The genetic contribution to non-syndromic human obesity

Andrew J. Walley, Julian E. Asher* and Philippe Froguel*‡*

Abstract | The last few years have seen major advances in common non-syndromic obesity research, much of it the result of genetic studies. This Review outlines the competing hypotheses about the mechanisms underlying the genetic and physiological basis of obesity, and then examines the recent explosion of genetic association studies that have yielded insights into obesity, both at the candidate gene level and the genome-wide level. With obesity genetics now entering the post-genome-wide association scan era, the obvious question is how to improve the results obtained so far using single nucleotide polymorphism markers and how to move successfully into the other areas of genomic variation that may be associated with common obesity.

Heritability
The proportion of the total phenotypic variation in a given characteristic that can be attributed to additive genetic effects. In the broad sense, heritability involves all additive and non-additive genetic variance, whereas in the narrow sense, it involves only additive genetic variance.

**Section of Genomic Medicine, Imperial College London, Burlington-Danes Building, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK. ‡CNRS8090-Institute of Biology, Pasteur Institute, 1 Rue du Professeur Calmette, 59019 Lille, France. Correspondence to A.J.W. and P.F. e-mails: a.walley@imperial.ac.uk; p.froguel@imperial.ac.uk*
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If current trends continue, over 50% of adults in the United States will be clinically obese by 2030 (REF. 1), with global projections of 1.12 billion obese individuals by 2030 (REF. 2). Although the prevalence of obesity increased by 24% between 2000 and 2005, extreme obesity (body mass index (BMI) ≥ 40) increased by more than 50%, with a growth of 75% seen in the super-obese (BMI ≥ 50)[3]. The growth in obesity among adults has been paralleled by increases in obesity among children. 17% of children in the United States are considered obese (sex-specific BMI ≥ ninety-fifth percentile for age)[4], which is projected to rise to 30% by 2030 (REF. 1). Obesity is a major contributor to morbidity and mortality worldwide, surpassing smoking and drinking in its negative effects on health[5], which will negatively affect life expectancy of generations born after the rise of the obesity epidemic.

Many hypotheses have been proposed to explain the origin of the epidemic (see BOX 1 for a summary). Although the impact of environmental factors is likely to be significant, it is clear that obesity has a large underlying genetic component. Stunkard's seminal studies[6,7] gave a heritability estimate of 0.78 for weight, increasing to 0.81 in a 25-year follow-up study. Further twin studies have revealed heritability estimates of ~0.7 for BMI in both adults and children[8,9]. In addition, admixture mapping has shown that obesity correlates closely with the percentage of ancestry deriving from ethnic groups with an elevated prevalence of obesity[10,11]. This clear genetic basis for human obesity initiated the search to identify the causal genes with a view to understand the pathways and networks that control body mass in humans and to provide insights that will lead to rational treatment and prevention strategies, given the clear failure of public health campaigns.

There are currently a number of theories explaining the genetic basis of obesity but there is no current consensus in the field, probably as a consequence of the complex genetic interactions affecting susceptibility to obesity. The identification of a significant number of genes in rare forms of obesity has not translated to an explanation of the genetics underlying common obesity. This is undoubtedly a consequence of the fact that, in contrast to the rare familial forms, common obesity is polygenic with no observable simple Mendelian inheritance pattern. There are a few exceptions to this, namely melanocortin 4 receptor (*MC4R*) and brain-derived neurotrophic factor (*BDNF*), with variants originally identified as causing rare monogenic obesity but now known to be frequent enough to account for a measurable proportion of common obesity cases. Initially, as most studies of complex disease used family based ascertainment strategies, genome-wide linkage scans were carried out. However, these were eventually superseded by genome-wide association (GWA) studies that provide far more accurate genomic locations for obesity-related genes. The reported associations are, by definition, genome-wide significant ($p < 10^{-6}$), and the studies have identified a whole range of genes with poorly understood functions. It is already obvious that the GWA study design alone will not allow us to elucidate the genetic architecture of common obesity, but alternative study designs and additional obesity-related phenotype data should provide avenues to identify more genes. This Review aims to give

Admixture mapping
Genetic mapping using individuals whose genomes are mosaics of fragments that are descended from genetically distinct populations. This method exploits differences in allele frequencies in the founders to determine ancestry at a locus in order to map traits to specific populations.

the reader a flavour of this exciting time in obesity genetics, together with insights into the future of research in this increasingly important area.

The physiological basis of obesity

The insights provided by genetics research have lead to the development of a number of theories to explain the physiological basis of obesity. These theories overlap substantially — it is the emphasis they place on the key roles of specific tissues or systems that differentiate them.

Obesity as a disorder of energy balance. Obesity has long been viewed as a disease of energy balance. In brief, obesity is due to an excess of energy intake or a lack of energy expenditure. The latter can be due to a diminished basal and exercise-driven calorie expenditure rate (owing to an impaired oxidation of fat) or to excessive fat storage with non-reactive lipolysis in adipocytes. The hypothesis of a 'thrifty genotype' (BOX 1), which can explain the well-known ethnic differences in adiposity, has been popular for the last 30 years. However, this has not been supported by human genetics research as no DNA variation in an obesity gene (for example, fat mass and obesity associated, *FTO*) has been found to be more prevalent in isolated obesity-prone populations.

Leptin, encoded by *LEP*, has a key role in the regulation of energy balance through two mechanisms, acting on both food intake and energy expenditure. It is released in response to increasing adiposity and functions to decrease appetite and induce satiety. In rodents, leptin acts to increase energy expenditure through brown adipose tissue (BAT) thermogenesis. Whereas white adipose tissue is the primary site of fat storage, BAT is involved in energy expenditure through thermogenesis. Thermogenesis in mitochondria-rich BAT occurs as a result of mitochondrial uncoupling mediated by uncoupling protein 1 (UCP1), which disconnects oxidation reactions from the production of ATP by promoting proton leakage across the mitochondrial membrane. Higher leptin levels in the rodent hypothalamus reverse the decrease in UCP1 mRNA expression observed in the fasting state[12] and lead to increased sympathetic activation of BAT[13]. The loss of BAT function in rodents is linked to metabolic dysfunction and obesity[14], whereas experimentally induced BAT hypertrophy results in a lean, healthy phenotype[15]. Until recently, BAT was not thought to have a major metabolic role in adult humans but there is now strong evidence of metabolically active BAT depots in adults[16–19]. In addition, abnormalities of the sympathetic nervous system that are consistent with defects in the sympathetic afferent branch of thermogenesis have been observed in leptin-deficient adults[20]. The central administration of leptin has also been found to increase postprandial thermogenesis in sheep — like humans, sheep have brown adipocytes dispersed through white adipose tissue rather than the circumscribed BAT depots found in rodents[21]. These findings, and recent discoveries elucidating the developmental pathways involved in BAT formation and differentiation, notably the roles of PR domain zinc finger protein 16 (PRDM16)[22] and bone morphogenetic protein 7 (BMP7)[23], emphasize that the role of BAT in human obesity may be significant.

Obesity as a disorder of the adipocyte. Abnormalities of fat storage and mobilization are another potential mechanism for obesity in humans. Adipocytes store surplus fat as triacylglycerol and, when fat stores are mobilized, non-esterified fatty acids are released into the bloodstream. The enlargement of adipocytes through increased fat storage is thought to play a key part in weight gain in adults through the enlargement of the fat depots. A seminal study[24] showed that fat mass in humans is determined by both adipocyte size and number, with larger populations of larger adipocytes in obese people. This study also established that the population of adipocytes increases steadily throughout

Box 1 | **Hypotheses explaining the genetics of obesity**

The thrifty gene hypothesis
Evolutionary pressures have shaped a system that favours weight gain in times of famine, and physiological controls act primarily to prevent starvation rather than to regulate weight gain. In times when food is plentiful, this leads to weight gain.

The fetal programming hypothesis
The predominant governing force is the fetal environment, with maternal overnutrition or undernutrition provoking an appropriate postnatal response in the child. This may be mediated by epigenetic mechanisms such as genomic imprinting.

The predation release hypothesis
In the early evolution of humans, obesity would have been selected against because obese humans would have been more easily captured by predators. Once humans developed ways of defending themselves this evolutionary pressure was released, and random genetic drift has lead to the accumulation of predisposing genes in the population. This hypothesis overtly argues against the thrifty gene hypothesis by suggesting that famine has not been a sufficiently strong evolutionary pressure in human history.

The sedentary lifestyle hypothesis
Over the last 50 years it has been proposed that the average lifestyle has been affected by large decreases in physical activity and an increase in intake of fat-rich, calorie-dense foods. However, there is now evidence that physical activity has not reduced significantly, placing the main effect on obesity on the rapid changes in diet. This would suggest that metabolic enzymes could be expected to have a significant role in obesity susceptibility.

The ethnic shift hypothesis
Certain ethnic groups have higher rates of obesity than others, for example, Hispanic Americans compared with European Americans. As the proportion of Hispanic Americans has increased, the overall rates of obesity have increased. This may or may not be due to genetic differences.

The increased reproductive fitness hypothesis
Number of offspring is positively correlated with BMI in women, and one possible reason for this is that adiposity increases fecundity and this will serve to select for genetic variants that predispose to obesity.

The assortative mating hypothesis
Although the correlation between the BMI of spouses is low it is still statistically significant, and is suggested to be due to assortative mating. The hypothesis states that, over time, assortative mating in the context of genetic variants affecting obesity will contribute to an increase in obesity.

The complex hypothesis
This would suggest that there is no single genetic basis for obesity, it is a consequence of a combination of the hypotheses outlined above.

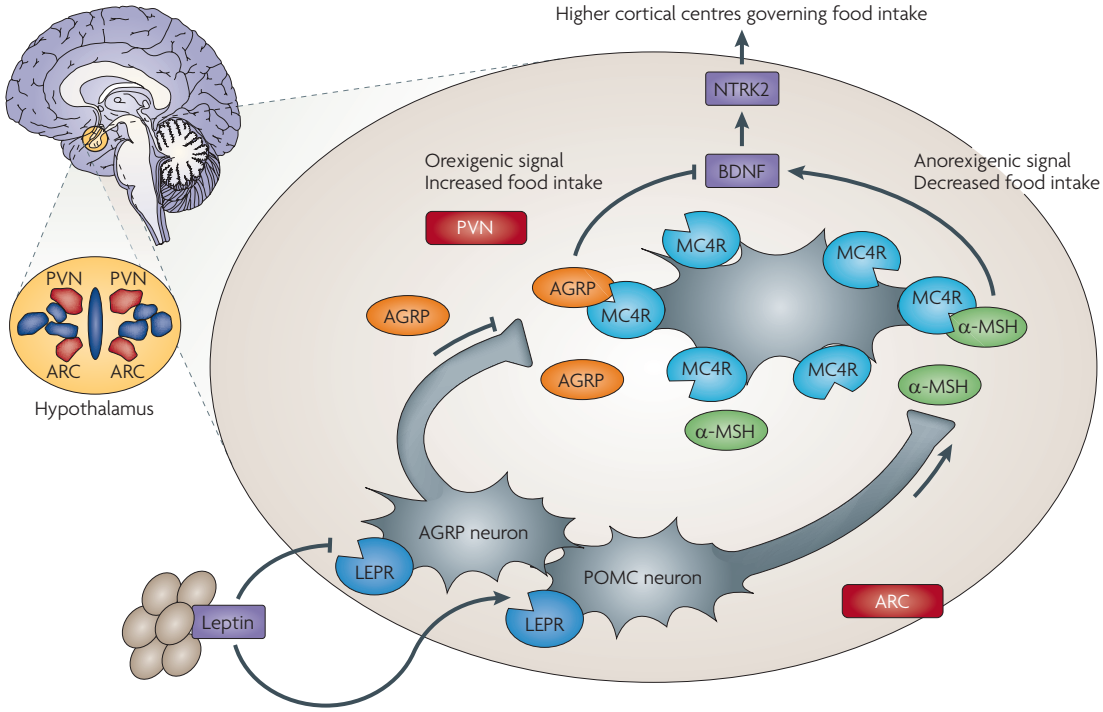

Figure 1 | **The leptin–melanocortin pathway.** The central nervous system plays a primary part in regulating food intake through the brain–gut axis[143], with the hypothalamus acting as the central regulator, receiving both long- and short-term food intake and energy expenditure feedback from the periphery. Signals are received from several tissues and organs, including: the gut, by hormones, such as ghrelin, peptide YY and cholecystokinin (CCK), and by mechanoreceptors measuring distension; and the pancreas, for example, through insulin and adipose tissue, and by hormones such as leptin and adiponectin[144,145]. The hypothalamus integrates these signals and acts through various downstream pathways to maintain energy balance. Although this system is well suited to preventing weight loss in times of starvation, it is rather less efficient at preventing weight gain. The rise in leptin levels that accompanies increasing adiposity has only a limited effect on food intake owing to cellular resistance to leptin, which may have evolved as a mechanism of preventing starvation[146]. The melanocortin 4 receptor (MC4R) is highly expressed in the paraventricular nucleus (PVN) of the hypothalamus, where it has a key role in the control of appetite. Leptin released from adipose tissue binds to leptin receptors (LEPR) on agouti-related protein (AGRP)-producing neurons and proopiomelanocortin (POMC)-producing neurons in the arcuate nucleus (ARC) of the hypothalamus. Leptin binding inhibits AGRP production and stimulates the production of POMC, which undergoes post-translational modification to generate a range of peptides, including α-, β- and γ-melanocyte-stimulating hormone (MSH). AGRP and α-MSH compete for MC4R — AGRP binding suppresses MC4R activity and α-MSH binding stimulates MC4R activity. Decreased receptor activity generates an orexigenic signal, whereas increased receptor activity generates an anorexigenic signal. Signals from MC4R govern food intake through secondary effector neurons that lead to higher cortical centres, a process that involves brain-derived neurotrophic factor (BDNF) and neurotrophic tyrosine kinase receptor type 2 (NTRK2; also known as tropomyosin-related kinase B, TRKB).

Genome-wide association study
A hypothesis-free method of investigating the association between common genetic variation and disease. This type of analysis requires a dense set of markers (for example, SNPs) that capture a substantial proportion of common variation across the genome, and large numbers of study subjects.

Hypothalamus
A brain region located below the thalamus, forming the main portion of the ventral region of the diencephalon and functioning to regulate bodily temperature, certain metabolic processes and other autonomic activities.

childhood and adolescence irrespective of weight, but then remains tightly regulated at a constant number during adulthood (although there is numerically neutral turnover of ~10% of cells in the cell population). Thus, changes in fat mass in adults are due to changes in adipocyte size rather than to an increase in adipocyte populations, and adipocyte populations are not affected by energy balance. One of the long-standing open questions in obesity research has been why over 75% of obese children go on to become obese adults, whereas only 10% of normal weight children become obese adults[25]. Spalding *et al.* found that adipocyte population growth starts at a younger age and involves a larger increase in adipocyte number in people with early-onset obesity, resulting in a larger number of adipocytes on reaching adulthood. Studies of previously obese individuals who have lost weight have shown an association between adipose tissue hypercellularity and leptin deficiency[26], which is likely to promote lipid accumulation in fat cells through increased appetite and lower energy expenditure.

Obesity as a neurobehavioural disorder. Until recently, the prevailing view of obesity has been as a disorder of energy balance. But another view has recently emerged of obesity as a neurobehavioural disorder[27], with defects in the neurological control of appetite and food intake playing a central part in pathogenesis. This view is borne out by the fact that a majority of the genes in which mutations result in monogenic obesity are involved in the control of appetite through the leptin–melanocortin pathway (FIG. 1).

Insights from monogenic obesity

After the identification of the leptin gene in mice and then in humans[28], leptin deficiency was the first cause of monogenic obesity to be demonstrated in a human patient[29]. Examination of cases of severe early-onset obesity have continued to provide information on obesity genes, leading to the identification of variants in additional genes in the leptin–melanocortin pathway, including leptin receptor (*LEPR*)[30], proopiomelanocortin (*POMC*)[31], pro-hormone convertase subtilisin/kexin type 1 (*PCSK1*)[32] and *MC4R*[33,34]. Mutations in three genes also involved in neural development have now been identified as the underlying cause of rare monogenic obesity: single-minded homologue 1 (*SIM1*)[35], *BDNF*[36] and neurotrophic tyrosine kinase receptor type 2 (*NTRK2*; also known as tropomyosin-related kinase B, *TRKB*)[37]. These are all involved in the functioning of the hypothalamus (the main control region for energy balance) and it is clear that the main consequence of inactivation of these genes is hyperphagia resulting in distortion of the bodily energy balance towards energy intake.

Linkage studies for common obesity

Family-based genome-wide linkage scans examine whether any genetic markers from a set of markers spanning the whole genome cosegregate with disease-related phenotypes. This design was the basis for many studies that successfully localized the causes of rare monogenic disease, and so it was natural to extend its use to analysing complex common disease. For obesity, more than 60 genome scans have been performed, resulting in the identification of 250 QTLs by 2006 (REF. 38). Positional cloning based on linkage results has identified promising candidate genes, including glutamate decarboxylase 2 (*GAD2*)[39], ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*)[40] and solute carrier family 6 (amino acid transporter), member 14 (*SLC6A14*)[41,42]. These three genes all have functions that can be directly related to obesity: GAD2 catalyses the formation of the neurotransmitter γ-aminobutyric acid, which upregulates food intake; ENPP1 inhibits insulin receptor activity and knockout mice for the insulin receptor are obese; and SLC6A14 is a tryptophan transporter — tryptophan is a precursor for the neurotransmitter serotonin, which regulates appetite. However, replication of these results has proved difficult. A recent meta-analysis of 37 published studies[43] containing more than 31,000 individuals did not detect strong evidence for linkage for BMI or BMI-defined obesity at any locus. Linkage analysis in common complex disease succeeds when a linkage peak is predominantly due to a few common variants of strong effect in one gene. However, the failure to replicate associations at many loci in studies of common disease suggests that the common variants only exert small genetic effects. This seems to hold true for obesity, with the most strongly associated gene variant so far, the *rs9939609* SNP in *FTO*, having only a ~1% effect on the variance observed in BMI[44].

Candidate gene association studies

Genetic association analysis has the advantages that it is a short-range effect compared with linkage and it can be carried out in unrelated individuals, who can be recruited more easily than complete families. Many genes underlying rare forms of monogenic obesity have been investigated for possible roles in common obesity, as well as others with more recently identified functional roles. TABLE 1 lists candidate genes reported in the period since our last Review in 2005 (REF. 45).

There is mounting evidence that missense mutations in these genes are associated with complex common obesity. Indeed, non-synonymous variants of *LEP* and *LEPR* have been associated with adult obesity[46–48], with *LEPR* also implicated in extreme childhood obesity[49]. More recently, polymorphisms in *LEP* and *LEPR* have been shown to be associated with sweet preference, suggesting an additional role for leptin signalling in obesity by regulating intake of sweet, typically calorie-rich foods[50]. A missense mutation disrupting *POMC* function was reported to increase susceptibility to early-onset obesity in several populations[51], and common non-synonymous coding variants in *PCSK1* have been associated with obesity in both adults and children[52,53]. Mutations in the *MC4R* gene resulting in amino acid substitutions that lead to loss of protein function typically cause monogenic obesity, but with variable penetrance[54]. By contrast, the infrequent gain-of-function mutations V103I and I251L (found in 0.5% to 2% of the population) have been consistently associated with a protective effect against obesity[55–57].

The common SNP –11391G>A, which is located in the proximal promoter of the adiponectin gene (*ADIPOQ*) and increases *ADIPOQ* expression (and adiponectin levels), has been associated with severe childhood and adult obesity in French Caucasians[58] and with adult obesity in other populations[59–61]. The discovery of associations between obesity and genes encoding cannabinoid receptor 1 (*CNR1*)[62], dopamine receptor 2 (*DRD2*)[63,64] and serotonin receptor 2C (*HTR2C*)[65,66] underscores the importance of neural signalling and the pathogenesis of obesity. Genes involved in regulating serotonin function (*SLC6A4*) and monoamine levels (*MAOA*) have also been shown to be predictive of BMI[67].

As mentioned above, none of the results of these studies reaches genome-wide significance and meta-analytical approaches have not improved this situation. For example, a meta-analysis of *LEPR* studies failed to find association between variants in this gene and obesity[68]. Overall, it is clear that candidate gene association studies have not provided unequivocal results, but the evidence is strong enough and replicated enough times to suggest that many of these genes contain variants that have a modest effect on obesity.

GWA studies

The foundation of the GWA study is the HapMap[69], an international project aimed at defining the range of common genetic variation in the human genome. By utilizing HapMap information on SNPs and linkage disequilibrium patterns[70,71], companies such as Illumina and Affymetrix have developed array-based platforms for the large-scale analysis of hundreds of thousands of SNPs in thousands of subjects, making GWA studies possible (see REF. 72 for a review).

QTL
A genetic locus that is identified through the statistical analysis of a quantitative trait, such as height or body weight.

Table 1 | **Recent candidate genes for common human obesity**

Gene	Gene symbol	Number of subjects*	Phenotype	*p* value*	Odds ratio	Refs
Ectonucleotide pyrophosphatase/ phosphodiesterase 1	*ENPP1*	6,147	Obesity	6×10^{-3} (adults)	1.50 (adults)	40
				6×10^{-4} (children)	1.69 (children)	
Proprotein convertase subtilisin/ kexin type 1	*PCSK1*	13,659	Obesity	7×10^{-8} (adults	1.34 (adults)	52
				2×10^{-12} (children)	1.22 (children)	
Nicotinamide phosphoribosyltransferase	*NAMPT*	4,559	Severe obesity	8×10^{-5} (adults)	NA	117
				6×10^{-9} (children)	NA	
Lamin A/C	*LMNA*	5,693	Obesity	1×10^{-2}	1.25	147
			Waist circumference	3×10^{-3}	1.14	
Growth hormone secretagogue receptor	*GHSR*	2,513	Obesity	7×10^{-4}	2.74	148
Suppressor of cytokine signalling 1	*SOCS1*	8,108	Obesity	4.7×10^{-2}	NA	149
Suppressor of cytokine signalling 3	*SOCS3*	1,425	BMI	3×10^{-3}	NA	150
			Waist to hip ratio	2×10^{-4}		
Krüppel-like factor 7	*KLF7*	14,818	Obesity	1×10^{-3}	0.90	151
Myotubularin related protein 9	*MTMR9*	3,220	BMI	5×10^{-4}	1.40	152
Delta-like homologue 1	*DLK1*	1,025 trios	Obesity	2×10^{-3}	1.34	153
Cannabinoid type 1 receptor	*CNR1*	5,750	Obesity	1.1×10^{-6} (adults)	1.85 (adults)	62
				3×10^{-5} (children)	1.52 (children)	
TBC1 (tre-2/USP6, BUB2, cdc16) domain family, member 1	*TBC1D1*	9 multiplex pedigrees, 423 population controls	Obesity	7×10^{-6}	NA	154
Neuropeptide Y receptor Y2	*NPY2R*	3,096	Obesity	2×10^{-3} (adults)	1.40 (adults)	155
				2×10^{-2} (children)	1.20 (children)	

Recent refers to 2005 to the present day. Results are those reported by the study authors. *Maximal sample sizes and *p* values from publication, for example, combined phase 1 and 2 results. NA, odds ratio figures not provided in publication.

Unlike candidate gene studies GWA is a hypothesis-free approach, typically using a case–control study design to increase the chances of recruiting large numbers of subjects, thereby enhancing statistical power. Statistical association analysis is used to identify the top hits for follow-up, comprising both the SNPs themselves and relevant candidate genes. Markers that may include those in nearby candidate genes, as well as SNPs that were identified in the initial genome-wide study, are then selected for targeted genotyping in a larger, independent cohort of cases and controls for replication purposes.

Several potential limitations of the GWA study have been noted. For example, this approach relies on the common disease–common variant hypothesis, which states that common diseases are caused by a few common gene variants rather than a large number of rare variants, and this has recently been challenged (see REF. 73 for a review). However, this does not negate the fact that the GWA approach has reaped large rewards in terms of identifying DNA variants associated with common complex diseases such as obesity. FIGURE 2 shows the distribution of odds ratios for the associations uncovered by these studies. TABLE 2 provides details of the main findings of the GWA work in obesity published so far, and it is immediately obvious that this approach has identified a group of genes that barely overlap with the candidate genes listed in TABLE 1 and in our previous Review[45]. It should be noted that most of the current GWA results are for markers that are not in known genes, something that is not immediately evident from the literature (TABLE 2). Meta-analysis of these data has already begun, with the GIANT consortium identifying additional associated loci using the largest available combined data set so far[74].

FTO*: the first common obesity gene.* In 2007, two groups simultaneously identified *FTO* as containing a common variant unequivocally associated with BMI and increased risk for obesity[44,75]. The Wellcome Trust Case Control Consortium performed a GWA scan for type 2 diabetes[76], resulting in the identification of *FTO* as strongly associated. However, after adjusting for BMI, the association with diabetes was abolished, establishing that the association is with BMI and not type 2 diabetes. In spite of this highly significant result, variation in *FTO* was estimated to account for only ~1% of the total heritability of BMI. The second study[75] reported quantitatively similar data. The *FTO* association has since been replicated in a wide range of child and adult subjects (see REF. 77 for a review), as well as in all the recently published GWA studies for obesity.

Case–control study
This is the comparison of cases (individuals with disease) with controls (otherwise similar individuals who do not have the disease) to determine whether genetic marker allele frequencies differ between the two groups, that is, are associated with susceptibility to or protection from disease.

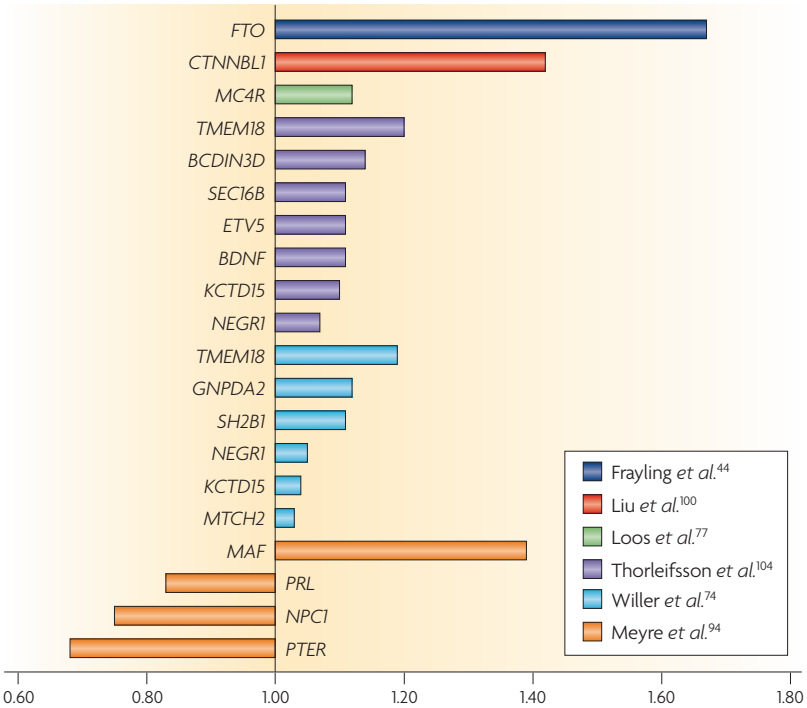

Figure 2 | **Odds ratios for genes associated with obesity in genome-wide studies.** Odds ratios from genome-wide scans are shown for the closest gene to the associated SNP marker[44,74,77,94,100,104]. *BCDIN3D*, BCDIN3 domain containing; *BDNF*, brain-derived neurotrophic factor; *CTNNBL1*, catenin, beta-like 1; *ETV5*, ets variant gene 5; *FTO*, fat mass and obesity associated; *GNPDA2*, glucosamine-6-phosphate deaminase 2; *KCTD15*, potassium channel tetramerization domain containing 15; *MAF*, v-maf musculoaponeurotic fibrosarcoma oncogene homologue; *MC4R*, melanocortin 4 receptor; *MTCH2*, mitochondrial carrier homologue 2; *NEGR1*, neuronal growth regulator 1; *NPC1*, Niemann–Pick disease type C1; *PRL*, prolactin; *PTER*, phosphotriesterase related; *SEC16B*, SEC16 homologue B; *SH2B1*, SH2B adaptor protein 1; *TMEM18*, transmembrane protein 18.

FTO is widely expressed in the brain, with evidence from animal studies indicating a particularly high level of expression in the hypothalamic nuclei, which are involved in regulating energy balance[78]. Both human and animal studies indicate that the gene may have a role in the regulation of appetite, with the risk allele associated with modestly increased food intake[79,80] and decreased satiety[81] in humans. The risk allele is also associated with decreased lipolytic activity in adipocytes, indicating a possible role in fat cell lipolysis[82]. Physical activity has been reported to modify the effects of the *FTO* risk allele, as it seems to have a stronger effect in people who are less active[83].

MC4R *variants and common obesity.* Two recent GWA studies have found strong association between SNPs located 188 kb away from the *MC4R* gene and BMI, waist circumference and obesity[84,85]. In the larger study[84], analysis of 660 nuclear families ascertained through an obese child or adolescent proband (BMI > ninety-fifth percentile) revealed significant overtransmission of the risk allele ($p = 2.4 \times 10^{-4}$). The association between this *MC4R* variant and obesity has also been replicated in a Danish study[86]. The variant has been associated with higher overall food intake and higher dietary fat intake[87]. This suggests that these intergenic obesity-associated variants may play a part in modulating *MC4R* activity and hence food intake behaviour (FIG. 1), although they are clearly physically distant from the gene. The increased effect on BMI in children is also consistent with the early-onset obesity observed in monogenic obesity caused by *MC4R* mutations.

GWA identification of novel candidate obesity genes. The GWA work carried out so far has produced a number of novel obesity genes, which are summarized in TABLE 2. Although an early first-generation array-based GWA study identified insulin-induced gene 2 (*INSIG2*) as a candidate obesity gene[88], this result was not supported by number of subsequent large studies[86,89–92]. One possible explanation is the lack of a robust genome-wide significant association ($p < 10^{-6}$) in the original study. The first current-generation GWA study was published in mid-2007 (REF. 93), and used families recruited from the general population. It found that *FTO* was strongly associated with BMI, hip circumference and weight. The first case–control GWA study using current-generation SNP microarrays and obese probands was published in late 2007 (REF. 53). The only gene variants reported to reach genome-wide significance and that were replicated were those previously identified in the *FTO* gene.

Our GWA study of 2,796 French Caucasians of extreme phenotype (early-onset obesity before the age of 6 for children and BMI ≥ 40 kgm^{-2} for adults), replicated in 14,186 European Caucasians, has identified three novel candidate genes: Niemann–Pick disease type C1 (*NPC1*), the proto-oncogene *MAF* and phosphotriesterase related (*PTER*)[94]. The association with *NPC1* is of particular interest, as the *NPC1* gene is expressed at particularly high levels in the brain (notably the hypothalamus)[95] and its protein product plays a part in endosomal cholesterol trafficking in the central nervous system, the immune system and the liver[96–98]. *Npc1* knockout mice show late-onset weight loss, poor food intake, a defect in cholesterol transport and neurological deficits[99].

Catenin, beta-like 1 (*CTNNBL1*) was recently identified in a GWA study of 1,000 US Caucasians adults sampled from the general population, with replication in 896 severely obese French Caucasians and 2,916 adult controls[100]. The most significant SNP was strongly associated with BMI and fat mass; this finding is particularly interesting as it may indicate a novel mechanism for the development of obesity — through the Wnt signalling pathway, which is strongly linked to type 2 diabetes genetics (see REF. 101 for a review). Wnt–β-catenin signalling has a number of functions that have implications for obesity, notably inhibiting adipogenesis[102] and initiating taste bud development[103].

A meta-analysis of 15 GWA studies performed by the GIANT consortium and involving a total of 32,387 individuals of European ancestry has revealed a further 6 candidate genes[74] (TABLE 2). As well as the within-study validation of the initial findings in 14 large independent samples (>58,000 individuals), the 5 variants with Illumina proxies (*KCTD15*, *MTCH2*, *NEGR1*, *SH2B1* and *TMEM18*) were found to be highly associated with

BMI in an independent GWA study[104]. In addition, they reported three additional candidate loci associated with variation in BMI and weight (TABLE 2).

Overall, the GWA approach has substantially increased the number of obesity-associated markers that we can have statistical confidence in. However, it is becoming clear that there is only a small overlap between genetic linkage and GWA. A potential explanation is that the linkage signals may be due to DNA variations of strong effect (odds ratio > 1.5) that are relatively infrequent compared with the observed associations from GWA studies, which are statistically robust and common but are not strong effects. The next step for all of these novel genes is to identify the causal variants and elucidate their biological role in obesity.

The future of genetic studies in obesity

The last few years have seen a major push to identify obesity genes and, on the evidence provided in this Review, there has been a considerable amount of success. However, this needs to be tempered by the fact that the contribution of these gene variants to obesity is currently estimated to be small; for example, the strongest association for obesity, that of *FTO*, is estimated to account for only ~1% of the heritability of obesity[77]. This may be for a number of reasons, for example: few of the

Table 2 | **Markers associated with obesity and body mass index (BMI) in genome-wide association studies**

Most significant marker	Nearest gene (distance from gene)	Number of subjects*	Phenotype	*p* value*	Odds ratio	Refs
rs9939609	*FTO*	28,587 adults	BMI	3×10^{-35}	1.67	44
		10,172 children		7×10^{-9}	1.27	
rs9930506	*FTO*	6148 subjects‡	BMI	8.6×10^{-7}	NA	93
rs17782313	*MC4R* (188 kb)	77,228 adults	BMI	2.8×10^{-15}	1.12	84
		10,583 children		1.5×10^{-8}	1.30	
rs10508503	*PTER* (180 kb)	8,128 adults	BMI	8.7×10^{-5}	0.68	94
		8,855 children		1.9×10^{-4}	0.64	
rs1805081	*NPC1*	8,128 adults	BMI	7.7×10^{-8}	0.75	94
		8,855 children		2.1×10^{-2}	0.75	
rs1424233	*MAF* (48 kb)	8,128 adults	BMI	1.9×10^{-8}	1.39	94
		8,855 children		1.6×10^{-6}	1.12	
rs6548238	*TMEM18* (33 kb)	84,823 adults	BMI	1.4×10^{-18}	1.19	74
		9,320 children		3.4×10^{-5}	1.41	
rs7561317	*TMEM18* (23 kb)	69,593 adults	BMI	4.2×10^{-17}	1.20	104
rs11084753	*KCTD15* (17 kb)	71,706 adults	BMI	2.3×10^{-8}	1.04	74
		9,156 children		9.7×10^{-4}	0.96	
rs29941	*KCTD15* (4.4 kb)	69,593 adults	BMI	7.3×10^{-12}	1.10	104
rs7498665	*SH2B1*	86,677 adults	BMI	5.1×10^{-11}	1.11	74
		69,593 adults		3.2×10^{-10}	1.08	104
rs10838738	*MTCH2*	80,917 adults	BMI	4.6×10^{-9}	1.03	74
rs10938397	*GNPDA2* (600 kb)	81,758 adults	BMI	3.4×10^{-16}	1.12	74
		9,309 children		2.0×10^{-2}	1.20	
rs2815752	*NEGR1* (3.5 kb)	83,499 adults	BMI	6.0×10^{-8}	1.05	74
rs2568958	*NEGR1* (16.7 kb)	69,593 adults	BMI	$1.2 \times 10^{-1}1$	1.07	104
rs6013029	*CTNNBL1*	1,000 adults	BMI	2.69×10^{-7}	1.42	100
		3,812 adults	Obesity	7.8×10^{-4}	1.42	
rs10913469	*SEC16B*	69,593 adults	BMI	6.2×10^{-8}	1.11	104
rs7647305	*ETV5* (7.4 kb)	75,043 adults	BMI	7.2×10^{-11}	1.11	104
rs925946	*BDNF* (9.2 kb)	69,593 adults	BMI	8.5×10^{-10}	1.11	104
rs7138803	*BCDIN3D* (10 kb)	69,593 adults	BMI	1.2×10^{-7}	1.14	104

Results are those reported by the study authors. *Maximal sample sizes and *p* values from publication, for example, combined phase 1 and 2 results. ‡Study is family-based with subjects from 14 to 102 years old. NA, odds ratio figures not provided in publication.

Minor allele frequency
The frequency of the less common allele of a biallelic genetic marker in a given population.

Prospective cohort
This is a group of subjects initially assessed for exposure to certain risk factors and then followed over time to evaluate the progression towards specific outcomes (often disease). This forms the basis of a longitudinal study.

current study designs include specifically selected obese subjects; the main phenotype studied is BMI, and this is only one of many possible obesity-related phenotypes; and the current generation of GWA study markers utilize SNPs with a minor allele frequency over 5%, and this approach will fail to detect rare SNPs of large effect.

Improving subject selection. Many studies in the obesity field were not initially designed as obesity studies but came about through the post hoc analysis of BMI or weight measured as part of a study of a different disease. However, if there are genes predisposing to severe obesity then extreme subjects must be recruited[105]. The first type of study is likely to identify genes that are important at the population level for modest increases in obesity; whether this can have a significant health impact is difficult to quantify. Studying extremely obese subjects is likely to identify genes of large effect in a small subgroup of the population, in which the health benefits of treatments informed by genetic study results will be significant. In addition, many studies do not consider the possible differences between analysing child and adult obesity, and the importance of this has recently been shown[106] by the identification of associations that vary in strength depending on the age of the subjects studied.

Improving the phenotype. The ascertainment of phenotype data is fundamental to all genetic association studies and is often not given enough consideration in the study design. Robust phenotypes that are accurate, reproducible and disease related are essential if the genetic study is going to provide useful information. One way of improving phenotype data is to refine anthropometric measurements, BOX 2 highlights some of the possibilities. The main concern here is that BMI is not an appropriate measure for certain groups of people — for example, athletes with significant muscle mass — and the bodily distribution of adipose tissue is now generally considered to be more important than the overall weight. A second approach is to look at phenotypes based on cellular and molecular measurements that may be much closer to measuring the effects of genes involved in obesity; with this approach, high correlation between a biological marker and the obese state can provide novel insights into the mechanisms underlying obesity.

A range of genomic techniques are now being used to generate novel intermediate molecular traits that can be analysed to explore the possibility of identifying novel genes associated with obesity. Transcriptomics has emerged as a valuable tool for the identification of novel disease-causing genes through the use of genetical genomics. In summary, the levels of all RNA transcripts in a set of tissue samples from related individuals are measured using a microarray-based technology, and the individuals are genotyped using a whole-genome marker set. The transcript levels are then analysed as quantitative traits for genetic linkage to the phenotype of interest[107]. In metabolomics, work has already identified different phenotypic profiles between obesity-prone and obesity-resistant mice fed on a high fat diet that correlate well with transcriptomics results[108]. Proteomic work is not far advanced in the field of obesity, but the first studies are starting to come through. For example, a recent analysis of endoplasmic reticulum stress-related proteins in adipose tissue from obese individuals identified three upregulated proteins: calreticulin, protein disulphide isomerase A3 and glutathione S-transferase P[109].

Improving genome-wide studies. There is good guidance available on the design of genetic studies[110,111], and the limitations of current GWA study designs are well known[72,112]. These include the use of SNP markers of >5% minor allele frequency, the use of case–control studies versus prospective cohort studies or families, and the analytical challenges presented by the large data sets.

Box 2 | **Advancing phenotype measurement**

Photonic scanners
Body mass index (BMI) and waist to hip ratio are simple and cheap measurements suitable for large numbers of subjects, and so have been widely used in genetic studies. However, although these measurements would seem to be simple to carry out reproducibly, there is evidence that this is not the case — particularly when these values are self-reported, as is often the case for epidemiological studies (see REF. 134 for a review). In addition, BMI fails to take into account the bodily distribution of fat and the contribution of muscle to the overall weight. One recent approach in anthropometric measurement is the use of photonic scanners to produce an accurate and reproducible three-dimensional topographic map of the whole body surface in a few seconds at a low cost[135].

Air-displacement plethysmography
To address the failure of BMI to give an accurate view of whether a subject is genuinely obese, the air-displacement plethysmograph has been developed, of which the BODPOD (Life Measurement Inc, Concord, USA) is probably the best-known example. This allows the measurement of the total body volume as well as weight, and the proportions of fat and fat-free body mass can be calculated. This measurement can be carried out in as little as 5 minutes, is reliable and reproducible, and the equipment is particularly suitable for measuring infants under 6 months age[136].

Computed tomography and magnetic resonance imaging
Cost is still the defining factor in whether to choose more accurate phenotyping methods, but routine use of advanced imaging techniques for phenotyping purposes is becoming more common. These techniques are non-invasive and can give highly accurate and reproducible measurements of body fat mass and distribution[137]. Although computed tomography, including dual-energy X-ray absorptiometry, has been widely used in obesity research, it uses ionizing radiation, which means its use in healthy individuals is unethical. It is also expensive and time consuming. Similarly, magnetic resonance imaging, although it is highly accurate, requires a large and ongoing financial investment in the equipment and is not currently a high-throughput technique.

Ultrasonography
Ultrasound imaging is widely used in medicine and few, if any, side-effects have been reported. It is also inexpensive and requires minimal training. A recent review of the field[138] highlighted that measurements taken by ultrasound imaging were highly correlated with those obtained by computed tomography or magnetic resonance imaging (80% or higher), and that they were also more highly correlated with obesity than BMI or waist to hip ratio.

Improving feeding behaviour measurement
The difficulty with measuring feeding behaviour is ensuring that the measurement technique is accurate and reproducible. Self-reporting notoriously underestimates food consumption[139], but newer methods such as recording children's meals using digital photographs can help reduce the variability[140]. Efforts by long-standing groups such as the Framingham Heart Study are also greatly contributing to improving the assessment of eating patterns in adults[141]. However, the field is not without problems — a recent report on breakfast skipping and BMI found that the detection of a positive association depends on the definition of breakfast skipping used[142].

It is true that no variant so far discovered accounts for more than a small fraction of the genetic variation, and it has been suggested that much larger case–control GWA approaches will be needed to obtain the statistical power that is needed to detect common variants of small effect[113]. However, this will require a considerable reduction in genotyping costs, with even a small GWA study (~1,000 subjects) currently costing over US$1,000,000 for high-density SNP arrays. Rapid advances in the development of the new generation of whole-genome sequencing gives the prospect that, in only a few years, large numbers of subjects will not be genotyped but sequenced instead.

Although case–control studies are popular because of the ease with which the subjects can be recruited, they are vulnerable to spurious results owing to population substructure and the difficulty in controlling for gene–environment interactions, something that family-based study designs can address[114]. In addition, prospectively recruited population samples[115], in which risk factors and exposures can be estimated prior to disease onset, need to be carried out to gain insights into gene–environment interactions. It should be noted that the GWA results obtained so far have been in North American or Western European subjects. A GWA study using subjects from the isolated Pacific island of Kosrae found little similarity in results for many quantitative traits, including no association between BMI and *FTO* or *MC4R* variants[116]. The extension of GWA studies to other populations will serve to highlight both shared variants influencing obesity and those that are specific to a population.

Obesity genetics: beyond common SNPs

Rare SNPs. In spite of the increasing numbers of GWA studies in a range of common diseases, on the basis of the common disease–common variant hypothesis the arrays are designed to use genetic markers with a minor allele frequency over 5%. However, there are now sufficient reports of rare variants of strong effect in complex common disease — for example, in obesity[117], susceptibility to infection[118] and type 1 diabetes[119] — to support the idea that both common and rare variants contribute to common disease. Sequencing all known coding DNA, known as exomic sequencing[120], and deep sequencing in specific genomic regions are now possible and are a fast way to identify all the sequence variants of interest. In addition, family-based study designs offer the possibility of using the new generation of genome sequencing machines to carry out deep sequencing of linked loci to determine the genetic basis of linkage peaks. This previously unavailable approach could revolutionize the field by identifying genes involved in obesity that are otherwise undetectable using case–control cohorts.

Copy number variation. Copy number variants (CNVs), which include copy number gains (duplications or insertions), losses (deletions) and rearrangements, have been estimated to account for nearly 18% of heritable variance in gene expression[121]. Of particular relevance to obesity, gene ontology analyses indicate that the genes overlapped by CNVs are enriched for those involved in brain development, sensory perception (including olfaction) and immune responses[122,123]. Furthermore, the GIANT consortium reported that the *NEGR1* obesity-associated SNPs that they detected seem to be in strong linkage disequilibrium with a nearby CNV[74], although there is currently no functional evidence to support the involvement of this CNV in obesity. The recent development of high-density SNP arrays that are specifically designed to enhance CNV discovery[124,125] and the simultaneous development of novel algorithms to detect CNVs from the data produced by these arrays (see REF. 126 for a review) have offered the possibility of simultaneous genome-wide SNP and CNV profiling to generate a more complete picture of genetic variation.

Epigenetic variation. Epigenetics is the study of heritable changes in the genome that are not the result of changes in the linear sequence of the DNA. These changes include DNA methylation, histone methylation and chromatin modification. The effect of epigenetics has long been known in syndromic obesity, in which genomic imprinting is crucial to the disease phenotype in Prader–Willi syndrome[127]. Imprinting defects in GNAS1 complex locus (*GNAS1*) give rise to the obesity-associated syndrome pseudohypoparathyroidism. There is also evidence of parent-of-origin effects, suggesting imprinting, being linked to common polygenic obesity in other areas of the genome[128,129]. Although it is difficult to distinguish between purely environmental effects and effects of the environment on epigenetic factors, epigenetics has been proposed as the mechanism underlying propagation of obesity from mother to child by a 'thrifty epigenotype'[130]. Genome-wide measurement of epigenetic variation has recently been made possible using techniques such as DNA-methylation-specific microarrays[131] and methylated DNA immunoprecipitation and resequencing[132]. This will allow us to progress towards a more global understanding of the role of epigenetics in obesity.

Systems-based genome-wide approaches. Integrated genomic and genetic or 'deep genome' analysis is the future of all human genetics, not just that of obesity. We are now at a point where we have extensive knowledge of the contribution that SNPs make to genomic variation, and we are poised to enter a post-SNP period in which we investigate the contribution of other forms of genomic variation to health and disease. A pioneering systems-based meta-analysis that focused on obesity drew on data from 49 genome-wide experiments — including microarrays, proteomic and gene expression analysis, and RNAi studies in humans, mice, rats and worms[133]. Using a simple model to integrate the data, essentially counting the number of positive reports for a gene in the scientific literature, this integrative approach resulted in the identification of 16 potential candidate genes that were positively associated with obesity by a minimum of 6 experiments, 15 of which had not previously been identified. Many of the genes identified are associated with obesity or obesity-related phenotypes. However, this type of analysis is dependent on the published literature and needs to be carried out regularly to incorporate new findings.

Population substructure
This is the presence of hidden subgroups in a population caused by, for example, admixture, population stratification or inbreeding. If this is not accounted for it may lead to increased type 1 error and decreased statistical power.

Conclusions

It is clear that the worldwide epidemic of obesity is not genetic in origin but is due to changes in lifestyle and environment. However, it is also clear that genetics greatly influences this situation, giving individuals in the same 'obesogenic' environment significantly different risks of becoming obese. The field of non-syndromic common human obesity has been transformed in the last few years by the contribution of cutting-edge genetics. The use of the GWA approach in particular has identified many genes with robust association to common obesity or BMI. Determining how these results fit into current models of the genetic architecture and physiology of obesity is now a major challenge, as no existing hypothesis explains all the data. In spite of our successes, it is also true that our current methods are only identifying minor contributors to the genetic effect in obesity, and this poses the question of how to explain the apparently high heritability of obesity. There is a lot more work needed, including larger-scale studies (possibly hundreds of thousands of subjects), studies using novel phenotypes, deep resequencing of the genome, studies investigating the contribution of copy number variation and epigenetics, and the long-term goal of identifying the causal variants and their biological roles in obesity. The next 10 years in obesity genetics will be exciting indeed.

1. Wang, Y., Beydoun, M. A., Liang, L., Caballero, B. & Kumanyika, S. K. Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic. *Obesity (Silver Spring)* **16**, 2323–2330 (2008).
2. Kelly, T., Yang, W., Chen, C. S., Reynolds, K. & He, J. Global burden of obesity in 2005 and projections to 2030. *Int. J. Obes. (Lond.)* **32**, 1431–1437 (2008).
3. Sturm, R. Increases in morbid obesity in the USA: 2000–2005. *Public Health* **121**, 492–496 (2007).
4. Ogden, C. L. *et al.* Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* **295**, 1549–1555 (2006).
5. Sturm, R. The effects of obesity, smoking, and drinking on medical problems and costs. *Health Aff. (Millwood)* **21**, 245–253 (2002).
6. Stunkard, A. J., Foch, T. T. & Hrubec, Z. A twin study of human obesity. *JAMA* **256**, 51–54 (1986).
The first twin study of obesity that reported the substantial role of genetics.
7. Stunkard, A. J. *et al.* An adoption study of human obesity. *N. Engl. J. Med.* **314**, 193–198 (1986).
8. Turula, M., Kaprio, J., Rissanen, A. & Koskenvuo, M. Body weight in the Finnish Twin Cohort. *Diabetes Res. Clin. Pract.* **10** (Suppl. 1), S33–S36 (1990).
9. Wardle, J., Carnell, S., Haworth, C. M. & Plomin, R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. *Am. J. Clin. Nutr.* **87**, 398–404 (2008).
A twin study showing that, even in an obesogenic environment, genetics has a significant effect on obesity.
10. Redden, D. T. *et al.* Regional admixture mapping and structured association testing: conceptual unification and an extensible general linear model. *PLoS Genet.* **2**, e137 (2006).
11. Williams, R. C., Long, J. C., Hanson, R. L., Sievers, M. L. & Knowler, W. C. Individual estimates of European genetic admixture associated with lower body-mass index, plasma glucose, and prevalence of type 2 diabetes in Pima Indians. *Am. J. Hum. Genet.* **66**, 527–538 (2000).
12. Sivitz, W. I., Fink, B. D. & Donohoue, P. A. Fasting and leptin modulate adipose and muscle uncoupling protein: divergent effects between messenger ribonucleic acid and protein expression. *Endocrinology* **140**, 1511–1519 (1999).
13. Rahmouni, K. & Morgan, D. A. Hypothalamic arcuate nucleus mediates the sympathetic and arterial pressure responses to leptin. *Hypertension* **49**, 647–652 (2007).
14. Lowell, B. B. *et al.* Development of obesity in transgenic mice after genetic ablation of brown adipose tissue. *Nature* **366**, 740–742 (1993).
The first report to show that loss of BAT in transgenic mice leads to obesity.
15. Ghorbani, M., Claus, T. H. & Himms-Hagen, J. Hypertrophy of brown adipocytes in brown and white adipose tissues and reversal of diet-induced obesity in rats treated with a β_3-adrenoceptor agonist. *Biochem. Pharmacol.* **54**, 121–131 (1997).
16. Nedergaard, J., Bengtsson, T. & Cannon, B. Unexpected evidence for active brown adipose tissue in adult humans. *Am. J. Physiol. Endocrinol. Metab.* **293**, E444–E452 (2007).
17. van Marken Lichtenbelt, W. D. *et al.* Cold-activated brown adipose tissue in healthy men. *N. Engl. J. Med.* **360**, 1500–1508 (2009).
18. Cypess, A. M. *et al.* Identification and importance of brown adipose tissue in adult humans. *N. Engl. J. Med.* **360**, 1509–1517 (2009).
19. Virtanen, K. A. *et al.* Functional brown adipose tissue in healthy adults. *N. Engl. J. Med.* **360**, 1518–1525 (2009).
20. Ozata, M., Ozdemir, I. C. & Licinio, J. Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects. *J. Clin. Endocrinol. Metab.* **84**, 3686–3695 (1999).
21. Henry, B. A., Dunshea, F. R., Gould, M. & Clarke, I. J. Profiling postprandial thermogenesis in muscle and fat of sheep and the central effect of leptin administration. *Endocrinology* **149**, 2019–2026 (2008).
22. Seale, P. *et al.* PRDM16 controls a brown fat/skeletal muscle switch. *Nature* **454**, 961–967 (2008).
23. Tseng, Y. H. *et al.* New role of bone morphogenetic protein 7 in brown adipogenesis and energy expenditure. *Nature* **454**, 1000–1004 (2008).
24. Spalding, K. L. *et al.* Dynamics of fat cell turnover in humans. *Nature* **453**, 783–787 (2008).
25. Freedman, D. S. *et al.* Childhood overweight and family income. *MedGenMed* **9**, 26 (2007).
26. Lofgren, P. *et al.* Long-term prospective and controlled studies demonstrate adipose tissue hypercellularity and relative leptin deficiency in the postobese state. *J. Clin. Endocrinol. Metab.* **90**, 6207–6213 (2005).
27. O'Rahilly, S. & Farooqi, I. S. Human obesity: a heritable neurobehavioral disorder that is highly sensitive to environmental conditions. *Diabetes* **57**, 2905–2910 (2008).
28. Zhang, Y. *et al.* Positional cloning of the mouse obese gene and its human homologue. *Nature* **372**, 425–432 (1994).
The paper that identified the first gene underlying obesity and that brought obesity research into the modern age.
29. Montague, C. T. *et al.* Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* **387**, 903–908 (1997).
The first reported evidence that monogenic obesity exists in humans.
30. Clement, K. *et al.* A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* **392**, 398–401 (1998).
31. Krude, H. *et al.* Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by *POMC* mutations in humans. *Nature Genet.* **19**, 155–157 (1998).
32. Jackson, R. S. *et al.* Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene. *Nature Genet.* **16**, 303–306 (1997).
33. Vaisse, C., Clement, K., Guy-Grand, B. & Froguel, P. A frameshift mutation in human MC4R is associated with a dominant form of obesity. *Nature Genet.* **20**, 113–4 (1998).
This paper, together with reference 34, first identified *MC4R* gene variants as the most prevalent form of monogenic human obesity.
34. Yeo, G. S. *et al.* A frameshift mutation in *MC4R* associated with dominantly inherited human obesity. *Nature Genet.* **20**, 111–112 (1998).
35. Holder, J. L. Jr, Butte, N. F. & Zinn, A. R. Profound obesity associated with a balanced translocation that disrupts the *SIM1* gene. *Hum. Mol. Genet.* **9**, 101–108 (2000).
36. Friedel, S. *et al.* Mutation screen of the brain derived neurotrophic factor gene (*BDNF*): identification of several genetic variants and association studies in patients with obesity, eating disorders, and attention-deficit/hyperactivity disorder. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **132B**, 196–199 (2005).
37. Yeo, G. S. *et al.* A *de novo* mutation affecting human TrkB associated with severe obesity and developmental delay. *Nature Neurosci.* **7**, 1187–1189 (2004).
38. Rankinen, T. *et al.* The human obesity gene map: the 2005 update. *Obesity (Silver Spring)* **14**, 529–644 (2006).
39. Boutin, P. *et al. GAD2* on chromosome 10p12 is a candidate gene for human obesity. *PLoS Biol.* **1**, E68 (2003).
40. Meyre, D. *et al.* Variants of *ENPP1* are associated with childhood and adult obesity and increase the risk of glucose intolerance and type 2 diabetes. *Nature Genet.* **37**, 863–867 (2005).
41. Suviolahti, E. *et al.* The *SLC6A14* gene shows evidence of association with obesity. *J. Clin. Invest.* **112**, 1762–72 (2003).
42. Durand, E. *et al.* Polymorphisms in the amino acid transporter solute carrier family 6 (neurotransmitter transporter) member 14 gene contribute to polygenic obesity in French Caucasians. *Diabetes* **53**, 2483–2486 (2004).
43. Saunders, C. L. *et al.* Meta-analysis of genome-wide linkage studies in BMI and obesity. *Obesity (Silver Spring)* **15**, 2263–2275 (2007).
44. Frayling, T. M. *et al.* A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* **316**, 889–894 (2007).
The first obesity gene identified through a GWA study, although the study was for type 2 diabetes rather than obesity.
45. Bell, C. G., Walley, A. J. & Froguel, P. The genetics of human obesity. *Nature Rev. Genet.* **6**, 221–34 (2005).
46. Jiang, Y. *et al.* Common variants in the 5′ region of the leptin gene are associated with body mass index in men from the National Heart, Lung, and Blood Institute Family Heart Study. *Am. J. Hum. Genet.* **75**, 220–230 (2004).
47. Li, W. D. *et al.* Sequence variants in the 5′ flanking region of the leptin gene are associated with obesity in women. *Ann. Hum. Genet.* **63**, 227–234 (1999).
48. Chagnon, Y. C. *et al.* Associations between the leptin receptor gene and adiposity in middle-aged Caucasian males from the HERITAGE family study. *J. Clin. Endocrinol. Metab.* **85**, 29–34 (2000).
49. Roth, H. *et al.* Transmission disequilibrium and sequence variants at the leptin receptor gene in extremely obese German children and adolescents. *Hum. Genet.* **103**, 540–546 (1998).
50. Mizuta, E. *et al.* Leptin gene and leptin receptor gene polymorphisms are associated with sweet preference and obesity. *Hypertens. Res.* **31**, 1069–1077 (2008).
51. Challis, B. G. *et al.* A missense mutation disrupting a dibasic prohormone processing site in pro-opiomelanocortin (POMC) increases susceptibility to early-onset obesity through a novel molecular mechanism. *Hum. Mol. Genet.* **11**, 1997–2004 (2002).

52. Benzinou, M. *et al.* Common nonsynonymous variants in *PCSK1* confer risk of obesity. *Nature Genet.* **40**, 943–945 (2008).
53. Hinney, A. *et al.* Genome wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (FTO) variants. *PLoS ONE* **2**, e1361 (2007).
The first GWA study to specifically recruit obese subjects.
54. Dubern, B. *et al.* Mutational analysis of melanocortin-4 receptor, agouti-related protein, and alpha-melanocyte-stimulating hormone genes in severely obese children. *J. Pediatr.* **139**, 204–209 (2001).
55. Geller, F. *et al.* Melanocortin-4 receptor gene variant I103 is negatively associated with obesity. *Am. J. Hum. Genet.* **74**, 572–581 (2004).
56. Heid, I. M. *et al.* Association of the 103I MC104R allele with decreased body mass in 7937 participants of two population based surveys. *J. Med. Genet.* **42**, e21 (2005).
57. Stutzmann, F. *et al.* Non-synonymous polymorphisms in melanocortin-4 receptor protect against obesity: the two facets of a Janus obesity gene. *Hum. Mol. Genet.* **16**, 1837–1844 (2007).
58. Bouatia-Naji, N. *et al.* ACDC/adiponectin polymorphisms are associated with severe childhood and adult obesity. *Diabetes* **55**, 545–550 (2006).
59. Nakatani, K. *et al.* Adiponectin gene variation associates with the increasing risk of type 2 diabetes in non-diabetic Japanese subjects. *Int. J. Mol. Med.* **15**, 173–177 (2005).
60. Sutton, B. S. *et al.* Genetic analysis of adiponectin and obesity in Hispanic families: the IRAS Family Study. *Hum. Genet.* **117**, 107–118 (2005).
61. Vimaleswaran, K. S. *et al.* A novel association of a polymorphism in the first intron of adiponectin gene with type 2 diabetes, obesity and hypoadiponectinemia in Asian Indians. *Hum. Genet.* **123**, 599–605 (2008).
62. Benzinou, M. *et al.* Endocannabinoid receptor 1 gene variations increase risk for obesity and modulate body mass index in European populations. *Hum. Mol. Genet.* **17**, 1916–1921 (2008).
63. Thomas, G. N., Tomlinson, B. & Critchley, J. A. Modulation of blood pressure and obesity with the dopamine D2 receptor gene *Taq*I polymorphism. *Hypertension* **36**, 177–182 (2000).
64. Epstein, L. H. *et al.* Food reinforcement, the dopamine D2 receptor genotype, and energy intake in obese and nonobese humans. *Behav. Neurosci.* **121**, 877–886 (2007).
65. McCarthy, S. *et al.* Complex *HTR2C* linkage disequilibrium and promoter associations with body mass index and serum leptin. *Hum. Genet.* **117**, 545–557 (2005).
66. Pooley, E. C. *et al.* A 5-HT_{2C} receptor promoter polymorphism (HTR2C - 759C/T) is associated with obesity in women, and with resistance to weight loss in heterozygotes. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **126B**, 124–127 (2004).
67. Fuemmeler, B. F. *et al.* Genes implicated in serotonergic and dopaminergic functioning predict BMI categories. *Obesity (Silver Spring)* **16**, 348–355 (2008).
68. Heo, M. *et al.* A meta-analytic investigation of linkage and association of common leptin receptor (LEPR) polymorphisms with body mass index and waist circumference. *Int. J. Obes. Relat. Metab. Disord.* **26**, 640–646 (2002).
69. The International HapMap Consortium. The International HapMap Project. *Nature* **426**, 789–796 (2003).
The original description of the project to map the human variation that underpins much of the current human genetic studies.
70. The International HapMap Consortium. A haplotype map of the human genome. *Nature* **437**, 1299–1320 (2005).
71. The International HapMap Consortium. A second generation human haplotype map of over 3.1 million SNPs. *Nature* **449**, 851–861 (2007).
72. McCarthy, M. I. *et al.* Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nature Rev. Genet.* **9**, 356–369 (2008).
73. Iyengar, S. K. & Elston, R. C. The genetic basis of complex traits: rare variants or "common gene, common disease"? *Methods Mol. Biol.* **376**, 71–84 (2007).
74. Willer, C. J. *et al.* Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nature Genet.* **41**, 25–34 (2009).
A meta-analysis of 15 GWA studies for BMI associations reporting six novel loci.
75. Dina, C. *et al.* Variation in *FTO* contributes to childhood obesity and severe adult obesity. *Nature Genet.* **39**, 724–726 (2007).
76. The Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661–678 (2007).
A large-scale GWA study of seven common diseases, including type 2 diabetes.
77. Loos, R. J. & Bouchard, C. *FTO*: the first gene contributing to common forms of human obesity. *Obes. Rev.* **9**, 246–50 (2008).
78. Gerken, T. *et al.* The obesity-associated *FTO* gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. *Science* **318**, 1469–1472 (2007).
79. Speakman, J. R., Rance, K. A. & Johnstone, A. M. Polymorphisms of the *FTO* gene are associated with variation in energy intake, but not energy expenditure. *Obesity (Silver Spring)* **16**, 1961–1965 (2008).
80. Wardle, J., Llewellyn, C., Sanderson, S. & Plomin, R. The *FTO* gene and measured food intake in children. *Int. J. Obes. (Lond.)* (2008).
81. Wardle, J. *et al.* Obesity associated genetic variation in FTO is associated with diminished satiety. *J. Clin. Endocrinol. Metab.* **93**, 3640–3643 (2008).
82. Wahlen, K., Sjolin, E. & Hoffstedt, J. The common *rs9939609* gene variant of the fat mass- and obesity-associated gene FTO is related to fat cell lipolysis. *J. Lipid Res.* **49**, 607–611 (2008).
83. Andreasen, C. H. *et al.* Low physical activity accentuates the effect of the *FTO* rs9939609 polymorphism on body fat accumulation. *Diabetes* **57**, 95–101 (2008).
84. Loos, R. J. *et al.* Common variants near *MC4R* are associated with fat mass, weight and risk of obesity. *Nature Genet.* **40**, 768–775 (2008).
85. Chambers, J. C. *et al.* Common genetic variation near *MC4R* is associated with waist circumference and insulin resistance. *Nature Genet.* **40**, 716–188 (2008).
86. Andreasen, C. H. *et al.* Non-replication of genome-wide based associations between common variants in *INSIG2* and *PFKP* and obesity in studies of 18,014 Danes. *PLoS ONE* **3**, e2872 (2008).
87. Qi, L., Kraft, P., Hunter, D. J. & Hu, F. B. The common obesity variant near *MC4R* gene is associated with higher intakes of total energy and dietary fat, weight change and diabetes risk in women. *Hum. Mol. Genet.* **17**, 3502–8 (2008).
88. Herbert, A. *et al.* A common genetic variant is associated with adult and childhood obesity. *Science* **312**, 279–283 (2006).
89. Dina, C. *et al.* Comment on "A common genetic variant is associated with adult and childhood obesity". *Science* **315**, 187b; author reply 187e (2007).
90. Rosskopf, D. *et al.* Comment on "A common genetic variant is associated with adult and childhood obesity". *Science* **315**, 187; author reply 187e (2007).
91. Loos, R. J., Barroso, I., O'Rahilly, S. & Wareham, N. J. Comment on "A common genetic variant is associated with adult and childhood obesity". *Science* **315**, 187c; author reply 187e (2007).
92. Lyon, H. N. *et al.* The association of a SNP upstream of *INSIG2* with body mass index is reproduced in several but not all cohorts. *PLoS Genet.* **3**, e61 (2007).
93. Scuteri, A. *et al.* Genome-wide association scan shows genetic variants in the *FTO* gene are associated with obesity-related traits. *PLoS Genet.* **3**, e115 (2007).
94. Meyre, D. *et al.* Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. *Nature Genet.* **41**, 157–159 (2009).
The first GWA study for severe adult and child obesity reporting three novel loci.
95. Su, A. I. *et al.* Large-scale analysis of the human and mouse transcriptomes. *Proc. Natl Acad. Sci. USA* **99**, 4465–4470 (2002).
96. Amigo, L. *et al.* Relevance of Niemann–Pick type C1 protein expression in controlling plasma cholesterol and biliary lipid secretion in mice. *Hepatology* **36**, 819–828 (2002).
97. Ikonen, E. Cellular cholesterol trafficking and compartmentalization. *Nature Rev. Mol. Cell Biol.* **9**, 125–138 (2008).
98. Vance, J. E. Lipid imbalance in the neurological disorder, Niemann–Pick C disease. *FEBS Lett.* **580**, 5518–5524 (2006).
99. Xie, C., Turley, S. D., Pentchev, P. G. & Dietschy, J. M. Cholesterol balance and metabolism in mice with loss of function of Niemann–Pick C protein. *Am. J. Physiol.* **276**, E336–E344 (1999).
100. Liu, Y. J. *et al.* Genome-wide association scans identified *CTNNBL1* as a novel gene for obesity. *Hum. Mol. Genet.* **17**, 1803–1813 (2008).
101. Cauchi, S. & Froguel, P. *TCF7L2* genetic defect and type 2 diabetes. *Curr. Diab. Rep.* **8**, 149–155 (2008).
102. Ross, S. E. *et al.* Inhibition of adipogenesis by Wnt signaling. *Science* **289**, 950–953 (2000).
103. Liu, F. *et al.* Wnt-β-catenin signaling initiates taste papilla development. *Nature Genet.* **39**, 106–112 (2007).
104. Thorleifsson, G. *et al.* Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nature Genet.* **41**, 18–24 (2009).
105. Froguel, P. & Blakemore, A. I. The power of the extreme in elucidating obesity. *N. Engl. J. Med.* **359**, 891–893 (2008).
106. Lasky-Su, J. *et al.* On the replication of genetic associations: timing can be everything! *Am. J. Hum. Genet.* **82**, 849–858 (2008).
107. Cookson, W., Liang, L., Abecasis, G., Moffatt, M. & Lathrop, M. Mapping complex disease traits with global gene expression. *Nature Rev. Genet.* **10**, 184–194 (2009).
108. Li, H. *et al.* Transcriptomic and metabonomic profiling of obesity-prone and obesity-resistant rats under high fat diet. *J. Proteome Res.* **7**, 4775–4783 (2008).
109. Boden, G. *et al.* Increase in endoplasmic reticulum stress-related proteins and genes in adipose tissue of obese, insulin-resistant individuals. *Diabetes* **57**, 2438–2444 (2008).
110. Zondervan, K. T. & Cardon, L. R. Designing candidate gene and genome-wide case–control association studies. *Nature Protoc.* **2**, 2492–2501 (2007).
111. Rao, D. C. An overview of the genetic dissection of complex traits. *Adv. Genet.* **60**, 3–34 (2008).
112. Teo, Y. Y. Common statistical issues in genome-wide association studies: a review on power, data quality control, genotype calling and population structure. *Curr. Opin. Lipidol.* **19**, 133–143 (2008).
113. Iles, M. M. What can genome-wide association studies tell us about the genetics of common disease? *PLoS Genet.* **4**, e33 (2008).
114. Cupples, L. A. Family study designs in the age of genome-wide association studies: experience from the Framingham Heart Study. *Curr. Opin. Lipidol.* **19**, 144–150 (2008).
115. Manolio, T. A., Bailey-Wilson, J. E. & Collins, F. S. Genes, environment and the value of prospective cohort studies. *Nature Rev. Genet.* **7**, 812–820 (2006).
116. Lowe, J. K. *et al.* Genome-wide association studies in an isolated founder population from the Pacific Island of Kosrae. *PLoS Genet.* **5**, e1000365 (2009).
117. Blakemore, A. I. *et al.* A rare variant in the visfatin gene (*NAMPT/PBEF1*) is associated with protection from obesity. *Obesity (Silver Spring)* (in the press).
118. Khor, C. C. *et al.* A Mal functional variant is associated with protection against invasive pneumococcal disease, bacteremia, malaria and tuberculosis. *Nature Genet.* **39**, 523–528 (2007).
119. Nejentsev, S., Walker, N., Riches, D., Egholm, M. & Todd, J. A. Rare variants of *IFIH1*, a gene implicated in antiviral responses, protect against type 1 diabetes. *Science* **324**, 387–389 (2009).
120. Jones, S. *et al.* Exomic sequencing identifies *PALB2* as a pancreatic cancer susceptibility gene. *Science* **324**, 217 (2009).
121. Stranger, B. E. *et al.* Relative impact of nucleotide and copy number variation on gene expression phenotypes. *Science* **315**, 848–853 (2007).
The first paper to describe the effects of copy number variation on gene expression.
122. de Smith, A. J. *et al.* Array CGH analysis of copy number variation identifies 1,284 new genes variant in healthy white males: implications for association studies of complex diseases. *Hum. Mol. Genet.* **16**, 2783–2794 (2007).
123. Feuk, L., Carson, A. R. & Scherer, S. W. Structural variation in the human genome. *Nature Rev. Genet.* **7**, 85–97 (2006).
124. Peiffer, D. A. *et al.* High-resolution genomic profiling of chromosomal aberrations using Infinium whole-genome genotyping. *Genome Res.* **16**, 1136–1148 (2006).
125. McCarroll, S. A. *et al.* Integrated detection and population-genetic analysis of SNPs and copy number variation. *Nature Genet.* **40**, 1166–1174 (2008).

126. Baross, A. *et al.* Assessment of algorithms for high throughput detection of genomic copy number variation in oligonucleotide microarray data. *BMC Bioinformatics* **8**, 368 (2007).
127. Horsthemke, B. & Wagstaff, J. Mechanisms of imprinting of the Prader–Willi/Angelman region. *Am. J. Med. Genet. A* **146A**, 2041–2052 (2008).
128. Dong, C. *et al.* Possible genomic imprinting of three human obesity-related genetic loci. *Am. J. Hum. Genet.* **76**, 427–437 (2005).
129. Guo, Y. F. *et al.* Assessment of genetic linkage and parent-of-origin effects on obesity. *J. Clin. Endocrinol. Metab.* **91**, 4001–4005 (2006).
130. Stoger, R. The thrifty epigenotype: an acquired and heritable predisposition for obesity and diabetes? *Bioessays* **30**, 156–166 (2008).
131. Bibikova, M. *et al.* High-throughput DNA methylation profiling using universal bead arrays. *Genome Res.* **16**, 383–393 (2006).
132. Weber, M. *et al.* Chromosome-wide and promoter-specific analyses identify sites of differential DNA methylation in normal and transformed human cells. *Nature Genet.* **37**, 853–862 (2005).
133. English, S. B. & Butte, A. J. Evaluation and integration of 49 genome-wide experiments and the prediction of previously unknown obesity-related genes. *Bioinformatics* **23**, 2910–2917 (2007).
The first attempt at a systems biology approach to integrating obesity research results identifies novel genes.
134. Gorber, S. C., Tremblay, M., Moher, D. & Gorber, B. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. *Obes. Rev.* **8**, 307–326 (2007).
135. Wells, J. C., Ruto, A. & Treleaven, P. Whole-body three-dimensional photonic scanning: a new technique for obesity research and clinical practice. *Int. J. Obes. (Lond.)* **32**, 232–238 (2008).
136. Ellis, K. J. *et al.* Body-composition assessment in infancy: air-displacement plethysmography compared with a reference 4-compartment model. *Am. J. Clin. Nutr.* **85**, 90–95 (2007).
137. Shen, W. & Chen, J. Application of imaging and other noninvasive techniques in determining adipose tissue mass. *Methods Mol. Biol.* **456**, 39–54 (2008).
138. Vlachos, I. S., Hatziioannou, A., Perelas, A. & Perrea, D. N. Sonographic assessment of regional adiposity. *AJR Am. J. Roentgenol.* **189**, 1545–1553 (2007).
139. Westerterp, K. R. & Goris, A. H. Validity of the assessment of dietary intake: problems of misreporting. *Curr. Opin. Clin. Nutr. Metab. Care* **5**, 489–493 (2002).
140. Swanson, M. Digital photography as a tool to measure school cafeteria consumption. *J. Sch. Health* **78**, 432–437 (2008).
141. Pencina, M. J., Millen, B. E., Hayes, L. J. & D'Agostino, R. B. Performance of a method for identifying the unique dietary patterns of adult women and men: the Framingham nutrition studies. *J. Am. Diet Assoc.* **108**, 1453–1460 (2008).
142. Dialektakou, K. D. & Vranas, P. B. Breakfast skipping and body mass index among adolescents in Greece: whether an association exists depends on how breakfast skipping is defined. *J. Am. Diet Assoc.* **108**, 1517–1525 (2008).
143. Morton, G. J., Cummings, D. E., Baskin, D. G., Barsh, G. S. & Schwartz, M. W. Central nervous system control of food intake and body weight. *Nature* **443**, 289–295 (2006).
144. Henry, B. A. & Clarke, I. J. Adipose tissue hormones and the regulation of food intake. *J. Neuroendocrinol.* **20**, 842–849 (2008).
145. Rosen, E. D. & Spiegelman, B. M. Adipocytes as regulators of energy balance and glucose homeostasis. *Nature* **444**, 847–853 (2006).
146. Spiegelman, B. M. & Flier, J. S. Obesity and the regulation of energy balance. *Cell* **104**, 531–543 (2001).
147. Wegner, L. *et al.* Common variation in *LMNA* increases susceptibility to type 2 diabetes and associates with elevated fasting glycemia and estimates of body fat and height in the general population: studies of 7,495 Danish whites. *Diabetes* **56**, 694–698 (2007).
148. Baessler, A. *et al.* Genetic linkage and association of the growth hormone secretagogue receptor (ghrelin receptor) gene in human obesity. *Diabetes* **54**, 259–267 (2005).
149. Gylvin, T. *et al.* Functional *SOCS1* polymorphisms are associated with variation in obesity in whites. *Diabetes Obes. Metab.* **11**, 196–203 (2009).
150. Talbert, M. E. *et al.* Polymorphisms near SOCS3 are associated with obesity and glucose homeostasis traits in Hispanic Americans from the Insulin Resistance Atherosclerosis Family Study. *Hum. Genet.* **125**, 153–162 (2009).
151. Zobel, D. *et al.* Variation in the gene encoding Kruppel-like factor 7 influences body fat: studies of 14,818 Danes. *Eur. J. Endocrinol.* **160**, 603–609 (2009).
152. Yanagiya, T. *et al.* Association of single-nucleotide polymorphisms in MTMR9 gene with obesity. *Hum. Mol. Genet.* **16**, 3017–3026 (2007).
153. Wermter, A. K. *et al.* Preferential reciprocal transfer of paternal/maternal DLK1 alleles to obese children: first evidence of polar overdominance in humans. *Eur. J. Hum. Genet.* **16**, 1126–1134 (2008).
154. Stone, S. *et al.* TBC1D1 is a candidate for a severe obesity gene and evidence for a gene/gene interaction in obesity predisposition. *Hum. Mol. Genet.* **15**, 2709–20 (2006).
155. Siddiq, A. *et al.* Single nucleotide polymorphisms in the neuropeptide Y2 receptor (*NPY2R*) gene and association with severe obesity in French white subjects. *Diabetologia* **50**, 574–84 (2007).

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DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
ADIPOQ | *BDNF* | *CNR1* | *CTNNBL1* | *DRD2* | *ENPP1* | *FTO* | *GAD2* | *HTR2C* | *INSIG2* | *KCTD15* | *LEP* | *LEPR* | *MAF* | *MAOA* | *MC4R* | *MTCH2* | *NEGR1* | *NPC1* | *NTRK2* | *PCSK1* | *POMC* | *PTER* | *SH2B1* | *SLC6A14* | *SLC6A4* | *TMEM18*

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Andrew J. Walley's homepage:
http://www1.imperial.ac.uk/medicine/people/a.walley
Julian E. Asher's homepage:
http://www1.imperial.ac.uk/medicine/people/j.asher
Philippe Froguel's homepage:
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