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Review

A new era in childhood obesity

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Advances in our understanding of hypothalamic control of energy homeostasis have resulted in the identification of genetic forms of obesity, both syndromic and nonsyndromic, with some precision treatments now being employed. In this review article, we examine the progress being made in identifying new genes involved in the hypothalamic leptin–melanocortin system and their possible implications in obesity, as well as other potential clinical features. We include an update on clinical trials in genetic obesity with specific pharmacological treatments, such as agonists for the melanocortin 4 receptor, and for glucagon-like peptide-1 receptor. The possibility of employing new precision drug targets in specific forms of obesity is modifying the approach to disease treatment in the pediatric clinic.

Highlights

Obesity associated with the melanocortin system can be diagnosed in childhood, including both monogenic and syndromic forms.

Genetic obesity is characterized by early onset and extreme hyperphagia, although there is no precise definition for these features.

Numerous polymalformative syndromes include obesity among their main phenotypic traits. Among these are ciliopathies, in which alterations in the neuronal ciliary system can disrupt hypothalamic proopiomelanocortin neuron signaling, helping to explain the hyperphagia and obesity frequently observed in some of these disorders.

Pharmacological treatment of patients with impairment of the leptin–melanocortin pathway can be classified into specific and nonspecific treatments.

The use of these therapies is expanding to new indications, and additional treatments are under clinical investigation for both monogenic and polygenic obesity.

Keeping body weight in check: role of the leptin–melanocortin system

Body weight is precisely controlled throughout the lifespan by the maintenance of metabolic and energy homeostasis. This results from the complex interplay of a myriad of regulatory signals relaying nutritional and environmental cues, with key hormonal factors being integrated by essential brain circuits responsible for the regulation of feeding and energy expenditure [1,2]. Among the brain areas physiologically involved in this phenomenon, the hypothalamus stands out as a major integrative center for body weight control (Box 1).

Along with milestones in preclinical research, such as the discovery of the adipose hormone leptin, with potent **anorexigenic actions** (see Glossary), identification of important players in body weight control has been guided by clinical studies addressing the pathogenic basis of early-onset severe forms of obesity [12]. This is well illustrated by the discovery and characterization of mutations in the leptin–melanocortin pathway (Figure 1), where preclinical findings on how leptin and melanocortins (MC) control feeding and metabolism have been corroborated and expanded by clinical data describing the phenotypic consequences of genetic inactivation of elements of this complex system. These include leptin (LEP) and its receptor, LEPR, as well as the genes encoding proopiomelanocortin (POMC), the precursor of MC, proprotein convertase subtilisin/kexin type 1 (PCSK1), an enzyme that processes POMC to form MCs, the main MC receptor, MC4R, and numerous cofactors involved in melanocortin production and signaling. These human cases of severe obesity, usually representing monogenic forms, have not only allowed better understanding of the pathophysiological control of body weight (Box 2) but have also helped to illuminate novel therapies for the management of obesity. Major recent advances in this area, focusing mainly on the leptin–melanocortin pathway, are summarized in this review. Moreover, we emphasize that obesity has a multifactorial etiology and that this must be taken into consideration in the diagnosis, especially in young children with severe early-onset obesity, as treatment protocols can be highly specific, impacting both their long-term metabolic and mental health.

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Box 1. Hypothalamic control of body weight—the arcuate nucleus perspective

The hypothalamus is a key brain area for the regulation of a wide diversity of vegetative functions, including metabolic and energy homeostasis [1,2]. The hypothalamic circuits controlling food intake and energy expenditure involve specific neuronal pathways that have orexigenic or anorexigenic actions [2] and circuits involved in thermogenic regulation and peripheral metabolism [3], with contributions from non-neuronal and neurovascular players [4,5]. These systems are organized into different hypothalamic nuclei that are profusely interconnected and hierarchically organized to control all aspects of systemic energy homeostasis, and whose deregulation can lead to obesity.

Among the various hypothalamic nuclei involved in feeding and body weight control, the arcuate nucleus (ARC) holds a prominent hierarchical role as the first-order center for the reception and initial processing of metabolic information, largely conveyed by peripheral hormones and nutritional signals. The ARC, in turn, sends projections to other hypothalamic nuclei or extrahypothalamic brain regions to drive fundamental aspects of metabolic homeostasis [1]. The most relevant neuronal circuit in the ARC is defined by the reciprocal connections between neurons expressing proopiomelanocortin (POMC) that is processed to melanocortins, which are powerful anorexigenic signals, and neurons expressing Agouti-related peptide (AgRP) and neuropeptide Y (NPY), with potent orexigenic actions [1,6,7]. These neurons express receptors for key metabolic hormones but with inverse responses, with conditions that activate POMC neurons inactivating AgRP neurons, and vice versa.

The melanocortin system integrates various ligands, including α-, β-, and γ-melanocyte-stimulating hormones (MSHs), derived from the proteolytic processing of POMC, and their five receptor subtypes, MC1R to MC5R [6,7]; MC4R, and to a lesser extent MC3R, are the most relevant in conveying the anorectic actions of melanocortins. AgRP is also part of the melanocortin system and produces its orexigenic actions by antagonizing the effects of α-MSH at the level of MC4R [6,7]. Ample evidence points to an essential role of POMC neurons in the ARC in transmitting the anorexic effects of leptin, a hormone produced in adipose tissue, on body weight control and in glucose homeostasis [6,7]. However, recent experimental data suggest that these POMC neurons are dispensable for the actions of leptin on body weight at least in mice [8]. Likewise, the function of AgRP neurons in maintaining body weight has been also disputed [9]. POMC neurons in the ARC also participate in the interplay between energy homeostasis and other essential bodily functions, such as reproduction [10,11].

Monogenic severe early-onset obesity associated with hyperphagia

Childhood obesity is not only a risk factor for adult obesity, diseases, and decreased life expectancy, but it is also associated with impairment of physical and mental health even during early ages [21]. In children, it is particularly important to recognize specific clinical features that could help to identify obesity subjects requiring specific treatments (e.g., genetic forms) and to reinforce counseling and psychological support. Obesity due to genomic, genetic, or epigenetic mechanisms is rare, with an unknown prevalence for most causes. The worldwide incidence of obesity in children aged 2 to 4 years is estimated to be around 7% [22], but 13% of patients with severe early-onset obesity are reported to have an underlying genetic cause [23]. This incidence will likely increase as new genetic anomalies associated with excess weight gain are identified and genetic testing in childhood obesity becomes more prevalent.

The discovery of leptin [24] launched the description of the leptin–melanocortin–MC4R signaling pathway (Box 1) and the subsequent identification of loss-of-function mutations in genes of this system associated with obesity in humans. The mutations identified to date cause severe early-onset obesity characterized by extreme **hyperphagia** that usually begins in the first months or years of life [13,25]. However, diagnosis is hindered as there is no consensus on the age limit to establish early-onset obesity, although the American Academy of Pediatrics recently proposed a limit of younger than 5 years of age [26], nor is there a precise method to determine hyperphagia [25]. Classification of childhood obesity severity based on either **body mass index (BMI)** excess or the presence of associated comorbidities has been proposed [21,26]. These patients do not usually present with other distinctive phenotypic features, but some **polymalformative syndromes** include hyperphagia and obesity due to impairment of some of the genes involved in this satiety signaling pathway among their key phenotypic hallmarks. The list of genes encoding

Glossary

Anorexigenic actions: a signal or factor that reduces appetite.
BMI score or *Z*-score: degree of severity of BMI excess during childhood and adolescence. Calculated for age and sex as [patient's BMI—mean population BMI]/SD.
Body mass index: ratio between weight (kilograms) and squared height (square meters), an indirect estimator of body fat mass.
Ciliopathies: a group of diseases/syndromes caused by a dysfunctional primary neuronal cilia system, including several identified polymalformative syndromes.
European Medicines Agency (EMA): the agency in charge of the approval and labeling of human drugs in the EU.
FDA: an agency in charge of the approval and labeling of human drugs in the United States.
Genome-wide association studies (GWAS): studies in which the DNA of subjects with different phenotypes for a specific disease or trait is compared with specific variants in genes that are more frequent in the disease or trait in question.
Hyperphagia: an uncontrollable drive to eat, usually resulting in the rapid and frequent consumption of large amounts of food, often interfering with a subject's activities, including sleep.
Hypogonadotrophic hypogonadism: defect in gonadal function due to defective gonadotrophin (FSH: follicle-stimulating and LH: luteinizing hormones in the pituitary), that can be due to a lack of the hypothalamic stimulating hormone (GnRH).
Online Mendelian Inheritance in Man Database (OMIM): an online accessible database of known human genes and genetically inherited conditions, periodically updated based on emerging scientific evidence.
Orexigenic actions: a signal or factor that induces appetite.
Polymalformative syndromes: human conditions encompassing several malformations and dysfunctions often due to a common genetic basis.
SD score: a statistical measurement used to indicate how far a data point is from the mean value of the studied population.

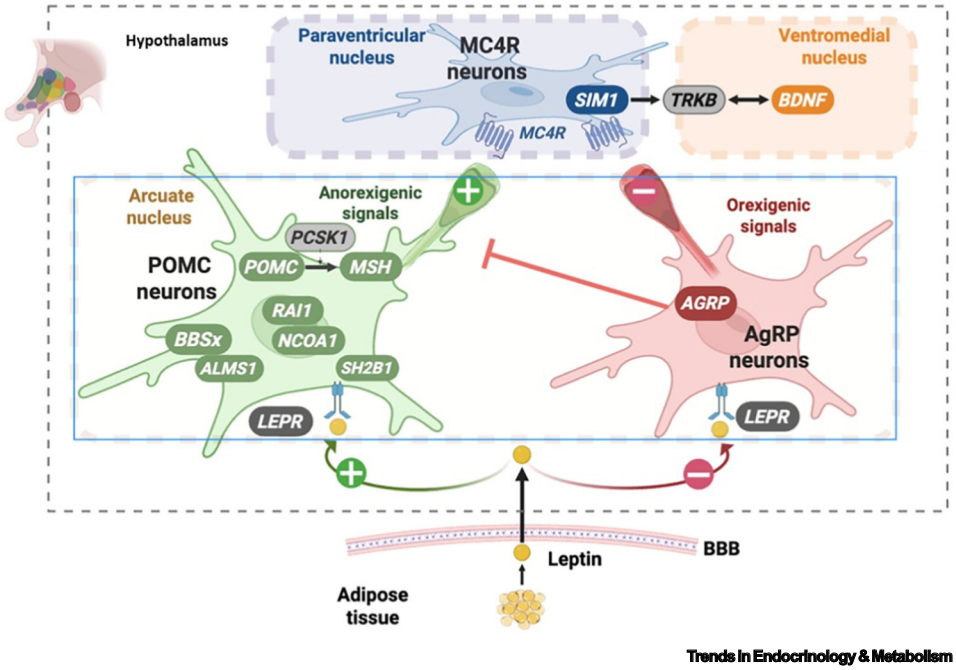

Figure 1. The leptin–melanocortin satiety signaling pathway: from adipocytes to the hypothalamus. Schematic representation of the leptin–melanocortin satiety signaling pathway. The adipose tissue secretes leptin that crosses the BBB reaching the arcuate nucleus in the hypothalamus, where it acts through its receptor (LEPR) to inhibit orexigenic AgRP neurons and to stimulate anorexigenic POMC neurons. The POMC precursor protein is cleaved by PCSK1 to produce alpha-MSH that can act on the MC4R in other hypothalamic nuclei to stimulate satiety and energy expenditure. AgRP is an antagonist of the MC4R and thus stimulates hunger and decreases energy expenditure. Other genes coding for proteins with a relevant role for the correct functioning of this pathway are shown in italics. AgRP: Agouti-related peptide; ALMS1: Alström syndrome gene; BBB: blood–brain barrier; BBSx: Bardet–Biedl syndrome genes; BDNF: brain-derived neurotrophic factor; LEPR: leptin receptor; MC4R: melanocortin-4 receptor; MSH: melanocyte-stimulating hormone; NCOA1: nuclear receptor coactivator 1; PCSK1: proprotein convertase subtilisin/kexin type 1; POMC: proopiomelanocortin.

proteins controlling the integrity of the leptin–melanocortin pathway and whose impairment can result in human obesity continues to grow (Table 1).

Comparison of clinical features due to variants in LEP, LEPR, POMC, MC4R, and PCSK1

Human obesity due to leptin deficiency is an ultra-rare condition inherited in an autosomal recessive fashion due to biallelic loss-of-function mutations in *LEP*. Although reported cases are rare, population genetics forecast a much higher prevalence of LEPR deficiency than is currently known [23], emphasizing the need for specific diagnostic strategies to detect these forms of obesity. The prevalence of PCSK1 deficiency appears to be even lower than that of LEP, LEPR, and POMC deficiencies [13,46], while monoallelic *MC4R* variants are accepted as the main cause of monogenic obesity [20,47], with an estimated prevalence of approximately 2.5% in patients with obesity and even higher when obesity onset occurs early in life. A 0.3% prevalence was reported in a general cohort at birth in the United Kingdom [48]. However, homozygous or compound heterozygous cases leading to more severe phenotypes with extreme hyperphagia are less prevalent.

Patients deficient in *LEP* or *LEPR* exhibit the most rapid and greatest weight gain, attaining an extremely high BMI in the first year of life, followed by a plateau up to 5 years of age [13]. In

Box 2. Early descriptions of monogenic obesity.

Genetic leptin deficiency [7q31.3, **Online Mendelian Inheritance in Man Database (OMIM)** #164160] was first reported in 1997, with few patients identified since. These patients usually have normal birth weight but reach an extremely elevated BMI by 1 year of age, with unexpectedly low or undetectable serum leptin levels. Insulin resistance, liver steatosis, and immunological alterations are often found during childhood [13–15]. **Hypogonadotrophic hypogonadism** is typical, supporting the role of leptin in puberty onset and progression [16]. Bioinactive and antagonistic leptin have also been associated with severe childhood obesity in patients with normal or high leptin levels. Subclassification based on how the underlying genetic variants modify the protein, causing leptin deficiency, bioinactivity, or antagonism, has been proposed [14].

Obesity due to LEPR deficiency, first described in patients carrying a homozygous loss of function variant in *LEPR* (1p31, OMIM# 601007), also have normal birth weight, intense weight gain due to uncontrollable hyperphagia before 6 months of age and hypogonadotrophic hypogonadism. Growth hormone and thyrotropin deficiencies may be present. Their clinical alterations are reported to be less severe than in patients with congenital leptin deficiency.

The first reported cases of genetically driven POMC deficiency (2p23.3, OMIM #176830) had normal birth weight and extreme weight gain during the first months of life as well as unexpected reddish hair, light skin pigmentation, and adrenal insufficiency of pituitary origin. However, red hair, hypopigmentation, and adrenal insufficiency were later shown to not be universal. These patients have a high prevalence of central hypothyroidism and type 1 diabetes mellitus, with possible impairment of growth and pubertal development [13,15,17].

The enzyme PCSK1 processes POMC in the hypothalamus and proinsulin and proglucagon in the pancreas. In 1997, a woman with extreme obesity that started in childhood, impaired glucose homeostasis, hypogonadotropic hypogonadism, low cortisol, high leptin, POMC, and proinsulin levels and very low insulin levels was found to have compound heterozygous loss of functional variants in *PCSK1* (5q15-q21, OMIM #162150). Possible clinical features were later expanded to include intestinal malabsorption in early life manifesting as persistent diarrhea [18] and dramatic hyperphagia possibly due to impaired processing of proinsulin in addition to disruption of the melanocortin pathway [19].

The first two cases of human obesity associated to heterozygous variants in *MC4R* (18q22, OMIM #155541) were reported in 1998, with more severe phenotypes due to biallelic variants subsequently identified, suggesting both autosomal dominant and recessive inheritance patterns [20].

contrast, in POMC-deficient patients, the early rise in BMI is less abrupt and progressively increases up to 5 years of age, lacking an early plateau [13]. Homozygous MC4R variants result in a BMI evolution and severity similar to that in LEP- or LEPR-deficient patients, while in patients with monoallelic MC4R variants, weight gain is usually less abrupt, resulting in BMI excess that is less severe at age 5 [13]. Monoallelic variants in *PCSK1* are also reported to cause obesity, but again, it is less severe than that due to biallelic impairment [49,50]. However, reports regarding the role of heterozygous variants in *POMC* [51,52], *LEP,* and *LEPR* [53–55] are conflicting. A recent multicentric study of a significant number of patients harboring biallelic variants in *LEP*, *LEPR*, *POMC,* or *MC4R* indicates that by 1 year of age, these patients almost invariably have a BMI above +2 **SD SCORE** and suggests that a genetic cause of obesity should be highly suspected if, by 2 years of age, a child's BMI is 24 kg/m^2 + 4.69 SD SCORE or above [13].

Other characteristics may differ between these monogenic forms of obesity, but they may not be sufficient to predict the specific genetic diagnosis. For example, although acceleration of growth and skeletal maturation are frequently observed in polygenic childhood obesity, overgrowth is postulated to be a hallmark of MC4R-associated obesity, beginning early in life and being greater than that observed in LEP or LEPR deficiency, but similar to that in POMC deficiency [13]. MC4R variants are also suggested to be associated with greater increases in insulin resistance and visceral and intrahepatic adipose content, but lower cholesterol and triglyceride levels and cardiovascular disease risk than would be predicted according to the severity of their obesity [56,57]. As POMC is a precursor for several bioactive molecules, including endorphins (α, β, and γ), melanocortins, and adrenocorticotropic hormone (ACTH), essential for adrenal gland stimulation and steroid synthesis, including cortisol, variants in this gene possibly result in other affectations.

Table 1. Genes involved in leptin–melanocortin signaling pathway function

Gene (Cytogenetic location; OMIM)	Protein	Pathophysiological mechanism involving leptin–melanocortin dysfunction associated with obesity due to loss of function variants[a]	Refs
ADCY3 (*2p23.3; OMIM*600291*)	Adenylate cyclase 3 (*enzyme*)	Adcy3 colocalizes with MC4R in neuronal primary cilia and regulates body weight in mice. Its inhibition in *Mc4r*-expressing neurons in mice increases food intake resulting in obesity. Autosomal recessive obesity predisposition syndrome described in humans (*OMIM*#617885).	[27]
BDNF (*11p14.1; OMIM*113505*)	Brain-derived neurotrophic factor (*preproprotein for growth factor*)	Hypothalamic development. *Agrp* and *Pomc* neurons act via *Bdnf*-expressing neurons in the hypothalamic paraventricular. Deletion of *Bdnf*-expressing neurons blunts plasticity of sympathetic innervation of adipose tissue, crucial for energy homeostasis.	[28]
CPE (*4q32.3; OMIM*114855*)	Carboxypeptidase E (*enzyme*)	*Pomc* neuron-specific ablation of *Foxo1* increases *Cpe* expression selectively increasing CPE-dependent processing of POMC. The resulting neuropeptide profile is associated with decreased food intake and normal energy expenditure. Autosomal recessive obesity syndrome described in humans (*OMIM*#619326).	[29]
FOXO1 (*13q14.11; OMIM*136533*)	Forkhead Box O1 (*transcription factor*)	*Pomc* neuron-specific ablation of *Foxo1* increases products of POMC associated with decreased food intake and normal energy expenditure in *pomc-Foxo1*$^{-/-}$ mice. This effect is mediated by CPE.	[29]
GNAS (*20q13.32; OMIM*139320*)	Guanine nucleotide-binding protein (*G protein*)	Colocalizes with MC4R and regulates its signaling. Autosomal dominant (influenced by imprinting) obesity syndrome described in humans (OMIM#103580).	[30]
ISL1 (*5q11.1; OMIM*600366*)	ISL LIM Homeobox 1 (*transcription factor*)	Early expression of *Isl1* in the developing hypothalamus promotes terminal differentiation of melanocortinergic neurons. Essential for hypothalamic *Pomc* expression throughout life.	[31]
KSR2 (*12q24.22-q24.23; OMIM*610737*)	Kinase suppressor of RAS 2 (*scaffold protein in the MAPK/ERK pathway*)	*KSR2* regulates feeding behavior, adaptive thermogenesis, and sensitivity to leptin and activators of the energy sensor AMPK.	[32]
MAGEL2 (*15q11.2; OMIM*615547*)	MAGE-like protein 2 (*ubiquitin ligase enhancer*)	*Magel2* is required for leptin-mediated depolarization of POMC neurons in the hypothalamic arcuate nucleus in mice. Autosomal dominant obesity syndrome described in humans (OMIM#615547).	[33]
MC3R (*20q13.2; OMIM*155540*)	Melanocortin receptor 3 (*receptor*)	*Mc3r* null mice have an increased fat to lean mass ratio. Autosomal dominant human obesity susceptibility syndrome due to mutations in *MC3R* described (OMIM#602025).	[10]
MRAP2 (*21q22.11; OMIM*609196*)	Melanocortin 2 receptor accessory protein (*accessory protein to MCRs*)	Determinant in the ciliary localization of MC4R and its correct signaling. Autosomal dominant human obesity susceptibility syndrome due to mutations in *MRAP2* described (OMIM#615457).	[34–36]
NCOA1 (*2p23.3; OMIM*602691*)	Nuclear/steroid receptor coactivator (*protein [SRC1], receptor coactivator*)	Interacts with phosphorylated STAT3, a target of leptin receptor activation, to potentiate POMC transcription. Deletion of *Ncoa1* in *Pomc* neurons in mice attenuates their depolarization by leptin, decreases *Pomc* expression, and increases food intake leading to high-fat diet-induced obesity.	[37]
NRP1 (*10p11.22; OMIM*602069*) *NRP2* (*2q33.3; OMIM*602070*)	Neuropilin 1 and Neuropilin 2 (*receptors*)	Receptor for semaphorins. In mice, deletion of the NRP2 in *Pomc* neurons disrupts their projections from the arcuate to the paraventricular nucleus, reduces energy expenditure, and causes weight gain. Variants in *NRP1 or 2* disrupt cell-surface localization of the receptor and its function.	[38]
NTRK2 (*9q21.33; OMIM*600456*)	Neurotrophic tyrosine kinase receptor type 2 (*receptor*)	Receptor for BDNF mediating its actions, including in hypothalamic development, synaptic plasticity, and cell signaling. Autosomal dominant obesity syndrome described in humans (OMIM#613886).	[39]
PHIP (*6q14.1; OMIM*612870*)	Pleckstrin homology domain-interacting protein (*insulin and melanocortin signal modulation*)	Whole exome sequencing in severe childhood obesity suggests a link between *PHIP* variants and repressed *POMC* transcription. Autosomal dominant obesity syndrome described in humans (OMIM#617991).	[40]
PLXNA1 (*3q21.3; OMIM*601055*) *PLXNA2* (*3q21.3; OMIM*601055*) *PLXNA3* (*3q21.3; OMIM*601055*) *PLXNA4* (*3q21.3; OMIM*601055*)	Plexin receptors (*receptor*)	Receptors for semaphorins. Variants in *PLXNA1-4* disrupt cell-surface localization of the receptor and function. Autosomal recessive obesity syndrome described in humans (OMIM#619955).	[38]

(continued on next page)

Table 1. (continued)

Gene (Cytogenetic location; OMIM)	Protein	Pathophysiological mechanism involving leptin–melanocortin dysfunction associated with obesity due to loss of function variants[a]	Refs
RAI1 (*17p11.2; OMIM*607642*)	Retinoic acid induced gene 1 (*gene expression regulator*)	*Rai1* haploinsufficiency reduces *Bdnf* expression resulting in hyperphagia, obesity, and altered fat distribution in mice. Autosomal dominant obesity syndrome described in humans (OMIM#182290).	[41]
SEMA3 A(*7q21.11; OMIM* 603961*) *SEMA3B* (*3p21.31; OMIM*601281*) *SEMA3C* (*7q21.11; OMIM*602645*) *SEMA3D* (*7q21.11; OMIM*609907*) *SEMA3E* (*7q21.11; OMIM*608166*) *SEMA3F* (*3p21.31; OMIM*601124*) *SEMA3G* (*3p21.1; OMIM*620997*)	Semaphorin 3 (*chemoattracting proteins*)	In mice, Sema3 signaling drives the development of *Pomc* neuron projections from the arcuate to the paraventricular nuclei in the hypothalamus, thus playing a role in the development of melanocortin circuits. Rare variants in *SEMA3*s affect their secretion and function in humans.	[38]
SH2B1 (*16p11.2; OMIM*608937*)	Src homology 2B adaptor protein 1 (*adaptor protein*)	Essential for JAK2-mediated leptin signaling. Neuron-specific overexpression of *SH2B1* dose-dependently protects against high-fat diet-induced leptin resistance and obesity. Autosomal dominant obesity syndrome described in humans (OMIM#613444).	[42]
SIM1 (*6q16.3; OMIM*603128*)	Single-minded Homolog of *Drosophila* (*transcription factor*)	Involved in hypothalamic development, particularly the supraoptic nucleus and *MC4R* neurons in the paraventricular nucleus.	[43]
TBX3 (*12q24.21; OMIM*601621*)	T-box transcription factor 3 (*transcription factor*)	Tbx3 directs the terminal specification of neurons and is required for maintaining their peptidergic identity. Loss of *Tbx3* function in hypothalamic neurons causes weight gain and metabolic disturbances by disrupting the development of *Pomc* and *Agrp/Npy* neurons. Autosomal dominant obesity syndrome described in humans (OMIM#181450).	[44]
TUB (*11p15.4; OMIM*601197*)	TUB bipartite transcription factor. A member of the Tubby family. (*transcription factor*)	Tub is a substrate of insulin receptor tyrosine kinase (IRTK) and leptin receptor (LEPR)–Janus kinase 2 (JAK2) in hypothalamic nuclei. Inhibition of *Tub* expression in the hypothalamus blunts the effect of insulin or leptin on POMC, thyroid-releasing hormone, melanin-concentrating hormone, and orexin expression. Autosomal recessive obesity syndrome described in humans (OMIM#616188).	[45]

[a]OMIM: Mendelian Inheritance in Man Database (URL: http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim).

Moreover, POMC neurons are involved not only in satiety but also in energy expenditure, stress responses, glucose metabolism, growth, and development [58]. In both mice [59,60] and humans [61] these neurons are vastly heterogeneous, and although there are many similarities, there are also notable differences that could predict disparate metabolic outcomes due to affectation of POMC neurons in these species [61]. For example, receptors for the gut peptides cholecystokinin and bombesin are expressed in specific subpopulations of POMC neurons in mice but not in humans, and expression of the receptors for leptin and GLP-1 in POMC neurons overlaps in humans but is expressed in separate populations in mice. The hypothalamic cell populations expressing MCR4 also differ between mice and humans. These observations are very important as they suggest that the responses to obesity therapies in preclinical studies may not necessarily predict human responses.

Other genes with described variants and targeted in clinical assays

The list of genes involved in the leptin–melanocortin satiety pathway and identified in cases of human obesity continues to grow [62] (Table 1), although the prevalence of obesity associated with pathogenic variants in these genes is currently unknown. Notwithstanding, increased

genetic testing and identification of associated clinical features, in addition to obesity, have resulted in some of these genes being selected for therapeutic clinical trials with an MC4R agonist. Among these is the coactivator of steroid receptor 1 (SRC1), encoded by *NCOA1*, which modulates leptin-induced POMC activity, and rare heterozygous variants in this gene result in severe obesity [37]. In mice, specific deletion of *Src-1* in POMC neurons decreases *Pomc* expression and increases food intake, leading to high-fat diet-induced obesity [37]. This protein is also involved in thyroid hormone signaling [63] and has been associated with protection against cognitive decline [64], suggesting other possible clinical traits.

Src homology 2B adaptor protein 1 (*SH2B1*) is involved in both hypothalamic development and leptin receptor signaling [42]. In humans, haploinsufficiency due to 16p11.2 deletions [65] and pathogenic *SH2B1* variants are associated with hyperphagia and severe insulin resistance/glucose intolerance, which is disproportionate to the degree of obesity [66]. Pleckstrin homology domain interacting protein (PHIP) directly affects POMC transcription enhancement, and rare predicted deleterious variants are more prevalent in patients with severe obesity, with pathogenic variants in *PHIP* also being associated with Chung–Jansen syndrome, which includes obesity among its main features [40].

Semaphorins, mainly *SEMA-3*, their receptors neuropilin (*NRP*) and plexin (*PLXNA*) [38], and numerous transcription factors, including T-box 3 (*TBX3*) [44,67] and single-minded homolog 1 (*SIM1*) [43], participate in the development of hypothalamic POMC neurons and their projections. Rare variants in this set of genes are significantly enriched in severely obese patients compared with controls [68]. Semaphorins also participate in inflammation, angiogenesis, and autoimmune processes in diseases such as diabetic retinopathy, rheumatic diseases, and osteoarthritis [69,70]. As NRP is also a coreceptor for transforming growth factor and vascular transforming growth factor, it is involved in physiological pathways in addition to neural development [71]. Alterations in PLXNA can also affect the development of the olfactory system and the reproductive axis [72]. Heterozygous variants in *TBX3* cause Ulnar–Mammary syndrome [73], which has a broad clinical spectrum. The impact of variants in *SIM1* ranges from nonsyndromic obesity to what was initially called pseudo Prader–Willi syndrome [74]. Indeed, human cases of obesity with pathogenic variants in genes involved in hypothalamic development and melanocortin signaling, such as *SIM1*, *BDNF*, *NTRK2,* or *SH2B1*, usually show intellectual disability and malformative stigmata, as these genes are involved in neuronal development in other brain areas. The resulting phenotypes may vary greatly depending on the variant and whether it is homozygous or heterozygous, as well as the individual's entire genetic makeup and numerous environmental factors. Indeed, genes involved in neuronal development can be greatly influenced by their environment, often in a temporal manner, adding to possible variations in the clinical features.

Genetic variants in syndromic forms of obesity

There is an extensive list of polymalformative syndromes with obesity among their main phenotypical traits, including some with relatively high prevalence, such as Down, Turner, or fragile-X syndromes. In these patients, intellectual disability, frequent use of psychoactive drugs with **orexigenic actions**, limitations on their ability to perform physical activity, and alterations in food preferences and eating patterns can underlie the development of obesity. Additionally, syndromes caused by large chromosomal deletions, for example, as previously stated for 16p11.2 deletion, can have pleiotropic phenotypic features due to the affectation of several genes.

In a subset of syndromic forms of obesity (Table 2) intrinsic impairment of the leptin–melanocortin pathway has been demonstrated, particularly in syndromes with early-onset

Table 2. Selected polymalformative human syndromes and nonsyndromic acknowledged susceptibility syndromes with obesity

Syndrome	Genetic basis	Main features	Refs
Alström Autosomal recessive	*ALMS* (*2p13.1*) Involved in the neuronal primary cilia	*Typical*: Cardiomyopathy, without intellectual disability. Obesity. *Frequent*: Neuro-ophthalmologic defects. Neurosensitive deafness. Type 2 diabetes mellitus. *Possible*: Hyperuricemia, hypertriglyceridemia, hypogonadism, hypothyroidism, GH deficiency.	(OMIM#203800)
Bardet–Biedl 1–26 Autosomal recessive/triallelic	26 known genes (*BBSome*) involved in neuronal primary cilia*	*Typical*: Hyperphagia and early onset obesity with intellectual disability (prominent speech delay). Polydactyly. Retinal degeneration. *Frequent*: Iridian coloboma (BBS 2), renal impairment, hypogonadism/microgenitalism (males). Anosmia/hyposmia. *Possible*: Cardiovascular abnormalities. Craniosynostosis.	(OMIM BBS 1–22) [a] [75]
BDV syndrome (Blakemore–Durmaz–Vasileiou) Autosomal recessive	*CPE* (*4q32.3*) Carboxypeptidase E	*Typical*: Early-onset severe obesity, hyperphagia, moderately impaired intellectual development, and infantile hypotonia. *Frequent*: Endocrine disorders (hypogonadotropic hypogonadism, hypothyroidism). *Possible*: Insulin resistance.	(OMIM#619326)
Chung–Jansen Autosomal dominant	*PHIP* (*6q14.1*) Pleckstrin homology domain interacting protein	*Typical*: Global developmental delay from infancy with impaired intellectual development (prominent speech delay), behavioral abnormalities, dysmorphic features, and obesity. *Frequent*: Dysmorphisms (full eyebrows/synophrys, upturned nose, large ears, tapering fingers).	(OMIM#617991)
Dworschak–Punetha neurodevelopmental syndrome Autosomal recessive	PLXNA1 (3q21.3) Plexin A1	Typical: Global developmental delay, mildly impaired intellectual development. Frequent: Behavioral abnormalities, including autism spectrum disorder and hyperactivity. Possible: Obesity. Optic disc hypoplasia, ptosis, hypo- or hyperpigmented skin lesions, dysmorphic facial features, brain imaging abnormalities of the ventricles or corpus callosum.	(OMIM#619955)
Joubert (types 1–40) Autosomal recessive	40 genes involved in the neuronal primary cilia***	*Typical*: Hypoplasia of the cerebellar vermix (neuroradiologic 'molar tooth sign'), dysregulation of breathing pattern, developmental delay, and neurologic abnormalities (hypotonia, tremor). Obesity. *Possible*: Retinal dystrophy. Renal abnormalities. Typical craniofacial gestalt (large head, prominent forehead, high rounded eyebrows, epicanthal folds, ptosis, upturned nostrils, open mouth, tongue protrusion, and low-set and tilted ears).	OMIM Joubert (types 1–40) [b] [76]
Meckel (types 1–14) Autosomal recessive	14 genes involved in the neuronal primary cilia**	*Typical*: Cystic renal disease. Central nervous system malformations (especially occipital encephalocele) and hepatic abnormalities, including portal fibrosis or ductal proliferation. Obesity. *Possible*: Polydactyly. Bowing of the long bones. Craniofacial abnormalities.	OMIM Meckel (types 1–14) [c] [76]
Obesity, susceptibility to BMIQ19 Autosomal recessive	*ADCY3* (*2p23.3*) Adenylate cyclase 3	*Typical*: Hyperphagia and obesity in the first 2 years of life *Frequent*: Hyposmia/anosmia. *Possible*: Intellectual disability, puberty impairment, dyslipidemia, insulin resistance.	(OMIM#617885)
OBHD syndrome: Obesity, hyperphagia, and developmental delay Autosomal dominant	*NTRK2* (*9q21.33*) TrkB receptor that binds BDNF	*Typical*: Global developmental delay and hyperphagia resulting in obesity. *Possible*: Seizures. Craniosynostosis.	(OMIM#613886)
Prader–Willi Autosomal dominant (imprinting influence)	*15q11-q13.* Involving *MAGEL2.*	*Typical*: Hypotonia, hypogonadism, intellectual and motor disability with behavioral abnormalities. Feeding difficulties in the first year of life followed by intense hyperphagia and obesity thereafter. *Frequent*: Small hands and feet, hypogenitalism, typical Gestalt (almond-shaped eyes, inverted V upper lip). Emotional lability. *Possible*: Insulin resistance. Polyhydramnios. Sparse fetal movements.	(OMIM#176270)
Pseudohypoparathyroidism 1A (Albright hereditary osteodystrophy) Autosomal dominant (imprinting influence)	*GNAS* (*20q13-32*) G-protein alpha subunit Gs-α	*Typical*: Short stature and trunk obesity (Albright osteodystrophy phenotype) and intellectual disability. *Frequent*: Calcifications. Hormone resistance (TSH, PTH, GHRH, and gonadotrophins).	(OMIM#103580)

Table 2. (continued)

Syndrome	Genetic basis	Main features	Refs
RDOB syndrome: Retinal dystrophy and obesity Autosomal recessive	TUB (11p15.4) TUB bipartite transcription factor (Tubby family)	Typical: Retinal dystrophy and obesity. No dysmorphic features or clinical features similar to BBS or Alström.	(OMIM#616188)
Schaaf–Yang Autosomal dominant	MAGEL2 (15q11.2) MAGE Family Member L2	Typical: Hypotonia, delayed motor development, and intellectual disability with behavioral abnormalities (initially described as 'Prader-Willi like'). Frequent: Dysmorphic facial features. Obesity and hyperphagia. Autism. Possible: Joint contractures, hypothyroidism, GH deficiency. Fetal akinesia.	(OMIM#615547)
Smith–Magenis Autosomal dominant	RAI1 (17p11.2) Retinoic acid induced 1	Typical: Dysmorphic craniofacial features (brachycephaly, prominent forehead, synophrys, epicanthal-folds, broad nasal bridge, ear anomalies, prognathism). Delayed motor development and intellectual disability with behavioral disturbances (self-injury, self-hugging stereotypes). Frequent: Obesity and hyperphagia. Otolaryngologic problems.	(OMIM#182290)
Ulnar Mammary Autosomal dominant	TBX3 (12q24.21) T-box transcription factor 3	Typical: Limb abnormalities, apocrine/mammary gland hypoplasia and/or dysfunction, abnormal dentition, delayed puberty and genital anomalies (mainly in males). Frequent: Obesity. Possible: Nipple hypoplasia.	(OMIM#181450)
16p11.2 deletion syndrome 220 Kb Autosomal dominant	*16p11.2* (involving *SH2B1*) SH2B adaptor protein 1	*Typical*: Intellectual disability, autism, developmental disorders. *Frequent*: Obesity and insulin resistance (highly dependent on *SH2B1* deletion). Attention deficit disorder.	(OMIM#613444)

See Table 1 for specific gene involvement in leptin–melanocortin signaling pathway.
GH: growth hormone; OMIM: Online Mendelian Inheritance in Man Database (URL: http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim); T2DM: type 2 diabetes mellitus.
[a]For detailed genetic basis, see OMIM ('Bardet–Biedl').
[b]For detailed genetic basis, see OMIM ('Meckel syndrome' types 1–14 in OMIM in February 2026).
[c]For detailed genetic basis, see OMIM ('Joubert syndrome' types 1–40 in OMIM in February 2026).

obesity and dramatic hyperphagia as major features. This has been pivotal for including some of these cases in therapeutic clinical trials with MC4R agonists, particularly in syndromes due to impairment of neuronal primary cilia, or **ciliopathies**, and in conditions potentially impairing *MAGEL2* expression. Impairment of *MAGEL2* expression is postulated to underlie, at least in part, the hyperphagia and obesity observed in Prader–Willi (deletions or uniparental maternal expression of 15q11.2-q13) and Schaaf–Yang (heterozygous pathogenic variants in the paternally derived copy of the maternally imprinted *MAGEL2*) syndromes. *MAGEL2* is highly expressed in the hypothalamus, is involved in neurodevelopment, and is required for leptin-mediated depolarization of POMC neurons [77]. It is involved in satiety and anxietylike behavior associated with food reward [78], traits altered in both syndromes [79].

Disruption of ciliary function can result in a wide variety of pathological outcomes including the ciliopathies Alström, Meckel, Joubert, and Bardet–Biedl syndrome, where hyperphagia and obesity are frequently observed [76,80]. Primary cilia are small protruding organelles on the surface of most cells in the human body and are integral to the correct functioning of diverse signaling cascades; thus, their affectation can have widespread effects. Indeed, these syndromes have diverse phenotypes, including skeletal, systemic (e.g., eye, urinary, or genital), neurobehavioral, and intellectual impairments. For example, Bardet–Biedl syndrome is associated with a broad range of clinical features but with no precise genotype–phenotype correlation, even considering that, to date, 26 genes are reported to cause this syndrome. Obesity in these syndromes is proposed to result from functional disruption of the leptin–melanocortin pathway, as the neural ciliary system plays a prominent role in hypothalamic POMC neuron signaling [81].

Current treatments

The pharmacological treatment of patients with impairment of the leptin–melanocortin pathway can be classified into specific treatments, for example, recombinant leptin and setmelanotide, and nonspecific treatments, mainly represented by liraglutide, semaglutide, phentermine–topiramate, and, in adult patients, tirzepatide. Specific treatments refer to those that replace or substitute a factor that is missing or not functioning. In leptin deficiency, including lack of leptin, bioinactive leptin, and antagonism of leptin's actions, treatment with subcutaneous recombinant human leptin leads to a rapid reduction in hyperphagia and subsequent weight loss [14,82,83]. It is of note that, to date, the **European Medicines Agency (EMA)** has approved recombinant leptin use in generalized or partial lipodystrophy (https://www.ema.europa.eu/en/medicines/human/EPAR/myalepta), but not in leptin deficiency.

Setmelanotide is a nonspecific melanocortin receptor agonist that stimulates hypothalamic MC4R signaling to regulate satiety and appetite. It was initially approved by the **FDA** and EMA for the treatment of obesity and hyperphagia in children aged 6 years or older, after its efficacy and safety were demonstrated in LEPR, POMC, and PCSK1 deficiency due to biallelic loss-of-function mutations [46], as well as in Bardet–Biedl syndrome [84,85]. In the latter, the beneficial effects of treatment included an improved quality of life [86] and metabolic profile [87]. Recently, indications for the treatment were extended to children from the age of 2 years, after a Phase 3, open-label, multicenter trial showed similar benefits to those observed in older patients, including a significant reduction in hunger and BMI **Z-scores** in all patients, with no significant side effects [88].

Preliminary data on setmelanotide treatment in patients harboring mutations in *PHIP*, *SEMA3*, *PLXNA*, *MAGEL 2*, *TBX3,* or *SIM1* indicate a significantly higher percentage of subjects achieving significant weight loss compared with placebo treatment. Although the sample size is limited, the response of patients with variants in *SEMA3E* appears to be better and more uniform than that of those with variants in *SEMA3A-G*. Similarly, weight loss and hyperphagia reduction appear to be greater and more consistent in patients with *PHIP* variants than in those harboring variants in *PLXNA* or *SIM1* [89,90]. In *SIM1* variants, weight reduction correlated better with the degree of loss of function predicted by functional analysis than with the variant class itself, with a postulated role for variable penetrance [91]. Skin hyperpigmentation is almost universal in response to setmelanotide treatment, with local irritation at the injection site, digestive symptoms, and headache also reported, although with lower frequency and intensity.

Data on the use of GLP1 receptor (GLP1R) agonists in patients with obesity secondary to a known impairment in the leptin–melanocortin pathway are limited, as setmelanotide is generally the first choice, except in patients carrying mutations in *MC4R*. Data in these patients are limited but indicate an initial beneficial effect with heterogeneous long-term results [92], similar to their reported response to bariatric surgery [93]. This is supported by a recent study showing that *MC4R* knockout mice respond well to GLP-1R agonists [94]. Data on the use of tirzepatide, a dual agonist for GLP-1 and GIP receptors, in MC4R mutation carriers suggest that the rate and intensity of weight reduction in these patients are similar to that of noncarriers, suggesting that tirzepatide may also be an effective treatment in MC4R deficiency [95] and requires further studies.

In syndromic obesity, therapeutic trials have largely focused on patients with Prader–Willi syndrome due to their intense hyperphagia, but with largely disappointing outcomes. Although clinical trials are still ongoing (NCT06772597[i]), initial results indicate that setmelanotide fails to significantly improve hyperphagia or induce weight loss (NCT02311673[ii]) [96], whereas GLP1R agonists have shown short-term positive results in some patients [97], but follow-up data and properly designed studies to evaluate their effects are lacking. The recent approval by the FDA (https://www.accessdata.fda.

gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=428214) of extended-release diazoxide-choline, which activates ATP-sensitive potassium channels, for weight management in Prader–Willi syndrome provides a novel therapeutic tool for these patients, even though the main benefits have been reported in quality of life and caregivers' perceived illness severity and burden of disease [98]. On the supposition that disruption of the leptin–melanocortin system is potentially involved in the hyperphagia and obesity associated with other genetic syndromic obesities, setmelanotide treatment has also been used in Smith–Magenis [99] or Alström syndrome [84], but with no evidence of a clinically significant benefit on weight loss demonstrated to date.

Further testing is needed to obtain approval for the use of leptin and setmelanotide in patients with affectation of other genes and clinical conditions, with some studies currently underway [15]. The use of setmelanotide in cases of acquired hypothalamic obesity due to postnatal hypothalamic damage [100] was recently approved by the FDA (https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Frhythmtx.com%2Fwp-content%2Fuploads%2F2026%2F03%2FIMCIVREE-prescribing-information.pdf&data=05%7C02%7Cj.ramkumar%40elsevier.com%7Cf6e6a307ab094e81d2aa08de8e305b22%7C9274ee3f94254109a27f9fb15c10675d%7C0%7C0%7C639104535649270261%7CUnknown%7CTWFpbGZsb3d8eyJFbXB0eU1hcGkiOnRydWUsIlYiOiIwLjAuMDAwMCIsIlAiOiJXaW4zMiIsIkFOIjoiTWFpbCIsIldUIjoyfQ%3D%3D%7C0%7C%7C%7C&sdata=vQCSdsrY1TxMVZbJlQe%2Bxq30QQJs3%2BhQ5vW4KLQeEwE%3D&reserved=0) and will hopefully be accepted by the EMA in the near future as data from Phase 3 trials (NCT05774756[iii]) is now available. Similarly, therapeutic clinical trials using setmelanotide that are being conducted in patients with obesity due to the presence of variants in several of the aforementioned genes such as *NCOA1*, *SH2B1*, *PHIP*, *TBX3*, *SIM1*, semaphorins (SEMA3(A-G)) and their receptors *NRP and PLXNA*, will hopefully also lead to the approval for employment in at least some of these cases. Finally, although it may not seem logical, setmelanotide, which requires functional MC4R, has been shown to induce weight loss in adult patients affected with obesity due to some *MC4R* variants, as this agonist is reported to reverse the reduced cell surface expression of *MC4R* caused by these variants [101]. Moreover, as most cases of MC4R-related obesity are heterozygous, this agonist should be effective through activation of those receptors expressed from the nonaffected allele. However, to date, no data on the treatment of children with MC4R obesity with setmelanotide have been published. In adults with obesity but no proven underlying genetic defect, setmelanotide increased resting energy expenditure and shifted substrate oxidation to fat [102], but further data in polygenic obesity are still pending (clinical trials NCT02041195[iv] and NCT01749137[v]).

As more hypothalamic genes and functional processes are identified, new entities amenable to treatment with current drugs may be discovered, as well as targets for new drugs. New routes (i.e., oral; NCT06046443[vi]) and posology (i.e., weekly; NCT06239116[vii]) for MCR agonists are currently under development, in addition to potential new agents such as pharmacological chaperones [103] and atomoxetine (NCT06899178[viii]), which are currently in the pipeline for future treatments of MC4R-related obesities.

Concluding remarks

In this review article, we summarized the known genetic causes of obesity and syndromes associated with obesity in humans, as well as specific pharmacological treatments that have been approved or that are in different clinical trial phases. In addition, the possibility of targeting new genes identified in the leptin–melanocortin system was also discussed. However, obesity is also associated with variants in genes that are expressed outside the leptin–melanocortin system, as **genome-wide association studies (GWAS)** have identified genes expressed in other brain areas as well as systemically. Drug development, however, is hindered by the fact that many proteins are involved in various actions in different tissues, often making it difficult to identify specific targets. Moreover, as most cases of obesity

Outstanding questions

What other genes involved in the melanocortin system are associated with obesity?

Should pharmacological treatments in childhood obesity be used for life?

Are new pharmacological treatments for childhood obesity expected to be approved soon?

are polygenic and have different underlying etiologies, the most likely scenario is that subpopulations of subjects with obesity will respond to one or another pharmacological treatment, but not all subjects will respond equally to any treatment. Studies that identify biomarkers to determine how an individual will respond to a given obesity drug are of utmost importance.

Although there are important questions that still need to be answered concerning genetic obesity in children (see outstanding questions), at present, the identification of genetic causes of obesity is fundamental for patient care, as specific treatments can be highly effective. Genetic analysis should be performed in children with severe early-onset obesity and hyperphagia, starting with a gene panel of the most common genes known to be involved in monogenic obesity, which can be increased or tailored according to the patient's features. Testing can also be extended to more complex analyses (e.g., exome or genome), as there are clearly genes involved in obesity that are yet to be identified. As new genes are identified, the protocols used in the clinic must be continuously updated, and treatment choices must also evolve as new targets are identified and drug options are expanded. However, it is also clear that an increase in the number and complexity of genetic testing could be accompanied by numerous genetic findings that are difficult to ascribe to the observed clinical characteristics, thus complicating the diagnosis. Indeed, the advancement of functional studies to interpret genetic variants that are currently classified as variants of uncertain significance (VUS), and thus to determine their pathogenicity and mechanism of action, will be highly relevant for new therapeutic indications in patients with monogenic obesity. To advance more rapidly and with precision, the creation of official reference centers specializing in genetic obesity is necessary. These centers would not only be useful in the diagnosis of new causes of genetic obesity but would also be of utmost importance in centralizing the studies on these rare diseases in an attempt to obtain sufficient patients to more clearly characterize the associated clinical features of the different affected genes and to determine their responses to specific treatments and long-term evolution.

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Declaration of interests

The authors have nothing to declare.

Resources

[i] https://clinicaltrials.gov/study/NCT06772597
[ii] https://clinicaltrials.gov/study/NCT02311673
[iii] https://clinicaltrials.gov/study/NCT05774756
[iv] https://clinicaltrials.gov/study/NCT02041195
[v] https://clinicaltrials.gov/study/NCT01749137
[vi] https://clinicaltrials.gov/study/NCT06046443
[vii] https://clinicaltrials.gov/study/NCT06239116
[viii] https://clinicaltrials.gov/study/NCT06899178

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