nature

REVIEWS

*Nature Reviews* referee guidelines

Review articles

*Nature Reviews* publishes timely, authoritative articles that are of broad interest and exceptional quality. Thank you for taking the time to help us to ensure that our articles meet these high standards.

Review articles in *Nature Reviews* journals provide accessible, authoritative and balanced overviews of a field or topic. These articles are targeted towards readers from advanced undergraduate level and upwards, including researchers, academics and clinicians, and should be accessible to readers working in any discipline.

Please submit your report in narrative form and provide detailed justifications for all statements. Confidential comments to the editor are welcome, but it is helpful if the main points are stated in the comments for transmission to the authors.

Please note that all *Nature Reviews* articles will be thoroughly edited before publication and all figures will be redrawn by our in-house art editors. We therefore request that you concentrate on the scientific content of the article, rather than any minor errors in language or grammar.

Please consider and comment on the following points when reviewing this manuscript:

• Is the article timely and does it provide a useful addition to the existing literature?

• Are the scope and aims of the article clear?

• Are the ideas logically presented and discussed?

• Is the article accessible to a wide audience, including readers who are not specialists in your own field?

• Does the article provide a balanced overview of the literature? Please bear in mind that it may not be possible to cover all aspects of a field within such a concise article.

• Does the article provide new insight into recent advances?

• Is the discussion fair and accurate? Although our authors are encouraged to be opinionated, they should not ignore alternative points of view.

• Do the figures, boxes and tables provide clear and accurate information? Are there any additional or alternative display items that you think that the authors should include?

• Are the references appropriate and up-to-date? Do they reflect the scope of the article?

• Are you aware of any undeclared conflicts of interest that might affect the balance, or perceived balance, of the article?

**The promise of new anti-obesity treatment options arising from identification and better understanding of genetic obesity traits**

Anke Hinney 1\*, Antje Körner 2, Pamela Fischer-Posovszky 3

**Affiliations**

1 Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy and Center for Translational Neuro- and Behavioral Sciences, University Hospital Essen, University of Duisburg-Essen, Germany

2 Leipzig University, Medical Faculty, Hospital for Children and Adolescents, Centre of Pediatric Research (CPL), Leipzig, Germany and LIFE Child, Leipzig Research Centre for Civilization Diseases, Leipzig, Germany and 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

3 Department of Pediatrics and Adolescent Medicine, Ulm University Medical Center, Germany

\* Corresponding author:

Prof. Dr. Anke Hinney

Contact: anke.hinney@uni-due.de

6.960 words (without abstract and bullet points)

192 references

Display items: 2 tables, 4 boxes, 1 figure

**Abstract (182)**

Obesity is a multifactorial and complex disease often manifesting in early childhood with a life-long burden. While common, multifactorial polygenic obesity is driven by the interaction of genetic predisposition with environmental factors, rare forms of monogenic obesity are caused by defined pathogenic variants in single genes. Most of these genes are involved in the central nervous regulation of hunger, satiety and energy expenditure. These variations mostly affect genes of the leptin-melanocortin pathway or its regulators. Clinically, patients present with impaired satiety, hyperphagia, and pronounced food seeking behavior in early childhood, ultimately leading to severe early-onset obesity. With the advent of novel pharmacological treatment options emerging for monogenic obesity targeting the central melanocortin pathway, genetic testing is recommended for patients with rapid weight gain in infancy and additional clinical suggestive features. Likewise, so far untreatable patients with hypothalamic damage or syndromic obesity involving energy regulatory circuits may benefit from these novel pharmacologic treatment options. Early identification of affected patients will lead to proper treatment, preventing the development of obesity sequelae, avoiding failure of conservative treatment approaches and alleviating patients and families from stigmatization.

**Bullet points (4-6, 30 words or fewer)**

* Most monogenic obesity traits result from pathogenic variants in single genes converging in leptin-melanocortin pathways.
* Targeting central pathways of energy expenditure with e.g., MC4R agonists provides new and promising treatment options for affected patients.
* Polygenic obesity results from an interplay of numerous genetic and environmental factors.
* Polygenic risk scores and massively parallel sequencing approaches will help to early identify obesity predisposition.
* New precision medicine approaches might help to tackle the obesity pandemic.

**Introduction**

According to the World Health Organization (WHO), approximately 39 million children under the age of 5 years had overweight or obesity in 2020 1. The prevalence of severe obesity is particularly alarming. Depending on the study and criteria applied, the reported prevalence numbers for severe childhood obesity range from 1.96% to 6.3% within the general population (overview in 2). Interestingly, a recent study by Geserick et al. discovered that adolescents with obesity had experienced the most rapid weight gain at an age of 2 – 6 years 3. In parallel to an increase in body mass index (BMI) in early childhood, the expansion of fat mass is paralleled by first signs of adipose tissue dysfunction (increased adipocyte size / adipocyte hypertrophy, inflammation/macrophage infiltration, and adipokines dysbalance) 4. The early onset of obesity is clearly linked to the development of cardiovascular and metabolic comorbidities, with (preclinical) manifestation 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. Common childhood obesity arises from the interaction of an individual genetic predisposition and our obesogenic environment. Recently, the Covid-19 pandemic illustrated the collision of these two pandemics, and showed particular vulnerability of children with existing obesity to further excessive weight gain and the clinical burden associated with the lock-down 8–10. Therefore, preventing and treating obesity as early as possible is of utmost clinical importance and social relevance.

Individuals living with obesity are often accused of failure to adopt to a healthy lifestyle, even among health care professionals. The latter assumption leads to stigmatization and is thus associated with psychological problems eventually leading to a vicious circle of weight gain – guilt – further weight increase 11. Knowledge about the pathological mechanisms including genetics involved helps to reduce weight stigma 12. Reduction of stigmatization through gain of knowledge and education is a superior aim of genetic studies in the context of body weight regulation and obesity.

**Genetic causes of obesity**

*Heritability of body weight*

Body weight, such as other anthropometric measures, is highly heritable. Seminal twin and adoption studies at the end of the 1980s and 1990s (e.g. 13) underscored that genetic factors play a remarkable role in body weight regulation (recently reviewed in 14). Twin studies have reported the highest and most consistent heritability rates ranging from 0.6 to 0.9 for explained BMI variance 15. Except for the newborn period, for which a lower heritability of 0.4 had been described, heritability estimates of BMI are not substantially affected by age 16. Heritability estimates derived from family and adoption studies are mostly considerably lower, in the range of 0.25 to 0.7 15. In general, twin studies are more informative if non-additive genetic factors play a larger role in body weight regulation. They also provide a better control for age effects on BMI. It is relevant to know that both direct and indirect genetic effects compose the genetic component. If, for example, in a monozygotic twin pair both infants are frequently hungry (direct genetic effect), the caretaker will feed them often (indirect genetic effect), even if the twins were separated at birth17. The genetic underpinnings of obesity are complex and apply to metabolic as well as behavioural factors: more than half of the variance 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 had been described in several studies 21. Twin and other family studies implied that the strong predictive value of parental BMI mainly arises from genetic rather than shared environmental factors 15, and that life style factors potentiate maternally-associated obesity risk 22. The socio-economic status is (SES) yet another important risk factor for pediatric obesity, increasing the odds ratio for obesity by more than 2-fold in children with low compared to high SES 19. Although genome-wide association studies (GWAS) provided valuable insights, the identified genetic variation only explains a comparatively small fraction of the heritability. Identified variants mostly have small effect sizes. A consensus explanation for this 'missing heritability' in complex diseases has not yet emerged (for review see 23 ). Briefly, possible explanations include analytical limitations, small effect sizes, rare variants, variants not picked up due to methodological approaches (e.g. 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 24.

**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 and therefore also regarded as syndromes. Thus, we suggest to distinguish the group of obesity syndromes from common, polygenic forms of obesity 25,26. Even this categorization might be an oversimplification as the influence of genetics on obesity can be seen as a continuous spectrum 26.

**Polygenic forms of obesity**

The most common form of obesity is multifactorial and driven by the interaction of polygenic predisposition with environmental factors. The polygenic factors commonly act additively, so that the effects of all single alleles sum up to a combined effect size. Information on polygenic variants is summarized in Box 3. A recent study identified and validated a polygenic predictor containing 2.1 million common variants to quantify obesity susceptibility. 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 gradient in weight was observed. Additionally, there was a 25-fold gradient in risk of extreme obesity across polygenic score deciles27. Hence, such polygenic risk scores may help to estimate individual risk for progressive severe obesity, which would, however, 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. However, in early childhood the gradient became significant and even reached 12 kg by 18 years of age. Thus the effect size of a polygenic score can be similar to that of rare, pathogenic variants leading to monogenic obesity 27. Despite the impressive sample size and number of variants included, the finding of 23.4% of BMI variability explained indicates that there are currently unknown or unidentified factors that might in the future explain this missing heritability.

**Obesity syndromes**

*Syndromal obesity with signs of neurodevelopmental disorder*

In obesity forms, which had been classically referred to as syndromal, obesity 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 28,29. Prominent examples are Prader-Willi syndrome and Bardet-Biedl syndrome 28,29. 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 28,29.

*Monogenic forms of obesity*

The monogenic forms of obesity are caused by genetic variations in single genes (**Table 1**). Of note, affected genes are usually involved in the central nervous regulation of hunger and satiety and are mostly linked to the hypothalamic leptin-melanocortin pathway (**Figure 1**) 30. Genetic risk variants as underlying cause of severe obesity are infrequent. The reported prevalence values (excluding studies which only investigated a single gene) range from 6% in general pediatric obesity cohorts investigating syndromic obesity and MC4R (see 31) up to 13% in children, who were referred to a tertiary center due to suspicion of an underlying medical cause of obesity 32 (with samples analyzed in an obesity gene panel or by microarray), or even higher in consanguineous populations 25,33,34. It can be expected that this rate might increase in the future with massive parallel sequencing technology 25. In fact, a recent re-scrutinization of the ALSPAC cohort found a frequency of 0.30% for pathogenic MC4R variants 35. But even with the use of specific obesity panels and modern exome sequencing technology, the identification of patients with known forms of monogenic obesity will only infrequently occur. In addition to classical genetic mechanisms, there is accumulating evidence that epigenetic mechanisms play a role in the development of obesity as reviewed in 36,37.

**Clinical features of early-onset obesity**

*Definitions and cut-offs*

To diagnose obesity and to perform comparable clinical studies clear and uniform definitions are urgently needed. The definitions provided in the current clinical practice guidelines on pediatric obesity from the Endocrine Society 25 are based on the Center Disease Control (CDC) growth charts in children aged 2-19 years old 38 and on WHO child growth standards in children under the age of two years 39 (Table 2). 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 (https://www.cdc.gov/healthyweight/bmi/calculator.html).

*Risk factors for pediatric obesity*

Beyond the three major risk factors for childhood obesity (genetics, parental overweight and lower socioeconomic status), large epidemiologic studies have identified perinatal factors (high maternal weight gain during pregnancy, high birthweight, formula feeding) imposing increased obesity risk with even stronger associations than life-style factors 19, and which should hence be regarded in the clinical evaluation of children with obesity. Of particular note, high birth weight was shown to be associated with later obesity 40 and children large for gestational age continued to have a higher BMI in childhood and adolescence 3. This needs to be differentiated from the increased risk for diabetes and cardiovascular disease in previously small-for gestational age born children according to the Barker hypothesis. In both instances, a (too) rapid catch-up growth around infancy drives a progressive transition to central obesity and insulin resistance 41. A recent population-based study analyzed the BMI dynamics in >51,505 children 3. Herein, 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. Normal or underweight children continued to have a stable BMI-SDS of around zero as expected. In contrast, children with overweight or obesity had increased BMI-SDS scores from infancy onwards, beginning at 1 year of age. As already mentioned above, the annual increase in BMI-SDS was highest between ages 2 and 6 years. As for the BMI, also growth dynamics in children with obesity are significantly distinct to normal-weight children. Children with obesity are significantly taller in early childhood with height-SDS ranging from 0.4 to 1 standard deviation above reference 42–45. Earlier puberty, blunted pubertal growth spurt, alterations in sex hormone profiles and advanced bone age might explain subsequent normalization at final height 43,44.

*Clinical features of genetic obesity*

The BMI trajectories of children with certain forms of monogenic obesity are clearly different from those with polygenic obesity 46. 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 alike had a BMI of >27 kg/m2 at the age of 2 years and their BMI was > 140% of the 95th percentile. At the age of 5 years the BMI was > 33 kg/m2 and > 184% of the 95th percentile in both patient groups 46. As such, their weight was conspicuous already in the first years of life. Patients with a deficiency in both, ligand and receptor, do not have normal pubertal development due to hypogonadotropic hypogonadism 47–49. Reports on linear growth are inconsistent. One study reports that patients with leptin deficiency were taller than the mid-parental median 50, while others report normal growth in childhood but reduced final height due to the absence of a pubertal growth spurt in both, ligand and receptor deficiency 48,51. Patients heterozygous for pathogenic variants in the *MC4R* showed less pronounced weight gain in the first 2 years of life, but severe obesity later on and frequently have tall stature 32.

Coherent with the impairment of central hypothalamic and neuroendocrine pathways in monogenic traits of obesity, patients and/or families frequently report hyperphagia with food-seeking or even food-stealing behavior and insatiable hunger, and some features more specific to certain gene alterations (see below) such as impaired pubertal development, increased predisposition to infections or diarrhea, hypopigmentation. Of note, cognitive development is usually normal in monogenic obesity traits. Motor development may appear to be delayed, which is, however, at least to some extent attributable to the mere excess body mass. Based on these observations, genetic testing should be considered if “red flags” indicative for monogenic obesity are present (see **Box 1**). As such, current clinical practice guidelines recommend genetic testing in patients with extreme early onset obesity (before 5 years of age) and clinical features of genetic obesity (in particular extreme hyperphagia) and/or a family history of extreme obesity 25.

Nevertheless, in the communication with the families the low likelihood of finding an underlying genetic cause should be openly communicated to prevent falsely high expectations. Furthermore, if a genetic variation is reported, particularly if it is a *de novo* variant, the functional impairment must be experimentally shown to prove causality for 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 52,53 but also for *LepR* and *PCSK1* variants 54–58.

**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 converging centrally to the MC4R receptor (**Figure 1**). An overview of genetic variants causing obesity syndromes is provided in Table 1 (**Table 1**).

*Congenital leptin deficiency*

Leptin is a 16 kD protein hormone and mainly secreted by adipocytes 59,60. It exerts its functions via binding to and activating the long form of the leptin receptor, resulting in the activation of various signaling cascades, such as phosphorylation of signal transducer and activator of transcription 3 (STAT3) 61. The serum levels of leptin correlate positively with body fat mass and BMI with a strong variability especially in extreme BMIs 62. Via central and peripheral routes, leptin affects a wide range of physiological processes including energy balance, metabolism, endocrine regulation and immune function 59,60. Leptin basically represents a peripheral signal for energy sufficiency to the central nervous system. A low level of the hormone corresponds to a low filling state of the adipose tissue energy stores. Critically low leptin levels induce a range of responses to preserve or restore the energy reservoir, among them altered behavioral, metabolic, endocrine, and immune responses 63.

Pathological variants in the *LEP* gene lead to congenital leptin deficiency or dysfunction 47,64–67. Coherent with the functional role of leptin, patients present with hyperphagia, increased food seeking, impaired satiety. For explanation, hyperphagia can be described as increased energy intake compared to controls or as eating an amount higher than predicted for body size or composition 68, often going along with a preoccupation for food presenting as *e.g.,* food seeking behavior 68. Satiety describes the control of appetite and refers to periods between meals, while satiation stands for the control of meal size 69. These processes can be measured by questionnaires 69. Born with normal weight, patients rapidly gain weight after birth and develop severe obesity associated with hyperinsulinemia, dyslipidemia, and hepatic steatosis 64. Another cardinal sign of leptin deficiency or dysfunction is hypogonadotropic hypogonadism and delayed pubertal development, while recurrent severe infections are reported in some but not all patients 64–66,70–72. In mice, hyperleptinemia promotes obesity-associated hypertension 73. 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 suffered from high blood pressure 74 suggesting leptin-independent pathomechanisms in the development of hypertension. Leptin was described to regulate the hypothalamic-pituitary-thyroidal axis in animal models 75,76, yet thyroid dysfunction is not a constant feature of leptin deficiency or dysfunction 65,71,77.

In 1997, congenital leptin deficiency was first described as autosomal recessive form of severe early-onset obesity in two children of a consanguineous Pakistani family 65. Of note, the circulating leptin levels 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 64. Several variants cause defects in leptin protein production and/or secretion, leading to classical leptin deficiency 47,64,65. This disease can be diagnosed by confirming the absence of immunoreactive leptin in the circulation. However, Wabitsch et al. described a variant (c.298G>T, p.D100Y), which is produced and secreted but biologically inactive. The genetic alteration lies within a region of the protein that is responsible for docking on to the receptor rendering the variant incapable of binding to the leptin receptor and therefore causing congenital leptin dysfunction 66. Whereas in patients with common obesity, total and bioactive leptin levels are concordant and adequate for the degree of obesity 78, the circulating leptin levels in the patients with bioinactive leptin are high and the correct diagnosis could be missed if just a classical leptin RIA or ELISA is performed for diagnostic purposes 66. Of note, a DNA sequencing approach can detect such pathogenic variants. Therefore, genetic testing is highly recommended in patients with suspected monogenic obesity, e.g. 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 with a phenotype highly comparable to ligand deficiency or dysfunction 48,79,80. It was first described in a consanguineous family from northern Algeria 79. According to a recent systematic literature research, 45 distinct *LEPR* variants were reported in the literature in a total of 88 patients 80. The genetic alterations include single amino acid changes, insertions, duplications, deletions, as well as nonsense risk variants predicted to cause truncation of the LEPR protein 80,81. The proof of functional impairment of these risk variants need to be performed to assess causality of the genetic variation and based on this may guide treatment decisions 82. 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 under diagnosis of the disease 80.

Patients with variants in the *LEPR* gene are normal weight at birth, but then rapidly exhibit pronounced food-seeking behavior, hyperphagia, and impaired satiety 29,48,79. This leads to rapid weight gain and severe obesity associated with hyperinsulinemia, dyslipidemia, and hepatic steatosis 29,48,79. Hypogonadotropic hypogonadism is a constant feature of leptin receptor deficiency 29,48,79,80, while recurrent severe infections are observed less frequently observed80,83. A recent review found pituitary hormone deficiencies in only one-third of patients 80.

*Sh2B1 deficiency*

The Src-homology-2B adaptor protein 1 (SH2B1) is a crucial molecule in leptin-mediated signal transduction enhancing the downstream signal by JNK2-dependent and -independent mechanisms 84. 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 displayed severe hyperphagia and severe insulin resistance 85. Shortly thereafter, loss of function (LoF) in *SH2B1* were identified as a monogenic cause of hyperphagia and early-onset obesity along with maladaptive behavior 86,87. SH2B1 also serves as an adaptor molecule in the insulin signaling cascade and might act as a central as well as peripheral regulator of glucose homeostasis and insulin sensitivity independently of body weight 88. Thus, it is not surprising that affected patients suffer from severe insulin resistance disproportionate for the degree of obesity 85. Considering its action as a promotor of leptin signaling in the MC4R pathway, treatment with MC4R agonists may be efficient in these patients. In first phase 2 trials, half of the patients with SH2B1 deficiency or 16p11.2 deletion responded with relevant weight loss. Such a clear separation of responders and non-responders may be due to heterogeneity in underlying genetic causes 89.

*POMC deficiency*

The proopiomelanocortin (*POMC)* gene encodes a pituitary preproprotein that is processed into several bioactive neuroendocrine peptides via the proproteinconvertase subtilisin/kexin-type 1 (PCSK1) 30. Among them is alpha-melanocyte-stimulating hormone (α-MSH), which acts via the MC4R to suppress appetite and food intake 30. Homozygous or compound heterozygous variants lead to POMC deficiency, also known as early-onset obesity, adrenal insufficiency, and red hair (OBAIRH). The autosomal recessive disorder was first described by Krude et al. 90 and is characterized by severe hyperphagia leading to severe early-onset obesity, secondary hypocortisolism, and pigmentary abnormalities such as pale skin and red hair, the latter being dependent on the genetic background of the individual. Hypoglycemia, hyperbilirubinemia, and life-threatening cholestasis might be observed in the first months of life 90. In total, 14 distinct variants have been described in 17 patients (summary in 91).In addition to these classical genetic alterations, variation in the DNA methylation status of the *POMC* gene was shown to be associated with obesity 92. DNA methylation is influenced by maternal nutrition during pregnancy 93, which underscores the modulating and direct role of environmental factors on molecular pathways regulating energy balance and hence body weight.

*PCSK1 deficiency*

PCSK1, as described above, is responsible for the cleavage of pro-hormones to yield active hormones: Variants in *PCSK1* in both the homozygous or heterozygous state lead to a complex clinical phenotype with early-onset obesity but also enteropathy with severe diarrhea and neuroendocrine problems, among them glucocorticoid deficiency, hypogonadism, and abnormal glucose homeostasis 94–97. These features result from the failure to process active hormones from prohormones, e.g. α-MSH from POMC in the hypothalamus or glucagon-like peptide-1 or -2 from proglucagon in the small intestine 56,94–97. 26 cases have been reported in the literature (summary in 98). Interestingly, variants in *PCSK1* have also been identified in genome-wide association analyses to be associated with childhood obesity 99. Hence, the association of *PCSK1* variants range from clear monogenic presentation to complex polygenic associations. Therefore, the functionality of the variant needs to be assessed 58 before treatment with MC4R agonists may be initiated.

*MC4R deficiency*

First described in 1998 as causative for severe obesity 100,101, MC4R deficiency so far is the most frequent form of monogenic obesity 53,102. It is estimated that variants in the MC4R gene are found in 2-5 % of pediatric and adult patients with obesity 30,53,103. Some of those patients may respond well to treatment with MC4R agonists such as setmelanotide 104. More than hundred variants have been described and both, homozygous compound heterozygous and heterozygous variants play a role in the development of obesity 30,53,103. Most variants reduce the function of the MC4R, leading to hyperphagia, severe obesity, severe hyperinsulinemia often along with increased lean mass and increased linear growth 105.

Effects on BMI for LoF 105 risk variants in the range of 15-30 kg increased weight and for gain of function (GoF)106 variants decreasing weight about 1.5 kg, had been described in 2004 already; recent data 107 confirm these findings. MC4R is a G protein coupled receptor. The functionality of variants was classically proven based on the capacity to induce Gsα signaling. However, recent insights leading to a more detailed view of the MC4R signaling uncovered that some variants (e.g. V103I, S127L) are biased towards Gq/11 pathway by endogenous agonists 108. This may explain why other previous agonists did not yield the expected beneficial results in some patients with MC4R deficiency and once more underscores the necessity for a detailed and comprehensive functional characterization of underlying signaling.

Furthermore, some variants can cause a gain of function of the receptor and were associated with lower BMI as well as lower odds of cardiometabolic sequelae such as type 2 diabetes and coronary artery disease 106,107. The GoF variants exhibited a signaling bias with an increased recruitment of β-arrestin to the MC4R along with increased cAMP levels in the cell and increased and sustained phosphorylation of ERK1/2 107.

Biased signaling is an interesting phenomenon known for G protein coupled receptors 109. Of note, in a recent study by Akbari et al. the exomes of 645.626 individuals were sequenced and 16 genes with an exome-wide association with the BMI were identified. Among them five brain-expressed G protein-coupled receptors 105,110. This suggests that not only the MC4R as most prominent representative of the leptin melanocortin pathway but also other GPCRs might act as fine tuners of body weight also in the heterozygous state.

*Aberrant expression of agouti-signaling protein (ASIP)*

Only recently, a heterozygous tandem duplication at the ASIP (agouti-signaling protein) gene locus causing ubiquitous, ectopic *ASIP* expression was identified as the cause of early onset extreme obesity (preliminary findings from a pre-print paper: Körner et al., https://doi.org/10.21203/rs.3.rs-1459517/v1) . The mutation places the *ASIP* coding region under control of the ubiquitously active itchy E3 ubiquitin protein ligase (ITCH) promoter, driving the ubiquitous generation of ASIP. The patient´s phenotype of early-onset obesity, overgrowth, red hair, and hyperinsulinemia is concordant with that of mutant mice ubiquitously expressing the homolog agouti. ASIP represses melanocyte-stimulating hormone-mediated activation as an inverse agonist of the melanocortin receptors, and thereby can affect eating behavior, energy expenditure, adipocyte differentiation, and pigmentation, as observed in the index patient. The type of mutation, i.e. the chromosomal rearrangement, is not readily detected by classical sequencing analysis algorithms and a second patient was only discovered by targeted screening. Thus, human obesity caused by ubiquitous ASIP expression is a novel monogenic trait, potentially treatable by melanocortin receptor agonists and with potentially many more patients yet undiscovered.

*GNAS deficiency*

The Gαs (stimulatory G-protein alpha subunit) protein is encoded by *GNAS* (guanine Nucleotide Binding Protein (G Protein), Alpha Stimulating Activity Polypeptide 1 gene). G protein-coupled receptor (GPCR) signaling is mediated by GNAS. The classical obesity syndrome Albright's hereditary osteodystrophy is caused by pathogenic variants in *GNAS*. Patients present with developmental delay, short stature, and skeletal abnormalities. Pathogenic variants on the maternal allele also cause, due to imprinting, obesity and hormone resistance to parathyroid hormone (pseudohypoparathyroidism). A recent sequencing approach in 2548 children with extreme obesity revealed 22 heterozygous *GNAS* carriers of pathogenic variants 111. Nearly all pathogenic variants in *GNAS* lead to impaired MC4R signaling. The authors suggested that screening of children with extreme obesity for GNAS deficiency may allow early diagnosis and improved clinical outcomes 111. Affected patients might benefit from treatment with melanocortin agonists. Variant frequencies in normal weight controls were not described.

*CPE deficiency*

Carboxypeptidase E (CPE) is an enzyme catalyzing the release of C-terminal arginine or lysine residues from polypeptides, after being processed by proprotein convertases 112. As such, it is involved in the biosynthesis of peptide hormones and neuropeptides. A truncating pathogenic variant is the gene encoding CPE resulted in undetectable mRNA expression in patient-derived blood cells. The patient suffered from morbid obesity along with hypogonadotropic hypogonadism, abnormal glucose homeostasis, and intellectual disability 113. Recently, novel homozygous CPE LoF variants were described in four individuals from three unrelated consanguineous families 114. All affected individuals had extreme obesity and showed endocrine anomalies (hypogonadotropic hypogonadism, central hypothyroidism) as well as neurodevelopmental delay. The authors of this study named this specific, recognizable clinical phenotype Blakemore-Durmaz-Vasileiou (BDV) syndrome 114.

*SRC1 deficiency*

Steroid Receptor Coactivator-1 (SRC-1) modulates the function of nuclear hormone receptors and transcription factors in enhancing or suppressing the expression of target genes 115. Based on the fact that mice with a deletion of Src-1 in Pomc neurons displayed increased food intake and obesity, Yang et al. analyzed exome sequencing and corresponding resequencing data from a cohort of patients with severe early-obesity and respective controls 116. In the obesity group they identified 15 heterozygous variants, which caused an impairment of leptin-induced POMC activity, while 4 other variants 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 analyzed the effect of a 1-year lifestyle intervention based on exercise, behavior, and nutritional counselling in pediatric patients with *MC4R* gene variants. Children with pathogenic variants lost weight to a comparable amount as age- and BMI-matched controls without such alterations 117,118 yet they had greater difficulties to maintain the weight loss 117. In contrast, a study in Danish children reports that an intervention program at a tertiary center for one year failed to reduce BMI-SDS in children suffering from MC4R-related obesity 119. Studies on surgical interventions in monogenic obesity are also scarce 120–122. Currently there are no clear statements on safety and efficacy 120, therefore we conclude the surgery is not a primary treatment option. 120.

Single case reports describe the diagnostic odyssey of patients suffering from congenital leptin receptor deficiency and the failure of several therapeutic approaches ranging from weight loss programs, outpatient and inpatient psychotherapy to bariatric surgery, mostly with unsatisfactory success 123,124 These examples once more demonstrate that early genetic diagnostics are required in severe early-onset obesity to avoid frustrating failure of therapy or even potential harmful surgical intervention 124.

**Pharmacological treatment options**

Treatment options for common obesity with long-term effects are very limited 125. There are a number of US Food and Drug Administration (FDA)-approved medications for weight loss in adults 125. Three of them were approved for adolescent obesity, the lipase inhibitor orlistat, the norepinephrine reuptake inhibitor phentermine, and the glucagon-like peptide-1 receptor (GLP-1R) agonist, liraglutide. In Europe, the GLP-1R agonist liraglutide is the only approved (but still not reimbursed) pharmacological treatment option. For more information please see 25,126–129.

In the last 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. Subcutaneous administration of human recombinant leptin at a dose of 0.03 mg per kilogram of lean body weight per day leads to rapid changes in eating behavior, a reduction of food intake, and subsequent loss of fat mass and body weight 66,70 in patients with leptin deficiency. Beneficial metabolic and endocrine effects are also observed, among them improvement of hyperinsulinemia, hyperlipidemia, and liver steatosis as well as onset of puberty 130–132. For example, a decrease in liver fat content can be observed as early as 3 days after onset of therapy 130. After its discovery in 1994, leptin was the big hope for the treatment also of common obesity 133. Unfortunately, exogenous administration of leptin in patients with common, polygenic obesity with elevated circulating levels of the hormone was disappointing as it turned out to have limited efficacy in clinical studies 133,134.

In 2014, the FDA approved Myalept® (metreleptin) as an orphan drug for the treatment of generalized lipodystrophy, a condition characterized by the absence or loss of body fat and, in consequence, very low levels of leptin 135. Comparable to congenital leptin deficiency or dysfunction, these patients show dramatic metabolic improvements under leptin substitution 135. Of note, metreleptin has recently been used to treat patients with anorexia nervosa, an eating disorder characterized by hypoleptinemia 136,137. The short-term off-label approach demonstrated beneficial cognitive, emotional, and behavioral effects.

Side effects of metreleptin treatment include the development of anti-leptin antibodies, which might have a neutralizing effect, and an elevated risk of lymphoma as three patients developed T cell lymphoma during therapy 135. Leptin was shown to exert pro-cancer effects via the activation of pro-proliferative or anti-apoptotic pathways 138. On the other hand, 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 and thereby reducing food intake is a reasonable approach 139,140. However, previous pharmacological attempts failed due to lack of effect or severe, in particular cardiovascular side effects 140.

In 2016, a milestone was reached in the treatment of monogenic obesity with the introduction of a novel MC4r agonist setmelanotide 139. After the first description of POMC deficiency 90, it was speculated that an agonist at the MC4R mimicking the POMC derivative α-MSH would decrease obesity in those patients. A first attempt revealed that treatment with a synthetic MC4R agonist caused hypertension 140. In a phase 2 trial in 2016, Kühnen et al. reported that a new compound targeting the MC4R named setmelanotide exerted beneficial effects in two patients with POMC deficiency, leading to a reduction in hunger and food intake and substantial weight loss, yet without an influence on blood pressure 139. No adverse events were reported. Of note, the skin color and the color of nevi darkened and the hair color changed from red to dark brown 139 due to cross-reactivity of the compound with melanocortin-1 receptor (MC1R). During a period of 46 months there were no malignant skin alterations 141. Regular skin examinations are crucial taking into account that specific variants in MC1R predispose to melanoma 142. 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 was rather subtle and comparable to the weight loss observed in controls with obesity (phase 1b trial, not designed to investigate treatment effects)143. It is at this point questionable if patients with common obesity might benefit from treatment with a MC4R agonist on the long term 143,144. The effect of setmelanotide was superior in POMC deficiency compared to LEPR deficiency. In a phase 3 trial, the majority (80%) of the 10 patients with POMC deficiency and nearly half (45%) of 11 patients with LEPR deficiency lost at least 10% of body weight after approximately 1 year 145. Phase 3 trials including patients with MC4R variants are currently ongoing.

In 2020, setmelanotide received FDA approval for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1, or leptin receptor deficiency 146. The European Agency of Medicines (EMA) approval followed in 2021 for the same age range and indications.

Setmelanotide is currently being evaluated in phase 2 and phase 3 trials (e.g. ENABLE study, EUDRACT 2021-002873-24 and DAYBREAK study, EUDRACT 2021-002855-12) as treatment option in many other genetic defects in the MC4R pathway. It is also evaluated for patients with syndromic (e.g., Bardet-Biedl syndrome 147,148 or Alström syndrome) and hypothalamic (NCT04725240) obesity, as well as chromosomal rearrangement of the 16p11.2 locus, SH2B1, CPE 0r SRC1 variants, heterozygous variants of monogenic obesity, and also in patients with leptin deficiency, who are unresponsive to leptin treatment 146. Beyond these defined monogenic and syndromic traits, patients with obesity secondary to hypothalamic damage due to tumors or trauma may benefit from this treatment options provided the MC4R neurons are intact.

Interestingly, setmelanotide had been used in a patient with partial lipodystrophy who developed neutralizing antibodies under metreleptin treatment 149. A slight decrease in hunger scales was reported, but no other metabolic benefits. This underlines that leptin exerts its beneficial function on metabolism by both, 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 150. An increased MC4R expression was observed in active lesions in multiple sclerosis 150. In vitro, setmelanotide proved robust anti-inflammatory effects 150. Therefore, targeting the MC4R might provide a potential strategy to delay or stop inflammation-associated neurodegeneration.

*GLP-1 agonists*

Based on the success of GLP-1 agonism in common adolescent obesity 151, studies were performed to find out if it might be beneficial in patients with monogenic obesity. Indeed, treatment with liraglutide induced weight loss (fat mass and lean mass) and improvement of metabolic parameters in case reports with pathogenic variants of MC4R 152–154.

**Innovative treatment approaches**

Enormous knowledge has been accumulated about the concerted regulation of glucose homeostasis, hunger and satiety, energy expenditure as well as eating behavior and the respective underlying molecular mechanisms 155.

**Unimolecular polypharmacology**

As most single-hormone targeting approaches for the treatment of obesity revealed a limited efficacy of approximately 5-10 % in terms of body weight reduction it was logical to analyze if the coadministration of compounds would outperform the effect of single drugs. Indeed, several studies in rodent models revealed that combination therapies can achieve metabolic improvements superior to the effect of single hormone therapies (for examples please see 155). 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 GLP-1 and glucagon for the treatment of glucose intolerance and obesity 155,156 . GLP-1 acts as anti-diabetic, but glucagon is known to have acute hyperglycemic effects making the combination not very intuitive. However, glucagon has several additional functions, among them inhibition of lipid synthesis and stimulation of lipolysis, browning in adipose tissue thereby increasing energy expenditure, decrease of food intake. Indeed, a rationally designed dual agonist at the GLP-1 and glucagon receptors normalized both, glucose tolerance and obesity in mice under a high fat diet 156. Since that time a plethora of different combinations of dual and even triple agonists has been designed and some of them are currently evaluated in clinical studies (overview in 155,157). Further approaches combine GLP-1R agonists with endocrine hormones such as estrogen or thyroid hormone, thereby exploiting the beneficial metabolic actions of the hormones targeted in cells of energy regulation by use of the GLP-1R shuttle but avoiding systemic side-effects (reviewed in 158). Patients with pathogenic variants in the leptin-melanocortin pathway downstream of the MC4R or with homozygous (and compound heterozygous) variants in the *MC4R* gene that are not suitable for treatment with setmelanotide, might benefit from these developments. For an excellent summary on recent advances in anti-obesity drug discovery please see 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. Novel approaches for the treatment of common obesity are introduced in Box 4.

Patients with monogenic forms of obesity might benefit from novel induced pluripotent stem cell (iPSC) technologies and CRISPR-mediate gene editing. In 2006, iPSCs were first produced from mouse fetal and adult fibroblasts 160 and the reprogramming of somatic cells into pluripotent cells then rapidly succeeded in human cells 161. Although hampered by the inherent risk factors tumorigenicity and immunogenicity, iPSCs have an enormous clinical potential as reviewed in 162. In the context of obesity, iPSCs are useful as disease models in a dish to study the influence of gene variants in different cell types. For example, hypothalamic-like neurons were generated from iPSCs of patients with extreme obesity (BMI > 50 kg/m²) 163. Capable of neuropeptide secretion and responsive to leptin and ghrelin, they retained the typical disease features and can therefore be used to study the role of certain gene variants, but also gene-environment interactions 163.

The ultimate aim would be to repair defective into functional variants by CRISPR-mediate gene editing. This could be the last resort for patients, who are not suitable for pharmacotherapy and where other treatment approaches failed. Up to now, two strategies are conceivable 164, either delivery of CRISPR-tools into target cells *ex vivo*, e.g. patient-derived iPSCs and subsequent transplantation of engineered cells back into the patient, or *in vivo* editing, where the CRISPR cargos are injected systemically or locally. The latter has been applied in leptin-deficient, extremely obese *ob/ob* mice using an adenoviral CRISPR system injected locally into white adipose tissue 165. Although less than 2% of alleles were repaired the production of leptin and its physiological functions such as inhibition of food intake were restored.

**Outlook**

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 25 but their successful implementation in the general population is questionable. Once obesity has manifested in children and adolescents, it has a high likelihood to persist 3. Hence, we need to identify children at risk for severe and progressive obesity before manifestation. For this, surveillance of individual growth data is pertinent 166. Once an accelerated weight gain is noted, validated polygenic risk scores (PRS) can further help to estimate the obesity risk. Beyond this, with more advanced understanding (and clinical studies) of obesity subphenotypes, PRS can help to tailor the components of classical as well as pharmacological treatment options to the individual patients to obtain utmost effectiveness in weight gain prevention or reduction. Improved recognition of patients with underlying medical causes of obesity such as polygenic, monogenic or syndromal obesity as well as a better access to diagnostic and genetic testing is of utmost importance. Even with current genetic diagnostic technologies, many patients with genetic obesity disorders are probably not identified 80,167 and only a minority of children that would be eligible for diagnostic tests according to current guidelines have actually undergone those tests 168. There is an urgent need for more personalized prevention and treatment strategies. Concepts such as nutritional and exercise genomics or metabolomic evaluations might be useful herein 169,170.

Novel genetic diagnostic advances hold the potential to 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.

**Acknowledgements**

We thank Luisa Sophie Rajcsanyi, MSc, for her help with the figure. AH was funded by Deutsche Forschungsgemeinschaft (DFG; HI 865/2-1), the BMBF (01GS0820, PALGER2017-33: 01DH19010), and the Stiftung Universitätsmedizin Essen. AK was supported by grants from the DFG, KO3512/3-1 and DFG funded Collaborative Research Center “ObesityMechanisms” CRC1052 (No 209933838) and the German Diabetes Association (DDG). PFP received funding from Deutsche Forschungsgemeinschaft (Heisenberg professorship, Projektnummer 398707781).

**Competing interests**

AK provided unpaid advice to Rhythm Pharmaceuticals.

**References**

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).

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. (Lond).* (2021) doi:10.1038/s41366-021-00968-2.

9. Nogueira-de-Almeida, C. A. *et al.* COVID-19 and obesity in childhood and adolescence: a clinical review. *J. Pediatr. (Rio. J).* **96**, 546–558.

10. The Lancet Public Health. Childhood obesity beyond COVID-19. *Lancet Public Heal.* **6**, e534 (2021).

11. Hill, B. *et al.* Weight stigma and obesity‐related policies: A systematic review of the state of the literature. *Obes. Rev.* obr.13333 (2021) doi:10.1111/obr.13333.

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**, 51–4 (1986).

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**, 325–51 (1997).

16. Vlietinck, R. *et al.* Genetic and environmental variation in the birth weight of twins. *Behav. Genet.* **19**, 151–61 (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 (LWW), 2007).

18. Plomin, R., DeFries, J., McClear, G. & Rutter, M. *Behavioral genetics*. (W.H.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**, 345–53 (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**, 1225–31 (2002).

22. Körner, A., Kiess, W. & Vogel, M. Persistence of Obesity from Early Childhood Onward. *N. Engl. J. Med.* **380**, 194–195 (2019).

23. Eichler, E. E. *et al.* Missing heritability and strategies for finding the underlying causes of complex disease. *Nat. Rev. Genet.* **11**, 446–450 (2010).

24. 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).

25. 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).

26. Loos, R. J. F. & Yeo, G. S. H. The genetics of obesity: from discovery to biology. *Nat. Rev. Genet.* **23**, 120–133 (2022).

27. Khera, A. V *et al.* Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood. *Cell* **177**, 587-596.e9 (2019).

28. 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).

29. Poitou, C., Mosbah, H. & Clément, K. Mechanisms in endocrinology update on treatments for patients with genetic obesity. *Eur. J. Endocrinol.* **163**, R149–R166 (2020).

30. Yeo, G. S. H. *et al.* The melanocortin pathway and energy homeostasis: From discovery to obesity therapy. *Mol. Metab.* 101206 (2021) doi:10.1016/j.molmet.2021.101206.

31. Reinehr, T. *et al.* Definable somatic disorders in overweight children and adolescents. *J. Pediatr.* **150**, 618–22, 622.e1–5 (2007).

32. 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).

33. 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).

34. 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).

35. 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).

36. Ling, C. & Rönn, T. Epigenetics in Human Obesity and Type 2 Diabetes. *Cell Metab.* **29**, 1028–1044 (2019).

37. Rohde, K. *et al.* Genetics and epigenetics in obesity. *Metabolism* **92**, 37–50 (2019).

38. Centers for Disease Control and Prevention. CDC Clinical growth Charts. https://www.cdc.gov/growthcharts/clinical\_charts.htm.

39. World Health Organisation. The WHO Child Growth Standards. https://www.who.int/toolkits/child-growth-standards/standards.

40. Qiao, Y. *et al.* Birth weight and childhood obesity: a 12-country study. *Int. J. Obes. Suppl.* **5**, S74–S79 (2015).

41. 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**, 2153–8 (2006).

42. 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).

43. Denzer, C. *et al.* Pubertal development in obese children and adolescents. *Int. J. Obes.* **31**, 1509–1519 (2007).

44. de Groot, C. J. *et al.* Determinants of Advanced Bone Age in Childhood Obesity. *Horm. Res. Paediatr.* **87**, 254–263 (2017).

45. Kempf, E. *et al.* Dynamic alterations in linear growth and endocrine parameters in children with obesity and height reference values. *EClinicalMedicine* **37**, 100977 (2021).

46. Kohlsdorf, K. *et al.* Early childhood BMI trajectories in monogenic obesity due to leptin, leptin receptor, and melanocortin 4 receptor deficiency. *Int. J. Obes.* (2018) doi:10.1038/s41366-018-0049-6.

47. 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).

48. 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).

49. 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**, 127–33 (2012).

50. 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).

51. Farooqi, I. S. & O’Rahilly, S. 20 YEARS OF LEPTIN: Human disorders of leptin action. *J. Endocrinol.* **223**, T63–T70 (2014).

52. Melchior, C. *et al.* Clinical and functional relevance of melanocortin-4 receptor variants in obese German children. *Horm. Res. Paediatr.* **78**, 237–46 (2012).

53. Hinney, A., Volckmar, A.-L. & Knoll, N. Melanocortin-4 Receptor in Energy Homeostasis and Obesity Pathogenesis. in 147–191 (2013). doi:10.1016/B978-0-12-386933-3.00005-4.

54. Farooqi, I. S. Monogenic human obesity syndromes. in 301–310 (2021). doi:10.1016/B978-0-12-820683-6.00022-1.

55. Creemers, J. W. M. *et al.* Heterozygous mutations causing partial prohormone convertase 1 deficiency contribute to human obesity. *Diabetes* **61**, 383–90 (2012).

56. 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**, 347–71 (2016).

57. 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. (Lond).* **40**, 973–81 (2016).

58. 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).

59. Mantzoros, C. S. *et al.* Leptin in human physiology and pathophysiology. *Am. J. Physiol. - Endocrinol. Metab.* **301**, (2011).

60. Park, H.-K. & Ahima, R. S. Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. *Metabolism.* **64**, 24–34 (2015).

61. Wauman, J., Zabeau, L. & Tavernier, J. The leptin receptor complex: Heavier than expected? *Front. Endocrinol. (Lausanne).* **8**, (2017).

62. Antunes, H., Santos, C. & Carvalho, S. Serum leptin levels in overweight children and adolescents. *Br. J. Nutr.* **101**, 1262–1266 (2008).

63. Pan, W. W. & Myers, M. G. Leptin and the maintenance of elevated body weight. *Nat. Rev. Neurosci.* **19**, 95–105 (2018).

64. Funcke, J.-B. *et al.* Monogenic forms of childhood obesity due to mutations in the leptin gene. *Mol. Cell. Pediatr.* **1**, 3 (2014).

65. Montague, C. T. *et al.* Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* **387**, 903–908 (1997).

66. Wabitsch, M. *et al.* Biologically inactive leptin and early-onset extreme obesity. *N. Engl. J. Med.* **372**, (2015).

67. 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**, (2015).

68. Heymsfield, S. B. *et al.* Hyperphagia: Current concepts and future directions proceedings of the 2nd international conference on hyperphagia. *Obesity* **22**, S1–S17 (2014).

69. 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).

70. 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).

71. 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).

72. 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**, (2010).

73. Gruber, T. *et al.* Obesity-associated hyperleptinemia alters the gliovascular interface of the hypothalamus to promote hypertension. *Cell Metab.* **33**, 1155-1170.e10 (2021).

74. Von Schnurbein, J. *et al.* Leptin Is Not Essential for Obesity-Associated Hypertension. *Obes. Facts* **12**, 460–475 (2019).

75. 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).

76. Nillni, E. A. *et al.* Leptin regulates prothyrotropin-releasing hormone biosynthesis: Evidence for direct and indirect pathways. *J. Biol. Chem.* **275**, 36124–36133 (2000).

77. Paz-Filho, G., Delibasi, T., Erol, H. K., Wong, M.-L. & Licinio, J. Congenital leptin deficiency and thyroid function. *Thyroid Res.* **2**, 11 (2009).

78. 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).

79. Clément, K. *et al.* A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* **392**, 398–401 (1998).

80. 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).

81. Nunziata, A. *et al.* Functional and phenotypic characteristics of human leptin receptor mutations. *J. Endocr. Soc.* **3**, 27–41 (2018).

82. 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).

83. Nunziata, A. *et al.* Functional and Phenotypic Characteristics of Human Leptin Receptor Mutations. *J. Endocr. Soc.* **3**, 27–41 (2019).

84. 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).

85. Bochukova, E. G. *et al.* Large, rare chromosomal deletions associated with severe early-onset obesity. *Nature* **463**, 666–670 (2010).

86. Doche, M. E. *et al.* Human SH2B1 mutations are associated with maladaptive behaviors and obesity. *J. Clin. Invest.* **122**, 4732–4736 (2012).

87. 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).

88. Rui, L. SH2B1 regulation of energy balance, body weight, and glucose metabolism. *World J. Diabetes* **5**, 511 (2014).

89. 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. *ESPE Abstr.* (2021).

90. 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).

91. 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).

92. 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).

93. 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).

94. 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).

95. 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).

96. 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).

97. 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).

98. 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).

99. Benzinou, M. *et al.* Common nonsynonymous variants in PCSK1 confer risk of obesity. *Nat. Genet.* **40**, 943–5 (2008).

100. Yeo, G. S. H. *et al.* A frameshift mutation in MC4R associated with dominantly inherited human obesity [1]. *Nat. Genet.* **20**, 111–112 (1998).

101. Vaisse, C., Clement, K., Guy-Grand, B. & Froguel, P. A frameshift mutation in human MC4R is associated with a dominant form of obesity [2]. *Nat. Genet.* **20**, 113–114 (1998).

102. 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).

103. Kühnen, P., Krude, H. & Biebermann, H. Melanocortin-4 Receptor Signalling: Importance for Weight Regulation and Obesity Treatment. *Trends Mol. Med.* **25**, 136–148 (2019).

104. Clément, K. *et al.* MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency. *Nat. Med.* **24**, 551–555 (2018).

105. Dempfle, A. *et al.* Large quantitative effect of melanocortin-4 receptor gene mutations on body mass index. *J. Med. Genet.* **41**, 795–800 (2004).

106. Geller, F. *et al.* Melanocortin-4 Receptor Gene Variant I103 Is Negatively Associated with Obesity. *Am. J. Hum. Genet.* **74**, 572–581 (2004).

107. Lotta, L. A. *et al.* Human Gain-of-Function MC4R Variants Show Signaling Bias and Protect against Obesity. *Cell* **177**, 597-607.e9 (2019).

108. Paisdzior, S. *et al.* Differential Signaling Profiles of MC4R Mutations with Three Different Ligands. *Int. J. Mol. Sci.* **21**, (2020).

109. Smith, J. S., Lefkowitz, R. J. & Rajagopal, S. Biased signalling: From simple switches to allosteric microprocessors. *Nat. Rev. Drug Discov.* **17**, 243–260 (2018).

110. Genomics, H. *et al.* Sequencing of 640,000 exomes identifies GPR75 variants associated with protection from obesity. **8683**, (2021).

111. Mendes de Oliveira, E. *et al.* Obesity-Associated GNAS Mutations and the Melanocortin Pathway. *N. Engl. J. Med.* **385**, 1581–1592 (2021).

112. 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).

113. 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**, 1–13 (2015).

114. 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).

115. York, B. & O’Malley, B. W. Steroid Receptor Coactivator (SRC) family: Masters of systems biology. *J. Biol. Chem.* **285**, 38743–38750 (2010).

116. Yang, Y. *et al.* Steroid receptor coactivator-1 modulates the function of Pomc neurons and energy homeostasis. *Nat. Commun.* **10**, 1–14 (2019).

117. Reinehr, T. *et al.* Lifestyle Intervention in Obese Children With Variations in the Melanocortin 4 Receptor Gene. *Obesity* **17**, 382–389 (2009).

118. 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).

119. Trier, C. *et al.* Obesity treatment effect in Danish children and adolescents carrying Melanocortin-4 Receptor mutations. *Int. J. Obes.* **45**, 66–76 (2021).

120. Vos, N. *et al.* Bariatric Surgery for Monogenic Non-syndromic and Syndromic Obesity Disorders. *Curr. Diab. Rep.* **20**, 44 (2020).

121. 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).

122. 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).

123. Kleinendorst, L., van Haelst, M. M. & van den Akker, E. L. T. Young girl with severe early-onset obesity and hyperphagia. *BMJ Case Rep.* bcr-2017-221067 (2017) doi:10.1136/bcr-2017-221067.

124. 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).

125. Heymsfield, S. B. & Wadden, T. A. Mechanisms, Pathophysiology, and Management of Obesity. *N. Engl. J. Med.* **376**, 254–266 (2017).

126. Cardel, M. I., Jastreboff, A. M. & Kelly, A. S. Treatment of Adolescent Obesity in 2020. *JAMA* **322**, 1707 (2019).

127. 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).

128. Sherafat-Kazemzadeh, R., Yanovski, S. Z. & Yanovski, J. A. Pharmacotherapy for childhood obesity: present and future prospects. *Int. J. Obes.* **37**, 1–15 (2013).

129. Peirson, L. *et al.* Treatment of overweight and obesity in children and youth: a systematic review and meta-analysis. *C. Open* **3**, E35–E46 (2015).

130. 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).

131. 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).

132. 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).

133. 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**, 353–9 (2015).

134. Heymsfield, S. B. *et al.* Recombinant Leptin for Weight Loss in Obese and Lean Adults. *JAMA* **282**, 1568 (1999).

135. Tsoukas, M. A., Farr, O. M. & Mantzoros, C. S. Leptin in congenital and HIV-associated lipodystrophy. *Metabolism.* **64**, 47–59 (2015).

136. 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**, 1–10 (2020).

137. 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* (2021) doi:10.1007/s00787-021-01778-7.

138. de Candia, P. *et al.* The pleiotropic roles of leptin in metabolism, immunity, and cancer. *J. Exp. Med.* **218**, 1–17 (2021).

139. Kühnen, P. *et al.* Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist. *N. Engl. J. Med.* **375**, 240–246 (2016).

140. Greenfield, J. R. *et al.* Modulation of Blood Pressure by Central Melanocortinergic Pathways. *N. Engl. J. Med.* **360**, 44–52 (2009).

141. Kanti, V. *et al.* A Melanocortin-4 Receptor Agonist Induces Skin and Hair Pigmentation in Patients with Monogenic Mutations in the Leptin-Melanocortin Pathway. *Skin Pharmacol. Physiol.* 1–10 (2021) doi:10.1159/000516282.

142. 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.* **Volume 10**, 1143–1154 (2018).

143. Collet, T. H. *et al.* Evaluation of a melanocortin-4 receptor (MC4R) agonist (Setmelanotide) in MC4R deficiency. *Mol. Metab.* **6**, 1321–1329 (2017).

144. Ryan, D. H. Setmelanotide: what does it mean for clinical care of patients with obesity? *Lancet Diabetes Endocrinol.* **8**, 933–935 (2020).

145. 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).

146. Markham, A. Setmelanotide: First Approval. *Drugs* **81**, 397–403 (2021).

147. 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).

148. Argente, J. *et al.* Phase 3 Trial of Setmelanotide in Participants With Bardet-Biedl Syndrome: Placebo-Controlled Results. in *European Society for Paediatric Endocrinology* (2021).

149. 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 Reports* **2020**, 1–9 (2020).

150. 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**, 1–13 (2019).

151. Kelly, A. S. *et al.* A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. *N. Engl. J. Med.* **382**, 2117–2128 (2020).

152. 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).

153. 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 Reports Med.* **1**, 100006 (2020).

154. Welling, M. S. *et al.* Effects of <scp>glucagon‐like</scp> peptide‐1 analogue treatment in genetic obesity: A case series. *Clin. Obes.* **11**, (2021).

155. 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).

156. Day, J. W. *et al.* A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. *Nat. Chem. Biol.* **5**, 749–757 (2009).

157. Clemmensen, C. *et al.* Emerging hormonal-based combination pharmacotherapies for the treatment of metabolic diseases. *Nat. Rev. Endocrinol.* **15**, 90–104 (2019).

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.* (2021) doi:10.1038/s41573-021-00337-8.

160. Takahashi, K. & Yamanaka, S. Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. *Cell* **126**, 663–676 (2006).

161. Takahashi, K. *et al.* Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. *Cell* **131**, 861–872 (2007).

162. Yamanaka, S. Pluripotent Stem Cell-Based Cell Therapy—Promise and Challenges. *Cell Stem Cell* **27**, 523–531 (2020).

163. 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).

164. Uddin, F., Rudin, C. M. & Sen, T. CRISPR Gene Therapy: Applications, Limitations, and Implications for the Future. *Front. Oncol.* **10**, (2020).

165. 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).

166. Keller, E. *et al.* Auxological computer based network for early detection of disorders of growth and weight attainment. *J. Pediatr. Endocrinol. Metab.* **15**, 149–56 (2002).

167. 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).

168. Dayton, K. & Miller, J. Finding treatable genetic obesity: strategies for success. *Curr. Opin. Pediatr.* **30**, 526–531 (2018).

169. Brennan, L. & de Roos, B. Nutrigenomics: lessons learned and future perspectives. *Am. J. Clin. Nutr.* **113**, 503–516 (2021).

170. Bouchard, C. Exercise genomics—a paradigm shift is needed: a commentary: Table 1. *Br. J. Sports Med.* **49**, 1492–1496 (2015).

171. Riveros-McKay, F. *et al.* Genetic architecture of human thinness compared to severe obesity. *PLoS Genet.* **15**, 1–25 (2019).

172. 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).

173. Orthofer, M. *et al.* Identification of ALK in Thinness. *Cell* **181**, 1246-1262.e22 (2020).

174. 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).

175. 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).

176. Hinney, A. & Hebebrand, J. Polygenic obesity in humans. *Obes. Facts* **1**, 35–42 (2008).

177. 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).

178. 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).

179. 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).

180. 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).

181. 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).

182. Dina, C. *et al.* Variation in FTO contributes to childhood obesity and severe adult obesity. *Nat. Genet.* **39**, 724–6 (2007).

183. 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**, 889–94 (2007).

184. 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).

185. Lan, N. *et al.* FTO - A Common Genetic Basis for Obesity and Cancer. *Front. Genet.* **11**, 559138 (2020).

186. Annapoorna, P. K. *et al.* FTO: An Emerging Molecular Player in Neuropsychiatric Diseases. *Neuroscience* **418**, 15–24 (2019).

187. Landgraf, K. *et al.* The Obesity-Susceptibility Gene TMEM18 Promotes Adipogenesis through Activation of PPARG. *Cell Rep.* **33**, (2020).

188. Zuk, P. A. *et al.* Human Adipose Tissue Is a Source of Multipotent Stem Cells. *Mol. Biol. Cell* **13**, 4279–4295 (2002).

189. 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. *Frontiers in Pharmacology* vol. 11 158 (2020).

190. 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).

191. Chouchani, E. T., Kazak, L. & Spiegelman, B. M. New Advances in Adaptive Thermogenesis: UCP1 and Beyond. *Cell Metab.* **29**, 27–37 (2019).

**Boxes**

**Box 1: *Red Flags* indicative for monogenic obesity**

* extreme obesity >3.5 BMI SDS (particularly in patients <5 years)
* rapid weight gain in first 2 years of life
* consanguinity of parents
* hyperphagia (constant food seeking)
* additive features or symptoms (e.g., short stature, red hair, adrenal insufficiency (POMC), hypogonadism (LEP, LEPR), infections (LEP/LEPR), intractable recurrent diarrhea (PCSK1), pituitary insufficiencies e.g. adrenal insufficiencies (POMC, PCSK1), hypothyroidism (LEP, LEPR), hypogonadism (LEP, LEPR), growth hormone deficiency (LEP, LEPR), diabetes insipidus (PCSK1).
* normal weight in parents

**Box 2: Genes associated with thinness and eating disorders**

Interestingly, heritability of thinness is as strong as of obesity. A GWAS of thinness vs extreme obesity identified 10 obesity loci. A novel obesity and BMI-associated locus (*PKHD1*) was also detected171. A previous GWAS on underweight versus extreme obesity identified *FTO* in rather small study groups (below 500 in each group)172. Both studies took advantage of extremes of the BMI range and implied that genetic mechanisms of thinness might help to understand the genetics of body weight regulation. Recently anaplastic lymphoma kinase gene (*ALK*) had been identified as candidate gene for thinness. Although the results were not genome wide significant, studies in drosophila and mice underscored the importance of the gene for weight regulation173. Genetic analyses in obesity can profit from similar analyses in eating disorders. The most recent GWAS for anorexia nervosa identified 8 chromosomal loci, one of which overlaps with a BMI locus174. A cross trait analysis of anorexia and BMI loci revealed three overlapping chromosomal regions175. The identification of genes and underlying biological mechanisms for obesity can greatly profit from the analysis of overlapping phenotypes.

**Box 3: GWAS-identified obesity candidate genes**

Polygenic variants are common at the population level (allele frequencies > 1%). Their effect sizes are small. Nevertheless, multiple risk variants add on to a relevant increase in obesity risk. In individuals with obesity the risk variants are more frequent than in a normal weight population 176. The shared genetic background between childhood and adult BMI is high 172,177. Currently more than one thousand variants have been described 178,179, the total number might well be much higher. The lowest estimated effect sizes are well below 100 grams and even the strongest risk variant in the fat mass and obesity-associated gene *(FTO)* confers an estimated 1.130 gram increase in adult body weight 180.

For obesity to emerge interaction of several of such polygenic variants and their (combined) interaction with environmental factors is necessary. Genome wide association studies (GWAS) are feasible since the advent of high-density single nucleotide polymorphisms (SNP) chips, which led to the identification of a large number of confirmed genes for different complex traits (https://www.ebi.ac.uk/gwas/). GWAS-derived candidate genes are located near genome-wide significant (p≤ 5x10-08) SNPs . It can take a long time from a GWAS-hit to a confirmed, functionally analyzed obesity gene. Innovative approaches that link several molecular traits (*e.g.* genomics, transcriptomics) with environmental exposure and detailed phenotype (phenomics) bear the potential to identify new and causal links 181.

Some genes that were identified in GWAS had previously been described for monogenic forms of obesity (e.g. MC4R, leptin, PCSK1) 178. Many others had not previously been associated with obesity, such as the strongest candidate *FTO* 172,182,183, which is not only associated with obesity but also with cancer 184,185 and neuropsychiatric traits 186. Likewise, for *TMEM18* the biological function is still not completely resolved, although it may have a role in adipose tissue remodeling 187.

**Box 4:** **Innovative cellular therapies for common 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. For clinical use they have mostly been isolated from bone marrow. Multipotent, self-renewing progenitor cells can also be isolated from white adipose tissue (adipose-derived stem/stromal cells, ASC) 188. This presents a huge advantage as adipose tissue is easily accessible and contains significantly higher numbers of progenitors compared to bone marrow. Therefore, ASCs have been extensively studied as a tool in regenerative medicine with clinical studies ongoing in the areas of diabetes, cardiovascular diseases, cancer, inflammatory and neurodegenerative diseases 189. It is, therefore, conceivable that ASCs could be useful in the context of obesity, e.g. to promote tissue remodeling to convert dysfunctional and inflamed obese adipose tissue into functional adipose tissue. Recently, preadipocytes isolated from human adipose tissue and then immortalized were subjected to molecular modification by CRISPR-Cas9 to develop a weight loss strategy 190. Specifically, cells were engineered for high expression of uncoupling protein-1 (UCP1). UCP1 is specifically expressed in brown and beige adipocytes and mediates their thermogenic activity by uncoupling the respiratory chain from ATP production leading to dissipation of energy as heat 191. Thus, beige or brown adipocytes can use up energy and 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 (HUMBLE) cells into mice prevented diet-induced obesity and improved glucose tolerance and insulin sensitivity 190. As ASCs are already intensively studied and used 189, the translation of such approaches into clinical studies seems within reach. New research investigates if transplantation of cells can be circumvented by the injection of their release products, i.e. small extracellular vesicles or exosomes 189.

**Figures**

**Figure 1: Central nervous regulation of body weight via the leptin-melanocortin pathway**

Leptin is produced and secreted from adipocytes in relation to fat mass and exerts its function as satiety factor in the hypothalamic arcuate nucleus. It binds to the leptin receptor present on specific neurons. The Src-homology-2B adaptor protein 1 (SH2B1) is a crucial molecule in leptin-mediated signal transduction. In agouti-related protein (AGRP) expressing neurons, leptin downregulates the expression of the anorexigenic AGRP, which acts as an inverse agonist at the melanocortin 4 receptor (MC4R). In pro-opiomelanocortin (POMC)-expressing neurons leptin induces the expression of the POMC gene. Proproteinconvertase subtilisin/kexin-type 1 (PCSK1) and carboxypeptidase (CPE) catalyze the processing of peptide hormones including alpha-melanocyte stimulating hormone (α-MSH), which serves as an anorexigenic agonist at the MC4R. Pleckstrin homology domain interacting protein (PHIP) serves as an enhancer of POMC transcription, while steroid receptor coactivator-1 (SRC-1) modulates the function of nuclear hormone receptors and transcription factors, both 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 the melanocortin-4 receptor (MC4R) present on neurons in the paraventricular nucleus (PVN), which controls appetite and links the filling state of long-term energy stores to feeding behavior. Melanocortin receptor accessory protein 2 (MRAP2) is an accessory protein of melanocortin receptors and regulates their function. Single-minded homolog 1 (SIM1) is a basic helix-loop-helix transcription factor and required for the development of neurons of the PVN. An agonist at the MC4R (Setmelanotide) is useful to treat monogenic forms of obesity affecting genes upstream of the MC4R and certain genetic variants of the MC4R. All monogenes (see Table 1) that can be treated with either a leptin analog (Metreleptin) or a MC4R –agonist (Setmelanotide) are depicted in bold.