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REVIEW

A Comprehensive Review of Syndromic Forms of Obesity: Genetic Etiology, Clinical Features and Molecular Diagnosis

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Abstract

Syndromic obesity refers to obesity occurring with additional clinical findings, such as intellectual disability/developmental delay, dysmorphic features, and congenital malformations.

Purpose of Review To present a narrative review regarding the genetic etiology, clinical description, and molecular diagnosis of syndromic obesity, which is a rare condition with high phenotypic variability and genetic heterogeneity. The following syndromes are presented in this review: Prader-Willi, Bardet-Biedl, Pseudohypoparathyroidism, Alström, Smith-Magenis, Cohen, Temple, 1p36 deletion, 16p11.2 microdeletion, Kleefstra, *SIM1*-related, Börjeson-Forssman-Lehmann, WAGRO, Carpenter, MORM, and *MYT1L*-related syndromes.

Recent Findings There are three main groups of mechanisms for syndromic obesity: imprinting, transcriptional activity regulation, and cellular cilia function. For molecular diagnostic, methods of genome-wide investigation should be prioritized over sequencing of panels of syndromic obesity genes. In addition, we present novel syndromic conditions that need further delineation, but evidences suggest they have a higher frequency of obesity.

Summary The etiology of syndromic obesity tends to be linked to disrupted neurodevelopment (central) and is associated with a diversity of genes and biological pathways. In the genetic investigation of individuals with syndromic obesity, the possibility that the etiology of the syndromic condition is independent of obesity should be considered. The accurate genetic diagnosis impacts medical management, treatment, and prognosis, and allows proper genetic counseling.

Keywords Syndromic obesity · Genetic etiology · Molecular diagnosis · Neurodevelopment · Hyperphagia

Introduction

Obesity is a growing public health problem with high prevalence [1], affecting an increasing number of countries worldwide [2]. This condition is formally defined as a body mass index [BMI = weight (Kg) / height $(m)^2$] ≥ 30 for adults [3]. For children and adolescents, the diagnosis is given when BMI is above the 95th centile considering population data of the same age and sex [4].

The etiology of obesity is mostly multifactorial [5] and its heritability is high. Evidence from twins, families and adoption studies have shown heritability estimates ranging from 40 to 70% [6]. Cases of major underlying medical causes (monogenic or endocrine disorders, cerebral or medication-induced obesity) are rare and a relatively low etiological diagnostic yield has been reported [7•]. Typically, obesity cases related to deleterious variants in leptin-melanocortin pathway genes such as *LEP, LEPR, POMC, MC4R, MC3R, PCSK1*, and *SH2B1* are classified as nonsyndromic monogenic forms [8••]. Kleinendorst et al. (2018) [9•] investigated 1230 patients with obesity; 48 (~4%) were diagnosed with genetic obesity, 29 (~2.4%) of whom had pathogenic variants in the above-mentioned genes. Another study

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conducted by the same research group [7•] focused only on cases of pediatric obesity (younger than 18 years); among 282 evaluated individuals, 37 (~13%) were diagnosed with genetic obesity - 17 of them (~6%) with pathogenic variants in these leptin-melanocortin pathway genes -, 8 (~3%) had cerebral injury affecting the hypothalamic centers for weight regulation (e.g., tumor in the hypothalamic region), and 9 (~3%) presented medication-induced obesities.

Syndromic obesity is a generic clinical term that refers to cases of obesity occurring with additional clinical findings [8••, 10••, 11–14]. The majority of cases present with developmental delay/intellectual disability [8••, 14–16] and may also exhibit dysmorphic features or congenital malformations [8••, 10••, 11–14]. Syndromic forms of obesity are rare [8••, 17–19] and present high phenotypic variability [8••, 13, 19]. Often, syndromic obesity has a monogenic origin (autosomal or X-linked) [8••].

Kaur et al. [8••], in a systematic review, reported 79 obesity syndromes with obesity considered to be a cardinal feature in 55 of them, while the prevalence of obesity in the other 24 syndromes was higher than that in the general population. Prader-Willi and Bardet-Biedl are the best-known genetic syndromes in which obesity is a central feature [8••]. Examples of genetic disorders in which obesity is often a relevant feature are briefly presented in Table 1 and they will be discussed in detail in this narrative review. Our focus are the syndromes of greatest interest in clinical practice, their clinical description, genetic etiology, and molecular diagnosis. There are different genetic causes associated with these described syndromes, including variants in genes with classic Mendelian patterns, copy number variations (CNVs) and imprinting alterations.

Genetic changes in the leptin-melanocortin pathway result in hypogonadotropic hypogonadism, low blood pressure, behavioral problems, cholestasis and seizures, in addition to obesity; we may consider that these pleiotropic clinical manifestations could fit the definition of syndromic obesity. However, we do not will describe these forms, which are most commonly described in the literature as nonsyndromic monogenic forms, although a gray area in the distinction between syndromic and nonsyndromic forms of obesity is discussed by Kaur and colleagues [8••]. In this manuscript, we will discuss forms of obesity that are usually classified as syndromic, in which obesity is considered a cardinal feature associated with additional clinical characteristics. We also briefly introduced a discussion about novel syndromic conditions for which obesity has been considered relevant, recently described and whose phenotypes are still under delineation.

Main Syndromic Forms of Obesity

Prader-Willi Syndrome

The prevalence of Prader-Willi syndrome is estimated at 1:8333 to 1:52,000 live births [20–26]. Frequent features of Prader-Willi syndrome patients include profound hypotonia in early childhood, hypogonadotropic hypogonadism, developmental delay, intellectual disability, and short stature [27, 28]. Patients often have a narrow forehead, almond-shaped eyes, and a narrow nasal bridge [27]. Hands are small [29], and the fingers can be tapered at the tips; hypopigmentation of the hair, eyes and skin is common due to the loss of a copy of the *OCA2* gene (Fig. 1A), relevant for melanocytes. Features such as strabismus and scoliosis are often also present [27]. In addition, some patients have a high pain threshold [28]. Another relevant feature is a decreased fetal movements and growth restriction compared with unaffected siblings [27].

Motor development is delayed. Regarding intellectual development, they can learn to read, write and do simple arithmetic calculations. They also have a special skill in assembling puzzles. The average intelligence quotient is between 60 and 70 [30] and behavioral problems are common (70–90%). Psychosis occurs in adulthood in 10 to 20% of cases [27]. Some individuals have depression, possessiveness, and a tendency to steal and lie. The habit of picking wounds is also frequent [28].

In Prader-Willi patients there are complex nutritional phases. Typically, up to 15 months (median age at completion: 9 months) the patients present with difficulty feeding due to hypotonia and may be failure to thrive. At 5 to 15 months (median 9 months), constant growth begins, and weight is increasing at a normal rate. The weight increases without a significant change in appetite or caloric intake around 2.08 years old. A most relevant weight gain is associated with a concomitant increased interest in food around 4.5 years old. Marked hyperphagia typically accompanied by food seeking and lack of sense of satiety begins at 8 years old (median), which leads to the development of severe obesity, primarily of central distribution (abdomen, buttocks, and thighs). Most individuals go through these typical nutritional phases [27]. Lack of satiety and cognition problems often cause patients to ingest inedible food (frozen, raw and even spoiled food) [30], but some adults progress and no longer have the insatiable appetite of the previous nutritional phase [27].

Obesity is the main cause of metabolic complications [31], and death in Prader-Willi syndrome patients [32]. Early dietary and lifestyle interventions, with restricted access to food and control food intake (food security

Table 1 Syndromic obesity disorders described in this review and classification by their main genetic etiology

Syndrome (OMIM number)	Gene(s) involved	Inheritance	Hypotonia (infancy)	Hyperphagia	Obesity	Other clinical findings
imprinting disorders						
Prader-Willi syndrome (#176270)	*NDN*, *SNRPN*	maternal imprinting	+	+	starts at 1–6 years old	ID; motor DD; behavioral problems; short stature; hypopigmentation; facial dysmorphisms; hypogonadism; small hands/feet
Pseudohypoparathyroidism 1a (#103580)	*GNAS*	paternal imprinting	–	+ (mild)	starts in the 2 first years of life	cognitive impairment (ID is rare); parathyroid hormone resistance; multiple hormone resistance; reduced erythrocyte Gsα activity; short stature; round facies; thickened calvaria; ectopic soft tissue or dermal ossification(s); brachydactyly
Pseudohypoparathyroidism 1c (#612462)			–	+ (mild)	starts in the 2 first years of life	cognitive impairment (ID is rare); parathyroid hormone resistance; multiple hormone resistance; normal erythrocyte Gsα activity; short stature; round facies; thickened calvaria; ectopic soft tissue or dermal ossification(s); brachydactyly
Pseudopseudohypoparathyroidism (#612463)		maternal imprinting	–	–	obesity is less common and, if present, it is not severe	cognitive impairment (ID is rare); no resistance to parathyroid hormone or other hormones; reduced erythrocyte Gsα activity; short stature; round facies; thickened calvaria; ectopic soft tissue or dermal ossification(s); brachydactyly
Temple syndrome (#616222)	*DLK1, RTL1, DIO3*	maternal imprinting	+	±	birth weight is frequently below average; obesity ~49% of patients; starts at 4–6 years old	low birth weight; motor DD/speech delay; short stature; precocious puberty; facial dysmorphisms; hyperextensible joints; small hands/feet
monogenic disorders						

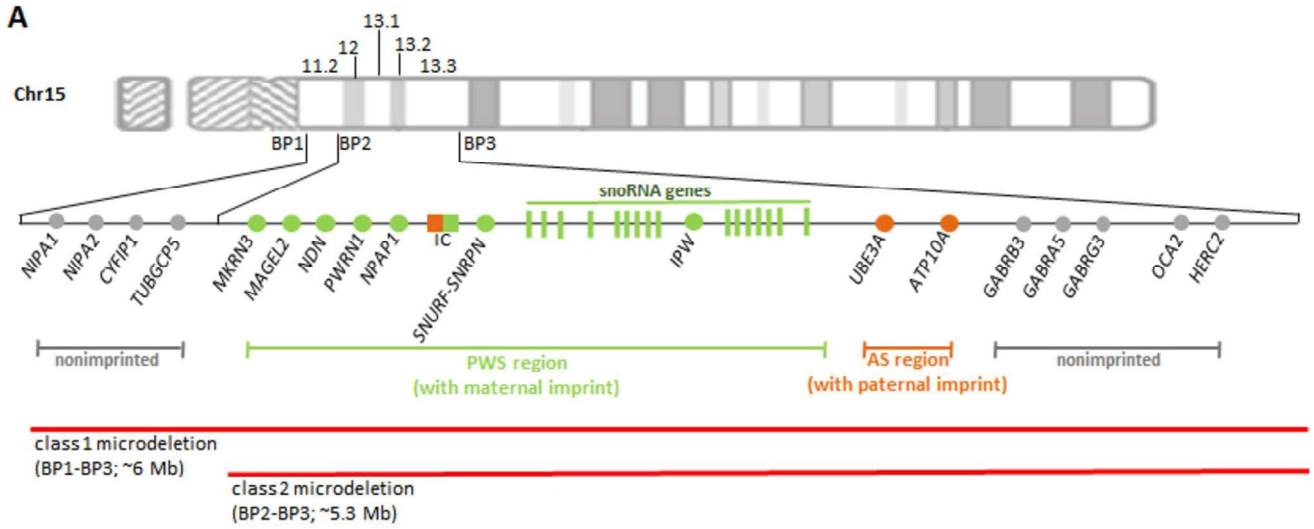
Table 1 (continued)

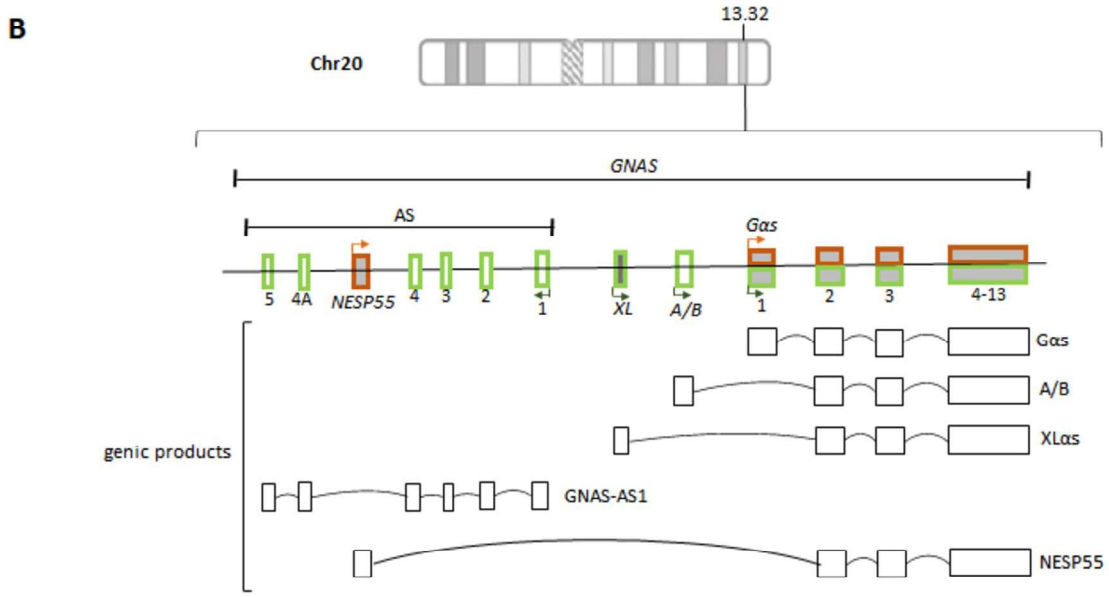
Syndrome (OMIM number)	Gene(s) involved	Inheritance	Hypotonia (infancy)	Hyperphagia	Obesity	Other clinical findings
Alström syndrome (#203800)	*ALMS1*	AR	–	+	excessive weight gain after the first year of life; BMI of most young children is >95th centile	early onset retinal degeneration; hearing loss observed in the first decade (progressive and severe); type 2 diabetes mellitus; dyslipidemia; arterial hypertension; low testosterone in males and hyperandrogenism in females; dilated cardiomyopathy; respiratory problems
Cohen syndrome (#216550)	*VPS13B*	AR	+	not characterized	truncal; increased waist circumference becomes evident at 5–12 years, but does not always lead to an obesity BMI	ID; motor DD; speech impairment; microcephaly; facial dysmorphisms; ophthalmologic problems; high-pitched crying and voice; joint hypermobility; narrow hands/feet; leukopenia (mainly neutropenia)
Börjeson-Forssman-Lehmann syndrome (#301900)	*PHF6*	XLR	+	not characterized	truncal obesity	ID (mild to moderate); motor DD; speech impairment; facial dysmorphisms; gynecomastia; hypogonadism; characteristic digit anomalies; hyperextensible fingers; abnormal hands/feet
Carpenter syndrome type 1 (#201000)	*RAB23*	AR	–	–	high birth weight; late obesity	central nervous system malformations; multiple suture craniosynostosis, facial dysmorphisms; heart defects; umbilical hernia; cryptorchidism; hypoplastic testes; broad or bifid thumbs, absent or small middle phalanges, polysyndactyly of hands/feet; bowed femur and tibia
Carpenter syndrome type 2 (#614976)	*MEGF8*	AR	–	–	tendency of high birth weight and childhood obesity	multisuture craniosynostosis; facial dysmorphisms; heart defects; hypoplastic and/or supernumerary nipples; umbilical hernia; cryptorchidism; polysyndactyly of hands/feet
Mental retardation, truncal obesity, retinal dystrophy, and micropenis (MORM - #610156)	*INPP5E*	AR	–	–	obesity apparent in childhood	ID/ speech impairment; retinal dystrophy (reduced visual acuity by 3 years old; usually not progressive); micropenis

Table 1 (continued)

Syndrome (OMIM number)	Gene(s) involved	Inheritance	Hypotonia (infancy)	Hyperphagia	Obesity	Other clinical findings
MYT1L-related syndrome (#616521)	*MYT1L*	AD	–	+	~58% of patients have overweight/obesity (usually beginning in early childhood)	ID; behavioral disorders; speech impairment; facial dysmorphisms
mono/digenic disorder						
Bardet-Biedl syndrome	various (see Table 2)	AR/DR	–	+	72–92% of patients; significant weight gain in the first year of life	ID; retinal degeneration with progressive visual impairment; blindness occurs, on average, at 15.5 years; kidney disorders; hypogonadism (in men); polydactyly
Genomic disorders						
Smith-Magenis syndrome (#182290)	*RAI1* CNV: 90%; SNV/indel: 10%	AD	+	satiety impairment	childhood-onset abdominal obesity	DD, mild-to-moderate ID, behavioral abnormalities, sleep disturbance, short stature; typical coarse facial features that progress with age
Kleefstra syndrome type 1 (#610253)	*EHMT1* more cases involving microdeletions than SNV/indel	AD	+	–	overweight at birth; early onset obesity	ID (moderate to severe); motor DD; severe delayed or absent speech; behavioral problems; sleep disorder; seizures; microcephaly; brachycephaly; facial dysmorphisms; congenital heart disease
SIM1-related syndrome (*603128)	*SIM1* more cases involving deletions than SNV/indel	AD	+	+	early onset obesity	developmental delay; hypothyroidism also has been reported in several cases
1p36 deletion distal syndrome (#607872)	*UBE4B, CASZ1*	AD	+	+	after infancy	DD; short stature; craniofacial dysmorphisms
16p11.2 deletion syndrome; 220 Kb; BP2 – BP3 (#613444)	*SH2B1*	AD	–	+	severe early-onset obesity	cognitive deficits; DD; autism
16p11.2 deletion syndrome; 593 Kb; BP4 - BP5 (#611913)	*KCTD13* and possibly *MAZ, TAOK2, CORO1A, PRRT2, TBX6,* and *CTD13*	AD	–	+	evolves throughout childhood; in adulthood, ~75% of patients have obesity	ID; speech impairment; motor coordination difficulties; autism; facial dysmorphisms
Wilms tumor, aniridia, genitourinary anomalies, DD/ID, and obesity (WAGRO - #612469)	*WT1, PAX6,* and *BDNF*	AD	+	+	childhood-onset obesity; 2/3 of individuals presenting deletion encompassing *BDNF* have obesity	Wilms tumor; aniridia; genitourinary anomalies; DD/ID; and obesity

AD - autosomal dominant, DR - digenic recessive, AR - autosomal recessive, ID - intellectual disability, DD - developmental delay, CNV - copy number variations, SNV - single nucleotide variations, BMI - body mass index


A
Chr15
13.1
12
13.2
11.2
13.3
BP1
BP2
BP3
snoRNA genes
NIPA1
NIPA2
CYFIP1
TUBGCP5
MKRN3
MAGEL2
NDN
PWRN1
NPAP1
IC
SNURF-SNRPN
IPW
UBE3A
ATP10A
GABRB3
GABRA5
GABRG3
OCA2
HERC2
nonimprinted
PWS region
(with maternal imprint)
AS region
(with paternal imprint)
nonimprinted
class 1 microdeletion
(BP1-BP3; ~6 Mb)
class 2 microdeletion
(BP2-BP3; ~5.3 Mb)


B
Chr20
13.32
GNAS
AS
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4A
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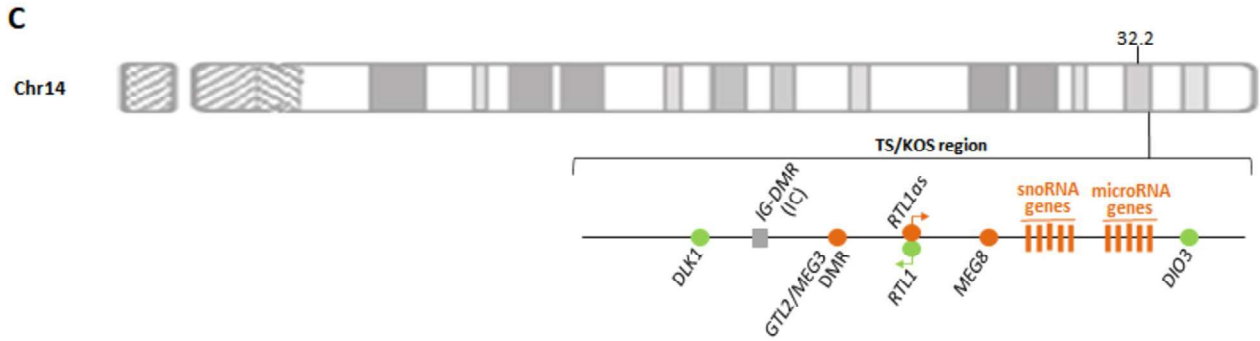
XLαs
GNAS-AS1
NESP55


C
Chr14
32.2
TS/KOS region
IG-DMR
(IC)
RTL1os
snoRNA
genes
microRNA
genes
DLK1
GTL2/MEG3
DMR
RTL1
MEG8
DIO3

◂**Fig. 1** Syndromic obesity mechanisms involving uniparental imprinting. **A, B, and C** - The genes expressed exclusively from the paternal chromosome (maternal imprinting) are in green, while those expressed from the maternal chromosome (paternal imprinting) are in orange. Not drawn to scale. **A** - PWS – Prader-Willi syndrome; AS - Angelman syndrome; BP1 - breakpoint 1; BP2 - breakpoint 2; BP3 - breakpoint 3; IC - imprinting centers for PWS (green) and AS (orange). **B** – *GNAS locus*. Exons expressed by the maternal chromosome are surrounded by the color orange, while those expressed by the paternal chromosome are surrounded by the color green; biallelic expression exons are circled in orange at the top and green at the base. Arrows indicate transcriptional start sites and transcriptional direction. Black line boxes and connecting lines depict exons and introns, respectively, that code for the named proteins. Several other transcripts arise from differentially methylated promoters, including the maternally expressed *NESP55* and the paternally expressed *XLαs* and *A/B*. **C** - TS – Temple syndrome; KOS - Kagami-Ogata syndrome; IC - imprinting center; IG-DMR - intergenic differentially methylated region. Arrows indicate the transcriptional direction for *RTL1as* and *RTL1*. In most tissues

approach), associated with the use of growth hormone therapy, have profound impact in preventing obesity and improving body composition in these patients [33].

The phenotype results from a lack of the expression of paternally inherited alleles of genes in the 15q11-q13 imprinted region [13, 27, 34], usually due to paternal microdeletion (approximately 65–75%) or maternal uniparental disomy 15 (20–30%), but imprinting defects also occur in a minority of cases (1–3%) [27, 35]. Chromosomal rearrangements can also cause Prader-Willi syndrome but are rarer [36]. Angelman syndrome is another genetic disorder related to changes in the same region of chromosome 15, but caused by the absence of expression of alleles on the maternal chromosome and with markedly distinct phenotypes [37].

The Prader-Willi region is crucial for hypothalamus development and function [36]. Figure 1A shows the structure of the 15q11-q13 region and specifies the genes that are expressed exclusively from the paternal chromosome (maternal imprinting) and those expressed from the maternal chromosome (paternal imprinting). Hypothalamic dysfunction is the basis of Prader-Willi syndrome pathophysiology, which includes a deficiency in growth and reproductive hormones, circadian rhythm abnormalities, and a lack of satiety. Structural hypothalamic changes include significantly smaller hypothalamic paraventricular nucleus volume and reduction in cell number [38].

High-level of ghrelin, a hormone produced by the gastric mucosa that has an orexigenic action, has been well documented [39], however, a clinical trial revealed that the use of a selective reversible inhibitor of ghrelin O-acyltransferase (GLWL-01) neither significantly reduced hyperphagia-related behavior nor changed global clinical end points [40]. Also, livoletide, a non-acylated or inactive ghrelin analogue that works by decreasing the amount of active ghrelin in the brain, was shown to be ineffective for hyperphagia [41].

The control of patients' eating behavior is the most important unmet need, but there are still no approved pharmacological treatments [41], although the results with diazoxide choline controlled release (DCCR) is promising. The use of DCCR led to a reduction in hyperphagic behavior in a small number of tested patients (11) and also in aggressive behavior, fat mass, waist circumference, and trends for improvements in lipids and insulin resistance [31].

Angelman/Prader-Willi syndrome imprinting centers (ICs – Fig. 1A) regulate imprinting in the SNURF-SNRPN gene cluster. Under normal conditions, Prader-Willi IC is methylated on the maternal allele, while it is unmethylated on the paternal allele. Silencing of the paternal allele or maternal uniparental disomy of the SNURF/SNRPN gene cluster results in loss of expression of several genes in the Prader-Willi region and leads to the development of the syndrome [42].

DNA methylation analysis is the only technique that can diagnose Prader-Willi syndrome in all three molecular genetic classes (microdeletion, maternal uniparental disomy and mutations in the imprinting center) and differentiate Prader-Willi from Angelman syndrome [35]. In the 15q11-q13 region, there are sequences more prone to rearrangements known as BP1, BP2 and BP3 (breakpoints 1, 2 and 3, respectively – Fig. 1A). Rearrangements between these breakpoints resulting in microdeletions are classified as class I (B1-B3; approximately 6.6 Mb) and II (B2-B3; approximately 5.3 Mb); both are almost always *de novo* events, but class 1 is usually associated with a more severe clinical condition. There are also cases involving minor or major microdeletions, but these are considered atypical [43, 44].

Bardet-Biedl Syndrome

Bardet-Biedl syndrome is a multisystem genetic syndrome [45, 46] that occurs in 1:13,000 (in isolated communities with high levels of consanguinity) to 1:160,000 [47–51] live births and has considerable interfamilial and intrafamilial variable expressivity [45, 52]. It is characterized mainly by retinal degeneration (>90%), truncal obesity with an age of onset usually in infancy (72–92% of patients), polydactyly (63–81%), intellectual disability (50–61%), hypogonadotropic hypogonadism in men (59–98%), and kidney disorders, including polycystic kidneys (20–53%) [53]. Most signs may not be present at birth, but they appear and progress during the first and second decades of life [52].

Diagnostic criteria for Bardet-Biedl were proposed by Schatchat and Maumenee [54] and modified by Beales et al. [55]. The clinical features were divided into primary (rod-cone dystrophy, polydactyly, obesity, learning disabilities, hypogonadism in males, and renal anomalies) and secondary features (speech disorder/delay; strabismus/cataracts/astigmatism; brachydactyly/syndactyly; developmental delay;

polyuria/polydipsia - nephrogenic diabetes insipidus -; ataxia/poor coordination/imbalance; mild spasticity - especially lower limbs -; diabetes mellitus; dental crowding/hypodontia/small roots/high arched palate; left ventricular hypertrophy/congenital heart disease; and hepatic fibrosis).

Bardet-Biedl syndrome should always be considered in patients with obesity and progressive visual impairment. Retinal dystrophy occurs in approximately 94% of cases. It usually begins in the first decade of life, with initial loss of rod photoreceptors followed by later cone photoreceptors compromise. There is a progressive night blindness, followed by photophobia and loss of central and color vision [56]. Differential diagnosis should be made, especially considering McKusick-Kaufman syndrome (OMIM # 236700) and other diseases in which there are visual difficulties and/or polydactyly.

One third of Bardet-Biedl syndrome patients present a widespread obesity in the first year and a more truncal deposition in adults. Different mechanisms contribute to obesity in Bardet-Biedl syndrome, including central and peripheral control of energy expenditure. Plasma leptin levels are higher in these individuals, and drugs targeting this pathway is emerging as a possible therapy for the management of obesity [57].

Bardet-Biedl syndrome is a ciliopathy [46, 58]; most related genes encode proteins involved in the formation and/or functioning of the BBSome, a multiprotein complex important for ciliary function [45, 46]. It is known that the primary cilium is an important structure in neurogenesis and development of the hippocampus. Its impairment is probably related to the neurological problems of Bardet-Biedl syndrome [45]. Additionally, BBSome is critical for regulation of the leptin receptor trafficking and pathway activity [59–61].

As shown in Table 2, many genes have been identified as related to this syndrome. *BBS1* and *BBS10* are the most

Table 2 Bardet-Biedl syndrome genetic data (OMIM)

	Locus	Genes involved	Inheritance
Bardet-Biedl syndrome 1 (#209900)	1p35.2	*CCDC28B* (also *MGC1203*)	AR/DR
	3q11.2	*ARL6* (also *BBS3*)	
	11q13.2	*BBS1*	
Bardet-Biedl syndrome 2 (#615981)	16q13	*BBS2*	AR
Bardet-Biedl syndrome 3 (#600151)	3q11.2	*ARL6* (also *BBS3*)	AR
Bardet-Biedl syndrome 4 (#615982)	15q24.1	*BBS4*	AR
Bardet-Biedl syndrome 5 (#615983)	2q31.1	*BBS5*	AR
Bardet-Biedl syndrome 6 (#605231)	20p12.2	*MKKS* (also *BBS6*)	AR
Bardet-Biedl syndrome 7 (#615984)	4q27	*BBS7*	AR
Bardet-Biedl syndrome 8 (#615985)	14q31.3	*TTC8* (also *BBS8*)	AR
Bardet-Biedl syndrome 9 (#615986)	7p14.3	*PTHB1* (also *BBS9*)	AR
Bardet-Biedl syndrome 10 (#615987)	12q21.2	*BBS10*	AR
Bardet-Biedl syndrome 11 (#615988)	9q33.1	*TRIM32* (also *BBS11*)	AR
Bardet-Biedl syndrome 12 (#615989)	4q27	*BBS12*	AR
Bardet-Biedl syndrome 13 (#615990)	17q22	*MKS1* (also *BBS13*)	AR
Bardet-Biedl syndrome 14 (#615991)	8q22.1	*TMEM67* (also *MKS3*)	AR
	12q21.32	*CEP290* (also *BBS14*)	
Bardet-Biedl syndrome 15 (#615992)	2p15	*WDPCP* (also *BBS15*)	AR
Bardet-Biedl syndrome 16 (#615993)	1q43-q44	SDCCAG8 (also *BBS16*)	AR
Bardet-Biedl syndrome 17 (#615994)	3p21.31	*LZTFL1* (also *BBS17*)	AR
Bardet-Biedl syndrome 18 (#615995)	10q25.2	*BBIP1* (also *BBS18*)	AR
Bardet-Biedl syndrome 19 (#615996)	22q12.3	*IFT27* (also *BBS19*)	AR
Bardet-Biedl syndrome 20 (#619471)	2p23.3	*IFT172*	AR
Bardet-Biedl syndrome 21 (#617406)	8q22.1	*C8ORF37*	AR
Bardet-Biedl syndrome 22 (#617119)	9p21.2	*IFT74*	AR

AR - autosomal recessive, DR - digenic recessive

frequently mutated genes among Bardet-Biedl cases, followed by *BBS12* [62]. For 20 to 30% of individuals with Bardet-Biedl syndrome clinical diagnosis there are no identifiable variants in known related genes, which means that other yet unidentified genes may be involved [53]. Bardet-Biedl syndrome is usually caused by individual *locus*, with an autosomal recessive pattern of inheritance and, therefore, is more common in consanguineous populations [46, 63], but there are reports of interaction of two or more *loci* [45]. In some families, three mutated alleles were observed for the manifestation of Bardet-Biedl syndrome (and not just two, as for autosomal recessive inheritance), suggesting a triallelic inheritance model (involving two *loci*), with an estimated frequency of less than 10% of bulletin board cases [53].

Knockout mouse models for the *BBS2* [64], *BBS4* [65] and *BBS6* [66] genes were developed. All of them exhibited obesity, retinopathy and male infertility, in addition to other signs particular to a single model, such as problems of social interaction, deficits in smell and polydactyly [64–66]. These three models had hyperleptinemia secondary to leptin (anorexigenic hormone) resistance and showed reduced hypothalamic POMC (anorexigenic neuropeptide) expression. The phenotype of these animal models suggest that Bardet-Biedl syndrome genes play an important role in maintaining neuronal sensitivity to leptin [67], and this is the probable mechanism of obesity [46].

Pseudohypoparathyroidism

Pseudohypoparathyroidism (or inactivating PTH/PTHrP signaling disorder [68]) is characterized by target organ resistance or unresponsiveness to parathyroid hormone, that leads to hypocalcemia, hyperphosphatemia, and increased circulating parathyroid hormone [69].

Pseudohypoparathyroidism prevalence was estimated in a Danish study as 1.1/100,000 inhabitants [70]. The three disorders, pseudohypoparathyroidism type 1a, 1c, and pseudopseudohypoparathyroidism, are caused by alterations in the *GNAS* gene [71], a gene subjected to imprinting and that produces four different transcripts (Fig. 1B) using alternative promoters, including G protein subunit alpha (Gαs). The five protein encoded are Gαs (expressed by both alleles in most tissues), A/B, XLαS and GNαS-AS1, which are paternally expressed, and *NESP55*, which is maternally expressed [72, 73]. Since exons 2–13 of *GNAS* are shared by XLαs, NESP55 and A/B proteins, variants in those exons lead to deficiency of not only Gsα, but also these other products; the phenotypes resulting from the deficiency of each of these *GNAS* products are unclear [74]. Gsα is a subunit of the stimulatory G protein [75], is ubiquitously expressed and plays roles in the regulation of various hormones [74] (e.g. epinephrin and calcitonin) [75]; resistance to additional hormones, such as thyroid stimulating hormone (TSH), growth hormone-releasing hormone (GHRH) and gonadotropins can also be observed in patients with pseudohypoparathyroidism 1a and 1c [74]. Gsα is responsible for the cAMP-mediated signaling by activating the enzyme adenylyl cyclase, which stimulates the cAMP formation and the subsequent protein kinase A (PKA) activation. Molecular alterations that deregulate the Gsα/cAMP/PKA pathway mostly affect the signaling of PTH/PTHrp (parathyroid hormone/parathyroid hormone-related peptide), activated by the PTHR1 (Parathyroid hormone 1 receptor) [75].

Typical pseudohypoparathyroidism physical findings are called Albright hereditary osteodystrophy (OMIM #300800), in which patients have round facies (approximately 92%), short stature (80%), thickened calvaria (62%), ectopic soft tissue or dermal ossification(s) (osteoma cutis – 56%), and obesity (50%). Subcutaneous calcifications (55%), dental hypoplasia (51%), cataract and band keratopathy (44%) are also common, likely consequences of longstanding hypocalcemia. Many patients have brachydactyly, involving one or both hands or feet; 68% have brachymetacarpia, 50% brachyphalangia, and 43% brachymetatarsia [76]. *GNAS* mutations in the paternal allele lead to pseudopseudohypoparathyroidism, which also manifests as Albright hereditary osteodystrophy, but without resistance to parathyroid or other hormones [74].

Pseudohypoparathyroidism 1a is associated with lower intelligence quotient scores, delayed adaptive behavior skills, and behavior problems; 93% received special education services [77]. In contrast, cognitive impairment is not prevalent in pseudopseudohypoparathyroidism [78].

Early-onset obesity and a significant overweight and obesity in adults characterizes *GNAS* alterations (BMI z-score: 1.4 ± 2.6 in pseudopseudohypoparathyroidism patients, 2.1 ± 2.0 in pseudohypoparathyroidism 1a, and 1.4 ± 1.9 in pseudohypoparathyroidism 1b) [79]. The obesity mechanism is likely related to Gsα signaling reduction at the melanocortin receptors, structures that mediate the central effects of leptin on satiety, with anorexigenic actuation [80].

Regarding birth weight and growth trajectories in disorders of *GNAS* inactivation, pseudohypoparathyroidism 1a and pseudopseudohypoparathyroidism patients are smaller at birth (length z-score -1.1 ± 1.8 and -3.0 ± 1.5, respectively) than healthy controls; 64% and 59%, respectively, have short stature. Pseudohypoparathyroidism 1b patients have an early post-natal overgrowth (height z-score at 1 year: 2.2 ± 1.3), but a normal adult height (z-score: -0.4 ± 1.1) [79].

Patients with pseudohypoparathyroidism type 1b show imprinting abnormalities at the complex *GNAS locus*, with parathyroid and other hormones resistance. Rarely, there are cases with an Albright hereditary osteodystrophy phenotype, including obesity. The molecular causes of autosomal dominant familial pseudohypoparathyroidism type 1b are microdeletions within the *GNAS locus* or the nearby *STX1*

(approximately 200 kb of distance). These results in isolated loss of imprinting at exon *A/B* or deletions involving the *NESP55* differentially methylated region resulting in loss of all maternal *GNAS* imprints [81]. In some cases of sporadic pseudohypoparathyroidism type 1b, an isodysomy of paternal chromosome 20 (entire [82, 83] or q arm [81, 83]) was identified.

In the cohort of 282 patients with pediatric obesity evaluated by Kleinendorst et al. (2020) [7•], 5 (~1.8%) presented *GNAS* variants. In the analysis of exome data from 2548 children with severe obesity, Mendes de Oliveira et al. (2021) [84] identified 22 (~0.86%) patients harboring deleterious variants in *GNAS* and without suspected pseudohypoparathyroidism. Usually, *GNAS* sequencing has been performed only in patients with clinical features suggestive of pseudohypoparathyroidism, but pathogenic variants in this gene may manifest only with obesity [84] and have been recognized as a cause of childhood obesity.

Alström Syndrome

Alström syndrome is a rare autosomal recessive disorder caused by variants in *ALMS1* [85, 86]. Obesity, retinal degeneration, type 2 diabetes mellitus and sensorineural deafness are the most important features of Alström syndrome [86, 87]. Intellectual disability is uncommon, but patients can have early learning difficulties and speech impairment; delay in early motor developmental milestones is seen in 27% of the patients [86]. The prevalence of Alström syndrome is not precisely known, but according to a review published in 2021, approximately 1200 cases of Alström syndrome have been identified worldwide [88].

Obesity is always present [87]. In general, birth weight is normal, but hyperphagia and excessive gain occurs after the first year of life [89]. The BMI of most young children is >95th centile [86], and obesity is central in childhood. In some individuals, body weight tends to normalize, decreasing after adolescence [89]. Height is normal in early childhood, but growth slows in adolescence, and final adult height is usually <5th centile [86].

The individuals with Alström syndrome exhibit early onset retinal degeneration of rods and cones, leading to progressive vision problems, nystagmus, and photophobia [89]. Many people lose all perception of light by the end of their second decade of life, albeit a minority retains the ability to read large prints by the third decade. Hearing loss is also progressive and severe (40–70 dB), observed in the first decade in up to 70% of the individuals [89].

In addition, patients have dyslipidemia, especially markedly increased levels of triglycerides and VLDL cholesterol. They are also often diagnosed with arterial hypertension around the age of two [87]. They may present with hypothyroidism, alterations in the insulin-like growth factor (IGF) system, low testosterone in males and hyperandrogenism in females; hyperinsulinemia and type 2 diabetes develop in childhood [86].

Dilated cardiomyopathy can occur suddenly in infancy (first months of life), and restrictive cardiomyopathy develops slowly in adolescents and adults. They may develop absence seizures and febrile epilepsy. Respiratory problems such as pulmonary fibrosis, chronic obstructive respiratory syndrome, and acute respiratory distress syndrome are also common. Liver dysfunction begins with hepatic steatosis and can progress to hepatic fibrosis and cirrhosis. Renal failure develops slowly in late adolescence and adulthood [86]. Birth complications include neonatal hypoxia and hypotonia [90].

The ALMS1 protein localizes to centrosomes and basal bodies of ciliated cells and operates in cell cycle regulation and intraciliary transport. Like Bardet-Biedl syndrome, Alström syndrome is also a ciliopathy [86] and there is an important phenotypic overlap between the two syndromes, however, patients with Alström syndrome do not have polydactyly or syndactyly [87].

Smith-Magenis Syndrome

Smith-Magenis syndrome is estimated to occur in 1:15,000 to 1:25,000 births [91]. This syndrome is characterized by typical coarse facial features that progress with age (particularly due to the disproportion between the midface retrusion and the increasing width and protrusion of the mandible, emphasizing prognathism). Patients exhibit developmental delay, mild-to-moderate range of intellectual disability, behavioral abnormalities, sleep disturbance, and childhood-onset abdominal obesity [91, 92]. Typical facial dysmorphisms include brachycephaly, broad face, frontal bossing, synophrys, upslanting palpebral fissures, deep-set eyes, midface retrusion, depressed nasal bridge, short and broad nose, low-set and/or abnormally shaped ears, everted and tented upper lip vermilion, and prognathism. Behavioral abnormalities include stereotypes, maladaptiveness, outbursts/temper tantrums, attention-seeking behaviors, opposition, aggression, self-injurious, and polyembolokoilamania. Infants have feeding difficulties, failure to thrive, hypotonia, hyporeflexia, prolonged napping or need to be awakened for feeds, and generalized lethargy. Hearing loss and speech disorders are also common [91]. According to Gouard et al. (2020), 30% of patients have a BMI ≥97th centile; considering only patients older than 10 years, 60% had a BMI ≥90 centile compared to 29% below this age. [93]. This syndrome has been shown to have food-related behaviors similar to Prader-Willi syndrome [94]. Smith et al. (2002) also demonstrated an increased risk of dyslipidemia [95].

Smith-Magenis syndrome is an autosomal dominant condition caused by pathogenic loss-of-function variants of *RAI1*, and the majority of them (90%) are interstitial 17p11.2

microdeletions [91, 93]. Familial cases are rare, with no sex bias [91]. According to Bruns et al., *Rai1*$^{+/-}$ mice are slightly smaller than wild-type (at five weeks old), are hyperphagic, presenting with altered abdominal and subcutaneous fat distribution from 20 weeks of age, behavioral abnormalities, variable penetrance of craniofacial defects and reduced fertility. Leptin levels were high in *Rai1*$^{+/-}$ mice and correlated with adiposity. A reduced expression of *Bdnf* was also found in *Rai1*$^{+/-}$ mice [96], a gene that has been linked to higher BMI in individuals with WAGRO syndrome [97], as will be further discussed in this manuscript. *RAI1* encodes a protein that acts as a transcriptional regulator involved in neurodevelopment, behavioral function, and circadian rhythms [91].

Cohen Syndrome

Cohen syndrome is an autosomal recessive disease with multisystem clinical features [98, 99] characterized by truncal obesity (develop in teenage years), hypotonia (usually detected during breastfeeding and may persist until adolescence), intellectual disability, and narrow hands and feet. Craniofacial features can include microcephaly [99], thick hair and eyebrows, long eyelashes [99, 100], hypertelorism [99], arched or wave-shaped eyelids [99, 100], high nasal bridge, bulbous nasal tip, short philtrum, high and narrow palate, prominent maxillary central incisors, maxillary hypoplasia, and micrognathia [99], but clinical facial recognition is difficult before the age of six [99, 101]. Patients may also have leukopenia (mainly neutropenia) [99, 102, 103], ophthalmologic changes (e.g., severe myopia and early-onset and progressive retinal dystrophy) [99, 102, 103], high-pitched crying and voice, possibly secondary to laryngeal abnormalities [99], and joint hypermobility [99, 102, 103]. There are also reports of congenital heart disease. Increased waist circumference becomes evident between 5 and 12 years, not always associated to an obesity BMI. Therefore, it has been suggested that the term "obesity" be replaced with "abnormal truncal fat distribution"[99].

All Cohen syndrome patients have some degree of intellectual disability, speech development is often impaired, and motor developmental milestones are significantly delayed. Friendly personality is common [99].

Cohen syndrome is caused by mutations involving the *VPS13B* gene (also known as *COH1*) [99, 104]. This syndrome is mainly described in the Finnish population [105], in which bottleneck events enriched for some pathogenic variants [106]. Cohen syndrome tends to be more heterogeneous with wide phenotypic variability in non-Finnish patients [99].

The *VPS13B* gene appears to be important in the development and function of the eyes, hematopoietic system, and central nervous system [99]. It encodes a membrane protein involved in Golgi integrity [98] and vesicle-mediated transport [99]. Deleterious *VPS13B* variants disturb the Golgi, leading to an unusual pattern of glycosylation of several proteins and an impairment in endosomal-lysosomal trafficking. Functional studies indicate that preadipocytes without *VPS13B* differentiate more easily, which probably justifies the accumulation of fat [99]. These biochemical and cellular changes are believed to be involved in the pathophysiology of Cohen syndrome [98].

Temple Syndrome

Temple syndrome is characterized by hypotonia (93%, with feeding difficulties frequently reported), small feet (96%) and hands (87%), low weight at birth (87% <5th centile), precocious puberty (86%), motor development delay (83%), short stature (79%), hyperextensible joints (63%), speech delay (59%), obesity (49%), intellectual disability (39%), premature birth (30%), scoliosis (23%), and low birth head circumference (27% <5th centile) [107]. Obesity is of the truncal type and develops as early as 4–6 years old [108]. Early-onset weight gain is associated with decreased resting energy expenditure and hyperphagic behavior. There are facial similarities between many of the patients, including a broad, tall forehead nose often short with a wide, fleshy nasal tip, and a short philtrum [107]. Facial features become distinguishable with age. It is worth mentioning that frontal bossing and micrognathia are common in infants [108]. In early childhood, patients with Tempe syndrome may have a phenotype that overlaps that of Silver-Russell syndrome.

Temple syndrome maps to the 14q32.2 region [109] and, like Prader-Willi syndrome, is an imprinting disorder [108]. Considering 51 Temple syndrome cases reviewed by Ioannides et al. (2014) [107], 40 had maternal chromosome 14 disomy, six had imprinting defects, and five had microdeletions on the paternal chromosome. Cases of Robertsonian translocations [110, 111] or mosaicism [112–114] are rare. All these mechanisms have the absence of paternal 14q32 expression in common [107]. To date, no SNV (single nucleotide variations) or indel mutations causing Temple syndrome have been identified [115, 116].

We present in Fig. 1C the 14q32.2 region highlighting the imprinting profile of the genes contained therein. Imprinting is controlled by an IC intergenic differentially methylated region or IG-DMR, which is normally methylated only on the paternal chromosome. IG-DMR methylation is acquired in the male germline and subsequently directs the acquisition of methylation on the paternal allele of a somatic DMR (differentially methylated region) within *GTL2/MEG3*. The unmethylated IG-DMR on the maternal allele is associated with the expression of *GTL2/MEG3* and *RTL1as*, which represses the expression of *DLK1* and *RTL1* in cis. Genetic testing based on ratiometric measurement of methylated/

unmethylated DNA within the IG-DMR can be used as a screening tests for Temple syndrome [107].

Loss-of-function *DLK1* mutations cause central precocious puberty and are also associated with metabolic disorders. DLK1, which inhibits adipogenesis, is likely involved in the Temple syndrome mechanisms of obesity, precocious puberty, and metabolic problems, such as type 2 diabetes mellitus and hyperlipidemia [117]. Furthermore, *DLK1* expression in the mouse hypothalamus and in kisspeptin neuron-derived cell lines suggests a neuroendocrine function [115].

1p36 Deletion Syndrome

1p36 deletions are the most common terminal deletions in humans [118] and are detected in approximately 1 in 5000 newborns [118, 119]. In a cohort of 279 syndromic obesity patients analyzed by genomic microarrays and negative for Prader-Willi, five (1.8%) presented 1p36 deletions [10••]. The major clinical features are developmental delay, hypotonia, short stature and craniofacial dysmorphisms such as large anterior fontanel, prominent forehead and chin, deep eyes, ear asymmetry, a flat nasal bridge, and maxillary hypoplasia. Other possible clinical manifestations are skeletal malformations, cardiac, gastrointestinal, and visual abnormalities, seizures, and behavioral problems [119]. There is also an association of 1p36 deletions with obesity and hyperphagia [120].

There are two critical portions related to the phenotype, one proximal/interstitial (OMIM #619343) and one distal/terminal (also called classic; OMIM # 607872) [118, 119] (Fig. 2A); the distal portion is associated with obesity [120]. Most of cases (52–67%) have a terminal deletion on chromosome 1. There is evidence of participation of *MMP23B, GABRD, SKI, PRDM16, KCNAB2, RERE, UBE4B, CASZ1, PDPN, SPEN, ECE1, HSPG2*, and *LUZP1* genes in the phenotype [96], and the deleted region and corresponding genomic content are related to phenotypic variations [119]. Regions related to specific features are presented in Fig. 2A, according to a review published by Jordan et al. (2015) [118]; we also represent the critical region for the manifestation of obesity and hyperphagia (1p36.33–36.32) [120].

16p11.2 Deletion Syndromes

Deletions of different genomic segments in the 16p11.2 region, not necessarily with overlapping gene content, cause syndromic obesity forms. In a cohort study of 680 unrelated children with syndromic obesity and without Fragile-X or Prader-Will syndromes, Gimeno-Ferrer and colleagues [121] identified by microarray analysis 11 cases (1.6%) with 16p11.2 CNVs. In this region, there are recurrent CNVs originating from nonhomologous allelic recombination between five breakpoints (BPs) (Fig. 2B) [122].

The 16p11.2 deletion between BP4 and BP5 (~600 kb, OMIM # 611913) is one of the most frequent CNVs identified in neurodevelopmental and autism spectrum disorders [122, 123], with a prevalence of 1:2000 in the general population [123]. Approximately 0.5% of the cases of autism spectrum disorders are related to this syndrome [123]. In this 16p11.2 deletion syndrome, obesity is associated with hyperphagia and evolves throughout childhood. In adulthood, 75% of patients have obesity (approximately 45% of them with grade III), although birth weight is frequently below average. Although head circumference is smaller at birth, there is an overall increase by 2 years of age, and macrocephaly (Z score ≥ 2) is present in 17% of patients. Frequent features are speech impairment (70%), motor coordination difficulties (60%), seizures (24%), and autism (20–25%). The intelligence quotient is shifted 1.8 standard deviations lower than that of noncarriers of 16p11.2 deletion. Facial dysmorphisms are present in half of the carriers [123], but there are no characteristic facial features [124]. Congenital anomalies are more frequent than in the general population, with the most common being vertebral segmentation abnormalities (hemivertebrae or kyphoscoliosis affect ~20% of carriers). Central nervous system alterations include increased brain volume, changes in white matter microstructural properties, and early electrophysiological cortical responses from the auditory cortex. The deletion between BP4 and BP5 is most often *de novo* [123].

The 16p11.2 deletion between BP2 and BP3 has 220 Kb (OMIM # 613444) [122] (Fig. 2B) and causes severe early-onset obesity with cognitive deficits, developmental delay, and autism [125]. This region encompasses nine genes, including *SH2B1*, postulated to be the principal responsible for obesity and intellectual disability [121, 126]. *SH2B1* is a critical regulator of body weight and metabolism in both animals and humans. SH2B1 acts as is an endogenous enhancer of leptin sensitivity in neurons. Mice with hypothalamus-specific ablation of *Sh2b1* develop obesity, insulin resistance, and liver steatosis. In contrast, *SH2B1* hypothalamic overexpression protects against high-fat diet-induced obesity and metabolic syndrome [127]. Other 16p11.2 deletions related to syndromic obesity phenotypes involve genes of the BP4-BP5 and/or BP2-BP3 portions. Some of them are represented in Fig. 2B.

Kleefstra Syndrome Type 1

Kleefstra syndrome type 1 is characterized by moderate to severe intellectual disability, severe delayed or absent speech, childhood hypotonia, delayed motor development [128–130] and sleep disorder [128]. Facial features include microcephaly, brachycephaly, hypertelorism, synophrys,

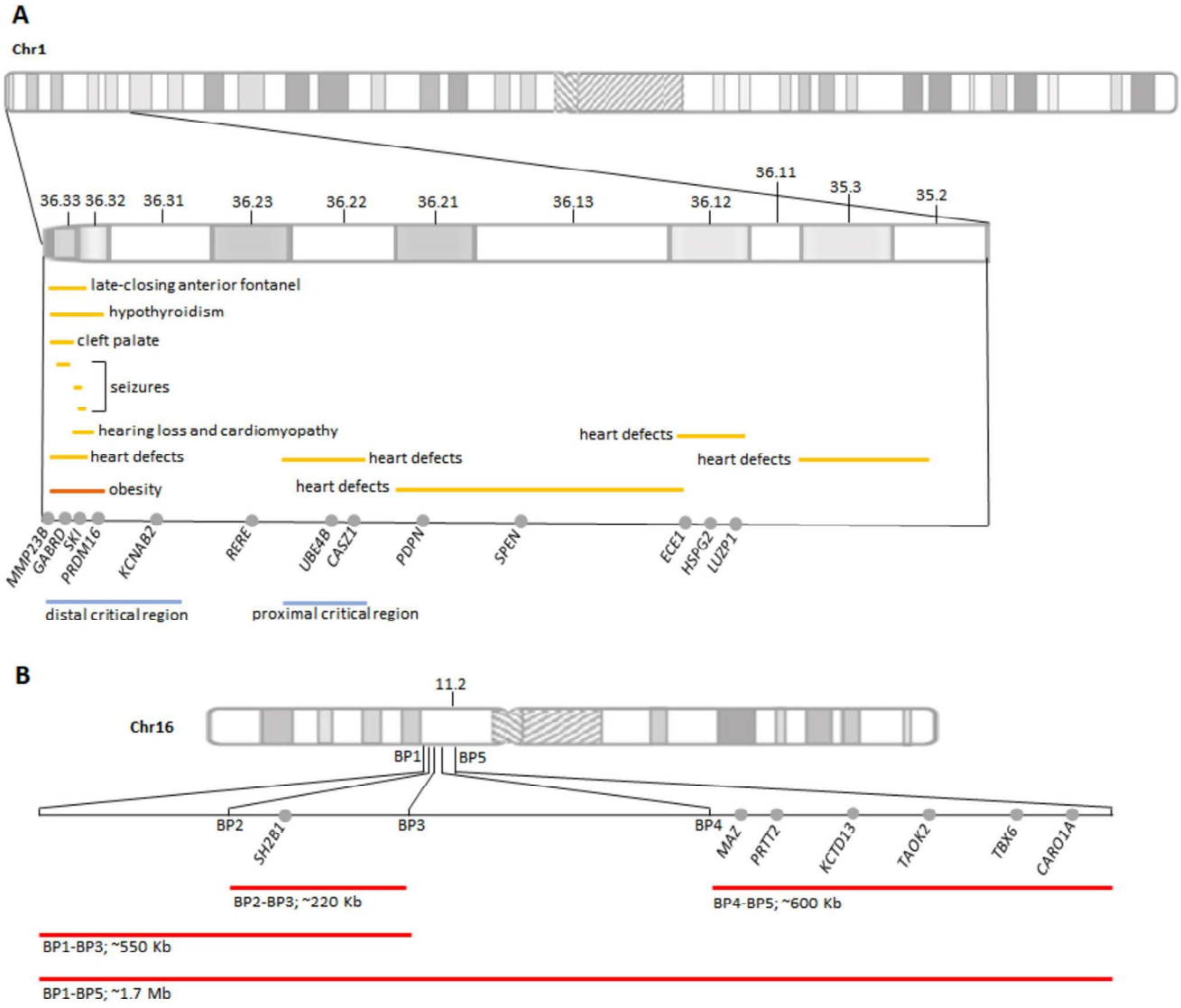


Fig. 2 Schematic representation of 1p36 and 16p11.2 microdeletions. **A** - 1p36 syndrome region. Critical regions (blue bars) associated with different phenotypes (yellow bars; for obesity, brown bar) have been narrowed. Only genes associated with phenotypes are represented. Not drawn to scale. **B** - 16p11.2 syndromes region. Five imbalance segments (red bars) have been defined for the 16p11.2 chromosomal region. Only genes that could be related to the phenotypes are represented. Not drawn to scale

midface hypoplasia, everted lower lip, prognathism, and macroglossia. Patients with Kleefstra syndrome type 1 are often large for gestational age and childhood obesity is very common. Congenital heart disease and seizures are also frequently reported [130]. The prevalence remains imprecise, but it is estimated to occur in 1:200,000 cases of intellectual disability [131]. Few cases of brain imaging tests exhibit dilated ventricles, myelination problems and other abnormalities [130].

Behavioral problems are common [128, 130], including apathy, aggression, psychosis, autistic features, catatonia, bipolar disorder, and regression in daily functions and cognitive abilities. In adulthood, they may also manifest severe psychiatric pathologies [130].

Kleefstra syndrome type 1 is an autosomal dominant disorder caused by *EHMT1* haploinsufficiency [132]. There are cases of terminal or interstitial deletions encompassing 9q34.3 and including at least part of *EHMT1*, and cases with intragenic *EHMT1* heterozygous variants. There are few reports of inherited cases, for example, from somatic mosaicism or balanced translocation [129].

EHMT1 is a major methyltransferase that acts for the mono- and dimethylation of lysine 9 on histone 3 (H3K9me1/2) and can also monomethylate both H3K27 and H3K56 in some contexts [133]. Its predominant histone

mark (H3K9me2) is related to transcriptional repression. EHMT1 also interacts with other transcription factors [132] and is essential for repressing gene transcription in a highly tissue- and temporal-specific manner [134]. Pyramidal CA1 hippocampal neurons of *Ehmt1*$^{+/-}$ mice had significant reductions in spine density, number of mature spines, and dendritic arborization, indicating a postsynaptic deficit [135].

In individuals presenting cardinal features of Kleefstra syndrome type 1 and not harboring *EHMT1* variants, heterozygous variants have been identified in *KMT2C* that also codes for a histone methyltransferase. In the reported six individuals, with age ranging from 7 years to 31 years, none of them presented weight 2 SD above the mean [132].

SIM1-Related Syndrome

It has been known for decades that deletions involving the 6q16.1-q21 region, often larger than 10 Mb, lead to a Prader-Willi-like syndromic form of obesity [136–139]. Common and overlapping features of Prader-Willi syndrome are neonatal hypotonia, early-onset obesity, and developmental delay [140]. However, these 6q deletions appear to have incomplete penetrance for the obesity phenotype (observed in 8/13 patients) [140]..

Holder et al. (2000) [141] identified in a girl with syndromic obesity a translocation t(1;6)(p22.1;6q16.2) disrupting *SIM1*. Further publications confirmed that the critical gene for the Prader-Willi-like phenotype is *SIM1* [142–144], as specific mutations in this gene also lead to the phenotype. *SIM1* is a relevant transcription factor in the formation of the paraventricular nucleus of the hypothalamus [145], which is probably related to the occurrence of obesity in patients. Heterozygous (*Sim1*$^{+/-}$) mice have hyperphagia, early obesity, hyperinsulinemia and hyperleptinemia. More recently, Matharu et al. (2019) [146] reversed the obesity phenotype in *Sim1* haploinsufficient mice using CRISPR-mediated activation (CRISPRa), technology based on the upregulation of the existing normal gene copy.

In 6q16 microdeletions, another gene that encodes a transcription factor also seems to be important for obesity and developmental delay phenotypes: *POU3F2*. This gene is important for the development and function of the hypothalamus [147]. Recently, a publication reported patients with truncated variants in *POU3F2* who shared autism spectrum disorder, developmental delay, low birth weight, infant feeding difficulties, and adolescent-onset obesity; they developed insulin resistance and hyperphagia during childhood [148].

Börjeson-Forssman-Lehmann Syndrome

Börjeson-Forssman-Lehmann syndrome is a rare syndrome in which mild to moderate intellectual disability is the main feature [149]; there is a delay in speech and in the development of motor skills. In adolescence, patients have generalized learning difficulties that make them dependent on the care of others [53].

Börjeson-Forssman-Lehmann syndrome is an X-linked recessive syndrome [150] that is caused by mutations involving the *PHF6* gene [151] that encodes an epigenetic regulator [152]. It manifests mainly in males; female carriers are usually unaffected or have only mild clinical signs [151], but recently *de novo* mutations in *PHF6* have been identified in women with a distinct and severe intellectual disability disorder [151, 153–155]. Obesity, which is common in male individuals, is not a striking feature in these female patients [155].

Some dysmorphisms with narrow palpebral fissures and large ears are also prevalent, especially with long and flaccid lobes, gynecomastia (97%), characteristic digit anomalies (96% - such as short, flat and hyperflexible fingers, short and separated toes, big and short hallux and/or hammer toe), hypogonadism (86%), and truncal obesity (76%) [53]. Patients may also have microcephaly (6%) or macrocephaly (15%). Epileptic seizures were observed in approximately 8% of patients. At birth, weight and head circumference are usually normal [149]. However, hypotonia occurs in the neonatal period and in infancy, which causes growth and developmental problems. Börjeson-Forssman-Lehmann syndrome has great interfamilial and intrafamilial phenotypic variability [53], and some clinical features only become more evident with age [149].

A transcriptome analysis of the cerebral cortex of mice with a CRISPR-generated *PHF6* mutation demonstrated that this gene promotes the expression of neurogenic genes and represses synaptic genes [156]. It was also shown in mice that the *PHF6* gene encodes a critical protein for the migration of neurons in the cerebral cortex. PHF6 dysregulation generates white matter changes and neuronal hyperexcitability, which may be relevant to the pathogenesis of intellectual disability and seizures in Börjeson-Forssman-Lehmann syndrome [149, 157].

WAGRO Syndrome

WAGR syndrome is a contiguous gene syndrome caused by heterozygous deletions of the chromosomal region 11p13, encompassing mainly the genes *WT1* and *PAX6*. The acronym WAGR refers to cardinal features of this syndrome: W (Wilms tumor), A (aniridia), G (genitourinary anomalies) and R (developmental delay/intellectual disability). Several case reports described individuals with WAGR syndrome presenting obesity, and this clinical finding was incorporated in the acronym (WAGRO) [158]. This clinical finding was further evaluated in large cohorts. In a study of 54 individuals with WAGR syndrome, showing a median age of 9.2 years, obesity was observed in 10 individuals (18%).

Thus, in the guidelines for healthy supervision in children with this syndrome proposed by the authors, they included the monitoring of the nutritional status, with particular attention to weight management [159]. More recently, in a cohort of 91 individuals ascertained from the WAGR Syndrome Patient Registry from 2014 to 2020, evaluating the rates of self-reported healthy issues, mostly from the United States and United Kingdom, obesity was reported in 39/74 individuals (52.7%) [160].

Although deletions of *WT1* and *PAX6* are associated with Wilms tumor and aniridia respectively, the role of other genes in the chromosome region 11p13 are poorly characterized [160]. Based on the role of brain-derived neurotrophic factor (*BDNF*) acting in the ventromedial hypothalamus to regulate energy homeostasis, downstream of the leptin-proopiomelanocortin signaling pathway in animal models, Han et al. (2008) [97] evaluated the possibility that haploinsufficiency of *BDNF* could be responsible for higher BMI in individuals with WAGR syndrome. In this study, 19 out of 33 individuals (58%) presented deletions encompassing *BDNF*, and in the comparison between this group and the one without deletion of *BDNF*, an increased prevalence of childhood-onset obesity was observed in the former group, a difference statistically significant, suggesting the role of this gene in energy homeostasis also in humans. According to the study conducted by Unger et al. (2007), a *Bdnf* deletion in the ventromedial and dorsomedial hypothalamus of adult mice resulted in hyperphagic behavior and obesity [161].

In a recent study [160], obesity was observe in almost 2/3 of the individuals presenting deletions encompassing *BDNF*. As mentioned earlier, *Rai1* haploinsufficiency leads to reduced expression of *Bdnf* in mice [96]. Thus, it is possible that there are overlaps between the obesity mechanisms of Smith-Magenis and WGRO syndrome.

Carpenter Syndrome

In humans, biallelic mutations involving the *RAB23* gene lead to Carpenter syndrome type 1 [162, 163], characterized by multiple suture craniosynostosis (sagittal, lambdoid, and coronal), with severe cases presenting cloverleaf skull, facial dysmorphisms, broad or bifid thumbs, absent or small middle phalanges, and polysyndactyly of hands and feet, in particular, preaxial polydactyly in the feet. Additionally, the characteristics of Carpenter syndrome type 1 are intellectual disability, high birth weight, postnatal obesity, congenital heart disease, umbilical hernia, cryptorchidism, hypoplastic testes, bowed femur and tibia, and malformations of the central nervous system [162]. The patients' obesity is of the central type. Overgrowth manifestations and advanced bone age have also been described [164, 165].

RAB23 is a GTPase that acts as a regulator in *sonic hedgehog* signaling [162], an important pathway in animal development [166]. Biallelic nonsense *RAB23* mutations in mice lead to neural tube defects and embryonic lethality [167]. Notably, RAB23 is implicated in ciliary trafficking [60, 168], including this syndrome in the group of ciliopathies.

As Carpenter syndrome type 1, Carpenter syndrome type 2 presents multiple congenital malformations, such as multisuture craniosynostosis, polysyndactyly of hands and feet, umbilical hernia, cryptorchidism and heart disease. It is caused by biallelic mutation in the *MEGF8* gene. Obesity is also a feature of Carpenter syndrome type 2. However, individuals harboring variants in *MEGF8* may also be seen with lateralization defects, like transposition of the great arteries, dextrocardia, to complete *situs inversus*. In addition, thoracic skeletal abnormalities and spaced, hypoplastic, and/or supernumerary nipples appear to be more frequent features in these individuals [169].

Megf8$^{-/-}$ mice have a disruption in axon guidance in the peripheral nervous system and exhibit defects in development of the limb, heart, and left-right patterning. Furthermore, *MEGF8* appears to be involved in BMP4 signaling [170], a protein that regulates a number of developmental processes, including the dorsal-ventral axis, neural patterning [171], and orofacial development [172].

MORM Syndrome

Biallelic pathogenic variants in the *INPP5E* lead to a syndrome characterized by intellectual disability (previously called "mental retardation"), truncal obesity, retinal dystrophy, and micropenis, or MORM syndrome [173, 174]. In MORM syndrome, retinal dystrophy is usually not progressive, except for one reported case that was progressive in the first decade of life, being of cone-rod type, similar to the ones seen in other ciliopathies. In the two cases reported in the literature, including the original large, consanguineous Pakistani family, the age of onset of the obesity varied from infancy to childhood, associated with insulin resistance and dyslipidemia [175]. Further reports are necessary for a fully delineation of the phenotypic spectrum of this newly recognized syndrome.

INPP5E plays an important role in the development and maintenance of ciliary homeostasis. Therefore, MORM is also a ciliopathy [173, 176].

MYT1L-Related Syndrome

According to the most comprehensive study of this syndrome, which involved the analysis of 62 cases, the main phenotypic features of *MYT1L*-related syndrome are developmental delay with behavioral disorders (98%), language impairment (95%), intellectual disability (70%), overweight/obesity (58%), and epilepsy (23%) [177]. hyperphagia is an

overarching mechanism leading to excessive weight gain in these patients. Strabismus and macrocephaly are also common features [178], but overall, a facial phenotype does not seem to be recognizable [178, 179]. The behavioral features include autism, aggressiveness [177, 178], attention deficit hyperactivity disorder, anxiety, nervous tics, and obsessive–compulsive disorder [177].

Microdeletions in 2p25.3 encompassing *MYT1L*, as well as heterozygous indels and SNVs in this gene are the underlying cause of this autosomal dominant form of syndromic obesity [177–181]. MYT1L is a zinc finger neural family of transcription factors [182]. It is an important regulator of neuronal differentiation [183–186], expressed in different parts of the brain, with peak expression in the fetal period [181]. As functional evidence, *Myt1l* haploinsufficient mice recapitulate several clinical phenotypes observed in humans carrying heterozygous *MYT1L* variants, such as obesity and behavioral alterations. The effect in weight gain was sex-dependent, with female mice showing a higher weight gain late in life. Abnormal development of the hypothalamus with loss of oxytocin expression in the preoptic neuroendocrine area has been observed in a zebrafish model. In humans, lesions in the equivalent area to this preoptic neuroendocrine zebrafish region are associated with hyperphagia and obesity. There is a hypothesis, therefore, that intellectual disability and obesity observed in patients with *MYT1L* mutations could be caused by dysregulation of gene expression and development of the neuroendocrine hypothalamus [178].

Discussion

In this article, we presented the main forms of syndromic obesity. Identifying the etiology of syndromic obesity in patients is challenging due to the great number of disorders, which are associated with different mechanisms and genetic heterogeneity. Furthermore, there are several syndromes in which obesity could be observed in a subset of individuals, particularly in the ones comprising intellectual disability, such as Kabuki and Rubinstein-Taybi syndromes [187, 188]; however, the current evidence is insufficient to establish them as forms of syndromic obesity.

Furthermore, some publications about syndromic obesity include overgrowth syndromes, such as Luscan-Lumish [189, 190], Beckwith-Wiedemann [191], and Tatton-Brown-Rahman syndromes [166, 167]. Although obesity could be part of these syndromes, overgrowth syndromes imply abnormally excessive growth in the size of the body or a body part [192]. In this manuscript, we did not include this category.

Although there is already a considerable number of syndromes in which obesity is considered a cardinal sign, this list is still growing, with the description of novel syndromes particularly leveraged by the use of modern and innovative techniques in recent decades, such as: Chung-Jansen (autosomal dominant; *PHIP* gene) [193, 194], White-Kernohan (autosomal dominant; *DDB1* gene) [195], *PRMT7*-related (autosomal recessive) [196], SINO (autosomal dominant; *KIDINS220* / *ARMS* gene) [197, 198], CLABAR (autosomal dominant; *TRIP12* gene) [199], and BDV (autosomal recessive; *CPE* gene) [200, 201] syndromes. However, the clinical profile of most of these syndromes are still under delineation, and the consistent association with obesity remais to be confirmed.

Genetic Investigation of Syndromic Obesity

In the present article, we focus on genetic syndromes in which the occurrence of obesity is frequent and well characterized. However, the obesity in syndromic patients can be directly due to underlying molecular mechanisms of hunger-satiety or can also be because generalized obesogenic behaviors associated with intellectual disability and/or psychiatric disorders.

Studies investigating the genetic etiology of syndromic obesity cases also identified genetic variants mapped to intellectual disability genes, in which obesity is not a central feature [1, 8••, 10••, 136, 202, 203••], and therefore, the obesity may not be directly related to the syndrome [203••], although there is higher prevalence of obesity among people with cognitive impairment [204–206]. Many factors may contribute to this higher prevalence, such as low levels of physical activity, poor nutritional habits [207], and psychiatric drugs [208]. Several publications also reported association of obesity with psychiatric disorders [209–212] - which are present in many syndromic patients - and syndromic intellectual disability with anxiety [213], which could drive binge eating events [214]. Thus, the possibility that the etiology of the syndromic condition can be independent of obesity can not be rule out.

Even before the manifestation of obesity, some clinical features may be indicative of the need for genetic investigation. Prader-Willi syndrome, for example, can be suspected during the neonatal period due to typical hypotonia and feeding problems [215] and even prenatal period, if asymmetrical intrauterine growth and polyhydramnios are detected [216]. Another relevant fact is that early-onset obesity (especially <5 years) is more likely to have a genetic origin [7•].

The genetic investigation of syndromic obesity requires the evaluation of multiple genetic mechanisms, considering that the etiology can be related to CNVs, SNVs, indels and alterations in the methylation pattern, with high genetic heterogeneity, posing substantial challenges for diagnosis.

Regarding the molecular diagnostic yield achieved in syndromic obesity cohort studies, the following publications deserve mention: (1) D'Angelo et al. (2018) [10••] evaluated by chromosomal micoarray patients previously tested

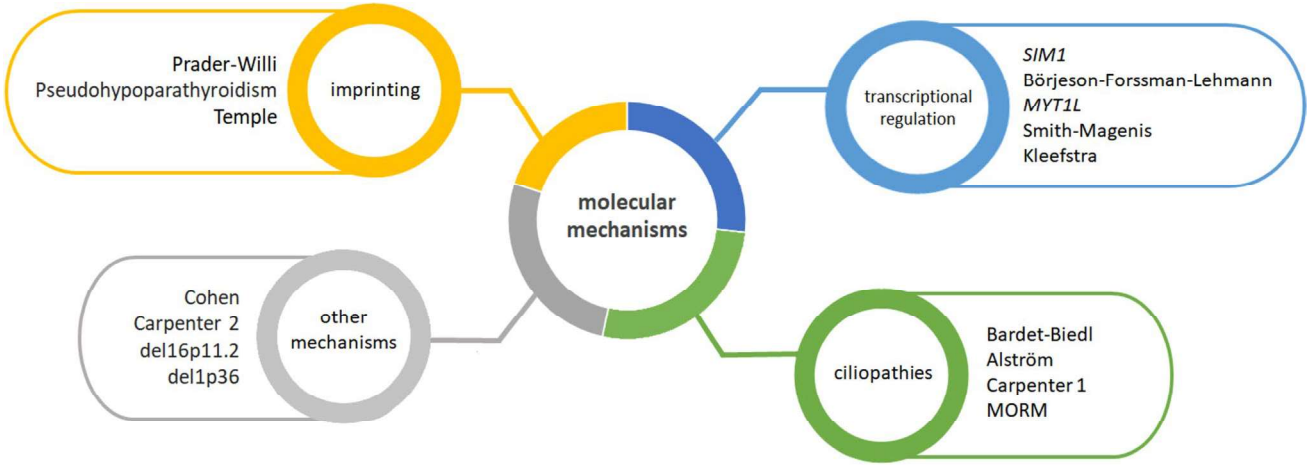


Fig. 3 Molecular causal mechanisms of syndromic forms of obesity. There are three main groups of mechanisms: imprinting disorders, alteration of genes direcly involved in regulation of transcriptional activity, and ciliopathies. For each mechanism, examples of syndromes are presented. However, not all syndromic forms of obesity seem to fit these three general mechanisms, which is represented by the gray band in the graph

negative for Prader-Willi syndrome (methylation analysis); pathogenic/likely pathogenic CNVs were detected in 24% (67/279) of them. (2) Carvalho et al. (2022) [203••] investigated- patients who previously tested negative for karyotype, Prader-Willi syndrome, Fragile X syndrome, and a limited panel of CNVs (MLPA); the combination of CNV and SNV/indel analysis using NGS data led to a high diagnostic yield (~47%).

Therefore, methods of genome-wide investigation (DNA microarray and whole exome/genome sequencing) should be prioritized over the target sequencing of well-characterized syndromic obesity gene panels. The simultaneous analysis of CNVs, SNVs and indels using NGS data is a cost-effective option for genetic investigation of syndromic obesity [203••]. Additionally, epigenetic platforms that can collectively analyze and distinguish between genomic imprinting disorders, such as Prader-Willi and Temple syndrome, are useful to aid in clinical diagnosis [108].

Biological Mechanisms

Although the biological pathways related to syndromic obesity genes are quite diversified, it is clear that the etiology tends to be central (linked to neurodevelopment), with less contribution of causal peripheral mechanisms. There are three main groups of mechanisms (Fig. 3):

1. imprinting disorders (e.g., Prader-Willi syndrome, pseudoparathyroidism, and Temple syndrome). Various imprinted genes are critical regulators of growth and development [217]. Prader-Willi, Temple and syndromes related to *GNAS* mutations have obesity and other clinical features possibly connected to hypothalamic disturbances.
2. mutations in genes directly involved in transcriptional activity (e.g., Kleefstra type 1, Börjeson-Forssman-Lehmann, *SIM1*-related, *MYT1L*-related, and Smith-Magenis syndromes). There is a significant overrepresentation of genes encoding proteins that alter chromatin structure in neurodevelopmental disorders [218].
3. ciliopathies (e.g., Bardet-Biedl, Alström, MORM, and Carpenter type 1 syndromes). Neuronal cilia likely play diverse signaling roles throughout the brain and impact several behaviors, including feeding. Additionally, cilia modulate peripheral tissue signaling and homeostasis. The relationship between cilia dysfunction and obesity is complex and not fully understood [60], but three possible mechanistic processes are described: (i) adipogenesis (ciliary proteins may influence in pro-adipogenic and anti-adipogenic signaling pathways); (ii) neuronal food intake regulation (cilia on hypothalamic neurons, particularly on the POMC neurons, contain the receptors for hormones that regulate food intake such as leptin, neuropeptide Y and MCH); and (iii) food odor perception (diminished ciliary signaling of the olfactory receptor neurons might reduce satiating) [219].

Conclusions

A correct genetic diagnosis impacts medical management, treatment, and prognosis, in addition to enabling proper genetic counseling. Additionally, it may benefit the family from the psychological point of view by ending the

diagnostic odyssey [220]. However, the etiology is not identified in most cases of syndromic obesity [8••, 202]. Kaur and colleagues (2017) [8••] reported that the genetic etiology has been elucidated for only a fraction of syndromic forms of obesity described in the literature (19 out of the 79). There are gaps in knowledge about syndromic obesity and a low genetic diagnostic rate, which impairs genetic counseling and hinders the development of therapeutic approaches. Knowledge of pathophysiology pathways could reveal therapeutic opportunities for syndromic forms of obesity.

Availability of Data and Materials Not applicable

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Compliance with Ethical Standards

Conflict of Interest The authors declare that there are no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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