

# Monogenic disorders of obesity and body fat distribution

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**Abstract** Recently, great progress has been made towards understanding the molecular basis of body fat regulation. Identification of mutations in several genes in spontaneous monogenic animal models of obesity and development of transgenic models have indicated the physiological roles of many genes in the regulation of body fat distribution. In humans, mutations in leptin, leptin receptor, prohormone convertase 1 (PC1), pro-opiomelanocortin (POMC), melanocortin 4-receptor (MC4-R), and peroxisome proliferator-activated receptor (PPAR)  $\gamma$ 2 genes have been described in patients with severe obesity. Most of these obesity disorders exhibit a distinct phenotype with varying degrees of hypothalamic and pituitary dysfunction and a recessive inheritance, whereas *MC4-R* mutation has a nonsyndromic phenotype with dominant inheritance. These mutations suggest the critical role of central signaling systems composed of leptin/leptin receptor and  $\alpha$ -melanocyte stimulating hormone/MC4-R in human energy homeostasis. Although the genetic basis of monogenic disorders of body fat distribution, such as congenital generalized lipodystrophy and familial partial lipodystrophy, Dunnigan variety, is still unknown, the genes for these have recently been localized to chromosomes 9q34 and 1q21-22, respectively. The advances in our knowledge of the phenotypic manifestations and underlying molecular mechanisms of genetic body fat disorders may lead to better treatment and prevention of obesity and other disorders of adipose tissue in the future.—Chen, D., and A. Garg. Monogenic disorders of obesity and body fat distribution. *J. Lipid Res.* 1999. 40: 1735–1746.

**Supplementary key words** obesity • congenital generalized lipodystrophy • familial partial lipodystrophy • leptin • leptin receptor • melanocyte-stimulating hormone • melanocortin receptors

Overall excess of body fat as well as regional adiposity are recognized risk factors for type 2 diabetes, dyslipidemia, hypertension, and coronary heart disease. Other disorders with extreme abnormalities in body fat distribution, such as familial and acquired lipodystrophies, are also frequently associated with marked insulin resistance, early-onset diabetes mellitus, hypertriglyceridemia, and low serum concentrations of high density lipoprotein (HDL) cholesterol (1). Recently, great progress has been made in identifying several genes and in understanding the molecular mechanisms underlying spontaneous syn-

dromes of obesity and abnormal body fat distribution in animal models and humans. Progress has also been made in establishing transgenic animal models with altered body adiposity and peculiar body fat distribution similar to that seen in familial forms of human lipodystrophy. This article reviews these advances in our knowledge of monogenic disorders of obesity and adipose tissue distribution in rodents and humans, and clinical features of these human disorders are reviewed in detail.

## Rodent monogenic models of obesity

Several well-described spontaneous monogenic rodent models of obesity syndromes have been known for over 4 decades, but only in the last 6 years have the molecular basis and the underlying pathophysiological mechanisms of obesity in these animals been elucidated (2).

**The *agouti* gene mutation.** The *agouti* was the first obesity gene cloned (3). The gene product, agouti signaling protein (ASP), is a 133-amino acid (16 kD) polypeptide. Although its mRNA has been detected in the skin, testis, and embryonal tissue (4), *agouti* is only known to function in the hair follicles in the neonatal period. It induces pheomelanin production in melanocytes to form the characteristic banded pattern of coat hair (yellow subapical band in black or brown hair). Dominant mutations, such as *A<sup>v</sup>* and *A<sup>w</sup>*, in the promoter region of the *agouti* gene result in its ectopic overexpression in all tissues (3–6). Mice with this mutation exhibit yellow coat color, hyperphagia, obesity, increased lean body mass, hyperinsulinemia, and infertility (4).

ASP competitively inhibits binding of  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH), a proteolytic product of proopiomelanocortin (POMC), to melanocortin receptors (Mc-rs), a family of G-protein coupled receptors (7).

Abbreviations: PC1, prohormone convertase 1; POMC, pro-opiomelanocortin; MC4-R, melanocortin 4-receptor; PPAR, peroxisome proliferator-activated receptor; HDL, high density lipoprotein; ASP, agouti signaling protein;  $\alpha$ -MSH,  $\alpha$ -melanocyte-stimulating hormone; Mc-rs, melanocortin receptors; AGRP, agouti related protein; C/EBP, CCAAT/enhancer-binding protein; SREBP, sterol regulatory element-binding protein; CGL, congenital generalized lipodystrophy.

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It has high affinity for Mc1-r and Mc4-r, two of the five receptors of this family. It has been shown that obesity and yellow coat in mice are in fact two independent phenotypic features. Mice with *e/e* genotype, which prevents eumelanin synthesis, are yellow but non-obese (8), whereas *A<sup>y</sup>* mice with a dominant *sombre* (*e<sup>so</sup>*) gene, which prevents pheomelanin synthesis, are black yet obese (9). Similarly, an inactivating mutation of *Mc1-r* results in yellow but non-obese animals (10), while knockout of *Mc4-r* gene causes obesity without yellow coat (11). These results suggest that *Mc4-r*, highly expressed in the hypothalamus, is important in controlling energy balance and is the link between *agouti* mutation and obesity. Besides  $\alpha$ -MSH, produced by the pituitary melanotrophs and the hypothalamic neurons (12), ligands for Mc4-r may include desacetylated  $\alpha$ -MSH (13) and *agouti*-related protein (AGRP) normally expressed in the hypothalamus. AGRP has partial homology to ASP, and its overexpression recapitulates many features of obese *yellow* or *Mc4-r* mutant mice (14, 15). Thus, ectopic expression of ASP may induce obesity by augmenting normal action of AGRP. There is also speculation that  $\gamma$ -MSH, another derivative of POMC with structural homology to  $\alpha$ -MSH, has a role in energy regulation by interacting with *Mc3-r* in the hypothalamus (16).

Recent studies of *mahogany* (*mg*) gene have revealed greater complexity of obesity related to *agouti* mutation. Homozygous mutation of *mg* gene prevents yellow fur coat color change and obesity in *A<sup>y</sup>* mice (17, 18) but not those with *Mc1-r* (17) or *Mc4-r* (19) mutations, suggesting that *mg* action involves molecular events downstream of *A<sup>y</sup>* mutation but upstream of Mc-rs. The *mg* gene encodes a 150-kD transmembrane protein that shares homology with extracellular matrix proteins and has wide tissue distribution, including in hypothalamus (19, 20). However, its interactions with other molecules remain to be elucidated.

**The *tubby* gene mutation (*tub*).** The mice homozygous for *tub* mutation develop late-onset obesity without diabetes (21). Affected mice also develop slow-onset deafness and retinal degeneration. This phenotype is due to a point mutation that results in an error in the transcript splicing and the loss of the carboxyl terminus of the protein product (22). The *tubby* belongs to a *tubby*-like gene family whose function is not fully understood. The human homologues of mouse *tubby* includes *TUB*, *tubby*-like protein 1 (*TULP 1*), *TULP 2* and *TULP 3* (23, 24). Although human obesity has not been associated with *TUB* family, mutations in *TULP 1* and *TULP 2*, are implicated in the development of retinitis pigmentosa and cone-rod dystrophy, respectively (23, 25, 26). Homology analyses suggest that the *tubby* gene product is a phosphodiesterase that may be involved in the control of apoptosis of the cochlear and retinal cells.

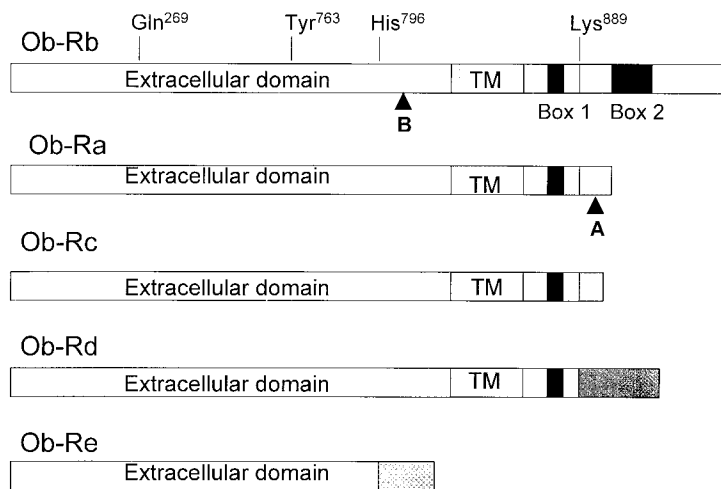
**The *carboxypeptidase E* (*Cpe*) gene mutation (*fat*).** Mice with homozygous *fat* mutation develop late-onset marked obesity, infertility, and striking hyperproinsulinemia (21, 27). However, hyperglycemia occurs only transiently in males. The T729C nucleotide point mutation in *Cpe* gene causes a Ser202Pro substitution in CPE and renders this protein

enzymatically inactive. CPE is present in many tissues, including the brain, pituitary, pancreas, and adrenals and is involved in the post-translational processing of many prohormones and neuropeptides, including proinsulin and POMC. Furthermore, CPE may function as an intracellular membrane receptor necessary for regulated release of these substances from the cells through secretory pathways (28, 29). The disruption of processing and secretion of POMC and its intermediates may be responsible for development of obesity due to reduced ligands for Mc4-r.

**The *leptin* (*Lep*) gene mutation (*ob*).** The *Lep* gene is one of the most extensively studied obesity genes. Homozygous *Lep* gene mutation, *ob/ob*, causes early-onset morbid obesity with diabetes in mice. In addition, affected mice exhibit hyperphagia, hypothermia, hypercorticosteronemia, decreased linear growth, and infertility (30–32). The *Lep* gene encodes a 167-amino acid (16-kD) protein, leptin, a member of class 1 cytokine superfamily. The primary structure of leptin is highly conserved, and there is 84% homology in amino acid sequences between the mouse and human homologues (33). The *ob* mutation is a single base substitution (C428T) that results in premature termination of the protein synthesis at codon 105 (33). Although *ob* trait is autosomal recessive (31), mice heterozygous for *Lep* mutation (*ob/+*) are more obese and hypoleptinemic than the wild-type (*+/+*) littermates (34), indicating that the recessivity of this mutation is not complete.

Leptin is produced primarily by the adipose tissue, and its plasma levels correlate well with body fat mass. As leptin administration normalizes all aspects of the obesity and diabetes syndrome and restores reproductive function in *ob/ob* mice by acting through leptin receptors in the central nervous system (35–38), it has been regarded as a signal crucial for energy balance, body adiposity, and reproduction. However, leptin may also play a role in the regulation of adrenal and thyroid function and chronic stress response (39, 40). Recent studies indicate that leptin is also produced from non-adipose tissues, such as the placental trophoblasts and amnion cells (41), gastric epithelium (42), and mammary epithelium (43), but the significance of these findings is yet unknown.

**The *leptin receptor* (*Lepr*) gene mutation (*db*).** The *db/db* mice have the same phenotype as *ob/ob* mice, but they are resistant to leptin (31, 35, 36). The mutation resides in the leptin receptor (44, 45), a member of class-1 cytokine receptor family. Leptin receptor exists in several isoforms due to alternative splicing of the transcript. Ob-Rb, the long form expressed most highly in the hypothalamus, is the main isoform mediating leptin signaling. It consists of a large extracellular domain, a single transmembrane domain, and an intracellular domain that contains a motif important for interaction with Janus kinase (JAK) and a motif of signal transducer and activator of transcription (STAT) (Fig. 1). Recently, it has been shown that the ob-Ra isoform may also be involved in signal transduction (46). The mouse and human leptin receptor (OB-R) molecules share 71% identity in the intracellular domain. The *db* mutation is a single base substitution (G→T) in the intracellular domain of ob-Ra, which creates a splice site ho-



**Fig. 1.** Structure and mutations of the leptin receptor. The longest isoform of the leptin receptor, Ob-Rb, consists of an extracellular domain, a single transmembrane domain (TM), and an intracellular domain that includes boxes 1 and 2 (solid dark). Boxes 1 and 2 represent JAK-binding and STAT motifs, respectively, critical for signal transduction. Ob-Ra, Ob-Rb, Ob-Rc, and Ob-Rd differ from one another due to alternative splicing after Lys889 in the intracellular domain. Ob-Re isoform is alternatively spliced after His796 in the extracellular domain and lacks the transmembrane and intracellular domains. The *ob* mutation (site A) in *obese* mice is a G→T transversion in the intracellular domain of Ob-Ra. The Gln→Pro at position 269 and Tyr763→stop codon mutations in the extracellular domain represent *fa* and *f* mutations in rats, respectively. The human *LEP* gene mutation (site B) is a G→A transversion in the extracellular domain (exon 16) leading to premature termination of protein synthesis.

mologous to that in the intracellular domain of ob-Rb. This results in the insertion of the C-terminus of ob-Ra into the cytoplasmic tail of ob-Rb transcript and subsequent premature termination of the ob-Rb synthesis (44, 47). The C-terminal motif of ob-Rb important for tyrosine kinase activation is thus lost in mice with *db/db* mutation.

The genetically obese Zucker and Koletsky rats both have mutations in the extracellular domain of the leptin receptor and exhibit dyslipidemia and hyperglycemia or impaired glucose tolerance as recessive traits. Koletsky rats are genetically hypertensive with marked insulin resistance (48). The *fa/fa* mutation in Zucker rats, an A880C nucleotide missense mutation resulting in Gln269Pro amino acid substitution, reduces the expression of the leptin receptor on the cell surface with marked intracellular retention, decreased leptin binding, and diminished signal transduction (45, 49–53). These rats have markedly decreased weight-reducing response to intracerebroventricular administration of leptin, compared to the *Fa/fa* heterozygotes (54, 55). In contrast, the *f/f* mutation in Koletsky rats is a T2349A nonsense and null mutation resulting in virtually undetectable leptin receptor mRNA in the tissue (56). Besides the predicted diminished cellular response

to leptin in *f/f* rats, lack of leptin receptor in the brain of *f/f* rats also leads to reduced transport of leptin from plasma to cerebrospinal fluid (56).

The mechanism by which *Lep* and *Lepr* mutations cause obesity has not been totally elucidated. Molecular events downstream of leptin receptor may involve signaling via POMC/melanocortins (57), AGRP, and other neuropeptides, such as neuropeptide Y (NPY) (58).

*Transgenic and knockout rodent models of altered body fat distribution.* Table 1 displays several mouse models with either transgenic or knockout of specific genes that alter the amount or the distribution of body fat. These animal models not only reveal that certain genes may affect body adiposity by influencing energy balance, but also indicate the critical role of genes in adipocyte proliferation and differentiation. These genes include transcription factors of the CCAAT/enhancer-binding protein (C/EBP) and sterol regulatory element-binding protein (SREBP) families. Knockouts of C/EBP  $\alpha$  (59),  $\beta$ , and  $\delta$  (60) result in partial or complete lack of accumulation of lipids in the adipose tissue. Overexpression of A-ZIP/F gene, whose product inactivates B-ZIP proteins in C/EBP and activator protein-1 (AP-1) families, produces mice devoid of white

TABLE 1. Transgenic and knockout models of obesity and altered body fat distribution

Models with Increased Body Fat or Obesity	Models with Decreased Body Fat or Lipodystrophy
Overexpression of <i>glut4</i> gene in adipose tissue (113, 114)	Overexpression of LPL gene in muscle and cardiac tissues (115)
Overexpression of <i>AGRP</i> gene (14, 15)	Overexpression of $\beta$ 1-adrenergic receptor gene in adipose tissue (116)
Ablation of brown fat A (117, 118)	Overexpression of uncoupling protein gene in adipose tissue (119)
Inactivation of GH transgene (120, 121)	Overexpression of A-ZIP/F gene (61) <sup>a</sup>
Knockout of neuropeptide Y-Y1 receptor gene (122)	Overexpression of nSREBP-1c gene (62)
Knockout of $\beta$ 3-adrenergic receptor gene (123)	Knockout of the <i>glut4</i> gene (124)
Knockout of <i>Mcf4-r</i> gene (11)	Knockout of C/EBP $\alpha$ , $\beta$ , and $\delta$ genes (59, 60)
Knockout of ICAM-1 gene or integrin $\alpha$ M $\beta$ 2 (Mac-1) gene (125)	Ablation of thyroid hormone production (126)
Knockout of bombesin receptor subtype-3 gene (127)	Knockout of RII beta subunit of protein kinase A gene (128)
Knockout of PPAR $\alpha$ gene (129)	Knockout of <i>mg</i> gene (18)
Knockout of 5-HT <sub>2c</sub> serotonin receptor gene (130, 131)	

AGRP, agouti-related protein; C/EBP, CCAAT enhancer-binding protein; *Glut4*, glucose transporter-4; GH, growth hormone; 5-HT, 5-hydroxytryptophan; ICAM-1, intercellular adhesion molecule-1; LPL, lipoprotein lipase; MC4-R, melanocortin-4 receptor; *mg*, mahogany gene; nSREBP, nuclear sterol regulatory element-binding protein; PPAR $\alpha$ , peroxisome proliferator-activated receptor  $\alpha$ .

<sup>a</sup> A-ZIP/F, a transgene engineered to inactivate transcription factors of C/EBP family.



adipose tissue while exhibiting a severely reduced amount of brown adipose tissue (61). Overexpression of SREBP-1c in adipose tissue in mice causes markedly reduced subcutaneous and omental adipose tissue but enlargement of interscapular fat pad (buffalo hump). These animals also have severe insulin resistance, hyperglycemia, hypertriglyceridemia, and lipid-laden internal organs, difficulty in thriving, and early death (62). There are, however, no reports of spontaneous mutations in these genes in association with obesity or lipodystrophy in mice.

### Human monogenic syndromes of obesity and body fat distribution

Following the lead of genetic studies in rodent models of obesity, several homologous single gene mutations underlying obesity syndromes in humans were identified in the last 2 years. In all reported cases, abnormal karyotype and gross abnormalities of brain structures were excluded. There was also no evidence for pleiotropic genetic obesity syndromes, such as Prader-Willi syndrome, in the affected subjects.

**Leptin (*LEP*) gene mutations.** An 8-year-old girl and her 2-year-old male cousin from a highly consanguineous family of Pakistani origin presented with early onset (at 4 and 3 months, respectively) severe obesity and hyperphagia (63). Serum leptin levels were very low. Fasting plasma glucose concentration was normal in both, but fasting plasma insulin level was elevated in the girl. Slightly elevated thyroid stimulating hormone (TSH) levels were noted in both patients, whereas gonadotropin and gonadal hormone levels were appropriate for prepubertal age. The family members were normal except that their mothers were moderately obese with borderline low serum leptin levels.

Both patients were homozygous for a single nucleotide deletion at position 398 of the leptin gene (Fig. 2). This mutation resulted in a frame-shift of the leptin-coding region after Gly132 and a premature termination of the peptide synthesis. All of their parents and one of the four siblings were heterozygous for this mutation. The other three siblings had normal leptin alleles. This study established relevance of leptin in regulating energy balance in humans.

A homozygous single nucleotide transversion in leptin gene resulting in Arg→Trp substitution in the mature peptide (Fig. 2) and low serum leptin levels has also been discovered in three other morbidly obese individuals, including two adults, from a highly consanguineous family (64). They were hyperinsulinemic, and an affected woman was hyperglycemic. The adult male patient exhibited characteristic hypothalamic hypogonadism and dysfunction of

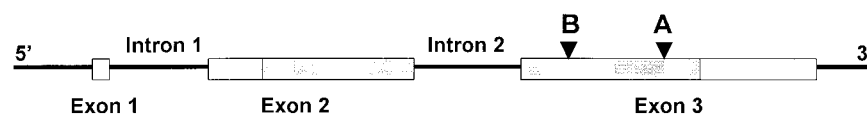
the sympathetic nervous system. The affected woman had primary amenorrhea. These findings suggest a role of leptin in the initiation of puberty and reproduction in humans. All the other family members studied were either heterozygous for the mutation or had normal alleles. The leptin gene mutation occurred at the same location as that found in the *ob/ob* mice, but this was a missense instead of nonsense mutation. Unlike *ob/ob* mice, the affected individuals did not have retarded linear growth or hypercortisolemia.

In addition, heterozygous missense leptin gene mutations have been reported in two unrelated obese Finnish men, both of whom had low serum leptin levels (65). As relevant information regarding inheritance of the genotypes and phenotypes is not available, whether these mutations were the cause of obesity in these men is unclear. Interestingly, the heterozygotes for leptin gene mutation from the first two pedigrees all had normal leptin levels for their body fat mass (63, 64). Although decreased leptin levels and increased fat mass are observed in *ob/+* heterozygous mice (34), whether heterozygous mutations in leptin gene can cause obesity in humans remains to be determined.

**Leptin receptor (*LEPR*) mutation (*OB-R*).** Three morbidly obese sisters (age 13–19 y) from a consanguineous family were noted to have markedly high serum leptin levels (66). They had developed hyperphagia and severe obesity within a few months after birth. Emotional lability and social disability, but not mental retardation, were also noted. These patients also had hypogonadotropic hypogonadism and failure of pubertal development, hypothalamic hypothyroidism, mild growth delay, and subnormal growth hormone response to hypoglycemia.

The three subjects were homozygous for a single nucleotide substitution at a splice site of exon 16 of the *LEPR* gene (Fig. 1). This mutation produced a protein of 831 amino acids (*OB-Rhd*), lacking both the transmembrane and intracellular domains. Both parents and four siblings who were heterozygous for the mutation had normal or slightly increased body fat, suggesting autosomal recessive inheritance for this disorder.

Documentation of *LEP* and *LEPR* mutations in obese humans establishes the role of leptin-leptin receptor system in energy balance and hypothalamic functions related to sexual maturation, linear growth, and thyroid physiology. Unlike *db/db* mice, however, the patients with *LEPR* mutation had normal fasting and postprandial blood glucose, insulin, and lipids levels and normal hypothalamic-pituitary-adrenal axis.



**Fig. 2.** Structure and mutations of the leptin gene. The leptin gene consists of three exons and two introns. Translated exon regions are represented by the shaded segments. Site A is a single base C-deletion at position 398 that results in a frame-shift and premature termination of leptin peptide synthesis. Site B is C314T transversion that results in an Arg→Trp substitution.

**Prohormone convertase 1 (PC1) gene mutation.** The proband for PC1 gene mutation was a 43-year-old moderately obese woman with a history of severe childhood obesity (67). She also had impaired glucose tolerance, postprandial hypoglycemia, hypogonadotropic hypogonadism, hypocortisolism, elevated plasma proinsulin and POMC concentrations, and very low plasma insulin concentration. Serum leptin concentration was appropriate for body mass index (BMI).

She was a compound heterozygote for two mutations in PC1 gene. A G→A substitution in exon 13 resulted in a Gly483Arg missense mutation in the PC1 peptide. This mutation abolished the autocatalytic cleavage ability of PC1 in the endoplasmic reticulum, resulting in reduced production of mature and functional PC1. The second mutation, an A→C substitution, occurred at a donor splice site in intron 5 of PC1 gene resulting in a frame shift and premature termination in the catalytic domain of PC1. All of her four children were heterozygous for one of the two mutations, but they were clinically normal, suggesting an autosomal recessive inheritance.

The phenotype of this patient is remarkably similar to that of *fat/fat* mice with *Cpe* gene mutation. PC1, like CPE, is involved in the post-translational processing of prohormones and neuropeptides (68). Processing of POMC by PC1 enables the formation of melanocortins, including  $\alpha$ -MSH. Thus, deficiency of melanocortins due to reduced production may be the cause of obesity in this patient. The other clinical features may be related to diminished processing of proinsulin, POMC, and precursor of gonadotropin-releasing hormone.

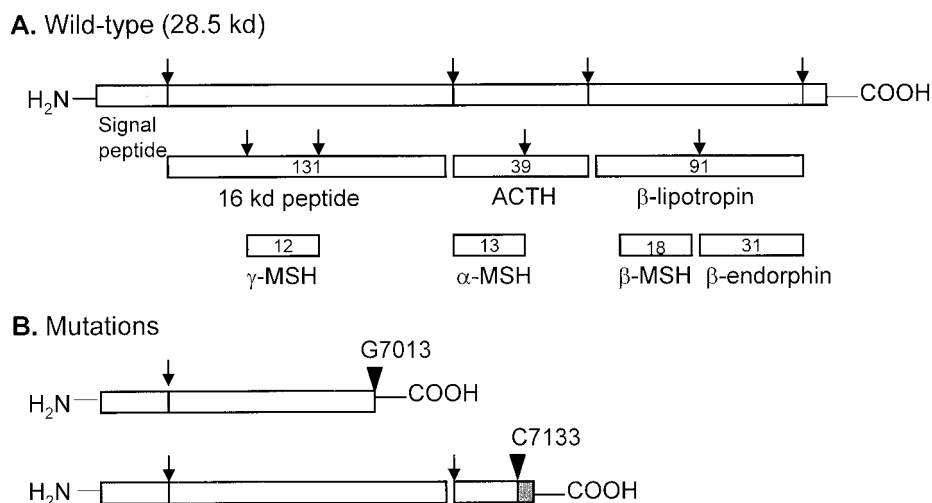
**POMC gene mutation.** Mutations in the POMC gene

have been described in a 5-year-old girl and a 5-year-old boy from unrelated families (69). Both patients developed early onset obesity with hyperphagia. They also had red hair pigmentation and adrenocorticotropin (ACTH) deficiency diagnosed during infancy. Both patients had undetectable serum ACTH levels after corticotropin-releasing hormone (CRH) stimulation. In response to thyrotropin-releasing hormone (TRH) stimulation,  $\alpha$ -MSH level was undetectable in the girl and only low normal in the boy. The older brother of the girl died at age 7 months with underlying adrenal hypoplasia suggestive of secondary adrenal insufficiency.

Two compound heterozygous mutations in exon 3 of POMC coding region were discovered in the girl and her older brother (Fig. 3). The G7013T nucleotide transversion in the paternal allele resulted in a premature termination at codon 79 and hence the complete loss of synthesis of  $\alpha$ -MSH and ACTH. The second mutation was a single nucleotide deletion at position 7133 in the maternal allele, resulting in a frame-shift and disruption of the receptor-binding core motif of  $\alpha$ -MSH and ACTH and a premature termination at codon 131.

The mutation in the 5-year-old boy was a homozygous C3804A substitution in exon 2 of POMC gene in the 5' untranslated region. This mutation created an out-of-frame initiation codon that interfered with the normal initiation of the wild-type peptide translation.

The clinical features of these patients resemble those seen in *A<sup>y</sup>* and *A<sup>y/y</sup>* mice and are likely related to the deficiency of the POMC-derived hormones and neuropeptides. The red hair pigmentation and obesity are thought to be due to deficiency of  $\alpha$ -MSH (70, 71). ACTH deficiency



**Fig. 3.** The structure and mutations of POMC. A: POMC is synthesized as a large precursor that is cleaved into bioactive molecules (such as  $\alpha$ ,  $\beta$ ,  $\gamma$ -MSH, ACTH,  $\beta$ -lipotropin, and  $\beta$ -endorphin) by post-translational processing (cleavage sites are marked by arrows). Number of amino acids in these molecules is indicated in the bars. The shaded region in the amino terminal represents signal peptide. Alpha-MSH is identical to the first 13 amino acids of ACTH. B: The three mutations discovered in humans include 1) G7013T transversion at codon 79 resulting in the loss of ACTH,  $\alpha$ -MSH, and  $\beta$ -endorphin; 2) C7133 deletion at codon 127 resulting in disruption of the receptor-binding motifs of ACTH and  $\alpha$ -MSH and premature termination; and 3) C3804A transversion in the 5' untranslated region (site not shown), resulting in the appearance of an aberrant, out-of-frame initiation codon that interferes with initiation of translation at the normal site.

causes secondary adrenal insufficiency. Normal phenotype of the heterozygous parents in both families suggests that this syndrome has a recessive mode of inheritance.

**Peroxisome proliferator-activated receptor (PPAR)  $\gamma$ 2 gene mutation.** PPAR $\gamma$ 2 is a nuclear transcription factor known to play a key role in adipocyte differentiation and insulin action. PPAR $\gamma$ 2 activity is stimulated by thiazolidinediones and certain unknown endogenous ligands, whereas it is inhibited by Ser114 phosphorylation, a process enhanced by insulin and certain growth factors (72). Screening of 121 obese subjects revealed a heterozygous G344T transversion and resultant Pro115Gln missense mutation of the PPAR $\gamma$ 2 gene in three men with type 2 diabetes mellitus and one nondiabetic woman, who were more obese than the others. This mutation was not found in 237 normal-weight subjects (73). Interestingly, fasting serum insulin levels were lower in the three diabetic men with PPAR $\gamma$ 2 gene mutation than in the other obese individuals, suggesting either lower insulin resistance or failure of insulin production in these men. In support of the former, it is shown that this mutation abolishes phosphorylation of Ser114 and increases triglyceride accumulation in cultured NIH 3T3 cells, suggestive of gain-of-function of the PPAR $\gamma$ 2 gene (73). A definite causal role of PPAR $\gamma$ 2 mutation in causing human obesity, however, remains to be established by more detailed characterization of the phenotype and genotype of affected individuals and their families.

**Melanocortin receptor (MC4-R) mutation.** Recently, obesity resulting from *MC4-R* mutations has been reported in several individuals and families, confirming an important role of MC4-R in energy balance in humans. In the first report, a heterozygous mutation of 4-nucleotide deletion at codon 211 of *MC4-R* gene was identified in 1 of 63 individuals with early onset obesity (74). This mutation resulted in a frame-shift that introduced 5 aberrant amino acids and caused premature termination of MC4-R in the fifth transmembrane domain, a critical site for G-protein binding and activation. The index patient was a 4-year-old boy who had normal birth weight but suffered progressive weight gain and obesity with hyperphagia at the age of 4 months. There was no evidence of other endocrine dysfunction, and serum leptin level was appropriate for BMI. The father of the boy, who was heterozygous for this mutation, also had early onset morbid obesity, whereas the mother was unaffected.

Another proband, a 35-year-old woman, with *MC4-R* mutation was identified as a result of screening 43 individuals with early onset severe obesity (75). Six severely obese members over four generations in her family carried a heterozygous 4-nucleotide insertion mutation at nucleotide position 732 (codon 244) of the *MC4-R* gene. This mutation was not found in 275 nonobese control subjects. In the mutant receptor, the sixth transmembrane domain and the rest of the C-terminal structure were replaced by a short and aberrant peptide. The proband had normal blood glucose, lipid, and leptin levels. She had normal pubertal development, and three of other affected women had normal reproductive function.

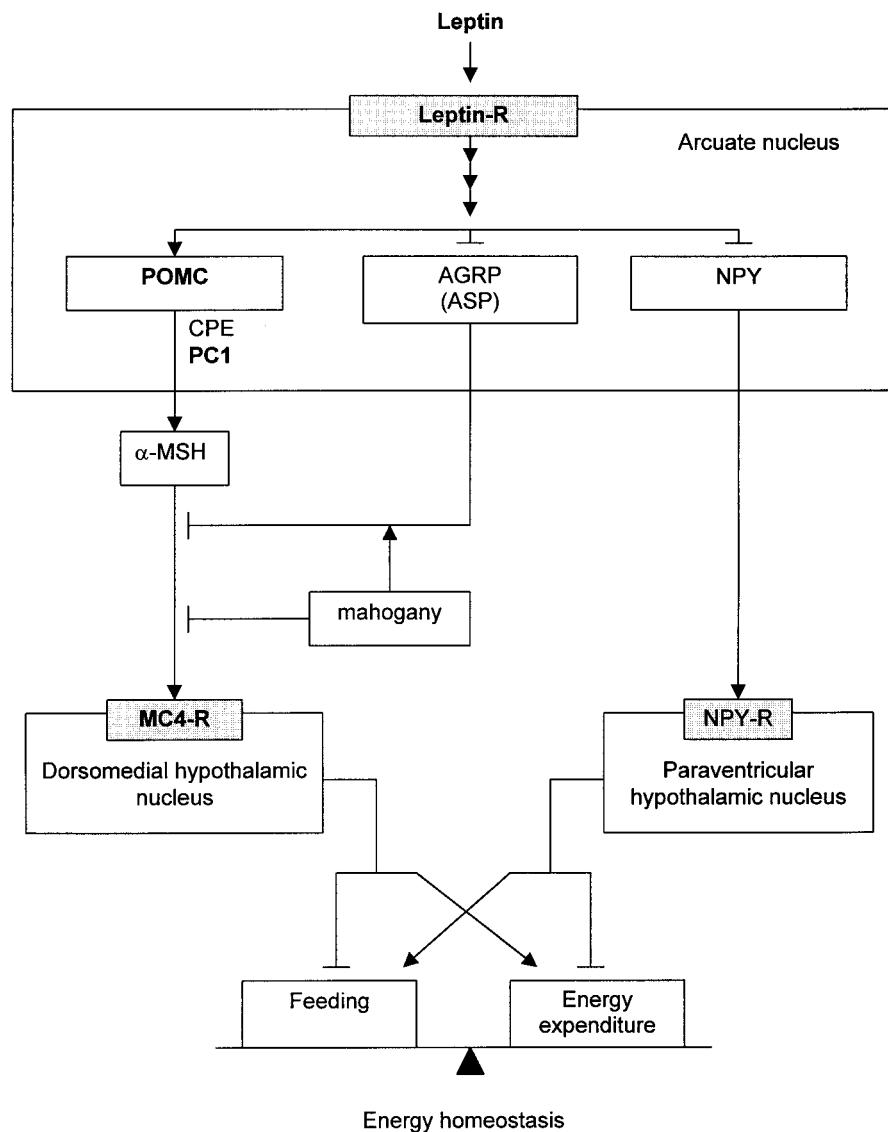
More recently, *MC4-R* mutations were identified in 10 probands in screening 461 individuals including healthy subjects and those with severe obesity, anorexia nervosa, and bulimia nervosa (76). All but one of the individuals with *MC4-R* mutations was obese. A 19-year-old female proband and her mother, both of whom were obese, were found to have the same 4-bp deletion at codon 211 as described above. Two other obese female index subjects, age 10 and 16 years old, respectively, were noted to have combined nonsense mutation (Tyr35stop in the extracellular domain of MC4-R) and a missense mutation (Asp37Val in the 3' untranslated region of MC4-R). These mutations were inherited from their respective mothers, who were also obese. One 15-year-old obese male had double missense mutations (Ser30Phe near the N-terminal and Gly252Ser in the sixth transmembrane domain, respectively). Four other males, age 9–19 years old, harbored 4 different missense mutations, including Pro78Leu, Thr112Met, Arg165Trp, and Ile317Thr of MC4-R. Two polymorphisms, Val103Ile and Ile251Leu, were also identified. Thus, *MC4-R* mutations are characterized by dominant inheritance and absence of apparent phenotypic abnormalities besides obesity. This dominant inheritance is thought to be due to haplo-insufficiency mechanism commonly seen in the mutations of the G-protein coupled receptors (77).

**Other genetic syndromes of obesity.** Approximately 25 other genetic obesity syndromes are known (78), but the genes of only a minority of them have been located to specific chromosomal regions (2). In this group of disorders, mutations in specific genes have not yet been identified. The genetic basis for Prader-Willi syndrome is among the better understood. Besides hyperphagia and obesity, Prader-Willi syndrome is characterized by hypotonia, hypogonadism, and mental retardation with somatic abnormalities, such as short stature, peculiar facial features, and small hands. This phenotype results from the loss of paternally imprinted gene expression in chromosome 15q11-13 region (79, 80). The gene defects in Prader-Willi syndrome include parental gene deletion or point mutation, uniparental disomy, and mutations in the imprinting center, the small nuclear ribonucleoprotein-associated polypeptide N (SNRPN) gene, causing error in methylation of the parental genes. Bardet-Biedl syndrome, another intriguing disorder, is an autosomal recessive disorder characterized by obesity, mental retardation, hypogonadism, pigmentary retinopathy, polydactyly, and renal structural abnormalities (79). Linkage studies indicate that this syndrome may be caused by genetic defects at various chromosomal loci, including chromosome 3p13-p12, 11q13, 15q22.3-q23, and 16q21 (2). Recent study of 17 Canadian kindreds suggests that additional chromosomal loci may be involved in Bardet-Biedl syndrome (81).

**Genetic disorders of body fat distribution.** There are at least two well-characterized genetic disorders with markedly abnormal body fat distribution and extreme insulin resistance, i.e., congenital generalized lipodystrophy (CGL) and familial partial lipodystrophy, Dunnigan variety (FPLD). CGL is an autosomal recessive disorder with near

complete absence of adipose tissue and markedly muscular appearance from birth (82). Patients with CGL have accelerated growth, increased basal metabolic rate, and voracious appetite during childhood. Other features include severe acanthosis nigricans, hepatosplenomegaly, acromegaloid appearance, hypertriglyceridemia, early-onset diabetes mellitus, menstrual abnormalities, and development of focal lytic lesions in the appendicular skeleton after puberty. These patients have complete absence of adipose tissue from most of the sc areas, intraabdomi-

nal and intrathoracic regions and bone marrow, the sites where metabolically active adipose tissue is located. However, mechanical adipose tissue, such as that in the orbits, sc regions of scalp, palms and soles, perineum, vulva and in the periarticular regions, is completely preserved (82–84). Plasma leptin concentrations are low (85). The genetic basis of CGL is unknown. Candidate genes, such as insulin receptor, insulin-like growth factor 1 receptor, insulin receptor substrate 1,  $\beta$ -3 adrenergic receptor, apolipoproteins A2, C2, and C3, fatty acid binding protein 2, muscle



**Fig. 4.** Schematic representation of the central control mechanisms of energy homeostasis and monogenic obesity disorders. Leptin interacts with leptin receptor in neurons in the arcuate nucleus and modulates expression of POMC, AGRP, or NPY, which in turn influences feeding behavior and energy expenditure. Alpha-MSH derived from POMC stimulates MC4-R in neurons in the dorsomedial hypothalamic nucleus. The  $\alpha$ -MSH/MC4-R interaction is inhibited by AGRP and ASP (ectopically expressed in *agouti* mutation), and it may also be inhibited by *mahogany* gene product directly or indirectly. NPY stimulates NPY receptor in neurons in the periventricular hypothalamic nucleus. Known mutations that cause obesity in humans are depicted in bold. Abbreviations: AGRP, agouti-related peptide; ASP, agouti signaling protein (ectopically expressed in *agouti* mutation); CPE, carboxypeptidase; mahogany, *mahogany* gene product; leptin-R, leptin receptor; MC4-R, melanocortin-4 receptor;  $\alpha$ -MSH,  $\alpha$ -melanocyte-stimulating hormone; NPY, neuropeptide Y; NPY-R, neuropeptide Y receptor; PC1, prohormone convertase 1; POMC, proopiomelanocortin. (→) indicates stimulatory effect; (⊥) indicates inhibitory effect.



glycogen synthase, hepatic lipase, hormone-sensitive lipase, lipoprotein lipase, leptin, and peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) have been excluded (86–89). It is hypothesized that the markedly abnormal body fat distribution in CGL is primarily due to a genetic defect causing poor growth and development of metabolically active adipose tissue (90).

FPLD is an autosomal dominant disorder with normal adipose tissue distribution during childhood but loss of subcutaneous adipose tissue from the extremities during pubertal years (91). Subsequently, patients with FPLD may accumulate excess fat in the face and neck. Intraabdominal, intrathoracic, bone marrow, and mechanical adipose tissue is well preserved (92). Patients are predisposed to develop diabetes mellitus, hypertriglyceridemia, and low levels of HDL-cholesterol. Using a genome-wide linkage analysis approach, we have localized the FPLD gene to a 5.2 cM region on chromosome 1q21-22 (93), and this location has been confirmed by others (94, 95). This region contains potential candidate genes, such as cellular retinoic acid-binding protein type 2 (*CRABP2*) and aryl hydrocarbon receptor nuclear translocator (*ARNT*). We hypothesize that a steroid-responsive adipose tissue protein/receptor involved in post-pubertal growth and maintenance of sc fat in the extremities is defective in FPLD.

## DISCUSSION

Taken together, five single obesity genes in rodents have been identified. All but the *tub* gene suggests the crucial role of leptin and melanocortin signaling systems in the pathogenesis of obesity. There is strong evidence to further suggest that there are high level cross-talks between these two systems to modulate their functions, both in the hypothalamus and in peripheral tissues (96–98). Their central actions in regulating energy homeostasis are integrated rather than independent of each other. The known components contributing to obesity are depicted in Fig. 4.

In humans, six single gene mutations associated with obesity have been reported. Except for PPAR $\gamma$ 2 mutation, they are causally related to obesity based on geno- and phenotyping of the affected subjects and families. These mutations have confirmed the involvement of leptin and melanocortin systems in the development of obesity in humans. Phenotypically, early onset severe obesity is a universal finding in all reported cases except for individuals with PPAR $\gamma$ 2 mutation, but the screening processes may have introduced selection bias in the characterization of these syndromes. Some clinical features of the reported cases with these mutations were quite distinct, depending upon the sites of disruption in the two systems and the involvement of components outside the two systems (Table 2). *MC4-R* mutations were unique in this group because of the dominant inheritance and absence of other endocrine abnormalities besides obesity.

The exact prevalence and significance of these single gene mutations or dysfunction of these signaling systems in human obesity are unknown. The prevalence of *MC4-R* mutation is estimated to be about 1% in extremely obese individuals (76). *LEP* gene mutations and associated leptin deficiency appear to be rare in humans according to the results of screening a large number of normal weight and obese subjects (99–101). However, chromosomal regions flanking *LEP* gene have been linked with obesity (102–105). As a negative feedback effect of leptin in appetite control, energy balance, and body adiposity is not apparent under usual circumstances, the physiological role of leptin in obese but otherwise healthy humans is unclear (106, 107). Indeed, an energy-conserving genotype, or thrifty genotype, has been shown to have survival advantage during prolonged starvation and may be evolutionarily favored (108). Leptin, therefore, is likely to be conserved in evolution for its role beyond anti-obesity function. Flier (39) has proposed a role of leptin in adaptation of starvation, but this remains to be established. The *MC4-R*, *MC5-R*, and *LEPR* genes have been linked to or found in association with obesity (109, 110). More re-

TABLE 2. Clinical features of human obesity syndromes with single gene mutations


	Genes with Mutations					
	LEP	LEP-R	PC1	POMC	PPAR $\gamma$ 2	MC4-R
Subjects (n)	5	3	1	3	4	19
Inheritance	AR	AR	AR	AR	?	D
Onset of obesity (mo)	3–4	4–5	<36	4–5	?	4–6
Age at report (y)	2–34	13–19	43	5	32–74	4–78
Early hyperphagia	+	+	?	+	?	+
Serum leptin level	low	high	normal	?	?	normal
Diabetes/IGT	–	–	–	–	+	–
Serum insulin level	high	high	low	?	low	normal
Hypogonadotropic hypogonadism	+	+	+	?	?	–
ACTH deficiency	–	–	+	+	?	–
Other clinical features	↑TSH	Emotional problems, growth delay, hypothalamic hypothyroidism, sympathetic dysfunction	Postprandial hypoglycemia, autoimmune thyroiditis, ↑proinsulin	Red hair, ↓ $\alpha$ -MSH	?	–

ACTH, adrenocorticotropin; AR, autosomal recessive; D, dominant (due to haplo-insufficiency); IGT, impaired glucose tolerance; TSH, thyrotropin; +, presence; –, absence; ?, unknown.



cently, the chromosomal region encompassing POMC gene has been linked to obesity-related quantitative traits in Mexican-American and French populations in two genome-wide scans (111, 112). Therefore, these or related mutations may have an important role in obesity in some populations.

So far, there has been no direct evidence showing that the genetic loci linked to the other genetic obesity syndromes or FPLD are associated with the common forms of obesity or body fat distribution. Therefore, the contribution of these genes in causing obesity or abnormal body fat distribution in otherwise healthy people remains unknown.

In summary, the past 2 years have witnessed a rapid increase in our knowledge of the clinical features as well as molecular basis of several monogenic disorders of human obesity. Progress has also been made in characterization of the clinical features and towards identification of genes involved in monogenic disorders of body fat distribution. This knowledge should also help in our understanding of the underlying mechanisms of the common forms of obesity and abnormal body distribution. A thorough understanding of the molecular mechanisms of body fat regulation will eventually lead to the development of better strategies for the treatment and prevention of obesity and other adipose tissue disorders. 

**Note Added in Proof:** Recent genome-wide linkage studies in 17 families with congenital generalized lipodystrophy revealed genetic heterogeneity but showed linkage to chromosome 9q34 (132). Two of the 17 families were unlinked.

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