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Lessons from Extreme Human Obesity: Monogenic Disorders

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The prevalence of common obesity in the United States has dramatically increased over the past 30 years [1]. This rise is largely attributed to the increased caloric richness of the common diet and the decreased physical activity in most individuals' lives. However, obesity is a multifactorial disease that is influenced by genetic and environmental factors. An inherited component to body weight accounts for 40% to 70% of an individual's predisposition to obesity [2]. Therefore, weight gain is caused by dietary and lifestyle choices on a background of genetic susceptibility. Most genes that contribute to this predisposition are still unknown, but the discovery and characterization of single gene defects that cause severe human obesity has provided some insight into the hereditary nature of body weight.

As indicated in Box 1, *monogenic obesity* is defined as obesity resulting from a mutation or deficiency of a single gene.

The known monogenic forms of obesity can be divided into three broad categories. The first category is obesity caused by mutations in genes that have a physiologic role in the hypothalamic leptin–melanocortin system of energy balance. Specifically, obesity caused by leptin, leptin receptor, melanocortin-4 receptor (MC4R), proopiomelanocortin (POMC), and prohormone convertase 1/3 (PC1/3) mutations are addressed. Because these disorders are well characterized and extensively reviewed by others [3–5], they are summarized here only to highlight key clinical points.

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Box 1. Useful definitions

Monogenic obesity: obesity explained by mutation in a single gene

Early-onset obesity: not clearly defined in the literature. Generally considered as abnormal weight gain occurring in children less than 10 years of age. In this article, referred to as the onset of rapid weight gain before the age of 2 years.

Common obesity: obesity that is most frequently encountered in the general population and is not associated with any developmental syndromes.

The World Health Organization body mass index classification in adults

Overweight: body mass index (BMI) between 25 and 29.99 kg/m^2

Obese: BMI greater than 30 kg/m^2

Obese class I: BMI between 30 and 34.99 kg/m^2

Obese class II (preferable to the term *severe obesity*): BMI between 35 and 39.99 kg/m^2

Obese class III (preferable to the term *morbid obesity*): BMI greater than 40 kg/m^2

Centers for Disease Control and Prevention body mass index classification in children aged 2 to 20 years

At-risk for overweight: BMI greater than or equal to the 85th percentile on BMI-for-age curves

Overweight: BMI greater than or equal to the 95th percentile on BMI-for-age curves

The term *obese* is not defined in children. However, for the purposes of discussion and recruitment for research studies, a child who has a BMI greater than the 97th percentile on BMI-for-age chart can be considered obese, and one with a BMI greater than the 99th percentile can be considered severely obese.

For most recent CDC BMI percentile curves, go to http://www.cdc.gov/growthcharts.

The second category is obesity resulting from mutations in the three genes necessary for development of the hypothalamus: *SIM1*, *BDNF*, and *NTRK2*. These genes have important roles during hypothalamic development and lead to severe obesity when mutated. These conditions further support the concept that the hypothalamus is critical for energy homeostasis, but the exact mechanisms through which these gene defects lead to obesity are not yet understood.

The third category is obesity presenting as part of a complex syndrome caused by mutations in genes whose functional relationship to obesity is

also unclear. This article focuses on three of these syndromes: Bardet-Biedl (BBS), Alström, and Carpenter's, the origins of which have recently been ascribed to the dysfunction of the primary cilium. Consideration of these syndromes emphasizes the ongoing discovery of new molecular mechanisms underlying the pathogenesis of obesity.

Obesity caused by gene mutations that affect the leptin–melanocortin system

Naturally occurring mutations in mice that cause severe obesity led to the discovery and understanding of a neuronal system that regulates long-term energy homeostasis in mammals [6]. Thereafter, the occurrence in humans of severe obesity-causing mutations affecting the same pathways as in mice has validated that this system of energy balance is conserved across species, and is in fact crucial to the maintenance of body weight in humans. Referred to as the *leptin-melanocortin system*, this specific network of neurons, centered in the hypothalamus, integrates information about peripheral energy stores relayed primarily by the hormone leptin. The effective output is a change in food intake behavior and basal energy expenditure. Fig. 1 briefly summarizes the current understanding of this system as it pertains to this discussion of monogenic obesity. A detailed description of all molecules and pathways implicated in energy balance is beyond the scope of this review [7–10].

Leptin

Severe early-onset obesity, extremely low serum leptin levels, and successful treatment with exogenous leptin distinguish congenital leptin deficiency from all other monogenic causes of obesity. This condition is a rare autosomal recessive disorder resulting from homozygous mutations in the leptin gene. Only 12 individuals in the world have been reported to have congenital leptin deficiency, all homozygous for one of two known mutations [11]. Two cousins from a consanguineous Pakistani family, homozygous for a frameshift mutation (ΔG133) that leads to a truncated, unsecreted leptin molecule, were first reported in 1997 [12]. Since then, three Turkish patients homozygous for a missense mutation (R105Y) [13] and six patients from four unrelated Pakistani families with the ΔG133 mutation have been described [14,15].

All reported patients share the clinical phenotype of severe obesity, hyperphagia, and serum leptin levels that are disproportionately low for their degree of fat mass. These patients are of normal birth weight, but their dramatic weight gain begins in the first 3 months of life and continues so that they weigh more than 20 kg by 1 year of age and more than 50 kg by 5 years of age [12]. Patients who have a leptin deficiency also have impressive adiposity with greater than 50% body fat, whereas normal children have 15% to 25% body fat [12].

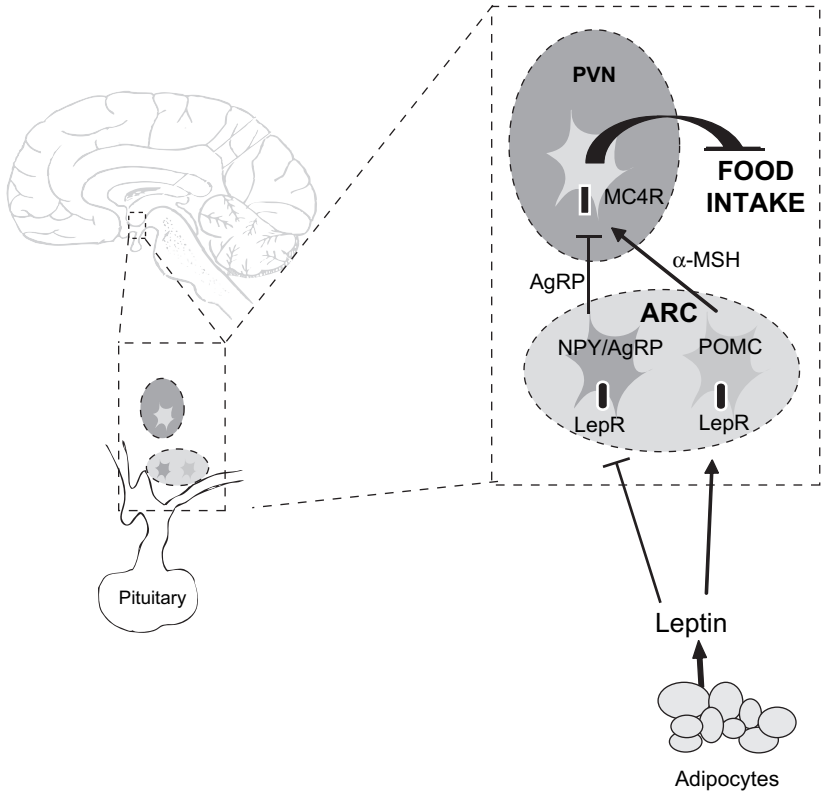

Fig. 1. Leptin–melanocortin system of energy balance. **H**ormones such as leptin convey information about the body's energy stores to the brain. Leptin is secreted by adipocytes in proportion to the body's fat mass. Leptin binds to its receptors on two populations of neurons in the arcuate nucleus of the hypothalamus (ARC): the orexigenic agouti-related peptide (AgRP)/neuropeptide Y -expressing neurons and the anorexigenic POMC-expressing neurons. These groups of neurons have projections to the paraventricular nucleus of the hypothalamus and to other regions of the brain. The paraventricular nucleus of the hypothalamus (PVN) has a dense neuronal population that expresses MC4R. When leptin binds its receptor (LepR) on POMC neurons, α-melanocyte-stimulating hormone (α-MSH), a cleavage product of the POMC transcript, is released. Activation of MC4R in the PVN by α-MSH relays a satiety signal and causes a decrease in food intake. AgRP is an antagonist of MC4R, and competes with α-MSH to bind MC4R. Binding of AgRP to MC4R leads to increased food intake. Leptin activates POMC neurons and inhibits AgRP neurons. Therefore, by activating its receptors on these two neuronal populations, leptin acts in a concerted way to increase MC4R activation by α-MSH and decrease its antagonism by AgRP, to cause a decrease in food intake. Mutations in genes with critical roles in the Leptin–melanocortin system cause early-onset and severe obesity. Autosomal recessive mutations in leptin, LepR, POMC and PC1/3, and autosomal dominant MC4R mutations have been described.

Aside from their striking weight phenotype, these patients come to clinical attention for their lack of pubertal development [13–15]. The absent or delayed puberty results from hypogonadotropic hypogonadism and highlights leptin's importance in the onset of puberty [16]. Abnormal T-cell number and function, which may present as frequent respiratory infections [17], also occurs in congenital leptin deficiency and is explained by leptin's role in proliferation of CD4+ T cells and release of cytokines from T-helper-1 cells. Additionally, leptin regulates prohormone convertase 1/3 (PC1/3), which is necessary for the synthesis of thyrotropin-releasing hormone (TRH) and growth hormone–releasing hormone (GHRH). This role may explain the thyroid and growth hormone dysfunction reported in some of these patients [18]. Because congenital leptin deficiency is so rare, extensive laboratory evaluation to uncover the hormonal and immunologic deficiencies associated with it can only be recommended if the degree of obesity and clinical presentation suggest this disorder.

Daily subcutaneous administration of recombinant human leptin to children who have congenital leptin deficiency results in dramatic weight loss, reduction in fat mass, resumed pubertal progression, and improved thyroid and immune function [14,15]. However, this is an exceptionally rare but remarkable example of effective treatment of obesity arising from an understanding of its physiologic basis. Furthermore, no similar benefit is seen from giving supraphysiologic doses of leptin to obese patients who are not leptin deficient [19]. Thus, congenital leptin deficiency is unique because it can be diagnosed based on a serum leptin level that is extremely low for the patient's fat mass, and daily administration of leptin can successfully treat the disorder.

However, direct sequencing of the leptin gene is still the mainstay of diagnosis because a mutation could arise that does not affect synthesis or secretion of leptin but impairs receptor binding or other downstream function. If a mutation such as this were to occur, the patient would have the clinical phenotype, but a serum leptin level that, similar to other forms of obesity, is proportional to the patient's fat mass rather than diagnostically low.

Leptin receptor

The first report of leptin receptor deficiency was that of a homozygous mutation in three sisters from a consanguineous Algerian family [20]. Much like the patients who had congenital leptin deficiency, these three patients who had no functional leptin receptor had severe, early-onset obesity. They had normal birth weight, rapid weight gain starting before 6 months of age, and weights greater than 15 kg at 1 year of age. When evaluated during adolescence, their BMIs were 50 to 70 kg/m^2, their body fat was greater than 65%, and they lacked pubertal changes because of hypogonadotropic hypogonadism. Impaired growth hormone and thyrotropin secretion were subtle findings only evident through dynamic testing [20].

Recently, eight more individuals who had homozygous or compound heterozygous leptin receptor mutations were identified in a highly consanguineous cohort of severely obese and hyperphagic patients. Functional studies of these mutant receptors showed complete or partial loss of receptor signaling in response to leptin [11]. The clinical features of severe obesity, hypogonadotropic hypogonadism, and impaired immune function were consistent with previous reports by Clement and colleagues [20], and as expected, leptin levels were elevated proportional to fat mass.

Leptin and leptin receptor deficiencies are extraordinarily uncommon. The obesity resulting from these conditions is incomparable in severity and associated with hypogonadism. If encountered in the clinical setting, a serum leptin level can help differentiate between the conditions. Although with leptin deficiency the leptin levels are typically low, serum leptin in leptin receptor deficiency reflects BMI and fat mass, as in common obesity and all other forms of monogenic obesity. The fact that serum leptin levels in leptin receptor deficiency are not any higher than would be predicted by the degree of obesity emphasizes an important point. It shows that leptin synthesis occurs normally independent of a functional leptin receptor. Therefore, no feedback occurs from leptin receptor signaling on the secretion of leptin from adipocytes [21].

Proopiomelanocortin

POMC is the precursor to five biologically active proteins made in the anterior pituitary or hypothalamus and skin. POMC has a prominent role in the leptin–melanocortin system in that *POMC*-expressing neurons are targets of leptin signaling, and α–melanocyte-stimulating hormone (α-MSH) is the POMC cleavage product that activates MC4R. PC1/3 and PC2 are necessary for the proteolytic cleavage of POMC to each of the active peptides (see Fig. 1; Fig. 2).

The unique feature of complete POMC deficiency is that patients present in the newborn period with adrenal insufficiency. Their profound hypocortisolism is caused by lack of the POMC substrate for adrenocorticotropic hormone (ACTH) synthesis in the anterior pituitary. Similar to patients who have panhypopituitarism, ongoing glucocorticoid replacement is required to prevent adrenal crises. The second salient feature of complete POMC deficiency that subsequently presents is the hyperphagia and severe obesity resulting from lack of MC4R activation by α-MSH. These patients have normal birth weight, onset of rapid weight gain before 6 months of age, and weights exceeding 15 kg by 1 year and 25 kg by 3 years.

The first two patients who had complete POMC deficiency were described in 1998. One patient was compound heterozygous for two nonsense mutations, and the other was homozygous for a base pair substitution that disrupted translation of the entire POMC protein [22]. Three more patients who had homozygous or compound heterozygous *POMC* mutations causing congenital POMC deficiency were described in 2003 [23]. The sixth

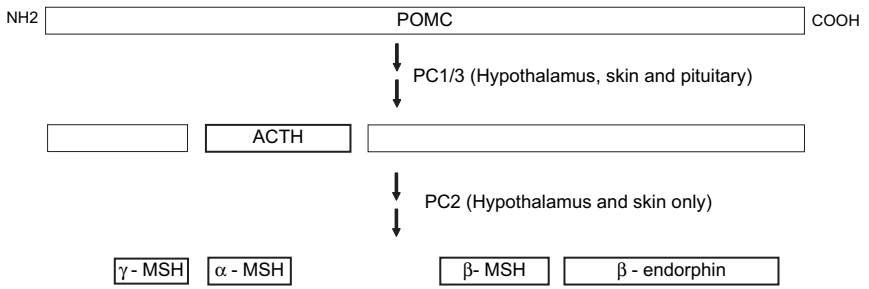

Fig. 2. Processing of POMC. POMC is processed by PC1/3 and PC2 into five biologically active proteins. In the corticotropes of the anterior pituitary, PC1/3 is expressed, but PC2 is not. Therefore, adrenocorticotropic hormone (ACTH) is the only biologically active POMC-derived peptide synthesized in the anterior pituitary. PC1/3 and PC2 are expressed in the melanotropes of the hypothalamus and skin. Thus, POMC is sequentially processed into α-, β-, and γ-MSH and β-endorphin in these tissues. The phenotype of POMC deficiency is explained by the tissue-specific lack of these cleavage products.

case was reported in a Turkish patient who had a homozygous frameshift loss of function mutation with severe obesity and ACTH deficiency, but dark hair [24]. Red hair, because of lack of α-MSH activating MC1R in melanocytes, was initially reported as part of the clinical spectrum of congenital POMC deficiency. However, this finding is not essential for diagnosis, because the Turkish patient who had complete POMC deficiency, and possibly his deceased similarly affected brother, had dark hair [24].

Prohormone convertase 1/3

PCs are a family of serine endoproteases that cleave inactive hormone precursors into biologically active secreted peptides. Of the seven proteins in this family, only PC1/3 and PC2 are selectively expressed in neuroendocrine tissues and involved in the regulated secretory pathway of hormone biosynthesis [25]. Substrates for PC1/3 and PC2 include proTRH, proinsulin, proglucagon, proGHRH, POMC, pro–neuropeptide Y, and pro–cocaine-amphetamine–related transcript [18]. Thus, PC1/3 and PC2 are required for proper synthesis of many peptides involved in energy homeostasis. Moreover, the catalytic activities of PC1/3 and PC2 are tissue-specific, as seen in the example of POMC being processed differentially to ACTH in the pituitary, and α-, β-, and γ-MSH in the hypothalamus (see Fig. 2). Another example of the tissue-specificity of PC1/3 and PC2 is the cleavage of proglucagon to glucagon in the pancreatic α-cell, and to GLP-2 in the intestinal L cell.

Three cases of *PC1/3* mutations that cause severe obesity have been reported [26–29]. All three patients had hyperphagia and early-onset obesity believed to result from improper processing of POMC to α-MSH in hypothalamic neurons. Two of the patients had reported weights of more than 35 kg at

3 years of age. These patients also had mild hypocortisolism caused by partial ACTH deficiency that was not as severe as in the patients who had complete POMC deficiency. All three patients also had malabsorption caused by small bowel dysfunction, although with considerably variable severity. Improper processing of proglucagon in the intestinal cells to GLP-2, which has trophic effects on small bowel epithelium, may contribute to poor integrity of the small bowel mucosa in these patients. Abnormalities of glucose homeostasis, namely postprandial hyperglycemia and subsequent reactive hypoglycemia, were noted in two of the three patients. This effect reflects abnormal processing of proinsulin to insulin in pancreatic β-cells [26,27]. Other findings, such as hypogonadotropic hypogonadism in one patient and central hypothyroidism in another, may be attributed to impaired proTRH and proGHRH processing by PC1/3.

These patients came to clinical attention because of reactive hypoglycemia in one case and intractable neonatal diarrhea in the other two, rather than because of severe obesity. Only three cases of PC1/3 deficiency are known, the variability in their clinical phenotype is considerable, and obesity is not the distinguishing feature. Therefore, heterozygous *PC1/3* mutations are currently extremely rare in the differential diagnosis of monogenic obesity. A better understanding of the various roles of PC1/3 in different tissues would improve the ability to clinically detect subtle deficiencies in its function. Currently, measuring proinsulin and insulin levels after a glucose load to show a high proinsulin-to-insulin ratio is the only laboratory evaluation available to determine PC1/3 deficiency.

Melanocortin-4 receptor

In 1998, two groups simultaneously reported the first two cases of severe obesity and hyperphagia caused by *MC4R* mutations [30,31]. Since then, MC4R has emerged as the most specialized and crucial molecule for body weight regulation in the leptin–melanocortin system. First, *MC4R* mutations are inherited in an autosomal dominant fashion, with marked obesity resulting from only one affected allele. Second, aside from severe obesity and hyperphagia, MC4R deficiency has no other physical, hormonal, or developmental consequence, making the function of this receptor very specific for energy balance. And third, mutations in *MC4R* are the most common cause of monogenic obesity known. Compared with the autosomal recessive mutations in genes for leptin, leptin receptor, POMC, and PC1/3 that together total only 32 reported cases of severe obesity in the world, the global prevalence of *MC4R* mutations is approximately 2.5% in severely obese individuals [32–35]. In a large cohort of obese patients and nonobese controls, Lubrano-Berthelier and colleagues [36] recently confirmed that the prevalence of heterozygous, obesity-causing *MC4R* mutations was 2.6% (2.83% in children who had early-onset obesity and 2.35% in adults who had later-onset obesity).

MC4R mutations segregate with obesity in the families of the probands, and are dominantly inherited with variable penetrance and expressivity. Therefore, the obesity phenotype of heterozygous *MC4R* mutation carriers can range from severely obese to lean. Functional studies of obesity-associated *MC4R* mutations show that more severely impaired receptor function in vitro correlates with earlier age of obesity onset and higher BMI. The in vitro studies also show that each mutation impairs receptor function differently through affecting membrane expression, response to agonist, and constitutive activity to a variable degree [36]. The obesity phenotype of *MC4R* mutations is therefore determined not only through variable penetrance and expressivity but also through allelic heterogeneity that contributes to different pathogenic mechanisms. Although no effective therapy for obesity caused by *MC4R* mutations currently exists, hope exists that ongoing research will provide a better understanding of the mechanisms through which *MC4R* mutations cause obesity and will lead to successful treatment options.

Heterozygous carriers of leptin, leptin receptor, and proopiomelanocortin mutations

Most obesity-causing *MC4R* mutations are heterozygous and dominantly inherited. Fewer than 10 cases of homozygous or compound heterozygous *MC4R* mutations have been reported [33,37,38]. These individuals, lacking both alleles of *MC4R*, are significantly more obese than the heterozygotes, and are comparable to patients who have leptin, leptin receptor, and POMC deficiency.

Some evidence exists that an intermediate-weight phenotype may exist for heterozygous carriers of mutations in genes for leptin, leptin receptor, and POMC, implicating these genes in the susceptibility to common obesity. Farooqi and colleagues [39] evaluated 13 heterozygous carriers of the leptin ΔG133 mutation and found that serum leptin levels were significantly lower, whereas BMI and body fat mass were significantly higher in the heterozygotes than in controls. However, interindividual variability in leptin measurements and the small sample-size make these results difficult to interpret. Heterozygous carriers of leptin receptor mutations were not severely obese, but had increased fat mass to the same extent as heterozygote leptin mutation carriers [11].

Significantly higher BMIs were reported in the heterozygous relatives of a patient with POMC deficiency [24], and screening cohorts of severely obese patients has shown heterozygous mutations in *POMC* that do not occur in controls [40–42]. These heterozygous *POMC* mutations segregate with obesity in the probands' families and cause hyperphagia and obesity without any other clinical manifestations, such as adrenal insufficiency. Thus, like heterozygous *MC4R* mutations, heterozygous *POMC* mutations may be a more common cause of monogenic obesity. The heterozygous

carriers of *PC1/3* mutations do not have an obvious phenotype, which is not surprising given the overlap of substrate specificity and functional redundancy between PC1/3 and PC2.

Obesity caused by gene mutations that affect neurodevelopment

Three genes, *SIM1*, *BDNF*, and *NTRK2* have been shown through mouse models to be important in hypothalamic development. Recently, mutations in these genes have also been implicated in the development of obesity in mice and humans. The mechanisms through which these genes regulate body weight are unknown. Abnormal development of the hypothalamus, postnatal impairment of the function of these genes, or both may be responsible for the obesity phenotype.

SIM1

In 2000, Holder and colleagues [43] described a girl who had early-onset, severe obesity, hyperphagia, increased linear growth, and normal energy expenditure. Her rapid weight gain began at 3 months of age, so that she was almost 20 kg by 2 years of age and more than 40 kg by 5 years. Her obesity was not associated with any developmental abnormalities, syndromic features, or endocrine dysfunction. This patient had a de novo translocation that disrupted one of her *SIM1* alleles on chromosome 6q [43].

Mice missing one copy of *Sim1* have the same phenotype as the patient, early-onset obesity with hyperphagia, normal energy expenditure, and increased linear growth, and also have a decrease in the total number of paraventricular nucleus (PVN) neurons [44,45]. Because the PVN is the location of *MC4R*-expressing neurons that are critical for energy balance, abnormal development of the PVN is hypothesized to cause obesity in *Sim1* heterozygous mice and *SIM1* haploinsufficient patients.

More recent evidence shows that SIM1 may have an ongoing, postdevelopmental role in energy balance, and specifically that it may function downstream of MC4R to control food intake [46–48]. However, the molecular pathways downstream of MC4R that regulate food intake are far from understood, and further studies are necessary to determine the exact role of SIM1 in these pathways.

Additional evidence for the role of SIM1 in the development of obesity is provided by patients who are obese because of interstitial deletions of chromosome 6q that involve the *SIM1* locus (6q16.2) [49–51], and from significant linkage of childhood obesity related traits to the chromosomal region (6q22.31-q23.2) that contains *SIM1* [52].

Therefore, haploinsufficiency of *SIM1* has been shown to relate to severe, early-onset obesity in one patient who has the translocation, and implicated in the cause of obesity in patients who have interstitial deletions of chromosome 6 that include the *SIM1* locus.

Finally, rare point mutations in *SIM1* were also shown to be significantly associated with obesity in a large screen of obese patients and matched controls [53]. The extent of this association between rare *SIM1* mutations and obesity was comparable only to that between *MC4R* mutations and obesity in this study. In vitro studies of these *SIM1* mutations are needed to determine the functional significance and confirm the role of these rare mutations in the development of obesity.

Brain-derived neurotrophic factor and tropomyosin-related kinase B

BDNF (brain-derived neurotrophic factor) and its receptor TRKB (tropomyosin-related kinase B) regulate proliferation, survival, and differentiation of neurons during development, and neuronal plasticity in the adult nervous system [54–56]. Specific to energy balance, BDNF and TRKB modulate the development and postnatal plasticity of hypothalamic neurons, but both have also been shown to be important for memory, behavior, and cognitive development [30,55,56]. Partial deficiency of Bdnf and TrkB in mouse models causes hyperphagia and obesity [57–59]. Bdnf decreases food intake in mice [58,60,61], likely through acting downstream of Mc4r [57].

The first human case of severe obesity caused by haploinsufficiency of *BDNF* was reported last year [62]. The patient was an 8-year-old girl who presented with hyperphagia and obesity. Her weight exceeded 20 kg at 2 years of age. She also had impaired cognition, memory, and nociception, and hyperactivity. The patient had a de novo paracentric inversion on chromosome 11 that included the *BDNF* locus. Although the inversion may disrupt other unknown genes contributing to the patient's phenotype, the marked similarity of this patient's presentation to that of a patient who had a mutation in *NTRK2*, the gene that encodes TRKB (see below), supports the hypothesis that her phenotype results from haploinsufficiency of *BDNF* [62]. As in *SIM1* haploinsufficiency, this patient's obesity may result from a lack of BDNF during hypothalamic development, or from its impaired postnatal role in MC4R signaling and control of food intake.

One human case of a heterozygous de novo mutation in *NTRK2* has been reported [63]. The 8-year-old boy presented with hyperphagia and early-onset obesity of a similar magnitude to the patient who had *BDNF* haploinsufficiency. He also had developmental delays, stereotyped behaviors, and impairment in memory, learning, and nociception. Functional studies of his missense mutation showed significantly decreased BDNF-induced receptor autophosphorylation and activation of downstream signaling molecules [63,64]. The authors also found reduced neurite outgrowth and cell survival in response to BDNF in cells transfected with the mutant receptor [64], suggesting that postdevelopmental neuronal plasticity is also affected by *NTRK2* mutations.

Screening of a cohort of individuals who had severe, early-onset obesity, and developmental delay showed three other rare mutations in *NTRK2*

(I98V, P660L and T821A) that were not present in controls, but in vitro studies of these mutations did not show a significant difference in receptor function compared with wild-type [64].

Although the exact role of SIM1, BDNF, and TRKB in the development of obesity has not been clearly delineated, their involvement in hypothalamic development and their postnatal function possibly downstream of MC4R is suggested by evidence from mouse models.

Obesity associated with a pleiotropic developmental syndrome

Several pleiotropic syndromes exist with obesity as a predominant phenotype in association with findings such as mental retardation, congenital organ defects, limb or facial dysmorphisms, and endocrine dysfunction. Prader-Willi syndrome is the most common, characterized by neonatal hypotonia and failure to thrive, and subsequent obesity caused by intense hyperphagia, along with developmental delay, mental retardation, hypogonadism, and small hands and feet. The genetic basis of these syndromes is complex. Although the genes or chromosomal regions implicated in the origin of many of these syndromes are known, their relationship to the development of obesity is unclear. Many monogenic obesity-associated syndromes have been reviewed elsewhere [5,65,66], and therefore are not addressed. Instead, this article focuses on three syndromes with multiple phenotypic similarities in addition to obesity, for which pathogenesis was recently linked to dysfunction of the primary cilium.

The primary cilium is an organelle extending from almost all eukaryotic cells. Its architecture differs from that of the more common motile cilium in that its axoneme is made up of 9 microtubule doublets only (9 + 0), without the additional central doublet present in motile cilia (9 + 2) [67]. Primary cilia are attached to the cell at the basal body and are important for chemo- and mechanosensation of the environment and transduction of intracellular signaling. Many important signaling pathways, such as hedgehog signaling and the Wnt pathway, localize to the primary cilium [68]. Because protein synthesis does not occur in cilia, a mechanism called *intraflagellar transport* (IFT) is required to carry proteins necessary for ciliary maintenance and function into and out of the cilia [67].

Bardet-Biedl syndrome

BBS is characterized by clinical findings of retinal degeneration, postaxial polydactyly, obesity, and structural or functional defects of the kidney. Other associated findings include anosmia, mental retardation, hepatic fibrosis, male hypogonadism or undescended testes, female urogenital tract abnormalities, type 2 diabetes mellitus, hypertension, cardiac abnormalities, Hirschsprung's disease, situs inversus, and predisposition to malignancies [69–71]. Obesity in patients who have BBS ranges from mild to severe,

and is reversible with caloric restriction and exercise. Rapid weight gain in the first year of life is associated with hyperphagia. No difference in resting metabolic rates have been observed between patients who have BBS and matched obese controls, but lower levels of spontaneous physical activity in patients who have BBS have been reported [72].

BBS is rare and genetically heterogeneous. Mutations in 12 genes, *BBS1–12*, have been identified that contribute to the development of the phenotype [73]. The functions of these genes are not well delineated but are somehow linked to the primary cilium [74].

Nachury and colleagues [73] recently showed that 7 of the 12 BBS-causing genes encode highly conserved proteins that are necessary for primary cilia function. These proteins form a complex, called the *BBSome*, and associate with another factor, Rab8GTP, to facilitate transport of proteins to the primary cilium.

Despite exciting advances in the understanding of BBS pathogenesis and its relationship to ciliary function, the origin of obesity associated with this syndrome is still largely unclear. Dysfunction of cilia in specific neurons could explain obesity caused by hyperphagia and impaired satiety, because Davenport and colleagues [75] showed that deletion of cilia from neurons throughout the central nervous system, and specifically from POMC-expressing neurons, causes obesity in mice. This finding is the first evidence that even a novel mechanism of pathogenesis such as primary ciliary dysfunction may relate to the hypothalamic regulation of food intake in causing obesity. However, this evidence is preliminary and further research is needed. Although it is well established that hypothalamic POMC neurons are critical for signaling satiety, how disruption of ciliary function in these neurons affects their role in energy balance is not.

Alström syndrome

Alström syndrome is another rare syndrome that shares many pleiotropic clinical findings with BBS, namely retinal degeneration, early-onset obesity, type 2 diabetes mellitus, and perceptive hearing loss. It is an autosomal recessive disorder caused by mutations in the *ALMS1* gene. It is also associated with cardiomyopathy, liver and kidney dysfunction, and delayed puberty. The pathogenesis of Alström syndrome has also been linked to dysfunction of the primary cilium, in that the ALMS1 protein localizes to the centrosome and ciliary basal body, and likely has a role in the formation or maintenance of primary cilia. Li and colleagues [76] show that ALMS1 has an important role in cilia formation in kidney cells. Human mutations in *ALMS1* known to cause Alström syndrome result in truncated ALMS1 proteins. These truncated proteins are able to support normal cilia formation but may cause a subtle and undetermined alteration in ciliary function that leads to the development of the Alström phenotype. Residual function of mutant ALMS1 in Alström syndrome explains the lack of a more severe developmental phenotype.

Carpenter's syndrome

Carpenter's syndrome is a pleiotropic disorder with the following features: craniosynostosis affecting primarily metopic and sagittal sutures, polydactyly, soft-tissue syndactyly, and obesity. Other associated findings include brachydactyly, molar agenesis, genu valgum, hypogenitalism, congenital heart defects, umbilical hernia, and learning disability. The disorder has an autosomal recessive inheritance and was recently described to be caused by a homozygous nonsense mutation *L145X* in *RAB23* in five affected individuals from three families [77]. Evaluation of additional patients who had Carpenter's syndrome identified four other mutations in *RAB23*. Similar nonsense mutations in the mouse *Rab23* gene lead to a far more severe phenotype of neural tube defect, causing exencephaly and embryonic lethality.

Rab23 is from Rab family of small GTPases that regulate intracellular trafficking of membrane-associated proteins. Rab23 negatively regulates the Sonic hedgehog signaling pathway [78–81]. Yoshimura and colleagues [82] recently showed that Rab23 is one of three Rab GTPases (Rab8a, Rab17, and Rab23) involved in the formation of the primary cilium.

The phenotype of Carpenter's syndrome shares findings of limb deformities (polysyndactyly and brachydactyly) with other syndromes that result from impaired hedgehog signaling. However, findings of craniosynostosis and obesity have not been previously associated with the hedgehog pathway. Given the evidence that obesity in BBS and Alström syndrome is associated with dysfunction of the primary cilium, and given that hedgehog signaling occurs on the primary cilium in many cell types, it is possible to implicate ciliary dysfunction that disrupts hedgehog signaling in the pathogenesis of Carpenter's syndrome.

Summary

Several lessons can be gleaned from the study of extreme human obesity. First, the long-term regulation of body weight in humans is centered in the hypothalamus. Within the hypothalamus, the leptin–melanocortin system is critical for energy balance, because disruption of these pathways that sense peripheral energy stores and signal satiety leads to the most severe forms of human obesity. Furthermore, MC4R is the most specialized molecule for body weight maintenance within this system because MC4R deficiency has no other clinical phenotype.

Second, the monogenic causes of obesity identified thus far account for less than 5% of severe obesity, and are in themselves very heterogeneous. BBS, for example, can result from alterations in at least 12 different genes, and obesity caused by *MC4R* mutations can result from different mechanisms that affect receptor function. Furthermore, novel mechanisms are emerging as important for pathogenicity of obesity, such as abnormal

hypothalamic development, alterations in neuronal plasticity, and dysfunction of the primary cilium. Therefore, the currently characterized monogenic forms of obesity can be viewed as the "tip of the iceberg," providing clues that the pathogenic mechanisms underlying common obesity is equally heterogeneous.

Third, treatment of congenital leptin deficiency with leptin is a rare but powerful example of successful therapy arising from an understanding of the molecular pathogenesis. Thus, further research to understand the pathogenic mechanisms underlying obesity is required for the development of similarly rational and effective treatments. However, this research is slow and challenging because of the great genetic heterogeneity of the disorder.

Fourth, the lack of specific therapies to treat the various genetic causes of obesity highlights a dichotomy in the approach to an obese patient. Although currently a patient experiences no direct benefit in knowing the genetic basis of his disease, it is important from a research perspective to further explore the genetic cause of this phenotype. Only through elucidating the molecular mechanisms underlying obesity can this devastating condition be rationally approached and effectively treated.

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