Review Article

Genes Implicated in Obesity and Overweight: Potential Biomarkers of Early Diagnosis

María Luz Gunturiz Albarracín[1*], Ana Yibby Forero[2], Pablo Enrique Chaparro[3]

[1]Project Bank Team, Public Health Research Division, National Institute of Health, Colombia

[2]Nutrition Group, Public Health Research Division, National Institute of Health, Colombia

[3]National Health Observatory Division, National Institute of Health, Colombia

*__Corresponding author:__ María Luz Gunturiz Albarracín, BsC, PhD. Project Bank Team, Public Health Research Division, National Institute of Health, Avenue Street 26 No 51-20 CAN, Bogotá, D.C., Colombia. Tel: +5712207700; +573123600581; Email: mgunturiz@ins.gov.co

Abstract

Obesity is a chronic, complex and multifactorial disease, characterized by excess body fat, positive imbalance between energy intake and energy expenditure. The adverse metabolic effects caused by obesity can increase the risk of type 2 diabetes, many forms of cancer, fatty liver disease, hormonal disorders, hypertension, cardiovascular disease, metabolic syndrome and increased mortality, among others. In children, childhood obesity increases the chances of an earlier adolescence, gynecomastia in children and polycystic ovary syndrome, among other diseases; In addition, obese children and adolescents are more likely to remain obese in adulthood and develop various cardiovascular and metabolic diseases that decrease their quality of life. Several studies of the human genome have led to the identification and characterization of multiple genes that contribute to obesity; however, relatively few studies have allowed the identification of genes or biomarkers involved in obesity and overweight, especially in low and middle income countries. They are used routinely in early diagnosis and as a tool for the management of this condition. In this article, we review different genes that can serve as early diagnostic markers in children and adolescents in countries like Colombia, where there is a high prevalence of overweight and predisposition to obesity from these ages.

Keywords: Biomarkers; Genes; Genetic; Obesity; Overweight

Abbreviations

ACTH	:	Adrenocorticotropin
ACP1	:	Acid Phosphatase 1
ADIPOR1	:	Adiponectin receptor 1
BMI	:	Body Mass Index
CARTPT	:	Cocaine- and Amphetamine-Regulated Transcript Prepropeptide Gene
DM2	:	Diabetes Mellitus type 2
ENPP1	:	Ectonucleotide Pyrophosphatase/Phosphodiesterase 1
FTO	:	Fat Mass and Obesity-Associated Gene

GHR	:	Ghrelin and Obestatin Prepropeptide
GRPR	:	Gastrin Receptor
LEP	:	Leptin
LEPR	:	Leptin Receptor
MACP	:	Anion Transport Proteins Mitochondrial
MC4R	:	Melanocortin 4 Receptor
MC-R	:	The Melanocortin Receptor Ligand
MSH	:	Melanocyte Stimulating Hormones
MYT1L	:	Myelin Transcription Factor 1
NR0B2	:	Nuclear Receptor Subfamily 0 Group B Member 2
PCGR	:	Protein-Coupled G-Receptors
POMC	:	Proopiomelanocortina
PPAR	:	Peroxisome Proliferator-Activated Receptor
PPARGC1β	:	Peroxisome Proliferative Activated Receptor, Gamma, Coactivator 1 beta
PXDN	:	Peroxidasin
SDC3	:	Syndecan-3
SIM1	:	Single-Minded 1
SNPs	:	Single Nucleotide Polymorphisms
TMEM18	:	Transmembrane Protein 18
UCPs	:	Uncoupling Proteins

Introduction

Overweight and obesity prevalence has dramatically increased during the last decade and reached epidemic dimensions. By 2030 it is expected that there will be 2.16 billion overweight individuals with 1.12 billion adults predicted to be clinically obese. With current trends, by 2030, some researchers project that 86.3% of American adults will be overweight ($25 <$ body mass index (BMI) ≤ 30) or obese (BMI > 30) and that overall 51.1% will be obese [1-6].

Obesity is the excessive deposition of adipose tissue resulting of energy imbalance. The changes in food availability and characteristics, as well as the decrease in physical activity during the last decades have favored the energy imbalance causing that energy intake exceeds energy expenditure. This trend has been observed in all age groups across different countries. The response to environmental changes affecting diet and physical activity is widely diverse and certain subjects and populations seem to be more prone to develop obesity and its related comorbidities. In early onset obesity it is important to differentiate between obesity due to rare genetic abnormalities from the common forms. Numerous genetic abnormalities are characterized by obesity. In some cases, single gene mutations can have a very important effect on Body Mass Index (BMI) [7].

Obesity is a multifactorial disease that occurs from the interaction between a genetic predisposition and the presence of certain external factors (caused by both genetic and non-genetic factors) [8,9]. It is characterized by an increase in body weight beyond the needs of the skeletal physical structure, as a result of the excessive accumulation of body fat [9-12]. Usually is defined in adults as a BMI greater than 30 kg/m^2, obesity has become a leading public health concern for both genders, all ages, and all ethnic groups [1].

The relationship between the increase in the obesity index, and the consequent risk of morbidity and mortality associated with it, such as dyslipidemia, hepatic steatosis, ovarian syndrome and hypogonadism, musculoskeletal problems, cholecystitis, cardiovascular diseases, diabetes, pseudotumor cerebri, and certain types of cancers, make obesity an important health problem [13].

Obesity is currently one of the main public health problems in Western countries, so it is important, in addition to promoting good habits, to study and understand its genetic bases, molecular mechanisms and the susceptibility of each person. that will contribute to improve the strategies of prevention and treatment and to diminish the negative impact that this disease exerts on society [14]. Childhood obesity is a serious public health problem associated with the development of several chronic diseases, such as type 2 Diabetes Mellitus (DM2), dyslipidemia, and hypertension (HTA) and the elevated prevalence of this condition is mostly due to inadequate diet and lifestyle, but it is also influenced by genetic factors [15].

Causes of Obesity

Obesity has become a serious health problem worldwide due to its close link with the main causes of morbidity and mortality in countries industrialized and developing [16]. This disease is a complex disorder metabolism that is frequently associated in addition to with DM2 and HTA with coronary heart disease, thrombosis, dyslipidemias, gallstones, hepatic steatosis, sleep apnea, dysfunctions endometrial cancer and cancer, among others [17,18].

The vast majority of cases of obesity are the result of a complex interaction of genetic, hormonal, nutritional, physical activity, environmental, physical and social factors, a condition that increases the risk of various cardiometabolic, pulmonary and psychosocial complications in children, that often continue until adulthood. In addition to those mentioned, the causes of obesity can be the increase in caloric intake, genetic predisposition, sedentary lifestyle and, exceptionally, neurological diseases.On the other hand, pathological obesity represents only a small percentage of these cases, therefore, prevention strategies and early intervention are key to reversing the obesity epidemic [19,20].

Monogenic, Polygenic and Syndromic Obesity

Obesity tends to aggregate in families, its form of inheritance does not correspond to known patterns, and is highly dependent on environmental factors [21-23]. Numerous studies have shown that predisposition to obesity, and their associated conditions are more similar among genetically related individuals than in those not related. The phenotypes associated with obesity have an additive heritability (h2) significant, this parameter being the proportion of the variability of a trait that is attributable to genetic factors. In the case of the Body Mass Index (BMI) the h2 has values from 40 to 70% in different studies in human groups [7,22-24].

The heritability of many other phenotypes associated with adiposity, such as body weight, percentage of body fat, or free mass of fat, circulating concentrations of adipocytokines, and other markers of inflammation, has been estimated in different populations and different age groups, with consistent observations of the contribution of genetic factors to the variation of these traits. Obesity is phenotypically expressed in a very heterogeneous way, with mechanisms very diverse molecular. The Scientific evidence indicates that genetic factors are involved in the development of obesity in approximately 30% to 40% of cases, not just in the forms monogenic, but also in common obesity [18,25,26].

Although in recent years has increased the study of genetic factors, there is still ignorance of the genetic control of common forms of obesity [18,25,26]. Currently, the contribution of genetic factors to this pathology can be summarized in:

- Monogenic obesity is caused by a single dysfunctional gene (simple mutations) and represents a small number of severe cases that appear in childhood and are accompanied by different neuroendocrine disorders, development and behavior. It is severe and rao character and is presented from the beginning of childhood. Monogenic obesity can be syndromic or non-syndromic. This ultim is produced by alterations of simple genes, but unlike the syndromic it does not produce characteristic phenotypes (are included mutations in genes of the leptin-melanocortin pathway which plays a key role in the hypothalamic control of food intake).

- Some genetic variants of high risk in common obesity; that is, polygenic obesity, in which, each susceptibility gene would only have a small effect on body weight and its contribution would be more significant when predisposing environmental factors are present for its phenotypic expression, as excessive feeding and reduction of physical activity.

- There are approximately 30 syndromes (syndromic obesity) that present obesity as part of the representation clinical and that are generally accompanied by mental retardation, dysmorphisms and other characteristics. Among the best characterized forms, are: Prader Willi syndromes, Bardet-Biedl, Albrigt bereditary osteodystrophy, Adler, Fragile X syndrome, Borjeson-Eorssman-Lebman, Coben, among others. Some of these syndromes are associated with chromosomal abnormalities, and others are monogenic forms with pleiotropic effects. Determine the origin of obesity in children with these syndromes, it is difficult because it is not possible to control all the factors surrounding them [7,27-29]. However, at least four of these syndromes are accompanied by severe hyperphagia and other signs of hypothalamic dysfunction, suggesting an origin at the level of the central nervous system, making it easier to diagnose [7,27-29].

Specifically, Prader-Willi syndrome is a complex genetic condition that affects many parts of the body. In infancy, this disease is characterized by weak muscle tone (hypotonia), feeding difficulties, poor growth, and delayed development. Beginning

in childhood, affected individuals develop an insatiable appetite, which leads to chronic overeating (hyperphagia) and obesity. Some people with Prader-Willi syndrome, particularly those with obesity, also develop type 2 diabetes [30].

Bardet-Biedl syndrome is considered a rare form of obesity and has a prevalence of less than 1/100.000. It is an autosomal recessive form that is frequently associated with central obesity, mental retardation, limb dysmorphia and other abnormalities. This is a heterogeneous syndrome that has been associated with 8 loci and seven of them have been located at the molecular level 18. The genes associated with this syndrome are BBS1 on chromosome Ilql3 and BBS2 on 16q2. In most cases the function of the proteins encoded by these genes is not known [31].

On the other hand, the Cohen syndrome is one of the rare autosomal recessive disorders characterized by nonprogressive mild to severe psychomotor retardation, motor clumsiness, microcephaly, characteristic facial features, childhood hypotonia and joint laxity, progressive retinochoroidal dystrophy, myopia, intermittent isolated neutropenia, and a cheerful disposition. Specific facial features include high-arched or wave-shaped eyelids; long, thick eyelashes; thick eyebrows; prominent root of nose; short philtrum (which is unable to cover the prominent upper central incisors); small or absent lobuli of the ears; thick hair and low hairline; narrow hands and feet; and mild syndactylies (in 50% to 60%) [32,33].

Obesity at an early age is a phenotype common to several monogenic forms of human obesity, and to syndromes caused by chromosomal abnormalities. Of course, these genetic alterations do not explain proliferation of obesity in recent years, however, the study of these forms of obesity has given valuable information on relevant metabolic pathways in the development of this condition [33-35].

Some studies have compared homogenous population groups of different ages and obese and thin. These groups have studied, among others, the energy consumption, the intestinal microbiome, the number of adipocytes, and several genetic markers and it has been shown that the energy consumption is lower in children who become overweight compared to other children. thin children; that the microbiome of the obese contains less Bacteriodes than the thin ones, which suggests that obesity would also have a microbial component, in which case the obese microbiome would have greater capacity to save energy from the diet. Additionally, it has been observed that the number of existing adipocytes of adults is acquired in childhood and adolescence, while in children it remains constant, both in obese and thin, even when they lose weight, changing in childhood and adolescence, and staying constant in adulthood. In this stage of life, neither destroy nor increase [15].

Numerous studies reported that single gene variants cause Mendelian forms of obesity, determined by mutations of major effect in single genes. Rare, non-syndromic forms of obesity are a result of loss-of-function mutations in genes that act on the development and function of the hypothalamus or the leptin-melanocortin pathway. These variants disrupt enzymes and receptors that play a role in energy homeostasis, resulting in severe early-onset obesity and endocrine dysfunctions.

Among the genes involved in the etiology of obesity are they find metabolic genes, genes that code for peptides that control the signals of hunger and satiety, regulatory genes of energy expenditure and genes that regulate the growth and differentiation of adipocytes There are many loci and several genes that have been associated with the predisposition for obesity and thinness, obesity development and classified according to their expression in different stages of this condition, such as in early onset, predisposition to obesity, late onset, severe obesity (morbid). Table 1 shows some of the genes associated with obesity in their different stages of presentation.

Gene	Aliases	Chromosome Location	Stages/ Type of obesity
Proopiomelanocortina	POMC Gene Also known as LPH; MSH; NPP; POC; ACTH; CLIP; OBAIRH	2p23.3	Early onset obesity
Nuclear receptor subfamily 0 group B member 2	NR0B2 gene Also known as SHP; SHP1	1p36.1	

Ghrelin and obestatin prepropeptide	GHRL gene	3p26-p25	Predisposition to obesity
Mitochondrial Uncoupling proteins	UCP1 and UCP3 genes	4q28-q31 and 11q13.4 respectively	
Cocaine- and Amphetamine-Regulated Transcript Prepropeptide	CARTPT gene	5q13.2	
Beta-2-adrenergic receptor	ADRB2 gene	5q31-q32	
Beta-3-adrenergic receptor	ADRB3 gene	8p12	
Ectonucleotide pyrophosphatase/ phosphodiesterase 1	ENPP1 gene	6q22-q23	
Melanocortin-3 and melanocortin-4 receptor antagonist	AGRP gene	16q22	Late-onset obesity
Leptin	LEP gene	7q31.3	Severe (morbid) obesity
Leptin receptor	LEPR gene	1p31	
Peroxisome proliferator-activated receptor	PPARG gene	3p25	
Peroxisome proliferative activated receptor, gamma, coactivator 1 beta	PPARGC1B gene Also known as PERC; ERRL1; PGC1B; PGC-1(beta)	5q32	
Fat mass and obesity-associated	FTO gene	ND	
Single-minded 1	SIM1 gene	6q16.3	
Melanocortin 4 receptor	MC4R gene	18q22	Obesity
Solute carrier organic anion transporter family member 4C1	SLCO4C1 gene Also known as OATPX; OATP-H; OATP-M1; OATP4C1; PRO2176; SLC21A20	5q21	
Syndecan 3	SDC3 gene Also known as SDCN; SYND3	1p35.2	
Adiponectin receptor 1	ADIPOR1 gene Also known as CGI45; PAQR1; ACDCR1; CGI-45; TESBP1A	1q32.1	
Acid phosphatase 1	ACP1 gene Also known as HAAP; LMWPTP; LMW-PTP	2p25.3	
Transmembrane protein 18	TMEM18 gene or lncND gene	2p25.3	
Peroxidasin	PXDN gene Also known as PXN; VPO; MG50; PRG2; ASGD7; COPOA; D2S448; D2S448E	2p25.3	
Myelin transcription factor 1	MYT1L gene Also known as NZF1; MRD39; myT1-L; ZC2H2C2; ZC2HC4B	2p25.3	
Glutamate ionotropic receptor kainate type subunit 1	GRIK1 gene Also known as EAA3; EEA3; GLR5; GLUR5; GluK1; gluR-5	21q21.3	
Gastrin-releasing peptide receptor	GRPR gene Also known as BB2; BB2R	Xp22.2	

Table 1: Some of the genes associated with monogenic obesity in different stages of this pathology.

Genes Associated with Early Onset and Predisposition to Obesity

Proopiomelanocortina (POMC) Gene

Also known as LPH; MSH; NPP; POC; ACTH; CLIP; OBAIRH is located on the short arm of chromosome 2 (2p23.3) encodes the precursor of the adrenocorticotropin sérica, ACTH in the pituitary gland. POMC is regulated by leptin and is cleaved by prohormone-convertases to produce ACTH, the Melanocortin Receptor ligand (MC-R) and alpha, beta and gamma Melanocyte Stimulating Hormones (MSH). The reddish pigmentation of the hair, adrenal insufficiency and obesity are caused by deficiencies in the ligands and the subsequent lack of activation of the MC1 MC2 and MC4 receptors, respectively. In addition to the total deficiency of POMC, some cases of isolated deficiency of beta-MSH, the ligand for MC4-R derived from POMC, have also been described. These individuals have a distinct POMC mutation in the region that codes for beta-MSH. This isolated deficiency of beta-MSH results in a clinical phenotype similar to that observed in MC4-R deficiency (childhood obesity, hyperphagia and increased linear growth) but is not associated with red hair or adrenal insufficiency [36-39]. POMC deficiency is a form of monogenic obesity that causes severe early onset obesity, adrenal insufficiency, red hair and pale skin.

Nuclear Receptor Subfamily 0 Group B Member 2, NR0B2 Gene

Also known as SHP; SHP1 is located on the short arm of chromosome 1 (1p36.1), it codes for a protein that interacts with the retinoid and thyroid receptor hormones, inhibiting its ligand-dependent transcriptional activation. In addition, when it interacts with estrogen receptors its function is inhibited. It has been suggested that the protein represses transactivation mediated by the nuclear hormone receptor through two separate stages, competition with coactivators and the direct effects of its transcriptional repressor function. 18 variations have been identified from this gene [40].

Ghrelin and Obestatin Prepropeptide (GHRL) Gene

Also known as MTLRP is located on the short side of chromosome 3 (3p26-p25), codes for ghrelin-obestatin preproprotein that is cleaved to produce two peptides, ghrelin and obestatin. Ghrelin is a powerful appetite stimulant and plays an important role in energy homeostasis and regulating multiple activities, including hunger, reward perception through the mesolimbic pathway, gastric acid secretion, gastrointestinal motility and secretion of the insulin stimulated by glucose. On the other hand, obestatin regulates the function of adipocytes and the metabolism of glucose. Four mutations, 3 of them without meaning, have been identified in the GHRL gene that increase the predisposition to obesity [10,41-47].

Uncoupling Proteins (UCP1 And 3) Gene

UCP1 is located on the long arm of chromosome 4 (4q28-q31), and encode mitochondrial uncoupling proteins, a member of the family of anion transport proteins mitochondrial (MACP). In general, UCPs are mitochondrial transport proteins that create proton leakage through the inner mitochondrial membrane, therefore decompose the oxidative phosphorylation of ATP synthesis, so that the energy is dissipated as heat [48,49].

On the other hand the UCP3 gene is located on the long arm of chromosome 11 (11q13.4), it codes for mitochondrial uncoupling proteins, from the family of mitochondrial anion transport proteins (MACP). These proteins create proton leakage through the inner mitochondrial membrane, causing the uncoupling of oxidative phosphorylation of ATP synthesis, so that energy dissipates as heat. 9 mutations in the UCP3 gene have been described [50].

Seven mutations in the UCP1 gene and 9 mutations in the UCP3 gene have been described, changes that have been associated with an increased susceptibility to obesity, generally of early onset [48,49].

Cocaine- and Amphetamine-Regulated Transcript Prepropeptide Gene (CARTPT)

Located on the long arm of chromosome 5 (5q13.2), codes for a satiety factor closely associated with the actions of leptin and neuropeptide Y. This anorectic peptide inhibits induced hunger and completely blocks the response of Feeding induced by neuropeptide Y, regulated by leptin in the hypothalamus. In addition, it promotes neuronal development and in vitro survival. Two mutations have been identified in the CARTPT gene, which have been associated with a greater predisposition to obesity, usually of early onset [51].

Beta-2-Adrenergic Receptor (ADRB2) Gene

Located on the long arm of chromosome 5 (5q31-q32), codes for the beta-2-adrenergic receptor that is a member of the superfamily of G-protein coupled receptors and is directly associated with one of its final effectors, class C calcium channel Ca type L (V) 1.2. This receptor-channel complex also contains a G protein, an adenylate cyclase, cAMP-dependent cAMP, and the PP2A phosphatase. The assembly of the signaling complex provides a mechanism that ensures specific and rapid signaling by this receptor coupled to protein G. Six mutations have been described in the ADRB2 gene, which have been associated with an increased susceptibility to obesity, generally from the beginning early [43,52].

Beta-3-Adrenergic Receptor (ADRB3) Gene

Located on the short arm of chromosome 8 (8p12), it codes for a protein that belongs to the family of beta adrenergic receptors,

which mediate the activation induced by catecholamines of adenylate cyclase through the action of proteins G. This receptor is located mainly in adipose tissue and is involved in the regulation of lipolysis and thermogenesis. Two nonsense mutations have been described in the ADRB3 gene, changes associated with a greater predisposition to obesity, generally of early onset [43,52,53].

Ectonucleotide Pyrophosphatase/Phosphodiesterase 1 (ENPP1) Gene

Located on the long arm of chromosome 6 (6q22-q23), codes for a protein called ectonucleotide pyrophosphatase/ phosphodiesterase 1 (ENPP1). This protein helps break down adenosine triphosphate (ATP), especially when it is outside the cell. The ENPP1 protein also plays a role in the control of cell signaling in response to the hormone insulin, through the interaction between a part of the ENPP1 protein, called the SMB2 domain, and the insulin receptor. They have been identified 54 variations in the ENPP1 gene, associated with a greater predisposition to obesity, generally of early onset [54-56].

Genes Implicated in Late-Onset Obesity

Melanocortin-3 and Melanocortin-4 Receptor Antagonist (AGRP) Gene

Located on the long arm of chromosome 16 (16q22), it encodes a melanocortin-3 and melanocortin-4 receptor antagonist that seems to regulate the hypothalamic control of feeding behavior through the melanocortin receptor and / or the regulation of the intracellular calcium, and therefore, plays a role in the homeostasis of body weight. Five mutations in the AGRP gene have been described, associated with late-onset obesity [39,57].

Genes Involved in Severe (Morbid) Obesity: Leptin (LEP) Gene

Located on chromosome 7 (7q31.3), it codes for the protein leptin, a hormone secreted primarily in white adipose tissue, which circulates in the blood in proportion to the fat content to regulate the amount of adipose tissue and the body mass by interacting with certain neuronal receptors that affect appetite and energy homeostasis. To this end, leptin receptors are highly expressed in neurons of the hypothalamus, which act as primary sensors for alterations in energy reserves, controlling food intake and energy expenditure. In this way, leptin regulates these two neuronal populations reciprocally, contributing to the regulation of appetite and energy homeostasis. In addition, leptin is expressed in the male and female reproductive organs, in the mammary glands and in the immune system. Mutations homozygous in it can generate a truncated protein with undetectable concentrations in serum, leading to severe obesity of early onset. The symptoms are heterogeneous, although it is common to observe severe obesity of early onset and hyperphagia and, frequently, also hyperinsulinemia. In this gene,

6 nonsense mutations, 1 splicing mutation, 2 regulatory mutations and 3 small deletions have been described [58-61].

Leptin Receptor (LEPR) Gene

Located on chromosome 1 (1p31), it encodes for the leptin receptor, a membrane protein homologous to the receptor of the family of class 1 cytokines. 3% of those affected by obesity have homozygous mutations in this gene, which cause the loss of all isoforms of the leptin receptor. In addition, heterozygous mutations are also associated with an increase in weight, but for the development of morbid obesity the loss of the two alleles is required, either as a result of a homozygous mutation or compound heterozygous mutations. Certain mutations that affect regions near the transmembrane domain of the leptin receptor can result in a truncated extracellular domain that it could act as a spurious binding protein, resulting in elevated levels of leptin. However, genetic alterations located in other areas of the LEPR gene do not usually generate large accumulations of leptin. In this gene, 11 nonsense mutations, 1 cut / splice mutation, 1 small insert, 1 major insert / duplication, and 1 repetition variation have been described [58-61].

In general, the results of leptin deficiency and those of leptin receptor deficiency are similar, observing that affected individuals experience a rapid increase in weight during the first months of life, with excessive accumulations of subcutaneous fat deposited on the trunk. and in the extremities. In line with the severity of obesity, hyperinsulinemia is observed and, in some adults, type 2 diabetes mellitus develops during the third or fourth decade of life. All cases are characterized by intense hyperphagia and may be associated with hypogonadotropic hypogonadism.

Peroxisome Proliferator-Activated Receptor (PPARG) Gene

Located on the short arm of chromosome 3 (3p25), it encodes the PPARgamma protein, a regulator of adipocyte differentiation and glucose homeostasis that acts as a critical regulator of bowel homeostasis by suppressing proinflammatory-kappa-β responses mediated by NF. Likewise, it plays a role in the regulation of cardiovascular circadian rhythms by regulating the transcription of Arntl / BMAL1 in blood vessels. 20 mutations have been described, 2 deletions and 1 insertion / deletion in the PPARG gene, variations related to severe obesity [62,63].

Peroxisome Proliferative Activated Receptor, Gamma, Coactivator 1 Beta (PPARGC1β) Gene

Also known as PERC; ERRL1; PGC1B; PGC-1(beta), is located on the long arm of chromosome 5 (5q32), it codes for a protein that stimulates the activity of several transcription factors and nuclear receptors, including alpha estrogen receptors, the nuclear respiratory factor 1, and the receptor glucocorticoids. The

encoded protein may be involved in the oxidation of fats, the non-oxidative metabolism of glucose, and the regulation of energy expenditure. Three mutations in this gene related to important obesity have been identified [62,63].

Fat Mass and Obesity-Associated (FTO) Gene

Polymorphisms in this gene are related to individual differences in food intake and energy balance and can also influence skeletal muscle phenotype [64,65]. Multiple Single Nucleotide Polymorphisms (SNPs) occur on the FTO gene that may influence adipogenesis and obesity [66-68]. Since the obesity-associated SNPs are on the intron 1 region of the FTO gene, the mechanisms through which they influence body mass are uncertain. However, it has recently been shown in humans that a T-C SNP at position 53,767,042 on the FTO gene (rs1421085) causes an increase in IRX3 and IRX5 protein expression during early adipocyte differentiation in favor of energy-storing/white adipocytes over energy-dissipating/beige adipocytes. The critical downstream effect of this is increased energy conservation in the form of augmented fat storage [10,64,68,69].

In FTO a great number of additional susceptibility variants have been identified altogether still accounting for a small percentage of the overall risk for obesity [9,55,65,70-72].

Single-Minded 1 (SIM1) Gene

Is a basic helix-loop-helix transcription factor involved in the development and function of the paraventricular nucleus of the hypothalamus, is located on the long arm of chromosome 6 (6q16.3), it encodes a transcription factor that can have pleiotropic effects during embryogenesis and in adults. A deletion and complex rearrangement in the SIM1 gene associated with severe obesity has been identified [73,74].

Other Genes Involved in Obesity

Melanocortin 4 Receptor, MC4R Gene

Located on the long arm of chromosome 18 (18q22), belongs to the superfamily of Protein-Coupled G-Receptors (PCGR). The neuropeptides that act as ligands bind to its central cavity causing a conformational change that induces its activation. Genetic abnormalities in the MC4R gene are the most common genetic alterations in obese individuals. Mutations in this gene give rise to obesity as an isolated trait. 137 variations have been described that cause disturbances in the binding of the ligand and alter the affinity of the receptor agonists against their antagonists, hindering ligand coupling and subsequent signal transduction, so this gene has been implicated in the dominant autonomic obesity [55,58,75].

Solute Carrier Organic Anion Transporter Family Member 4C1 (SLCO4C1) Gene

Also known as OATPX; OATP-H; OATP-M1; OATP4C1;

PRO2176; SLC21A20 is located on the long arm of chromosome 5 (5q21), belongs to the organic anion transporter (OATP) family that are involved in the membrane transport of bile acids, conjugated steroids, thyroid hormone, eicosanoids, peptides, and numerous drugs in many tissues [76]. Specifically, SLCO4C1 is involved, among other functions, in the transport of thyroid hormones that have been linked in numerous occasions with weight variations, being hypothyroidism a frequent cause of overweight [77,78].

Syndecan 3, SDC3 Gene

Also known as SDCN; SYND3 is located on the short arm of chromosome 1 (1p35.2), it codes for a protein that belongs to the proteoglycan family "sindican" that could play a role in the organization of the cell form by affecting the actin cytoskeleton, possibly by transferring signals from the surface of the cell in a carbohydrate-dependent mechanism. Two nonsense mutations in the SDC3 gene that have been associated with obesity have been described [79-82].

Adiponectin Receptor 1 (ADIPOR1) Gene

Located on chromosome 1 (1q32.1), it receptor regulates several physiological aspects, including lipid metabolism and is overexpressed in peripheral white cells of obese children. Has also been reported that higher levels of receptor expression are associated with insulin resistance, which could be a compensatory mechanism to mitigate the effects of decreased adiponectin levels [10,83-85].

Acid Phosphatase 1, (ACP1) Gene

Also known as HAAP, LMW-PTP, LMWPTP is located on chromosome 2 (2p25.3) and expressed in adipocytes. Polymorphisms in this gene have been associated with severe obesity and with total cholesterol and triglyceride levels [86,87]. There is an overall positive association between obesity and low activity of ACP1 suggesting that the heterozygous loss of this gene could contribute to the obesity observed in your patients [55,87-90].

Transmembrane Protein 18 (TMEM18) Gene or lncND Gene

Located on chromosome 2 (2p25.3) and expressed in all brain sites, including the hypothalamus. Genome-wide association studies by the GIANT consortium have shown a direct and significant association between an single-nucleotide polymorphism, SNP near the TMEM18 gene and obesity (BMI and weight) [88,91]. Almen et al. [92] reported the involvement of TMEM18 in adult and childhood obesity and DM2, nevertheless, the role of haploinsufficiency for TMEM18 is still debated [93].

Furthermore, peroxidasin (PXDN) and MYT1L genes are located in the smallest region of overlap when looking at the

common deleted genes in obese patients with distal or interstitial deletion. PXDN also known as PXN; VPO; MG50; PRG2; ASGD7; COPOA; D2S448; D2S448E is located on the short arm of chromosome 2 (2p25.3) encodes for a heme-containing peroxidase enzyme, that is secreted into the extracellular matrix and is involved in extracellular matrix formation and may function in the physiological and pathological fibrogenic response in fibrotic kidney [94]. The function of the PXDN gene is not clearly defined in humans, but mutations in this gene cause corneal opacification and other ocular anomalies, and also microphthalmia and anterior segment dysgenesis.

On the other hand, Myelin transcription factor 1, MYT1L also known as NZF1; MRD39; myT1-L; ZC2H2C2; ZC2HC4B is located on the short arm of chromosome 2 (2p25.3), has not yet been described as candidate gene in obesity but in sixsome patients are deleted for MYT1L and show hyperphagia [95]. This gene encodes a member of the zinc finger superfamily of transcription factors whose expression, thus far, has been found only in neuronal tissues; the encoded protein belongs to a novel class of cystein-cystein-histidine-cystein zinc finger proteins that function in the developing mammalian central nervous system. Forced expression of this gene in combination with the basic helix-loop-helix transcription factor NeuroD1 and the transcription factors POU class 3 homeobox 2 and achaete-scute family basic helix-loop-helix transcription factor 1 can convert fetal and postnatal human fibroblasts into induced neuronal cells, which are able to generate action potentials. Mutations in this gene have been associated with an autosomal dominant form of cognitive disability and with autism spectrum disorder, in addition to those mentioned above [93,96,97].

Finally, several of the genes studied have interrelated functions with the regulation of appetite, the sensation of satiety and hormonal processes, among them the Glutamate receptors are the predominant excitatory neurotransmitter receptors in the mammalian brain and are activated in a variety of normal neurophysiologic processes. The GRIK1 and GRM7 genes are members of this family, which have various roles in the physiology of the central nervous system, one of them the regulation of energy balance and intake. GRIK1 also known as EAA3; EEA3; GLR5; GLUR5; GluK1; gluR-5, located on the long arm of chromosome 21 (21q21.3), his gene product belongs to the kainate family of glutamate receptors, which are composed of four subunits and function as ligand-activated ion channels and a mutation in this gene has been associated with reduction of body mass index in heavy drinkers [14,98].

In studies with mice, it has been seen that the absence of another glutamate receptor of the same family (mGLUR5) leads to a considerable decrease in weight. On the other hand, GRPR is the gene that gives rise to the gastrin-releasing peptide receptor,

a hormone responsible for facilitating digestion in the stomach and promote the sensation of fullness and whose malfunction can cause difficulties to feel satiated and, consequently, cause a greater eating of food [14,62,63,99].

Conclusion

The cases of obesity derived from chromosomal alterations or monogenic conditions in humans represent a very small proportion of the cases of obesity and overweight. On the other hand, to make an adequate diagnosis and rule out genetic anomalies associated with obesity at early ages, it is necessary to study other characteristics, such as developmental delay, dysmorphisms, etc.

Common obesity and the phenotypes related to it have a significant genetic component and there is ample evidence of the influence of multiple genes on the development of this disease. The study of the genetics of obesity has shown that some of the most likely mechanisms that predispose to its development are found in the pathways that regulate appetite and energy expenditure; however, there is no genetic variant that is consistently associated with the common obesity risk. The identification of the genes involved or associated with obesity and overweight is relevant to the understanding of the pathophysiology of these conditions and allows the establishment of early diagnosis biomarkers that in the future contribute to improve the prevention and proper management of obesity in children and adolescents.

Acknowledgments

References

1. Flegal KM, Carroll MD, Ogden CL, Curtin LR (2010) Prevalence and trends in obesity among US adults, 1999-2008. JAMA 303: 235-241.

2. Wang YF, Beydoun MA, Liang L, Caballero B, Kumanyika SK (2008) Will all Americans become overweight or obese? estimating the progression and cost of the US obesity epidemic. Obesity (Silver Spring) 16: 2323-2330.

3. Kelly T, Yang W, Chen CS, Reynolds K, He J (2008) Global burden of obesity in 2005 and projections to 2030. Int J Obesity 32: 1431-1437.

4. OMS (2016) Obesidad y sobrepeso. Nota Descriptiva N° 311.

5. World Health Organization (2006) WHO Child Growth Standards. Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age. Methods and development. Department of Nutrition for Health and Development.

6. WHO (2014) Global Nutrition Targets 2025: Stunting Policy Brief (WHO/NMH/NHD/14.3). World Health Organization, Geneva.

7. Tejero ME (2008) Genética de la obesidad. Bol Med Hosp Infant Méx 65: 441-450.

8. Böttcher Y, Körner A, Kovacs P, Kiess W (2012) Obesity genes: impli-

cation in childhood obesity. Pediatrics and Child Health 22: 31-36.

9. O'Rahilly S (2009) Human genetics illuminates the paths to metabolic disease. Nature 462: 307-314.

10. Ulloa-Martínez M, Burguete-García AI, Murugesan S, Hoyo-Vadillo C, Cruz-Lopez M, et al. (2016) Expression of candidate genes associated with obesity in peripheral white blood cells of Mexican children. Arch Med Sci 12: 968-976.

11. Herrera BM, Lindgren CM (2010) The genetics of obesity. Curr Diab Rep 10: 498-505.

12. Zhu J, Su X, Li G, Chen J, Tang B, et al. (2014) The incidence of acute myocardial infarction in relation to overweight and obesity: a meta-analysis. Arch Med Sci 10: 855-862.

13. https://www.ivami.com/en/genetic-testing-human-gene-mutations-diseases-neoplasias-and-pharmacogenetics/4224-genetic-testing-obesity-obesity-genes-nr0b2-pomc-ghrl-ucp1-cartpt-adrb2-enpp1-i-pc1-i-adrb3-agrp-lep-lepr-pparg-sim1-ucp3-mc4r-sdc3-and-ppargc1b

14. Serra-Juhé C, Martos-Moreno GÁ, Bou de Pieri F, Flores R, González JR, et al. (2017) Novel genes involved in severe early-onset obesity revealed by rare copy number and sequence variants. PLoS Genet 13: e1006657.

15. Da Fonseca ACP, Mastronardi C, Johar A, Arcos-Burgos M, Paz-Filho G (2017) Genetics of non-syndromic childhood obesity and the use of high-throughput DNA sequencing technologies. J Diabetes Complications 31: 1549-1561.

16. Pucarin-Cvetković J, Mustajbegović J, Jelinić JD, Senta A, Nola IA, et al. (2006) Body mass index and nutrition as determinants of health and disease in population of Croatian Adriatic islands. Croat Med J 47: 619-626.

17. Cao Y (2007) Angiogenesis modulates adipogenesis and obesity. J Clin Invest 117: 2362-2368.

18. Soca PEM, Cruz LA, Marrero MM, Mosqueda Batista L, Pérez López LM (2009) Clasificación de obesidad monogénica. Medical Scientific Mail of Holguín 13.

19. Gurnani M, Birken C, Hamilton J (2015) Childhood Obesity: Causes, Consequences, and Management. Pediatr Clin North Am 62: 821-840.

20. Williams EP, Mesidor M, Winters K, Dubbert PM, Wyatt SB (2015) Overweight and Obesity: Prevalence, Consequences, and Causes of a Growing Public Health Problem. Curr Obes Rep 4: 363-370.

21. Hill JO, Peters JC (1998) Environmental contributions to the obesity epidemic. Science 280: 1371-1374.

22. Cummings DE, Schwartz MW (2003) Genetic and pathophysiology of human obesity. Ann Rev Med 54: 453-471.

23. Güngör NK (2014) Overweight and obesity in children and adolescents. J Clin Res Pediatr Endocrinol 6: 129-143.

24. Loos RJ, Bouchard C (2003) Obesity -is it a genetic disorder? J Intern Med 254: 401-425.

25. Clément K (2006) Genetics of human obesity. C R Biol 329: 608-622.

26. López-Alarcón MG, Rodríguez-Cruz M (2008) Epidemiología y genética del sobrepeso y la obesidad. Perspectiva de México en el contexto mundial. Bol Med Hosp Infant Méx 65: 421-430.

27. Bell CG, Walley AJ, Froguel P (2005) The genetics of human obesity. Nat Rev Genet 6: 221-234.

28. Chung WK, Leibel RL (2005) Molecular physiology of syndromic obesities in humans. Trends Endocrinol Metab 16: 267-272.

29. Warden CH, Fisler JS (2008) Gene-nutrient and gene-physical activity summary--genetics viewpoint. Obesity (Silver Spring) 16: S55-S59.

30. Genetics Home Reference (2018) Prader-Willi syndrome. U.S. Department of Health & Human Services.

31. Parakh R Md, Nairy DM Md (2016) Bardet-Biedl Syndrome with End Stage Renal Disease. Iran J Med Sci 41: 539-542.

32. (2018) E Cohen Syndrome.

33. Farooqi IS, O'Rahilly S (2016) Cohen Syndrome. In: Endocrinology: Adult and Pediatric (Seventh Edition).

34. Bastarrachea R, Kent JW, Williams JT, Cai G, Cole SA, et al. (2006) The genetic contribution to obesity. In: Overweight and the metabolic syndrome: from bench to bedside. Bray GA, Ryan DH (Editors). Springer.

35. Farooqi S (2007) Insights from the genetics of severe childhood obesity. Horm Res 68: 5-7.

36. Hilado MA, Randhawa RS (2018) A novel mutation in the proopiomelanocortin (POMC) gene of a Hispanic child: metformin treatment shows a beneficial impact on the body mass index. J Pediatr Endocrinol Metab 31: 815-819.

37. Rodrigues KCDC, Pereira RM, de Campos TDP, de Moura RF, da Silva ASR, et al. (2018) The Role of Physical Exercise to Improve the Browning of White Adipose Tissue via POMC Neurons. Front Cell Neurosci 12: 88.

38. da Silva AI, Braz GRF, Silva SCA, Pedroza AADS, de Lima-Júnior NC, et al. (2019) Body composition, biochemical, behavioral and molecular alterations in overfed rats after chronic exposure to SSRI. Behav Brain Res 356: 62-70.

39. Mountjoy KG (2015) Pro-Opiomelanocortin (POMC) Neurones, POMC-Derived Peptides, Melanocortin Receptors and Obesity: How Understanding of this System has Changed Over the Last Decade. J Neuroendocrinol 27: 406-418.

40. Vega A, Martinot E, Baptissart M, De Haze A, Saru JP, et al. (2015) Identification of the link between the hypothalamo-pituitary axis and the testicular orphan nuclear receptor NR0B2 in adult male mice. Endocrinology 156: 660-669.

41. Ghalandari H, Hosseini-Esfahani F, Mirmiran P (2015) The Association of Polymorphisms in Leptin/Leptin Receptor Genes and Ghrelin/Ghrelin Receptor Genes with Overweight/Obesity and the Related Metabolic Disturbances: A Review. Int J Endocrinol Metab 13: e19073.

42. Luperini BC, Almeida DC, Porto MP, Marcondes JP, Prado RP, et al. (2015) Gene polymorphisms and increased DNA damage in morbidly obese women. Mutat Res 776: 111-117.

43. Saliba LF, Reis RS, Brownson RC, Hino AA, Tureck LV, et al. (2014) Obesity-related gene ADRB2, ADRB3 and GHRL polymorphisms and the response to a weight loss diet intervention in adult women. Genet Mol Biol 37: 15-22.

44. Ovsyannikova IG, White SJ, Larrabee BR, Grill DE, Jacobson RM, et al. (2014) Leptin and leptin-related gene polymorphisms, obesity, and influenza A/H1N1 vaccine-induced immune responses in older individuals. Vaccine 32: 881-887.

45. Zhuang L, Li M, Yu C, Li C, Zhao M, et al. (2014) The Leu72Met polymorphism of the GHRL gene prevents the development of diabetic nephropathy in Chinese patients with type 2 diabetes mellitus. Mol Cell Biochem 387: 19-25.

46. Li P, Tiwari HK, Lin WY, Allison DB, Chung WK, et al. (2014) Genetic association analysis of 30 genes related to obesity in a European American population. Int J Obes (Lond) 38: 724-729.

47. Scerif M, Goldstone AP, Korbonits M (2011) Ghrelin in obesity and endocrine diseases. Mol Cell Endocrinol 340: 15-25.

48. Lee KH, Chai VY, Kanachamy SS, Say YH (2015) Association of UCP1 -3826A/G and UCP3 -55C/T gene polymorphisms with obesity and its related traits among multi-ethnic Malaysians. Ethn Dis 25: 65-71.

49. Brondani LA, Assmann TS, Duarte GC, Gross JL, Canani LH, et al. (2012) The role of the uncoupling protein 1 (UCP1) on the development of obesity and type 2 diabetes mellitus. Arq Bras Endocrinol Metabol 56: 215-225.

50. Musa CV, Mancini A, Alfieri A, Labruna G, Valerio G, et al. (2012) Four novel UCP3 gene variants associated with childhood obesity: effect on fatty acid oxidation and on prevention of triglyceride storage. Int J Obes (Lond) 36: 207-217.

51. Lisa Y, Sook HF, Yee HS (2012) Association of the Cocaine- and Amphetamine-Regulated Transcript Prepropeptide Gene (CARTPT) rs2239670 Variant with Obesity among Kampar Health Clinic Patrons, Malaysia. Malays J Med Sci 19: 43-51.

52. Szendrei B, González-Lamuño D, Amigo T, Wang G, Pitsiladis Y, et al. (2016) Influence of ADRB2 Gln27Glu and ADRB3 Trp64Arg polymorphisms on body weight and body composition changes after a controlled weight-loss intervention. Appl Physiol Nutr Metab 41: 307-314.

53. Daghestani M, Daghestani M, Daghistani M, Eldali A, Hassan ZK, et al. (2018) ADRB3 polymorphism rs4994 (Trp64Arg) associates significantly with bodyweight elevation and dyslipidaemias in Saudis but not rs1801253 (Arg389Gly) polymorphism in ARDB1. Lipids Health Dis 17: 58.

54. Meyre D, Bouatia-Naji N, Tounian A, Samson C, Lecoeur C, et al. (2005) Variants of ENPP1 are associated with childhood and adult obesity and increase the risk of glucose intolerance and type 2 diabetes. Nat Genet 37: 863-867.

55. Mejía-Benítez A, Klünder-Klünder M, Yengo L, Meyre D, Aradillas C, et al. (2013) Analysis of the contribution of FTO, NPC1, ENPP1, NEGR1, GNPDA2 and MC4R genes to obesity in Mexican children. BMC Med Genet 14: 21.

56. Hsiao TJ, Lin E (2016) The ENPP1 K121Q polymorphism is associated with type 2 diabetes and related metabolic phenotypes in a Taiwanese population. Mol Cell Endocrinol 433: 20-25.

57. Dietrich MO, Liu ZW, Horvath TL (2013) Mitochondrial dynamics controlled by mitofusins regulate Agrp neuronal activity and diet-induced obesity. Cell 155: 188-199.

58. Saeed S, Bonnefond A, Manzoor J, Shabbir F, Ayesha H, et al. (2015) Genetic variants in LEP, LEPR, and MC4R explain 30% of severe obesity in children from a consanguineous population. Obesity (Silver Spring) 23: 1687-1695.

59. Jiang Y, Wilk JB, Borecki I, Williamson S, DeStefano AL, et al. (2004) Common variants in the 5' region of the leptin gene are associated with body mass index in men from the National Heart, Lung, and Blood Institute Family Heart Study. Am J Hum Genet 75: 220-230.

60. Roth H, Korn T, Rosenkranz K, Hinney A, Ziegler A, et al. (1998) Transmission disequilibrium and sequence variants at the leptin receptor gene in extremely obese German children and adolescents. Hum Genet 103: 540-546.

61. Morris DL, Rui LY (2009) Recent advances in understanding leptin signaling and leptin resistance. Am J Physiol Endocrinol Metab 297: E1247-E1259.

62. Huang J, Jia Y, Fu T, Viswakarma N, Bai L, et al. (2012) Sustained activation of PPARα by endogenous ligands increases hepatic fatty acid oxidation and prevents obesity in ob/ob mice. FASEB J 26: 628-638.

63. Ridderstrale M, Johansson LE, Rastam L, Lindblad U (2006) Increased risk of obesity associated with the variant allele of the PPARGC1A Gly482Ser polymorphism in physically inactive elderly men. Diabetologia 49: 496-500.

64. Sonestedt E, Gullberg B, Ericson U, Wirfält E, Hedblad B, et al. (2011) Association between fat intake, physical activity and mortality depending on genetic variation in FTO. Int J Obes (Lond) 35: 1041-1049.

65. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, et al. (2007) A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 316: 889-894.

66. Dina C, Meyre D, Gallina S, Durand E, Körner A, et al. (2007) Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet 39: 724-726.

67. Andreasen CH, Stender-Petersen KL, Mogensen MS, Torekov SS, Wegner L, et al. (2008) Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. Diabetes 57: 95-101.

68. Claussnitzer M, Hui CC, Kellis M (2015) FTO Obesity Variant and Adipocyte Browning in Humans. N Engl J Med 373: 895-907.

69. Han Z, Niu T, Chang J, Lei X, Zhao M, et al. (2010) Crystal structure of the FTO protein reveals basis for its substrate specificity. Nature 464: 1205-1209.

70. Villalobos-Comparán M, Teresa Flores-Dorantes M, Teresa Villarreal-Molina M, Rodríguez-Cruz M, García-Ulloa AC, et al. (2008) The FTO gene is associated with adulthood obesity in the Mexican population. Obesity (Silver Spring) 16: 2296-2301.

71. Klöting N, Schleinitz D, Ruschke K, Berndt J, Fasshauer M, et al. (2008) Inverse relationship between obesity and FTO gene expression in visceral adipose tissue in humans. Diabetologia 51: 641-647.

72. Church C, Moir L, McMurray F, Girard C, Banks GT, et al. (2010) Overexpression of Fto leads to increased food intake and results in obesity. Nat Genet 42: 1086-1092.

73. Bonnefond A, Raimondo A, Stutzmann F, Ghoussaini M, Ramachandrappa S, et al. (2013) Loss-of-function mutations in SIM1 contribute to obesity and Prader-Willi-like features. J Clin Invest 123: 3037-3041.

74. Ramachandrappa S, Raimondo A, Cali AM, Keogh JM, Henning E, et al. (2013) Rare variants in single-minded 1 (SIM1) are associated with severe obesity. J Clin Invest 123: 3042-3050.

75. Lee YS, Poh LK, Kek BL, Loke KY (2007) The role of melanocortin 3 receptor gene in childhood obesity. Diabetes 56: 2622-2630.

76. Mikkaichi T, Suzuki T, Tanemoto M, Ito S, Abe T (2004) The organic anion transporter (OATP) family. Drug Metab Pharmacokinet 19: 171-179.

77. Morrison AC, Srinivas SK, Elovitz MA, Puschett JB (2010) Genetic variation in solute carrier genes is associated with preeclampsia. Am J Obstet Gynecol 203: 491.e1-491.e13.

78. Talmud PJ, Drenos F, Shah S, Shah T, Palmen J, et al. (2009) Gene-centric association signals for lipids and apolipoproteins identified via the HumanCVD BeadChip. Am J Hum Genet 85: 628-642.

79. Zheng Q, Zhu J, Shanabrough M, Borok E, Benoit SC, et al. (2010) Enhanced anorexigenic signaling in lean obesity resistant syndecan-3 null mice. Neuroscience 171: 1032-1040.

80. Ha E, Kim MJ, Choi BK, Rho JJ, Oh DJ, et al. (2006) Positive association of obesity with single nucleotide polymorphisms of syndecan 3 in the Korean population. J Clin Endocrinol Metab 91: 5095-5099.

81. Schüring AN, Lutz F, Tüttelmann F, Gromoll J, Kiesel L, et al. (2009) Role of syndecan-3 polymorphisms in obesity and female hyperandrogenism. J Mol Med (Berl) 87: 1241-1250.

82. Strader AD, Reizes O, Woods SC, Benoit SC, Seeley RJ (2004) Mice lacking the syndecan-3 gene are resistant to diet-induced obesity. J Clin Invest 114: 1354-1360.

83. Yamauchi T, Kadowaki T (2008) Physiological and pathophysiological roles of adiponectin and adiponectin receptors in the integrated regulation of metabolic and cardiovascular diseases. Int J Obes (Lond) 32: S13-S18.

84. Rasmussen MS, Lihn AS, Pedersen SB, Bruun JM, Rasmussen M, et al. (2006) Adiponectin receptors in human adipose tissue: effects of obesity, weight loss, and fat depots. Obesity (Silver Spring) 14: 28-35.

85. Akingbemi BT (2013) Adiponectin receptors in energy homeostasis and obesity pathogenesis. Prog Mol Biol Transl Sci 114: 317-342.

86. Paggi A, Borgiani P, Gloria-Bottini F, Russo S, Saponara I, et al. (1991) Further studies on acid phosphatase in obese subjects. Dis Markers 9: 1-7.

87. De Lorenzo A, Di Renzo L, Puja A, Saccucci P, Gloria-Bottini F (2009) A study of acid phosphatase locus 1 in women with high fat content and normal body mass index. Metabolism 58: 351-354.

88. Doco-Fenzy M, Leroy C, Schneider A, Petit F, Delrue MA, et al. (2014) Early-onset obesity and paternal 2pter deletion encompassing the ACP1, TMEM18, and MYT1L genes. Eur J Hum Genet 22: 471-479.

89. Gloria-Bottini F, Bottini N, Bottini E (2006) Effect of ACP1*C on early life viability. Hum Biol 78: 365-369.

90. Bottini N, MacMurray J, Peters W, Rostamkhani M, Comings DE (2002) Association of the acid phosphatase (ACP1) gene with triglyceride levels in obese women. Mol Genet Metab 77: 226-229.

91. Thorleifsson G, Walters GB, Gudbjartsson DF, Steinthorsdottir V, Sulem P, et al. (2009) Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nat Genet 41: 18-24.

92. Almén MS, Jacobsson JA, Shaik JH, Olszewski PK, Cedernaes J, et al. (2010) The obesity gene, TMEM18, is of ancient origin, found in majority of neuronal cells in all major brain regions and associated with obesity in severely obese children. BMC Med Genet 11: 58.

93. Stevens SJ, van Ravenswaaij-Arts CM, Janssen JW, Klein Wassink-Ruiter JS, van Essen AJ, et al. (2011) MYT1L is a candidate gene for intellectual disability in patients with 2p25.3 (2pter) deletions. Am J Med Genet A 155A: 2739-2745.

94. Péterfi Z, Donkó A, Orient A, Sum A, Prókai A, et al. (2009) Peroxidasin is secreted and incorporated into the extracellular matrix of myofibroblasts and fibrotic kidney. Am J Pathol 175: 725-735.

95. Blanchet P, Bebin M, Bruet S, Cooper GM, Thompson ML, et al. (2017) MYT1L mutations cause intellectual disability and variable obesity by dysregulating gene expression and development of the neuroendocrine hypothalamus. PLoS Genet 13: e1006957.

96. Lee Y, Mattai A, Long R, Rapoport JL, Gogtay N, et al. (2012) Microduplications disrupting the MYT1L gene (2p25.3) are associated with schizophrenia. Psychiatr Genet 22: 206-209.

97. Kepa A, Martinez Medina L, Erk S, Srivastava DP, Fernandes A, et al. (2017) Associations of the Intellectual Disability Gene MYT1L with Helix-Loop-Helix Gene Expression, Hippocampus Volume and Hippocampus Activation During Memory Retrieval. Neuropsychopharmacology 42: 2516-2526.

98. Kranzler HR, Feinn R, Gelernter J, Pond T, Covault J (2014) Topiramate's reduction of body mass index in heavy drinkers: lack of moderation by a GRIK1 polymorphism. Exp Clin Psychopharmacol 22: 419-423.

99. Bradbury MJ, Campbell U, Giracello D, Chapman D, King C, et al. (2005) Metabotropic glutamate receptor mGlu5 is a mediator of appetite and energy balance in rats and mice. J Pharmacol Exp Ther 313: 395-402.