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Monogenic, Polygenic and Multifactorial Obesity in Children: Genetic and Environmental Factors

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Abstract

Obesity is a chronic disease that has increased alarmingly in recent years. It is considered a risk factor for the development of diseases such as type 2 diabetes, cardiovascular diseases, dyslipidemia, and some types of cancer. Two genetic profiles have been described: monogenic obesity, in which a single gene is mutated, usually leading to loss-of-function or haploinsufficiency, and polygenic obesity, which involves several polymorphic genes with complex interactions between genes and environmental factors. In the latter case, the frequency of polymorphisms can be very high, depending on the population analyzed. In both cases, the genes of interest are associated with changes in body composition through different mechanisms, including hyperphagia, energy expenditure, adipocyte differentiation and lipolysis. However, most studies have analyzed genes associated with obesity in other populations, and the results are often inconsistent, so it is important to study the context of obesity, such as genetics, biochemical biomarkers and environmental factors. Environmental factors include physical activity, nutritional status, and an intake of foods rich in fats and carbohydrates that favor obesity in children. In addition, several chemical compounds have been described as potential endocrine disruptors that increase BMI and produce obesity, and some biological agents can alter the homeostasis of adipose tissue. In this review, we analyzed the genetic and environmental factors that influence obesity, particularly in children.

Keywords: Obesity; Overweight; Mutation: Polymorphisms; Environment; Children; Biomarkers

Abbreviations

OECD: Organization for Economic Cooperation and Development; BMI: Body Measured Index; LEP: Leptin; LEPR: Leptin Receptor; POMC: Proopiomelanocortin; PCSK1: Prohormone convertase 1/3; MC4R: Melanocortin 4 Receptor; SIM1: Single Minded Homologue 1; GWAS: Genome Wide Association Studies; PPARG: Peroxixome Proliferator-Activated Receptor γ; ADIPOQ: Adiponectin; FTO: Fat-Mass and Obesity Associated Gene; SNP: Single Nucleotide Polymorphism; CED: Chemical Endocrine Disrupters; DDE: Diphenyl-dichloro-Ethylene (DDE); BPA: Bisphenol A

Introduction

Obesity is a chronic disease of diverse etiology. In the genetic context, monogenic obesity is associated with loss-of-function mutations in a single gene. These mutations are very rare and are in some cases unique to a patient or several members of a family; in some populations with high rates of consanguinity, the mutations are more frequent [1]. In polygenic obesity, there is an interaction between several polymorphic genes; in this case, the frequency is greater than 1% and varies by the population analyzed. In this type of obesity, the risk that is attributed to each allele is generally small, but the additive effect of several risk alleles can considerably increase susceptibility to obesity [2]. Multifactorial obesity refers the involvement of other environmental factors, or the obesogenic environment. These factors include: a) physical agents, such as the specific diet of each population, the nutritional status of individuals, and physical activity; b) chemical agents, such as pesticides and other compounds that function as endocrine disrupters and modify signaling pathways, particularly alterations in the leptin/adiponectin pathway, insulin/glucose, fatty acid metabolism, and the hypothalamic-pituitary-thyroid axis; and c) biological agents, such as viruses that may have obesogenic potential and microbiota involved in metabolism and bioavailability of various nutritional components [3,4]. Figure 1 shows the relationship between all factors leading to obesity.

Epidemiology of Obesity in Children

Obesity is a risk factor for the development of chronic non-communicable diseases, such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular diseases, and some types of cancer [5]. It has become a very costly public health problem, and in 2009, it was estimated that the cost in different countries worldwide ranged from 0.7% to 2.8% of national health expenditure [6]. In 2014, the global economic impact of obesity was estimated in the US to be $2.0 trillion or 2.8% of its national health expenditure. Another important consideration is profit losses due to low productivity, disability, or even permanent disability [7].

A report by the Commission on Ending Childhood Obesity (2016) shows that at least 41 million children under age five are overweight or obese, and most of them live in developing or underdeveloped countries [8]. The Organization for Economic Cooperation and Development (OECD) reports that one in six children (under 15 years

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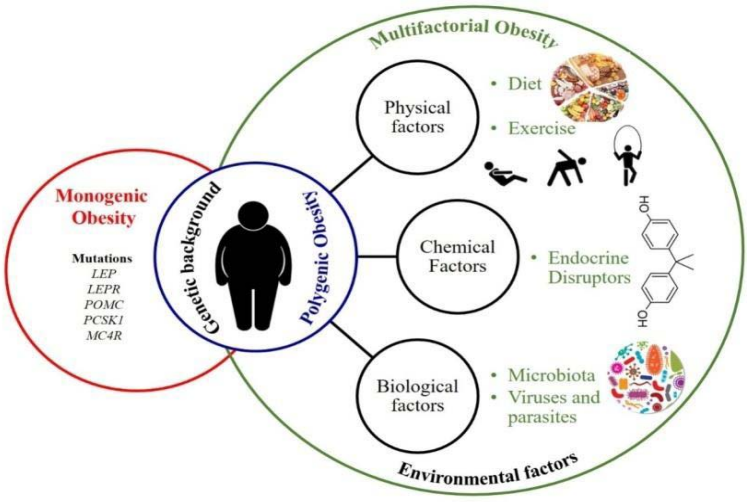

Figure 1: Factors associated and related with obesity in children. In monogenic obesity, a mutation in a single gene is sufficient to develop the disease, children are the most affected. In polygenic obesity, several candidate genes have been associated with obesity; however, studies are inconsistent across populations due to gene - environment interactions. In addition, exist evidence that diet, physical activity, the presence of chemical compounds such as endocrine disruptors and the specific microbiota of everyone may be risk factors for obesity.

old) is overweight or obese. According to OECD projections, by 2030, the prevalence of obesity will increase in the United States, Mexico, and England to 47%, 39%, and 35%, respectively [9]. In a review of studies of the global burden of disease, they evaluated the prevalence of overweight and obesity worldwide between 1980 and 2013 in 1769 studies. They found that the number of overweight or obese people increased from 857 million in 1980 to 2.1 billion in 2013. In the case of children, the prevalence of overweight and obesity increased from 16.55% in 1980 to 23.2% in 2013 in developed countries and followed a similar pattern in developing countries where it increased from 8.25% to 13.15% [10].

Intrinsic Factors Involved in Obesity: Genetic Backgrounds

The terms mutation and polymorphism refer to changes in the DNA sequence; these may be a point change, deletion, or insertion. Although both terms refer to the same event, the mutation is usually associated with the disease and has a very low frequency. Mutations are mapped in familial studies of genetic linkage and therefore may differ between families and have extremely low frequencies; in the literature, they are defined as rare mutations. On the other hand, a polymorphism is a change in the DNA sequence that is associated with natural genetic variability and is highly represented in human populations; at least 1% are carriers. Polymorphisms do not necessarily lead to disease, though they increase susceptibility if associated with other genetic (polygenic model) or environmental factors (multifactorial model). High heritability of obesity has been observed in both monogenic and polygenic-multifactorial contexts, and the most frequent associations in children are described below.

Genes involved in monogenic childhood obesity

Obesity associated with monogenic factors refers to the presence of mutations in a single gene. They are often autosomal loss-of-function mutations that have a dominant or codominant effect, resulting in haploinsufficiency. A mutated copy of the gene is sufficient to develop the phenotype, heterozygous individuals are obese, and in homozygous individuals this condition is more severe. This type of mutation has been reported in children with morbid obesity who generally present with high BMI, compulsive hyperphagia, endocrine abnormalities and in some cases developmental delays. Among the most important genes in this category are *LEP* (Leptin), *LEPR* (Leptin Receptor), *POMC* (Proopiomelanocortin), *PCSK1* (Prohormone convertase 1/3), *MC4R* (Melanocortin 4 receptor) and *SIM1* (Single minded homologue 1).

Leptin (*LEP*)

Leptin is a 16-kD protein that consists of 167 amino acids and is mainly secreted from white adipose tissue. This protein acts on the hypothalamic regions of the brain, which control eating behavior, and plays a critical role in the regulation of body weight by inhibiting food intake and stimulating energy expenditure [11]. In addition, leptin has a variety of other functions, including the regulation of hematopoiesis, angiogenesis, wound healing, and the immune and inflammatory response; therefore, it is a hormone with pleiotropic effects [12]. Defects in leptin production cause early and severe hereditary obesity, an absence of circulating leptin, and hyperphagia. Several mutations have been described in different populations, most frequent in families with high conguinity rates. A consistent change is the mutation N103K; children with this mutation have very low serum leptin levels, suggestive of a functional impact [13-16]. In studies of leptin deficiency, leptin replacement therapy has had a positive impact by preventing weight gain and obesity; treatment with recombinant human leptin (metreleptin) rapidly normalized eating behavior and resulted in weight loss [17].

Leptin receptor (*LEPR*)

Leptin receptor belongs to the glycoprotein 130 (gp130) family of cytokine receptors and has six known isoforms (LEPR a – f); LEPR-b is the longest. Leptin receptor is found in many tissues in several alternatively spliced forms, raising the possibility that leptin exerts effects on many tissues, including the hypothalamus. Leptin acts

Table 1: Genetic factors associated with monogenic obesity in children.

Gene/Function	Mutations	Biological effect or characteristics	Design of the studies	Reference
***LEP*/Leptin** Hormone involved in the regulation of food intake and energy expenditure.	p.L72S, p.N103K, p.R105W, p.H118L, p.S141C, p.W121X c.104_106delTCA, c.135del3bp, c.398delG, c.481_482delCT, c.163C>T.	Deficiency or inefficiency.	Review	[20]
	p.N103K	Change of amino acid. Deficiency in energy regulation pathway.	Screening 457 subjects of Pakistan, 1 child was carrier.	[22]
	1-44del42, c.350G>A (p.C117Y), c.313C>T (p.R105W), c.398delG (p.G133_VfsX14).	42 bp deletion intron 1,missense mutation, truncated protein, missense mutation. Severe obesity.	Cohort of 73 Pakistani children from consanguineous families	[23]
	W121X	Novel homozygous nonsense mutation, leptin deficiency. Severe obesity.	Case report/Egypt	[24]
	c.144del TAC (G1n49Thrfs*23)	Novel homozygous frameshift mutation. Excessive weight gain and hyperphagia.	Case report/ Saudis parents with known consanguinity	[25]
	c.298G>Tp.D100Y	Novel homozygous transversion, leading to a change from aspartic acid to tyrosine at amino acid and high immunoreactive levels of leptin. Severe obesity	Case report/Turkish parents	[26]
***LEPR*/Leptin receptor** The binding of leptin to its receptor triggers hormone-mediated signaling.	1.3 - 58.8 kb del, c.1810T>A (p.C604S), c.2396-1G>T, c.1675G>A (p.W558*)	Homozygous deletion, missense mutation, splice site, nonsense mutation. Severe obesity	Cohort of 73 Pakistani children from consanguineous families	[23]
	Chromosome 1 isodisomy	Frameshift exon 14. Severe obesity with hyperphagia and delayed puberty.	Case report/France	[27]
***POMC*/Promelanocortin** Precursor protein of several active peptides of the melanocortin system.	Heterozygosity for c.-11C>A/p.W84X mutations	Frameshift mutation, truncated preprohormone. Growth acceleration, moderate obesity and recurrent cholestasis.	Case report/Russia	[31]
	Heterozygosity for R236G	Abnormal processing. Obese subject	Cross-sectional/Pakistan	[32]
	Homozygous mutation c.64delA	Deletion, no protein. Rapid weight gain, obesity, and episodes of hypoglycemia	Case report/Turkey	[33]
	Homozygous 5' untranslated region mutation11C>A.	Abolish normal synthesis. Severe obesity, adrenocorticotropic hormone deficiency.	Cases report/USA	[34]
	Homozygous single substitution C202T (p.Gln68X).	Stop codon, no protein. Severe obesity and hypoglycaemia.	Case report/Italy Non-consanguineous family of Egyptian ancestry	[35]
	p.Arg86Term	Stop codon, no protein. Hypocortisolism, hyperphagia, early-onset obesity, skin pigmentation.	Case report/India	[36]
	662A>G (Tyr221Cys), 394C>G (Pro132Ala), 511G>T (Ala171Ser), 706C>G (Arg236Gly).	Change amino acid. BMI increased and family history of obesity.	Screening Case-control/ Norway	[37]
***PCSK1*/Prohormone convertase** Endoprotease that process large precursor proteins into mature bioactive products.	909C>A (Phe303Leu), 989C>T (Ser330Phe), 1405G>A (Val469Ile), 1096-10C>T Splice, 397-10T>C Splice	Change amino acid and spliced variants. BMI increased and family history of obesity.	Screening Case-control/ Norway	[37]
	Novel heterozygous variants (c.1095 þ 1G > A and p.S24C)	Loss enzymatic activity. Extreme obesity, impaired glucose tolerance.	Study on 52 obese children of Obesity Childhood cohort / Germany	[38]
	Missense: c.625G>A (p.G209R), c.772C>A (p.P258T), c.1269C>A(p.N423K), c.1643T>C (p.F548S), c.1777G>A (p.G593R). Nonsense: c.2T>C (p.M1X), c.693C>G (p.Y231X), c.1009C>T (p.Q337X), c.1213C>T (p.R405X). Deletion: c.1349_1352delTGGA (p.V450fsX1) Splice site: c.1095+1T (IVS8þ1G>T) c.1095+1A (IVS8þ1G>A).	Missense mutations in the catalytic domain, nonsense, deletions and splice mutations that cause loss activity. Neonates had severe mal-absorptive diarrhea and failure to thrive.	Screening identified from the UCLA Pediatric Diarrhea Research Database / USA.	[39]
	c.544-2A>G	Skipping of exon 5, the generation of a premature termination codon. Congenital diarrhea and polyuria.	Case report/Turkey	[40]

***MC4R*/Melanocortin 4 receptor** Binding of MC4R to α-MSH leads to stimulation of receptor activity and suppression of food intake, AgRP has opposite effects.				
	Homozygous mutationc.947T>C (p.I316S), c.482T>C (p.M161T)	Deleterious protein with loss of function. Excessive bodyweight and hyperphagia.	Cohort of 73 Pakistani children with severe obesity from consanguineous families.	[23]
	237G>C (Met79Ile), 493C>T (Arg165Trp), 494G>A (Arg165Gln), 926T>A (Leu309Gln), 751A>C (Ile251Leu)	Change amino acid. BMI increased and family history of obesity.	Screening Case-control/ Norway	[37]
	Heterozygosity for S94N, C293R	Missense mutations with loss of function Progressive weight gain, hyperphagia, hyperinsulinemia.	Case report / Canada	[45]
	Homozygous mutation c.216C>A (N72 K)	Inactivation of receptor by aberrant retention in the cytoplasm. Early-onset obesity and hyperphagia	Case report/Netherlands	[46]
***SIM1*/Single minded homologue 1** Transcription factor that controls target genes.	Novel heterozygous variant p.D134N	Predicted pathogenic. Severe obesity	Screening with 4 positive/ Slovak and Moravia	[48]
	Del 6q16.1. Deletion unknow, downstream of SIM1.	Variable developmental delay, intellectual disability, and susceptibility to obesity and hyperphagia.	10 probands-Six families/ UK	[49]
	Del 6q16. Deletion unknow	1.73 to 7.84 Mb. Severe obesity with Prader-Willi-like phenotype	8 patients positive/France	[50]
	c.886A>G (p.R296G), c.925A>G (p.S309G)	Loss of function.Develop delay and obesity	Screening 283 children with 2 positives/France	[51]

through the LEPR. Patients with functional deficiencies in LEPR have phenotypic similarities to LEP-deficient patients; they have rapid weight gain in the first few months of life, with severe hyperphagia and endocrine abnormalities [18]. These patients cannot benefit from recombinant leptin treatment because the receptor does not respond to its ligand; in these cases, serum leptin levels are high [19].

Proopiomelanocortin (*POMC*)

The melanocortin system consists of proopiomelanocortin and its derived peptides β endorphin, α, β, and γ, melanocyte stimulating hormone (MSH), and adrenocorticotropic hormone (ACTH), which interact with different melanocortin receptors. The *POMC* gene is expressed in the hypothalamus, pituitary gland, and several peripheral tissues, including skin. Mutations that cause deficient signals in this pathway involve a wide range of processes, including regulation of body weight, adrenal steroidogenesis, and hair pigmentation [20]. Experimental studies in Labrador retriever dogs [21] and *in vitro* transcription of the *POMC* 11C >A mutation confirmed that loss-of-function causes obesity and predicts adrenal insufficiency [22]. Other mutations have also been described in consanguineous families [23-27].

Proprotein convertase (*PCSK1*)

The proprotein convertase subtilisin kexin type 1 gene encodes proprotein convertase 1/3 (PC1/3), which is a neuroendocrine convertase that belongs to a family of subtilisin-like serine endoproteases and processes large precursor proteins into mature bioactive products [28]. This enzyme is tissue-specific and processes precursors within the regulated neuroendocrine secretory pathway. PC1 activity is essential for the activating cleavage of many peptide hormone precursors implicated in the regulation of food ingestion, glucose homeostasis, and energy homeostasis, such as proopiomelanocortin, proinsulin, proglucagon, and proghrelin. Rare mutations in PCSK1 cause obesity, severe malabsorptive diarrhea, and endocrine abnormalities; even a heterozygous status causes obesity in several population studies. Löffler, et al. [29] reported elevated proinsulin levels and/or impaired glucose tolerance in children, and they found eight known variants and two novel heterozygous variants (c.1095 + 1G >A and p.S24C) by sequencing the *PCSK1* gene. Patients with the new variants presented with extreme obesity and impaired glucose tolerance. Functionally, c.1095 + 1G > A mutation caused the skipping of exon 8 translation and a complete loss of enzymatic activity [30,31]. Similarly, Stijnen, et al. [32] reported common mutations and polymorphic variants associated with endocrinopathies and obesity.

Melanocortin 4 receptor (*MC4R*)

The melanocortin 4 receptor is a G protein-coupled receptor that responds to an agonist, α-melanocyte-stimulating hormone (α-MSH) and to an antagonist/inverse agonist, agouti-related peptide (AgRP), both of which are released by upstream neurons. Binding to α-MSH leads to stimulation of receptor activity and suppression of food intake, whereas AgRP has opposite effects [33]. MCR4 is expressed in neurons of the hypothalamus and is essential for regulation of appetite and energy expenditure; its dysfunction in humans causes hyperphagia, impaired satiety, and obesity. Therefore, homozygous mutations are associated with severe obesity [34].

A study reported a novel human *MC4R* antagonist, Ipsen 17 that acted as a pharmacological chaperone of human MCR4. They tested it against 12 obesity-causing human *MC4R* variants, including S58C, E61K, N62S, I69T, P78 L, C84R, G98R, T162I, R165 W, W174C, C271Y, and P299H; Ipsen 17 was found to be the most universal pharmacological chaperone of MC4R because it can completely rescue the function of mutant receptors [35]. Other mutations have also been reported in several studies [36,37].

Single-minded 1 (*SIM1*)

The *SIM1* gene belongs to the bHLH/PAS (basic helix-loop-helix/Per-Arnt-Sim) family of transcription factors, which is characterized by an N-terminal bHLH domain required for DNA binding and dimerization and a PAS domain that acts as a secondary dimerization interface. Transcriptional control of target genes requires heterodimerization with another transcription factor, aryl-hydrocarbon receptor nuclear translocator, or a homolog prevalent in the central nervous system, ARNT2 [38]. Loss-of-function mutations in *SIM1* cause early-onset obesity and developmental delay, as observed in multiple different populations [39]. The phenotype has

also been reported to be very similar to that of Prader-Willi patients [40-42].

More details about the *LEP, LEPR, POMC, PCSK1, MC4R* and *SIM1* genes, types of mutation, phenotypes or biological effects, and type of studies are described in Table 1.

Genes Involved in Polygenic and Multifactorial Obesity

In polygenic obesity, several genes have been analyzed by different approaches, such as the identification of polymorphisms in candidate genes, Genome Wide Association Studies (GWAS) and exome analysis, and case-control and cohort studies. Each approach has advantages and disadvantages. In the case of candidate gene studies, specific genes that have some biological association with the development of the disease are analyzed; however, the results in each population are generally different, generating inconsistencies that are re-analyzed by meta-analysis, though they are sometimes not comparable by ethnic stratification, sample size, and the methodologies used to identify polymorphisms [43].

In GWAS, the whole genome is analyzed, and the case *vs*. control variants are compared in order to identify the most frequent variants-these are risk genotypes. However, in most cases, the biological relationship of the gene with the disease is not found, or it is a variant in a non-coding region that requires detailed analysis. However, these studies have provided important evidence for the regulation of candidate genes by identifying polymorphic variants affecting promoter regions, enhancers, and alternative splicing sites. The first gene associated with polygenic obesity by GWAS was FTO, which is associated with fat tissue associated with obesity, confirmed in different age groups and populations of different ancestry [44].

More recently, massive sequencing techniques targeting the exome were developed to analyze functional variants that were identified in GWAS and may affect the structure-function of the encoded proteins. A recent GWAS meta-analysis of BMI in 339,224 adults identified 97 loci that accounted for approximately 2.7% of BMI variation. Although most GWAS have focused on polymorphic variants with relatively high frequency, few have been conducted on childhood obesity. Sabo, et al. [45] explored the contributions of both rare and common exonic variants to childhood obesity, and through whole genome analysis, they found a novel obesity gene, *PEX1*, in the VIVA LA FAMILIA cohort of 916 Hispanic children. The authors concluded that *PEX1* rs141510219 was strongly associated with multiple indices of obesity-weight, BMI, waist circumference, fat mass, and trunk fat mass and, despite its rarity, was found to be highly penetrant in the 10 affected children from three pedigrees.

In multifactorial polygenic obesity studies, there are often inconsistencies; results obtained in one population are not replicated in another, which can be attributed to several factors, including the pleiotropic effect of transcription factors that affect the differential expression of several target genes (e.g., *FTO* and *PPARG*) and the levels of circulating hormones that affect endocrine signaling in different pathways (e.g., leptin and insulin). Additionally, several studies have shown that these genes have cis and trans regulation. Trans regulation is generally induced by external factors, such as diet and exposure to various physical, chemical and/or biological agents, and causes disease through the interaction between genetics and environment [46]. Interaction between multiple genes can result in epistasis, where the action of one gene affects another, such that the expected phenotype or association is not observed. Animal models have been used to understand such interactions in complex diseases like obesity [47].

The important characteristics of the most studied polymorphic genes, their biological or biochemical implications, and their association with obesity in children are described below. A more detailed analysis is shown in Table 2.

Peroxixome proliferator-activated receptor γ (*PPARG*)

PPARG is a member of the nuclear receptor superfamily that regulates the transcription of genes involved in cell growth, adipocyte differentiation, cholesterol and fatty acid metabolism, cell survival, ubiquitination, and adaptive thermogenesis. It is activated by lipophilic hormones, dietary fatty acids, and their metabolites [48]. Single Nucleotide Polymorphisms (SNPs), the most common of which is Pro12Ala (rs1801282) in *PPARG2*, have been associated with obesity. These studies show that the Ala variant has lower DNA binding capacity and lower transactivation ability compared to the Pro variant [49]. Some *PPARG* polymorphisms have been associated with obesity and type 2 diabetes. In addition, differences in glucose, cholesterol, triglyceride levels, insulin resistance, and changes in anthropometric measurements have been found, though results between populations are variable [50-56].

Adiponectin (*ADIPOQ*)

The *ADIPOQ* gene encodes the hormone adiponectin, which is produced exclusively in adipose tissue and released into plasma for distribution. Its receptors are mainly found in the liver and skeletal muscle, where it participates in the translocation of the glucose receptor and in the β-oxidation of fatty acids. Its transcription is dependent on PPARG, and the signaling cascade of adiponectin receptors promotes its transcription. Adiponectin levels are negatively associated with obesity and insulin resistance [57].

Several polymorphisms have been reported in non-coding and coding regions, including T-19148C, A-19119C, C-17760T, C-11377G, INS CA-11156, -7950G, C-4120A, 45TG and 276GT. Some of these SNPs have been associated with increased BMI and other anthropometric measures, as well as an increase in the level of adiponectin, the ratio of leptin/adiponectin, total cholesterol, HDL and LDL; therefore, they are considered to be risk genotypes for obesity and type 2 diabetes [58-63].

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

The *FTO* gene is a nuclear protein of the AlkB-related non-heme iron and 2-oxoglutarate-dependent oxygenase superfamily, but the exact physiological function of this gene is not known. Other non-heme iron enzymes function to reverse alkylated DNA and RNA damage by oxidative demethylation [64]. Several polymorphisms in the gene have been associated with obesity in children and adults of different ethnicities; in addition, it has been related to increased BMI and related anthropometric measures, caloric intake, and compulsive hyperphagia behavior [65–70].

Leptin (*LEP*)

Leptin is a lipo-regulating hormone produced primarily in

Table 2: Genetic factors associated with polygenic and multifactorial obesity in children.

Gene/Name	Polymorphism	Biological effect or frequency minor allele	Design studies	Reference
PPARG	Pro12Ala, 1431C>T	Pro12Ala was associated with a lower BMI. Poor COMPX was associated with the *PPARG* T1431 allele.	Prospective, 84 children aged 4 –10 years / Scotland	[59]
	Pro12Ala	Homozygous *PPARG* 12Pro carriers had slightly higher total and LDL-cholesterol levels compared with carriers of 12Ala.	Prospective, 285 children aged 11 – 16 years / Sweden	[60]
	Pro12Ala	*PPARG* 12Ala-carriers presented higherglucose levels than Pro/Pro homozygotes.	Cohort of 325 children followed up from birth to 4 years old / Brazil	[61]
	Pro12Ala	Carriers of the Ala/Alagenotype had increased HOMA-IR compared to individuals with Pro/Pro + Ala/Pro genotypes.	Groups of obese children and a control group / Russian	[62]
	Several SNP in *PPARG*	Interaction between SNP's had a marginal association with dietary fats	Cohort European Diet, Obesity and Genes	[63]
	Pro12Ala	Low levels of triglycerides	Prospective, 215 children aged 6 – 12 years / Mexico	[64]
	Pro12Ala	Association between Pro12Ala genotype and fasting insulin, HOMA-IR and IR in children with high total cholesterol or LDL-cholesterol	Prospective, 1457 children aged 6–14 years / Mexico	[65]
ADIPOQ	G276T	Homozygous *ADIPOQ* 276 T/T had higher total and LDL-cholesterol levels compared with carriers of the 276 G allele.	Prospective, 285 children aged 11 – 16 years / Sweden	[60]
	SNPrs4632532 and rs182052	Effect on HDL cholesterol	Prospective, 215 children aged 6 – 12 years / Mexico	[64]
	SNP rs17300539	A variant was associated with higher adiponectin levels, this SNP may increase the risk for childhood obesity and insulin resistance.	Cohort of children of European origin, 1,852 children	[68]
	SNP rs1501299	Association with obesity	Meta-analysis: 62 reports	[69]
	SNP rs2241766	Association with overall obesity in adults	Case – Control study adult and cohort of children / Mexico	[70]
	-11377 C/G, +45 T/G and +276 G/T	G-G-T haplotype carriers had higher total and LDL cholesterol levels than non-carriers	Prospective, 687 childrenaged 7 – 11 years / Korea	[71]
	-11377C>G	Genotype G/C or G/G associated with obesity and 25% more leptin / adiponectin than C/C genotype	Prospective, 100 children aged 5–10 years	[72]
FTO	SNP rs9939609	Associated with obesity and anthropometric-related measures, total cholesterol and LDL.	Prospective, 215 children aged 6 – 12 years / Mexico	[64]
	SNP rs9939609	No association with BMI in children	Prospective, 1218 children aged 6 – 15 years / Mexico	[70]
	SNPrs9939609, rs17817449	SNP rs9939609 AA genotype was associated with obesity and carriers of rs17817449 SNP had higher values of weight, body mass index, waist and hip circumference, total cholesterol, triglycerides, adiponectin, and fasting glucose.	Prospective, 387 children aged 1 – 18 years / Romania	[74]
	SNP rs9939609	Improvement of measured obesity related after physical intervention	Intervention study: 36 school children / Brazil	[75]
	SNP rs9939609	No association with obesity or overweight	Case – Control study: 153 controls and 195 obese/overweight children / Brazil	[76]
	SNP rs9939609	Associated with obesity and high BMI in children with familiar history of obesity	Prospective, 406 children aged 7 – 17 years / Brazil	[77]
	SNP rs9939609	Association between disorder of corporeality and emotional eating was found only in A-allele carriers	Case – control study, 250 Eating Disorders patients aged 18 – 60 years and 119 controls / Italia	[78]
	SNP rs9939609	*FTO* genotype was associated with greater caloric consumption	Randomized experiment, 200 children aged 9-10 years	[79]
LEP	G-2548	No association with obesity or related parameters	Meta-analysis: 62 reports	[69]
	G-2548A, A19G	Association with weight, height, BMI, WC, HDL cholesterol and serum leptin levels	Case – Control study, 475 subjects aged 10 – 78 / Pakistan	[81]
	G-2548A	Association with BMI, WC, HC, fasting blood glucose and serum leptin levels	Case – control study, 394 subjects aged 5 – 45 years	[82]
	G-2548A, A19G	Genotypes GG(19A>G) and AA (2548G>A) had lowest relative mRNA level and serum leptin concentration	Prospective, 48 children aged 9 – 15 years / Poland	[83]
	G-2548A	Association with variations in leptin levels, BMI and HC, G allele was associated with overweight in girls	Prospective, 880 healthy children aged 12-16 years	[84]
	G-2548A	Association inconclusive with overweight/obesity and the related metabolic disturbances. The results may be due to unidentified gene-environment interactions	Review: 24 studies	[85]
	G-2548A, A19G	No significant differences between *LEP* polymorphisms and serum leptin levels	Prospective cross-sectional 80 healthy Caucasian infants under 6 months of age	[86]

adipose tissue, where it maintains intracellular lipid homeostasis. Upon binding to its receptor, it initiates a signaling cascade to decrease the activity of lipogenic transcription factors, primarily PPARG in the liver and the SRBP-1C sterol regulatory element carrier protein, thus inducing the decrease of lipogenic enzymes [71]. Several polymorphisms have been described in the gene, but the most studied is G-2548A, which has been associated with obesity, low circulating leptin levels (GA genotype, AA), increased BMI, and other anthropometric measures [72-77].

Leptin receptor (*LEPR*)

LEPR is expressed in different tissues and exerts its function in the hypothalamus via the JAK/STAT pathway to promote the

transcription of genes encoding anorexigenic proteins, such as alpha-melanocyte-stimulating hormone (α-MSH), the transcript regulated by cocaine and amphetamine (CART) and corticotropin releasing hormone (CRH), thus initiating leptin-induced satiety signal [71]. Several *LEPR* polymorphisms have been associated with obesity, increased BMI and anthropometric measures, and alterations in leptin, adiponectin, insulin and elevated cholesterol levels [78–85].

Extrinsic Factors Involved in Obesity: Environment Agents

Environmental factors such as physical activity, nutritional status, and an intake of foods rich in fats and carbohydrates favor an obesity in children. In addition, several chemical compounds have been described as potential endocrine disruptors that increase BMI and lead to obesity, and some biological agents alter the homeostasis of adipose tissue. These factors are part of multifactorial obesity.

Diet and physical activity

Through diet, energy is acquired in the form of macronutrients (carbohydrates, proteins, and lipids) and micronutrients (vitamins and minerals). The composition of the diet determines the accumulation of adipose tissue, not only the number of calories that a food contributes but also the type of macronutrient those calories come from; however, controversy remains. A diet rich in fats and lipids, compared with a diet rich in another macronutrient with the same caloric component, stimulates the transcription of genes involved in adipogenesis [86]. This has been observed in randomized clinical trials, where a low-fat diet leads to weight reduction, but the results are variable among cohort studies [87].

A review of different cohort, intervention, or transverse studies on carbohydrates explored the controversy over the intake of beverages with added sugar and the risk of overweight and obesity in childhood, independent of age, sex, ethnicity, and physical activity [88]. In the Avon Longitudinal Study of Parents and Children - Bristol University cohort, it was found that food with added sugar increased energy intake and was associated with overweight and obesity in children and adolescents [89]. On the other hand, high protein intake may also increase the risk of overweight and obesity, as shown in a randomized study in which a low-protein diet reduced the risk of obesity at age 6 [90]; in The Environmental Determinants of Diabetes in the Young Study, energy intake and protein amount increased the risk of obesity in 5.5-year-old children [91].

An important factor in the excessive consumption of macronutrients are ultra-processed foods and fast food, where most of the ingredients are sugars and saturated fats, with little nutritional quality. In Brazil, the Household Budget Survey showed a high risk of obesity (OR= 3.72) in people who had ultra-processed foods in their homes [92]. In Saudi Arabia and China, an increase in overweight and obesity has been observed mainly in regions that have become westernized and have fast food chains [93,94].

Another factor in the development of obesity is energy expenditure, which includes basal metabolic expenditure, the thermal effect of food, and physical activity. The recommended activity for children ages 5 to 18 is a minimum of 60 minutes per day of moderate to vigorous physical activity, and children under 6 years of age should engage in at least 3 hours per day of play and exercise [95]. Various studies in both adults and children and adolescents suggest a minimum of 180 minutes of physical activity per week [96].

Similar results have been reported in children from Sweden [97] and Finland [98], where moderate to vigorous physical activity for one year was associated with an increase in muscle mass and better physical or cardiorespiratory fitness in children. In the International Study of Childhood Obesity, Lifestyle and the Environment and ENERGY project, there was an association between moderate to vigorous physical activity and a lower risk of obesity and lower anthropometric measures independent of other sedentary behavior [99,100] or birth weight [101].

Chemical compounds as endocrine disruptors

In vitro, animal and epidemiological evidence has shown interference of some chemical contaminants with hormone pathways, which may result in endocrine disorders such as obesity and type 1 and type 2 diabetes. Exposure to these Chemical Endocrine Disrupters (CEDs) can be through ingestion, inhalation, injection, transdermal contact, or during gestation. In cell culture and animal models, chemical contaminants such as tributiltin, diethylstilbestrol, 4-nonylphenol, and mono-2 ethylhexylphthalate have been observed to promote adipogenesis through interaction with PPAR, C/EBPβ, aP2, and LPL [102].

Some studies in different cohorts of the European Union found that the CEDs Dichloro-Diphenyl-Dichloro-Ethylene (DDE), bisphenol A (BPA), and phthalates contributed significantly to the development of obesity and type 2 diabetes in early childhood and even in adulthood [103]. In cohort studies from Greece [104], they found an association between exposure to polychlorinated biphenols, as measured by urinary levels of BPA, with higher anthropometric measures, elevated blood pressure, and obesity in children aged 4 years; however, no association was found with prenatal exposure [105]. In two different cohorts of Denmark (Faroe Islands), they found an association between exposure to organochlorines and higher levels of insulin in girls but not in boys [106], and levels of perfluorooctanoic acid and perfluorooctyl sulfonate in maternal serum were associated with obesity in children at 18 months and 5 years of age [107]. In addition to the observed effects of each pollutant, in a cohort of pregnant women in Spain, the concentration of 27 contaminants was measured, and exposure to organochlorines was associated with obesity in children 7 years of age [108]. However, there are inconsistent results in the CHAMACOS cohort of children born in the USA to Mexican mothers who were exposed to dicloro difenil tricloroetano and dietilestilbestrol during pregnancy but not after birth; in this study, there was no association with obesity, but rather with low growth in girls [109].

In the birth cohort Columbia Center for Children's Environmental Health, they found an association between urinary levels of BPA with fat percentage and waist circumference at 7 years of age [110]. In obese children, an inverse correlation was found between urinary levels of BPA and levels of adiponectin; adipocytes extracted from these same children showed a low expression of adiponectin and increased expression of resistin when treated with BPA [111]. However, in the Mount Sinai Children's Environmental Health Study cohort, there was no association between urinary levels of BPA and triclosan and obesity, but 2,5-dichlorophenol was associated with

the highest percentage of fat, while levels of benzophenone-3 were associated with a lower percentage of fat in girls. Most of the evidence indicates an association between exposure to chemical contaminants and an increased risk of obesity, and different results may be due to the genetic structure of populations as well as other environmental factors.

Metallic elements generally exist in the environment and in food. Although the metallic elements in the human body are usually in small quantities, some of them play important biological roles in enzymes, hormones, vitamins, and normal metabolism [112]. Recently, Fan et al. [113], used the National Health and Nutrition Examination Survey data from 2011-2014 to investigate the relationships between serum metallic elements (Cu, Zn, Mn, Pb, Hg, and Se) and BMI, triglyceride, low density lipoprotein cholesterol, cholesterol, insulin, and the homeostasis model assessment of insulin resistance index (HOMA-IR), in 5404 children and adolescent subjects 6-19 years of age. This study reported significant associations between the highest quartile of copper concentrations in blood with obesity status and cholesterol; the highest concentrations of manganese in the blood were associated with obesity in those aged 6-19 years. Moreover, blood mercury and selenium showed positive relationships with cholesterol. Further, a negative association existed between lead and zinc in blood, and obesity was observed.

On the other hand, arsenic is an endocrine disruptor that although has been recognized as a risk factor for type 2 diabetes with [114], it is still uncertain whether arsenic is also an obesogen. The currently available information suggests that arsenic can negatively affect white adipose tissue metabolism resulting a potential obesogen [115].

Biological agents associated with obesity

Another environmental factor that has recently been studied is the human adenovirus type 36 (Ad36). Ad36 induces adipogenesis by increasing: 1) cell membrane glucose receptors (Glut4 and Glut1), leading to an increase in intracellular glucose independent of insulin; 2) enzymatic activity of acetyl Co-A caroboxylase-1 and fatty acid synthase, which converts glucose into fatty acids; and 3) transcription of the PPARγ and C/EBPβ genes, which are involved in the differentiation of stem cells into adipocytes [116-118]. In addition, it diminishes the expression of genes involved in β oxidation [119].

In animals and humans, it has been observed that Ad36 participates in increasing body fat [120-122] in addition to decreasing the effect of diet and exercise on weight loss in children and teenagers. However, it has been associated with lower levels of glucose, total cholesterol, non-esterified fatty acids, and insulin levels [123,124]. Weight loss has been different in the case of adults, where a greater decrease has been reported in those who were seropositive for Ad36 after non-pharmacological treatment [125]. Ad36 infection has been associated with increased levels of leptin [126] and lower levels of adiponectin, as well as increased pro-inflammatory cytokines TNF-α, IL-6, VEGF, and MCP1 [127-129].

In meta-analyses, which included individuals of different nationalities and different methods of antibody determination against Ad36, an increased risk of obesity was found in seropositive subjects, higher in the case of children, but this was not associated with glucose levels, lipid profile, or blood pressure [130-132]. In the Family Heart Study, Ad36 infection was associated with higher adiposity and better glycemic control in a 10-year follow-up study in children who were seropositive for Ad36 [133,134]. However, in the Cardiovascular Risk in Young Finns Study, after 30 years of follow-up, there was no association between being seropositive in childhood and weight gain in adulthood, but a cross-sectional association was found between seropositive individuals and higher prevalence of obesity [135].

Metabolic disorders and obesity are closely linked to lifestyle and diet, and obesity also is associated with microbial dysbiosis, decreased intestinal barrier function, gut inflammation, metabolic endotoxemia, chronic low-grade systemic inflammation, and desensitization of vagal afferent nerves. The gut microbiota is a complex community of bacteria residing in the intestine. Animal models have demonstrated that several factors contribute to and can significantly alter the composition of the gut microbiota, including genetics, the mode of delivery at birth, the method of infant feeding, the use of medications, especially antibiotics, and diet [136]. Recent evidence suggests that altered gut microbiota, together with decreased gut barrier function, allows for the passage of bacterial components or metabolites in obese individuals, leading to the disruption of vagal afferent signaling and consequently resulting in further increases in body weight [137].

In healthy individuals, bacterial translocation is blocked by a single layer of highly specialized intestinal epithelial cells that form a strong barrier lining the gut wall. This structure is responsible for the efficient absorption of nutrients, but in susceptible individuals, for incompletely understood reasons, either defective epithelial barrier function or dysregulated microbial composition or microbial pathogens drive intestinal inflammation [138]. In addition, intestinal microbiota can be modulated by a high-fat diet that induces intestinal dysbiosis through changes in composition and distribution of bacteria [139]. Other studies have reported that prebiotics and probiotics are a safe and effective dietary substance that can therapeutically alter the gut microbiota of the host to improve the health of obese subjects [140]. Finally, several studies have demonstrated the ability of parasites to alter microbial communities within their shared niche, leading to alterations in inflammatory processes. Few reports have addressed how these changes to the microbiome may be a mechanism by which parasites influence not only inflammation but also metabolic states [141].

Conclusion

Obesity is a pandemic that has reached alarming levels and gravely concerns government health systems because of its association with other chronic degenerative diseases that represent high costs in health services. The infant population is especially vulnerable and, although monogenic obesity mainly affects children, its frequency is very low compared with multifactorial polygenic obesity, which involves several polymorphic genes related to obesity and their interaction with environmental factors. These include diet, physical exercise, distribution of nutrients, the role of the microbiome, and the presence of other biological agents such as viruses and parasites; in addition, exposure to chemical contaminants can alter gene expression or nutrient distribution. It is necessary to develop comprehensive strategies that consider several elements (genetic and environmental) that can lead a population to a state of obesity in order to control and prevent their complications.

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