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Genes Predisposing to Monogenic, Polygenic, and Syndromic Obesity: A Review of Current Trends and Prospects for Standard Obesity Genetic Testing

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Abstract

Objective: The burden of obesity is currently enormous, necessitating a novel strategy to complement the existing ones. Accordingly, genetic predisposition is suspected in many cases of the disease, which can potentially be used as therapeutic targets. However, there are differing viewpoints on the suspect genes, prompting the current review to articulate the genes and their mechanisms. Eight (16%) of the genes singularly predispose humans to obesity (called monogenic obesity), 22 (43%) interact with other genes and the environment to predispose humans to obesity (called polygenic obesity), and 21 (41%) cause syndromic obesity. Monogenic obesity is often caused by three genes [the leptin (*LEP*), the leptin receptor (*LEPR*), and the melanocortin 4 receptor (*MC4R*) genes], polygenic obesity [fat mass and obesity-associated (*FTO*) gene], and syndromic obesity (Prader-Willi Syndrome). These genes control food intake and energy expenditure, and so mutations in them cause overeating, adiposity, and hyperphagia. Based on these findings, two genetically-based drugs, named recombinant human leptin and setmelanotide, have been formulated and shown to significantly reduce food intake, body weight, and fat mass. This suggests that when the genetic etiology of obesity is fully understood, the disease's treatment and prevention will improve. Healthcare providers are urged to develop genetically-based personalized treatments for obese patients.

Keywords: Adiposity, Body weight, Hyperphagia, Leptin, Obesity

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Introduction

Obesity is described as excessive fat accumulation that is harmful to health (1,2). There is no perfect method for measuring obesity. However, the most commonly utilized methods are body mass index (BMI) and waist circumference (3,4). The BMI of a person is computed by multiplying the weight in kilograms by the height in meters squared (5). A BMI of 25 or more is considered overweight, whereas a BMI of 30 or above is considered obese (6,7). Waist circumference is a less common method for determining obesity in adults, which involves measuring the waist (8). Females with a waist circumference of 80 cm or more are regarded as unhealthy, while males with a waist circumference of 94 cm or more are deemed unhealthy (9,10).

Obesity and overweight prevalence have skyrocketed in recent years, reaching epidemic proportions with the incidence rate more than doubling since 1980 (11). Obesity was thought to be an issue only in advanced countries, but it is currently highly prevalent in developing countries, particularly in urban areas (12). This is a consequence of industrialization and economic globalization, which have aided the spread of obesogenic products (calorie-laden western diets) such as sugar-sweetened beverages and packaged foods to developing countries (13). As of 2016, about 44% of adults (more than 2 billion) worldwide were overweight or obese, with over 70% of them living in low- or middle-income nations. This information debunks the belief that obesity is only a problem in high-income countries (14). Overweight and obesity affect about 30% and 10% of adults in Sub-Saharan Africa, respectively (15). In Nigeria, approximately 21 million and 12 million people aged 15 and above were overweight or obese in 2020, accounting for a 20.3% and 11.6% age-adjusted prevalence, respectively (16).

Obesity and being overweight can cause several potentially fatal illnesses (17). The most prevalent of these illnesses include high cholesterol, high blood pressure, heart disease, diabetes mellitus, gallbladder disease, stroke, osteoarthritis, sleep apnea, respiratory problems, and cancers (17,18). Obesity can also cause dyslipidemia, non-alcoholic fatty liver disease (NAFLD), lower quality of life, psychosocial problems, and a shorter lifespan (19). Over 2.8 million people die each year from the mentioned diseases and other obesity-related disorders (2). Obesity was responsible for around 4 million fatalities in 195 countries in 2015, the majority of which were due to cardiovascular complications (20). In advanced countries, obesity and its accompanying chronic conditions, such as diabetes, cardiovascular disease, and cancer, lower life expectancy by an average of 2.7 years (21).

Aside from the health burden, the increasing prevalence of obesity is also causing a huge threat to economies worldwide. The rise in weight- and obesity-related disorders has not only harmed the health of billions of people, but has also resulted in enormous economic costs. Obese people miss more days of work than people who are not obese, and they operate at a lower capacity while they are at work (22). Obesity also raises the risk of being laid off and has a negative influence on income (22). In many developed nations, 8.4% of the health budget is spent on treating the consequences of being overweight (21). Obesity reduces GDP by 3.3% on average in many developed countries (21). In Nigeria, there is a scarcity of data on the cost of healthcare services for obese people. However, a clinical study showed that obese Nigerians spend more money on medical treatments than non-obese Nigerians (23,24).

Available treatment options for obesity include lifestyle and diet adjustment, regular exercise, weight loss, medication, and surgery (25). However, considering the disease's huge burden, a novel therapeutic strategy is necessary to reverse the rising trend. To this end, genetic predisposition, as well as

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epigenetic, environmental factors, and lifestyle are suspected of the disease's rising burden. Genetic factors, in particular, account for about 40-70% of the incidence, and many candidate genes have been identified (26). However, the list of suspect genes is growing. This study was conceived to provide current information on the identified genes and their obesogenic pathophysiology. This will aid healthcare providers in making accurate diagnoses and developing appropriate therapies for those who are affected.

Pathogenesis of obesity

The first law of thermodynamics, when applied to body weight, states that body weight will remain unchanged if energy intake and expenditure are equal during a given time period. So, overweight or obesity is caused by overeating or poor energy expenditure (27,28). The body is in energy equilibrium when energy intake matches energy expenditure and body energy (often equivalent to body weight) is stable (27,29). In healthy individuals, adipose tissues play a critical role in maintaining this equilibrium at both the organ and systemic levels (30). White adipose tissue stores excess energy as a lipid and regulates lipid mobilization and distribution in the body (30). It does this by recruiting more adipocytes to accumulate more fat and undergo cellular hypertrophy. White adipose tissue also functions as an endocrine organ and produces several bioactive substances such as adipokines, which communicate with other organs to regulate several metabolic pathways (30). Brown and beige adipose tissues, on the other hand, burn lipid by dissipating energy in the form of heat during a calorie shortfall (30). Adipose tissues, along with the pancreas and digestive tract, send signals to the central nervous system, which help regulate appetite and thus calorie intake and energy expenditure (31). Obesity, on the other hand, reduces adipose tissue storage capacity, resulting in energy imbalance and fat buildup in visceral adipose depots as well as ectopic tissues such as the liver, skeletal muscle, and heart (30,32). Small deviations from the homeostatic mechanisms, as low as less than 2% of daily energy intake, can cause significant long-term changes in body weight (~20 kg) (31,33). To sum it up, when energy intake exceeds energy expenditure, body fat mass (of which 60 to 80% is usually body fat) increases, while it decreases when energy expenditure exceeds intake (27,34). Factors that modulate the association between dietary intake and obesity include physical activity, genetic and epigenetic factors, chemical or pollutant exposure, poor sleep pattern, microbiota, energy-dense diets, over-nutrition, and adipose tissue dysfunction (30,33,34). These factors disrupt either energy intake, expenditure, storage, or all (27).

Genetic basis of obesity

The brain employs the signals sent into the central nervous system by adipose tissues, the pancreas, and the digestive tract to instruct the body on its energy needs (35,36). These signals are transmitted by hormones such as insulin, ghrelin, leptin, and some molecules, all of which are coded for by genes. Thus, any changes in these genes can affect their expressions and functions (35). This underscores the importance of genes in energy homeostasis, obesity pathogenesis, prevention, and treatment. To this end, studies have demonstrated that genetic predisposition contributes to about 40–70% of cases of obesity, and so far, over 50 genes are strongly linked with the disease (25,37). Some of these genes alone predispose people to obesity (referred to as monogenic obesity), whereas others combine with others and the environment to predispose people to obesity (referred to as polygenic obesity) (38,39). There is also syndromic obesity, which is severe obesity associated with phenotypes such as neurodevelopmental and organ abnormalities (38,39). Monogenic causes are primarily involved in signal transmission and embedded mainly in the hypothalamic leptin/melanocortin axis, while the polygenic interacts with the environment (38,39).

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Polygenic causes are the most prevalent in the obese population, while monogenic causes account for just about 5% (38). The most frequent causes of monogenic obesity are mutations in leptin (*LEP*), the leptin receptor (*LEPR*), and the melanocortin 4 receptor (*MC4R*) genes (40). The fat mass and obesity-associated gene (*FTO*) is the commonest causes of polygenic obesity and, by extension, the commonest causes of obesity, found in up to 43% of the obese (35). Prader-Willi Syndrome (PWS) is the commonest cause of syndromic obesity and is found in 1 in 15,000–25,000 births (39,41).

The current review identified over 100 obesity candidate genes. However, some were not replicated in follow-up studies, so only 51 genes that were regularly linked with the disease were included in this study. Of the 50 genes, 8 (16%) cause monogenic obesity, 22 (43%) cause polygenic obesity and 21 (41%) cause syndromic obesity.

Genetic testing for obesity: progress, benefits, and costs

There is no standard genetic testing panel for obesity yet. Some hospitals, laboratories, research institutions, and pharmaceutical corporations, however, sequence well-known candidate genes in order to find the functional mutation that may be causing a patient's body weight gain (159). Some of these laboratories and companies include Sequencing.com, 23andMe, Dante Labs, AncestryDNA, and MyHeritage (160). These laboratories often sequence the cheek swab of the affected person using whole-genome sequencing (160). DNA test kits are also available from the companies.

The results of the DNA test are being used in weight-loss programs. Some people approach a nutritionist or licensed dietitian to develop a personalized nutrition plan based on their test results (160). Obesity genetic testing has helped reduce some of the burdens of the disease, which includes feelings of shame by patients and stigmatization by the public. Importantly, the test results are being used to personalize treatment for individual patients. Currently, two such personalized and genetically-based drugs have been produced and approved, and they are recombinant human leptin and setmelanotide (159,161). Leptin replacement therapy has been found to help patients who are lacking in leptin caused by *LEP* gene mutations (159,161). Setmelanotide is a selective *MC4R* agonist that helps patients with *POMC*, *PCSK1*, or *LEPR* deficiency compensate for the lack of melanocyte-stimulating hormone (MSH) (159,162). A daily dermal injection of setmelanotide significantly decreased weight and hunger (159). However, setmelanotide has minor adverse effects, which include nausea, hyperpigmentation, vomiting, darkening of skin, injection site reactions, and penile erections (159,162). Generally, testing for obesity genes early in life, especially for those with a family history of obesity, has been demonstrated to be beneficial as it allows affected individuals to plan their diet ahead of time and lower their risk of becoming obese (26,163). If a large number of obese people get access to this facility, the disease's incidence and burden will undoubtedly decrease.

In recent years, the cost of genetic testing for various diseases has been reduced, unlike in the past when the human genome was first sequenced. According to Medline Plus (164), the cost of genetic testing in the United States ranges from below $100 to over $2,000. The costs are higher if several tests are required or several members of the family need to be tested before a meaningful result can be obtained. The cost of genetic screening for newborns depends on the state. Some states pay some of the costs, but most tests cost between $30 and $150 per infant. The decreasing cost has made genetic testing more accessible to millions of people around the world (160). This has definitely had a positive impact on the cost of obesity genetic testing. Some laboratories, like sequencing.com and personal diagnostics, sell obesity DNA test kits for between $69 and £39.98 (160,165). A pharmaceutical company in the US named

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"Rhythm" even offers a free genetic testing program for patients (166). When these costs are compared with the attendant obesity burden reduction that follows genetic testing, the cost is worthwhile. With the current trend, the costs are likely to be reduced further. With increasing knowledge, a standard obesity genetic panel could be developed, making testing more affordable and effective. However, poverty and a lack of facilities, proper planning, and information may hinder the progress of developing nations.

Conclusion

Mutations in the genes that control food intake and energy expenditure may cause overeating, adiposity, and hyperphagia, resulting in overweight or obesity. These genes accounted for between 40 and 70% of cases of obesity. Given the huge contribution of genetics to the incidence of obesity, treatments tailored to the causal genes and their pathophysiology in affected individuals will significantly improve the condition. To this end, two genetically-informed drugs, named recombinant human leptin and setmelanotide, have been formulated and found to be effective. As such, healthcare providers are encouraged to design drugs and treatments based on the pathophysiology of the causal genes in the affected individuals. The strength of this study lies in its ability to articulate genes and variants based on the types of obesity they cause, which may aid in effective diagnosis and treatment procedures. The weakness of the study lies in its inability to take into account the prevalent obesity genes in each region of the world, among ethnic groups, and genders. This weakness is a pointer for future study.

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Conflict of Interest

The authors declare that there is no conflict of interest in this study.

Table 1. Genes/mutations predisposing to monogenic obesity

Gene/Variant	Full name	Locus	Biological function	Pathophysiology	References
***NTRK2* or *BDNF* or *NT-3* growth factors receptor */rs1211166, rs1401635*, and Y722C**	Neurotrophic Receptor Tyrosine Kinase 2	9q21.33	Energy homeostasis regulation. The migration, development, differentiation, and survival of fetal neurons are all regulated by *BDNF*/*TrkB* neurotrophic signaling, which also regulates food intake.	TrkB's ability to stimulate neurite outgrowth in response to *BDNF* is altered by mutations in this gene. Hypothalamic neurogenesis is reduced, which causes severe hyperphagia and obesity	(42,43)
MC4R*/ More than 170 variants have been reported including rs17782313, *L325I, E308K, D298N, F261L, T248A, D111V, Y80F, L325I, and S270F	Melanocortin 4 receptor	18q21.32	*MC4R* regulates energy homeostasis and body weight in the hypothalamus.	Loss of functions generates orexigenic signals, resulting in hyperphagia and obesity	(35,44, 45)
LEP*/*rs7799039, rs2167270,	Leptin	7q32.1	The *LEP* produces leptin, which regulates body weight through energy homeostasis.	Mutations in the gene cause congenital leptin deficiency, which disrupts feelings of satiety, resulting in excessive hunger and weight gain.	(46)
LEPR*/At least 18 LEPR gene mutations that cause leptin receptor deficiency have been identified which include *rs113710I, rs1137100, rs3736228,* and *rs320	Leptin receptor	1p31.3	*LEPR* gene suppresses appetite when bound by leptin. The gene codes for the leptin receptor, which is important in body weight regulation.	*LEPR* gene mutations increased hunger and weight gain.	(35,47)

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Gene/Variant	Full name	Locus	Biological function	Pathophysiology	References
PCSK1/rs72552, rs6232, rs6234,* and *rs6235	Proprotein convertase subtilisin /kexin type 1	5q15	It controls the production of insulin (35). *PCSK1* encodes prohormone convertase 1/3 (PC1/3), which is important for the activating cleavage of many peptide hormone precursors involved in the regulation of food ingestion, glucose homeostasis, and energy homeostasis	Loss-of-function mutations cause *PC1/3* deficiency, characterized by a complex set of endocrinopathies and obesity (48). *PCSK1* deficiency in infants causes severe intestinal malabsorption during the first years of life, requiring controlled nutrition. These children then become hyperphagic, with associated obesity	(48)
SH2B1/rs147094247, rs7498665, rs60604881, rs62037368 and rs62037369,	Src homology 2 B adapter protein 1	16p11.2	It helps to keep the body's energy and glucose levels in check. *SH2B1* promotes leptin signaling and obesity-regulating activity in the brain. *SH2B1* increases insulin signaling in peripheral tissues. *SH2B1* is essential for compensatory beta cell growth in pancreatic islets in response to insulin insensitivity and β-cell stress.	*SH2B1* mutations cause leptin resistance, energy imbalance, and insulin resistance, resulting in hyperphagia.	(49,50)
POMC/ Tyr221Cys	Proopiomelanocortin	2p23.3	It produces several peptides, one of which is beta-melanocyte stimulating hormone, which regulates weight by binding to the *MC4R* receptor. The brain's signaling through this receptor serves to maintain the balance between the energy consumed by the body and the energy expended by the body.	It causes proopiomelanocortin insufficiency, which is characterized by a lack of α-MSH and β-MSH-mediated signaling in the brain, causing the body's energy balance to be disrupted, resulting in overeating and severe obesity.	(51,52)
SIM1/p.D134N , p.T481K, p.A517V, p.T46R, p.H323Y, and p.T714A	Single-minded homolog 1	6q16	SIM1 interacts with pathways controlling melanocortin signaling to play a major role in neuronal differentiation of the nucleus paraventricularis in the hypothalamus, which is important for energy homeostasis. *SIM1* is a downstream regulator of the *MC4R* gene, and mutations in this gene are a common cause of monogenic obesity in humans.	*SIM1* gene deletion causes hyperphagia and food impulsivity. *SIM1* deficiency is associated with severe obesity, either with or without Prader–Willi syndrome–like features.	(52,53,54)

Table 2. Genes/mutations predisposing to polygenic obesity

Gene/Variant	Full name	Locus	Biological function	Pathophysiology	References
FTO/rs1421085, rs9939609, rs1861868, rs17817449, rs3751812, rs7202116*, and *rs9939609	Fat mass and obesity-associated gene	16q12.2	It regulates feeding behavior and energy expenditure.	It increases the tendency to be sedentary and store body fat by increasing hunger and calorie intake, d ecreasing satiety and controlling overeating.	(26,55,56)
ANK2/R1788W* and *L1622I	Ankyrin 2	4q25-q26	The *ANK2* gene produces ankyrin-B, a protein that helps organize the cell's structural framework (cytoskeleton) and connects some proteins that traverse the cell membrane to the framework. Ankyrins also play a role in cell movement (migration) and cell growth and division (proliferation).	Causes increased glucose intake by fat cells, which results in increased weight and culminates in obesity when the metabolism ages or a high-fat diet is eaten. This eventually results in the spilling of lipids in the fat cells onto the liver and muscles, causing inflammation in the tissues and insulin resistance, a hallmark of type II diabetes.	(57,58)
CDKAL1/rs22067304, rs7756992 A/G, rs35612982*, and *rs10811661.	CDK5 Regulatory Subunit Associated Protein 1 Like 1.	6p22.3	*CDKAL1* codes for Cyclin-dependent kinase 5 (CDK5), a regulatory subunit-associated protein 1 found in a variety of tissues, including neurons and β-cells. CDK5 boosts the survival of pancreatic cells and regulates mitochondrial function in adipose tissue.	Suppresses *CDKAL1* mRNA expression in adipose tissue, reducing energy expenditure by disrupting mitochondrial function in primary differentiated brown adipocytes and isolated mitochondria.	(59,60,61)
TNNI3K/rs151416	TNNI3 interacting kinase	1p31.1	TNNI3 codes for a MAP kinase kinase kinase protein. The protein contains ankyrin repeats whose functions have been mentioned earlier.	Nutritional imbalance, particularly a lower intake of dietary protein.	(62,63)

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Gene/Variant	Full name	Locus	Biological function	Pathophysiology	References
GIPR/rs1167166, rs2302382,* and *rs8111428	Gastric inhibitory polypeptide receptor	19q13.2	Modulates body weight and glucose homeostasis by increasing resistin and ghrelin levels.	Decreased expression, which raises plasma leptin levels, increasing food intake and weight 52.	(64,65)
GIP/rs4794008, rs9904288,* and *rs1390154	Glucose-dependent insulinotropic polypeptide	17q21.32	Modulates fat distribution and glucose metabolism either through incretin function or independently of incretin function	Mutations in *GIP* increases the visceral fat area (VFA) and the VFA/SFA ratio SFA = subcutaneous fat area.	(66)
NPC1/rs1805081	NPC intracellular cholesterol transporter 1	18q11	The *NPC1* gene directs the production of a protein found in lysosomes and endosomes, which digest and recycle materials. The protein helps cholesterol and other forms of fat move around within cells and across cell membranes	Mutations in *NPC1* or *NPC2* causes Niemann-Pick disease. The disease is a rare neurovisceral lipid storage disorder that disrupts intracellular lipid transport, causing lipid products to accumulate in late endosomes and lysosomes	(67, 68)
ADIPOQ/rs26679* and *rs2241766	Adiponectin, C1Q and collagen domain containing	3q27.3	The gene is embedded exclusively in the adipose tissues, where it produces adiponectin, which promotes energy expenditure.	Mutation causes adiponectin deficiency 56.	(35,69, 70)
INSIG2/rs756665	Insulin-induced gene 2	2q14	*INSIG2* is embedded in the endoplasmic reticulum and controls cholesterol and fatty acid production. In rats, *INSIG2* modulates triglyceride levels.	Mutations in *INSIG2* promote cholesterol and fatty acid production, resulting in obesity.	(35,71, 72)
PPARα or G/rs1801282* and *PPARG Pro12Ala	Peroxisome proliferator-activated receptor α or gamma	3p25.2 for gamma For alpha 22q13.31	*PPAR* family members increase lipid absorption and fat tissue growth. *PPARG* codes for a protein that promotes adipocyte production and development. *PPARα* controls genes that are involved in fatty acid catabolism and is found in active metabolic tissues such as the skeletal muscles, heart, liver, and brown fat.	*PPARα* mutations cause excessive circulating fatty acid, abnormal accumulation of lipids in the liver and heart, resulting in obesity. *PPARG* knockout mice lack adipose tissue, indicating that PPARG is a key regulator of adipocyte development.	(35,73,74 ,75)
NEGR1/rs2815752	Neuronal Growth Regulator 1	1p31.1	NEGR1 gene regulates energy balance and thus body mass index in the hypothalamus.	Causes reduced NEGR1 expression in the periventricular hypothalamus, which results in weight gain, likely due to increased food intake. The gene has been linked to Niemann-Pick Disease Type C (NPC2), a rare genetic disease characterized by mal-absorption of cholesterol and lipids in the cells. This results in an inappropriate buildup of these substances in numerous tissues, including brain tissue.	(36,76, 77)
MTCH2* or *MIMP/rs1064608	Mitochondrial Carrier 2	11p11.2	It regulates mitochondrial metabolism and related cell death.	Overexpression inhibits fatty acid or lipid metabolism, leading to lipid accumulation. However, loss of function increases energy utilization and protects against diet-induced obesity.	(78,79, 80)
KCTD15/rs17782313, rs11084753*, and *rs29941	Potassium channel tetramerization domain containing 15	19q13.11	*KCTD15* regulates adipocyte differentiation.	Loss of function causes leptin deficiency and disruption of adipogenesis.	(81)
FAIM2/rs7138803* and *rs7132908	Fas apoptotic inhibitory molecule 2	12q13.12	It is an anti-apoptotic protein that protects cells from Fas-induced apoptosis. It inhibits caspase-8 activation, which regulates Fas-mediated apoptosis in neurons.	It causes adiposity and an increase in overall body size.	(82,83)
ADRB3/rs4994	Adrenergic β3 receptor	8p11.23	It is an adrenergic receptor found in brown adipose tissue, where it controls thermogenesis and lipolysis to prevent fat accumulation.	Mutations cause lower lipolytic activity, which predisposes to obesity and resistance to weight loss.	(84)
CNR1/rs1049353, rs6454674*, and *rs10485170	Cannabinoid receptor 1	6q15	*CNR1* regulates lipolysis and insulin resistance in adipose tissues.	Causes abnormal lipid homeostasis.	(85,86, 87)

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Gene/Variant	Full name	Locus	Biological function	Pathophysiology	References
SLC6A14/ rs2011162, rs2071877, rs369615885, rs199531433, rs200351649, rs182839907,* and *rs376518536	Solute carrier family 6 member 14	Xq24	It synthesizes a protein that controls appetite and body weight by regulating the availability of tryptophan for serotonin synthesis.	It causes fatty liver and metabolic syndrome, which leads to an increase in food consumption.	(88,89)
KSR2/p.Arg224Trp, p.Asp294Glu, p.Arg253Trp, p.Asp323Glu, p.Ala344Th, p.Ala373Thr, p.His536Tyr, p.Arg525Gln, p.Thr143Thr,* and *p.Arg434Gln	Kinase suppressor of Ras 2	12q24.23	*KSR2* secretes a protein which is involved in a signaling pathway associated with energy homeostasis.	Loss of function disrupts signaling, which impairs cellular fatty acid and glucose oxidation, causing hyperphagia in children, and insulin insensitivity.	(90,91)
CPE/c.76_98del; p.E26RfsX68, rs1946816, rs4481204,* and *Ser202Pro	Carboxypeptidase E	4q32.3	Carboxypeptidase E regulates hunger and glucose metabolism. As a result, it controls human body weight and metabolism.	It causes abnormal energy homeostasis, hypogonadotrophic hypogonadism, and late-onset obesity.	(92)
TUB/ c.1194_1195delAG, p.Arg398Serfs, rs2272382, rs2272383,* and *rs1528133	*TUB* bipartite transcription factor	11p15.4	It is embedded in the hypothalamus and is involved in energy balance.	It increases carbohydrate energy intake, raising blood glucose. It has also been linked with obesity and insulin resistance.	(93,94,95)
RAI1/p.R1089X	Retinoic acid induced 1	17p11.2	*RAI1* gene regulates circadian rhythm and lipid metabolism.	Mutations in the *RAI1* gene cause hypothalamic dysfunction by disrupting *BDNF* expression in the hypothalamus, interfering with leptin-melanocortin transmission, culminating in hyperphagia	(96,97)
CTNNBL1/ rs6020846 rs6013029, rs16986921, rs6020712, rs6020395	Cadherin-associated protein, beta-like 1	20q11.23	*CTNNBL1* produces a protein that is extensively embedded in skeletal muscle and is involved in energy metabolism	It causes overeating, which leads to adiposity and chronic inflammation as white adipose tissue expands	(98,99)

Table 3. Genes/mutations predisposing to syndromic obesity

Gene/Variant	Full name	Locus	Biological function	Pathophysiology	References
CUL4B/ p.R388X, rs121434615, rs121434616, rs786200913, rs797044862,* and *rs869320682	Cullin-4B	Xq24	The gene promotes mitochondrial activity and glycolysis.	Mutations in the gene cause X-linked mental retardation syndrome, which is characterized by central obesity.	(39,100,101)
UBE2A or HR6A/Xq24 deletion, G23R, and R11Q	Ubiquitin Conjugating Enzyme E2 A	Xq24	*UBE2A* attaches to the E3 ligase parkin, which promotes mitochondrial function. This gene aids in DNA damage repair.	It causes X-linked intellectual disability type Nascimento, characterized by seizures and obesity.	(102,103)
ALMS1/ c.3902C > A, p.S1301X, c.6436C > T, and p.R2146X	Alstrom syndrome 1	2p13.1	The *ALMS1* protein resides in most of the body's tissues where it controls body weight and boosts pancreatic functions.	Mutations in this gene cause Alstrom syndrome, characterized by insulin resistance and obesity.	(39,104,105)
TBX3	T-Box transcription factor 3	12q24.21	*TBX3* is embedded in the hypothalamus and controls energy homeostasis.	It predisposes to Ulnary Mammary syndrome, a rare developmental disorder characterized by obesity. Loss of *TBX3* function in the neurons causes obesity in mouse models.	(39,106,107)

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Gene/Variant	Full name	Locus	Biological function	Pathophysiology	References
BDNF/rs6265	Brain-derived neurotrophic factor	11p14.1	This gene resides in the brain, where it boosts the survival of nerve cells. The protein synthesized by the *BDNF* gene regulates eating, drinking, and body weight.	It causes WAGRO syndrome, characterized by childhood-onset obesity and pancreatitis, among others. It is also called 11p deletion syndrome.	(39,108,109)
NIPBL/ A c.6954 + 3A > C* substitution and a *c.5862 + 1delG deletion	Nipped-B-like protein	5p13.2	The *NIPBL* codes for delangin, a protein that is involved in cell development, chromatin structure, and cell communication, particularly between promoters and transcriptional enhancers.	It results in Cornelia de Lange syndrome (CdLS), which is characterized by overweight and obesity, constipation, epilepsy, hearing, and visual problems.	(110,111, 112)
GNAS/ c.585delGACT in exon 8* and *c.344C>TP115 L in exon 5	Guanine nucleotide binding protein, alpha stimulating activity polypeptide	20q13.32	It regulates energy homeostasis and metabolism.	It leads to Albright hereditary osteodystrophy or pseudohypoparathyroidis Type 1, characterized by small stature, hyperphagia and excessive weight gain from childhood.	(39,113,114, 115)
RAI1/rs9907986,rs4925102,* and *c.3440G > A	Retinoic acid-induced 1 gene	17p11.2	*RAI1* is a transcriptional factor involved in cell growth, skeletal muscle development, and lipid and glucose metabolism.	*RAI1* mutations predispose to Smith-Magenis Syndrome, characterized by sleep disturbance, feeding abnormalities, hyperphagia, and childhood-onset abdominal obesity	(116,117, 118).
RBMX/p.V170 I* and *p.R647C	RNA binding motif protein X-linked	Xq26.3	*RBMX* is necessary for the normal development of the brain.	It results in Shashi-X-linked mental retardation, which is characterized by mild intellectual retardation, obesity, and macroorchidism.	(119,120, 121)
CREBBP/c.40 A>G, c.1108C>T, c.1270C>T, c.1984C>T, c.3351_3352d upCC, c.3517C>T, c.3715_3716de lAA, c.4435G>T, c.4445A>G, c.4627G>T, c.4728+1G>A, c.4963delC, c.6043delA*, and *c.6065_6071de lAGCAGGC	CREB binding protein	16p13.3	The *CREBBP* gene regulates cell growth and division.	It predisposes to Rubinstein-Taybi syndrome, characterized by obesity.	(39,122,123, 124)
MKRN3/ZNF1 27	Makorin ring finger protein 3/ Zinc finger protein 127	15q11.2	*MKRN3* is expressed in the hypothalamus and functions as a putative E3-ubiquitin ligase.	It triggers Prader-Willi Syndrome. Affected individuals exhibit hypothalamic dysfunction characterized by developmental delay, hyperphagia, and childhood-onset obesity.	(39,125,126)
MAGEL2/SNR N	MAGE family member L2/ Small Nuclear Ribonucleoprotein Polypeptide N	15q11.2	*MAGEL2* regulates leptin receptor cell surface abundance through ubiquitination pathways.	It leads to Prader-Willi Syndrome, which is characterized by developmental delay and childhood-onset obesity. Mice lacking *MAGEL2* are obese and lack leptin sensitivity in the hypothalamus.	(39,127)
INPP5E	Inositol polyphosphate-5-Phosphatase E	9q34.3	Inositol phosphatases regulate cell signaling and membrane trafficking.	It predisposes to MORM syndrome. Affected people show mental retardation and truncal obesity.	(39,128,129)
EHMT1/ c.2712+1G>A	Euchromatin histone methyltransferase 1	9q34.3	The *EHMT1* codes for euchromatic histone methyltransferase 1, an enzyme which functionally modifies proteins called histones.	It triggers Kleefstra syndrome, characterized by developmental delay, high birth weight, and childhood obesity.	(39,130,131)

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Gene/Variant	Full name	Locus	Biological function	Pathophysiology	References
KMT2D* or *MLL2* or *ALR* or *KABUK1 or KMT2B/ c.8200C > T, c.10582C>G, c.10625T>C, c. 1658G>T, c.10745G >A,* and *c.10744C>T	Histone-lysine N-methyltransferase 2D	12q13.12	The *KMT2D* gene codes for lysine-specific methyltransferase 2D, an enzyme that is embedded in many organs and tissues, where it controls cell growth and division.	It causes Kabuki syndrome, also known as Niikawa-Kuroki syndrome, which is characterized by obesity or overweight in middle childhood or adolescence.	(39,132,133,134,135)
AFF4	AF4/FMR2 Family Member 4	5q31.1	The *AFF4* gene codes for a component of the super elongation complex (SEC). The SEC is a protein complex that is involved in gene transcription during embryonic development. The SEC helps ensure that development occurs normally before birth by resuming transcription of particular genes following pauses that occur naturally during the process.	It causes CHOPS syndrome, which is characterized by several congenital anomalies. The acronym "CHOPS" stands for "cognitive impairment, coarse facial features, heart and lung defects, obesity, short stature, and skeletal abnormalities,"which are all symptoms of the condition.	(39,136, 137).
RAB23/L145X, c.482-1G>A, c.481G>C,* and *c.86dupA,	Ras-related protein Rab-23	6p12.1-p11.2	The *RAB23* gene codes for a protein that is involved in vesicle trafficking, a process that transports proteins and other molecules within cells in sac-like structures known as vesicles. The *RAB23* protein regulates a specific developmental pathway termed the hedgehog signaling pathway, which is important in cell proliferation, cell specialization, and the normal shape of various parts of the body during embryonic development by transporting certain proteins.	It predisposes to Carpenter syndrome-2, a disorder characterized by obesity.	(39,138,139,140,141, 142).
PHF6/p.C45Y, c.999-1001delTGA, c.413C > G,* and *c.1A>G; pM1V	Plant homeodomain finger protein 6	Xq26.2	It codes for a protein with two PHD-type zinc finger domains, suggesting it plays a role in transcriptional regulation in the nucleolus.	Mutations result in Borjeson-Forssman-Lehmann Syndrome, characterized by intellectual disability and obesity.	(39,143,144,145,146, 147).
***BBS1-BBS21 (Variants in BBS 1* and 10 constitute most of the syndrome)**	Bardet-Biedl syndrome 1-21	11q13 (BBS1), 16q21 (BBS2), 3p13-p12 (BBS3), 15q 22.3-q23 (BBS4),2q31 (BBS5), and 20p12 (BBS6), 4q27 (BBS7),14q32.1 (BBS8), 7p14.3 (BBS9),12q21.2 (BBS10)	Many BBS proteins reside in the basal bodies, ciliary axonemes, and pericentriolar regions of cells, where they play a role in intracellular trafficking via microtubule-related transport.	Mutations in the gene cause Bardet-Biedel syndrome (BBS), characterized by obesity and decreased renal function.	(39,148, 149,150, 151)
VPS13B or COH1/ c.3666 + 1G > T , c. 9844 A > T:p.K3282 X, c.5272dupG,* and *c.62T>G	Vacuolar protein sorting 13 homolog B	8q22.2	This gene produces a protein that is essential for nerve cell growth and development. It may also play a role in adipocyte growth and development, as well as fat storage and distribution throughout the body	It causes Cohen syndrome, which is characterized by obesity and mental deficiency.	(39,152,153,154,155, 156)
ATRX /c.109C>T	Alpha-thalassemia/ mental retardation, X-linked	X21.1	The *ATRX* gene instructs the production of a protein that is required for proper development. Although the *ATRX* protein's exact function is uncertain, research suggest that it aids in the regulation of other genes' expression via chromatin remodeling.	This causes Chudley-Lowry syndrome. It is also known as *ATRX* syndrome, and is characterized by mental impairment, short stature, mild obesity, and hypogonadism.	(39,157, 158)

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