THE GENETICS OF HUMAN OBESITY

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Abstract | Obesity is an important cause of morbidity and mortality in developed countries, and is also becoming increasingly prevalent in the developing world. Although environmental factors are important, there is considerable evidence that genes also have a significant role in its pathogenesis. The identification of genes that are involved in monogenic, syndromic and polygenic obesity has greatly increased our knowledge of the mechanisms that underlie this condition. In the future, dissection of the complex genetic architecture of obesity will provide new avenues for treatment and prevention, and will increase our understanding of the regulation of energy balance in humans.

BODY MASS INDEX (BMI). An anthropometric measure of body mass that is calculated by dividing a person's weight in kilograms by the square of their height in metres.

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Almost 1 in 3 adults in the United States can currently be defined as clinically obese[1]; that is, with a BODY MASS INDEX (BMI) that is greater than 30 kg m^{-2}. The prevalence rates in other developed countries follow closely behind, and those in the developing world are rapidly catching up as they increasingly adopt a 'westernized' lifestyle. Obesity can therefore be seen as a global pandemic. The consequences of this are not only the social and psychological effects of excessive weight, but also the significant morbidity and premature mortality associated with the serious medical conditions that obesity predisposes to, including type II diabetes, hypertension, coronary artery disease and many forms of cancer[2,3]. If rates continue to rise in line with current trends, obesity is predicted to surpass smoking as the leading risk-factor for mortality in the United States within the next few years[4]. Furthermore, among the increasing number of affected children, the associated reduction in life expectancy is found to be even more extreme[5], and markers that are predictive of cardiovascular disease can already be detected in some cases[6].

Industrialization and its economic consequences have led to an increasingly urbanized and sedentary workforce. Coupled with ease of access to food, which has been aided by the globalization of this market, this basic reduction in energy expenditure and increase in caloric intake has contributed to what is now termed the 'obesogenic' environment[7]. In this respect, excess fat cannot be considered as a disease (a condition that is due to an individual biological abnormality), but as a collective adaptation to the pathological environmental pressure to eat too much and exercise too little.

Although inhabitants of the developed world share an increasingly homogeneous environment and the proportion of overweight adults has risen, there has been a particularly pronounced increase in those who can be defined as morbidly obese (BMI >40 kg m^{-2}), which exceeds what would be expected from a shift in population mean alone[1]. This implies that the 'obesogenic' environment that has developed since the mid-to-late twentieth century has caused a subgroup of the population, who are genetically susceptible to severe weight gain, to become excessively obese[8]. A theory to explain this has its origins in the classic paper by J. V. Neel that outlines the 'thrifty gene' hypothesis, whereby genes that predispose to obesity would have had a selective advantage in populations that frequently experienced starvation[9]. People who possess these genes in today's obesogenic environment might be those that 'overreact' — that not merely become slightly overweight, but become extremely obese. This can be seen in certain high-risk groups, such as Pima Indians and Pacific Islanders[8], and recent studies in the United States have shown that there is also a disproportionate level of obesity in African-Americans and Hispanic-Americans compared with Caucasians[10]. These differences cannot be explained by lifestyle, economic or environmental factors alone, indicating an important role of genetics.

Here, we provide an overview of the physiological basis of weight regulation, a description of monogenic and syndromic forms of obesity, and the genetic contribution to complex polygenic obesity — common obesity — that is caused by the interaction between

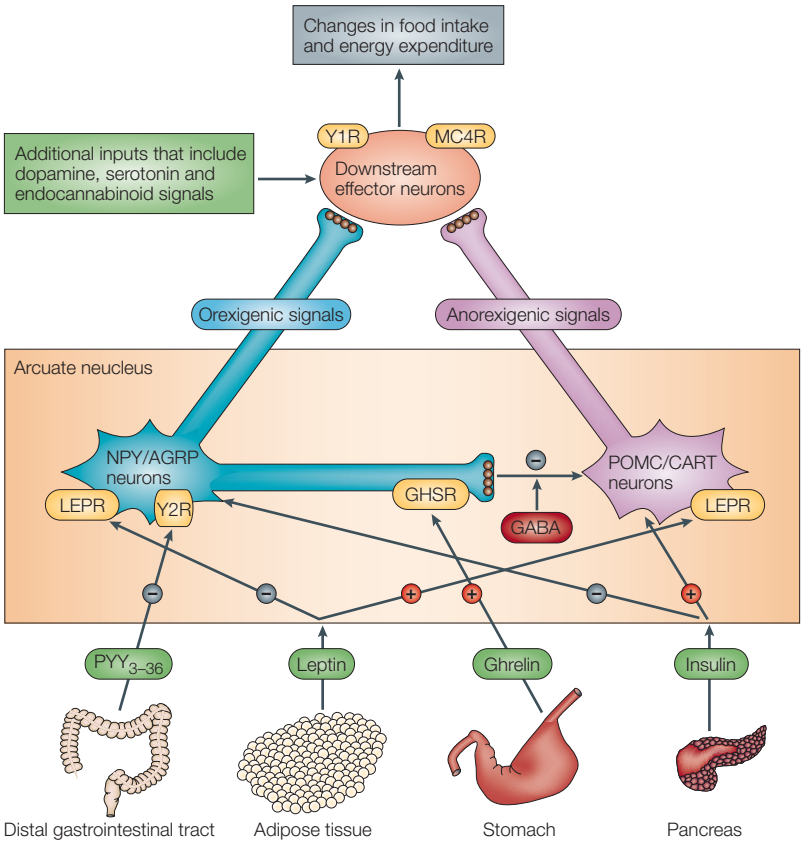


Figure 1 | **Physiological regulation of energy balance.** The neuropeptide Y (NPY)/agouti-related protein (AGRP) neurons, and the pro-opiomelanocortin (POMC)/cocaine and amphetamine related transcript (CART) neurons in the arcuate nucleus of the hypothalamus have key roles in the regulation of energy balance. Activation of the NPY/AGRP neurons has an orexigenic effect, promoting food intake, whereas the POMC/CART neurons have the opposite anorexigenic effect. POMC is activated through its post-translational modification to α-melanocyte stimulating hormone (α-MSH; not shown). These two sets of neurons receive input from several endocrine hormones as follows. Leptin is secreted from adipose tissue, circulating at levels that are proportional to body adipose stores, and exerts its effects through the leptin receptor (LEPR), inhibiting the NPY/AGRP neurons and stimulating the POMC/CART neurons. The pancreas secretes insulin, which has an anorexigenic influence on the arcuate nucleus. Ghrelin is produced by the stomach and duodenum, and stimulates the NPY/AGRP neurons through their growth hormone secretagogue receptors (GHSRs). The peptide $YY_{3–36}$ ($PYY_{3–36}$) is secreted from the distal gastrointestinal tract and signals through Y2 receptors (Y2Rs) to produce an inhibitory effect on the NPY/AGRP neurons. The NPY/AGRP neurons also have an inhibitory effect on the POMC/CART neurons through the release of γ-aminobutyric acid (GABA), which might be stimulated by the binding of ghrelin to GHSRs. The orexigenic and anorexigenic signals that are produced by the NPY/AGRP and POMC/CART neurons are then sent to second-order downstream effector neurons, which also receive modifying inputs from dopamine, serotonin and endocannabinoid signals. These effector neurons express receptors that include the Y1 receptor (Y1R) and the melanocortin 4 receptor (MC4R). These various inputs come together to provide the overall balance between food intake and energy expenditure.

multiple genes and the environment. We also discuss the progress that has been made so far in the identification of novel metabolic pathways that are involved in the physiology of weight regulation and in the pathophysiology of obesity, which might lead to improved preventive and therapeutic strategies. Finally, emerging strategies for gene identification are considered, concluding with a brief discussion of the future goals of research into the genetics of obesity.

Physiological basis of obesity

Obesity is caused by perturbations of the balance between food intake and energy expenditure, which is regulated by a complex physiological system that requires the integration of several peripheral signals and central coordination in the brain. The hypothalamus functions as a central regulator in this system. It receives information about energy balance through neuronal and hormonal signals to several tissue nuclei within it — particularly the ventro-medial, paraventricular and arcuate nuclei — and to the lateral hypothalamic area[11] (FIG. 1). The arcuate nucleus has an essential role in this system; it contains two sets of neurons, one produces agouti-related protein (AGRP) and neuropeptide Y (NPY) and the other produces pro-opiomelanocortin(POMC) and cocaine- and amphetamine-related transcript (CART). The first type are orexigenic, promoting food intake and reducing energy expenditure, and the second type produce the opposite anorexigenic effect[12].

Peripheral endocrine signals exert their effects through this system over both long- and short-term time-frames. Insulin has a role in the CNS as a signal of the level of adiposity over a moderate- to long-term period and has an anorexigenic effect through stimulation of POMC/CART neurons and inhibition of AGRP/NPY neurons[13]. The anorexigenic hormone leptin seems to be the principal adiposity indicator and signal of the state of nutrition, as its plasma levels are highly correlated to adipocyte number and fat content[14]. However, leptin is involved in the long-term regulation of adiposity, and other peptides are responsible for the short-term regulation of appetite. One of these, the orexigenic peptide ghrelin, is secreted primarily by the stomach and duodenum, and shows a rise in serum levels before eating and a decrease after eating[15]. Another mediator, peptide $YY_{3–36}$ ($PYY_{3–36}$), is secreted from the distal gastrointestinal tract on ingestion of food, with concentrations peaking within approximately 1 hour. It binds to presynaptic Y2 receptors in the NPY neurons that have putative inhibitory effects, which might lead to decreased food intake. Satiety is mediated by the response to other factors, such as gut distension and the release of the peptide cholecystokinin (CCK)[16].

The central arcuate nucleus processes these different inputs and exerts its effects by signalling to various downstream effector neurons. These include the orexigenic melanin-concentrating hormone (MCH) neurons and orexin or hypocretin neurons in the lateral hypothalamus[16], the thyrotrophin-releasing hormone (TRH) neurons that are involved in regulating the hypothalamic–pituitary–thyroid axis[17] and the γ-aminobutyric acid (GABA)-releasing interneurons in the paraventricular nucleus (PVN), which modulate orexigenic or anorexigenic effector neurons. Further inputs to this system include the dopamine, serotonin and endocannabinoid signalling systems (FIG. 1).

This weight-regulatory system is a powerful protection against weight loss; however, the same cannot be said for weight gain[18]. With increasing adiposity, the consequent rise in leptin has a limited effect on reducing

food intake and averting obesity[19]. The anti-obesity role of leptin is limited by cellular resistance to this signal, which might have developed in response to evolutionary pressure to promote fat storage and so protect against starvation[16]. Various mechanisms have been proposed for the occurrence of leptin resistance, including impairment of leptin transport[20], as well as the presence of negative regulators of leptin and insulin signalling[21–23].

Analysis of these physiological pathways has highlighted possible candidate genes that might underlie the genetic basis of obesity. In turn, genetic studies have contributed significantly to understanding the physiology of weight regulation, through both the use of animal models and the investigation of the genetics of rare and common human forms of obesity.

Monogenic forms of obesity

It is well established that mutations in genes that encode proteins with likely roles in appetite regulation are responsible for Mendelian disorders in which obesity is the most obvious phenotype. The elucidation of the causes of some of these monogenic forms of obesity has benefited from the positional cloning of a series of mouse obesity genes, including those that encode leptin[24], the leptin receptor (LEPR)[25], carboxypeptidase E (responsible for processing prohormone intermediates, such as proinsulin)[26] and the orexigenic protein agouti[27]. Targeted genetic manipulation has also established the vital regulatory role of molecules such as the melanocortin 4 receptor (MC4R), which is vital in the melanocortin pathway, and the orexigenic protein AGRP[28,29] (FIG. 1). These discoveries were rapidly followed by the identification of rare monogenic recessive forms of human obesity that are caused by mutations in the genes that encode leptin[30], LEPR[31], prohormone convertase 1(an endopeptidase that is involved in processing prohormones, including insulin and POMC)[32] and POMC[33], all of which result in a phenotype of excessive energy intake relative to energy expenditure.

A key role of leptin in some monogenic forms of obesity was further supported by the striking effect of leptin replacement in an extremely obese child with congenital leptin deficiency. In this 9-year-old child, the daily subcutaneous injection of recombinant human leptin for a year led to a complete reversal of obesity, with sustained fat-mass loss[34]. Moreover, partial leptin deficiency in 13 Pakistani subjects, owing to a heterozygous frameshift mutation in the leptin gene, was found to be associated with increased body fat[35]. However, only a handful of families with extreme forms of obesity in early infancy have mutations in these genes.

By contrast, more frequent autosomal-dominant forms of obesity are caused by mutations in the gene that encodes MC4R[36,37]. MC4R deficiency represents the most common monogenic obesity disorder that has been identified so far. It is present in 1–6% of obese individuals from different ethnic groups, with a higher prevalence in cases with increased severity and earlier age of onset[38,39]. In children with *MC4R* mutations, the degree of obesity and HYPERPHAGIA correlates with the extent of impairment of MC4R signalling, but the correlation disappears in adult carriers who cannot be phenotypically distinguished from obese non-carriers[40]. The characteristic intense feeling of hunger during childhood in patients with MC4R deficiency seems to lessen in adolescence, and levels of hyperinsulinaemia also become less marked[41]. Interestingly, MC4R-deficient mice are not hyperphagic when fed a low-fat diet, whereas hyperphagia is observed after the introduction of diets that have increased fat content, indicating gene–environment interactions[42]. Although difficult to assess in humans, such environmental effects for genes that are involved in the control of food intake might also contribute to explaining the increase in childhood obesity that has occurred in the past 20 years.

Syndromic forms of obesity

At least 20 rare syndromes that are caused by discrete genetic defects or chromosomal abnormalities, both autosomal and X-linked, are characterized by obesity. Most of these obesity syndromes are distinguished by the presence of mental retardation. It might be difficult to determine the origin of the obesity in children with these syndromes, who often live in institutions in which excess adiposity might be largely due to environmental factors. However, at least four syndromes seem to share severe hyperphagia, and/or other signs of hypothalamic dysfunction, indicating an origin at the level of the CNS[43].

The most frequent of these syndromes (1 in 25,000 births) is Prader–Willi syndrome (PWS), an autosomal-dominant disorder that is characterized by obesity, hyperphagia, diminished foetal activity, muscular HYPOTONIA, mental retardation, short stature and HYPOGONADOTROPIC HYPOGONADISM. It is usually caused by a paternally inherited deletion at the chromosomal region 15q11.2–q12, and less frequently by maternal UNIPARENTAL DISOMY; in rare cases it is caused by a defect that affects imprinting on this chromosome[44]. The cause of hyperphagia in PWS remains elusive, although PWS phenotypes are consistent with a combined hypothalamic impairment, causing several endocrine abnormalities. Recently, it was also suggested that the elevated production of the stomach-secreted peptide ghrelin seen in PWS might increase appetite by interacting with the POMC/CART and NPY hypothalamic neurons[45].

The loss of the single minded homologue 1 *(SIM1)* gene has also been associated with hyperphagia in syndromic obesity. This gene encodes a transcription factor that has a pivotal role in neurogenesis. Mice that are homozygous for a null allele of *SIM1* lack the PVN of the hypothalamus and die perinatally, whereas heterozygous null *SIM1* mice are hyperphagic and develop early-onset obesity, presumably related to the presence of on average 24% fewer cells in the PVN than in wild-type animals[46]. In humans, deletion or disruption of the *SIM1* region results in either a 'Prader–Willi-like' phenotype or a form of early-onset obesity that is associated with excessive food intake, similar to the hyperphagia seen in the mouse model[47,48].

HYPERPHAGIA
Ingestion of a greater than optimal quantity of food; an abnormally increased appetite for and consumption of food.

HYPOTONIA
Decreased muscle tone from the average and reduced resistance to passive stretching of muscles.

HYPOGONADOTROPIC HYPOGONADISM
Absent or decreased function of the male testis or the female ovary (the gonads). It results from the absence of the gonadal stimulating pituitary hormones, FSH (follicle stimulating hormone) and LH (luteinizing hormone).

UNIPARENTAL DISOMY
The presence in a cell of homologous chromosomes from the same parent, with no chromosome of that pair from the other parent. This can result from non-disjunction events during meiosis, and might be composed of both homologous chromosomes from one parent (heterodisomy) or a duplicate of one chromosome (isodisomy).

G_s PROTEIN
The heterotrimeric guanine nucleotide-binding protein (G protein) that stimulates adenylyl cyclase and functions as a molecular switch in many signal-transduction pathways.

ROD-CONE DYSTROPHY
Hereditary, progressive degeneration of the neuroepithelium of the retina that is characterized by night blindness and progressive contraction of the visual field.

POLYDACTYLY
A developmental anomaly that is characterized by the presence of more than five fingers on the hand or more than five toes on the foot.

HERITABILITY
The proportion of phenotypic variance that is due to genetic effects.

Pseudohypoparathyroidism type 1A (PHP1A) syndrome is due to a maternally transmitted mutation in *GNAS1*, which encodes the α-subunit of the G_s PROTEIN. Food-intake abnormalities in patients with this syndrome might be due to the expression of the resulting variant G_s protein in the hypothalamic circuitry that controls energy balance, which involves many G-protein coupled receptors[49].

The origin of obesity is more complex in Bardet–Biedl syndrome (BBS), which is characterized by six main features: ROD-CONE DYSTROPHY (the most frequent phenotype), POLYDACTYLY, learning disabilities, hypogonadism in males, renal abnormalities and obesity. In BBS patients, obesity occurs with an early onset, usually arising within the first few years of life[50]. However, one study of post-pubertal BBS patients found that only 52% were clinically obese[50]; therefore, this syndrome can present with a heterogeneous phenotype. Mutations in seven of the eight genetic loci that are associated with BBS have been identified in various pedigrees, but the functions of these genes remain poorly understood[51,52]. The genetic basis of BBS is typically autosomal recessive; however, the occurrence of triallelic inheritance has been suggested in some families[53].

It is clear from the descriptions above that the molecular causes that underlie the aetiology of syndromic obesity are more complex than for monogenic cases, and further studies are required to elucidate their genetic basis.

Genetics of common obesity

Perhaps surprisingly, the first evidence that genetics is important in common, non-syndromic obesity came from a study that was published nearly 30 years ago. In 1977, the National Heart, Lung and Blood Institute (NHLBI) Twin Study first indicated the possibility that the observed familial aggregation for obesity was due to genetic factors rather than environment[54]. Subsequently, in 1986, Stunkard used 1,974 monozygotic and 2,097 dizygotic twin pairs, and estimated a HERITABILITY value for weight of 0.78, which increased to 0.81 on completion of a 25-year follow-up[55]. These values were similar to the heritability value of 0.80 for height that was estimated in the same study. An adoption study at the same time showed similar results in support of a genetic influence on body weight, with adopted children having body sizes more similar to those of their biological parents than their adopted parents across the whole range of body size[56]. These studies were effectively combined in a seminal paper in 1990 that examined identical and fraternal twins that were reared together and apart[57]. Intra-pair correlation coefficients

Table 1 | **Phenotypes that are commonly used in obesity genetics research**

Phenotypes	Measurement methods	Comments
Physical phenotypes		
Weight	Scales	Quick, easy, cheap. Self-reported, so can be inaccurate.
Waist circumference Waist–hip ratio	Tape measure	Quick, easy, cheap. Used to define central obesity. Correlates well with BMI, visceral fatness and total body fatness.
Body mass index (BMI)	Scales and tape measure	Quick, easy, cheap. Used to define clinical obesity that is due to high correlation with fatness. Often calculated retrospectively for study groups that have been recruited for other reasons.
Caloric intake	Questionnaire or subject recall observation	Cheap and relatively simple if it is questionnaire-based. Complex and time-consuming if observation is required in controlled conditions.
Feeding behaviour	Questionnaire or subject recall observation	Cheap and relatively simple if it is questionnaire-based. Complex and time-consuming if observation is required in controlled conditions.
Skinfold thickness	Skin callipers	A relatively simple measure of subcutaneous fat. Usually used as the sum of several measures or as a ratio of thicknesses.
Central fat mass (CFM) Visceral fat mass (VFM) CFM–VFM ratio	DEXA	Precise and accurate, but expensive, complex and time-consuming. Unsuitable for large-scale screening.
Body-fat distribution	CT MRI	Precise and accurate, but expensive, complex and time-consuming. Unsuitable for large-scale screening.
Molecular phenotypes		
Hormone levels	ELISA RIA	Typically assessed in blood samples. Difficult to do *in vivo* for differentiated organs and tissues; for example, adipose tissue. Reflects the sum of all influences on a particular hormone. Expensive for large-scale studies.
Transcription levels	RT-PCR Real-time PCR Microarray	A wide range of tissues can be investigated; comparisons of different physiological states are possible. Only small numbers are used as it is currently expensive. Large datasets present analytical challenges. Measures relative RNA levels and not levels of biologically active proteins.
Metabolic profiling	HPLC NMR	Typically assessed in body fluids. Sample acquisition is relatively easy, but generates a complex metabolic profile, is expensive and is not easily applicable to solid tissues.

This is a list of categories of phenotypes that are used in many obesity genetics studies. Most are relatively broad, but demonstrate the relative strengths and weaknesses of each. CT, computed tomography; DEXA, dual energy x-ray absorptiometry; ELISA, enzyme-linked immunosorbent assay; HPLC, high-performance liquid chromatography; MRI, magnetic resonance imaging; NMR, nuclear magnetic resonance; RIA, radioimmunoassay; RT-PCR, reverse-transcriptase PCR.

Table 2 | **A selective list of genes that are associated with obesity phenotypes**

Gene*	Gene name*	Location‡	Phenotypes measured‖	References
ACDC	Adipocyte, C1Q and collagen domain containing, adiponectin	3q27	BMI, waist circumference BMI	137 138,139
ADRA2A	Adrenergic receptor α-2A	10q24–q26	Skinfold ratio, abdominal fat Skinfold ratio	140,141 142
ADRA2B	Adrenergic receptor α-2B	2p13–q13	Basal metabolic rate, weight-gain	143,144
ADRB1	Adrenergic receptor β-1	10q24–q26	Weight, fat mass, BMI	145
ADRB2	Adrenergic receptor β-2 surface	5q31–q32	WHR, obesity, BMI, subcutaneous fat Fat accumulation, obesity Adipocyte lipolysis	146–152 151,152 153
ADRB3	Adrenergic receptor β-3	8p12–p11.2	WHR, BMI, weight-gain capacity, earlier onset	154–160
LEP	Leptin (obesity homologue, mouse)	7q31.3	Obesity, BMI	161–164
LEPR	Leptin receptor	1p31	BMI, fat mass, overweight Fat mass, overweight Fat mass	165–167 168 169
NR3C1	Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	5q31	Obesity, overweight	170–172
PPARG	Peroxisome proliferative activated receptor, γ	3p25	BMI, weight, fat mass BMI, overweight, fat mass	173–182 175,177,183
UCP1	Uncoupling protein 1 (mitochondrial, proton carrier)	4q28–q31	Weight, BMI WHR	184–188 189
UCP2	Uncoupling protein 2 (mitochondrial, proton carrier)	11q13	Obesity BMI, obesity, skinfold thickness	190 191–194
UCP3	Uncoupling protein 3 (mitochondrial, proton carrier)	11q13	Caloric intake, fat intake, fat mass, WHR, BMI Skinfold thickness BMI	189,195,196 196 197,198

The list includes genes for which markers have been shown to be associated with obesity-related phenotypes in multiple published studies. A more complete list can be found at the Obesity Gene Map Database (see Online links box). *Official gene symbols and names are from the HUGO nomenclature committee web site (see Online links box). ‡Chromosomal band location is as listed in the NCBI database. ‖Short-hand descriptions of associated phenotypes that are statistically significant at $p < 0.05$. BMI, body mass index; WHR, weight–hip ratio.

for obesity phenotypes of 0.70 for men and 0.66 for women were reported a similar measure of heritability to previous studies. Shared environment seemed to have no measurable effect and non-shared personal environment contributed about 30% of the variance.

Although body weight and BMI are simple measures and are suitable for general population samples such as those described above, they are relatively crude and various more informative phenotypes have been used more recently, as described in TABLE 1. In 1989, Hasstedt and colleagues suggested a recessive mode of inheritance for a phenotypic measure that is derived by calculating the ratio of SUBSCAPULAR SKINFOLD THICKNESS to the sum of subscapular and SUPRAILIAC SKINFOLD THICKNESSES[58]. In the same year, using the same ratio as a measure of central body fat in the NHLBI cohort, a heritability of 0.43 was determined after correction for overall obesity[59]. The Finnish Birth Cohort Study[60] and the Muscatine Ponderosity Family Study reported similar values[61]. A large study of 4,884 twins and 2,509 singletons from Finland, aged between 16- and 17-years, estimated that 80% of the inter-individual variation in BMI was due to genetic effects[62], and this was supported by a similar UK-based study[63]. A recent investigation into the heritability of BMI, skinfold thickness and waist circumference in 102 Caucasian families reported an estimate of 0.46–0.60 for measures of fatness, such as BMI, and 0.29–0.48 for measures of fat distribution, such as waist circumference adjusted for BMI, independent of overall fatness[64]. These values fit in well with the estimates from twin studies, and indicate a minimum heritability of 0.4 for fatness and/or obesity.

The relative contribution of energy intake and expenditure in the development of obesity has also been explored using twin studies. In 1990, Bouchard and coworkers overfed pairs of twins and found that, within twin pairs, weight-gain correlation was high (>70%), despite the fact that some twin pairs gained as little as 4.3 kg and others as much as 13.3 kg (REF. 65). Interestingly, after the study, most subjects spontaneously returned to their original food intake behaviour and lost weight, and this reduction was also found to be genetically driven. This phenomenon was confirmed in Czech twins that were submitted to a low calorie diet, with an intra-pair correlation of 0.88 in fat loss during treatment and a correlation of 0.77 for METABOLIC EFFICIENCY[66]. Recently, a familial association with total energy and macronutrient intakes, independent of anthropometric measures such as height and weight, was reported, indicating genetic or home-environmental influences that are specific to these behaviours[67]. There is currently little evidence to support a genetic contribution to alterations in energy intake, probably owing to the fact that this is almost impossible to measure in an unperturbed, freely observed state.

SUBSCAPULAR SKINFOLD THICKNESS
The skinfold measure that is taken below the inferior angle of the scapula.

SUPRAILIAC SKINFOLD THICKNESS
The skinfold measure that is taken midway between the hip joint and the bottom of the ribcage.

METABOLIC EFFICIENCY
Energy intake per kilogram that is required to maintain bodyweight.

Familial clustering for obesity has also been observed, with a RELATIVE RISK of 3–7 in adults[68] and up to 10 in morbid obesity with childhood onset (P.F., unpublished observations). The study of populations with different degrees of ADMIXTURE also supports a role of genetic factors in obesity. Indeed, in the obesity-prone Pima Indians and in African-Americans, the degree of admixture is inversely correlated with obesity and diabetes, indicating that the admixed genes have a strong effect on disease susceptibility[69].

With the increasing scale of the obesity problem and the body of evidence outlined above for a strong genetic contribution to development of the disease, many groups have started to study the genetics of polygenic obesity to better understand the pathogenesis of the disease and highlight possible pharmacological targets. Two approaches that are commonly used across the whole field of complex human genetics have been used to identify the underlying genes: candidate-gene and whole-genome approaches, which are discussed in the sections that follow.

Approaches to identifying obesity genes

Candidate-gene studies. The design of the candidate-gene approach is simple; the fundamental requirements are the identification of a gene that is involved in the disease phenotype, a polymorphic marker within that gene and a suitable set of subjects to genotype for that marker. Identification of the potential candidate genes is the main stumbling block. There are two main types of candidate that are generally considered in such studies: functional and positional. Functional candidates are genes with products that are in some way involved in the pathogenesis of the disease. Clearly, this is highly dependent on the current state of knowledge about a disease, and in the case of obesity, the identification of signalling molecules such as leptin and POMC has provided a great stimulus to the field. Positional candidates are genes that are identified because they lie within genomic regions that have been shown to be genetically important in linkage or association studies, or by the detection of chromosomal translocations that disrupt the gene. Positional candidates are discussed in the context of whole-genome screens; we begin with a discussion of functional candidates.

The candidates discussed here and listed in TABLE 2 are only a small selection of those published, and a more complete list can be found at the Obesity Gene Map database (see Online links box). As would be expected, owing to both experimental and statistical variation, there have been studies that have reported no association for all of these genes; however, from the available functional data, they are all plausible candidates for genes that are involved in common obesity. These genes are involved in the regulation of energy metabolism, appetite control or autocrine–paracrine signalling by adipocytes.

A possible role of less deleterious variants of genes that are responsible for monogenic forms of obesity (described above) has been proposed for common obesity. Currently, there is little evidence for this, although recent reports indicate that rare variants in these genes might have a greater influence than first thought. A non-synonymous SNP that affects *POMC* is associated with childhood obesity in various populations[70]. This variant is responsible for the abnormal generation of a fusion protein between β-melanin stimulating hormone (β-MSH) and β-endorphin, which binds MC4R with an affinity that is similar to its natural ligands, but has a reduced ability to activate the receptor. This might affect melanocortin signalling pathways, thereby leading to increased food intake. The potential role of common SNPs within the *POMC* locus is currently under intense investigation, and the association of multiple HAPLOTYPES with obesity phenotypes is a plausible hypothesis (J. Blanjero, personal communication). A haplotype in the leptin promoter has also been shown to be strongly associated with obesity[71], although surprisingly this is the only evidence to indicate a role for leptin variants in common obesity so far. In the case of the *MC4R* gene, the most common missense mutation has been shown to be significantly associated with protection from obesity, in spite of having a low MINOR ALLELE FREQUENCY[72].

It is noteworthy that there are no convincing meta-analyses of variants in candidate genes that unambiguously support their contribution to the genetic risk for obesity, as has been recently shown in type II diabetes for the nuclear receptor peroxisome proliferative activated receptor-γ (PPARG) or for the potassium channel KCNJ11 (previously known as Kir6.2) (REF. 73). It is possible that the current state of our knowledge of mechanisms that control weight maintenance has not yet revealed the most promising candidates. On the other hand, obesity is so heterogeneous in human populations that meta-analyses of genetic studies for obesity can be difficult to evaluate; for example, this could be due to the widely differing obesogenic environments that subjects are recruited from. The way forward now is to investigate the functional roles of the current candidate genes in model organisms and *in vitro* cell systems. This will allow the development of functional assays that can then be used to test putative activator or inhibitor molecules as possible therapeutic agents.

Genome-wide linkage studies

Genome-wide linkage scans involve the typing of families using polymorphic markers that are positioned across the whole genome, followed by calculating the degree of linkage of the marker to a disease trait. Positional candidate genes can then be identified by examining the regions around the peaks of linkage that are obtained from the study. This is a useful approach as, unlike the candidate-gene studies described above, it does not rely on any pre-existing knowledge of the genes that underlie the trait being studied. There has been success using this method in other complex traits, such as inflammatory bowel disease , with the identification of caspase recruitment domain family, member 15 (*Card15*), also called *NOD2* (REF. 74), ischaemic stroke with phosphodiesterase 4D (*PDE4D*) (REF. 75), and asthma with a disintegrin and metalloproteinase domain 33 (*ADAM33*) (REF. 76) and the dipeptidylpeptidase 10 (*DPP10*) genes[77].

RELATIVE RISK
The ratio of the risk of the expression of a phenotype among individuals with a particular exposure, genotype or haplotype to the risk among those without that exposure, genotype or haplotype.

ADMIXTURE
The mixture of two or more genetically distinct populations.

HAPLOTYPE
A set of closely linked genetic markers on a single chromosome.

MINOR ALLELE FREQUENCY
The frequency of the less common allele of a polymorphism. It has a value between 0 and 0.5, and can vary between populations.

PROBAND
A subject that is ascertained on the basis of their phenotype; often used to identify affected families for genetic studies.

QUANTITATIVE TRAIT
A continuously varying trait; for example, weight, height and skin colour.

VARIANCE COMPONENTS METHOD
The variance components (VC) approach is a method that expresses the phenotypic variances and covariances among individuals as a function of the estimated number of shared alleles that are identical by descent at a given locus.

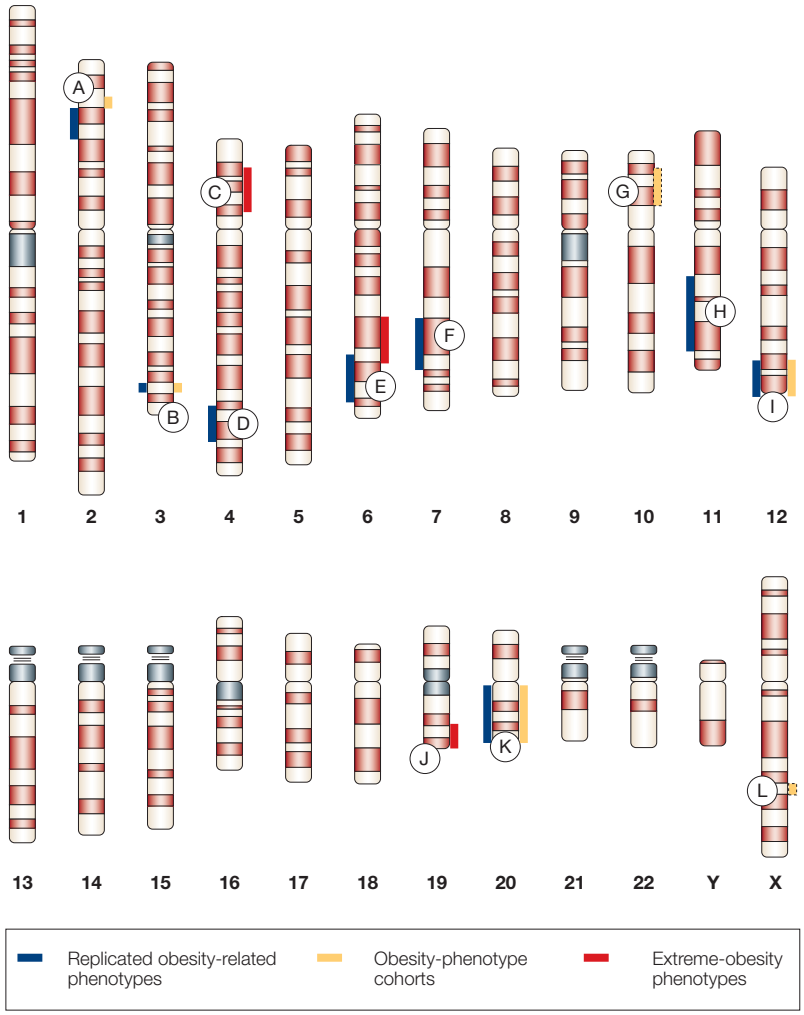


Figure 2 | **Genetic-linkage map for obesity.** Loci that have been found to be linked with obesity are shown. The blue bars indicate regions that have been replicated in several studies. The yellow bars represent those loci that were found in cohorts that were selected specifically for obesity, and dotted lines around these bars indicate replication with other obesity cohorts. The red bars indicate those regions that were identified in groups with extreme-obesity phenotypes. A, 2p21–p23 (REFS 78,79,81,82); B, 3q27 (REFS 96–101); C, 4p15–p14 (REF. 102); D, 4q31–q32 (REFS 83,84); E, 6q22.31–q23.2 (REFS 91,107,108); F, 7q31–q32 (REFS 84–86); G, 10p11–p12 (REFS 79,87,88); H, 11q14–q24 (REFS 89–91); I, 12q23–q24 (REFS 84,136); J, 19q13.33–q13.43 (REF. 105); K, 20q11–q13 (REFS 92–95); L, Xq24 (REFS 79,102,106).

These all provide evidence that this technique can successfully reveal new aetiological pathways. Here, we discuss how this strategy has been applied with some success, to the genetic basis of common obesity.

Sampling strategies in linkage studies. In obesity, genome-wide scans have been performed in two kinds of sample sets: families that are representative of general populations and families that are studied because they include an obese PROBAND. The former studies are of great interest for QUANTITATIVE TRAIT analyses in large pedigrees from populations with a high prevalence of obesity using the powerful VARIANCE COMPONENTS METHOD for linkage analyses. Indeed, using this method, the first genome scan for an obesity phenotype located a quantitative trait locus (QTL) for leptin levels and fat mass at 2p21 in a cohort of Mexican Americans from the San Antonio Family Heart Study[78]. The first genome-wide analysis using NUCLEAR FAMILIES ascertained specifically for obesity also found a locus for obesity at 2p21 and reported another at 10p12 (REF. 79). Subsequently, more than 165 loci have been identified[80], with evidence of linkage with numerous obesity-related phenotypes.

Many of these studies have only analysed BMI for linkage, as height and weight data are readily available for almost all patient samples, allowing retrospective analysis of subjects that were recruited for other purposes. Cohorts gathered for studies of type II diabetes, osteoporosis, hypertension, sleep apnoea (the cessation of breathing during sleep caused by upper airway obstruction), sedentary life style, for LONGITUDINAL PROSPECTIVE STUDIES, or ethnic groups of genetic or phenotypic interest, have all been subsequently analysed for linkage to BMI. So, what many of these studies have been investigating is linkage to the genes that govern the 'normal' variation in weight. The overlap between these genes and those contributing to extreme obesity might be minimal, because the extreme phenotype could be due to different pathophysiological pathways, and genes that predispose to it might be rare in the general population. Perhaps surprisingly, some loci — 2p21–p23 (REFS 78,79,81,82), 4q31–q32 (REFS 83,84), 7q31–q32 (REFS 84–86), 10p11–p12 (REFS 79,87,88), 11q14–q24 (REFS 89–91) and 20q11–q13 (REFS 92–95) — have nevertheless been replicated from these differing phenotypes in disparate cohorts (FIG. 2). A locus on chromosome 3q27 has also been reproducibly identified in METABOLIC SYNDROME cohorts[96–101].

Increasing the likelihood of replication. By adopting similar ascertainment criteria for obesity, the likelihood of replicating linkage in genome-wide scans is increased. In addition, it is clear that phenotypes must be measured as reproducibly as possible to allow replication. The linkage on chromosome 10p12 that was first reported in French Caucasians[79] was subsequently supported by the identification of the same locus in German adults[87] and in African- and European-Americans[88]. The French study used an obesity cohort that consisted of morbidly obese probands with at least one sibling with a BMI ≥27, and the replication studies used similar phenotypes. Hunt *et al.* replicated identification of the chromosome 20q11–q13 locus, initially found in the Pima Indian population[92], using patients who had undergone gastric bypass operations for extreme obesity, as well as families with individuals that have a BMI ≥32 (REF. 94). In the study by Kissebah *et al.*, which supported the linkage of metabolic syndrome to 3q27, as well as identifying a possible epistatic site on chromosome 17p12, the subjects were drawn from a weight-loss programme and from families with at least two obese sib-pairs with BMIs ≥30 (REF. 96).

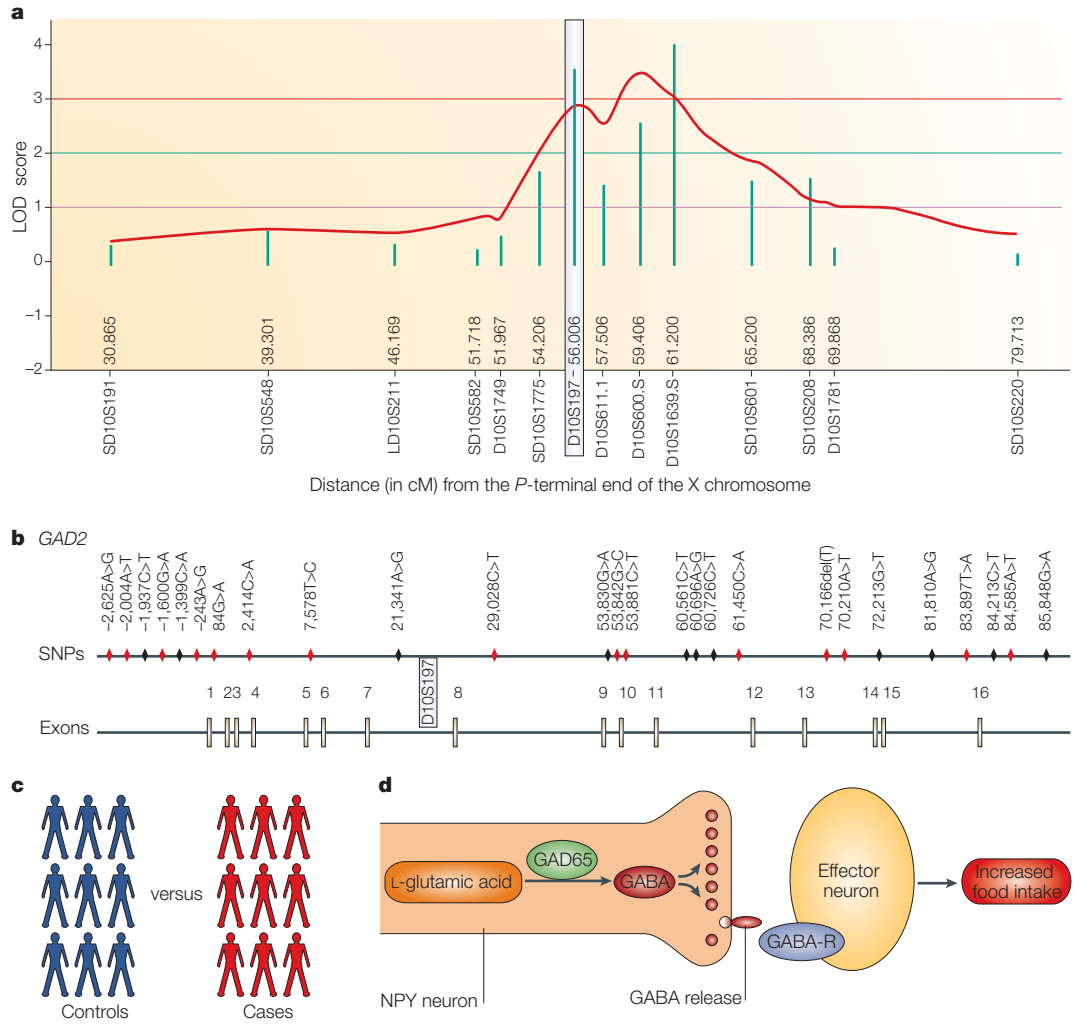
Enriching for a genetic component. A few studies have used families that contain several extremely obese individuals to attempt to select pedigrees with a significant

NUCLEAR FAMILY
A family that is composed of a father, mother and their children.

LONGITUDINAL PROSPECTIVE STUDIES
Studies in which individuals are followed up over time to assess who develops a certain outcome (often disease).

METABOLIC SYNDROME
The occurrence of hyperinsulinaemia, glucose intolerance, dyslipidaemia, hypertension and obesity in an individual.

Box 1 | **Identification of *GAD2* as a candidate gene for obesity**



The characterization of the chromosome 10p locus — initially identified in a French population[79] and subsequently replicated in German[87], African-American and European-American[88] cohorts — led to the first potential success in positional cloning of a novel susceptibility gene from an obesity-linkage region. The microsatellite D10S197 was found to be closest to the peak of linkage in the original and replication studies, as illustrated in **a** (the horizontal green lines on this graph indicate single-point logarithm of the odds (LOD) scores; the red lines indicate the multipoint score). This polymorphic marker is located in intron 7 of the glutamate decarboxylase 2 (*GAD2*) gene (**b**), and a protective haplotype (+61,450C and +83,897T) and an at-risk SNP in the *GAD2*-promoter region (–243A>G) were identified in both case-control and familial studies[109] (**c**). Functional studies showed a six-fold increase in *GAD2*-promoter activity for this allele.

GAD2 encodes the glutamic acid decarboxylase enzyme GAD65, which is involved in the formation of γ-aminobutyric acid (GABA) from L-glutamic acid (**d**). GABA functions together with the neuropeptide Y in the paraventricular nucleus to increase food intake[128], and leptin is known to function presynaptically to reduce GABA release from pro-opiomelanocortin (POMC) neurons[129]. Anti-GAD65 antibody concentrations have been shown to be associated with high body mass index (BMI), and this is thought to be due to obesity-associated hyperinsulinaemia[130]. Significant correlations between GAD65 antibody levels and the *GAD2* SNPs –243A>G, 61,450C>A and 83,897T>A were found, which indicate a functional effect of each of these SNPs on protein expression. Therefore, polymorphisms in *GAD2* might affect the GAD65 enzyme and so result in the increased production of GABA, which has a significant orexigenic role. In adults, the *GAD2* –243A>G SNP is associated with higher scores for hunger and disinhibition for food intake. In addition, in children, *GAD2* SNPs are associated with obesity in which there is an increase risk for 'binge eating' behaviour, especially in girls (D. Meyre *et al.*, unpublished observations).

Although *GAD2* SNPs cannot account for all of the linkage to the 10p region, these data highlight the importance of the GABA-related pathways in the regulation of food intake in humans. Genes that are involved in the GABA- and glutamate-signalling pathways, including those that encode the receptors and transporters of these molecules, are therefore among the potential candidates for polygenic obesity. The linkage peak and gene diagram are modified from REF. 109.

genetic component to obesity. Using morbidly obese subjects with obese siblings from a US population, Lee *et al.* reported linkage at 20q13 (REF. 95). In addition, by examining morbidly obese US subjects in 'affected clusters' — that is, groups of three or more closely related individuals with BMI ≥40 — Stone *et al.* identified a female-only predisposition locus at chromosome 4p15–p14, although the authors made no claims that this was a genuine sex-specific effect[102]. Subsequently, the company Myriad Genetics claimed in non-scientific journals that a so-called 'Obesity 1' gene had been identified in this region, but the identity of the gene has not been released so far.

The French population is under less obesogenic environmental pressure than that of the United States[103], and this is consistent with a considerably lower rate of morbid obesity (0.6% versus 4.6% in the US population)[104]. This indicates that morbidly obese French individuals are more likely to have a strong genetic predisposition, as the environmental effect is clearly weaker. Using a French cohort with severe and morbidly obese sib-pairs, a genome-scan recently found significant linkage at 19q13.33–q13.43 and suggestive linkage at 17q23.3–q25.1 (REF. 105). In a Finnish cohort, with a similar environmental pressure to the French sample, but with the extra advantage of considerable genetic homogeneity that is due to a relatively isolated population, a genome-scan of morbidly obese probands with an obese sibling found significant linkage at Xq24 (REF. 106).

There is a reduced time of environmental impact in extreme childhood obesity, so that studying such cases helps to reduce the contribution of environmental effects. A genome scan by Meyre *et al.* in children with a BMI that is greater than or equal to the ninety-seventh percentile localized significant linkage at 6q22.31–q23.2 (REF. 107). This was supported by the identification of linkage in the same region, using BMI and waist-circumference measurements, in the US Framingham Heart Study — a longitudinal prospective study of a general population sample for factors that influence cardiovascular disease[91,108]. Interestingly, this result is based on the genome-wide linkage analysis of six separate measurements of BMI taken over 28 years, from 1971 to 1998. This has showed that linkage studies of BMI values are robust with respect to the measurement errors that occur due to the inevitable minor variabilities that arise when different people take measurements at different times.

Therefore, making use of extreme phenotypes, reduced environmental pressure and homogeneous populations have been useful strategies in attempting to increase the genetic effects of obesity that apply to the groups studied and to improve the power of studies to detect linked loci.

Candidate genes from linkage studies. The definitive proof-of-concept that a genome-wide search for obesity genes has been successful is the identification of novel genes that contribute to the regulation of energy balance. In this regard, two positional candidate genes have been recently reported: *GAD2* at 10p, identified in French Caucasians (BOX 1), and *SLC6A14* at Xq24, identified in Finnish populations[109,110] (BOX 2). Interestingly, in both cases, the proposed molecular mechanisms that link mutations in these genes to obesity are connected with the hypothalamic regulation of food intake. Although it is clear that these genes do not account for large percentages of the genetic influence on obesity, and evidence for a role of these genes is still relatively preliminary, their discovery and replication in other sample sets provides evidence that the linkage approach can be fruitful in identifying genes that underlie genetic predisposition to common obesity. Other replicated loci that are linked to obesity phenotypes at 2p, 6q and 20p are currently the subject of intensive SNP analyses in various ethnic groups, and more strong positional candidates are likely to be identified soon.

New strategies for gene identification

Both the candidate-gene and whole-genome approaches to identifying genes that are associated with obesity have been partially successful, although they are more difficult than might originally have been expected. How could they be improved to identify novel genes more easily and with greater accuracy? Improving the power of a study by increasing the number of subjects, refining the phenotype, increasing the numbers of phenotypes available and using extreme phenotypes are important strategies, but can be expensive. Collaborations between groups to share existing datasets have resulted in significant increases in statistical power in other complex diseases — for example, type I diabetes[111] and asthma[112] — in spite of the complexity of analysing heterogeneous data. In addition, the proposed new 'genebanks' — collections of as many as a million DNA samples (see Austin *et al.*[113] for a review) — could provide advantages. They should allow large increases in statistical power without the compromise of introducing STRATIFICATION and other analytical challenges that arise from mixing together disparate groups of subjects, who are ascertained using varying criteria and by different research teams.

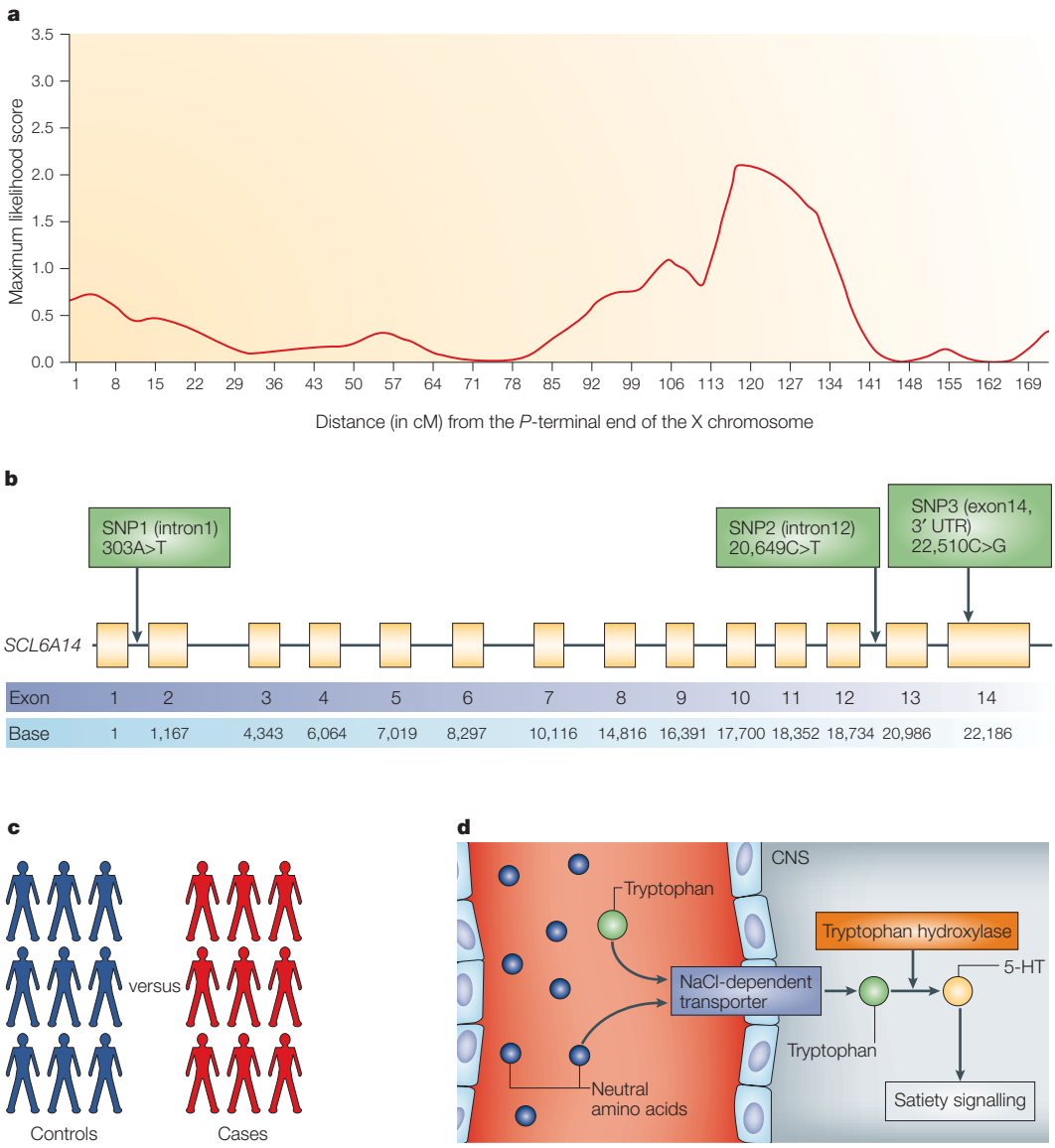
The increase in the number of subjects available for analysis that is offered by genebank projects needs to be matched by increases in the quality and specificity of phenotypic data. As shown in TABLE 1, many phenotypes have been used in genetic studies of obesity, and there is little agreement on the best phenotype to use, with advantages and disadvantages to each. As the field of complex genetics advances, it becomes increasingly clear that comprehensive and accurate phenotypic measurements are essential. End-phenotypes such as obesity or BMI are valuable, but represent the sum of all genetic and environmental influences; the future identification of genetic effects is likely to be achieved through the use of intermediate phenotypes, such as fat location or hormone levels, with consequent increases in the funding needed for such studies.

One source of novel intermediate phenotypes has emerged with the recent use of microarray technology to provide information on mRNA expression from thousands of genes in tissues of interest. In obesity,

STRATIFICATION
The presence of several subgroups within a study group, either through genuine population subdivision or recruitment bias. Differences in both allele frequency and disease prevalence between these subgroups can lead to spurious associations with disease.

Box 2 | **The *SLC6A14* candidate gene**

Significant linkage at Xq24 (**a**), with a peak at around 117 cM, was identified in a genome-scan of a Finnish population[106]. Microsatellite and SNP data were used to construct haplotypes within the linkage region, and evidence of shared haplotypes allowed the candidate region to be reduced from 15 Mb to 4 Mb. Analysis of candidate genes within this region in a case-control study detected a significant association of variants in the solute carrier family 6 member 14 gene (*SLC6A14*) with obesity[110] (**b**,**c**). This was based on a SNP in the 3′ untranslated region (SNP3; 22,510C>G) and haplotypes that comprise three non-coding SNPs, including SNP3. Recently, the association between the same *SLC6A14* SNPs and obesity was confirmed in a study in a French population where they were also found to modulate hunger and satiety scores[131]. Variants that affect non-coding regions can have many unpredictable effects, which can be difficult to determine[132], and no functional studies have been reported for these *SCL6A14* variants so far. The *SLC6A14* gene encodes a sodium- and chloride-dependent transporter of neutral and cationic amino acids[133] that has a high affinity for the non-polar amino acid tryptophan (**d**). In the brain, the enzyme tryptophan hydroxylase converts tryptophan into serotonin (5-hydroxytryptamine (5-HT))[134]. This neurotransmitter is known to be strongly involved with the central signalling of satiety by mechanisms that include effects on downstream effector neurons in the hypothalamus[135] (FIG. 1). Therefore, a possible hypothesis is that a reduction in the concentration of serotonin owing to reduced tryptophan transport might be the link with lower *SLC6A14* activity, and thereby increasing susceptibility to obesity by reducing satiety. The linkage peak in **a** is modified, with permission, from REF. 106 © (2000) Endocrine Society and the gene diagram in **b** is modified, with permission, from REF. 110 © (2003) American Society of Clinical Investigation.



comparing adipocytes from obese cases and lean controls offers the opportunity to identify genes that are up- or downregulated in these two physiological states. Such studies, which were initially carried out in mouse models[114,115] and have more recently been done for humans[116–118], show the strengths and weaknesses of microarray data. Their advantage is the ability to analyse the relative expression levels of thousands of genes simultaneously. However, the requirement for fresh tissue samples and high-quality RNA, together with the significant costs that are associated with running microarray experiments, has until recently limited these studies to small numbers of samples, greatly reducing the statistical power to detect significant differences in expression levels.

The use of microarrays on a larger scale, coupled with the use of gene-expression patterns as QTLs has, however, been carried out successfully in mice in one study of obesity genetics[119]. This study identified loci that are linked to expression levels of obesity-related genes, with the strongest linkage on mouse chromosome 2. It is notable that the syntenic region in humans, at 20q12–q13.2, has previously been identified as a locus that is linked to obesity[94,95]. This work has been followed by a microarray analysis of the basal expression levels of 3,554 human genes that are expressed in lymphoblasts, which demonstrated that using expression levels as QTLs in genome-wide linkage analysis allowed the identification of both *cis*- and *trans*-acting loci that regulate the basal expression of genes[120]. On the basis of these results, the use of expression levels as intermediate phenotypes (QTLs), as measured using microarrays, should prove to be a powerful technique for exploring the differences between lean and obese states in humans.

Another technique that is poised to make an enormous contribution to the field of complex human genetics is the whole-genome association study, which effectively merges the association and linkage approaches to gene identification. Until recently, the enormous amount of genotyping that is required to achieve even a moderate density of coverage across the genome was beyond even the largest laboratories. Now, with the development of large-scale sequencing facilities, the advent of medium- to high-throughput technologies for SNP typing and new DNA-pooling strategies, such genotyping projects are within the grasp of many researchers. Large-scale SNP-discovery projects, such as the SNP Consortium, and the International HapMap Project (see Online links box) are currently providing the necessary SNP information to online resources such as the dbSNP database (see Online links box). So, large-scale SNP studies of both large numbers of specific genes[121] and low-density whole-genome screens[122,123] are now becoming a reality. It is only a matter of time before the first whole-genome screens are carried out at the high SNP densities that are required for a single-pass genomic screen that will identify disease-specific genes (this requires >1 SNP per 5 kb, at a total of approximately 600,000 SNPs) in a large case-control or nuclear family collection (>1000 individuals).

The main problem with genome-wide studies that use SNPs lies in the analysis of the results. Genotyping technology is currently ahead of the statistical tools that are available, and it remains to be seen how quickly the problem of MULTIPLE-HYPOTHESIS TESTING using very large numbers of markers that show substantial linkage disequilibrium with each other will be solved. Theoretical and practical issues that surround whole-genome association studies are discussed in REFS 124,125. However, despite these concerns, the high density of SNP information that is available might provide the answer to an important problem for researchers who study complex genetic disease — the possibility that disease occurrence is due to the sum of many rare variants, which are not detectable using other methods because of the low level of risk that each variant confers. This has already been demonstrated in the case of the genetic basis of plasma high-density lipoprotein (HDL) levels[126]. Although this might complicate candidate-gene analysis, in the foreseeable future genotyping technologies will allow analysis of all the known SNPs in a gene. Alternatively, sequencing technologies might be developed that would allow the rapid sequencing of large genomic regions in sufficient numbers of subjects to capture all the relevant genetic information[127].

Conclusions

The most important message after nearly a decade of searching for genes that are involved in human obesity is that such genes, perhaps surprisingly, really do exist — despite the key role of modern lifestyles in the current obesity epidemic. These genes seem to be important in the development of most severe early-onset forms of obesity that have strong effects on morbidity and mortality. Their characterization has still to be completed, but should unravel the molecular mechanisms of an affliction that affects hundreds of millions of people, opening up new avenues in the management of a disease for which no efficient treatment, apart from major surgery, currently exists. By the discovery of novel genes that are involved in this condition, new aetiological pathways will be revealed that should lead to innovative therapies, preventive measures and insights into the pharmacogenetics of such strategies.

It is striking that despite constant statements from governments, charities and the media that childhood obesity is a world-wide threat, few convincing efforts have been made so far to collect and extensively phenotype large sample sets of obese children and their parents or to carry out PROSPECTIVE population-based studies of young obese individuals. However, the causes of some cases of childhood obesity have already been identified, and even cured — for example, in the case of leptin deficiency — which is better than the situation for many other complex diseases. Families with putative recessive forms of obesity have been identified for future studies, and several promising obesity-related candidate loci have already been identified from genome-wide linkage analyses, which await further analysis in association and functional studies. These strategies are sound and should provide new insights into obesity, an increasingly important disease in the early twenty-first century.

MULTIPLE-HYPOTHESIS TESTING
Testing more than one hypothesis in an experiment. As a result, the probability of an unusual result occurring by chance in the entire experiment is higher than the individual significance value associated with that result.

PROSPECTIVE STUDY
A study in which participants are divided into groups that are exposed or not exposed to the intervention(s) of interest before the outcomes have occurred.

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Competing interests statement

The authors declare no competing financial interests.

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