in thecentral nervous system (CNS, which regulates whole-body energy homeostasis, which seems to have a relatively high appetite and decreased satiety in all of these circumstances of

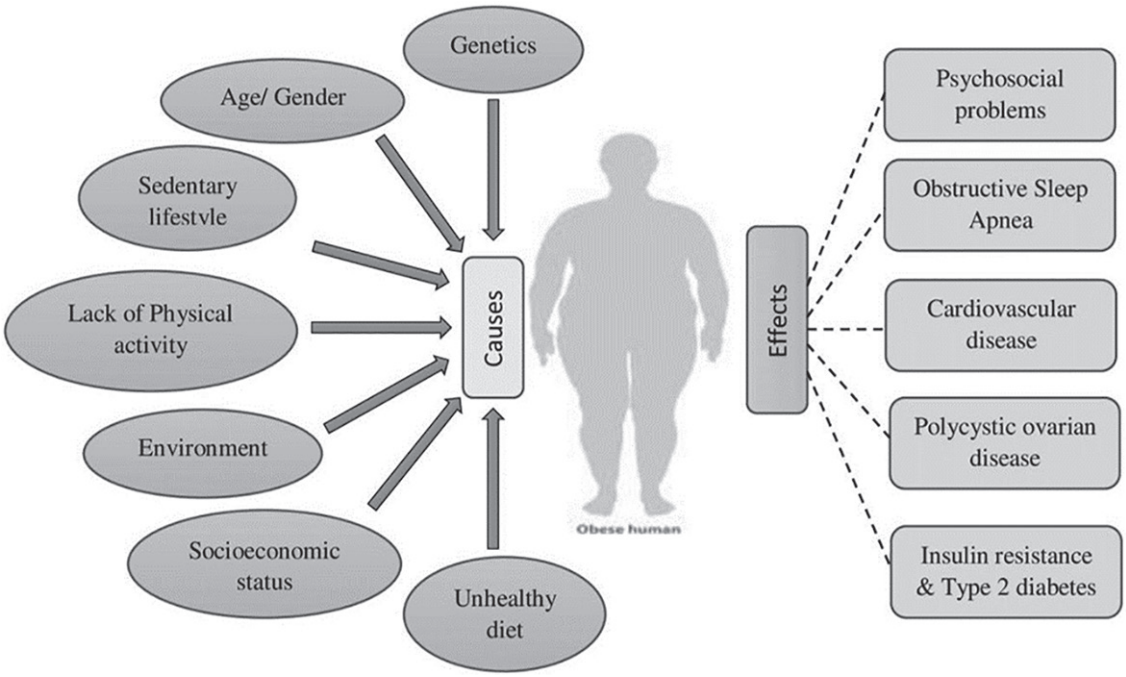

Figure 2 Various risk factors for obesity

obesity[7,8]. Both monogenic and syndrome forms of obesity are pervasive, and the identification of causal genetic variants has been quite successful[9]. It should be noted that gender and age are linked to obesity and body composition variations. Females, for example, process and collect more fat subcutaneously than in the visceral adipose tissue[10]. There are two general patterns of fat distribution: android (adiposis deposition in the abdomen) and gynoid (adipose deposition around the hips). One of the primary genetic variables related to obesity is the existence of specific genetic variations or mutations that influence the control of appetite and metabolism. Figure 3 demonstrates the role of genes in obesity.

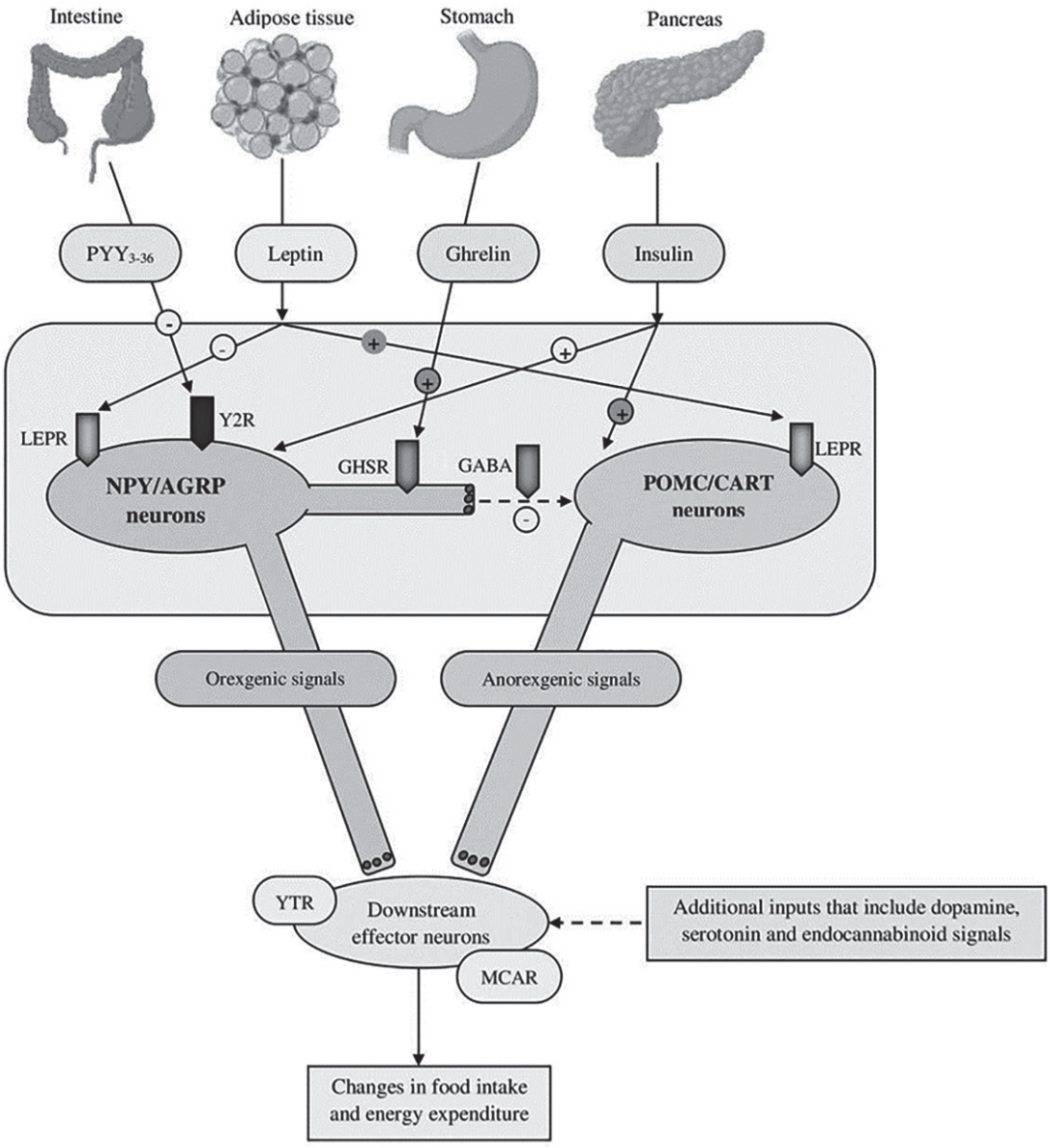

Figure 3 Genetic aspects and mechanisms of weight gain/obesity

Candidate genes linked to obesity

The genes selected from studies published in literature publications published over the last thirty years and catalogued on the Web of Sciences, PubMed, Google Scholar, Embase, and numerous other databases. Titles and abstracts were extracted form the literature and two reviewers reviewed the published articles. The papers were divided into two sections. The first category of publications focused on obesity as a chronic illness, while the second focused on themes, genes, and their links to obesity. The selected genes contained both intronic and exonic mutations, and the studies have reported gene expression in different regions leads to single nucleotide polymorphisms (SNP) (Figure 4). Table 1 describes the genes and functions associated with obesity and obesity-related health problems.

First, it may assist in a better understanding of the underlying biological mechanisms that lead to the development of obesity. This insight may be used to create novel therapies or interventions for obese people. Second, finding the genes linked to obesity might help us identify those more likely to become obese. Personalized preventative and treatment strategies, including dietary and lifestyle modifications or targeted drug therapies, may be developed by using this knowledge. Lastly, knowing the genetic causes of obesity might help us understand how genetics affects other diseases, including cardiovascular disease, type 2 diabetes, and some malignancies often associated with fat. This review found that many genes which have been identified as potential contributors to the development of this disease.

Fat mass and obesity-associated gene (*FTO*)

The *FTO* gene is located on chromosome 16q12.2 and has a maximum length of 410.50 kb, nine exons, and eight introns[11]. It is broadly expressed in human adipose and skeletal muscle tissues, with the most significant expression in the hypothalamic regions, regulating energy balance, especially the arcuate nucleus. Throughout 2007, genomewide research assessed multiple SNPs directly correlated with body fat percentage, hip circumference, body composition, and energy consumption. In addition, *FTO* was identified as an obesity sensitivity gene[12]. N6-methyladenosine demethylase (m6A) was discovered in mRNA and associated with *FTO's* carcinogenesis and adipogenesis.

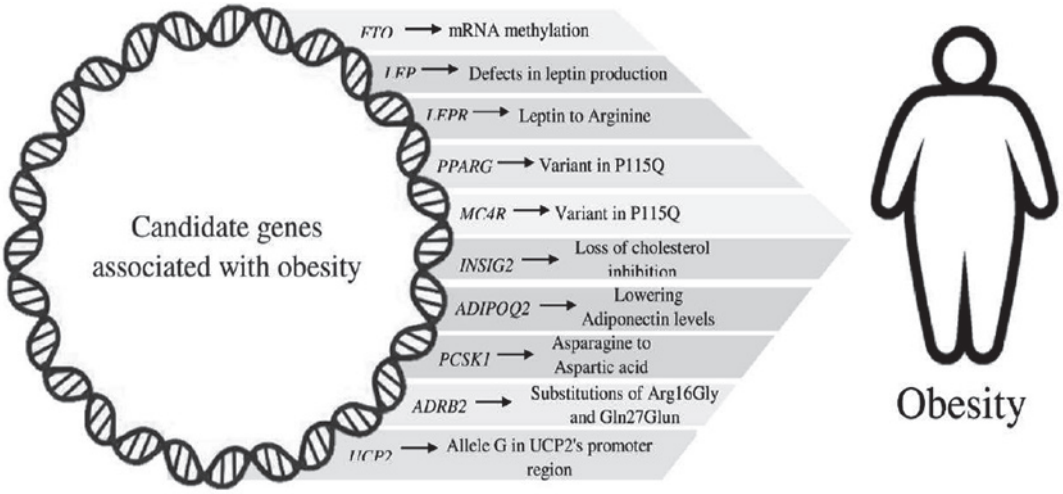

Figure 4 Candidate genes associated with obesity

Table 1 Candidate genes associated with obesity

Gene symbol	Gene name	Chromosome Location	Gene ID	Exons	Amino acids	Functions	Polymorphic sequence	Reference
FTO	FTO alpha-ketoglutarate-dependent dioxygenase	16q12.2	79068	16	505	In human skeletal muscles and adipose tissues, the strongest expression is in the arcuate nucleus of the hypothalamus, which regulates energy balance. Thus, it may be essential for appetite regulation and energy metabolism	rs9939609	[13]
LEP	Leptin	7q32.1	3952	3	167	It provides instructions for making a hormone called leptin, which is involved in the regulation of body weight	rs7799039	[17]
LEPR	Leptin receptor	1p31.3	3953	24	1165	It plays an important role in regulating adipose-tissue mass	K109R, Q223R	[24]
PPARG	Peroxisome proliferator-activated receptor gamma	3p25.2	5468	14	505	It plays a crucial role in adipogenesis and adipocyte gene expression and is the receptor for the thiazolidinedione class of insulin-sensitizing drugs.	rs1801282	[29]
MC4R	Melanocortin 4 receptor	18q21.32	4160	1	332	It is an essential regulator of energy homeostasis, food intake, and body weight in the hypothalamus.	rs17782313	[37]
INSIG2	Insulin-inducedgene 2	2q14.1-q14.2	51141	7	225	It plays a role in fat metabolism and insulin resistance regulation	rs7566605	[44]
ADIPOQ	Adiponectin, C1Q, and collagen domain-containing protein	3q27.3	9370	4	244	Controlling insulin sensitivity and lipid metabolism.	rs2241766	[49]
PCSK1	Proprotein convertase subtilisin/kexin type 1	5q15	5122	15	753	It regulate the calcium and pH dependence of prohormone convertases	rs6232, rs6234, and rs6235	[57]
ADRB2	Adrenoceptor beta 2	5q32	154	1	413	Lipid mobilization from fat stores is activated by lipolysis regulation	rs1042714, Arg16Gly, rs1042713	[65]
UCP2	Uncoupling protein 2	11q13.4	7351	10	309	In the development and treatment of obesity, UCP2 plays a vital role as a mitochondrial transporter involved in glucose/lipid metabolism.	Ala55Val	[69]

As a result of this discovery, the molecular mechanism linking *FTO* to increased overweight and obesity susceptibility was elucidated. One study found a link between the high risk of obesity and *FTO* expression (rs9939609 T/A), lower levels of the m6A ghrelin mRNA methylation, and higher ghrelin hormone levels[13]. An increase in the "hunger hormone," ghrelin, leads to an increased desire for high-calorie meals like sweets and salty snacks; this may affect weight gain and obesity[14]. Another study revealed that the *FTO* genotype at the *FTO* rs9939609 locus affects food intake and corticolimbic activity. Obesity-related adipose tissue accumulation is an important energy storage mechanism[15]. The m6A demethylation modulated by *FTO* mediates the splicing of mRNA, which is essential in regulating adipogenesis. They discovered that *FTO* function is inversely proportional to m6A levels throughout adipogenesis, and *FTO* deficiency prevents differentiation, whereas wild-type *FTO* (but not *FTO* mutant) maintains adipogenesis. *FTO* regulates m6A demethylation, which controls mRNA splicing, which controls adipogenesis. The same study reported that m6A levels and *FTO* function were negatively correlated with adipogenesis. *FTO* deficiency impairs differentiation, while wild-type *FTO* (but not mutant *FTO*) maintains adipogenesis. By stabilizing m6A levels across splice sites, the *FTO* controls RUNX1T1 exonic splicing, which affects differentiation. A low m6A level prevents *FTO* function and adipogenesis, whereas wild-type *FTO* generates fat. The adipogenic regulator factor RUNX1T1's exonic splicing is monitored by *FTO*, which regulates differentiation by stabilizing m6A levels across splice sites[16]. FTO gene variants may cause an imbalance in these processes, eventually resulting in weight gain and obesity. The FTO gene seems to be involved in diet and energy expenditure regulation.

Leptin gene (*LEP*)

The *LEP* gene encodes for leptin. It is situated in humans on chromosome 7q32.1 and comprises three exons divided by two introns[17]. Leptin is a 167-amino acid protein and is an essential signal in regulating body weight and adipose-tissue mass; and is activated by constraining food intake and motivating energy expenditure. Deficiencies in leptin production cause severe obesity. Multiple studies have identified the leptin gene as a vital cog in obesity, but the results have been mixed. Mammes et al.[18] became the first to demonstrate that the *LEP* promoter's rs7799039 (G-2548A) variant was closely linked with BMI reduction in obese women.

Regarding adipocyte growth and metabolism, CCAAT/enhancer-binding protein-alpha may have a natural target in the "obese" promoter[19]. It highly expressed the human *LEP* gene in the submucosa and adipose tissue of obese individuals[20]. Changes in CCAAT/enhancer-binding protein alpha levels or activity may affect *LEP* gene expression[21]. Various microsatellite markers the *LEP* gene have also been identified. However, the potential connections with obesity seem to be incongruent. C (-188) other reported diverse forms of the human *LEP* gene have been found to contain polymorphisms in the promoter region, unusual mutagenesis at codon F17L, and a mutation at codon V110M[22]. A recent study also found a variation in the *LEP* gene promoter untranslated exon 1 (A19G)[23]. Thus, although leptin gene alterations cause rare instances of obesity, obesity is more often brought on by a complex interaction of genetic, environmental, and lifestyle variables.

Leptin receptor gene (*LEPR*)

One experimental study examined the importance of *LEPR1* (primarily found in the brain's hypothalamus region but not in other tissues) in leptin signal transmission to the cell.[26] *LEPR* is located on the 1p31 chromosome in humans and has five isoforms. It is a glycoprotein with a single transmembrane-spanning domain, 1165 amino acids, and is related to the class 1 cytokine receptor family[24]. Homodimer leptin receptors do have the potential to modulate Janus kinases, which in turn stimulate transcription activators.

The long variant of the leptin receptor is closely linked to leptin signaling via Janus kinases and transcription system activation[25]. While the long forms are concentrated in specific organs, short forms may be found throughout the body in the kidney, lung, and choroid plexus. Variants commonly occur, leading to two non-conservative modifications: glutamine being replaced by arginine at codon 223 and a conservative alteration leading to lysine substitution at codon 109.[27] The human hypothalamus contains the leptin receptor, and researchers have found that the receptor's abilities affect leptin's sensitivity to energy restriction. Minimal impact of the Q223R, K109R, and K656N genetic variants was noted on the *LEPR* gene's symptomatic depletion of leptin upon energy restriction[28]. The leptin signaling system may change due to mutations or changes in the *LEPR* gene, which may help explain how obesity develops. Some *LEPR* gene variations may be linked to an increased incidence of obesity, according to detailed research, especially in specific populations. It's essential to keep in mind that there are many other variables than genetics that might cause obesity. Diet, lifestyle, and environmental variables are other factors affecting illness.

Peroxisome proliferator activated receptor-gamma gene (*PPARG*)

The *PPARG* gene is nearly 100 bp ong and contains one exon. It is located on chromosome 3p25.2. It codes for the *PPARG* subfamily of nuclear hormone receptor transcription factors in the immune system and adipose tissue. These receptors regulate the formation of adipocytes and the balance of glucose metabolism[29]. The *PPARG* forms a heterodimer that regulates gene transcription in fat metabolism, insulin production, cancer, and inflammation[30]. SNP rs1801282, in general, has been related to obesity across many populations, with the risk allele G identified[31]. Several gene mutations have been linked to obesity, including P115Q, a very peculiar gain-of-function variant[32]; V290M and P467L, two failure mutations discovered in three patients with metabolic syndrome but maintaining homeostasis weight[33]. The CG exchange at NR1C3 protein residue twelve (P12A) changes pyrrolidine-2-carboxylic acid to alanine, which may cause obesity and adult-onset diabetes[34]. The CT change in exon six at nucleotide one-sixty-one may alter adult susceptibility to obesity and diabetes. It has been demonstrated that the Pro12Ala mutation reduces metabolic syndrome and obesity caused by a ketogenic diet[35]. The P12A variant's expression is not dissimilar in obese individuals who have one of the two allele variants[36]. PPARG is a crucial gene in the control of adipogenesis and lipid metabolism overall, and its dysregulation may lead to the onset of obesity and related metabolic diseases. Hence, altering PPARG activity may be a viable therapeutic approach for obesity treatment and associated conditions.

Melanocortin 4 receptor (*MC4R*)

The *MC4R* gene is found on chromosome 18q21.3, which contains 332 amino acids that regulate energy expenditure, eating habits, and weight management at the hypothalamic level[37]. The precise mechanisms underlying the emphasis of the *MC4R* genetic polymorphism in metabolic disease molecular pathways are unknown. Specific *MC4R* polymorphisms have been correlated with increased weight gain in genomewide studies, most notably rs17782313, which is associated withhigher BMIs and overeating behaviors. Obesity, hyperphagia, and hyper insulin in children have been linked to *MC4R* gene variants. Abnormalities in the *MC4R* gene have been noticed in 3% to 5% of patients with early-onset extreme adult adiposity[38]. By affecting the *MC4R* genome, abnormalities that lead to the loss of function of the gene result in adverse consequences of fat loss after exercise[39]. According to detailed research on infants, the polymorphism rs17782313 has been linked to differences in BMI during the first 14 days of life, body fat, and BMI at 14 days[40]. The *MC4R* rs17782313 variant, inserted 188 kb downstream of the gene, has been

associated with BMI and rates of obese conditions in various populations[41]. Abnormalities produce orexigenic signals in the melanocortin system that reduce *MC4R* activity[42]. The leptin–pro–opiomelanocortin pathway, including the *MC4R* gene, regulates appetite and energy expenditure[43]. Overall, the PPARG gene plays a significant role in the control of adipocyte development and metabolism.

Insulin–Induced Gene 2 (*INSIG2*)

One of the most prominent roles of *INSIG2* in lipid metabolism is in fatty acid and endogenous cholesterol production feedback inhibition. On chromosome 2q14.1–q14.2, the gene measures 21.5 kilobases (Kb). It is an endoplasmic reticulum membrane–bound protein that prevents SREPs from becoming proteolytically activated[44]. A familiar SNP, rs7566605, around the *INSIG2* gene, has been associated with obesity in both children and adults. Regardless of ethnicity, roughly 10% of individuals bear the CC genotype, frequently leading to obesity[45]. Obesity is recessively associated with the C [minor] allele[46]. In three independent family–based samples and three studies of unrelated individuals, obesity was associated with the rs7566605 CC genotype. However, confirmation was associated with a single study group. A few efforts have been made or are being made to recreate the *INSIG2* discovery. Both positive and negative results have been reported[47,48]. Data are currently being consolidated for a large–scale meta–analysis, which will shortly assist in understanding whether *INSIG2* is a true polygenic Overall, there is some indication that INSIG2 may contribute to the development of obesity, but the findings of the studies have been contradictory, and further studies are required to completely understand the processes at play.

Adipocyte, C1Q, and Collagen Domain Containing protein (*ADIPOQ*)

ADIPOQ, a gene associated with obesity predisposition, has been found in many genomewide association studies on chromosome 3q27.3[49]. "Adipocyte complement–related protein of 30 kDa [ACRP30]," "gelatin binding protein 28" (GBP28), and "adipose most extensive gene transcript 1" are all names given to the protein generated by adipocytes, and it was discovered separately in the 1990s by several researchers (APM1)[50]. AMPK is encoded by the adiponectin gene, which regulates glucose levels and fat oxidation in the body[51]. Furthermore, obesity, diabetes, and myocardial infarction patients have been reported significantly lower adiponectin rates[52]. Numerous studies have found that *ADIPOQ* gene variations, including the rs2241766 G/T polymorphism, were positively associated with plasma adiponectin levels[53]. The *ADIPOQ* gene polymorphism (rs2241766) has been considered a potential obesity–related single nucleotide polymorphism (SNP)[54], although there have been discrepancies among various ethnic groups. Mutations have been shown to affect stable mRNA production by changing RNA splicing or stability in experimental designs, indicating that adiponectin expression varies by allele. In heterozygous subjects' adipose tissue, the G allele transcribed much higher levels of stable mRNA than the T allele[55]. This may be tested since obesity has been connected to *ADIPOQ*–rs2241766 G/T polymorphisms. ACDC is a crucial protein in obesity and may act as a marker for metabolic dysfunction and an elevated risk of cardiovascular disease at higher levels.

Proprotein Convertase Subtilisin/Kexin Type 1 (*PCSK1*)

Genetic variations in the *PCSK1* gene have been closely connected to monogenic obesity[58]. The gene encodes an enzyme that converts prohormones to active hormones in brain endocrine cells and regulates energy and metabolism[56]. This gene contains 15 exons in humans and is found on chromosome 5, with 753 amino acids[57]. This gene is also attributed to glucose metabolism, lipogenesis, and resting energy expenditure. One case of a patient with genetically inherited *PCSK1* deficiency and morbid

obesity has been reported[59]. Benzinou et al. reported in 2008 on the affiliation of three SNPs – rs6232, rs6234, and rs6235 – with obesity[60]. Numerous SNPs have been found to be significantly associated with BMI, but *PCSK1* SNPs have only been mildly attributed to BMI[61]. this enzyme plays a significant role in mass body control based on PC1/3 expression and physiological substrates. There is widespread activity of stress in the hypothalamic arcuate and para-ventricular nuclei[62], which regulates hunger and satiety.

Recent research has found minor mutant alleles of three familiar non-single nucleotide genetic variants (SNPs) at the *PCSK1* gene region, rs6232, rs6234, and rs6235, to be associated with an elevated threat of obesity[63] or glucose metabolic disturbance[64]. It is known that rs6234 and rs6235, two SNPs located in exon 14, cause amino acid changes at positions 665 in (Gln to Glu) and 690 (Ser to Thr) (Q665E and S690T, in the PC1/3 CT domain), respectively. An amino acid change (Asn to Asp) at position 221 (N221D) in the catalytic domain of PC1/3 was found with the rs6232 variation, which included a CNT distortion in exon 6. The secretory compartments of endocrine and neuroendocrine cells may have PC1/3 activity, although further research is needed to elucidate this possibility. Therefore, although there is still much to learn about PCSK1's involvement in obesity, the evidence indicates its significance in controlling appetite, satiety, and body weight.

Adrenoceptor beta 2 (*ADRB2*)

Human fat cells have the *ADRB2* gene, which codes for a lipolytic receptor protein. The *ADRB2* gene is found on chromosome 5 between the q31 and q32 bands[65]. Multiple diseases, including hypertension and obesity, have been linked to two common ADRB2 gene polymorphisms characterized by amino acid substitutions of Arg16Gly and Gln27Glun[66]. The beta-2 adrenergic receptor. Arg16Gly polymorphism has been linked to altered activity of *ADBR2*, resulting in reduced sensitivity[67]. This variation has also been associated with obesity in several groups. According to studies conducted on people of both genders, it has been linked to increased body fat, subcutaneous fat, elevated levels of the hormone leptin, and high triglycerides[68]. Overall, metabolic imbalances and associated health issues may occur due to diminished expression and signaling of β2-AR in obesity. Hence, a possible therapeutic approach for treating obesity and associated metabolic problems involves targeting β2-AR signaling.

Uncoupling protein 2 (*UCP2*)

In humans, the *UCP2* gene is found in the chromosomal region 11q13.4, a region associated with energy balance and obesity, and it comprises 309 amino acids with a molecular weight of 33 kDa. Several human investigations have found a link between the *UCP* polymorphism and exercise efficiency, substrate oxidation, type 2 diabetes risk, bodyweight fluctuations, resting calorie expenditure, BMI, glucose metabolism, obesity risk, physical activity, leptin, fat accumulation, and other factors[69]. These gene variants include a G/A polymorphism in the promoter region (866G/A), an (Ala55Val), and a 45 base pair insertion in the untranslated exon region 8[70]. The relationship between these *UCP2* polymorphisms and many characteristics of obesity have been frequently researched. Allele G in the *UCP2* promoter region has been associated with increased obesity risk while decreasing the chance of developing type 2 diabetes. A genetic variant called Ala55Val has been associated with greater exercise efficiency.[71] *UCP2* exon eight insertion allele findings have been unclear so far. Thus, further studies are required to fully unravel UCP2's impacts on energy metabolism and body weight control since its function in obesity is still unknown.

Conclusion concerning insulin resistance, type 2 diabetes

Obesity is caused by disparities in food intake, basal metabolic activity, and energy expenditure and is a significant risk factor for numerous metabolic disorders such as type 2 diabetes, insulin sensitivity, and non-alcoholic fatty liver disease[72,73], and associated with an increased likelihood of developing several diseases and conditions, including diabetic complications, heart disease, high blood pressure, osteoarthritis, and some cancers. An combination of genetic, environmental, and lifestyle factors may lead to obesity. Genetics have been proven to substantially impact the development of obesity, even if the precise causes of this disorder are still not completely understood. Many genes undergoing extensive research have been connected to a greater chance of obesity. These genes may affect many biological functions, such as how the body reacts to food, metabolism, and energy expenditure, raising the risk of obesity and weight gain. The study's findings include identifying multiple genetic variations linked to an elevated risk of obesity and a greater body mass index. Our study found that selected gene polymorphisms are related to obesity and play a role in developing obesity among children, adolescents, and young adults. Although GWAS have identified various obesity loci, they only account for a tiny portion of interindividual variance, indicating that more genetic variables are waiting to be identified. However, these discoveries will lead to meaningful treatments, identifying functional variations, and additional molecular and physiologic characterization of the genes and pathways implicated]. However these genes are subject to research restrictions based on race, gender, climate, and biology. Gene alterations may significantly influence the development of obesity. Recently, the investigation of gene alterations linked to obesity has increased substantially. To prevent and treat obesity effectively, lifestyle changes such as diet and exercise must be combined with medical management. Therefore, further empirical research with the appropriate data is required to examine the improvement and treatment of genetic variations associated with obesity.

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Conflict of interest

All authors have no relevant financial or non-financial competing interests to report

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