Leptin signaling defects in a mouse model of Prader-Willi syndrome
An orphan genetic obesity syndrome no more?

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Prader-Willi syndrome (PWS) is a rare (~1 in 12,000) genetic disorder that involves at least six genes on chromosome 15q11–q13. Children with PWS not only rapidly gain weight and become severely obese because of reduced voluntary activity and increased food intake, but also exhibit growth hormone deficiency, excessive daytime sleepiness, endocrine dysregulation and infertility. These phenotypes suggest dysfunction of the hypothalamus, the brain region that regulates short- and long-term energy balance and other body functions. The physiological basis for obesity in children with PWS has eluded researchers for decades. Mercer et al. now demonstrate that Magel2, the murine ortholog of one of the PWS genes, is a component of the hypothalamic leptin-melanocortin pathway that is critical for energy balance. Most interestingly, disruptions of other components of this pathway cause obesity in both mice and humans, suggesting a mechanistic link between PWS and other rare genetic forms of severe childhood-onset obesity.

Obesity and obesity-associated complications are a leading cause of morbidity, mortality and excess health care costs.1 While the heritability of body mass index in adults is estimated at 40–70%,2 genetic factors contribute to over 80% of weight variation in children and adolescents.3 Many obesity susceptibility genes act in the central nervous system, interacting with each other and with an environment that provides easy access to cheap, calorically dense and highly palatable food.4-6 Studies that identify and characterize novel obesity genes and pathways have already been shown to have great potential to help us understand, prevent and treat obesity.

Most childhood-onset, severe, syndromic or heritable forms of obesity are caused by rare mutations in genes important in energy balance control circuits in the hypothalamus (Fig. 1).2-12 This small region of the brain coordinates the nervous and endocrine systems to regulate energy balance and other homeostatic activities.13 Both rare mutations and common variants have been found in genes encoding proteins that are involved in the neural responses to leptin, a key hormone produced by adipose tissue. Mutations in these genes profoundly affect body weight and are not compensated for by other genes or pathways, highlighting their physiological importance. Further, leptin resistance is a hallmark of diet-induced obesity.14 The recent report by Mercer et al. demonstrating that loss of a protein named Magel2 impairs leptin signaling in the hypothalamus introduces a new member to the cast of characters essential for energy homeostasis.15 Magel2 is the murine ortholog of MAGEL2,16-23 one of the genes that is inactivated in the orphan genetic obesity disorder Prader-Willi syndrome (PWS).21,24-26 This raises a question about this rare and poorly understood disease: is PWS still an orphan genetic obesity disorder or is it too caused by a defect in hypothalamic leptin signaling?

Severely obese children with mutations in the genes encoding leptin, its receptor and downstream signaling components have intractable feelings of hunger (hyperphagia) and aggressive behavior around
In this respect, the genetic odds have not been in our favor. Multiple genes, including at least five protein-coding genes and a gene that produces a long non-coding RNA are simultaneously inactivated either by this microdeletion, by uniparental disomy or by a mutation that disrupts the imprinting process. Nature has thrown almost every possible genetic twist at the PWS region: in addition to genomic imprinting, clusters of small nucleolar RNAs are encoded in the introns of the non-coding RNA that also serves as an antisense RNA for the UBE3A gene responsible for Angelman syndrome. Other inactivated genes encode proteins of unknown function. One protein-coding gene located in the human PWS region is not found in rodents, complicating the studies of animal models. The PWS region is in the pericentromeric region of chromosome 15, so the genomic DNA is littered with repeated elements and sequence coverage is poor. In spite of this complexity, researchers have been systematically investigating the genes involved, one by one. They have identified mutants in the leptin or melanocortin pathway, with parallel food foraging behavior and reduced energy expenditure observed in food-deprived animals. For this reason, PWS has been described as a genetic model of starvation, because parallel food foraging behavior and reduced energy expenditure are observed in food-deprived animals. In contrast to most human genetic childhood obesity disorders where the causative genes disrupt the leptin, melanocortin, BDNF or related pathways, the cause of hyperphagic obesity in PWS is unknown. A priori, a genetic defect involving the leptin-melanocortin pathway is the most parsimonious explanation for obesity in PWS. However, until now, a mechanistic link between any one PWS gene and a specific pathway in the brain had not been made.

PWS is most commonly caused by a microdeletion that occurs on the paternally inherited chromosome 15 and genomic imprinting that silences the maternal allele of six key genes in this region. In this respect, the genetic odds have not been in our favor. Multiple genes, including at least five protein-coding genes and a gene that produces a long non-coding RNA are simultaneously inactivated either by this microdeletion, by uniparental disomy or by a mutation that disrupts the imprinting process. Nature has thrown almost every possible genetic twist at the PWS region: in addition to genomic imprinting, clusters of small nucleolar RNAs are encoded in the introns of the non-coding RNA that also serves as an antisense RNA for the UBE3A gene responsible for Angelman syndrome. Other inactivated genes encode proteins of unknown function. One protein-coding gene located in the human PWS region is not found in rodents, complicating the studies of animal models. The PWS region is in the pericentromeric region of chromosome 15, so the genomic DNA is littered with repeated elements and sequence coverage is poor. In spite of this complexity, researchers have been systematically investigating the genes involved, one by one.
one, in clusters or by studying deletions of the entire region of conserved synteny. A first clue that MAGEL2 could be implicated in obesity in PWS came with the observation that Magel2 is most highly expressed in regions of the hypothalamus that control circadian rhythm and energy balance.6 Gene targeted knockout mice lacking Magel2 are overweight and have twice the fat mass, proportionately higher leptin, low lean mass and low bone mass. Other hypothalamic deficiencies include blunted circadian rhythm, progressive infertility and neuroendocrine deficits, recapitulating phenotypes seen in progressive infertility and neuroendocrine cies include blunted circadian rhythm, one, in clusters or by studying deletions mass.16,17 Other hypothalamic deficien -mice lacking Magel2.

Many neurons in the brain respond to leptin, but the leptin-sensitive neurons considered most critical for energy homeo-stasis are located in the arcuate nucleus of the hypothalamus.7 Two distinct neuronal subtypes respond to leptin within the arcuate nucleus: neurons that produce Agouti-related peptide (AgRP) and Neuropeptide Y (NPY) and neurons that produce pro-opiomelanocortin (POMC). Leptin hyperpolarizes (inhibits) AgRP/ NPY neurons, reducing the release of orexigenic (appetite-inducing) peptides. In contrast, leptin depolarizes (excites) POMC neurons, promoting the release of anorexigenic (appetite-suppressing) peptides. One such peptide is α-MSH (melanocyte-stimulating hormone), which acts on melanocortin receptors in other brain sites to promote satiety and increase energy expenditure.8.9 Both the anti-orexigenic and pro-anorexigenic responses to leptin are blunted in animals with acquired (diet-induced obese) or congeni-tal (leptin receptor mutation) leptin insensi-tivity. To test leptin-mediated electrical activity in hypothalamic neurons, Mercer et al. used whole-cell patch recordings in individual neurons, which surprisingly revealed a defect specific to the anorexi-genic POMC neurons in Magel2 mice. That is, while POMC neurons are present in near normal numbers in the ARC of the hypothalamus, they fail to depolarize in response to leptin, while normal hyperpolarizing responses were detected in AgRP/ NPY cells.

The finding that Magel2 mice have a primary defect in leptin responses in the POMC-expressing class of anorexigenic neurons was intriguing because previous studies had shown that mice with inactivation of the leptin receptor in only the POMC neurons have increased fat mass, but like Magel2 mice are not massively obese.48 This is presumably because their AgRP/NPY and other neurons still respond to leptin, as is the case with Magel2 mice that retain responses to leptin in non-POMC neurons. Likewise, inactivating the signaling protein STAT3 in only POMC neurons causes mild obesity similar to that of Magel2 mice,49 and inactivating ciliary function in only POMC neurons is sufficient to cause obe-sity.50 The murine Magel2 and human MAGEL2 genes share 72% amino acid similarity,22,36 and likely share a conserved function in POMC neurons. A defect in the leptin-melanocortin system in children with PWS who lack MAGEL2 would explain many aspects of their disorder, including but not limited to excess fat mass, lower lean mass, reduced voluntary activity and infertility. Further studies, including clinical trials, will be needed to address whether the melanocortin system can be manipulated pharmacologically to improve appetite control in children with PWS.

We still have far to go in understanding the neural basis for PWS. Mice lacking Magel2 do not eat voraciously when freely fed, so they do not become morbidly obese like mice with leptin-pathway mutations or like children with PWS whose food environment is not strictly controlled. Their body weight regulation is abnormal though, as they return more slowly to a normal body weight after under- and over-feeding. The loss of other genes, such as the NDN gene encoding necdin43-45 and the clusters of small nucleolar RNAs have also been proposed to account for other endophenotypes in PWS, including neonatal respiratory insufficiency46 and failure to thrive in infancy.57 Nonetheless, we now have a foothold into energy imbalance in one of the last remaining and arguably most intriguing rare genetic dis-orders causing obesity. The new actor on this stage—Magel2—will have to find its niche in the complex protein network in hypothalamic neurons that governs the delicate balance between food intake and energy expenditure. This discovery also adds a new pharmacological target for improving hormone sensitivity and activating pathways downstream of appetitive hormones, both promising avenues for treatment of the obesity that has become rampant in today’s society.

Disclosure of Potential Conflicts of Interest
No potential conflict of interest was disclosed.

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