TABLE 415e-1 SELECTED OBESITY GENES IN HUMANS AND MICE

Gene	Gene Product	Mechanism of Obesity	In Human	In Rodent
Lep (ob)	Leptin, a fat-derived hormone	Mutation prevents leptin from delivering satiety signal; brain perceives starvation	Yes	Yes
LepR (db)	Leptin receptor	Same as above	Yes	Yes
POMC	Proopiomelanocortin, a precursor of several hormones and neuropeptides	Mutation prevents synthesis of melanocyte-stimulating hormone (MSH), a satiety signal	Yes	Yes
MC4R	Type 4 receptor for MSH	Mutation prevents reception of satiety signal from MSH	Yes	Yes
AgRP	Agouti-related peptide, a neuropeptide expressed in the hypothalamus	Overexpression inhibits signal through *MC4R*	No	Yes
PC-1	Prohormone convertase 1, a processing enzyme	Mutation prevents synthesis of neuropeptide, probably MSH	Yes	No
Fat	Carboxypeptidase E, a processing enzyme	Same as above	No	Yes
Tub	Tub, a hypothalamic protein of unknown function	Hypothalamic dysfunction	No	Yes
TrkB	TrkB, a neurotrophin receptor	Hyperphagia due to uncharacterized hypothalamic defect	Yes	Yes

(Fig. 415e-5). The results of genomewide association studies to identify genetic loci responsible for obesity in the general population have so far been disappointing. More than 40 replicated loci linked to obesity have been identified, but together they account for less than 3% of interindividual variation in BMI. The most replicated of these is a gene named *FTO*, which is of unknown function, but like many of the other recently described candidates, is expressed in the brain. Because the heritability of obesity is estimated to be 40–70%, it is likely that many more loci remain to be identified. It is possible that epistatic interactions between causative loci or unknown gene-environment interactions explain the poor success at identifying causal loci.

In addition to these human obesity genes, studies in rodents reveal several other molecular candidates for hypothalamic mediators of human obesity or leanness. The *tub* gene encodes a hypothalamic peptide of unknown function; mutation of this gene causes late-onset obesity. The *fat* gene encodes carboxypeptidase E, a peptide-processing enzyme; mutation of this gene is thought to cause obesity by disrupting production of one or more neuropeptides. AgRP is coexpressed with NPY in arcuate nucleus neurons. AgRP antagonizes α-MSH action at MC4 receptors, and its overexpression induces obesity. In contrast, a mouse deficient in the peptide MCH, whose administration causes feeding, is lean.

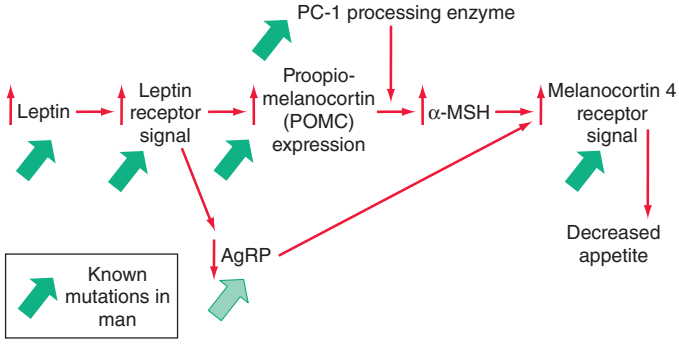

FIGURE 415e-5 A central pathway through which leptin acts to regulate appetite and body weight. Leptin signals through proopiomelanocortin (POMC) neurons in the hypothalamus to induce increased production of α-melanocyte-stimulating hormone (α-MSH), requiring the processing enzyme PC-1 (proenzyme convertase 1). α-MSH acts as an agonist on melanocortin-4 receptors to inhibit appetite, and the neuropeptide AgRp (Agouti-related peptide) acts as an antagonist of this receptor. Mutations that cause obesity in humans are indicated by the *solid green arrows*.

A number of complex human syndromes with defined inheritance are associated with obesity (Table 415e-2). Although specific genes have limited definition at present, their identification will likely enhance our understanding of more common forms of human obesity. In the Prader-Willi syndrome, a multigenic neurodevelopmental disorder, obesity coexists with short stature, mental retardation, hypogonadotropic hypogonadism, hypotonia, small hands and feet, fish-shaped mouth, and hyperphagia. Most patients have reduced expression of imprinted paternally inherited genes encoded in the 15q11-13 chromosomal region. Reduced expression of Snord116, a small nucleolar RNA highly expressed in hypothalamus, may be an important cause of defective hypothalamic function in this disorder. Bardet-Biedl syndrome (BBS) is a genetically heterogeneous disorder characterized by obesity, mental retardation, retinitis pigmentosa, diabetes, renal and cardiac malformations, polydactyly, and hypogonadotropic hypogonadism. At least 12 genetic loci have been identified, and most of the encoded proteins form two multiprotein complexes that are involved in ciliary function and microtubule-based intracellular transport. Some evidence suggests that mutations might disrupt leptin receptor trafficking in key hypothalamic neurons, causing leptin resistance.

Other Specific Syndromes Associated with Obesity • ***CUSHING'S SYNDROME*** Although obese patients commonly have central obesity, hypertension, and glucose intolerance, they lack other specific stigmata of Cushing's syndrome (Chap. 406). Nonetheless, a potential diagnosis of Cushing's syndrome is often entertained. Cortisol production and urinary metabolites (17OH steroids) may be increased in simple obesity. Unlike in Cushing's syndrome, however, cortisol levels in blood and urine in the basal state and in response to corticotropin-releasing hormone (CRH) or ACTH are normal; the overnight 1-mg dexamethasone suppression test is normal in 90%, with the remainder being normal on a standard 2-day low-dose dexamethasone suppression test. Obesity may be associated with excessive local reactivation of cortisol in fat by 11β-hydroxysteroid dehydrogenase 1, an enzyme that converts inactive cortisone to cortisol.

HYPOTHYROIDISM The possibility of hypothyroidism should be considered, but it is an uncommon cause of obesity; hypothyroidism is easily ruled out by measuring thyroid-stimulating hormone (TSH). Much of the weight gain that occurs in hypothyroidism is due to myxedema (Chap. 405).

INSULINOMA Patients with insulinoma often gain weight as a result of overeating to avoid hypoglycemic symptoms (Chap. 420). The increased substrate plus high insulin levels promote energy storage in fat. This can be marked in some individuals but is modest in most.

CRANIOPHARYNGIOMA AND OTHER DISORDERS INVOLVING THE HYPOTHALAMUS Whether through tumors, trauma, or inflammation, hypothalamic dysfunction of systems controlling satiety, hunger, and energy expenditure can cause varying degrees of obesity (Chap. 402). It is uncommon to identify a discrete anatomic basis for these disorders. Subtle hypothalamic dysfunction is probably a more common cause of obesity than can be documented using currently available imaging techniques. Growth hormone (GH), which exerts lipolytic activity, is diminished in obesity and is increased with weight loss. Despite low GH levels, insulin-like growth factor (IGF) I (somatomedin) production is normal, suggesting that GH suppression may be a compensatory response to increased nutritional supply.