

Mutations in ligands and receptors of the leptin–melanocortin pathway that lead to obesity

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SUMMARY

Obesity is associated with increased morbidity and mortality from cardiovascular disease, diabetes mellitus and certain cancers. The prevalence of obesity is increasing rapidly throughout the world and is now recognized as a major global public-health concern. Although the increased prevalence of obesity is undoubtedly driven by environmental factors, the evidence that inherited factors profoundly influence human fat mass is equally compelling. Twin and adoption studies indicate that up to 70% of the interindividual variance in fat mass is determined by genetic factors. Genetic strategies can, therefore, provide a useful tool with which to dissect the complex (and often heterogeneous) molecular and physiologic mechanisms involved in the regulation of body weight. In this Review, we have focused our attention on monogenic disorders, which primarily result in severe, early-onset obesity. The study of these genetic disorders has provided a framework for our understanding of the mechanisms involved in the regulation of body weight in humans and how these mechanisms are disrupted in obesity. The genes affected in these monogenic disorders all encode ligands and receptors of the highly conserved leptin–melanocortin pathway, which is critical for the regulation of food intake and body weight.

KEYWORDS genetics, leptin, melanocortin, mutation, obesity

REVIEW CRITERIA

We searched PubMed for original articles published between 1997 and 2008 that focused on the leptin–melanocortin pathway. All papers identified were English-language, full-text papers. We also searched the reference lists of identified articles for further papers.

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INTRODUCTION

The evidence for the heritability of body weight is very strong¹ and is comparable to that for height, another phenotype that has strong genetic determinants but whose expression can be modified by environmental factors, such as diet and physical activity. As with other common, complex traits, the genetic determinants of interindividual variation in body fat mass are likely to be multiple and interacting, with each single variant producing only a moderate effect. The genetics of obesity has been hampered for many years by a profusion of studies that have examined candidate genes, most of which have been inadequately powered to generate firm conclusions. In the past 2 years, however, genome-wide association studies involving large cohorts of participants have been undertaken that have proven extremely valuable for unraveling the etiology of complex diseases.

Reports of the first common genetic variant associated with human adiposity were published in 2007.^{2,3} Individuals homozygous for the high-risk allele (AA) of an intronic polymorphism (rs9939609) of the fat mass and obesity associated gene (*FTO*) weigh around 3 kg more than those individuals homozygous for the low-risk allele (TT), whereas heterozygous individuals display an intermediate phenotype.² This finding has since been replicated in multiple studies and the statistical evidence for the association of *FTO* with adiposity is overwhelming, at least in white populations.⁴ Gerken *et al.*⁵ have demonstrated that *FTO* encodes a member of the 2-oxoglutarate-dependent dioxygenase family. Of note, the highest level of *FTO* mRNA expression is detected in the brain and the arcuate nucleus of the hypothalamus, where expression is altered by fasting and feeding.⁵ Although the polymorphisms most associated with obesity are located within an intron of the *FTO* gene, it is still possible that these variants affect the expression of other genes adjacent to the *FTO* locus.⁶ As a consequence, it is not yet conclusively proven whether alteration in the function or concentration of the *FTO* protein is the key determinant

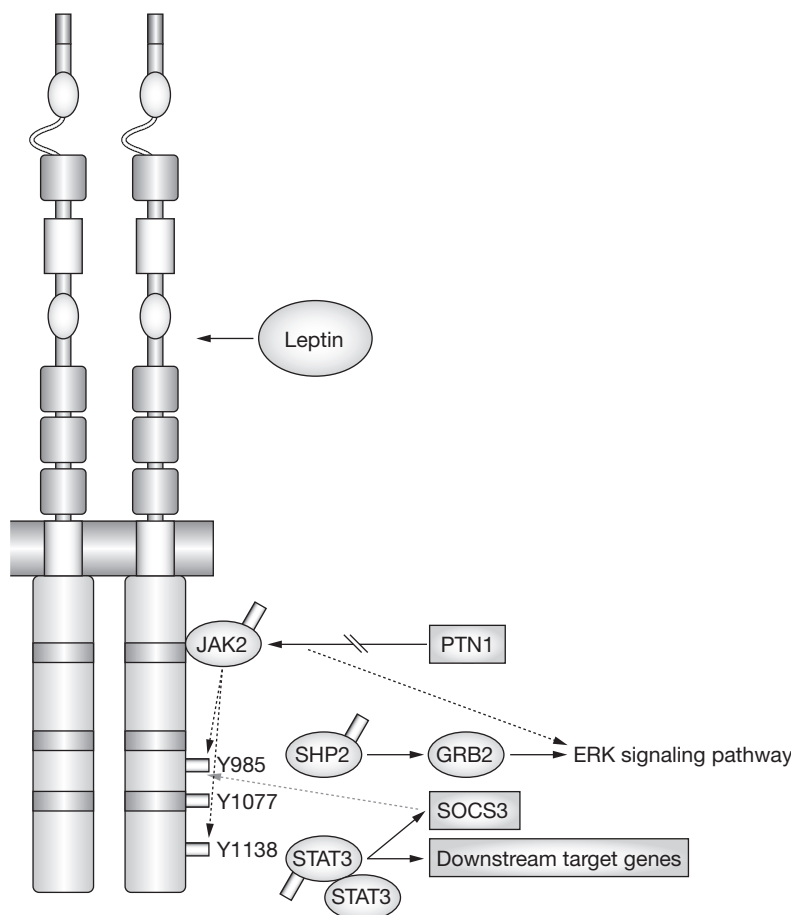


Figure 1 Leptin-induced signal transduction. The unliganded, full-length leptin receptor exists as a preformed homodimer. Leptin binding alters the conformation of the receptor, which enables transphosphorylation of specific tyrosine residues. Activation of intracellular JAK2 results in phosphorylation of the leptin receptor at tyrosine residues 985 and 1138. Phosphorylation of tyrosine 985 leads to activation of the ERK signaling pathway via SHP2 and GRB2. Phosphorylated tyrosine 1138 recruits STAT3, which dimerizes and is translocated to the nucleus, where it activates downstream target genes such as the gene that encodes SOCS3, an inhibitor of leptin signaling. PTN1 is also involved in negative regulation of the leptin receptor by dephosphorylation of JAK2 after internalization of the leptin–leptin receptor complex. Abbreviations: ERK, extracellular signal-regulated kinase; GRB2, growth factor receptor-bound protein 2; JAK2, janus kinase 2; PTN1, tyrosine–protein phosphatase nonreceptor type 1 (also known as protein-tyrosine phosphatase 1B); SHP2, Src homology 2 domain-containing protein tyrosine phosphatase; SOCS3, suppressor of cytokine signaling 3; STAT3, signal transducer and activator of transcription 3; Y, tyrosine.

of body weight. Nonetheless, studies in carefully characterized cohorts, in which detailed measurements of eating behavior and metabolic rate have been performed, suggest that intronic variation in the *FTO* gene influences obesity through effects on the central regulation of food intake⁷ rather than by effects on energy expenditure.⁸

A large number of additional genetic variants and potential candidate genes are likely to

emerge in the near future, when the results of genome-wide association studies are pooled and replicated. Initial results suggest that these data will reveal variants in a number of other genes expressed in the central nervous system.⁹ In this Review, we focus on monogenic disorders, which primarily result in severe, early-onset obesity. The genes affected in these disorders all encode ligands and receptors involved in the highly conserved leptin–melanocortin pathway, which is critical for the regulation of food intake and body weight.

LEPTIN AND LEPTIN RECEPTOR DEFICIENCY Leptin-induced signal transduction pathways

Leptin is a 16-kDa adipocyte-derived hormone¹⁰ whose circulating levels correlate closely with fat mass.¹¹ Prolonged fasting or starvation results in a fall in leptin levels, which triggers a series of changes in energy intake, energy expenditure and neuroendocrine function in order to maintain energy homeostasis.¹² Many of the physiologic effects of leptin are mediated through the central nervous system, particularly in the hypothalamus, which is the site of the highest mRNA expression of the long isoform of the leptin receptor.¹³ This receptor is a member of the interleukin-6-receptor family of class 1 cytokine receptors. Multiple isoforms of the leptin receptor have been described, which result from alternative splicing of the mRNA transcript of the leptin receptor gene (*LEPR*) and/or from post-translational proteolytic processing.¹⁴ The long isoform of the leptin receptor contains intracellular motifs necessary for activation of the JAK (Janus kinase) and STAT (signal transducers and activators of transcription) signal transduction pathway. Binding of leptin to the leptin receptor activates phosphorylation of several tyrosine residues on JAK2. As a consequence, JAK2 phosphorylates tyrosine residues 985 and 1138 on the intracellular tail of the leptin receptor, which in turn leads to downstream signaling events, such as the activation and nuclear translocation of STAT3 (Figure 1).¹⁵

The contribution of the JAK–STAT pathway to energy homeostasis has been addressed directly by studying a ‘knock-in’ mouse model that harbors an amino acid substitution of serine for tyrosine at position 1138 in the STAT3 binding site of the leptin receptor.¹⁶ Mice homozygous for this substitution share many of the features of the leptin-receptor null diabetic (*db/db*) mouse, such as hyperphagia and severe early-onset

obesity; however, they retain relatively normal gonadal function.¹⁶ These findings suggest that the STAT3 signal is important in the regulation of feeding behavior, but is not required for the regulation of the other hypothalamic functions of leptin, such as the control of reproduction and growth.

Leptin–melanocortin pathway

Leptin stimulates *POMC* (pro-opiomelanocortin) and *CARTPT* (cocaine and amphetamine related transcript prepropeptide) gene expression in primary neurons located in the arcuate nucleus of the hypothalamus (Figure 2).¹⁷ *POMC*-derived transcripts undergo extensive post-translational processing to generate a range of smaller, biologically active melanocortin peptides. These peptides are agonists for the melanocortin receptors and mediate the anorectic response.¹⁸ Leptin inhibits orexigenic pathways mediated by neurons that express the melanocortin antagonist, Agouti-related protein, and neuropeptide Y. These first-order, leptin-responsive neurons project to other sites of the hypothalamus that express the melanocortin receptor 4 (MC4R). These signal transduction pathways then interact with other brain centers to coordinate eating behavior, and modulate autonomic responses and other efferent signals to the periphery that regulate intermediary metabolism and energy expenditure. The identification of human mutations in ligands and receptors of the leptin–melanocortin pathway, and the characterization of the associated clinical phenotypes, have provided insights into the role of this signal transduction pathway in the regulation of many biological processes. These processes include food intake, energy expenditure, and lipid and carbohydrate metabolism, as well as reproductive, thyroid and immune function.

Prevalence and mode of inheritance of human leptin mutations

Homozygous frameshift, nonsense and missense mutations of the leptin gene (*LEP*) have been identified in 12 patients to date.^{19–22} These mutations result in an inability to produce the leptin protein, with undetectable levels in the serum of affected individuals. Furthermore, up to 3% of patients with severe obesity have been found to harbor mutations in *LEPR* that are associated with a loss of function in the protein, as measured by an inability to phosphorylate STAT3 *in vitro*.²³ Some of these mutations are homozygous frameshift or nonsense mutations

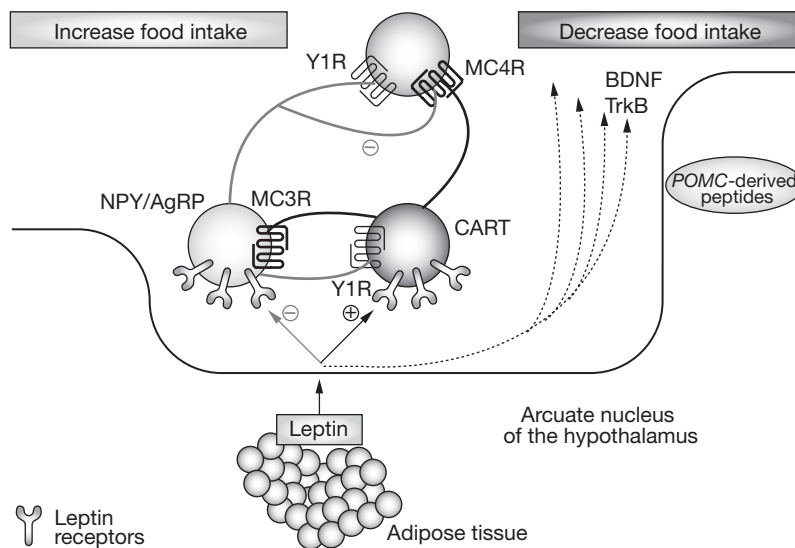


Figure 2 Leptin-induced signaling in the hypothalamus. Leptin is secreted by the adipose tissue and binds to hypothalamic leptin receptors. Leptin binding stimulates the expression of *POMC*-derived peptides and *CART* but inhibits the expression of *NPY* and *AgRP*. Neurons that express *POMC*-derived peptides and *CART* project to other sites of the hypothalamus that express *MC4R* and *Y1R*. Leptin also regulates *BDNF*–*TrkB* signaling through as yet unknown pathways. Abbreviations: *AgRP*, Agouti-related peptide; *BDNF*, brain-derived neurotrophic factor; *CART*, cocaine and amphetamine related transcript; *MC3R*, melanocortin 3 receptor; *MC4R*, melanocortin 4 receptor; *NPY*, neuropeptide Y; *POMC*, pro-opiomelanocortin gene; *TrkB*, tyrosine kinase receptor B; *Y1R*, neuropeptide Y receptor Y1.

that result in the loss of all isoforms of the leptin receptor. In addition, missense mutations that affect the extracellular domain of the leptin receptor have been reported.²³ Heterozygosity for *LEP* or *LEPR* mutations is associated with an increase in body weight.^{23,24} By contrast, development of severe obesity requires the loss of two alleles, either as a result of homozygous mutation or compound heterozygous mutations (i.e. different mutations on both alleles). Serum leptin levels are not disproportionately elevated in patients with leptin-receptor deficiency.²³ Nonetheless, certain mutations that affect regions close to the transmembrane domain of the leptin receptor can result in a truncated extracellular domain that might act as a spurious binding protein, and so result in abnormally elevated leptin levels.²⁵

Clinical phenotype and response to leptin administration

The clinical phenotypes associated with congenital deficiency of either leptin or its receptor are very similar. Individuals with leptin or leptin-receptor

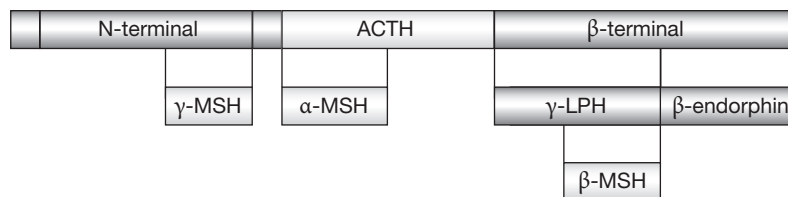


Figure 3 Structure of the pro-opiomelanocortin gene product. *POMC*-derived peptides undergo post-translational cleavage by prohormone convertases to yield the biologically active melanocortin peptides ACTH, α -MSH, β -MSH and γ -MSH. Other peptides produced by enzymatic cleavage include N-terminal peptide, β -LPH, γ -LPH, and β -endorphin. The significance of these peptides is unknown. Abbreviations: ACTH, adrenocorticotrophic hormone; LPH, lipotropin; MSH, melanocyte-stimulating hormone; *POMC*, pro-opiomelanocortin gene.

deficiency are of normal weight at birth but exhibit rapid weight gain in the first few months of life that eventually results in severe obesity. Body composition measurements show that leptin deficiency is characterized by the preferential deposition of fat mass, which results in a distinct clinical appearance, with excessive amounts of subcutaneous fat deposited over the trunk and limbs. Hyperinsulinemia consistent with the severity of obesity is observed, and some adults develop type 2 diabetes mellitus in the third or fourth decade of life. All affected individuals are characterized by intense hyperphagia, with food-seeking behavior and aggressive behavior when food is denied.²⁶ In addition, they display an inability to discriminate between appetizing and bland food items.²⁷ Although there are no detectable changes in the resting metabolic rate or total energy expenditure, abnormalities of sympathetic nerve function have been reported.²²

Leptin and leptin-receptor deficiency are associated with hypothalamic hypothyroidism²⁰ and hypogonadotropic hypogonadism,^{21,28} however, there is some evidence for a delayed, but spontaneous, onset of menses in affected women.²³ Children with leptin or leptin-receptor deficiency have normal linear growth in childhood and normal insulin-like growth factor I levels.²³ Nevertheless, the absence of a pubertal growth spurt leads to a reduction in the final adult height.²³ In addition, children with leptin deficiency have impaired T-cell number and function,²⁹ consistent with high rates of childhood infection and a high reported rate of childhood mortality.^{22,29}

Congenital leptin deficiency can be treated with daily subcutaneous injections of recombinant human leptin, which can correct all the phenotypic abnormalities seen in these patients.^{29,30} Leptin administration reduces food intake and modulates the reward value of

food, a response that is mediated by activation of striatal brain regions, as measured by functional MRI.²⁷ Treatment of children with leptin permits the progression of appropriately timed pubertal development,²⁶ and induces the development of secondary sexual characteristics and pulsatile gonadotropin secretion in adults with leptin deficiency.³⁰

Leptin resistance in common obesity

Most individuals with obesity have elevated circulating leptin levels and are resistant to the effects of exogenous leptin administration, consistent with a form of leptin resistance.³¹ Several potential mechanisms have been postulated to underlie leptin resistance, such as defects of impaired leptin transport across the blood–brain barrier and impaired leptin-receptor signaling.¹⁵ Suppressor of cytokine signaling 3 (SOCS3) is an intracellular protein that binds to JAK2 in a leptin-dependent fashion and inhibits JAK2-mediated autophosphorylation and phosphorylation of the leptin receptor.¹⁵ As a potent inhibitor of leptin signaling, SOCS3 has been implicated in the leptin resistance observed in patients with obesity. In mice, a complete lack of *Socs3* results in embryonic lethality; however, mice that are haploinsufficient for *Socs3*, or with neuron-specific deletion of *Socs3*, are lean and exhibit leptin sensitivity.³² Another molecule that has also been implicated as a negative regulator of leptin–JAK–STAT signaling is tyrosine-protein phosphatase nonreceptor type 1 (PTN1; also known as protein-tyrosine phosphatase 1B). JAK2 has a consensus recognition motif for PTN1 and is dephosphorylated by this enzyme in *in vitro* transfection studies.³³ *Ptn1* knockout mice show increased leptin sensitivity, enhanced STAT3 phosphorylation and weight loss.³⁴ To date, however, the relevance of these pathways to the phenomenon of obesity-associated leptin resistance in humans remains to be explored.

PRO-OPIOMELANOCORTIN DEFICIENCY SYNDROME

Pro-opiomelanocortin-derived transcript processing

POMC-derived transcripts undergo extensive, tissue-specific post-translational processing by proprotein convertases to yield a number of biologically active peptides (Figure 3).¹⁸ Pituitary corticotrophs express proprotein convertase subtilisin/kexin type 1 inhibitor (PCSK1; also known as proSAAS), but not PCSK2, resulting in

the production of N-terminal peptide, joining peptide, adrenocorticotrophic hormone (ACTH) and β -lipotropin.¹⁸ By contrast, expression of PCSK2 within the hypothalamus leads to the production of the melanocortins, α -melanocyte-stimulating hormone (α -MSH), β -MSH and γ -MSH, but not ACTH. The melanocortins mediate their effects through a family of five related G-protein-coupled receptors, two of which, MC3R and MC4R, are highly expressed within the central nervous system.³⁵ Study of genetic defects that impair the synthesis and processing of *POMC*-derived transcripts and the function of receptors for the constituent melanocortin peptides has clearly established that the melanocortin system plays a critical part in energy homeostasis in rodents and humans.³⁶

Of the two centrally expressed melanocortin receptors, MC4R is the most closely linked to energy homeostasis. Humans and mice lacking *MC4R* and *Mc4r*, respectively, are markedly obese and hyperphagic and display increased linear growth and severe hyperinsulinemia from a young age.^{37,38} Mice lacking *Mc3r* have subtle abnormalities of body composition, which occur later in life.³⁹ Although heterozygous loss-of-function *MC3R* mutations have been identified in humans,⁴⁰ the absence of data from control individuals of the relevant ethnic background, and of co-segregation of these mutations in affected families, means that the relevance of *MC3R* mutations is still unclear.

Mode of inheritance and clinical phenotype of pro-opiomelanocortin deficiency syndrome

In 1998, Krude *et al.*⁴¹ provided the first description of humans with congenital deficiency of all *POMC* gene products. Subsequently, four additional European children with congenital *POMC* deficiency syndrome have been reported, who were either homozygous or compound heterozygous for *POMC* mutations.^{41,42} One individual was a compound heterozygote for two nonsense mutations, whereas a second patient was homozygous for a mutation in the 5'-untranslated region of *POMC*, which introduced an additional out-of-frame start site that interfered with translational initiation. Patients with *POMC* deficiency syndrome all presented in early life with features of hypocortisolemia secondary to ACTH deficiency, leading to hypoglycemia, prolonged jaundice, susceptibility to the effects of infection, and (in one case) neonatal death. The children responded well to physiologic replacement with

glucocorticoids but all subsequently developed marked obesity in association with hyperphagia.

Notably, all the children with *POMC* deficiency syndrome reported to date have pale skin and striking red hair, features consistent with the known role of *POMC*-derived peptides in the determination of the pheomelanin to eumelanin ratio in melanocytes.⁴² The pigmentation phenotype was more subtle, however, in a Turkish patient with *POMC* deficiency syndrome who had brown hair with red roots.⁴³ This difference can probably be explained by his genetic background, as the other patients were all white individuals of European ancestry. The retention of dark hair in this child, and in his similarly affected deceased sibling, indicates that the synthesis of eumelanin in humans is not absolutely dependent upon the presence of melanocortin peptides.

Heterozygous mutations in pro-opiomelanocortin-derived melanocortin peptides

The markedly increased prevalence of obesity and overweight in the heterozygous *POMC* mutation carriers provides compelling support for the idea that loss of a single copy of this gene is sufficient to confer a predisposition to obesity.^{42,43} This finding is particularly relevant as we and others have described a variety of heterozygous point mutations in *POMC*, including loss-of-function mutations in α -MSH and β -MSH, which appreciably increase obesity risk but are not always associated with the development of this condition. An amino acid substitution of glycine for arginine at position 236 (Arg236Gly) of the *POMC*-derived transcript disrupts a dibasic cleavage site between β -MSH and β -endorphin, which results in a fusion protein that binds to MC4R but has a reduced ability to activate it.⁴⁴ The presence of this mutation in both individuals with obesity and control individuals without obesity reflects the results of previous studies that suggest Arg236Gly is not a highly penetrant cause of inherited obesity, but might increase the risk of obesity in carriers.⁴⁵ Children with obesity who carry a β -MSH variant, in which tyrosine at position 221 is replaced by a cysteine residue (Tyr221Cys), are hyperphagic and display increased linear growth.⁴⁶ Both of these features are characteristic of MC4R deficiency. These studies, therefore, support a previously unrecognized role for β -MSH in the control of human energy homeostasis.^{46,47}

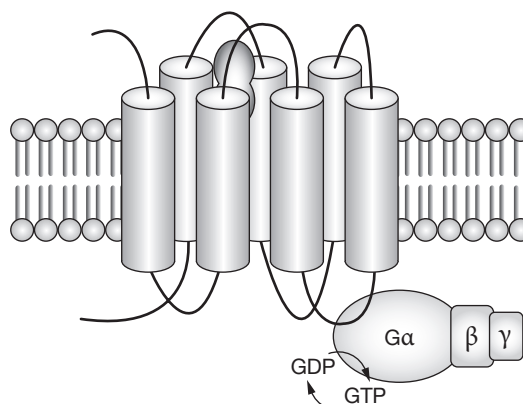


Figure 4 Melanocortin receptor 4 is a seven transmembrane domain G-protein-coupled receptor. Endogenous neuropeptide ligands α -MSH, β -MSH, and γ -MSH bind to a well-defined cavity within the transmembrane domain of MC4R resulting in a conformational change and receptor activation. MC4R is positively coupled to adenylate cyclase via the stimulatory heterotrimeric G proteins (α , β and γ). Abbreviations: MC4R, melanocortin receptor 4; MSH, melanocyte-stimulating hormone.

Proprotein convertase 1 deficiency

Many biologically inactive prohormones and neuropeptides are cleaved by serine endoproteases to release biologically active peptides.¹⁸ PCSK1 and PCSK2 are expressed in neuroendocrine tissues and act upon a range of substrates that include proinsulin, proglucagon and POMC-derived peptides.

Two patients were found to be compound heterozygous, and one was homozygous, for mutations of *PCSK1* that impair catalytic activity and processing of propeptides *in vitro*.^{48–50} A prominent clinical feature of affected individuals is severe, small-intestinal absorptive dysfunction in neonatal life. This symptom is likely to be attributable to impaired processing of propeptides within the enteroendocrine cells and nerves that express PCSK1 throughout the gut, with elevated levels of both progastrin and proglucagon reported.⁴⁸ Postprandial hypoglycemia, which occurs as a result of impaired processing of proinsulin to insulin, is a key clinical feature of PCSK1 deficiency, and provides the basis of a convenient diagnostic test. Elevated plasma levels of proinsulin and 32,33 split proinsulin in the context of low levels of mature insulin are found in patients with PCSK1 deficiency.⁴⁹ Hypogonadotropic

hypogonadism as a result of the impaired processing of preprogonadotropin-releasing hormone contributes to the infertility seen in this disorder, and impaired processing of POMC-derived transcripts contributes to the hyperphagic, severe, early-onset obesity.^{48,50}

MELANOCORTIN 4 RECEPTOR DEFICIENCY

MC4R belongs to the family A superfamily of G-protein-coupled receptors (GPCRs) that includes rhodopsin and the adrenergic receptors. MC4R comprises a hydrophobic core of seven transmembrane-spanning α -helices, three intracellular loops, three extracellular loops, an extracellular amino-terminal domain and an intracellular carboxyl-terminal domain (Figure 4). Neuropeptide ligands bind to the cavity within the transmembrane bundle and so result in a conformational change and receptor activation.⁵¹ MC4R is positively coupled to adenylate cyclase via the stimulatory heterotrimeric G proteins (Figure 4).

Prevalence and mode of inheritance

Mutations in *MC4R* have been reported in up to 6% of patients with severe, early-onset obesity,⁵² and are found at a frequency of approximately 1 in 1,000 in the UK general population,⁵³ making MC4R deficiency one of the most common human monogenic diseases. Although we found a 100% penetrance of early-onset obesity in heterozygous individuals, others have described carriers who were not obese.⁵⁴ Given the large number of potential influences on body weight, it is perhaps not surprising that both genetic and environmental modifiers will have important effects in some pedigrees. Taking account of all these observations, co-dominance—with modulation of expression and penetrance of the phenotype—is the most appropriate mechanism for the mode of inheritance in cases of MC4R deficiency.^{52,55} This finding is supported by the pattern of inheritance of obesity seen in heterozygous and homozygous *Mc4r* knockout mice.³⁸

Clinical phenotype

The clinical features of MC4R deficiency include hyperphagia, which often starts in the first year of life.⁵² In addition to the observed increase in fat mass, patients with MC4R deficiency also have an increase in lean mass and a marked increase in BMD. Affected individuals exhibit accelerated linear growth in early childhood, which does not seem to be caused by dysfunction of the growth hormone axis, and might be a consequence of

the disproportionate early hyperinsulinemia seen in these patients.⁵² The accelerated linear growth and the disproportionate early hyperinsulinemia are consistent with observations in the *Mc4r* knockout mouse.³⁸

Although patients with MC4R deficiency are objectively hyperphagic, *ad libitum* energy intake at a test meal is not as great as is observed with leptin deficiency.⁵² Of particular note is the finding that the severity of receptor dysfunction detected in *in vitro* assays can predict the amount of food ingested at a test meal by a patient harboring that particular mutation.⁵² An elevated respiratory quotient (i.e. the ratio of carbohydrate to fat oxidation) in MC4R deficiency is consistent with the impaired ability to mobilize fat seen in *Mc4r* knockout mice.⁵⁶

Functional characterization of MC4R mutations

Over 100 different *MC4R* mutations have been described. Around 30% are frameshift or nonsense mutations, whereas 70% are missense mutations that impair signaling through cyclic AMP *in vitro*.^{57,58} Approximately 70% of all naturally occurring, disease-causing *MC4R* missense mutations disrupt normal trafficking of the receptor to the cell surface.⁵⁸ Mutations have also been described, however, that do not seem to impair localization to the plasma membrane. These mutations disrupt ligand binding, alter the relative affinity of the receptor for agonists versus antagonists, impair the coupling of ligand binding to downstream signal transduction, or result in constitutive receptor activation (with presumed accelerated downregulation of receptor expression).^{57,58} Importantly, we and others have been unable to demonstrate any evidence for a dominant-negative effect associated with these mutations,⁵⁷ which suggests that *MC4R* mutations are more likely to result in a phenotype through haploinsufficiency.

At the time of writing, there is no specific therapy for MC4R deficiency. Nonetheless, it seems highly likely that affected individuals would respond well to pharmacotherapy that targeted the observed reduction in hypothalamic-melanocortinerig tone. As most patients are heterozygous *MC4R* mutation carriers, with one functional allele still intact, it is possible that in the future small-molecule MC4R agonists might provide excellent treatments for this disorder. The mechanism of GPCR dysfunction is also of potential interest, as pharmacologic

chaperones have been shown to increase the cell-surface expression of mutant GPCRs.

BRAIN-DERIVED NEUROTROPHIC FACTOR AND ITS RECEPTOR TRKB

The neurotrophins are involved in the development and maintenance of neurons, and in mediating synaptic plasticity in the brain and peripheral nervous system.⁵⁹ Evidence has emerged that implicates brain-derived neurotrophic factor (BDNF) and its receptor TrkB (tyrosine kinase receptor B; also known as NTRK2) in the regulation of mammalian eating behavior and energy balance.⁶⁰ Mice that lack one copy of the *Bdnf* gene, or harbor a hypomorphic mutation in the TrkB gene (*Ntrk2*) that results in reduced levels of expression (25% of the normal level), develop increased food intake and severe obesity.⁶¹ We have identified a single patient with a *de novo* mutation in *NTRK2* that was associated with severe hyperphagia and obesity, delayed speech and language development, impaired short-term memory, and loss of nociception.⁶² We have also identified a patient with a comparable obesity and neurobehavioral phenotype who harbors a *de novo* chromosomal inversion that disrupts expression of BDNF.⁶³ These findings provide direct evidence for a role of BDNF in human energy homeostasis, as well as in cognitive function, memory and behavior.

CONCLUSIONS

Monogenic obesity syndromes are comparatively rare. Nonetheless, an improved understanding of the precise nature of the inherited component of severe obesity might help dispel the notion that obesity represents an individual defect in behavior with no biological basis, and so is an important first step in destigmatizing the condition. Investigation of these genes could have practical implications for genetic counseling of affected families and might lead to a successful mechanism-based therapy. Given the rapid pace of genetic and molecular technologies, it is very likely that new genes, proteins and mechanisms will emerge to explain a variety of previously unrecognized obesity syndromes. As more is learnt about these genes, and as more syndromes are described, the need to evaluate patients with severe obesity in recognized centers will grow. Close collaboration with academic centers that have experience in this field will be needed to ensure that advances in the laboratory led to treatments that can be made available to the patients who need them.

The identification and characterization of monogenic obesity syndromes has contributed to our understanding of the pathways responsible for the regulation of body weight in humans. In turn, this knowledge has clarified the relevance of the leptin–melanocortin pathway as a target for pharmacologic intervention in patients with severe obesity. Peptide agonists of the leptin receptor,⁶⁴ β -MSH-derived agonists,⁶⁵ and small molecule and peptide MC4R agonists⁶⁶ are all potential therapies under development. The regulation of food intake and body weight is complex. Many additional molecules and neural circuits are involved,¹⁷ and it will be increasingly important to determine the role of these complex systems in human physiology and pathophysiology.

KEY POINTS

- Leptin regulates eating behavior, T-cell-mediated immunity and the onset of puberty
- Mutations in the pro-opiomelanocortin gene (POMC) cause adrenocorticotrophic hormone deficiency, severe obesity and hypopigmentation
- Melanocortin receptor 4 (MC4R) deficiency is dominantly inherited with variable penetrance and expression
- Genetic disruption of the brain-derived neurotrophic factor gene (BDNF) and the tyrosine kinase receptor B gene (TrkB) causes developmental delay, severe obesity, hyperactivity and impaired memory

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Competing interests

The authors declared no competing interests.