The promise of new anti-obesity therapies arising from knowledge of genetic obesity traits

Anke Hinney[1,2]✉, *Antje Körner*[3,4,5] *and Pamela Fischer-Posovszky*[6]

Abstract | Obesity is a multifactorial and complex disease that often manifests in early childhood with a lifelong burden. Polygenic and monogenic obesity are driven by the interaction between genetic predisposition and environmental factors. Polygenic variants are frequent and confer small effect sizes. Rare monogenic obesity syndromes are caused by defined pathogenic variants in single genes with large effect sizes. Most of these genes are involved in the central nervous regulation of body weight; for example, genes of the leptin–melanocortin pathway. Clinically, patients with monogenic obesity present with impaired satiety, hyperphagia and pronounced food-seeking behaviour in early childhood, which leads to severe early-onset obesity. With the advent of novel pharmacological treatment options emerging for monogenic obesity syndromes that target the central melanocortin pathway, genetic testing is recommended for patients with rapid weight gain in infancy and additional clinical suggestive features. Likewise, patients with obesity associated with hypothalamic damage or other forms of syndromic obesity involving energy regulatory circuits could benefit from these novel pharmacological treatment options. Early identification of patients affected by syndromic obesity will lead to appropriate treatment, thereby preventing the development of obesity sequelae, avoiding failure of conservative treatment approaches and alleviating stigmatization of patients and their families.

According to the World Health Organization (WHO), approximately 39 million children under the age of 5 years had overweight or obesity in 2020 (REF.[1]). The prevalence of severe obesity is particularly alarming. Depending on the study and criteria (TABLE 1) applied, the reported prevalence of severe childhood obesity ranges from 1.96% to 6.30% within the general population[2]. Interestingly, a 2018 study discovered that adolescents with obesity experienced the most rapid weight gain at an age of 2–6 years[3]. In parallel to an increase in BMI in early childhood, adipose tissue mass expands and the first signs of adipose tissue dysfunction appear, such as adipocyte hypertrophy, inflammation and macrophage infiltration, and dysregulation of adipokine secretion[4]. The early onset of obesity is clearly linked to the development of cardiovascular and metabolic comorbidities, with preclinical manifestations occurring in adolescence, and ultimately leading to an increase in mortality in adulthood[5]. Obesity is a frequent, serious, complex and chronic, relapsing disease, recognized as such by the leading professional societies[6,7]. Based on the genetic contribution, obesity can be classified into two main groups: syndromic obesity (which includes obesity syndromes associated with neurodevelopmental disorders as well as monogenic obesity syndromes) and common polygenic obesity. Common childhood obesity arises from the interaction of individual genetic predisposition and our obesogenic environment.

Since early 2020, the COVID-19 pandemic has intersected with the obesity pandemic, and showed the particular vulnerability of children with existing obesity to further excessive weight gain and the clinical burden associated with lockdowns[8–10]. Therefore, preventing and treating obesity as early as possible is of the utmost clinical importance and social relevance.

Individuals living with obesity are often accused of failure to adopt a healthy lifestyle, even by health-care professionals. This assumption leads to stigmatization and is associated with psychological harm[11]. Knowledge about the pathological mechanisms of obesity, including genetics, helps reduce weight stigma[12]. Reduction of stigmatization through the gain of knowledge and education is an important aim of genetic studies in the context of body weight regulation and obesity.

In this Review, we consider the heritability of body weight and genetic classifications of obesity, including

✉*e-mail:* *anke.hinney@uni-due.de*

https://doi.org/10.1038/s41574-022-00716-0

Key points

- Obesity is a complex, multifactorial disease that can be classified into common polygenic obesity and rare obesity syndromes, including monogenic obesity.
- Most monogenic obesity traits result from pathogenic variants in single genes converging in the leptin–melanocortin pathway.
- Targeting central pathways of energy expenditure with, for example, MC4R agonists provides new and promising treatment options for patients with monogenic obesity.
- Polygenic obesity results from an interplay among numerous genetic and environmental factors.
- Polygenic risk scores and massively parallel sequencing approaches will help the early identification of obesity predisposition.
- New precision medicine approaches based on genetic obesity traits might help tackle the obesity pandemic.

Heritability estimates
The proportion of variation that is attributable to genetic as opposed to environmental factors for a given phenotype.

Polygenic predictor
An estimation of the genetic liability to a complex human trait using genome-wide genetic variants.

common polygenic obesity and rare monogenic obesity. We discuss clinical features of early-onset monogenic obesity, as well as the hallmarks of monogenic obesity caused by pathogenic variants in different single genes. Finally, we highlight novel pharmacological treatment options for monogenic obesity targeting the central melanocortin pathway, as well as other innovative potential therapeutic avenues.

Heritability of body weight

Body weight variance, similar to other anthropometric measures, is highly heritable (BOX 1). Seminal twin and adoption studies at the end of the 1980s and 1990s[13] underscored that genetic factors have a remarkable role in body weight regulation[14]. Twin studies have found the highest and most consistent heritability estimates ranging from 0.6 to 0.9 for explained BMI variance[15]. Except for the postnatal period, for which a heritability of 0.4 had been found, heritability estimates of BMI are not substantially affected by age[16]. Heritability estimates of body weight and obesity derived from family and adoption studies are mostly considerably lower than in twin studies (0.25–0.7)[15]. Of note, both direct and indirect genetic effects compose the genetic component of obesity. For example, if in a monozygotic twin pair both infants are frequently hungry (a direct genetic effect), the carer will probably feed them often, even if the twins were separated at birth (an indirect genetic effect)[17]. The genetic underpinnings of obesity are complex and apply to metabolic as well as behavioural factors; more than half of the variance in body weight is genetically determined[18].

In large epidemiological studies, parental obesity is by far the strongest risk factor for obesity in childhood and adolescence[19], particularly if both parents are affected[20]. Stronger maternal than paternal effects have been found in several studies[21]. Twin and other family studies have implied that the strong predictive value of parental BMI mainly arises from genetic rather than shared environmental factors[15]. Socio-economic status is another important risk factor for paediatric obesity: in children with a low socio-economic status the odds ratio for obesity is more than twofold higher than in children with a high socio-economic status[19].

Although genome-wide association studies (GWAS) have provided valuable insights, the identified genetic variation only explains a small fraction of the heritability of body weight. Identified variants mostly have small effect sizes. A consensus explanation for this 'missing heritability' in complex diseases has not yet emerged[22]. Possible explanations include analytical limitations, small effect sizes, rare variants, variants not picked up owing to methodological limitations (for example, chromosomal rearrangements), imprecise heritability estimates, developmental aspects, non-additive or epistatic mechanisms, parental contributions, epigenetic effects, interactions between variants, expression of non-coding RNAs or transgenerational genetic effects[23].

Genetic classification of obesity

Based on the genetic contribution, obesity was historically classified into three main groups, common polygenic obesity, syndromic obesity and monogenic obesity. This traditional view has been revisited, as certain forms of monogenic obesity can be accompanied by neurodevelopmental and/or psychiatric disorders; therefore they can also be regarded as syndromes. Thus, we suggest that the group of obesity syndromes should be distinguished from common, polygenic forms of obesity[24,25]. Even this categorization might be an oversimplification, as the influence of genetics on obesity can be seen as a continuous spectrum[25].

Polygenic forms of obesity

The most common form of obesity is multifactorial and driven by the interaction between polygenic predisposition and environmental factors. The polygenic factors commonly act additively, so that the effects of all single alleles sum up to a combined effect size (BOX 2). A 2019 study identified and validated a polygenic predictor containing 2.1 million common variants to quantify obesity susceptibility[26]. The predictor was tested in more than 300,000 individuals from birth to middle age. In the group of middle-aged adults, a 13-kg weight difference (gradient) was observed between those with a high risk score and those with a low risk score. Additionally, a 25-fold gradient in risk of severe obesity was observed across polygenic score deciles[26]. Hence, polygenic risk scores (PRS) might help to estimate individual risk of progressive severe obesity. However, such risk scores would be even more precise if additional non-genetic clinical and environmental factors could be incorporated. Within a longitudinal birth cohort, the differences in birthweight across score deciles were minimal[26]. However, in early childhood the gradient became substantial and even reached 12 kg by 18 years of age.

Author addresses

[1]Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy and University Hospital Essen, University of Duisburg-Essen, Essen, Germany.
[2]Center for Translational Neuro- and Behavioral Sciences, University Hospital Essen, University of Duisburg-Essen, Essen, Germany.
[3]Leipzig University, Medical Faculty, Hospital for Children and Adolescents, Centre of Paediatric Research (CPL), Leipzig, Germany.
[4]LIFE Child, Leipzig Research Centre for Civilization Diseases, Leipzig, Germany.
[5]Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG) of the Helmholtz Zentrum München at the University of Leipzig and University Hospital Leipzig, Leipzig, Germany.
[6]Department of Paediatrics and Adolescent Medicine, Ulm University Medical Center, Ulm, Germany.

Table 1 | **Definitions of paediatric obesity**

Age (years)	Definition	Source	Diagnosis
<2	Specific weight for recumbent height ≧97.7 percentile	WHO child growth standards	Obesity
>2	85–95 BMI percentile	CDC growth charts	Overweight
>2	BMI ≧120% of the 95th percentile or BMI ≧35 kg/m^2		Severe obesity (class 2)[a]
>2	BMI ≧140% of the 95th percentile or BMI ≧40 kg/m^2		Severe obesity (class 3)[b]

Definitions of paediatric obesity are based on the current clinical practice guidelines on paediatric obesity from the Endocrine Society[24]. [a]Relates to class 2 obesity in adults. [b]Class 3 paediatric obesity has been proposed but is not fully accepted yet[24]. CDC, Centers for Disease Control and Prevention; WHO, World Health Organization.

Thus the effect size of a polygenic score can be similar to that of rare, pathogenic variants that cause monogenic obesity. Despite the impressive sample size and number of variants included[26], the finding of only 23.4% of BMI variability explained indicates that unknown or unidentified factors exist that might in the future explain this missing heritability.

Obesity syndromes

Syndromic obesity with signs of neurodevelopmental disorder. The form of obesity that was historically referred to as syndromic usually starts early in life and is associated with other clinical characteristics such as dysmorphic features, short stature, organ-specific developmental abnormalities and malformations, as well as neurodevelopmental deficits such as delayed learning and walking, intellectual impairment and autism spectrum disorders[27,28]. Prominent examples are Prader–Willi syndrome and Bardet–Biedl syndrome. More than 80 distinct syndromes have been described to date to be associated with childhood obesity and their genetic causes and phenotypes are described elsewhere[27,28].

Monogenic forms of obesity. Monogenic obesity is caused by genetic variations in single genes (TABLE 2). Of note, affected genes are usually involved in the central nervous system regulation of hunger and satiety and are mostly linked to the hypothalamic leptin–melanocortin pathway[29] (FIG. 1). The genetic risk variants that cause monogenic obesity are infrequent. However, in children who were referred to a tertiary centre due to suspicion of an underlying medical cause of obesity, the reported prevalence values can reach 13%[30]. Frequencies higher than 13% have been reported in consanguineous populations[24,31,32]. This rate might be expected to increase in the future with the emergence of massive parallel sequencing technology[24]. In fact, an analysis of the Avon Longitudinal Study of Parents and Children cohort of English children found a frequency of 0.30% for pathogenic melanocortin 4 receptor gene (*MC4R*) variants[33]. However, even with the use of specific obesity gene panels and modern exome sequencing technology, the identification of patients with known forms of monogenic obesity will only infrequently occur. In addition to classic genetic mechanisms, accumulating evidence indicates that epigenetic mechanisms have a role in the development of obesity[34,35].

Barker hypothesis
This hypothesis postulates that the origins of chronic diseases in adult life lie in fetal responses to the intrauterine environment.

Clinical features of early-onset obesity

Definitions and cut-offs

To diagnose early-onset obesity and to perform comparable clinical studies, clear and uniform definitions are urgently needed. The definitions provided in the current clinical practice guidelines on paediatric obesity from the Endocrine Society[24] are based on the Centers for Disease Control and Prevention (CDC) growth charts in children aged 2–19 years and on WHO child growth standards in infants aged <2 years (TABLE 1). Of note, national guidelines might differ from international definitions and recommendations. The CDC provides a BMI and BMI-for-age percentile calculator for children and teens on their website.

Risk factors for paediatric obesity

Three major risk factors for childhood obesity exist; these are genetic predisposition, parental overweight and lower socio-economic status. Beyond these factors, large epidemiological studies have identified that perinatal factors (such as high maternal weight gain during pregnancy, high birthweight and formula feeding) impose an increased obesity risk, with even stronger associations than 'classic' lifestyle factors (such as sleep duration, media consumption or physical activity)[19]. Thus, perinatal factors should be regarded in the clinical evaluation of children with obesity. Of particular note, high birthweight was shown to be associated with obesity later in life[36] and children large for gestational age were more likely to have a high BMI in childhood and adolescence than children born with a normal weight[3]. This association needs to be differentiated from the increased risk for type 2 diabetes mellitus (T2DM) and cardiovascular disease in children who were born small for gestational age according to the Barker hypothesis. In particular, rapid catch-up growth in infancy drives the progressive transition to central obesity and insulin resistance in those children born small for gestational age[37].

A 2018 population-based study analysed the BMI dynamics in 51,505 children[3]. The annual change in BMI standard deviation score (BMI-SDS) during childhood was assessed in relation to the occurrence of underweight, normal weight, or overweight and obesity in adolescence. The respective groups were assigned based on national (German) reference data[3]. As expected, normal weight or underweight children had a stable BMI-SDS of around zero, across the range of measurements. In contrast, children with overweight or obesity had increased BMI-SDS scores from infancy onwards, beginning at 1 year of age. As already mentioned, the annual increase in BMI-SDS was highest between the ages 2 years and 6 years. Similar to BMI, growth dynamics in children with obesity are substantially different from that in children with normal weight. Children with obesity are significantly taller in early childhood, with height SDS ranging from 0.4 to 1 standard deviations above the reference[38–41]. In children with obesity, earlier puberty, a blunted pubertal growth spurt, alterations in sex hormone profiles and advanced bone age might explain subsequent normalization in final height compared with children with normal weight[39,40].

Box 1 | **Genes associated with thinness and eating disorders**

Interestingly, the heritability of thinness is as strong as that of obesity. A genome-wide association study (GWAS) of thinness (defined as a BMI <18 kg/m^2) versus severe obesity (BMI standard deviation score >3; onset of obesity before the age of 10 years) identified ten loci that were previously associated with obesity. A novel obesity and BMI-associated locus (*PKHD1*) was also detected[172]. A previous GWAS comparing children and adolescents with underweight (mean BMI *Z*-score −1.38 ± 0.35; BMI <15th age percentile) and those with severe obesity (mean BMI *Z*-score 4.63 ± 2.27) identified *FTO* as an obesity-associated locus in small study groups (fewer than 500 individuals in each group)[173]. Both studies included individuals with BMI at the extremes of the range and implied that genetic mechanisms of thinness might help understand the genetics of body weight regulation. In 2020, *ALK* was identified as a candidate gene for thinness in a GWAS on healthy thin (lowest 6th percentile of the population-wide BMI spectrum) Estonian individuals and controls (30–50% BMI centile). Although the results were not significant genome-wide, additional studies in *Drosophila* and mice underscored the importance of the gene for weight regulation[174].

Genetic analyses in obesity can profit from similar analyses in eating disorders. A GWAS published in 2019 in anorexia nervosa identified eight chromosomal loci, one of which overlaps with a BMI locus[175,176]. A cross-trait analysis of anorexia and BMI loci revealed three overlapping chromosomal regions[177]. The identification of genes and underlying biological mechanisms for obesity can greatly benefit from the analysis of overlapping phenotypes.

Features of monogenic obesity syndromes

The BMI trajectories of children with certain forms of monogenic obesity are clearly different from those with polygenic obesity[42]. Most monogenic forms are characterized by a rapid onset of weight gain after birth, with the most rapid increase in BMI in the first year of life. For example, patients with congenital leptin or leptin receptor deficiency had a BMI of >27 kg/m^2 at the age of 2 years and their BMI was >140% of the 95th percentile. At the age of 5 years their BMI was >33 kg/m^2 and >184% of the 95th percentile in both patient groups[42]. Patients with congenital leptin or leptin receptor deficiency do not have normal pubertal development due to hypogonadotropic hypogonadism[43–45]. Reports on linear growth are inconsistent. In one study, patients with leptin deficiency were taller than the mid-parental median[46]. By contrast, in other studies, patients with leptin or leptin receptor deficiency had normal growth in childhood but reduced final height due to the absence of a pubertal growth spurt[44,47]. Patients heterozygous for pathogenic variants in *MC4R* show less pronounced weight gain in the first 2 years of life, but severe obesity later in childhood[42] and frequently have tall stature[30].

In monogenic obesity, central hypothalamic and neuroendocrine pathways can be impaired[24,48], which is consistent with reports from patients and/or their families of hyperphagia with food-seeking or even food-stealing behaviour and insatiable hunger. Hyperphagia can be described as increased energy intake compared with control individuals or as eating an amount higher than predicted for body size or composition[49]. This trait often accompanies a preoccupation for food, presenting, for example, as food-seeking behaviour[49]. Satiety describes the control of appetite and refers to periods between meals, whereas satiation is the control of meal size[50]. These processes can be measured by questionnaires[50].

Some features of monogenic obesity are more specific to certain gene alterations (see below), such as impaired pubertal development, increased predisposition to infections or diarrhoea and hypopigmentation. Of note, cognitive development is usually normal in patients with monogenic obesity. Motor development might seem to be delayed, but this effect is at least to some extent attributable to excess body mass. Based on these observations, genetic testing should be considered if 'red flags' indicative for monogenic obesity are present (BOX 3). Current clinical practice guidelines recommend genetic testing in patients with severe early-onset obesity (before 5 years of age) and clinical features of genetic obesity (in particular severe hyperphagia) and/or a family history of severe obesity[24].

If genetic testing is proposed, the low likelihood of finding an underlying genetic cause should be openly communicated to patients with obesity and their families, to prevent falsely high expectations. Furthermore, if a genetic variant is reported, particularly a de novo variant, the functional impairment must be shown experimentally to be the cause of the phenotype. The clinical cause is furthermore dependent on the presence and degree of impairment of function, which has been shown for *MC4R* pathogenic variants[51,52] but also for *LEPR* and *PCSK1* variants[48,53–56].

Hallmarks of monogenic obesity traits

The most common forms of monogenic obesity and those with indication for available pharmacological treatments are outlined here, in the order from peripheral signals that converge centrally to MC4R (FIG. 1 and TABLE 2).

Congenital leptin deficiency

Leptin is a 16-kDa protein and adipokine[57,58]. It exerts its functions via binding to and activating the long form of the leptin receptor, which results in the activation of various signalling cascades, such as phosphorylation of STAT3 (REF.[59]). The serum levels of leptin correlate positively with body adipose mass and BMI, with strong variability in the levels occurring at extremes of BMI[60]. Via central and peripheral routes, leptin affects a wide range of physiological processes including energy balance, metabolism, endocrine regulation and immune function[57,58]. Leptin represents a peripheral signal for energy sufficiency to the central nervous system. A low level of the hormone corresponds to a low energy state of the adipose tissue lipid stores. Critically low levels of leptin induce a range of responses to preserve or restore the energy reservoir, among them altered behavioural, metabolic, endocrine and immune responses[61].

Pathological variants in *LEP* lead to congenital leptin deficiency or dysfunction[43,62–65]. Patients present with hyperphagia, increased food seeking and impaired satiety. Born with normal weight, patients rapidly gain weight after birth and develop severe obesity associated with hyperinsulinaemia, dyslipidaemia and hepatic steatosis[62]. Another cardinal sign of leptin deficiency or dysfunction is hypogonadotropic hypogonadism and delayed pubertal development, whereas recurrent severe infections are reported in some but not all patients[62–64,66–68]. In mice, hyperleptinaemia promotes obesity-associated hypertension[69]. Thus, one might expect that a disturbance in the leptin–leptin receptor

system leads to hypotension. However, four out of six studied patients with leptin deficiency had high blood pressure[70], which suggests leptin-independent pathomechanisms in the development of hypertension. In rats, leptin was found to regulate the hypothalamic–pituitary–thyroidal axis[71,72]. However, thyroid dysfunction is not a constant feature of leptin deficiency or dysfunction[63,67,73].

In 1997, congenital leptin deficiency was first described as an autosomal recessive form of severe early-onset obesity in two children of a consanguineous family originating from Pakistan[63]. Of note, circulating levels of leptin were almost non-detectable in both patients. Since this initial description, a total of 18 distinct variants have been reported in over 60 patients worldwide[62]. Several variants cause defects in leptin protein production and/or secretion, which leads to classic leptin deficiency[43,62,63]. This disease can be diagnosed by confirming the absence of immunoreactive leptin in the circulation. However, a *LEP* variant (c.298G>T, p.D100Y) was described that is produced and secreted but is biologically inactive. The genetic alteration lies within a region of the protein that is responsible for docking on to the receptor, thereby rendering the variant incapable of binding to the leptin receptor and causing congenital leptin dysfunction[64]. In patients with common polygenic obesity, total immunoreactive and bioactive blood levels of leptin are concordant[74,75]. By contrast, immunoreactive blood levels of leptin in the patients with congenital leptin dysfunction are high, whereas bioactive blood levels of leptin are below the detection limit[74]. Therefore, the correct diagnosis of congenital leptin dysfunction could be missed if just a classic leptin radioimmunoassay or enzyme-linked absorbance assay is performed for diagnostic purposes[64]. Of note, a DNA sequencing approach can detect such pathogenic variants. Therefore, genetic testing is highly recommended in patients with suspected monogenic obesity, for example, through an obesity gene panel or exome-based sequencing.

Congenital leptin receptor deficiency

Congenital leptin receptor deficiency is a rare disease with autosomal recessive inheritance and a phenotype that is highly comparable to that in leptin deficiency or dysfunction[44,76,77]. It was first described in a consanguineous family from northern Algeria[76]. In a 2019 paper, 45 distinct *LEPR* variants were reported in the literature in a total of 88 patients[77]. The genetic alterations include single amino acid changes, insertions, duplications and deletions, as well as nonsense risk variants predicted to cause truncation of the leptin receptor protein[77,78]. The functional impairment caused by these risk variants needs to be proven to assess the causality of the genetic variation, and this knowledge might guide future treatment decisions[79]. The predicted prevalence of *LEPR* deficiency is 1.34 per 1 million people. Based on these numbers, one would expect that there are 998 patients with *LEPR* deficiency in Europe. The fact that the number of published cases is substantially lower suggests considerable underdiagnosis of this disease[77].

Patients with variants in the *LEPR* gene are normal weight at birth, but then rapidly exhibit pronounced food-seeking behaviour, hyperphagia and impaired satiety[28,44,76]. This phenotype leads to rapid weight gain and severe obesity associated with hyperinsulinaemia, dyslipidaemia and hepatic steatosis[28,44,76]. Hypogonadotropic hypogonadism is a constant feature of leptin receptor deficiency[28,44,76,77], whereas recurrent severe infections are less frequently observed[77]. Pituitary hormone deficiencies are found in one-third of patients[77].

SH2B1 deficiency

The SH2B adapter protein 1 (SH2B1) is a crucial molecule in leptin-mediated signal transduction that enhances the downstream signal by JNK2-dependent and JNK2-independent mechanisms[80]. In 2010, deletions on chromosome 16p11.2, an area where *SH2B1* is located, were found to co-segregate with obesity, and heterozygous carriers of deletions display severe hyperphagia and severe insulin resistance[81]. Shortly thereafter, loss of function variants in *SH2B1* were identified as a monogenic cause of hyperphagia and early-onset obesity along with maladaptive behaviour[82,83]. SH2B1 also serves as an adaptor molecule in the insulin signalling cascade and might act as a central as well as a peripheral regulator of glucose homeostasis and insulin sensitivity independently of body weight[84]. Thus, it is not surprising that affected patients have severe insulin resistance that is disproportionate to the degree of obesity[81]. Considering its action as a promoter of leptin signalling in the MC4R pathway, treatment with MC4R agonists might be effective as a therapy in these patients. In the first phase II trials, half of the patients with *SH2B1* deficiency or 16p11.2 deletion responded with clinically relevant weight loss. Such a clear separation of responders and non-responders might be due to heterogeneity in the underlying genetic causes[85].

Box 2 | **GWAS-identified obesity candidate genes**

Polygenic variants associated with obesity are common at the population level (allele frequencies >1%); however, their effect sizes are small. Nevertheless, multiple risk variants add on to a relevant increase in obesity risk. In individuals with obesity, risk variants occur more frequently than in a population of normal weight individuals[178]. The shared genetic background between childhood and adult BMI is high[173,179]. Currently, >1,000 variants have been described[180,181], but the total number might well be much higher. The lowest estimated effect sizes are well below 100 g of weight. Even the strongest risk variant (in *FTO*) confers an estimated increase in body weight in adults of 1,130 g[182].

For obesity to develop, interaction between several polygenic variants, either separately or combined, and environmental factors is necessary. Genome-wide association studies (GWAS) have become feasible since the advent of high-density single nucleotide polymorphism (SNP) chips, which led to the identification of a large number of confirmed genes for different complex traits. GWAS-derived candidate genes are located near SNPs that achieved genome-wide significance ($P \leq 5 \times 10^{-8}$). It can take a long time for research to progress from a GWAS hit to a confirmed, functionally analysed obesity gene. Innovative approaches that link several molecular traits (for example, genomics and transcriptomics) with environmental exposure and detailed phenotype (phenomics) have the potential to identify new and causal links[183].

Some genes that were identified in GWAS had previously been described for monogenic forms of obesity (for example, *MC4R*, *LEP* and *PCSK1*)[180]. Many others were not previously associated with obesity, such as the strongest candidate *FTO*[173,184,185], which is not only associated with obesity but also with cancer[186,187] and neuropsychiatric traits[188]. For another GWAS hit, *TMEM18*, the biological function is still not completely resolved, although it might have a role in adipose tissue remodelling[189].

Table 2 | **Genes implicated in severe monogenic and syndromic obesity**

Gene	Protein	OMIM[a]	Inheritance pattern	Clinical phenotype	Targeted pharmacological treatment option
Forms with specific treatment options					
CPE	Carboxypeptidase E	619326	AR	Obesity, hypogonadotropic hypogonadism, developmental delay	Setmelanotide
LEP[b]	Leptin	614962	AR	Obesity, hyperphagia, hypogonadism, frequent infections, neurological and endocrine dysfunctions	Metreleptin, setmelanotide
LEPR[b]	Leptin receptor	614963	AR	Obesity, hyperphagia, hypogonadism, neuroendocrine dysfunctions	Setmelanotide[c]
MC4R[b]	Melanocortin 4 receptor	618406	AD	Obesity, hyperphagia, accelerated growth	Setmelanotide
PCSK1 and *PCSK3*[b]	Proprotein convertase subtilisin–kexin	600955	AR	Obesity, endocrinopathy due to impaired processing of prohormones, postprandial hypoglycaemia, small-bowel enteropathy	Setmelanotide[c]
POMC[b]	Pro-opiomelanocortin	609734	AR	Obesity, red hair pigmentation, ACTH deficiency	Setmelanotide[c]
SH2B1[b]	SH2B adaptor protein 1	608937	AR	Obesity	Setmelanotide
SIM1	Single-minded homologue 1	603128	AR	Obesity, developmental delay	Setmelanotide
NCOA1 (otherwise known as *SRC1*)	Nuclear receptor coactivator 1	602691	AR	Obesity	Setmelanotide
BBS1-22	Bardet–Biedl syndrome	Bardet–Biedl syndrome; 209900, total of 22 entries	AR	Heterogeneous ciliopathy, retinitis pigmentosa, obesity, kidney dysfunction, polydactyly, behavioural dysfunction, hypogonadism	Setmelanotide
ALMS1	Alström syndrome protein 1	Alström syndrome; 203800	AR	Blindness, hearing loss, childhood obesity, hyperinsulinaemia, type 2 diabetes mellitus, dilated cardiomyopathy	Setmelanotide
Interstitial deletion of *17p11.2* or mutation or deletion of *RAI1*	Retinoic acid-induced protein 1	Smith–Magenis syndrome; 182290	AD	Obesity, facial abnormalities; congenital heart defect, structural renal anomalies; scoliosis, brachydactyly, speech delay, mental retardation, sleep disturbance, structural brain abnormalities, peripheral neuropathy, decreased pain sensitivity, decreased or absent deep tendon reflexes, hyperactivity, polyembolokoilamania, behavioural problems	Setmelanotide
Several genes in the Prader–Willi syndrome region of chromosome 15	Several proteins in the Prader–Willi syndrome region	Prader–Willi syndrome; 176270	AD; caused by deletion or disruption of a gene or several genes on the proximal long arm of the paternal chromosome 15 or maternal uniparental disomy 15	Diminished fetal activity, obesity, muscular hypotonia, mental retardation, short stature, hypogonadotropic hypogonadism, small hands and feet	Setmelanotide

Table 2 (cont.) | **Genes implicated in severe monogenic and syndromic obesity**

Gene	Protein	OMIM[a]	Inheritance pattern	Clinical phenotype	Targeted pharmacological treatment option
Forms with no current specific treatment options					
ADCY3[b]	Adenylate cyclase type 3	600291	AR to intermediate	Obesity	NA
BDNF	Brain-derived neurotrophic factor	113505	AR	Obesity, hyperphagia, impaired memory, impaired pain sensation, hyperactivity, developmental delay	
GNAS	Guanine nucleotide-binding protein G(s) subunit α isoforms XLas	139320	AR, paternally imprinted (maternal allele expressed)	Obesity, pseudohypoparathyroidism	
KSR2	Kinase suppressor of Ras2	610737	AR	Obesity, hyperphagia, severe insulin resistance	
MC3R	Melanocortin 3 receptor	155540	AD	Obesity, timing of sexual maturation, rate of linear growth, accrual of lean mass	
MRAP2	Melanocortin 2 receptor accessory protein 2	615410	AR	Obesity, hyperphagia, hyperglycaemia, hypertension	
NRP1, *NRP2*	Neuropilin 1, neuropilin 2	602069, 602070	AR	Obesity	
NTRK2	Neurotrophic receptor tyrosine kinase 2	600456	AR	Obesity, hyperphagia, impaired memory, impaired pain sensation, hyperactivity, developmental delay	
PLXNA1–4	Plexin A1–4	601055	AR	Obesity	
PHIP	Pleckstrin homology domain interacting protein	612870	AR	Obesity, developmental delay	
SEMA3A–G	Semaphorin 3A–G	603961, 602181, 602645, 609907, 608166, 601124	AR	Obesity, hypogonadotropic hypogonadism with or without anosmia	

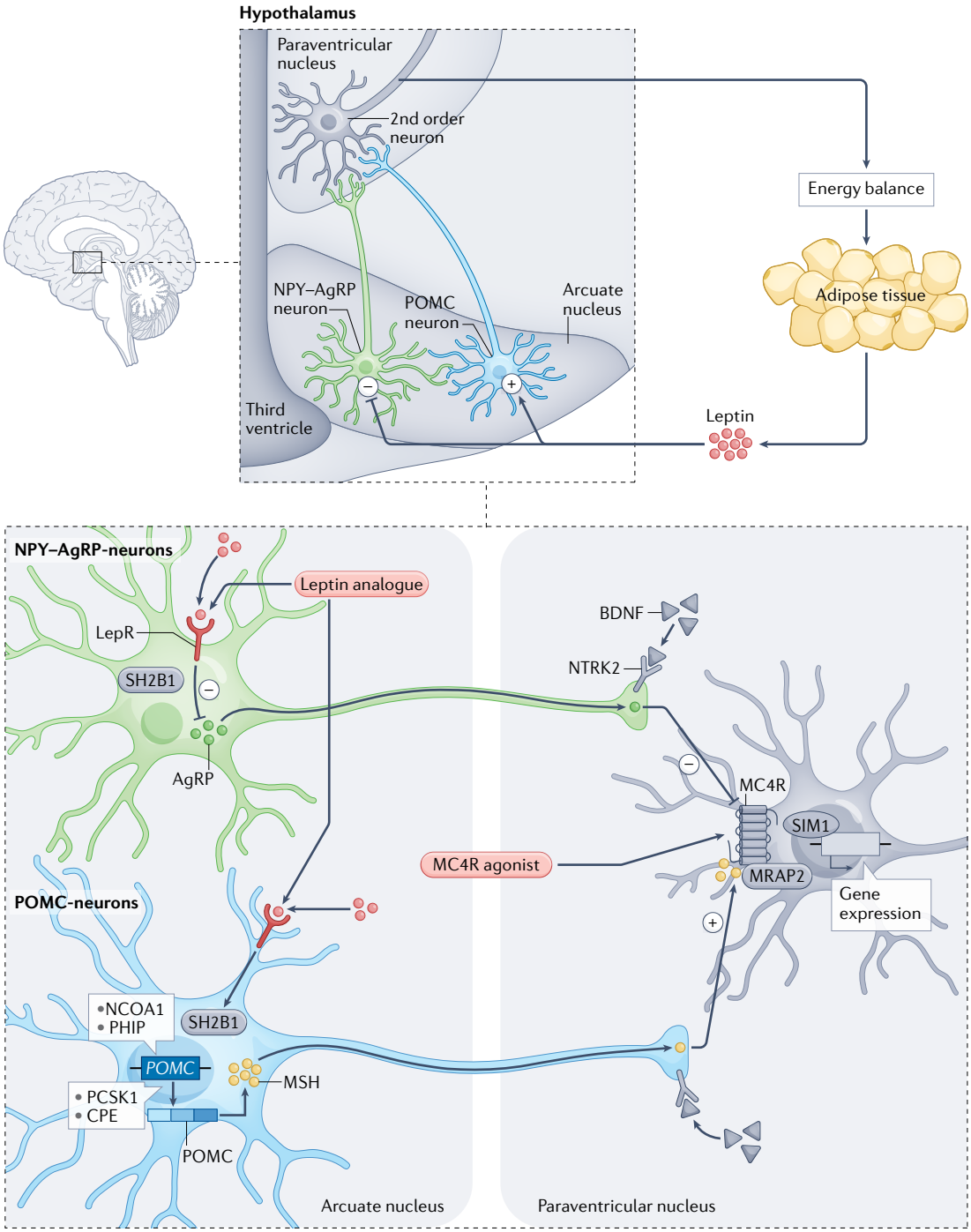
ACTH, adrenocorticotropic hormone; AD, autosomal dominant; AR, autosomal recessive; NA, not applicable; OMIM, Online Mendelian Inheritance in Man. [a]OMIM numbers can be accessed via the OMIM database, an online catalogue of human genes and genetic disorders. [b]Genes with strong pathophysiological evidence that clearly links genetic variants to obesity. [c]The FDA approved setmelanotide (Imcivree) for chronic weight management (weight loss and weight maintenance for at least 1 year) in patients aged 6 years and older with obesity due to three rare genetic conditions: *POMC* deficiency, *PCSK1* deficiency and *LEPR* deficiency, confirmed by genetic testing that demonstrates pathogenic variants in *POMC*, *PCSK1* or *LEPR*; all other treatments listed are currently in clinical trials.

POMC deficiency

The proopiomelanocortin (*POMC*) gene encodes a pituitary preproprotein that is processed into several bioactive neuroendocrine peptides via the proprotein convertase subtilisin/kexin type 1 (PCSK1)[29]. Among them is α-melanocyte-stimulating hormone (α-MSH), which acts via the MC4R to suppress appetite and food intake[29]. Homozygous or compound heterozygous variants lead to *POMC* deficiency, also known as 'early-onset obesity, adrenal insufficiency and red hair'. This autosomal recessive disorder was first described in 1998 (REF.[86]) and is characterized by severe hyperphagia that leads to severe early-onset obesity, secondary hypocortisolism and pigmentary abnormalities such as pale skin and red hair, with the pigment phenotype being dependent on the genetic background of the individual. Hypoglycaemia, hyperbilirubinaemia and life-threatening cholestasis might be observed in the first months of life[86]. In total, 14 distinct variants have been described in 17 patients[87]. In addition to these classic genetic alterations, variation in the DNA methylation status of *POMC* was shown to be associated with obesity[88]. DNA methylation is influenced by maternal nutrition during pregnancy[89], which underscores the modulating and direct role of environmental factors on molecular pathways that regulate energy balance and hence body weight.

PCSK1 deficiency

Variants in *PCSK1* in the homozygous or compound heterozygous state lead to a complex clinical phenotype, with early-onset obesity but also enteropathy with severe diarrhoea and neuroendocrine problems, among them glucocorticoid deficiency, hypogonadism and abnormal



glucose homeostasis[90–93]. These features result from the failure of PCSK1 to process active hormones from pro-hormones; for example, α-MSH from POMC in the hypothalamus or glucagon-like peptide 1 (GLP1) or GLP2 from proglucagon in the small intestine[54,90–93]. To date, 26 patients have been reported in the literature[94]. Interestingly, variants in *PCSK1* have also been identified in GWAS to be associated with childhood obesity[95]. Hence, the influence of *PCSK1* variants on obesity ranges from clear monogenic presentation to complex polygenic associations. Therefore, the functionality of an individual's gene variant needs to be assessed[56] before treatment with MC4R agonists can be initiated.

MC4R deficiency

First described in 1998 as a relevant factor for severe obesity in humans[96,97], MC4R deficiency so far is the most frequent form of monogenic obesity[52,98]. Variants in *MC4R* are estimated to be found in 2–5% of paediatric and adult patients with obesity[29,52,99]. Some of these patients might respond well to treatment with MC4R agonists such as setmelanotide[100]. More than 150 variants have been described, and homozygous, compound heterozygous and heterozygous variants have a role in the development of obesity[29,52,99]. Most variants reduce the function of the MC4R, which leads to hyperphagia, severe obesity and severe hyperinsulinaemia, which

Fig. 1 | **Central nervous system regulation of body weight via the leptin–melanocortin pathway.** Leptin is produced and secreted from adipocytes in proportion to the amount of adipose tissue mass and exerts its function as a satiety factor in the hypothalamic arcuate nucleus. It binds to the leptin receptor (LepR) present on specific neuron populations: neuropeptide Y (NPY)–agouti-related protein (AgRP) neurons and pro-opiomelanocortin (POMC) neurons. The Src-homology-2B adaptor protein 1 (SH2B1) is a crucial molecule in leptin-mediated signal transduction. In NPY–AgRP neurons, leptin downregulates the expression of the orexigenic AgRP, which acts as an inverse agonist at the melanocortin 4 receptor (MC4R). In POMC neurons, leptin induces the expression of *POMC*. Proprotein convertase subtilisin/kexin-type 1 (PCSK1) and carboxypeptidase (CPE) catalyse the processing of peptide hormones including α-melanocyte stimulating hormone (MSH), which serves as an anorexigenic agonist at the MC4R. Pleckstrin homology domain interacting protein (PHIP) serves as an enhancer of *POMC* transcription. Nuclear receptor coactivator 1 (NCOA1) modulates the function of nuclear hormone receptors and transcription factors by enhancing or suppressing the expression of target genes. Brain-derived neurotrophic factor (BDNF), via its receptor neurotrophic receptor tyrosine kinase 2 (NTRK2), modulates leptin-mediated synaptic plasticity of neurons. α-MSH binds to and actives MC4R present on neurons in the paraventricular nucleus, which controls appetite and links the energy state of long-term adipose stores to feeding behaviour. Melanocortin receptor accessory protein 2 (MRAP2) is an accessory protein of melanocortin receptors and regulates their function. Single-minded homologue 1 (SIM1) is a basic helix–loop–helix transcription factor and is required for the development of neurons of the paraventricular nucleus. An agonist at the MC4R (setmelanotide) is useful for treating monogenic forms of obesity affecting genes upstream of the MC4R and certain genetic variants of the MC4R.

sometimes occurs along with increased lean mass and increased linear growth[101].

Effects on body mass for loss of function *MC4R* risk variants are in the range of 15–30 kg increased weight[101]. Also, in 2004, a gain of function *MC4R* variant (V103I) was described that decreases body weight by ~1.5 kg[102]. Data published in 2019 confirmed the relevance of both loss of function and gain of function variants in weight regulation[103]. MC4R is a G protein-coupled receptor (GPCR) and the functionality of variants was typically proven based on the capacity to induce Gs signalling. However, insights published in 2020 led to a more detailed view of MC4R signalling, which uncovered that some variants (for example, V103I and H158R) are biased towards the Gq/11 pathway by endogenous agonists[104]. This finding once more underscores the necessity for a detailed and comprehensive functional characterization of genetic variants.

Carriers of gain of function variants in *MC4R* present with lower BMI as well as lower odds of cardiometabolic sequelae such as T2DM and coronary artery disease than non-carriers of these variants[102,103]. These gain of function variants exhibit a signalling bias, with an increased recruitment of β-arrestin to the MC4R along with increased cAMP levels in heterologous cell systems and increased and sustained phosphorylation of ERK1/2 (REF.[103]).

Biased signalling is an interesting phenomenon known for GPCRs[105]. Of note, the exomes of 645,626 individuals were sequenced and 16 genes with an exome-wide association with BMI were identified. Among them were five brain-expressed GPCRs[106]. This finding suggests that other GPCRs might act as fine tuners of body weight, also in the heterozygous state.

GNAS deficiency

The Gαs protein is encoded by *GNAS* and mediates GPCR signalling. The classic obesity syndrome Albright hereditary osteodystrophy is caused by pathogenic variants in *GNAS*. Patients present with developmental delay, short stature and skeletal abnormalities. Owing to maternal imprinting, pathogenic variants on the maternal allele also cause obesity and hormone resistance to parathyroid hormone (pseudohypoparathyroidism). A sequencing approach published in 2021 in 2,548 children with severe obesity revealed 22 were heterozygous carriers of *GNAS* pathogenic variants[107]. Nearly all pathogenic variants in *GNAS* lead to impaired MC4R signalling. The authors suggested that screening of children with severe obesity for *GNAS* deficiency might enable early diagnosis and improved clinical outcomes[107]. Affected patients might benefit from treatment with melanocortin agonists. Variant frequencies in normal weight control individuals were not described.

CPE deficiency

Carboxypeptidase E (CPE) is an enzyme that catalyses the removal of carboxy-terminal arginine or lysine residues from polypeptides, after being processed by proprotein convertases[108]. This enzyme is involved in the biosynthesis of peptide hormones and neuropeptides. A truncating pathogenic variant in *CPE* resulted in undetectable mRNA expression in blood cells derived from a patient with severe obesity. In addition to severe obesity, the patient had hypogonadotropic hypogonadism, abnormal glucose homeostasis and intellectual disability[109]. In 2021, novel homozygous *CPE* loss of function variants were described in four individuals from three unrelated consanguineous families[110]. All affected individuals had severe obesity and showed endocrine anomalies (hypogonadotropic hypogonadism and central hypothyroidism) as well as neurodevelopmental delay. The authors of this study named this specific, recognizable clinical phenotype Blakemore–Durmaz–Vasileiou syndrome[110].

NCOA1 deficiency

Nuclear receptor coactivator-1 (NCOA1; also known as steroid receptor coactivator 1, SRC1) modulates the function of nuclear hormone receptors and transcription factors in enhancing or suppressing the expression of target genes[111]. Based on the fact that mice with a deletion of *Ncoa1* in POMC neurons display increased

Box 3 | **Red flags indicative of monogenic obesity**

- Severe obesity with a BMI standard deviation score of >3.5 (particularly in patients aged <5 years).
- Rapid weight gain in the first 2 years of life.
- Consanguinity of parents.
- Hyperphagia (constant food seeking).
- Additive features or symptoms; for example: short stature, red hair, adrenal insufficiency (*POMC* deficiency), hypogonadism or increased predisposition to infection (*LEP* or *LEPR* deficiency), intractable recurrent diarrhoea (*PCSK1* deficiency), or pituitary insufficiencies such as adrenal insufficiencies (*POMC* or *PCSK1* deficiency), hypothyroidism, hypogonadism or growth hormone deficiency (*LEP* or *LEPR* deficiency), diabetes insipidus (*PCSK1*).
- Normal weight in parents.

food intake and obesity, exome sequencing and corresponding resequencing data from a cohort of patients with severe early-onset obesity and respective control individuals were analysed[112]. In the obesity group, the authors identified 15 heterozygous variants in *NCOA1*, which caused an impairment of leptin-induced POMC expression, whereas four other variants in *NCOA1* found in the control group had no effect. A detailed phenotypic description of patients with these variants is not available at this point.

Treatments for monogenic obesity

Non-pharmacological treatments

Data on lifestyle interventions in patients with monogenic obesity are scarce. One study analysed the effect of a 1-year lifestyle intervention based on exercise, behaviour counselling and nutritional counselling in paediatric patients with *MC4R* variants[113]. Children with pathogenic variants lost weight to an amount comparable to that in age-matched and BMI-matched control children without such alterations[113,114]; however, they had greater difficulties in maintaining the weight loss[113]. By contrast, a study in Danish children found that an intervention programme at a tertiary centre for 1 year failed to reduce BMI-SDS in children with MC4R-related obesity[115]. Studies on surgical interventions in monogenic obesity are also scarce[116–118]. Currently, no clear statements have been made on safety and efficacy[116]; therefore we conclude that surgery is not a primary treatment option[116].

Single case reports describe the diagnostic odyssey of patients with congenital leptin receptor deficiency and the failure of several therapeutic approaches. These include weight loss programmes, outpatient and inpatient psychotherapy and bariatric surgery, that mostly have unsatisfactory results[119,120]. These examples demonstrate that early genetic diagnostics are required in severe early-onset obesity to avoid the frustrating failure of therapy or even potentially harmful surgical intervention[120].

Pharmacological treatment options

Pharmacological treatment options for common polygenic obesity with long-term effects are very limited[121]. A number of medications for weight loss in adults have received FDA approval[121]. Three of them were approved for use in adolescent obesity: the lipase inhibitor orlistat, the norepinephrine reuptake inhibitor phentermine, and the GLP1 receptor (GLP1R) agonist liraglutide. In Europe, liraglutide is the only pharmacological treatment option[24,122–125] approved by the EMA, but is largely not reimbursed by health insurance providers (for example, in Germany).

In the past 10 years, genetic analyses have led to individualized treatment options for some types of monogenic obesity.

Metreleptin. Comparable to other endocrine disorders characterized by the absence of certain hormones, congenital leptin deficiency or leptin dysfunction can be treated by hormone supplementation therapy. In patients with leptin deficiency, subcutaneous administration of human recombinant leptin at a dose of 0.03 mg/kg of lean body mass per day leads to rapid changes in eating behaviour, a reduction of food intake and subsequent loss of adipose mass and body weight[64,66]. Beneficial metabolic and endocrine effects are also observed, among them improvement of hyperinsulinaemia, hyperlipidaemia and liver steatosis as well as resolved central hypogonadism with onset of puberty, as seen by the induction of gonadotropin secretion and menarche[126]. For example, a decrease in liver lipid content can be observed as early as 3 days after onset of therapy[126]. After its discovery in 1994, leptin was the big hope for the treatment of common obesity[127]. Unfortunately, exogenous administration of leptin in patients with common, polygenic obesity had limited efficacy in clinical studies[127,128].

In 2014, the FDA approved metreleptin as an orphan drug for the treatment of generalized lipodystrophy, a condition characterized by the absence or loss of body adipose tissue and, in consequence, very low levels of leptin[129]. Comparable to patients with congenital leptin deficiency or dysfunction, patients with generalized lipodystrophy show dramatic metabolic improvements under leptin substitution[129]. Of note, metreleptin has also been used to treat patients with anorexia nervosa, an eating disorder characterized by hypoleptinaemia[130,131]. The short-term off-label approach demonstrated beneficial cognitive, emotional and behavioural effects. These findings demonstrate that a protein that is relevant in obesity can have major effects in conditions with disordered body weight regulation or adipose tissue development.

Adverse effects of metreleptin treatment include the development of anti-leptin antibodies, which might have a neutralizing effect, and an elevated risk of lymphoma; three patients developed T cell lymphoma during therapy[129]. Leptin was shown to exert pro-cancer effects via the activation of pro-proliferative or anti-apoptotic pathways[132]. By contrast, patients with lipodystrophy might have a predisposition to lymphoma. Future studies are needed to establish a causal connection between leptin substitution therapy and lymphoma development.

Setmelanotide. Considering that most monogenic obesity traits finally converge at the central energy balance regulating MC4R pathway, treatment with MC4R agonists is a reasonable approach that might reduce food intake[133,134]. However, previous pharmacological attempts have failed due to lack of effect or severe adverse effects, in particular cardiovascular effects[99,134].

In 2016, a milestone was reached in the treatment of monogenic obesity with the introduction of a novel MC4R agonist setmelanotide[133]. After the first description of POMC deficiency[86], an MC4R agonist that could mimic the POMC derivative α-MSH was speculated to have the potential to decrease obesity in patients with POMC deficiency. A first pharmacological study conducted in healthy volunteers with overweight or obesity revealed that treatment with a synthetic MC4R agonist caused hypertension[134]. In a phase II trial in 2016, a new MC4R agonist named setmelanotide exerted beneficial effects in two patients with POMC deficiency; treatment was associated with a reduction in hunger and food intake and substantial weight loss, without an influence

on blood pressure[133]. No adverse events were reported. Of note, skin tone and the colour of naevi darkened and hair colour changed from red to dark brown[133] due to cross-reactivity of the compound with melanocortin 1 receptor (MC1R). During a period of 46 months, no malignant skin alterations were recorded[135]. Regular skin examinations are crucial, taking into account that specific variants in *MC1R* predispose to melanoma[136].

Since this first report, setmelanotide has been investigated additionally in patients with deficiencies in the central leptin–melanocortin pathway, namely leptin receptor deficiency and MC4R deficiency, showing overall beneficial results. However, for six heterozygous carriers of pathogenic variants in *MC4R*, the weight effect associated with setmelanotide was rather subtle and comparable to the weight loss observed in control individuals with obesity who also took the drug[137]. The effect of setmelanotide was superior in patients with *POMC* deficiency compared with its effect in patients with *LEPR* deficiency. In a phase III trial, the majority (80%) of ten patients with *POMC* deficiency and 45% of 11 patients with *LEPR* deficiency lost at least 10% of body weight after approximately 1 year[138]. Phase III trials including patients with MC4R variants are currently ongoing.

In 2020, setmelanotide received FDA approval for chronic weight management in adult and paediatric patients aged 6 years and older with obesity due to POMC, PCSK1 or leptin receptor deficiency[139]. The EMA approval followed in 2021 for the same age range and indications.

Setmelanotide is being evaluated in phase II and phase III trials (for example, NCT03013543, NCT02311673, NCT05093634 (EMANATE) and NCT04963231 (DAYBREAK)) as a treatment option in many other genetic defects in the MC4R pathway. The drug is also being evaluated in patients with syndromic obesity (for example, Bardet–Biedl syndrome[140,141] and Alström syndrome), as well as chromosomal rearrangement of the 16p11.2 locus, *SH2B1*, *CPE* or *SRC1* variants, heterozygous variants of monogenic obesity, and also in patients with leptin deficiency who are unresponsive to leptin treatment[139]. Beyond these defined monogenic and syndromic traits, patients with obesity secondary to hypothalamic damage due to tumours or trauma might benefit from this treatment option (NCT04725240), provided the MC4R neurons are intact. Whether patients with common polygenic obesity might benefit from treatment with a MC4R agonist on the long term is questionable at this point[137,142].

Interestingly, setmelanotide has been used in a patient with partial lipodystrophy who developed neutralizing antibodies under metreleptin treatment[143]. A slight decrease in hunger scores as evaluated by questionnaires was reported, but no other metabolic benefits. This finding underlines that leptin exerts its beneficial function on metabolism by central and peripheral modes of action that cannot be mimicked by MC4R agonism. As a side note, MC4R is not only highly expressed on neurons but also on astrocytes, and its activation has potent anti-inflammatory and neuroprotective effects[144]. Increased astrocytic MC4R expression was observed in active lesions in patients with multiple sclerosis[144]. In vitro, setmelanotide showed robust anti-inflammatory effects in astrocytes and promoted an anti-inflammatory phenotype in macrophages[144]. Therefore, targeting the MC4R might provide a potential strategy to delay or stop inflammation-associated neurodegeneration.

GLP1 agonists. Based on the success of GLP1 agonism in adolescents with common obesity[145], studies were performed to investigate if it might be beneficial in patients with monogenic obesity. Indeed, in case reports, treatment with liraglutide induced weight loss (adipose mass and lean mass) and improved metabolic parameters in individuals with pathogenic variants of MC4R[146–148].

Innovative treatment approaches

Enormous knowledge has accumulated about the concerted regulation of glucose homeostasis, hunger and satiety, energy expenditure and eating behaviour, and the respective underlying molecular mechanisms[149]. This knowledge has led to the development of some innovative treatment approaches for both common polygenic obesity and obesity syndromes.

Unimolecular polypharmacology

Most single-hormone targeting approaches for the treatment of polygenic obesity reveal a limited efficacy of less than 5% and rarely more than 10% body weight reduction[149]. Thus, it was logical to analyse if the drugs perform better when administered together than when administered singly. Indeed, several studies in rodent models revealed that combination therapies can achieve metabolic improvements superior to the effect of single hormone therapies[149]. Based on this premise the principle of unimolecular polypharmacology was developed.

The journey started with the development of a dual agonist unifying the features of GLP1 and glucagon for the treatment of glucose intolerance and obesity[149,150]. GLP1 exerts anti-diabetic actions, whereas glucagon is known to have acute hyperglycaemic effects, making this combination seem not very intuitive. However, glucagon has several additional functions; for example, inhibition of lipid synthesis and stimulation of lipolysis, inducing browning in adipose tissue that increases energy expenditure, and decreasing food intake[149]. Indeed, a rationally designed dual GLP1 and glucagon receptor agonist normalized glucose tolerance and improved obesity in mice receiving a high-fat diet[150], with improved efficacy relative to treatment with the individual single hormones. Since that time a plethora of different combinations of dual and even triple agonists have been designed and some of them are currently being evaluated in clinical studies for T2DM and obesity[149,151]. Based on the results of phase III studies[152–156], tirzepatide (a dual glucose-dependent insulinotropic polypeptide and GLP1 receptor agonist) has received FDA approval for the treatment of adults with T2DM. The compound induces clinically relevant weight loss in patients with T2DM. Remarkably, in individuals with overweight or obesity without T2DM, tirzepatide treatment resulted in a weight loss of 22.5%[157].

Other approaches in preclinical development combine GLP1R agonists with nuclear hormones such as

Box 4 | **Innovative cellular therapies for common polygenic obesity**

Mesenchymal stem cells are an attractive tool for regenerative medicine as they can differentiate into different mesenchymal lineages, such as osteoblasts, chondrocytes, muscle and nerve cells and adipocytes. They were first isolated from bone marrow[190]. Multipotent, self-renewing progenitor cells can also be isolated from white adipose tissue (adipose-derived stem cells (ASC), otherwise referred to as adipose-derived stromal cells)[191]. Adipose tissue is easily accessible and contains substantially higher numbers of progenitor cells than bone marrow, which is a huge advantage[192]. Therefore, ASCs have been extensively studied as a tool in regenerative medicine, with clinical studies ongoing in the areas of diabetes mellitus, cardiovascular diseases, cancer, and inflammatory and neurodegenerative diseases[192]. ASCs could conceivably be useful in the context of obesity; for example, to promote tissue remodelling and convert dysfunctional and inflamed adipose tissue in obesity into functional adipose tissue.

In 2020, preadipocytes isolated from human adipose tissue and then immortalized were subjected to molecular modification by CRISPR–Cas9 in order to develop a weight loss strategy[193]. Specifically, cells were engineered to express high levels of UCP1. UCP1 is specifically expressed in brown and beige adipocytes and mediates their thermogenic activity by uncoupling the respiratory chain from ATP production, which leads to dissipation of energy as heat[194]. Thus, the browning of white adipose tissue or the activation of brown adipose tissue are attractive targets for weight loss therapies. Indeed, transplantation of these modified human brown-like cells into mice prevented diet-induced obesity and improved glucose tolerance and insulin sensitivity[193]. As ASCs are already intensively investigated in preclinical and clinical studies[192], the translation of such approaches into clinical studies in patients with obesity seems within reach.

oestrogen or thyroid hormone, thereby restricting the nuclear hormone cargo to act favourably on the cells expressing GLP1R[158]. Patients with pathogenic variants in the leptin–melanocortin pathway downstream of the MC4R or with homozygous, heterozygous and compound heterozygous variants in *MC4R* who are not suitable for treatment with setmelanotide, might benefit from these developments in the area of unimolecular polypharmacology. For an excellent summary on advances in anti-obesity drug discovery see REF.[159].

Future innovative therapies

Besides novel pharmacotherapies, other types of innovative therapeutic approaches might find their path into the area of obesity and body weight regulation[160] (BOX 4). Patients with monogenic forms of obesity might benefit from novel induced pluripotent stem cell (iPSC) technologies and CRISPR-mediated gene editing. In 2006, iPSCs were first produced from mouse fetal and adult fibroblasts[161]. Subsequently, the reprogramming of somatic cells into pluripotent cells rapidly succeeded in human cells[162]. Although hampered by the inherent risk factors of tumorigenicity and immunogenicity, iPSCs have enormous clinical potential[163]. In the context of obesity, iPSCs are useful as in vitro disease models to study the influence of gene variants in different cell types. For example, hypothalamic-like neurons were generated from iPSCs of patients with polygenic, severe obesity (BMI >50 kg/m^2)[164]. Capable of neuropeptide secretion and responsive to leptin and ghrelin, they retained the typical disease features, such as dysregulated cellular respiration and molecular signatures related to metabolic disease, and can therefore be used to study the role of certain gene variants, but also gene–environment interactions[164].

The ultimate aim would be to functionally repair defective gene variants that lead to monogenic obesity by CRISPR–Cas9-mediated gene editing. This approach might be considered as a last resort in patients who are not suitable for pharmacotherapy and in whom other treatment approaches have failed. Up to now, two strategies are conceivable[165]. First, delivery of CRISPR tools into target cells ex vivo and subsequent transplantation of engineered cells back into the patient. This approach has been useful in haematological disorders and in cancer immunotherapy, but it is not suitable for many other tissue types[165]. To our knowledge, this option has not been investigated in the context of monogenic obesity. Second, in vivo editing, where the CRISPR cargos are injected systemically or locally. The latter approach has been applied in leptin-deficient, obese *ob*/*ob* mice using an adenoviral CRISPR system injected locally into white adipose tissue[166]. Although less than 2% of alleles were repaired, the production of leptin and its physiological functions, such as inhibition of food intake, were restored. Comprehensive preclinical studies are needed to bring these novel therapeutic approaches into clinical practice.

Conclusions

For children and adolescents with common polygenic obesity, the main focus is prevention of weight gain as early as possible. Generalized recommendations have been developed[24] but their successful implementation in the general population is questionable. Once obesity has manifested in children and adolescents, it has a high likelihood of persisting into adulthood[3]. Hence, we need to identify children at risk of severe and progressive obesity before manifestation. For this, surveillance of individual growth data is pertinent[167]. Once an accelerated weight gain is noted, validated PRS can further help estimate the obesity risk. As our understanding of obesity subphenotypes advances, PRS can help tailor the components of non-pharmacological and pharmacological treatment options to individual patients to obtain maximum effectiveness in weight gain prevention or weight reduction. Improved recognition of patients with underlying medical causes of obesity such as polygenic or syndromic obesity including monogenic forms, as well as a better access to diagnostic and genetic testing is of the utmost importance. Even with current genetic diagnostic technologies, many patients with genetic obesity disorders are probably not identified[77,168]. Furthermore, only a minority of children who are eligible for diagnostic tests according to current guidelines have actually undergone such testing[169]. An urgent need exists for more personalized prevention and treatment strategies. Concepts such as nutritional and exercise genomics or metabolomic evaluations might be useful here[170,171].

Novel genetic diagnostic advances hold the potential to achieve rapid diagnosis of patients with known forms of monogenic or syndromic obesity, but also give hope for the discovery of so far unknown causes of obesity. Eventually, variant detection can lead to precision medicine and personalized treatment. Early and correct diagnosis of early-onset obesity will lead to proper treatment, prevent the development of obesity sequelae, avoid failure of conservative treatment approaches and protect patients and families from stigmatization.

Published online 28 July 2022

CRISPR-mediated gene editing
CRISPR–Cas9 enzymes were developed from a naturally occurring genome editing system, important for immune defence in bacteria, and can be used to edit parts of the genome.

1. World Health Organization. Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (2021).
2. Moreno, L. A. Early severe obesity in children. *Nat. Rev. Endocrinol.* **14**, 194–196 (2018).
3. Geserick, M. et al. Acceleration of BMI in early childhood and risk of sustained obesity. *N. Engl. J. Med.* **379**, 1303–1312 (2018).
This study adresses the question of whether there is a critical age window for the manifestation of childhood obesity.
4. Landgraf, K. et al. Evidence of early alterations in adipose tissue biology and function and its association with obesity-related inflammation and insulin resistance in children. *Diabetes* **64**, 1249–1261 (2015).
5. Twig, G. et al. Body-mass index in 2.3 million adolescents and cardiovascular death in adulthood. *N. Engl. J. Med.* **374**, 2430–2440 (2016).
6. Fastenau, J. et al. A call to action to inform patient-centred approaches to obesity management: development of a disease-illness model. *Clin. Obes.* **9**, e12309 (2019).
7. Frühbeck, G. et al. The ABCD of obesity: an EASO position statement on a diagnostic term with clinical and scientific implications. *Obes. Facts* **12**, 131–136 (2019).
8. Vogel, M. et al. Age- and weight group-specific weight gain patterns in children and adolescents during the 15 years before and during the COVID-19 pandemic. *Int. J. Obes.* **46**, 144–152 (2021).
9. Nogueira-de-Almeida, C. A. et al. COVID-19 and obesity in childhood and adolescence: a clinical review. *J. Pediatr.* **96**, 546–558 (2020).
10. The Lancet Public Health. Childhood obesity beyond COVID-19. *Lancet Public. Heal.* **6**, e534 (2021).
A large study analysing the obesity and COVID-19 pandemics in childhood.
11. Hill, B. et al. Weight stigma and obesity-related policies: a systematic review of the state of the literature. *Obes. Rev.* **22**, e13333 (2021).
12. Hilbert, A. Weight stigma reduction and genetic determinism. *PLoS ONE* **11**, e0162993 (2016).
13. Stunkard, A. J., Foch, T. T. & Hrubec, Z. A twin study of human obesity. *JAMA* **256**, 51–54 (1986).
A seminal study depicting heritability estimates for BMI.
14. Silventoinen, K. & Konttinen, H. Obesity and eating behavior from the perspective of twin and genetic research. *Neurosci. Biobehav. Rev.* **109**, 150–165 (2020).
15. Maes, H. H., Neale, M. C. & Eaves, L. J. Genetic and environmental factors in relative body weight and human adiposity. *Behav. Genet.* **27**, 325–351 (1997).
16. Vlietinck, R. et al. Genetic and environmental variation in the birth weight of twins. *Behav. Genet.* **19**, 151–161 (1989).
17. Hebebrand, J. Obesity. in *Lewis's Child and Adolescent Psychiatry* (eds. Martin, A., Bloch, M. H. & Volkmar, F. R.) 602–614 (Lippincott Williams & Wilkins, 2007).
18. Plomin, R., DeFries, J., McClear, G. & Rutter, M. *Behavioral Genetics* (Freeman, 1997).
19. Kleiser, C., Schaffrath Rosario, A., Mensink, G. B. M., Prinz-Langenohl, R. & Kurth, B.-M. Potential determinants of obesity among children and adolescents in Germany: results from the cross-sectional KiGGS study. *BMC Public. Health* **9**, 46 (2009).
20. Hebebrand, J. et al. Epidemic obesity: are genetic factors involved via increased rates of assortative mating? *Int. J. Obes. Relat. Metab. Disord.* **24**, 345–353 (2000).
21. Magnusson, P. K. E. & Rasmussen, F. Familial resemblance of body mass index and familial risk of high and low body mass index. A study of young men in Sweden. *Int. J. Obes. Relat. Metab. Disord.* **26**, 1225–1231 (2002).
22. Eichler, E. E. et al. Missing heritability and strategies for finding the underlying causes of complex disease. *Nat. Rev. Genet.* **11**, 446–450 (2010).
23. Hebebrand, J., Volckmar, A.-L., Knoll, N. & Hinney, A. Chipping away the 'missing heritability': GIANT steps forward in the molecular elucidation of obesity – but still lots to go. *Obes. Facts* **3**, 294–303 (2010).
24. Styne, D. M. et al. Pediatric obesity-assessment, treatment, and prevention: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **102**, 709–757 (2017).
25. Loos, R. J. F. & Yeo, G. S. H. The genetics of obesity: from discovery to biology. *Nat. Rev. Genet.* **23**, 120–133 (2022).
26. Khera, A. V. et al. Polygenic prediction of weight and obesity trajectories from birth to adulthood. *Cell* **177**, 587–596.e9 (2019).
27. Kaur, Y., de Souza, R. J., Gibson, W. T. & Meyre, D. A systematic review of genetic syndromes with obesity. *Obes. Rev.* **18**, 603–634 (2017).
28. Poitou, C., Mosbah, H. & Clément, K. Mechanisms in endocrinology update on treatments for patients with genetic obesity. *Eur. J. Endocrinol.* **163**, R149–R166 (2020).
29. Yeo, G. S. H. et al. The melanocortin pathway and energy homeostasis: from discovery to obesity therapy. *Mol. Metab.* **48**, 101206 (2021).
30. Kleinendorst, L. et al. Identifying underlying medical causes of pediatric obesity: results of a systematic diagnostic approach in a pediatric obesity center. *PLoS ONE* **15**, e0244508 (2020).
31. Farooqi, I. S. & O'Rahilly, S. Mutations in ligands and receptors of the leptin-melanocortin pathway that lead to obesity. *Nat. Clin. Pract. Endocrinol. Metab.* **4**, 569–577 (2008).
32. Saeed, S. et al. Genetic causes of severe childhood obesity: a remarkably high prevalence in an inbred population of Pakistan. *Diabetes* **69**, 1424–1438 (2020).
33. Wade, K. H. et al. Loss-of-function mutations in the melanocortin 4 receptor in a UK birth cohort. *Nat. Med.* **27**, 1088–1096 (2021).
34. Ling, C. & Rönn, T. Epigenetics in human obesity and type 2 diabetes. *Cell Metab.* **29**, 1028–1044 (2019).
35. Rohde, K. et al. Genetics and epigenetics in obesity. *Metabolism* **92**, 37–50 (2019).
36. Qiao, Y. et al. Birth weight and childhood obesity: a 12-country study. *Int. J. Obes. Suppl.* **5**, S74–S79 (2015).
37. Ibáñez, L., Ong, K., Dunger, D. B. & de Zegher, F. Early development of adiposity and insulin resistance after catch-up weight gain in small-for-gestational-age children. *J. Clin. Endocrinol. Metab.* **91**, 2153–2158 (2006).
38. He, Q. & Karlberg, J. BMI in childhood and its association with height gain, timing of puberty, and final height. *Pediatr. Res.* **49**, 244–251 (2001).
39. Denzer, C. et al. Pubertal development in obese children and adolescents. *Int. J. Obes.* **31**, 1509–1519 (2007).
40. de Groot, C. J. et al. Determinants of advanced bone age in childhood obesity. *Horm. Res. Paediatr.* **87**, 254–263 (2017).
41. Kempf, E. et al. Dynamic alterations in linear growth and endocrine parameters in children with obesity and height reference values. *eClinicalMedicine* **37**, 100977 (2021).
42. Kohlsdorf, K. et al. Early childhood BMI trajectories in monogenic obesity due to leptin, leptin receptor, and melanocortin 4 receptor deficiency. *Int. J. Obes.* **42**, 1602–1609 (2018).
43. Strobel, A., Issad, T., Camoin, L., Ozata, M. & Strosberg, A. D. A leptin missense mutation associated with hypogonadism and morbid obesity. *Nat. Genet.* **18**, 213–215 (1998).
44. Farooqi, I. S. et al. Clinical and molecular genetic spectrum of congenital deficiency of the Leptin receptor. *N. Engl. J. Med.* **356**, 237–247 (2007).
A comprehensive description of genetic variants in LEPR and the relevance for obesity.
45. von Schnurbein, J. et al. Leptin substitution results in the induction of menstrual cycles in an adolescent with leptin deficiency and hypogonadotropic hypogonadism. *Horm. Res. Paediatr.* **77**, 127–133 (2012).
46. Beghini, M. et al. Serum IGF1 and linear growth in children with congenital leptin deficiency before and after leptin substitution. *Int. J. Obes.* **45**, 1448–1456 (2021).
47. Farooqi, I. S. & O'Rahilly, S. 20 years of leptin: human disorders of leptin action. *J. Endocrinol.* **223**, T63–T70 (2014).
48. Farooqi, I. S. Monogenic human obesity syndromes. *Handb. Clin. Neurol.* **181**, 301–310 (2021).
49. Heymsfield, S. B. et al. Hyperphagia: Current Concepts and Future Directions. Proceedings of the 2nd International Conference on Hyperphagia. *Obesity* **22**, S1–S17 (2014).
50. Gibbons, C., Hopkins, M., Beaulieu, K., Oustric, P. & Blundell, J. E. Issues in measuring and interpreting human appetite (satiety/satiation) and its contribution to obesity. *Curr. Obes. Rep.* **8**, 77–87 (2019).
51. Melchior, C. et al. Clinical and functional relevance of melanocortin-4 receptor variants in obese German children. *Horm. Res. Paediatr.* **78**, 237–246 (2012).
52. Hinney, A., Volckmar, A.-L. & Knoll, N. Melanocortin-4 receptor in energy homeostasis and obesity pathogenesis. *Prog. Mol. Biol. Transl. Sci.* **114**, 147–191 (2013).
53. Creemers, J. W. M. et al. Heterozygous mutations causing partial prohormone convertase 1 deficiency contribute to human obesity. *Diabetes* **61**, 383–390 (2012).
54. Stijnen, P., Ramos-Molina, B., O'Rahilly, S. & Creemers, J. W. M. PCSK1 mutations and human endocrinopathies: from obesity to gastrointestinal disorders. *Endocr. Rev.* **37**, 347–371 (2016).
55. Stijnen, P. et al. Endoplasmic reticulum-associated degradation of the mouse PC1/3-N222D hypomorph and human PCSK1 mutations contributes to obesity. *Int. J. Obes.* **40**, 973–981 (2016).
56. Löffler, D. et al. Functional and clinical relevance of novel and known PCSK1 variants for childhood obesity and glucose metabolism. *Mol. Metab.* **6**, 295–305 (2017).
57. Mantzoros, C. S. et al. Leptin in human physiology and pathophysiology. *Am. J. Physiol. - Endocrinol. Metab.* **301**, E567–E584 (2011).
58. Park, H.-K. & Ahima, R. S. Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. *Metabolism* **64**, 24–34 (2015).
59. Wauman, J., Zabeau, L. & Tavernier, J. The leptin receptor complex: heavier than expected? *Front. Endocrinol.* **8**, 30 (2017).
60. Antunes, H., Santos, C. & Carvalho, S. Serum leptin levels in overweight children and adolescents. *Br. J. Nutr.* **101**, 1262–1266 (2008).
61. Pan, W. W. & Myers, M. G. Leptin and the maintenance of elevated body weight. *Nat. Rev. Neurosci.* **19**, 95–105 (2018).
62. Funcke, J.-B. et al. Monogenic forms of childhood obesity due to mutations in the leptin gene. *Mol. Cell. Pediatr.* **1**, 3 (2014).
63. Montague, C. T. et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* **387**, 903–908 (1997).
The first description of leptin deficiency in humans.
64. Wabitsch, M. et al. Biologically inactive leptin and early-onset extreme obesity. *N. Engl. J. Med.* **372**, 48–54 (2015).
The first description of biologically inactive variants in the leptin gene.
65. Wabitsch, M. et al. Severe early-onset obesity due to bioinactive leptin caused by a p.N103K mutation in the leptin gene. *J. Clin. Endocrinol. Metab.* **100**, 3227–3230 (2015).
66. Farooqi, I. S. et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N. Engl. J. Med.* **341**, 879–884 (1999).
A comprehensive description of leptin treatment in severe obesity due to leptin deficiency.
67. Farooqi, I. S. et al. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J. Clin. Invest.* **110**, 1093–1103 (2002).
68. Fischer-Posovszky, P. et al. A new missense mutation in the leptin gene causes mild obesity and hypogonadism without affecting T cell responsiveness. *J. Clin. Endocrinol. Metab.* **95**, 2836–2840 (2010).
69. Gruber, T. et al. Obesity-associated hyperleptinemia alters the gliovascular interface of the hypothalamus to promote hypertension. *Cell Metab.* **33**, 1155–1170.e10 (2021).
70. Von Schnurbein, J. et al. Leptin is not essential for obesity-associated hypertension. *Obes. Facts* **12**, 460–475 (2019).
71. Kim, M. S. et al. The central melanocortin system affects the hypothalamo-pituitary thyroid axis and may mediate the effect of leptin. *J. Clin. Invest.* **105**, 1005–1011 (2000).
72. Nillni, E. A. et al. Leptin regulates prothyrotropin-releasing hormone biosynthesis: evidence for direct and indirect pathways. *J. Biol. Chem.* **275**, 36124–36133 (2000).
73. Paz-Filho, G., Delibasi, T., Erol, H. K., Wong, M.-L. & Licinio, J. Congenital leptin deficiency and thyroid function. *Thyroid. Res.* **2**, 11 (2009).
74. Wabitsch, M. et al. Measurement of immunofunctional leptin to detect and monitor patients with functional leptin deficiency. *Eur. J. Endocrinol.* **176**, 315–322 (2017).
75. Stanik, J. et al. Concordance of bioactive vs. total immunoreactive serum leptin levels in children with severe early onset obesity. *PLoS ONE* **12**, e0178107 (2017).

76. Clément, K. et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* **392**, 398–401 (1998). **Detection of the first patients with *LEPR* deficiency**.
77. Kleinendorst, L. et al. Leptin receptor deficiency: a systematic literature review and prevalence estimation based on population genetics. *Eur. J. Endocrinol.* **182**, 47–56 (2019).
78. Nunziata, A. et al. Functional and phenotypic characteristics of human leptin receptor mutations. *J. Endocr. Soc.* **3**, 27–41 (2018).
79. Voigtmann, F. et al. Identification of a novel leptin receptor (LEPR) variant and proof of functional relevance directing treatment decisions in patients with morbid obesity. *Metabolism* **116**, 154438 (2021).
80. Li, Z., Zhou, Y., Carter-Su, C., Myers, M. G. & Rui, L. SH2B1 enhances leptin signaling by both Janus kinase 2 Tyr813 phosphorylation-dependent and -independent mechanisms. *Mol. Endocrinol.* **21**, 2270–2281 (2007).
81. Bochukova, E. G. et al. Large, rare chromosomal deletions associated with severe early-onset obesity. *Nature* **463**, 666–670 (2010).
82. Doche, M. E. et al. Human SH2B1 mutations are associated with maladaptive behaviors and obesity. *J. Clin. Invest.* **122**, 4732–4736 (2012).
83. Volckmar, A.-L. et al. Mutation screen in the GWAS derived obesity gene SH2B1 including functional analyses of detected variants. *BMC Med. Genomics* **5**, 65 (2012).
84. Rui, L. SH2B1 regulation of energy balance, body weight, and glucose metabolism. *World J. Diabetes* **5**, 511 (2014).
85. Argente, J. et al. Efficacy and safety results of a phase 2 trial of setmelanotide in obesity due to SH2B1 variants and 16p11.2 deletion syndrome [abstract]. *ESPE Abstr.* **94**, FC2.1 (2021).
86. Krude, H. et al. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat. Genet.* **19**, 155–157 (1998).
87. Graves, L. E., Khouri, J. M., Kristidis, P. & Verge, C. F. Proopiomelanocortin deficiency diagnosed in infancy in two boys and a review of the known cases. *J. Paediatr. Child Health* **57**, 484–490 (2021).
88. Kühnen, P. et al. Interindividual variation in DNA methylation at a putative POMC metastable epiallele is associated with obesity. *Cell Metab.* **24**, 502–509 (2016).
89. Candler, T., Kühnen, P., Prentice, A. M. & Silver, M. Epigenetic regulation of POMC; implications for nutritional programming, obesity and metabolic disease. *Front. Neuroendocrinol.* **54**, 100773 (2019).
90. O'Rahilly, S. et al. Impaired processing of prohormones associated with abnormalities of glucose homeostasis and adrenal function. *N. Engl. J. Med.* **333**, 1386–1391 (1995).
91. Jackson, R. S. et al. Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene. *Nat. Genet.* **16**, 303–306 (1997).
92. Jackson, R. S. et al. Small-intestinal dysfunction accompanies the complex endocrinopathy of human proprotein convertase 1 deficiency. *J. Clin. Invest.* **112**, 1550–1560 (2003).
93. Farooqi, I. S. et al. Hyperphagia and early-onset obesity due to a novel homozygous missense mutation in prohormone convertase 1/3. *J. Clin. Endocrinol. Metab.* **92**, 3369–3373 (2007).
94. Pépin, L. et al. A newcase of PCSK1 pathogenic variant with congenital proprotein convertase 1/3 deficiency and literature review. *J. Clin. Endocrinol. Metab.* **104**, 985–993 (2019).
95. Benzinou, M. et al. Common nonsynonymous variants in PCSK1 confer risk of obesity. *Nat. Genet.* **40**, 943–945 (2008).
96. Yeo, G. S. H. et al. A frameshift mutation in MC4R associated with dominantly inherited human obesity. *Nat. Genet.* **20**, 111–112 (1998).
97. Vaisse, C., Clement, K., Guy-Grand, B. & Froguel, P. A frameshift mutation in human MC4R is associated with a dominant form of obesity. *Nat. Genet.* **20**, 113–114 (1998). This study and the study by Yeo et al. (1998) are the first studies delineating the effect of MC4R mutations on obesity.
98. Farooqi, I. S. et al. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *N. Engl. J. Med.* **348**, 1085–1095 (2003).
99. Kühnen, P., Krude, H. & Biebermann, H. Melanocortin-4 receptor signalling: importance for weight regulation and obesity treatment. *Trends Mol. Med.* **25**, 136–148 (2019).
100. Clément, K. et al. MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency. *Nat. Med.* **24**, 551–555 (2018).
101. Dempfle, A. et al. Large quantitative effect of melanocortin-4 receptor gene mutations on body mass index. *J. Med. Genet.* **41**, 795–800 (2004).
102. Geller, F. et al. Melanocortin-4 receptor gene variant I103 is negatively associated with obesity. *Am. J. Hum. Genet.* **74**, 572–581 (2004). **First study describing a robust polygenic effect of BMI**.
103. Lotta, L. A. et al. Human gain-of-function MC4R variants show signaling bias and protect against obesity. *Cell* **177**, 597–607.e9 (2019).
104. Paisdzior, S. et al. Differential signaling profiles of MC4R mutations with three different ligands. *Int. J. Mol. Sci.* **21**, 1224 (2020).
105. Smith, J. S., Lefkowitz, R. J. & Rajagopal, S. Biased signalling: from simple switches to allosteric microprocessors. *Nat. Rev. Drug. Discov.* **17**, 243–260 (2018).
106. Akbari, P. et al. Sequencing of 640,000 exomes identifies *GPR75* variants associated with protection from obesity. *Science* **373**, eabf8683 (2021).
107. Mendes de Oliveira, E. et al. Obesity-associated GNAS mutations and the melanocortin pathway. *N. Engl. J. Med.* **385**, 1581–1592 (2021).
108. Ji, L., Wu, H. T., Qin, X. Y. & Lan, R. Dissecting carboxypeptidase E: properties, functions and pathophysiological roles in disease. *Endocr. Connect.* **6**, R18–R38 (2017).
109. Alsters, S. I. M. et al. Truncating homozygous mutation of carboxypeptidase E (CPE) in a morbidly obese female with type 2 diabetes mellitus, intellectual disability and hypogonadotrophic hypogonadism. *PLoS ONE* **10**, e0131417 (2015).
110. Bosch, E. et al. BDV syndrome: an emerging syndrome with profound obesity and neurodevelopmental delay resembling Prader-Willi syndrome. *J. Clin. Endocrinol. Metab.* **106**, 3413–3427 (2021).
111. York, B. & O'Malley, B. W. Steroid receptor coactivator (SRC) family: masters of systems biology. *J. Biol. Chem.* **285**, 38743–38750 (2010).
112. Yang, Y. et al. Steroid receptor coactivator-1 modulates the function of Pomc neurons and energy homeostasis. *Nat. Commun.* **10**, 1718 (2019).
113. Reinehr, T. et al. Lifestyle intervention in obese children with variations in the melanocortin 4 receptor gene. *Obesity* **17**, 382–389 (2009).
114. Hainerová, I. et al. Melanocortin 4 receptor mutations in obese Czech children: studies of prevalence, phenotype development, weight reduction response, and functional analysis. *J. Clin. Endocrinol. Metab.* **92**, 3689–3696 (2007).
115. Trier, C. et al. Obesity treatment effect in Danish children and adolescents carrying melanocortin-4 receptor mutations. *Int. J. Obes.* **45**, 66–76 (2021).
116. Vos, N. et al. Bariatric surgery for monogenic non-syndromic and syndromic obesity disorders. *Curr. Diab. Rep.* **20**, 44 (2020).
117. Poitou, C. et al. Long-term outcomes of bariatric surgery in patients with bi-allelic mutations in the POMC, LEPR, and MC4R genes. *Surg. Obes. Relat. Dis.* **17**, 1449–1456 (2021).
118. Cooiman, M. I. et al. Long-term weight outcome after bariatric surgery in patients with melanocortin-4 receptor gene variants: a case–control study of 105 patients. *Obes. Surg.* **32**, 837–844 (2022).
119. Kleinendorst, L., van Haelst, M. M. & van den Akker, E. L. T. Young girl with severe early-onset obesity and hyperphagia. *BMJ Case Rep.* **2017**, bcr2017221067 (2017).
120. Zorn, S., von Schnurbein, J., Kohlsdorf, K., Denzer, C. & Wabitsch, M. Diagnostic and therapeutic odyssey of two patients with compound heterozygous leptin receptor deficiency. *Mol. Cell. Pediatr.* **7**, 15 (2020).
121. Heymsfield, S. B. & Wadden, T. A. Mechanisms, pathophysiology, and management of obesity. *N. Engl. J. Med.* **376**, 254–266 (2017).
122. Cardel, M. I., Jastreboff, A. M. & Kelly, A. S. Treatment of adolescent obesity in 2020. *JAMA* **322**, 1707–1708 (2019).
123. Viner, R. M., Hsia, Y., Tomsic, T. & Wong, I. C. K. Efficacy and safety of anti-obesity drugs in children and adolescents: systematic review and meta-analysis. *Obes. Rev.* **11**, 593–602 (2009).
124. Sherafat-Kazemzadeh, R., Yanovski, S. Z. & Yanovski, J. A. Pharmacotherapy for childhood obesity: present and future prospects. *Int. J. Obes.* **37**, 1–15 (2013).
125. Peirson, L. et al. Treatment of overweight and obesity in children and youth: a systematic review and meta-analysis. *CMAJ Open* **3**, E35–E46 (2015).
126. von Schnurbein, J. et al. Rapid improvement of hepatic steatosis after initiation of leptin substitution in a leptin-deficient girl. *Horm. Res. Paediatr.* **79**, 310–317 (2013).
127. Farr, O. M., Gavrieli, A. & Mantzoros, C. S. Leptin applications in 2015: what have we learned about leptin and obesity? *Curr. Opin. Endocrinol. Diabetes Obes.* **22**, 353–359 (2015).
128. Heymsfield, S. B. et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *JAMA* **282**, 1568–1575 (1999).
129. Tsoukas, M. A., Farr, O. M. & Mantzoros, C. S. Leptin in congenital and HIV-associated lipodystrophy. *Metabolism* **64**, 47–59 (2015).
130. Milos, G. et al. Short-term metreleptin treatment of patients with anorexia nervosa: rapid on-set of beneficial cognitive, emotional, and behavioral effects. *Transl. Psychiatry* **10**, 303 (2020). **The first clinical use of metreleptin in the treatment of patients with the eating disorder anorexia nervosa**.
131. Antel, J. et al. Rapid amelioration of anorexia nervosa in a male adolescent during metreleptin treatment including recovery from hypogonadotropic hypogonadism. *Eur. Child. Adolesc. Psychiatry* https://doi.org/10.1007/s00787-021-01778-7 (2021).
132. de Candia, P. et al. The pleiotropic roles of leptin in metabolism, immunity, and cancer. *J. Exp. Med.* **218**, e20191593 (2021).
133. Kühnen, P. et al. Proopiomelanocortin deficiency treated with a melanocortin-4 receptor agonist. *N. Engl. J. Med.* **375**, 240–246 (2016). **The first report on the weight-lowering effects of the MC4R agonist setmelanotide in patients with POMC deficiency**.
134. Greenfield, J. R. et al. Modulation of blood pressure by central melanocortinergic pathways. *N. Engl. J. Med.* **360**, 44–52 (2009).
135. Kanti, V. et al. A melanocortin-4 receptor agonist induces skin and hair pigmentation in patients with monogenic mutations in the leptin-melanocortin pathway. *Ski. Pharmacol. Physiol.* **34**, 307–316 (2021).
136. Tagliabue, E. et al. MC1R variants as melanoma risk factors independent of at-risk phenotypic characteristics: a pooled analysis from the M-SKIP project. *Cancer Manag. Res.* **10**, 1143–1154 (2018).
137. Collet, T. H. et al. Evaluation of a melanocortin-4 receptor (MC4R) agonist (setmelanotide) in MC4R deficiency. *Mol. Metab.* **6**, 1321–1329 (2017).
138. Clément, K. et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *Lancet Diabetes Endocrinol.* **8**, 960–970 (2020).
139. Markham, A. Setmelanotide: first approval. *Drugs* **81**, 397–403 (2021).
140. Haws, R. et al. Effect of setmelanotide, a melanocortin-4 receptor agonist, on obesity in Bardet-Biedl syndrome. *Diabetes Obes. Metab.* **22**, 2133–2140 (2020).
141. Argente, J. et al. Phase 3 trial of setmelanotide in participants with Bardet-Biedl syndrome: placebo-controlled results [abstract]. *ESPE Abstr.* **94**, FC2.2 (2021).
142. Ryan, D. H. Setmelanotide: what does it mean for clinical care of patients with obesity? *Lancet Diabetes Endocrinol.* **8**, 933–935 (2020).
143. Akinci, B. et al. The complicated clinical course in a case of atypical lipodystrophy after development of neutralizing antibody to metreleptin: treatment with setmelanotide. *Endocrinol. Diabetes Metab. Case Rep.* **2020**, 19–0139 (2020).
144. Kamermans, A. et al. Setmelanotide, a novel, selective melanocortin receptor-4 agonist exerts anti-inflammatory actions in astrocytes and promotes an anti-inflammatory macrophage phenotype. *Front. Immunol.* **10**, 2312 (2019).
145. Kelly, A. S. et al. A randomized, controlled trial of liraglutide for adolescents with obesity. *N. Engl. J. Med.* **382**, 2117–2128 (2020).
146. Iepsen, E. W. et al. Patients with obesity caused by melanocortin-4 receptor mutations can be treated with a glucagon-like peptide-1 receptor agonist. *Cell Metab.* **28**, 23–32.e3 (2018).
147. Iepsen, E. W. et al. GLP-1 receptor agonist treatment in morbid obesity and type 2 diabetes due to pathogenic homozygous melanocortin-4 receptor mutation: a case report. *Cell Rep. Med.* **1**, 100006 (2020).

148. Welling, M. S. et al. Effects of glucagon-like peptide-1 analogue treatment in genetic obesity: a case series. *Clin. Obes.* **11**, e12481 (2021).
149. Müller, T. D., Clemmensen, C., Finan, B., DiMarchi, R. D. & Tschöp, M. H. Anti-obesity therapy: from rainbow pills to polyagonists. *Pharmacol. Rev.* **70**, 712–746 (2018).
150. Day, J. W. et al. A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. *Nat. Chem. Biol.* **5**, 749–757 (2009).
151. Clemmensen, C. et al. Emerging hormonal-based combination pharmacotherapies for the treatment of metabolic diseases. *Nat. Rev. Endocrinol.* **15**, 90–104 (2019).
152. Frías, J. P. et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N. Engl. J. Med.* **385**, 503–515 (2021).
153. Rosenstock, J. et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet* **398**, 143–155 (2021).
154. Ludvik, B. et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet* **398**, 583–598 (2021).
155. Del Prato, S. et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet* **398**, 1811–1824 (2021).
156. Dahl, D. et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes. *JAMA* **327**, 534–545 (2022).
157. Jastreboff, A. M. et al. Tirzepatide once weekly for the treatment of obesity. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2206038 (2022).
158. Brandt, S. J., Götz, A., Tschöp, M. H. & Müller, T. D. Gut hormone polyagonists for the treatment of type 2 diabetes. *Peptides* **100**, 190–201 (2018).
159. Müller, T. D., Blüher, M., Tschöp, M. H. & DiMarchi, R. D. Anti-obesity drug discovery: advances and challenges. *Nat. Rev. Drug Discov.* **21**, 201–223 (2022). **Comprehensive review of the state of the art in anti-obesity drug discovery**.
160. Angelidi, A. M., Belanger, M. J., Kokkinos, A., Koliaki, C. C. & Mantzoros, C. S. Novel noninvasive approaches to the treatment of obesity: from pharmacotherapy to gene therapy. *Endocr. Rev.* **43**, 507–557 (2022).
161. Takahashi, K. & Yamanaka, S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* **126**, 663–676 (2006).
162. Takahashi, K. et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* **131**, 861–872 (2007).
163. Yamanaka, S. Pluripotent stem cell-based cell therapy—promise and challenges. *Cell Stem Cell* **27**, 523–531 (2020).
164. Rajamani, U. et al. Super-obese patient-derived iPSC hypothalamic neurons exhibit obesogenic signatures and hormone responses. *Cell Stem Cell* **22**, 698–712. e9 (2018).
165. Uddin, F., Rudin, C. M. & Sen, T. CRISPR gene therapy: applications, limitations, and implications for the future. *Front. Oncol.* **10**, 1387 (2020).
166. Zhu, L. et al. Leptin gene-targeted editing in ob/ob mouse adipose tissue based on the CRISPR/Cas9 system. *J. Genet. Genomics* **48**, 134–146 (2021).
167. Keller, E. et al. Auxological computer based network for early detection of disorders of growth and weight attainment. *J. Pediatr. Endocrinol. Metab.* **15**, 149–156 (2002).
168. Ayers, K. L. et al. Melanocortin 4 receptor pathway dysfunction in obesity: patient stratification aimed at MC4R agonist treatment. *J. Clin. Endocrinol. Metab.* **103**, 2601–2612 (2018).
169. Dayton, K. & Miller, J. Finding treatable genetic obesity: strategies for success. *Curr. Opin. Pediatr.* **30**, 526–531 (2018).
170. Brennan, L. & de Roos, B. Nutrigenomics: lessons learned and future perspectives. *Am. J. Clin. Nutr.* **113**, 503–516 (2021).
171. Bouchard, C. Exercise genomics — a paradigm shift is needed: a commentary. *Br. J. Sports Med.* **49**, 1492–1496 (2015).
172. Riveros-McKay, F. et al. Genetic architecture of human thinness compared to severe obesity. *PLoS Genet.* **15**, e1007603 (2019).
173. Hinney, A. et al. Genome wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (FTO) variants. *PLoS ONE* **2**, e1361 (2007).
174. Orthofer, M. et al. Identification of ALK in thinness. *Cell* **181**, 1246–1262.e22 (2020).
175. Watson, H. J. et al. Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nat. Genet.* **51**, 1207–1214 (2019).
176. Zheng, Y. et al. PTBP2 - a gene with relevance for both anorexia nervosa and body weight regulation. *Transl. Psychiatry*. **12**, 241 (2022).
177. Hinney, A. et al. Evidence for three genetic loci involved in both anorexia nervosa risk and variation of body mass index. *Mol. Psychiatry* **22**, 192–201 (2017).
178. Hinney, A. & Hebebrand, J. Polygenic obesity in humans. *Obes. Facts* **1**, 35–42 (2008).
179. Felix, J. F. et al. Genome-wide association analysis identifies three new susceptibility loci for childhood body mass index. *Hum. Mol. Genet.* **25**, 389–403 (2016).
180. Yengo, L. et al. Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. *Hum. Mol. Genet.* **27**, 3641–3649 (2018).
181. Pulit, S. L. et al. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. *Hum. Mol. Genet.* **28**, 166–174 (2019).
182. Loos, R. J. F. & Yeo, G. S. H. The bigger picture of *FTO* – the first GWAS-identified obesity gene. *Nat. Rev. Endocrinol.* **10**, 51–61 (2014).
183. Zeggini, E., Gloyn, A. L., Barton, A. C. & Wain, L. V. Translational genomics and precision medicine: moving from the lab to the clinic. *Science* **365**, 1409–1413 (2019).
184. Dina, C. et al. Variation in FTO contributes to childhood obesity and severe adult obesity. *Nat. Genet.* **39**, 724–726 (2007).
185. Frayling, T. M. et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* **316**, 889–894 (2007).
186. Wang, J.-Y., Chen, L.-J. & Qiang, P. The potential role of N6-methyladenosine (m6A) demethylase fat mass and obesity-associated gene (FTO) in human cancers. *Onco. Targets Ther.* **13**, 12845–12856 (2020).
187. Lan, N. et al. FTO – a common genetic basis for obesity and cancer. *Front. Genet.* **11**, 559138 (2020).
188. Annapoorna, P. K. et al. FTO: an emerging molecular player in neuropsychiatric diseases. *Neuroscience* **418**, 15–24 (2019).
189. Landgraf, K. et al. The obesity-susceptibility gene TMEM18 promotes adipogenesis through activation of PPARG. *Cell Rep.* **33**, 108295 (2020).
190. Han, Y. et al. Mesenchymal stem cells for regenerative medicine. *Cells* **8**, 886 (2019).
191. Zuk, P. A. et al. Human adipose tissue is a source of multipotent stem cells. *Mol. Biol. Cell* **13**, 4279–4295 (2002).
192. Shukla, L., Yuan, Y., Shayan, R., Greening, D. W. & Karnezis, T. Fat therapeutics: the clinical capacity of adipose-derived stem cells and exosomes for human disease and tissue regeneration. *Front. Pharmacol.* **11**, 158 (2020).
193. Wang, C.-H. et al. CRISPR-engineered human brown-like adipocytes prevent diet-induced obesity and ameliorate metabolic syndrome in mice. *Sci. Transl. Med.* **12**, eaaz8664 (2020).
194. Chouchani, E. T., Kazak, L. & Spiegelman, B. M. New advances in adaptive thermogenesis: UCP1 and beyond. *Cell Metab.* **29**, 27–37 (2019).

Acknowledgements
The authors thank L.S. Rajcsanyi (University of Duisburg-Essen, Essen, Germany) for her help with the first version of the figure. A.H. acknowledges the support of funding from Deutsche Forschungsgemeinschaft (DFG; HI 865/2-1), the BMBF (01GS0820, PALGER2017-33: 01DH19010) and the Stiftung Universitätsmedizin Essen. A.K. acknowledges the support of grants from the DFG, KO3512/3-1 and the DFG-funded Collaborative Research Center "Obesity-Mechanisms" CRC1052 (no. 209933838), and the German Diabetes Association (DDG). P.F.-P. acknowledges the support of funding from Deutsche Forschungsgemeinschaft (Heisenberg professorship, project number 398707781).

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
A.K. provided unpaid advice to Rhythm Pharmaceuticals. The other authors declare no competing interests.

Peer review information
Nature Reviews Endocrinology thanks ELT van den Akker who co-reviewed the manuscript with Ozair Abawi, Jesus Argente and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

RELATED LINKS
CDC growth charts: https://www.cdc.gov/growthcharts/clinical_charts.htm
Clinical trials: https://clinicaltrials.gov/ct2/home
Confirmed genes for different complex traits: https://www.ebi.ac.uk/gwas/
FDA approval: https://www.fda.gov/news-events/press-announcements/fda-approves-novel-dual-targeted-treatment-type-2-diabetes
OMIM database: https://www.omim.org/
WHO child growth standards: https://www.who.int/tools/child-growth-standards