New Thoughts on Pediatric Genetic Obesity: Pathogenesis, Clinical Characteristics and Treatment Approach

Provisional chapter

New Thoughts on Pediatric Genetic Obesity: Pathogenesis, Clinical Characteristics and Treatment Approach

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Abstract

Historically, some genetic syndromes and monogenic forms of obesity have been identified by clinical features and by sequencing candidate genes in patients with severe obesity. The phenotypic expression of genetic factors involved in obesity is variable, thereby allowing to distinguish several clinical pictures of obesity. Monogenic obesity is described as rare and severe early-onset obesity with abnormal feeding behavior and endocrine disorders. Many of the findings emerged from studying families who displayed a classical Mendelian pattern of inheritance. On the contrary, patients with syndromic obesity show a various degree of intellectual disability, different dysmorphic features, and organ-specific abnormalities. But to date, not all involved genes have been identified so far. New diagnostic tools, such as genome-wide studies, array CGH, and whole-exome sequencing, have highlighted more complex models of inheritance, and even more candidate genes were identified. This increase of knowledge may provide insights into the mechanisms involved in the regulation of body weight and finally lead to specific treatments. In these patients, hyperphagia is often a primary phenotypic component. Substantial gaps in understanding the molecular basis of inherited hyperphagia syndromes are present today with a lack of mechanistic targets that can serve as a basis for pharmacologic and behavioral treatments. We have evaluated retrospectively the literature data on weight, body mass index (BMI), clinical features, treatments, and treatment response in pediatric patients with forms of genetic obesity. However, this chapter provides an updated picture of emerging knowledge outlined by the more comprehensive genetic approaches, trying to outline more candidate genes for these forms of genetic obesity. Relevant papers will be identified through systematic searches of the PubMed, EMBASE and Cochrane databases. All published studies in the English language concerning these disorders will be evaluated. Keywords in the literature search will be entered in all combinations. Searches will be augmented by

manually reviewing the reference lists of all original articles and all systematic review articles, with each study being evaluated for inclusion.

Keywords: obesity, children, adolescence, next-generation sequencing, array CGH, pediatrics, diabetes, hyperphagia

1. Introduction

The World Health Organization defines being overweight and obesity as a "clinical condition characterized by an abnormal or excessive fat accumulation that may impair health" [1]. In 2014, an estimated 41 million children under the age of 5 were overweight or obese [1]. Once considered a problem only in high-income countries, being overweight and obesity are now dramatically on the rise in low- and middle-income countries, particularly in urban settings [1].

Therefore, obesity is considered a global epidemic and can cause serious health repercussions. In fact, in addition to causing a significant morbidity and premature mortality and to have psychological and social consequences, it is associated with medical conditions, such as type II diabetes (non-insulin-dependent diabetes mellitus or NIDDM), hypertension, coronary artery disease and many forms of cancer [2].

In order to create the best management programs and to determine novel therapeutic targets, it has become essential to understand the factors causing today's rising epidemic of childhood obesity [3].

Obesity is a complex condition, caused by multiple factors. It is characterized by an altered energy system, determined by the interaction of biological, social, and behavioral factors that cause an increase in food intake and a reduction in energy expenditure [4].

This global epidemic and the increase of its prevalence show that this condition is the result not only of genetic causes, but also of environmental factors (high availability of palatable and energy dense foods) [4]. However, some individuals manage to maintain a healthy body weight in an "obesogenic" environment, but the weight gain may be determined by their genetic susceptibility [4].

Recently, major advances in obesity research emerged concerning the molecular mechanisms contributing to the obese condition. However, several studies and data concerning the genetics and other important factors in the susceptibility risk of developing obesity are became increasingly evident [5]; in fact, available data suggest that 40–77% of the observed variance in human body weight can be accounted for, by inherited factors [6–8].

The strongest risk factor for childhood and adolescent obesity is parental obesity [9]. The risk becomes especially elevated if both parents are obese [10]. On the contrary, the pattern of inheritance of monogenic obesity is different (which may or may not be related to specific syndromes). In fact, they are attributable to a Mendelian model which recognizes a rare

causative mutation to load a single gene that can be expressed in the heterozygous and homozygous state [11].

Patients can be affected by monogenic forms, in which obesity is the predominant feature but it is not associated with malformations, or by syndromic obesity: in the latter case, they show also a pattern of clinical features, including developmental delay, dysmorphic features, and/or other developmental abnormalities [12].

Furthermore, historically, some genetic syndromes and monogenic forms of obesity have been identified by clinical features and by sequencing candidate genes in patients with severe obesity. Many of the initial findings emerged from studying families who displayed a classical Mendelian pattern of inheritance; however, more comprehensive genetic approaches, such as genome-wide studies, array CGH, and next-generation sequencing examinations, have highlighted more complex models of inheritance, and ever more candidate genes were identified [13]. In broad terms, most cases of patients with genetic forms of obesity are oligogenic, determined by interaction between genetic and environmental factors. In these cases, the genetic make-up influences weight and the individual responses to nutrition and physical activity. In addition to this form of obesity, there are others caused by a single gene or it appears to be related to a specific syndrome. Monogenic obesity typically is caused by a single gene mutation with severe obesity as the main symptom; syndromic obesity, on the other hand, has many characteristics, of which obesity is one symptom [13].

The increase of knowledge about the functional and physiological features of these different obesity forms may provide insights into the mechanisms involved in the regulation of body weight and finally lead to specific treatments. In these patients, hyperphagia is frequently a primary phenotypic component. Substantial gaps in understanding the molecular basis of inherited hyperphagia syndromes are present today with a lack of mechanistic targets that can serve as a basis for pharmacologic and behavioral treatments.

The comprehension of the molecular mechanisms of obesity progressed enormously in the last years thanks to the development of faster and more precise genetic screening tools applied in cohort studies or in examinations with focus on subjects and their families.

Several clinical presentations in obesity depend on the genes involved:

1. Monogenic obesity, described as rare and severe early-onset obesity, associated with endocrine disorders. The impact of genetics is high and only little dependent on environmental factors.
2. Syndromic obesity that corresponds to severe obesity associated with additional phenotypes (mental retardation, dysmorphic features, and organ-specific developmental abnormalities). Prader-Willi (PWS) and Bardet-Biedl (BBS) syndromes are the two most frequently linked to obesity, but more than 100 syndromes are now associated with obesity.
3. Oligogenic obesity, characterized by a variable severity, partly dependent on environmental factors and the absence of a specific phenotype. This type of obesity is responsible for 2–3% in adults and children.

Rare genetic forms of obesity are important to be detected clinically because it allows to progress in understanding the physiopathology of obesity. On the other hand, there is a specific management of these forms of obesity provided by specialized and multidisciplinary teams.

2. Monogenic obesity

A "monogene" is by textbook definition, a gene with a strong effect on the phenotype (Mendelian traits or Mendelian—single gene conditions), giving rise to a one-on-one relationship between genotype and phenotype.

So, monogenic and not syndromic obesity is caused by a single mutation of a gene.

This form of obesity occurs in infancy and is often associated with additional behavior, developmental or endocrinological disabilities, such as hyperphagia and hypogonadism; however, significant developmental delays are not visible, and the obesity is often not associated with other clinical manifestations [3, 6, 8, 13–17].

The types of monogenic obesity are summarized in **Table 1** [10–12, 18].

Monogenic obesity	Gene name	Main distinguishing features in addition to obesity
LEP deficiency	*LEP*	Hypogonadism, absent or delayed puberty, frequent infections, undetectable serum leptin
LEPR deficiency	*LEPR*	Hypogonadism, absent or delayed puberty
SH2B2 deficiency	*SH2B1*	Severe insulin resistance and disproportionate to degree of obesity; in rare cases presence of developmental delay
POMC deficiency	*POMC*	Hypogonadism, absent or delayed puberty, hair and cute hypopigmentation, isolated ACTH deficiency
MC4-R deficiency	*MC4-R*	Accelerated growth, increased final height
PCSK1 deficiency	*PCSK1*	Hypogonadism, absent or delayed puberty, postprandial hypoglycemia, elevated plasma proinsulin, severe malabsorption in the neonatal period
SIM1 deficiency	*SIM 1*	Spectrum of developmental delay
BDNF/trkB deficiency	*BDNF o NTRK2*	Developmental delay, hyperactivity, impaired memory, impaired pain sensation
CART deficiency	*CART*	Anxiety and depression

Adapted with permission from Ramachandrappa and Farooqi [19].

Table 1. Main features of monogenic not syndromic obesity.

These types of monogenic obesity are caused by mutations in leptin–melanocortin hypothalamic pathway genes. These genes regulate the sense of appetite and hunger (**Figure 1**).

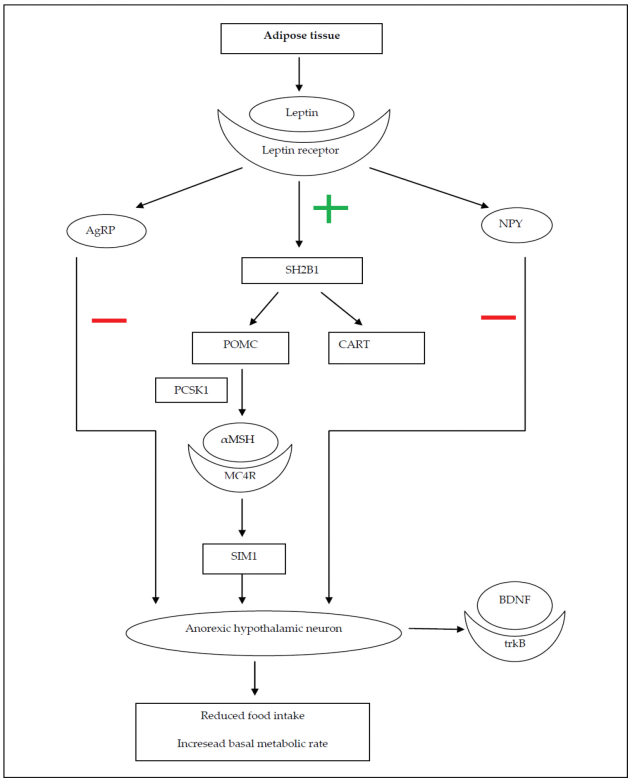

Figure 1. Appetite regulation: inhibitory (-) and favoring (+) mechanisms. Adapted with permission from Perrone et al. [11].

2.1. Congenital leptin deficiency (OMIM #614962)

In 1997, two severely obese cousins (an 8-year-old female child with a weight of 86 kg and a 2-year-old male child with a weight of 29 kg) were reported from a highly consanguineous family of Pakistani origin [20]. Despite their severe obesity, both children had undetectable levels of serum leptin and a mutation in the gene encoding leptin mapped at 7q32.1. The disease is caused by mutations in the *LEP* gene (OMIM *164160) typically leading to defects in protein synthesis or secretion, and therefore to the absence or very low blood levels of this hormone [21–23].

However, recently the first cases of functional leptin deficiency have been described [23, 24]. This entity is characterized by detectable immunoreactive levels of circulating leptin, but bioinactivity of the hormone due to defective receptor binding [23, 24].

So, serum leptin may be a useful marker in patients with severe early-onset obesity as an undetectable serum leptin is highly suggestive of a diagnosis of congenital leptin deficiency due to homozygous loss of function mutations in the *LEP* gene [12]. Leptin-deficient subjects are born of normal birth weight but exhibit rapid weight gain in the first few months of life resulting in severe obesity [25].

Leptin deficiency causes the loss of appetite control, so it is associated with hyperphagia, increased energy intake and aggressive behavior when food is denied. Other phenotypic features include hypothalamic hypothyroidism, hypogonadotropic hypogonadism (because leptin stimulates hypothalamic gonadotropin-releasing hormone [GnRH] production), elevated plasma insulin, T-cell abnormalities (because leptin also stimulates the inflammatory response and proliferation of T cells and cytokines Th1 mediated), and advanced bone age [26]. Currently, the prevalence of mutations in leptin is about 1% [12].

Leptin deficiency is entirely treatable with daily subcutaneous injections of recombinant human leptin with beneficial effects on the degree of hyperphagia, reversal of the immune defects and infection risk and permissive effects on the development of puberty [25]. The major effect of leptin administration is the normalization of hyperphagia and enhanced satiety [25, 27].

2.2. Congenital leptin-receptor deficiency (OMIM #614963)

In 1998 (1 year after the discovery of the congenital leptin deficiency), patients with similar phenotypic characteristic of leptin deficiency, but with a high blood level of leptin, were reported [28]. In these patients, a mutation in the leptin receptor (*LEPR*, OMIM *601007), mapped at 1p31.3, has been described [28].

One subsequent study has demonstrated that 3% of a group of patients with severe, early-onset obesity had a pathogenic *LEPR* mutation, but blood levels of leptin were not very high, suggesting that blood leptin levels cannot be used as a marker for leptin-receptor deficiency [29].

In literature, many mutations of the leptin receptor are described. Most recently, three novel mutations have been reported in the *LEPR* in two unrelated affected obese girls when latest genetic analysis techniques like whole-exome sequencing and targeted sequencing have been used for the mutational analysis in this gene [30, 31].

The clinical phenotypes associated with congenital leptin-receptor deficiency are similar to those of leptin deficiency, with severe obesity from the first few months of the life, hypothalamic hypothyroidism and hypogonadotropic hypogonadism [12, 26].

On the contrary, in these patients, because of a non-functional LEPR, leptin treatment is ineffective. Other factors could possibly bypass normal leptin delivery systems, but these are not yet currently available for the treatment of these patients [32].

2.3. SH2B1 deficiency

The Src-homology-2 B adaptor protein 1 (*SH2B1*, OMIM *608937) is a key intermediary in leptin signaling, promoting the activation of the leptin signaling pathway downstream of Janus kinase 2 (*JAK2*, OMIM *147796) [15]. So, leptin-stimulated activation of hypothalamic JAK2 is dramatically attenuated in *SH2B1* knockout mice [33].

In 2010, it was described that the 220-kb 16p11.2 deletion (28.73–28.95 Mb) seen in three patients co-segregated with severe early-onset obesity alone [14]. This deletion includes a small number of genes, one of which was *SH2B1*, known to be involved in leptin and insulin signaling [12]. However, several mutations in the *SH2B1* gene have also been reported in association with early-onset obesity, severe insulin resistance and behavioral abnormalities in some patients [34].

The phenotype of the children with *SH2B1*-containing deletions is characterized by extreme hyperphagia and fasting insulin levels disproportionately elevated compared to age and obesity-matched controls [15]. As expected, obese *SH2B1* KO mice develop hyperglycemia, hyperinsulinemia, glucose intolerance, and insulin resistance and NIDDM [35]. Interestingly, central and peripheral SH2B1 seem to regulate insulin sensitivity and glucose metabolism independently of its action on body weight in man and mice [36].

In these patients, there is no specific treatment, but care must be taken in starting a specific follow-up on the hyperphagia, obesity and alteration of gluco-insulinemic metabolism.

2.4. POMC deficiency (OMIM #609734)

In 1997, a role of central melanocortin signaling in the control of energy homeostasis was known [37]. Proopiomelanocortin (POMC) acts on anorectic targets of leptin in the brain [38]. The POMC, through to proconvertase 1 (PCSK1), is the precursor of a-melanocyte-stimulating-hormone anorectic peptide (a-MSH); the latter acts on melanocortin 4 receptor (MC4-R) anorectic neurons and suppresses the appetite and food intake [39].

Monogenic obesity from POMC deficiency manifests itself when there are homozygous null mutations. Heterozygous carriers of null *POMC* gene mutations have a significantly higher risk of being obese or overweight but are not invariably associated with obesity [19].

Since POMC is the precursor of adrenocorticotropic hormone (ACTH) and melanocyte-stimulating-hormone anorectic peptide (MSH), POMC-deficient newborns have adrenal crisis and pale skin and hair. Also, POMC deficiency causes hyperphagia and childhood obesity [3, 40]. The clinical features are comparable to those reported in patients with mutations in the receptor for POMC-derived ligands, MC4R (see below in the next chapter) [12].

Two important *POMC* mutations have been described in literature: the first is the rare mutation *R236G* that disrupts a di-basic cleavage site between β-MSH and β-endorphin, resulting in a β-MSH/β-endorphin fusion protein that binds to MC4R but has reduced ability to activate the receptor [38, 41]. The second is a rare missense mutation in the region encoding β-MSH, *Tyr221Cys* that cannot bind to and activate signaling from the MC4R, and obese children

carrying the *Tyr221Cys* variant are hyperphagic and showed increased linear growth, features of MC4R deficiency [42].

Specific treatment was not available until January 2016, when the US Food and Drug Administration awarded orphan drug status to the first α-MSH-based therapy for obesity. The α-MSH analog RM-493 [43, 44], also known as setmelanotide, was awarded orphan drug status for POMC deficiency and Prader-Willi syndrome [37].

2.5. Melanocortin-4 receptor deficiency (MC4R)

Among all forms of monogenic obesity, the most common is caused by MC4-R deficiency. Heterozygous mutations have been reported in many ethnic groups of obese patients and prevalence varies from 0.5 to 1.0% in obese adults, up to 6% in individuals with severe infantile onset obesity [45]. In 2014, a case of childhood obesity associated with compound heterozygosity for two mutations of *MC4R* gene (OMIM *155541), mapped at 18q21.32, was described [46]. In the same year, another new inactivating homozygous mutation of the *MC4R* gene in a girl with the severe obesity and hyperphagia was reported [47].

Mutations of this gene are codominant with variable penetrance and expressivity in heterozygous carriers [48]. Both heterozygous and homozygous mutations in *MC4R* have been implicated in obesity, but extreme obesity is incompletely penetrant in heterozygous patients [3]. Also, in these patients, genetic and environmental factors influence the severity of obesity associated with mutations of *MC4-R*.

The main clinical features include hyperphagia in early appearance (but not as severe as that seen in leptin deficiency) and an increase in fat mass, lean mass and bone mineral density [45]. These patients also have an accelerated growth that seems to be a consequence of hyperinsulinemia which such patients present from the earliest periods of life. It is apparently not related to a dysfunction of the GH axis [3, 49]. Despite this early hyperinsulinemia, obese adult subjects who are heterozygous for mutations in the *MC4R* gene are not at increased risk of developing glucose intolerance and NIDDM compared to controls of similar age and adiposity [12, 45].

Currently, there are no specific therapies for the MC4-R deficiency, but these individuals may benefit from surgical therapies, which could be taken into consideration in adults [12].

2.6. PCSK1 deficiency (OMIM #600955)

Pro-protein convertases (PCs) are a family of serine endoproteases that cleave inactive propeptides into biologically active peptides [50]. Two of these pro-protein, proprotein convertase, subtilisin/kexin-type 1 (PCSK1) and PCSK2 are selectively expressed in neuroendocrine tissues and cleave pro-hormones such as POMC, thyrotropin-releasing hormone (TRH), GnRH, proinsulin, proglucagon [12].

Patients with heterozygous or homozygous mutations in the *PCSK1* gene (OMIM *162150), mapped at 5q15, present small bowel enteropathy, early-onset obesity and complex neuroendocrine effects due to a failure to process the pro-hormones such as diabetes insipidus, glucocorticoid deficiency, hypogonadism, and altered glucose homeostasis [51, 52].

A typical characteristic of these patients is a history of severe intestinal malabsorption in the neonatal period, probably due to altered cleavage of intestinal peptides in the enteroendocrine cells [51].

Over the past few years, two meta-analysis about *PCSK1* mutations have been published: the first in 2014 confirmed the association of *PCSK1* SNPs with obesity and provides the first evidence that the association between *PCSK1 rs6232* and obesity is stronger for childhood obesity than for adult obesity; the second meta-analysis tried to study the association of *PCSK1* variants *rs6232* and *rs6234*/*rs6235* with quantitative BMI variation and common obesity risk in subjects from diverse ethnic groups. In this study, cohort age-group significantly modulated the association between *rs6232*, *rs6234*/*rs6235* and obesity with the effect sizes for both SNPs being stronger in children/adolescents than in adults.

It is thought also that the most common PCSK1 variants predispose to obesity especially in an "obesogenic" environment with free access to high-caloric food [53].

Currently, there are no specific therapies for the PCSK1 deficiency, but these individuals frequently required a prolonged course of parenteral nutrition therapy, particularly in the first year of life [54]. However, exogenous administration of several hormone may be necessary in relation to the hormonal deficiencies diagnosed [54].

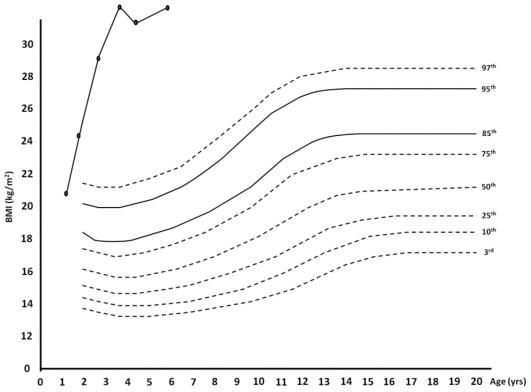

Figure 2. Girl with 6q16.3 deletion involving *SIM1* gene. It is evident that the extreme increase of the BMI of the patient and the reduction after the interdisciplinary approach.

2.7. SIM1 deficiency

Single-minded 1 (SIM1) is a transcription factor involved in the development of the supraoptic and paraventricular nuclei, acting downstream signal cascade of MC4-R. Obesity and hyper-

phagia have been reported in a patient with a balanced translocation disrupting *SIM1* [55] and multiple heterozygous missense mutations (6q16.3; OMIM *603128) [56]. However, some mutations of *SIM1* have incomplete penetrance and variable phenotype [57]. The similar phenotype between patients with SMI1 and MC4-R deficiency suggests that some effects of SIM1 are mediated by altered melanocortin signaling. On the other hand, some children with *SIM1* mutations have neuro-behavioral disorders including autism spectrum and "Prader-Willi-like" phenotype (**Figure 2**) [3, 12].

In mice, hyperphagia associated with SIM1 deficit can be improved by the administration of oxytocin, a neurotransmitter involved in the modulation of emotion (impaired oxytocinergic signaling is also one possible mechanism implicated in the obesity) [58].

2.8. Other types of non-syndromic genetic obesity

Mutations of the *BDNF* (*brain-derived neurotrophic factor*, OMIM *113505, mapped at 11p14.1) and its receptor TrKb (*tyrosin kinase B receptor*, OMIM *600456, mapped at 9q21.33) are rare causes of monogenic obesity acting downstream signal cascade of MC4-R and blocking translation [59].

BDNF's role in energy homeostasis emerged in the 1990s with the observation that intracerebroventricular BDNF administration suppresses appetite and induces weight loss in rodents, and *Bdnf* heterozygous knockout mice exhibit hyperphagia and obesity [60]. Complete lack of BDNF during embryologic development is perinatally lethal, but haploinsufficiency for BDNF or inactivating mutations of the BDNF receptor was associated with increased ad libitum food intake, severe early-onset obesity, hyperactivity, and cognitive impairment [60, 61]. Multiple genome-wide association studies of obesity in children and adults of different racial and ethnic populations have found associations for single-nucleotide polymorphisms (SNPs) at the BDNF locus and BMI, in particular for *G196A* variant (*rs6265*), which leads to a valine to methionine substitution at the 66th amino acid position (*Val66Met*) of the N-terminal prodomain of pro-BDNF. Furthermore, modifying factors—particularly sex, lifestyle behaviors, and psychotropic medication use—appear to be important confounders for the association between rs6265 and BMI [60–62]. In addition, the minor C allele of intronic *rs12291063* SNP was associated with lower BDNF expression and higher BMI [63].

NTRK2 (*TrkB*) mutation (which interferes with receptor autophosphorylation) causes the same symptoms of BDNF deficiency such as hyperphagia, obesity, impaired nociception, and intellectual disability [64, 65]. Recently, a *de novo* mutations in *TrkB* was found in a boy with severe obesity and impairment in learning, memory and nociception, and in a girl with hyperphagia and severe obesity [66].

Another cause of non-syndromic monogenic obesity is due to a gene mutation of *CART* (*cocaine- and amphetamine-regulated transcript*, OMIM *602606), mapped at 5q13.2. CART is an anorexigenic peptide produced by specific hypotalamic neurons in response to the stimulus of leptin. It would appear to mediate the termogenetic effects and energy expenditures characteristic of leptin. It has been shown that mutations in the *CART* gene are associated with

reduced levels of the peptide encoded by it. Adolescents carrying a missense mutation in the *CART* gene exhibit severe obesity associated with anxiety and depression [11, 67, 68].

Other recent forms of monogenic obesity, still being defined, are associated with *MRAP2* (*melanocortin 2 receptor accessory protein 2*, OMIM *615410, mapped at 6q14.2) mutation encoding a *MC4-R* co-receptor, and with *KSR2* (*Kinase suppressor of Ras 2*. OMIM *610737, mapped at 12q24.22-q24.23) mutation, a protein involved in intracellular signal with a role in energy homeostasis [69–72].

3. Syndromic obesity

To date have been identified syndromic forms (e.g., Prader-Willi Syndrome) in which obesity can be associated with other signs and symptoms, such as intellectual disability, dysmorfic features and unusual behaviors.

In these syndromes, obesity can be caused by hyperphagia because are involved genes related to central nervous system appetite control centers.

Recently, the genetic bases for some of these syndromes have been elucidated and are beginning to provide insights into the pathogenesis of the derangements of energy homeostasis.

Table 2 reports the main syndromic forms of obesity. High-throughput technologies, and in particular copy number variants (CNVs) detection, are likely to result in the identification and recognition of multiple new syndromes where obesity and developmental delay are closely associated [12].

Syndrome	Clinical features in addition to obesity	Prevalence	Genetic
Bardet-Biedl	Mental retardation, retinal dystrophy or pigmentary retinopathy, dysmorphic extremities, hypogonadism, kidney anomalies	1/125,000 to 1/175,000 births	BBS1 (11q13); BBS2 (16q12.2); BBS3 (*ARL6*, 3q11); BBS4 (15q24.1); BBS5 (2q31.1); BBS6 (*MKKS*, 20p12); BBS7 (4q27); BBS8 (*TTC8*, 14q31); BBS9 (*PTHB1*, 7p14); BBS10 (*C12ORF58*, 12q21.2); BBS 11 (*TRIM32*, 9q33.1); BBS12 (*FLJ35630*, 4q27); BBS13 (*MKS1*, 17q23); BBS14 (*CEP290*, 12q21.3); BBS15 (*WDPCP*, 2p15); BBS16 (*SDCCAG8*, 1q43); BBS17 (*LZTFL1*, 3p21); BBS18 (*BBIP1*, 10q25); BBS19 (*IFT27*, 22q12)
Prader-Willi	Neonatal hypotonia, mental retardation, hyperphagia, facial dysmorphy,	1/25,000 births	Lack of the paternal segment 15q11-q13 (microdeletion, maternal disomy, imprinting

Syndrome	Clinical features in addition to obesity	Prevalence	Genetic
	hypogonadotrophic hypogonadism, short stature		defect or reciprocal translocation)
Cohen	Retinal dystrophy, prominent central incisors, dysmorphic extremities, microcephaly, cyclic neutropenia	Diagnosed in fewer than 1000 patients worldwide	Autosomal recessive *COH1* gene (chr 8q22-q23)
Alström	Retinal dystrophy, neurosensory deafness, diabetes, dilated cardiomyopathy	Diagnosed in about 950 patients worldwide	Autosomal recessive *ALMS1* gene (chr 2p13-p14)
X fragile	Mental retardation, hyperkinetic behavior, macroorchidism, large ears, prominent jaw	1/2500 births	X-linked *FMR1* gene (Xq27.3)
Borjeson-Forssman-Lehmann	Mental retardation, hypotonia, hypogonadism, facial dysmorphy with large ears, epilepsy	Approximately 50 reported patients	X-linked *PHF6* gene (Xq26-q27)
Albright hereditary osteodystrophy	Short stature, skeletal defects, facial dysmorphy, endocrine anomalies	1/1,000,000 births	Autosomal dominant *GNAS1* gene (20q13.2)
Ulnar–mammary	Upper limb malformation (from hypoplasia of the terminal phalanx of the fifth digit to aplasia of hand and upper limbs on the ulnar side), abnormal development of mammary glands and nipples, teeth, genitalia, and of apocrine glands		Autosomal dominant *TBX3* gene (12q24.21)
Simpson-Golabi-Behmel	Multiple congenital abnormalities, pre-/post-natal overgrowth, distinctive craniofacial features, macrocephaly, and organomegaly.		X-linked *GPC4* gene (Xq26)
MEHMO syndrome	Mental retardation, epileptic seizures, hypogenitalism, microcephaly and obesity	Approximately <1/1,000,000 births	X-linked locus MEHMO (Xp22.13-p21.1)
1p36 deletion syndrome	Delayed growth, malformations, moderate to severe intellectual disability, seizures, hearing and vision impairment, and certain particular facial features.	1/5000 to 1/10,000 live births	Autosomal dominant microdeletion of 1p36
16p11.2 deletion syndrome	Developmental delay, intellectual disability, autism spectrum disorders, impaired communication, socialization skills	Approximately 3/10,000 births	Autosomal dominant microdeletion of 16p11.2
***ACP1*, *TMEM18*, *MYT1L* deletion**	Hyperphagia, intellectual deficiency, severe behavioral difficulties	Approximately 13 reported patients	Paternal deletion encompassing the *ACP1*, *TMEM18*, *MYT1L* genes (2p25)

Table 2. Main forms of syndromic obesity.

3.1. Developmental obesity syndromes involving ciliary dysfunction

Some genes linked to obesity have been associated with the function or formation of primary cilia, subcellular organelles, which serve a sensory function for most cell types. The ciliopathies form a class of genetic disease whose etiology lies with primary ciliary dysfunction. Some peculiar features can be found, such as retinal degeneration. This feature is of particular interest for its clinical relevance, rarity, and diagnostic power. Between these groups of diseases, we can include the Bardet-Biedl syndrome (BBS) and Alström syndrome (ALMS).

BBS has become a model ciliopathy because it became the first disease whose etiology lay in primary ciliary disorder [73]. It is a rare autosomal recessive genetic disorder with severe multiorgan impairment [74]. Its frequency in Europe and North America falls below 1:100,000 [75]. The disease symptoms may significantly vary between the patients; therefore, the diagnosis relies on the number of primary and secondary features of BBS [74]. Multiple articles summarize the data on frequencies of various symptoms in BBS patients [75, 76]. However, it is very important to realize that almost all clinical studies analyzed patients of various ages. Many individuals with BBS look virtually healthy at birth unless they were born with a polydactyly. Other symptoms of BBS tend to gradually emerge during or after the first decade of life; thus, patients diagnosed at early childhood tend to have fewer clinical features of the disease [74]. There are six primary features of BBS, that is, rod-cone dystrophy, polydactyly, obesity, genital abnormalities, renal defects, and learning difficulties. Secondary features include developmental delay, speech deficit, brachydactyly or syndactyly, dental defects, ataxia or poor coordination, olfactory deficit, diabetes mellitus, and congenital heart disease [75]. Some authors also mention hypertension, liver abnormalities, bronchial asthma, otitis, rhinitis, craniofacial dysmorphism, etc. [75–78].

However, the phenotype can be different: generally, obesity occurs early in life of patients affected by BBS, but the literature shows that 52% of post-pubertal BBS patients are obese [79]. It is recommended to assign BBS diagnosis to patients bearing at least 4 out of 6 primary features of the disease. If only three primary features are detected, two secondary features are required to confirm the presence of BBS.

These criteria describe BBS mainly as a clinical entity; they do not fully account to the existence of patients with attenuated forms of the disease as well as to possible gene-specific manifestations of BBS [80, 81].

At least 20 BBS genes have already been identified, and all of them are involved in primary cilia functioning. Genetic diagnosis of BBS is complicated due to lack of gene-specific disease symptoms; however, it is gradually becoming more accessible with the invention of multigene sequencing technologies [74].

The first five BBS loci were identified via linkage analysis of large BBS pedigrees [82–86] with corresponding genes cloned some years later [87–92]. The first gene assigned to BBS was *MKKS* (*MKS*; OMIM *604896) already known to induce McKusick-Kaufman syndrome; given that it did not belong to previously identified BBS loci, it was named *BBS6*. At present, there are already 21 known BBS genes (*BBS1*–*BBS20* and *NPHP1*), and their number is likely to increase due to the invention of exome sequencing and analysis of previously unstudied populations

[74]. Strikingly, all BBS genes participate in cilia functioning, being a part of BBSome (*BBS1* [11q13.2; OMIM *209901], *BBS2* [16q13; OMIM *606151], *BBS4* [15q24.1; OMIM *600374], *BBS5* [2q31.1; OMIM *603650], *BBS7* [4q27; OMIM *607590], *BBS8* [14q31.3; OMIM *608132], *BBS9* [7p14.3; OMIM *607968], *BBS17* [3p21.31; OMIM *606568], and *BBS18* [10q25.2; OMIM *613605]); chaperonin complex (*BBS6* [20p12.2; OMIM *604896], *BBS10* [12q21.2; OMIM *610148], and *BBS12* [4q27; OMIM *610683]); basal body (*BBS13* [17q22; OMIM *609883], *BBS14* [12q21.32; OMIM *610142], *BBS15* [2p15; OMIM *613580], and *BBS16* [1q43-q44; OMIM *613524]) or having some related biological function (*BBS3* [3q11.2; OMIM *608845], *BBS11* [9q33.1; OMIM *602290], *BBS19* [22q12.3; OMIM *615870], *BBS20,* and *NPHP1* [2q13; OMIM *607100]) [74].

Many of these genes appear to affect proteins localized to the basal body, a key element of the monocilium thought to be important for intercellular sensing in mammalian cells including neurons [73]. The literature shows that ciliary function is associated with leptin signaling [93]. As evidenced by some studies in mice, hyperphagia and obesity are caused by conditional post-natal knockout of proteins involved in intraflagellar transport [94], but they occur also when the loss of cilia affects the neurons, in particular POMC neurons [94].

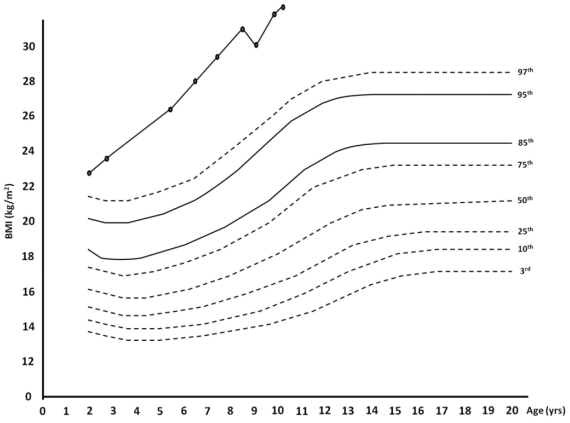

Figure 3. BMI growth chart in a girl with Alström syndrome.

Alström syndrome (ALMS; OMIM #203800) is a rare genetic disorder that has been included in the ciliopathies group, in the last few years [95].

The estimated prevalence for ALMS is one to nine cases per 1,000,000 individuals with nearly 900 cases described worldwide to date. Symptoms first appear in infancy and progressive development of multi-organ pathology lead to a reduced life expectancy. Variability in age of

onset and severity of clinical symptoms, even within families, are likely due to genetic background [95].

Children typically develop obesity by age 5 years, associated with hyperinsulinemia, chronic hyperglycemia and neurosensory deficits (**Figure 3**) [6]. Children affected by ALMS, like children with BBS, have visual impairment and deafness that occurs early in life but its incidence is higher in these patients as well as NIDDM, found in up to 70% of individuals by age 20 years [96, 97].

In addition, ALMS is also associated with cardiomyopathy, renal anomalies and endocrinopathies such as hypertriglyceridemia, pubertal delay, and hyperandrogenism and growth hormone deficiency [97].

Until now, disease-causing mutations in the *ALMS1* (2p13.1; OMIM *606844) gene have been involved in this disorder.

The diagnosis is based on the phenotype of the patient, and it is confirmed when two mutations in *ALMS1* gene are identifies through molecular analysis.

However, it is difficult to diagnose early ALMS first of all because symptoms arise gradually and secondly because the phenotypes overlap, in particular with BBS in the case of ALMS [98].

In recent times, thanks to the discovery of new genetic tools, in particular next-generation sequencing (NGS) technology, a large number of patients have been diagnosed. The advent of these new techniques allows early diagnosis also in those patients who do not have a characteristic phenotype, thus preventing long-term complications that can be caused by a delay in diagnosis [99].

Today, the most used genetic techniques are whole-exome sequencing (WES) and whole-genome sequencing, thanks to their low cost. However, they are also important because they allow to exclude the mutations in other genes [99, 100].

The WES is a rapid and easier technique because it analyzes all coding regions in the genome [100]. Thanks to it, in fact, mutations in *ALMS1* gene have been identified in individuals, whose phenotype did not seem to be typical of ALMS; therefore, it is fundamental to identifying pathogenic mutations in compound heterozygous state in *ALMS1* gene, overcoming also limitation of genetic panels in patient suffering from familial dilated cardiomyopathy and severe heart failure [101].

In fact, as reported in literature, the association of WES and a previous linkage analysis has allowed to identify the pathogenic mutations in *ALMS1* gene in a consanguineous Turkish family with severe dilated cardiomyopathy although it did not present the typical phenotype of ALMS [102].

Moreover, these mutations have been shown also in consanguineous Leber congenital amaurosis families through homozygosity mapping followed by WES [103].

As evidenced by these studies, the simultaneous use of different genetic techniques is fundamental both in the case of consanguineous families that in patients without the typical ALMS phenotype [95].

For management of the disease and to identify an accurate treatment, it is important for both the present of typical clinical features that an appropriate genetic diagnosis, which may be carried out by NGS techniques, thanks to its low cost compared with traditional polymerase chain reaction and direct Sanger sequencing [103].

4. Imprinted genetic syndromes

Prader-Willi syndrome (PWS, OMIM #176270) is a disorder caused by errors in genomic imprinting, which generally occur during both male and female gametogenesis. In particular, there is the loss of expression of paternal genes normally active and located in the chromosome 15q11-q13 region [104–108]. Conversely, a loss of expression of the preferentially maternally expressed *UBE3A* (OMIM *601623) gene in this region leads to Angelman syndrome (AS; OMIM #105830), an entirely different clinical disorder that causes developmental disabilities and neurological problems, such as difficulty speaking, balancing and walking, and, in some cases, seizures [109, 110].

According to several studies, most individuals with PWS (about two-thirds) have a de novo paternally inherited deletion of the chromosome 15q11-q13 region; about 25% of cases have maternal disomy 15 (chromosome 15 is inherited from the mother) [111]; less than 3% of patients have defects in the genomic imprinting center due to microdeletions or epimutations [104, 106, 112, 113], while rearrangements of the 15q11-q13 region or chromosomal translocations are rare [104, 114].

However, this syndrome, whose prevalence is around of 1/10,000–1/30,000, is considered the most common cause of syndomic obesity [115].

The cardinal features of PWS include infantile hypotonia, feeding difficulties due to a poor suck and failure to thrive (FTT), followed in later infancy or early childhood by excessive appetite with gradual development of obesity, short stature and/or decreased growth velocity due to growth hormone (GH) deficiency, intellectual disabilities (average IQ of 65), behavioral problems (e.g., temper tantrums, outburst and skin picking) and particular facial appearance (e.g., a small upturned nose, narrow bifrontal diameter with almond-shaped eyes, down-turned corners of the mouth with sticky salivary secretions and generally lighter skin, hair and eye color than other family members) [105, 106]. Hypothalamic dysfunction has been implicated in many manifestations of this syndrome including hyperphagia, temperature instability, high pain threshold, sleep-disordered breathing and multiple endocrine abnormalities [105, 107, 108].

Initially, two nutritional phases have been described in children with PWS:

- phase 1: the individual often presents FTT; he exhibits hypotonia with difficult feeding;
- phase 2: the individual is hyperphagic, and this condition will lead to obesity [105, 108].

To date, instead, seven different nutritional phases (five main phases and sub-phases in phases 1 and 2) have been identified.

As following, focusing on nutrition, although in the early phases, the child has poor appetite, the latter increases in phase 2b and leads progressively to hyperphagia, evident in phase 3 (**Table 3**).

Phases	Median ages	Clinical characteristics
0	Prenatal to birth	Decreased fetal movements and lower birth weight than sibs
1a	0–9 months	Hypotonia with difficulty feeding and decreased appetite. Needs assistance with feeding either through feeding tubes [nasal/oral gastric tube or gastrostomy tube] or orally with special, widened nipples
1b	9–25 months	Improved feeding and appetite and normal growth
2a	2.1–4.5 years	Weight increasing without appetite increase or excess calories. Will become obese if given the recommended daily allowance [RDA] for calories. Typically needs to be restricted to 60–80% of RDA to prevent obesity
2b	4.5–8 years	Weight and appetite are increased but can feel full
3	8 years to adulthood	Hyperphagic, rarely feels full
4	Adulthood	Appetite is no longer insatiable

Adapted with permission from Cassidy et al. [107].

Table 3. Clinical characteristics of the nutritional phases seen in Prader-Willi syndrome.

Analyzing the seven phases, we highlight the following:

- phase 0: the infant has growth restriction and decreased fetal movements;
- sub-phase 1a: the infant is hypotonic with difficulty feeding and with or without FTT;
- sub-phase 1b: the infant grows normally, and he improves appetite, also if weight gain is normal;
- sub-phase 2a: the child has a weight gain although there is not an increased appetite or caloric intake;
- sub-phase 2b: in addition to weight gain, there is an increased appetite;
- phase 3: the individual is hyperphagic; he seeks foods and presents the loss of sense of satiety;
- phase 4: it is typical of adults, who have an insatiable appetite and are able to feel full [107].

As said previously, individuals with PWS present an appetite that gradually increases and leads to obesity. In recent years, some studies have been conducted to understand the mechanisms controlling appetitive behavior, energy expenditure and body composition.

The central nervous system, in particular the hypothalamus that determines changes in energy balance, is involved in these processes.

One of the determining factors for the development of obesity in these patients is ghrelin, a 28 amino acid peptide produced in the stomach, that transmit satiety signal and whose level in obese PWS individuals is high [116, 117]. Circulating ghrelin levels are elevated in young children with PWS long before the onset of hyperphagia, especially during the early phase of poor appetite and feeding [118].

The literature reports that about 25% of the adults with PWS presents NIDDM (non-insulin-dependent diabetes mellitus) [119]; however, some studies show that in PWS, children fasting insulin concentrations and homeostasis model assessment insulin resistance index are lower than in obese control [120].

This syndrome, as mentioned, represents an human disorder related to genomic imprinting.

Although the DNA sequence of the imprinted maternally and paternally inherited alleles is the same, multiple epigenetic factors (such as DNA methylation, histone modifications and chromatin conformation) ultimately will determine whether the imprinted allele is expressed or repressed [121, 122].

DNA methylation analysis is the most efficient way to start the genetic workup if PWS is suspected clinically, but it cannot distinguish the molecular class (i.e., deletion; uniparental disomy, UPD; or imprinting defect, ID). Therefore, once the diagnosis of PWS is established by DNA methylation analysis, determination of the molecular class is the next step.

There are different genetic testing used in PWS: CMA-SNP array or FISH (fluorescence in situ hybridization) for deletion of 15q11.2-q13, DNA polymorphism analysis for UPD or ID or testing with MS-MLPA analysis for an IC deletion, important for the diagnosis of both of these individuals who do not have sufficient features because they are too young than of those who do not exhibit the typical phenotype [107].

4.1. Cohen syndrome

Cohen syndrome (CS) is an inherited disorder characterized by developmental delay, intellectual disability, microcephaly and hypotonia. Other features include progressive myopia, retinal dystrophy, hypermobility and distinctive facial features [6, 12]. Characteristic facial features include thick hair and eyebrows, long eyelashes, down-slanting and wave-shaped, a bulbous nasal tip, a smooth or shortened philtrum, and prominent upper central teeth [6, 12]. Children with CS tend to manifest failure to thrive in infancy and early childhood but subsequently become significantly overweight in the late childhood and adolescence. The obesity tends to be truncal in nature [6, 12]. In contrast to PWS, appetite and food intake are not increased during this time period, and activity is not noticeably decreased. Among individuals with CS, the prevalence of short stature is approximately 65% and delayed puberty 74%; clinical endocrinologic evaluations did not identify explanations for these findings [6, 12].

4.2. 1p36 deletion syndrome

1p36 deletion syndrome is a disorder characterized by severe intellectual disability, hypotonia, heart defects, hearing impairment and typical craniofacial features. In fact, patients with this

syndrome show straight eyebrows, deeply set eyes, midface hypoplasia, broad and flat nasal root/bridge, long philtrum, pointed chin, large, late-closing anterior fontanel, microbrachycephaly, epicanthal folds and posteriorly rotated, low-set, abnormal ears. Other typical findings include brachy/camptodactyly and short feet. Developmental delay and intellectual disability of variable degree are present in all, and hypotonia in 95%. Seizures occur in 44–58% of affected individuals. Other findings include prenatal-onset growth deficiency, structural brain abnormalities, congenital heart defects, vision problems, deafness, skeletal anomalies, abnormalities of the external genitalia and renal abnormalities. Obesity, which occurs as the consequence of hyperphagia, is also frequently observed in patients with the 1p36 deletion syndrome [123]. In this recent report [124], 40% of patients had obesity and hypercholesterolemia, and 1 patient developed NIDDM. Some authors suggested candidate regions for hyperphagia and obesity, such as *PRKCZ*, that may be associated with obesity because this gene is involved in carbohydrate or lipid metabolism, or insulin signaling [123]. It is suggested that genetic or environmental factors more likely contribute to the development of obesity and DM. However, a subset of patients may become overweight and obese with hyperphagia and NIDDM [125]. Previous studies observed that obesity was found exclusively in female patients with 1p36 deletion who showed growth restriction during the fetal period [126]. Because patients with 1p36 deletion show hypotonia and hyperphagia with obesity and NIDDM, which are also characteristic features of patients with PWS, some patients with 1p36 deletion may be misdiagnosed as having PWS.

4.3. 16p11.2 deletion syndrome

16p11.2 microdeletion syndrome is a chromosomal anomaly characterized by developmental and language delays, intellectual disability, social impairments represented by autism spectrum disorders, variable dysmorphisms and predisposition to obesity. In fact, in a screening cohort of patients with extreme obesity, enriched for patients with birth defects and/or neurocognitive deficiencies using method to detect copy number variations, recurrent, *de novo* deletions of 16p11.2 were identified in approximately 3% of cases. In these patients, durable weight loss has not been reported. So durable weight control is recommended although no data are available on the efficacy of early intervention in deletion carriers. However, impaired cognition may also result in abnormal eating behavior contributing to the obesity [127, 128]. Some data seem to hypothesize that this deletion may affect the neural circuitry involved in the energy balance. The early increase in head circumference seems to precede the onset of obesity [129]. The 16p11.2 deletion includes the *SH2B1* gene, an adaptor protein involved in leptin and insulin signaling which may be involved in the pathogenesis of the obesity and insulin resistance observed in this deletion [130].

Additionally, deficiencies of *SIM1* (single minded), *BDNF* (brain-derived neurotrophic factor) and *NTRK2* (neurotrophic tyrosine receptor kinase encoding the TrK protein, the receptor for BDNF) genes are associated with syndromic conditions involved in the functioning of the hypothalamus downstream of MC4R-expressing neurons and leading severe hyperphagic obesity. For example, haplodeficiency of *BDNF* has also been implicated in the

obesity occurring in a subset of patients with WAGR (Wilms tumor, aniridia, genitourinary malformations and retardation) syndrome [62].

4.4. Oligogenic obesity

Oligogenic obesity or common obesity is the result of the set of behavioral, environmental and genetic factors that may influence individual responses to diet and physical activity [131] (**Figure 4**).

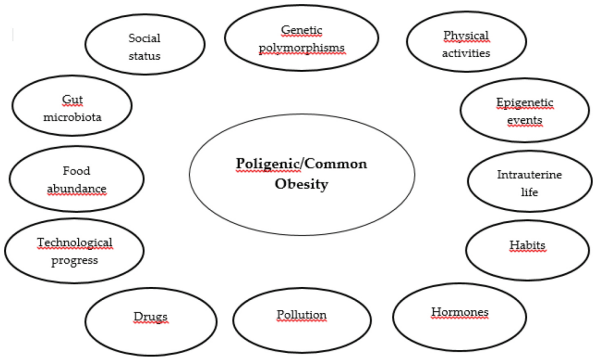

Figure 4. Gene–environment interactions in common obesity. Adapted with permission from Mutch and Clément [131].

The obesogenic changes of our environment in recent decades, especially the unlimited supply of cheap food with high palatability and high energy density, associated with genetic susceptibility are the causes of the current obesity epidemic [132].

The recent rapid rise in prevalence of childhood obesity suggests that, probably, environmental factors have a large impact on body weight in patients with common obesity although individual responses to these environmental factors are influenced by genetic factors called susceptibility genes [3].

Any of a group of alleles, at distinct gene loci that collectively control the inheritance of a quantitative phenotype or modify the expression of a qualitative character, are termed "polygenic" variants. A polygenic variant by itself has a small effect on the phenotype; only in combination with other predisposing variants does a sizeable phenotypic effect arise. Potentially, many such polygenic variants play a role in body weight regulation. It is estimated that the total number of genes with a small effect most likely exceeds [133]. These genes are involved in a variety of biological functions such as the regulation of food intake, energy expenditure, carbohydrate and lipid metabolism and adipose tissue development [131].

Therefore, unlike monogenic obesity, many genes and chromosome regions contribute to common obesity phenotype.

Genome-wide association studies have identified genetic risks for obesity. In less than 4 years, 52 genetic loci have been identified to be unequivocally associated with obesity-related traits [134]. However, these loci have only small effects on obesity susceptibility and explain just a fraction of the total variance. As such, their accuracy to predict obesity is poor and not competitive with the predictive ability of traditional risk factors such as parental and childhood obesity. The first convincing GWAS discovery for any obesity-related trait was made in 2007 for BMI when the *FTO* locus was found to be associated with obesity-related traits and specifically with extreme and early-onset obesity in children and adolescents [134–136]. Following the discovery of the *FTO* locus, one new locus near the *MC4R* was identified, a gene in which mutations are known to be the commonest cause of extreme childhood obesity. Also in recent years, other new BMI-associated loci were discovered such as near *TMEM18* (*transmembrane protein 18*, OMIM *613220, 2p25.3), near *KCTD15* (*potassium channel tetramerization domain-containing protein 15*, OMIM *615240, 19q13.11), near *GNPDA2* (*glucosamine-6-phosphate deaminase 2*, OMIM *613222, 4p12), in *SH2B1* (*SH2B adaptor protein 1*, OMIM *608937, 16q11.2), in *MTCH2* (*mitochondrial carrier homolog 2*, OMIM *613221, 11p11.2), near *NEGR1* (*neuronal growth regulator 1*, OMIM *613173, 1p31.1), near *FAIM2* (*FAS apoptotic inhibitory molecule 2*, OMIM *604306, 12q13.12), near *SEC16B* (*SEC16, homolog of S. cerevisiae B*, OMIM *612855, 1q25.2), near *ETV5* (*ETS variant gene 5*, OMIM *601600, 3q27.2) and in *BDNF* (*brain-derived neurotrophic factor*, OMIM *113505, 11p14.1). Although for many of these loci, association with BMI has been observed in children and in adolescents [64, 137], and in populations of non-white origin, their replication has been less consistent than for the *FTO* and near-*MC4R* loci for relatively small sample size of the replication studies [134].

Furthermore, longitudinal studies have been published in recent years that have followed up children over time; these studies indicated that GWAS-discovered risk variants influence the development of obesity in part by accelerating weight gain during infancy and childhood [138–140], but the mechanisms by which this occurs are not yet fully elucidated. One of the mechanisms involved may be the different sense of appetite, but the results of the studies are controversial [141, 142].

5. Epigenetics and obesity

Heritability estimates of BMI from twin studies range from 50 to 90% [143], so it plays a fundamental role in determining body weight. However, this latest figure appears in contradiction to the evidence of an epidemic increase in pediatric obesity over the last 20 years, time totally inadequate to record permanent changes in the genome. Only the reprogramming of gene expression through epigenetic modifications resulting from relevant environmental changes that have taken place mostly in the early periods of life may partially justify this phenomenon [11]. Epigenetic regulation of gene expression emerged in the last few years as a potential factor that might explain individual differences in obesity risk

[144]. Epigenetics can be defined as heritable changes that are mitotically stable (and potentially meiotically) and affect gene function but do not involve changes in the DNA sequence [145].

Currently, there is a growing interest in the study of the relationship between genetic variation, epigenetic variation and disease simultaneously. The two main mechanisms that lead to epigenetic changes are DNA methylation, and the alterations to histone proteins that alter the likelihood that specific genes are transcribed [146, 147].

Interindividual variations in epigenetic changes like CpG methylation can potentially alter gene function and predispose to obesity. The variation in the degree of methylation, in fact, is able to modulate the expression of genes involved in controlling hypothalamic appetite [148]. Using a genome-wide approach, obesity has been related to changes in DNA methylation status in peripheral blood leukocytes of lean and obese adolescents for two genes: in the *UBASH3A* (*ubiquitin-associated and SH3 domain-containing protein A*, OMIM *605736, 21q22.3) gene, a CpG site showed higher methylation levels in obese cases, and one CpG site in the promoter region *TRIM3* (*tripartite motif-containing protein 3*, OMIM *605493, 11p15.4) gene, showed lower methylation levels in the obese cases [149]. Also the obesity risk allele of *FTO* has been associated with higher methylation of sites within the first intron of the *FTO* gene, suggesting an interaction between genetic and epigenetic factors [150]. In addition, the obesity risk allele of *FTO* affects the methylation status of sites related to other genes (*KARS* [16q23.1; OMIM *601421], *TERF2IP* [16q23.1; OMIM *605061], *MSI1* [12q24.31; OMIM *603328], *STON1* [2p16.3; OMIM *605357] and *BCAS3* [OMIM *607470]), showing that the *FTO* gene may influence the methylation level of other genes [151]. Finally, a recent work has demonstrated that hypermethylation of the *POMC* gene plays an important role in preparing to obesity by reducing the expression of the gene itself [148].

Epigenetic changes usually occur during prenatal development or the early post-natal period. Already *in utero*, in fact, there may be a switch of energy balance resulting from exposure to specific environmental factors, resulting in epigenetic changes that can affect the potential of the fat mass of offspring. For example in a recent work, the methylation status of CpG from five candidate genes in umbilical cord tissue DNA from healthy neonates was measured, and it was found that higher methylation levels within promoter region of *RXRA* (*retinoid X receptor, alpha*, OMIM *180245, 9q34.2) gene, measured at birth, were strongly correlated with greater adiposity in later childhood [152]. Maternal nutrition is a major factor leading to epigenetic changes. Thus, the levels of vitamins consumed in pregnancy such as folate, methionine and vitamin B12, which affect methylation, become very important [147]. One study showed that prenatal exposure to malnutrition can determine abnormal DNA methylation resulting in epigenetic modifications that remain for the whole existence and that predispose to obesity and metabolic and cardiovascular risk in later life [153]. On the other hand also glycemic status during pregnancy is an important factor; in fact, hyperglycemia, as well as having a strong impact on the child's weight, can increase the risk of developing insulin resistance and obesity [147].

6. Steatosis and genetic of steatosis

Non-alcoholic fatty liver disease (NAFLD) actually represents the most frequent cause of chronic liver disease in industrialized countries in children and adolescents, as a direct consequence of the rise in childhood obesity [154]. Italian epidemiological data indicate that NAFLD affects approximately 3–10% of general pediatric population. This percentage increases up to >70%, with a male-to-female ratio of 2:1, in obese children [155]. NAFLD is defined by hepatic fat infiltration >5% hepatocytes, in the absence of other causes of liver pathology (such as daily alcohol utilization and either viral, autoimmune or drug-induced liver disease). It includes a spectrum of disease ranging from intrahepatic fat accumulation (steatosis) to various degrees of necrotic inflammation and fibrosis (non-alcoholic steatohepatatis [NASH]); simple steatosis has generally a benign course, but, rarely in children, NASH may progress to advanced and severe liver damage like cirrhosis and its complications (hepatocellular carcinoma and portal hypertension) [154, 156].

The pathogenesis of NAFLD appears to be multifactorial. The principal risk factor for fatty liver in childhood is obesity, but several other factors contribute to NAFLD development, including race/ethnicity, genetic factors, environmental exposures and alterations in the gut microbiome [157]. The dramatic rise in the prevalence of pediatric NAFLD is closely associated with the epidemic of obesity and metabolic syndrome; as in adulthood, pediatric NAFLD is associated with severe metabolic impairments such as insulin resistance, hypertension and abdominal obesity, determining an increased risk of developing type 2 diabetes mellitus, the metabolic syndrome and cardiovascular diseases [157, 158]. In addition, unhealthy food choices and the excessive fructose consumption in particular the fructose contained in the most common soda can promote the development of fatty liver [159].

The prevalence of hepatic steatosis varies among different ethnic groups. The ethnic group with the highest prevalence is the American Hispanic one (45%) followed by the Caucasian (33%) and the African-American (24%). The fatty liver prevalence in Europe, Australia and Middle East encompasses from 20 to 30%. In India, the fatty liver prevalence in urban populations encompasses from 16 to 32%; but in rural India, where there are traditional diets and lifestyles, the prevalence is lower (about 9%); this evidence suggests that a sedentary lifestyle and globalization of Western diet could be associated with an increase in the fatty liver prevalence in developing nations. In all the ethnicity, NAFLD is more prevalent in boys than in girls with a male to female ratio of 2:1 [160, 161].

Regarding to genetic factors, one of the most important gene involved in determining hepatic steatosis is the *patatin-like phospholipase-containing domain 3* gene (*PNPLA3*). Genome-wide association studies and other pediatric studies have revealed that the *rs738409* (I148M) variant for *PNPLA3* confers susceptibility to NAFLD-promoting hepatic accumulation of triglycerides and cholesterol by inhibition of triglyceride hydrolysis [162]. In addition, a recent case-control study has demonstrated that the *rs9939609A* allele of the fat mass and obesity-associated gene (*FTO*) increases the risk of NAFLD [157].

Another gene that acts together with *PNPLA3* in determining hepatic steatosis is the glucokinase regulatory protein (*GCKR*) gene which encodes for the glucokinase regulatory protein

(GCKRP) that inhibits the glucokinase (GCK) activity competing with the glucose, substrate of GCK. It has been demonstrated that the GCKRP L466 variant encodes for a protein that indirectly increased GCK activity. This increase in GCK hepatic activity promotes hepatic glucose metabolism, raises the concentrations of malonyl coenzyme A, a substrate for de novo lipogenesis, and contributes in liver fat accumulation [160, 163]. In addition, a study conducted in Chinese children has shown that that the polymorphism *rs11235972* of the *uncoupling protein 3* (*UCP3*) gene is associated with the occurrence of NAFLD. *UCP3* is a mitochondrial protein with a highly selective expression in skeletal muscle, a major site of thermogenesis in humans. Genetic variants of *UCP3* have been associated with NIDDM and obesity [164].

Apolipoprotein C3 gene (*APOC3*) *rs2854117* and *rs2854116* variants and *farnesyl-diphosphate farnesyltransferase 1* (*FDFT1*) gene *rs2645424* variant have been also associated with NAFLD in adult [160]. Also in the recent years, genetic studies have demonstrated that single-nucleotide polymorphisms (SNPs) in genes involved in lipid metabolism (*Lipin 1, LPIN1*), oxidative stress (*superoxide dismutase 2, —SOD2*), insulin signaling (*insulin receptor substrate-1, IRS-1*) and fibrogenesis (*Kruppel-like factor 6, KLF6*) have been associated with a high risk for NAFLD development and progression [154]. Finally, a recent study evaluated the combined effect of four-polymorphisms genetic risk score in predicting NASH in NAFLD obese children with increased liver enzymes to help NASH diagnosis with the other non-invasive diagnostic tests [165].

In conclusion, obesity and fatty liver disease often go hand in hand even in the pediatric population, and both are pathologies related to genetic and environmental factors.

7. Genetic approach to obesity

Recognizing the monogenic syndromic and not syndromic obesity is really very important for at least two reasons: firstly, because it is hoped that, in the near future, making use of the results of other research in the field of obesity, obese patients can benefit from specific treatment (such as leptin administration and MC4R receptor agonists); secondly, because it is hoped that they will benefit from a multidisciplinary approach to the management of the symptoms, however, the clinical features of patients with genetic obesity are often very blurred, so that diagnosis can escape at first. **Figure 5** shows a diagnostic classification algorithm which can be useful in territorial pediatrics to suspect monogenic obesity and in the second and third levels in hospitals to orientate themselves in the execution of all the diagnostic tests in order to confirm the final diagnosis [12].

The genetic contribution to common obesity has been established initially through family, twin and adoption studies. Twin studies have shown a relatively high heritability ranging from 40 to 77% [6]. Gene identification for the last 15 years has been based on two genetic epidemiological approaches (candidate gene and genome-wide linkage methods). Recently, genome-wide association studies have brought great information on obesity-related genes.

Candidate-gene studies: The design of the candidate gene approach is simple; candidate genes are genes that, according to their characteristics, can be considered causally related to the

disease. This method is based on the following resources: animal models using gene knockout and transgenic approaches and cellular model systems showing their role in metabolic pathways involved in glucose metabolism. There are two main types of candidates that are generally considered in such studies: functional and positional. Functional candidates are genes with products that are in some way involved in the pathogenesis of the disease. Positional candidates are genes that are identified because they lie within genomic regions that have been shown to be genetically important in linkage or association studies, or by the detection of chromosomal translocations that disrupt the gene [2, 3]. The latest update of the Human Obesity GeneMap reported 127 candidate genes for obesity-related traits. Results of large-scale studies suggest that obesity is strongly associated with genetic variants in the *MC4R* gene, *adrenergic β3 receptor* (*ADRB3*) gene, *PCSK1* gene, *BDNF* gene and *endocannabinoid receptor 1* (*CNR1*) gene [16].

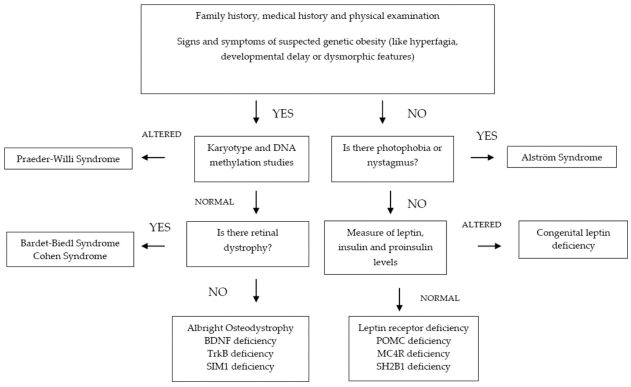

Figure 5. Diagnostic approach to genetic obesity. Adapted with permission from Farooqi and O'Rahilly [12].

Genome-wide linkage studies: Genome-wide linkage studies (GWLS) identify new, unforeseen genetic variants associated with a disease or a feature of interest. They rely on kinship of study participants and seek to identify chromosomal regions that tend to be co-inherited by individuals. The limit of genome-wide linkage studies is that they have a rather coarse resolution and typically identify broad intervals that require follow-up genotyping to pinpoint the genes that underlie the linkage signal [17]. The latest Human Obesity Gene Map update reported 253 loci from 61 genome-wide linkage scans, of which 15 loci have been replicated in at least three studies [16].

Genome-wide association studies: Genome-wide association studies (GWAS) are used in genetic research to look for associations between many (typically hundreds of thousands) specific genetic variations (more commonly, single-nucleotide polymorphisms, SNP) and particular diseases or traits. Genome-wide association studies have a higher resolution levels and are

able to narrow down the locus associated with greater accuracy, so this approach took place in the genome-wide linkage studies for common disease [3]. This new approach has found about 30 loci associated with obesity and high BMI. The strongest association is with FTO gene (the fat-mass and obesity-related gene) mutations. Also BDNF, SH2B1 e NEGR1 mutations are associated with obesity and support that obesity is a disorder of hypothalamic function [17].

Since the beginning of the genome-wide association study (GWAS) era in 2005, a number of large GWASs have been conducted on obesity-related traits in humans. A large meta-analysis from 46 studies conducted by the Genetic Investigation of Anthropometric Traits (GIANT) [166] consortium identified 32 SNPs robustly associated with adult BMI. The majority of these SNPs demonstrated directionally consistent effects in age- and sex-adjusted BMI in children and adolescents. However, even in combination, the 32 established SNPs explain <2% of the variation in BMI in either adults or children. The mismatch between the high heritability estimates from twin and other family studies (40–70%) and the small percentage of variation explained through GWAS (<2%) is called the problem of "missing heritability" [167, 168]. A portion of the missing heritability appears to be due to rare genetic variants and some non-additive genetic effects that are not found in analyses GWAS that showed only additional effects of common SNPs with minor allele frequencies (MAF) of >5%. Another part of the missing heritability can be explained by the fact that multiple additional common genetic mutations contribute to obesity, but they have a small effect that cannot be found by GWAS analyses [168].

New types of analyses, such as genome-wide complex trait analysis (GCTA), analysis of uncommon (MAF 0.5–1%) or rare (MAF 0.5%) variants and structural variants not detected by GWAS arrays, epigenetic analysis and gene–gene interactions (epistasis), are helping to fill that gap [167]. The purpose of the novel approach called genome-wide complex trait analysis (GCTA) is not to identify specific SNPs related to the target phenotype, but rather to estimate the total additive genetic effect of the common SNPs used on currently available DNA arrays [168].

The rare variant—common disease hypothesis—suggests that rare variants contribute significantly to complex traits. Probably, the obese phenotype is the consequence of additive effects and interactions among multiple alleles with varying magnitude of effect. Actually, we know that only 1% of the human genome is transcribed into mRNA and translated into proteins. An additional 0.5% is regulatory regions that control gene expression. Functions of the remaining 98.5% of the genome remain unknown. Rare variants might be identified by massive genotyping or deep sequencing in large families thanks to novel techniques that sequence millions of DNA strands in parallel and at low cost such as next-generation sequencing techniques [169].

Copy number variants (CNVs) represent another source of the heritability that is missed by GWAS studies. Copy number variants (CNVs) are products of genomic rearrangements, resulting in deletions, duplications, inversions and translocations [167, 170]. The most established CNV in the obesity field is a large, rare chromosomal deletion at 16p11.2; this deletion includes a small number of genes, one of which is *SH2B1*, known to be involved in leptin and insulin signaling. The search for CNVs in the context of obesity has proved fruitful,

and it has become quite clear they play a role in the missing heritability that still needs to be explained for the disease [19, 170].

8. Treatment options in patients with genetic obesity

The use of pharmacologic treatment for obesity is recommended by the American Academy of Pediatrics (AAP) as an adjunct to lifestyle changes when obesity-related health risks exist and lifestyle changes have not been effective for an individual. In addition, the AAP recommends pharmacotherapy only for children with BMI ≥99th percentile [171]. On the other hand, the Endocrine Society has suggested limiting pharmacotherapy to patients with a BMI over the 95th percentile who have failed diet and lifestyle intervention, or in limited cases with a BMI over the 85th percentile and severe comorbidities [147]. Overweight children should not be treated with pharmacotherapeutic agents unless significant, severe comorbidities persist despite intensive lifestyle modification. In these children, a strong family history of NIDDM or cardiovascular risk factors strengthens the case for pharmacotherapy [172].

There are currently only a few drugs approved for the treatment of obesity; such drugs belong to different pharmacologic categories with different mechanisms of action. A major class of medications used in weight treatment is appetite suppressants also called anorexigenic agents. These drugs increase hypotalamic levels of norepinephrine, dopamine and serotonin-promoting satiety and decreasing hunger [173]. Among the appetite suppressant drugs, sibutramine was used to treat obesity in children until recently. In 2010, sibutramine was withdrawn by the United States Federal Drug Administration (US FDA) and European Medicine Agency (EMA) for increased cardiovascular risk for individuals taking the medication [174]. As well, other drugs of the same class like ephedrine and fenfluramine were withdrawn from the market for their adverse effects [147]. With the withdrawal of sibutramine, orlistat and metformin are now the only available drugs for the treatment of pediatric obesity.

Orlistat, an inhibitor of pancreatic lipases, prevents the breakdown of triglycerides into absorbable fatty acids and monoglycerols. Thus, about one-third of the dietary intake, triglycerides is not absorbed. It reduces body weight, total cholesterol and LDL cholesterol, and the risk of NIDDM in adults with abnormal carbohydrate metabolism. In USA, orlistat is approved by the FDA in adolescents older than 12 years [175]. It is associated with a significant fall in BMI of 0.7 kg/m^2, but treatment is associated with increased rates of side effects including abdominal discomfort, pain, steatorrhoea and decreased absorption of the fat-soluble vitamins A, D, E and K. So, it is important to take those fat-soluble vitamins supplementation 2-h distance from orlistat administration [147]. Side effects are usually mild to moderate and generally decrease in frequency with continued treatment; this decrease may result from patients learning to consume less dietary fat to avoid these side effects. Typically, doses of 120 mg by mouth three times daily are needed for effectiveness [176, 177].

Although metformin has not been approved by the US FDA for the treatment of obesity, it may be effective as a weight loss agent in addition to its effects as a hypoglycemic agent. Its major site of action is the liver: the drug increases glucose uptake, decreases hepatic gluconeogenesis

and reduces hepatic glucose production; also, metformin inhibits lipogenesis and increases insulin sensitivity and may have an effect as an appetite suppressant. The major benefits of the medication are reduction of food intake, weight loss, visceral fat reduction, improvement of the lipid profile and of the carbohydrate intolerance [172, 175, 178]. A systematic assessed five randomized controlled trials all with follow-up of at least 6 months; compared to placebo, metformin reduced BMI by 1.42 kg/m^2 in obese children [179]. Patients treated with metformin report abdominal discomfort, which improves when the drug is taken with food. There is also a risk of vitamin B12 deficiency; therefore, a multivitamin is recommended. The risk of lactic acidosis has been observed in adults but not seen in pediatric patients [147].

Octreotide, a somatostatin analogue, has been investigated as a treatment for hypothalamic obesity. It binds receptors on the beta cells of the pancreas and inhibits insulin release [147]. A study comparing octreotide with placebo has demonstrated statistically significant weight loss and statistically significant mean decreases in BMI among those treated with octreotide for 6 months [180]. Octreotide works better in patients with insulin hypersecretion and insulin resistance. A study has demonstrated that greater weight loss correlated with a greater degree of insulin hypersecretion [181]. The high cost of the drug and the various side effects (gastrointestinal problems, gallstones, GH and TSH suppression, cardiac dysfunction) limit currently use [175].

In the case of monogenic obesity, subcutaneous injection of recombinant human leptin in children and adults with *LEP* mutations resulted in weight loss, mainly of fat mass, with a major effect on reducing food and hyperphagia, induction of puberty (even in adults) and improvement in T-cell responsiveness [24, 25, 27, 182]. Leptin treatment works in patients with leptin deficiency or with bioinactive leptin, but on the other hand, leptin treatment is useless in LEPR-deficient subjects, because the receptor mutations make it inactive [24, 183].

In the case of children with PWS, GH therapy can improve growth, body composition, muscle thickness, physical strength and agility, motor performance, fat utilization, and lipid metabolism [184–186]. The best response to GH in PWS patients is observed in the first 12 months of treatment. Although early treatment is important for the improvement in body composition, generally, in practice, it is possible to start treatment only after 2 years of age. Treatment can be started in a dose of 0.034 mg/kg/day (0.24 mg/kg/week) in infants, and toddlers and IGF-1 and IGFBP-3 levels are used to specify the dose of GH therapy. Benefits of continuing GH therapy in adulthood remain unclear although an improvement has been observed in body composition and cognitive functions in patients who received treatment only in adulthood. Contraindications for GH therapy in PWS patients are severe obesity, uncontrolled diabetes mellitus, untreated severe OSA, active cancer and psychosis [108].

A number of the PWS features, such as hyperphagia, obesity and behavioral anomalies, may be due to consequent hypothalamic hyposecretion of oxytocin for the reduction of paraventricular nucleus neurons. A few studies have investigated the capacity of exogenous oxytocin to improve these PWS features, but other research is necessary [183].

For MC4R-deficient obese patients, currently, there are no specific treatments. Different MC4R agonists were studied in vivo in animal and human studies, and almost all studies are currently

in the preclinical phase. These pharmacological MC4R agonists can restore normal activity in mutated receptors, and in obese animal, models cause decreased food intake, increased total energy expenditure, weight loss and weight-independent improvement of insulin sensitivity after 8 weeks of treatment [43, 187].

Finally, most recent studies on the treatment of obesity have focused on the potential role of plants used for obesity and its metabolic disorders treatments, exerting a positive effect on lipid and glucose metabolism, and anti-inflammatory activity [188]. For example, green tea disclosed anti-obesity effects in both *in vitro* and *in vivo*, decreasing adipose tissue through the reduction of adipocytes differentiation and proliferation, showing a positive effect in lipid profile, and lipid and carbohydrates metabolisms, and anti-inflammatory activity [188].

However, in literature, the anti-obesity properties and the mechanisms of action of some plants such as *Camellia sinensis*, *Hibiscus sabdariffa*, *Hypericum perforatum*, *Persea americana*, *Phaseolus vulgaris*, *Capsicum annuum*, *Rosmarinus officinalis*, *Ilex paraguariensis*, *Citrus paradisi*, *Citrus limon*, *Punica granatum*, *Aloe vera*, *Taraxacum officinale* and *Arachis hypogea* have been described [1[illegible]3]. However, polysaccharide macromolecules slowing the rate of carbohydrate and fat absorption have been resulted help reduce insulinemic peaks, enhancing β-cell function and potentially restoring the insulin secretory reserve in patients with IGT or NIDDM and genetic obesity history [189].

Another possible therapy for childhood obesity is bariatric surgery. There are 3 types of bariatric procedures: malabsorptive, restrictive and combination procedures. The first procedures are the jejunoileal bypass and the biliopancreatic diversion with duodenal switch that manage to lose weight by reducing nutrient absorption through the gut anatomical rearrangements; however, these procedures are not approved in children for their high morbidity and mortality. The Roux-en-Y gastric bypass (RYGB) is a combination procedure; it has become the most commonly performed bariatric surgical procedure, and it involves a reduction of stomach size and the reduction of intestinal absorptive capacity via the creation of a gastrojejeunal anastomosis [171, 172, 190]. Laparoscopic adjustable gastric banding (LAGB) is a wholly restrictive procedure, and it has been used more recently. This bariatric procedure is to place a balloon around the esophagogastric junction and inflate it with saline until you get the desired effect of the stomach size reduction. This procedure is recommended in children because it is reversible and does not create permanent intestinal rearrangements [171, 172, 191]. Laparoscopic sleeve gastrectomy (LSG) is a new and attractive option for young patients. It is a new restrictive procedure without the malabsorptive component present in other bariatric procedures. This technique involves the removal of a large portion of the stomach through a vertical resection, and the remaining stomach has a volume drastically reduced, with a capacity of around 100/150 ml. Weight loss outcomes in some study were similar between pediatric and adult patients at all time points, suggesting that LSG is similarly safe and effective in young and adult patients through at least 1 year of follow-up [192].

The criteria for access to bariatric surgery in childhood are very restrictive: BMI >35 kg/m^2 with severe comorbidities or >40 kg/m^2 with comorbidities, Tanner stage 4 or 5, to achieve at least 95% of the growth estimate in the case of malabsorptive procedures, the ability to follow the post-operative diet and exercise, an adequate social support, ability to follow constantly

medical indications and treatment and appropriate treatment of psychological problems [190]. Also it is recommended that bariatric surgery be done only in centers that can provide a multidisciplinary pre- and post-operative evaluation and psychological support both before and after the surgery [193].

Currently, data on bariatric surgery in children and adolescents with genetic obesity are limited and still controversial [183]. To date, bariatric surgery experience in treating children and adolescents with monogenic and syndromic forms of obesity is limited, and different bariatric procedures have been used with varying success [194]. Some studies have demonstrated the efficacy of bariatric surgery (in terms of weight loss and reduction of comorbidities such as obstructive sleep apnea, dyslipidemia, hypertension, diabetes mellitus and poor mobility) in patients with monogenic obesity (such as LEPR-deficient patients and patients with heterozygous *MC4R* mutations, but not in patients with homozygous *MC4R* mutation [195]) and syndromic obesity (such as PWS, BBS, Alström syndrome) but, due to the limited number of cases, the long-term efficacy and safety of bariatric surgery in genetic forms of obesity need further evaluation [183].

Even more in the early days are studies that try to correlate specific polymorphisms with response to bariatric surgery: For example, a study tried to find the presence of an association between several polymorphisms (including the *FTO* and *MC4R* genes) with post-operative weight loss [196]; another study found that a 15q26.1 locus is significantly associated with weight loss after Roux-en-Y gastric bypass surgery [197]. Thus, there is some evidence for the use of genomics to identify response to surgical procedures; the identification of genetic contributors could be useful to select those individuals who will obtain a greater benefit from a bariatric surgery. However, these results have yet to be confirmed.

9. Hyperphagia: etiopathogenesis and treatment

In the modern environment of plenty, obesity is favored by biological features that generally are advantageous in a restrictive environment, such as attraction to palatable and energy dense foods, slow satiety mechanisms and high metabolic efficiency [198].

The control of food intake and energy expenditure consists of a complex network of neural and hormonal systems that involving many genes [199]: in particular, the informations are collected at the peripheral level (intestine, stomach, adipose tissue); then, they are processed at the hypothalamic level and, finally, generate behavioral, endocrine and autonomic output [198].

In particular, much larger portions of the nervous system of animals and humans, including cortex, basal ganglia, and the limbic system, are concerned with the procurement of food as a basic and evolutionarily conserved survival mechanism to defend body weight [200]. These systems are directly and primarily involved in the interactions of the modern environment and lifestyle with the human body [198]. By focusing on the neural reward systems and the interaction between reward and homeostatic functions, it is possible to infer that the disturbance of this relationship determines obesity (**Figure 6**).

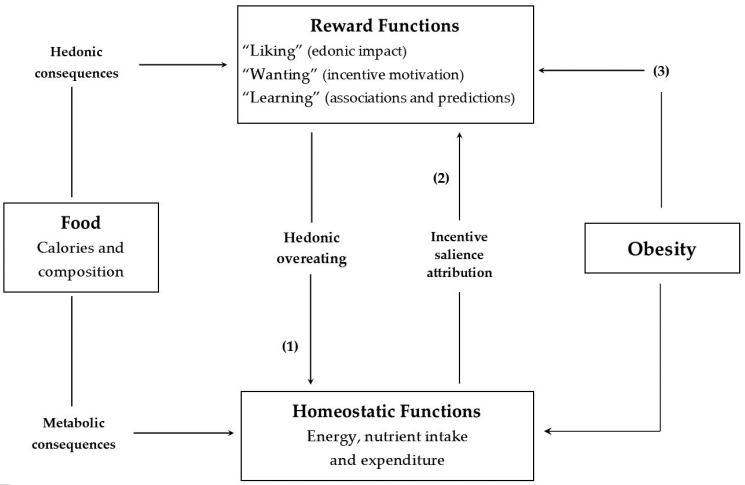

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Figure 6. Relationship between metabolic and hedonic controls of food intake and energy balance. Adapted with permission from Berthoud et al. [196].

This process can generate hedonic and metabolic consequences, which are independent from each other: in particular, the hedonic consequences are regulated by reward functions while the metabolic consequences of food (defined in terms of their input of energy and their effects on body composition, particularly increased fat accretion as in obesity) are regulated by homeostatic functions.

The alteration of reward functions may be a cause (i.e., excessive caloric intake modulated by hedonic value of food (1)) and/or a consequence (induced by obese state (3)) of obesity [198].

As schematically depicted in **Figure 6**, several potential interactions exist between food reward and obesity.

In particular, there are three fundamental mechanisms involved in the development of obesity, which are not mutually exclusive, but a combination of all three is operative in most individuals: excessive intake of palatable and energy dense foods, differences (genetic and other pre-existent) in reward functions and increase of obese state consequently to alterations of reward functions induced by obesity [198].

It is also important to realize that hyperphagia is not always necessary for obesity to develop, as the macronutrient composition of food can independently favor fat deposition.

In this regard, there is the "*gluttony hypothesis*" emerged from several studies in animals: in particular, although reward functions are not altered unlimited access to palatable food and

food cues leads to excessive caloric intake (hedonic overeating) and, consequently, to obesity (defined as diet-induce obesity) [198].

However, it is important to underline that not all individuals exposed to environment of plenty show an increased food intake and weight gain; this means that there are genetic and epigenetic pre-existing alterations that make some individuals more vulnerable to the increased availability of palatable food and food cues [198].

One of the key questions is how the motivation to get a reward will translate into action. In most cases, the motivation for something comes from the pleasure that this has generated in the past, or in other words, to obtain what has been helpful. The dopamine signal seems to be a critical component in this process [198].

The limited information available suggests that repeated sucrose access can upregulate dopamine release [201] and dopamine transporter [200] and change dopamine D1 and D2 receptor availability [201] in the nucleus accumbens. AQ1

As demonstrated by some observations, such pleasing foods have a high potential for addiction for which the withdrawal from it can cause symptoms such as anxiety, stress, depression resulting behavior of relapse because of occurring neural and molecular changes. Therefore, it is critical for switching the cycle of addiction and the prevention of a further spiral of addiction [198].

An issue on which to focus is that excessive caloric intake, as part of a disease, can gradually worsen: in fact at the beginning, there is overeating; then, the individual eats also in the absence of physiological hunger. Subsequently, there will be loss of control over eating (binge eating), and finally, hyperphagia defined as a hallmark of inherited disorders, in which obesity is present [203].

The term "hyperphagia" includes a series of conditions, such as binge eating disorder, hormonal imbalances such as glucocorticoid excess, leptin signaling abnormalities, syndromes associated with obesity and cognitive impairment (e.g., PWS) [203] and can be used in different situations: for example, to evaluate hunger and satiety through appropriate scales for pathological individuals compared to healthy individuals [203], to evaluate excessive caloric intake and the impact on body size and body composition in pathological individuals [203] or to evaluate preoccupation and psychological symptoms such as anxiety, stress due to hyperphagic behavior and the consequences that it determines (e.g., continuous search for food, night eating, ingestion of inedible food, theft of food, etc.) [203].

A person with hyperphagia has an obsessive and compulsive behavior towards food and often continues to eat for a long time, even if he/she feels full. This excessive nutriment can cause abdominal pain, guilt or drowsiness.

In particular, obesity is associated with dysregulated signaling systems, such as leptin and insulin resistance, as well as increased signaling through proinflammatory cytokines and pathways activated by oxidative and endoplasmatic reticulum stress [204] (**Figure 7**).

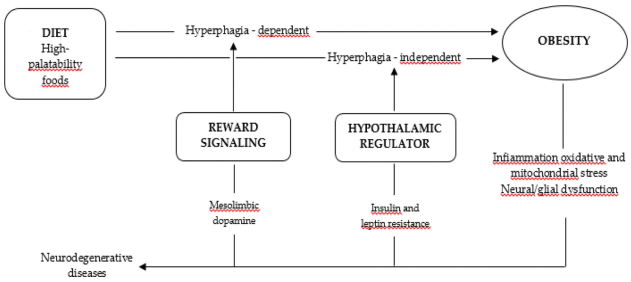

Figure 7. Secondary effects of obesity on reward circuitry and hypothalamic energy balance regulation. Adapted with-permission from Berthoud et al. [198].

As schematically depicted in **Figure 7**, obesity and, in turn, neurodegenerative diseases may be caused by leptin resistance, central insulin and altered regulation of energy balance, controlled by hypothalamus. About the latter, the literature shows that mitochondrial and oxidative stress increase due to high-fat diets leading to neural/glial dysfunction and, consequently, cytotoxic effects [198].

However, these toxic effects do not stop at the level of the hypothalamus but can also affect brain areas involved in reward processing [198].

10. Nutritional and behavioral approach to genetic obesity

The approach to the child with genetic obesity is very complex considering that obesity is associated with a number of complications that include the health of the child, and it must be focused on the entire family. Awareness about the problem by all family members and, in particular, changes in lifestyle and nutrition of the family are the most effective means both to ensure the compliance to the treatment, the success of the therapy and the maintenance of the long-term results.

The family, especially the parents, should be actively involved in the therapeutic program and become protagonists. The targeted intervention with "individual" programs only for the child, on the contrary, is often unsuccessful and frustrating for the child himself [205].

According to NICE guidelines on weight management in children dating from 2014 [206], it is important to:

- coordinate the care of children and young people around their individual and family needs [206];
- assess and intervene to improve child's health, considering his age and maturity. It is important to set goals based on needs and preferences both of the child that of the whole family [206];

- create an environment that promotes lifestyle changes within the family and in social settings. Parents (or carers) are responsible of these changes, especially if children are younger than 12 years old [206].

The initial assessment is important to collect data necessary for diagnosis and subsequent treatment. In particular, these informations regarding patient history (personal, familiar, healthy and social history), food/nutrition-related history (eating patterns, diet experience, physical activity, beliefs and attitudes about eating, etc.), anthropometric measures (current weight, weight history, etc.), biochemical data and medical tests (e.g., lipid profile, glucose profile, etc.); what the person has already tried and how successful this has been will be discussed, and what they learned from the experience; the person's readiness to adopt changes and their confidence in making changes will be assessed [206].

Multicomponent interventions are the treatment of choice. Weight management programs must include behavior change strategies to increase people's physical activity levels or decrease inactivity, improve eating behavior and the quality of the person's diet and reduce energy intake [206].

In particular, nutrition offered to obese children must also ensure the maintenance of adequate rhythms of growth and promote the maintenance of lean body mass (in particular of muscle mass), which represents the metabolically active compartment, and it is the large part of the total energy expenditure. Therefore, it must necessarily guarantee the macro- and micro-nutrients intake in relation to their age [205].

In overweight and obese children and young people, it is important a multidisciplinary intervention that includes dietary recommendations appropriate for age and complies with the principles for a healthy nutrition (in these patients, total energy intake should be below their energy expenditure) [206].

Dietary changes should be tailored to food preferences and allow for a flexible and individual approach to reducing calorie intake; it is important not to use unduly restrictive and nutritionally unbalanced diets because they are ineffective in the long term and can be harmful [206].

In these patients, it is also necessary that an intervention about physical activity is important not only for lose weight, but also for other health benefits, such as reduction risk of type 2 diabetes or heart diseases [206].

Therefore, obese and overweight children must be encouraged to become more active and to reduce inactive behaviors, such as sitting and watching television, using a computer or playing video games and to do at least 60 min of moderate or greater intensity physical activity each day. The activity can be in 1 session or several sessions lasting 10 min or more [206].

It is important to make the choice of activity with the child and ensure that it is appropriate to the child's ability and confidence, giving children the opportunity and support to do more exercise in their daily lives (e.g., walking, cycling, using the stairs and active play) or to do more regular, structured physical activity (e.g., football, swimming or dancing) [206].

Children affected by genetic obesity (e.g., PWS) often eat more than necessary for anxiety, sadness, boredom: in this case, it is important not only to reduce the amount of foods but also

to search for reasons of suffering causing the overeating. It is important, therefore, to reconstruct the individual's self-esteem [206].

There are, however, barriers to parental involvement in the child's treatment: in some families, for cultural or psychological reasons, parents do not perceive their child as obese. In other families, parents may acknowledge that the child is obese but denies that this condition can have consequences.

Therefore, it is crucial to raise awareness among parents of the need to intervene, especially when behavioral changes are needed in the family [207].

Focusing on hyperphagic children, particularly those affected by Prader–Willi syndrome, parents must learn to celebrate each small goal, large or small, and to appreciate the acquisition of any new skill [208].

In these children, there are behavior changes that become more apparent and severe with age: in fact, they are concerned about food, hypersensitive, agitated, aggressive, impulsive, anxious. These behaviors are caused specially by their insatiable appetite that causes physical, emotional and social problems [209].

For these reasons, it is important to intervene to reduce stress not only for children, but also for the whole family.

However, to control the anxious behavior in children with PWS, the following information may be useful:

- having a regular daily routine, following appropriate food program;
- giving your child transitional warnings—that is, "after you finish that puzzle, it is time for bath" [209];
- preparing your child ahead of time if there is going to be a change in routine;
- re-directing your child to another activity;
- using positive reinforcement;
- speaking to your child in a calm, yet firm matter-of-fact tone [209].

In children with PWS, it is essential management food, based also on control food access, to ensure adequate nutrition, weight regulation and appropriate eating behaviors.

Crucial in this regard is the role of parents, who must support their children in these changes by adopting appropriate strategies.

However, each family will find the best way for them and for the specific need of their child.

First of all, it is important to follow an adequate food program that helps parents to monitor their food intake and reassures the child that the food will always be available: therefore, it represents the beginning for him to acquire the habit of eating healthy so that food can be controlled and could become a part of his daily routine [209].

This program is based on three main meals (breakfast, lunch, and dinner) and two or three snacks (mid-morning snack, afternoon snack, and perhaps evening snack) [209]. It is fundamental to respect scheduled times (food must be given every 2–3 h), avoiding giving food outside mealtimes. Whenever possible, all family members should eat at the same time and others should not eat in front of the child when it is not their scheduled meal/snack time [209].

Portion control is another adequate strategy: it must not be excessive, but appropriate for the child's age to ensure adequate growth [209].

However, food must be healthy considering that in children with PWS, calorie needs are lower due to reduced metabolism. Food must be given only by parents/caregivers and served on the plate prior to being eaten, avoiding other platters/bowls of food visible on the table and to share or offer them other food [209].

At the end of the meal, it is important to remove the empty plate from the table and encourage the child to play away from the table or from the kitchenette until all food has been taken away. It is important to keep food out of sight and reach of children, keeping it under lock and key if necessary (**Figure 8**). AQ2

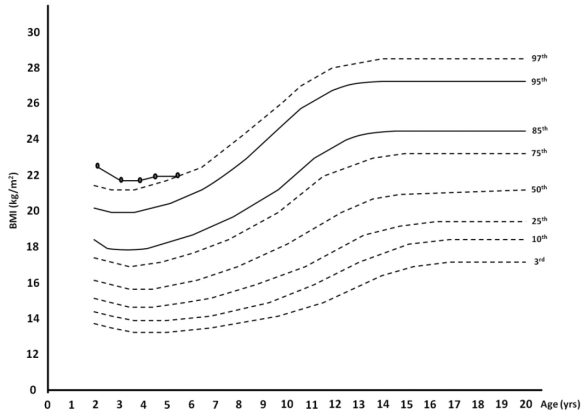

Figure 8. Girl with Bardet-Biedl syndrome. You can see the amelioration of the BMI after the interdisciplinary approach to hyperphagia.

11. Conclusions

This chapter may bring a significant contribution to the updating of knowledge of the genetic susceptibility and provide a better clarification of which variants are truly associated with the

predisposition to develop an obese phenotype. This chapter may also help to understand better the genetic diversity that could be associated in subjects with genetic forms of obesity. However, this chapter may help to understand this complex problem and the different approaches to treatment. In these forms of genetic obesity, the team approach to therapy (nurse educators, nutritionists, exercise physiologists, and counsellors) is the basis for treatment. Dramatic reductions in BMI are difficult to achieve and sustain, so counselling and therapy should start with realistic goals that emphasize gradual reductions of body fat and BMI and maintenance of weight loss. Finally, this chapter may provide news on the need for new therapeutic approaches in the field of childhood obesity as the basis of the hyperphagia treatment, a typical feature of these syndromes.

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