Chapter 3
Genome-Wide Association Studies of Obesity

Åsa K. Hedman, Cecilia M. Lindgren, and Mark I. McCarthy

Abstract Genome-wide association studies (GWAS) have accelerated the discovery of genetic variants associated with susceptibility to common complex diseases, such as obesity. Following the first robust GWAS of BMI and risk of obesity identified in 2007, GWAS have delivered 70 additional common loci associated with a wide range of obesity-related traits. These loci highlight a variety of molecular and physiological mechanisms involved in shaping these traits. However, even in combination, these loci explain only a small proportion of overall phenotypic heritability indicating that much of the genetic variation in obesity traits remains unexplained. Here, we discuss how the GWAS approach has been applied to the study of anthropometric phenotypes related to overall obesity and fat distribution and describe some of the clues to trait biology that are emerging. We also highlight some of the limitations of this work and future directions for research in this field.

Å.K. Hedman
Wellcome Trust Centre for Human Genetics, University of Oxford,
Roosevelt Drive, Oxford OX3 7BN, UK
e-mail: asah@well.ox.ac.uk

C.M. Lindgren
Broad Institute of Harvard and Massachusetts Institute of Technology,
Cambridge, MA 02142, USA

Wellcome Trust Centre for Human Genetics, University of Oxford,
Roosevelt Drive, Oxford OX3 7BN, UK
e-mail: celi@well.ox.ac.uk

M.I. McCarthy (✉)
Wellcome Trust Centre for Human Genetics, University of Oxford,
Roosevelt Drive, Oxford OX3 7BN, UK

Oxford Centre for Diabetes, Endocrinology and Metabolism,
Churchill Hospital, University of Oxford, Oxford OX3 7LJ, UK

Oxford National Institute for Health Research Biomedical Research Centre,
Churchill Hospital, Oxford, UK
e-mail: mark.mccarthy@drl.ox.ac.uk

S.F.A. Grant (ed.), *The Genetics of Obesity*, DOI 10.1007/978-1-4614-8642-8_3,

Abbreviations

BMI	Body mass index
CNV	Copy number variation
GIANT	Genetic Investigation of ANthropometric Traits
GWAS	Genome-wide association studies
LD	Linkage disequilibrium
MAF	Minor allele frequency
SNP	Single nucleotide polymorphism
T2D	Type 2 Diabetes
WC	Waist circumference
WHR	Waist–hip ratio

The rise in the prevalence of obesity in recent decades has been spectacular: recent estimates indicate that over 500 million adults worldwide are now classed as obese [1]. While the increased prevalence of obesity is almost certainly a reflection of secular changes in environmental and lifestyle factors, including an increased intake of nutrient-dense foods coupled with reduced physical activity [2], the familial aggregation of obesity is consistent with some degree of genetic influence on body mass index (BMI) and individual predisposition to obesity. More conclusive evidence for a genetic component comes from studies that have examined the correlation of BMI between identical twins raised apart and the relationship between the BMI of adoptees and both their biological and adoptive parents [3–5]. These consistently highlight the importance of genetic factors in modulating individual susceptibility to obesity in contemporary environments. Furthermore, in controlled experiments of excessive calorie intake, consequent changes in weight and body composition were highly correlated in monozygotic twins, once again consistent with a powerful role of genetic variation in the regulation of weight [6]. Estimates for the heritability of BMI vary widely between studies, but typical figures range between 0.47 and 0.90 in twin studies and between 0.24 and 0.81 in family-based studies [7].

Other obesity related traits, including measures of fat distribution are also heritable (even after adjusting for BMI). Estimates for the heritability of waist–hip ratio (WHR), a proxy of fat distribution, range between $h^2 \sim 0.31$–0.70; and ~0.22–0.61 after accounting for BMI [8–11]. The heritability of WHR is higher in women and estimates of genetic correlation of WHR between men and women indicate a sex specific genetic influence on the trait [11].

The Genetics of BMI and Obesity Pre-GWAS

Genetic studies aim to find DNA sequence variants that are causally associated with the trait of interest, in the expectation that such discoveries will help to reveal fundamental mechanisms responsible for human disease. The earliest studies in this

field focused on the application of family-based linkage studies to individuals and families with rare monogenic forms of obesity. The rare variants of large effects revealed by these efforts, such as those in *LEP* (encoding the hormone leptin, a crucial component of energy balance mechanisms) [12–14], *LEPR* (encoding the leptin receptor) [15], and *POMC* (encoding the proopiomelanocortin protein which is cleaved to form a number of key neuroendocrine messengers) [16], helped to define components of hypothalamic circuitry involved in body weight regulation in man. However, the application of linkage approaches to population-level variation in BMI and risk of common forms of obesity met with little success in terms of robust, replicated signals even in relatively well-powered meta-analysis [17]. This indicates that the genetic contribution to these traits is not dominated by the kinds of highly penetrant variants which linkage methods are best suited to detect [18].

The shift from linkage to association approaches was initially focused on the analysis of candidate genes [19], a strategy reliant on the quality of the prior biological hypotheses used to select them. One of relatively few successes from this approach was the demonstration that low frequency variants in the gene encoding the melanocortin 4 receptor (*MC4R*) were associated with severe, early-onset obesity [20]. These variants remain the commonest known genetic cause of morbid obesity contributing to a few percent of these cases [21]. These findings provided confirmation of the role of signalling through the hypothalamic leptin–melanocortin pathway for the maintenance of body mass in man [22]. However, the major impetus to the discovery of BMI- and obesity-associated variants has been provided by the ability to perform genome-wide scans for association.

Genome-Wide Association Studies

Genome-wide association studies (GWAS) (reviewed in [23, 24]) use dense genotyping arrays to determine how variation in genomic sequence (predominantly that due to single nucleotide polymorphisms, SNPs) associates with phenotypic traits of interest. Those traits may be categorical (e.g., obese cases and non-obese controls) or continuous (e.g., BMI or WHR). Array content and the correlation structure of variation across the genome (i.e., linkage disequilibrium) mean that GWAS to date have favored the interrogation of common variants (minor allele frequency [MAF] > 5 %). Since GWAS assay such variants across the genome, suitably powered studies enable the discovery of associated loci in an agnostic fashion, without the need for prespecified hypotheses concerning the genomic location of the association and the transcripts through which they may operate.

In the remainder of this chapter, we focus on the loci which have been shown by GWAS to be associated with overall obesity or fat distribution. We distinguish between studies of traits of overall obesity (including BMI, fat percentage, and dichotomized indices of extreme obesity) and those of fat distribution (including WHR, waist circumference (WC), and measures of visceral and subcutaneous fat). In total 70 genome-wide significant loci have been associated with these traits and most of these (50 in number) are common variant loci influencing continuous

obesity-related traits found in European samples. Others derive from equivalent studies in non-European samples (4 loci), and some have emerged exclusively from case–control studies in individuals selected from the extremes of the BMI distribution (9 loci) or by clinical classifications of overweight and obesity (7 loci).

Overall Obesity

Genome-Wide Association Studies of BMI

The first report from a GWA study claiming to have identified variants associated with common forms of overall obesity came in 2006 [25]. The researchers used a two-stage family-based design to identify a signal mapping close to the *INSIG2* encoding insulin induced gene 2 [25]. However, this association has not been proven robust to replication in the much larger samples that have been examined in subsequent studies (see below). In fact, the association p-value observed in this study fell short of the now-widely accepted threshold ($p < 5 \times 10^{-8}$: based on $p < 0.05$ corrected for a million independent tests [26]), highlighting the value of such stringent criteria as a means of avoiding inflation of the type 1 error, and the attribution of biological significance to loci which, like *INSIG2*, are likely to have been false positives.

The first report of a robust genome-wide significant locus influencing BMI and risk of obesity locus came from Frayling et al. [27] in 2007, and concerned a cluster of common variants close to the *FTO* ("Fat mass and obesity-associated") gene. These variants account for ~0.35 % of the phenotypic variance in BMI in Europeans [28] such that the two groups of homozygotes differ in weight by around 2.5 kg. The BMI association has now been widely replicated [28–33] and it is also clear that the same *FTO* variants are associated with risk of obesity at all grades of severity [27, 34].

Given that the only locus emerging from this first round of GWA studies [25, 27] had a relatively modest effect size, it was clear that larger sample sizes would be needed to extend these discoveries, both to common alleles of lesser effect, and to less frequent risk alleles. This provided the motivation for ever-larger meta-analyses efforts, which have dominated discovery efforts over the past few years. The largest of the studies published to date assembled data from almost 250,000 individuals [28]. The current count of BMI-associated loci detected in Europeans by these studies, most of them conducted under the aegis of the Genetic Investigation of ANthropometric Traits (GIANT) consortium [28–30], is 32 (Fig. 3.1).

The first such meta-analyses uncovered common regulatory variants influencing BMI near *MC4R* (encoding melanocortin receptor 4) [29]: low-frequency coding variants in this same gene had previously been implicated in severe obesity [20]. Subsequently, the parallel publications from GIANT [30] and the deCODE group [31] added nine BMI loci (mapping near *GNPDA2*, *KCTD15*, *MTCH2*, *NEGR1*, *SH2B1*, *TMEM18*, *BDNF*, *ETV5*, and *SEC16B*) to the list. It is of note that *BDNF*, encoding a brain derived neurotrophic factor involved in regulation of development

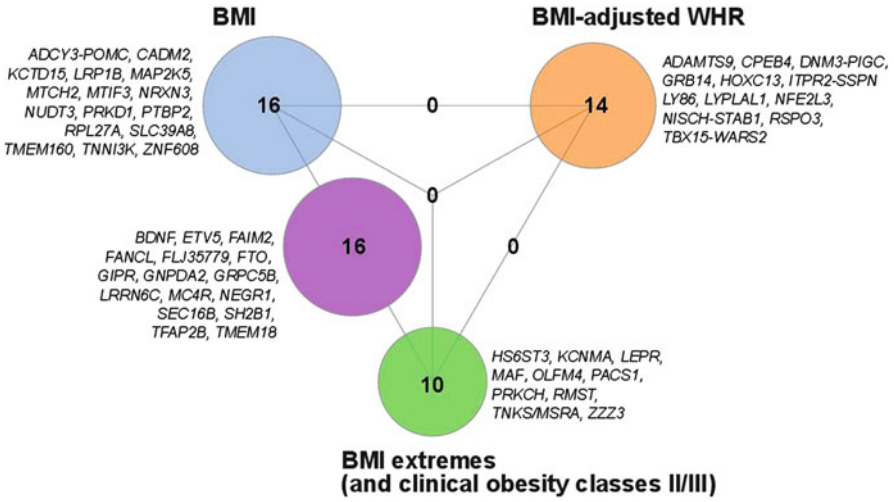

Fig. 3.1 Overlap of genome-wide significant loci of overall obesity (BMI), fat distribution (BMI-adjusted WHR) and BMI extremes (or clinical obesity classes) in European populations. Diagram depicts the overlap of reported GWAS loci ($p < 5 \times 10^{-8}$) of BMI [27–31], BMI-adjusted WHR [98], and BMI extremes or clinical obesity classes II–III [34, 38, 51–53, 55, 120]

of neuronal circuits [35], is also involved in monogenic forms of obesity [36]. The largest meta-analysis of BMI associations added 18 further loci to the tally [28] including regions near known obesity genes such as *POMC* (proopiomelanocortin) [16], known to be involved in neuroendocrine regulation of weight, as well as associations in or near novel genes such as *GPRC5B* (G protein-coupled receptor, family C, group 5, member B), implicated in regulation of adipose inflammatory processes and progression to insulin resistance in obesity in mice [37].

The studies above mostly focused on the analysis of SNPs but there is some evidence that copy number variations (CNVs) may be causal at some loci. For example, in the study by Willer et al. the BMI-associated SNP at the *NEGR1* (neuronal growth regulator 1) locus detected by GWAS was shown to tag a 45 kb deletion that might have stronger functional grounds for being causal [30]. More detailed studies published recently locate the causal allele at this locus to a second 8 kb deletion near *NEGR1* [38]. Rare CNVs have also been implicated in syndromic forms of obesity. For example, a rare deletion in the 16p11.2 region is associated with the combination of severe obesity and mental retardation [39, 40], and duplication of the same region is associated with underweight [41].

To date, most GWAS studies have been performed in populations of European origin but studies in other ethnic groups can help to identify novel loci, to characterize the extent of aetiological overlap, and to fine-map causal variants (such as in the *FTO* locus [42, 43]). Two large GWAS meta-analyses of BMI in East Asian populations were recently published [32, 33]. Between them, seven of the known loci in Europeans could be replicated to genome-wide levels of significance.

Furthermore, evaluating the associations in East Asians of previously reported BMI loci, an additional 11 loci, besides those genome-wide significant, were associated with BMI at lesser levels of significance (Okada et al. [32], $p < 0.02$; Wen et al. [33], $p < 0.05$), indicating considerable overlap in signals between East Asian and European populations. As in populations of European origin, the association at *FTO* locus explained the largest proportion of phenotypic variance (~0.2 %).

In addition, these studies identified four novel loci, mapping near *CDKAL1*, *KLF9*, *PCSK1* and *GP2* [32, 33]. Mutations in *PCSK1* cause monogenic obesity [44] and, while a candidate study previously associated nonsynonymous variants in *PCSK1* with common obesity risk in a European population [45], the *PCSK1* signal in East Asians (also nominally associated with BMI in Europeans in GIANT [28]) likely represents an independent signal. Genetic variants in *CDKAL1* (a CDK5 regulatory associated protein 1-like 1 with methythiotransferase function [46]), in strong LD ($r^2 \sim 0.8$) with the BMI GWAS SNPs in East Asians, have previously been associated with increased risk of Type 2 Diabetes (T2D) [47, 48]. The T2D risk allele(s) is associated with decreased glucose-stimulated insulin secretion [47, 49, 50]. Furthermore, the BMI-lowering allele of rs2206734 (also nominally associated with BMI in Europeans) was associated with increased risk of T2D in the same study population [32], indicating that variation near *CDKAL1* may play a complex role with respect to variation in both BMI and T2D-risk.

Case–Control Studies of Dichotomized BMI

In addition to studies of the variance in BMI in population-based studies, a complementary approach treats obesity in terms of a dichotomous "case–control" analysis. A variety of different schemes for this dichotomization are possible (Table 3.1). In the largest study of this type [51], featuring case–control analyses restricted to the "tails" of the BMI distribution using data from studies previously included in GIANT meta-analyses [28], Berndt et al. found considerable overlap in the pattern of association signals seen as compared to those observed in population- or cohort-wide analyses. However, where such studies focus on cases of more extreme definitions of obesity and/or leanness (that is, individuals several standard deviations away from the population mean), there may be the opportunity to detect additional, novel, signals that may have limited impact on overall population-level variance and which are therefore difficult or impossible to detect using GWAS approaches. The rare, penetrant variants causal for monogenic and syndromic forms of obesity provide the most obvious example of this phenomenon.

Indeed, whilst several of the loci reaching genome-wide significance in dichotomous analyses focused on extreme obesity in adults overlap with those previously reported (e.g., *BDNF*, *FTO*), there are several signals that appear unique to dichotomous analyses including *KCNMA1*, *NPC1*, *PTER*, and *HS6ST3* (Table 3.1, Fig. 3.1) [51–53]. However, most of these have appeared in a single study and have not, as yet, been replicated, even in other extreme case–control analyses. In equivalent

Table 3.1 Novel GWAS loci identified in case–control analyses of dichotomized BMI

Study type	Selection criteria for cases	Sample size in stage 1, cases/controls	Loci not described in BMI GWAS	Reference
Extreme obesity in children and adults	Early onset obesity (≤6 years) and extreme adult obese (BMI ≥ 40)	1,380/1,416	*MAF* (rs1424233), *NPC1*[a] (rs1805081), *PTER*[a] (rs10508503)	[52]
Extreme obesity in children and adolescents	BMI >97 % percentile	1,138/1,120	*TNKS/MSRA* (rs17150703), *SDCCAG8*[a] (rs12145833)	[55]
Extreme obesity in adults	BMI ≥ 40	164/163	*KCNMA1* (rs2116830)	[53]
Distributional tails in children	BMI ≥95 % percentiles	5,530/8,313	*BC041448* (rs4864201), *HOXB5* (rs9299), *OLFM4* (rs9568856)	[54]
Extreme obesity in children	BMI standard deviation score (SDS) ≥3, and onset at 10 years	1,509/5,380	*LEPR* (rs11208659), *PACS1* (rs564343), *PRKCH* (rs1957894) *RMST* (rs11109072)	[38]
Clinical class: obesity II	BMI ≥ 35	9,889/62,657	*HS6ST3* (rs7989336), *ZZZ3* (rs17381664)	[51]
Clinical class: obesity I	BMI ≥ 30	32,858/65,839	*GNAT2* (rs17024258), *HNF4G* (rs4735692), *MRPS33P4* (rs13041126), *ADCY9* (rs2531995)	[51]
Clinical class: overweight	BMI ≥ 25	93,015/65,840	*HNF4G* (rs4735692), *RPTOR* (rs7503807)	[51]

[a]Not genome-wide significant ($p < 5 \times 10^{-8}$)

case–control analyses in children, the more relaxed criteria adopted by Bradfield et al [54] detected many of the known adult BMI association signals but also highlighted novel signals near *OLFM4* and *HOXB5*. In contrast, studies of children selected from the extremes of the distribution have detected signals at (or approaching) genome-wide significance near *LEPR*, *PACS1*, *PRKCH*, *RMST*, *SDCCAG8*, and *TNKS/MSRA* (Table 3.1, Fig. 3.1) [38, 55], the latter locus also detected in some studies of fat distribution [56].

Genome-Wide Association Studies of Fat Percentage

BMI, although a widely used proxy of overall obesity, represents an aggregate measure of the lean and the fat mass of the individual. In an effort to better define the genetic determinants of obesity, Kilpeläinen et al. focused on body fat

percentage, as a more direct measure of adiposity, generating a GWAS meta-analysis of 36,626 individuals [57]. As well as detecting *FTO*, these analyses recovered two loci (*IRS1* and *SPRY2*) not previously associated with BMI. The body fat-increasing alleles at the *IRS1* (insulin receptor substrate 1 signalling protein) signal are, intriguingly, associated with a healthy metabolic profile (including reduced risk of T2D [58] and unhealthy lipid profile [59]). The *IRS1* locus is associated with measures of subcutaneous, but not visceral fat, indicating that the effect on fat mass at the *IRS1* locus is through regulation of subcutaneous fat deposition [57, 60]. The *SPRY2* locus has also been implicated in T2D risk [61, 62], though the body fat-associated SNP is not coincident with this previously reported T2D SNP. Contrary to the observations at *IRS1*, the body-fat increasing allele at the *SPRY2* locus is associated with an adverse metabolic profile [57].

Genetic Architecture of Overall Obesity (BMI)

Despite the success in identifying a growing numbers of loci to genome-wide significance, in European populations these signals, in combination, explain no more than 1.5 % of phenotypic variance in BMI. Of the established loci, the *FTO* locus has the largest effect accounting for ~0.35 % of population variance [28]. These numbers fall well short of estimates of the heritability of this trait (see above). The basis for this "missing" genetic variance remains unclear, though there is no lack of possible explanations [63, 64]. At least part of the "missing" genetic variance can be attributed to the effects of additional common variants that lie below the genome-wide significance threshold. Using full GWAS data sets (not just the "proven" hits), Yang and colleagues could recover approximately 17 % of the phenotypic variance in BMI that was tagged by common variants [65]. Part of the remaining shortfall likely reflects incomplete linkage disequilibrium between the variants genotyped on GWAS arrays and those which are causally responsible for the BMI associations [66], but other mechanisms are almost certainly involved [63, 67].

There is also the possibility that the estimates of heritability against which these measures of explained variance are evaluated, are themselves inaccurate. For example, intrauterine events that lead to epigenetic modifications with long-term phenotypic impacts can lead to increased sibling resemblance, inflating heritability estimates under some designs. Similarly, estimates derived from the comparison of the phenotypic correlations observed between monozygotic and dizygotic twin pairs are based on the assumption that both types of twin are exposed to a similar degree of shared environment [68], an assumption that may not be appropriate for intrauterine exposures.

Notwithstanding the above, it seems likely that an appreciable component of the genetic variance remains unexplained, and that at least part of this will be attributable to low frequency and rare variants not well captured by GWAS studies to date. The current wave of sequencing studies should shed some light on the extent to which these variants are contributing to inherited risk.

From GWAS Associations to Potential Functional Roles in Overall Obesity

As we have seen, GWAS have powered the identification of many genetic regions associated with BMI and obesity. However, this information is of limited value unless it can be translated into improved understanding of the pathophysiology of disease, and thereby into novel clinical approaches. However, in BMI, as with most other complex traits, the regions revealed by GWAS do not lend themselves to easy biological inference. The effect sizes are modest, and most signals map to non-coding sequence, frustrating efforts to identify the "causal" transcript (that is, the specific gene that is mediating the association signal). At the same time, the extensive local correlations between common variants (that is, linkage disequilibrium) can make fine-mapping of the causal variants challenging.

The *FTO* locus provides an excellent example of the difficulties inherent in moving from an association signal—in this case, a comparatively strong one—to a clear mechanism of action. We have now known for more than 6 years that a cluster of highly correlated common variants in the first intron of the *FTO* gene is associated with BMI and obesity [27]. Epigenetic analyses have suggested that the BMI-associated haplotype may influence local methylation status [69] but fine-mapping efforts have yet to provide compelling localization of the causal variant. When it comes to defining downstream effects, we still have no convincing evidence from man that the *FTO* transcript itself is in any way involved. There is for example, no instance of the co-occurrence of loss of function alleles in *FTO* and severe obesity in humans [70, 71]. On the other hand, the adjacent gene *RPGRIP1L* (or *FTM*), which is known to be coordinately regulated with *FTO* via a common promoter [72], and to display a similar pattern of hypothalamic expression, has an intriguing connection to obesity through its known causal role with respect to monogenic ciliopathies [73] some of which result in marked early obesity.

In fact, the most compelling evidence implicating *FTO* comes from mouse models: transgenic knockdown of the murine homologue *Fto* results in reduced weight, and overexpression to weight gain compared to control mice [74, 75]. One possible explanation consistent with these data is that the common intronic variants within *FTO* identified by GWAS, exert their effects on energy balance in man through coordinate dysregulation of both *FTO* and *RPGRIP1L*.

The identification of the signal at *FTO* naturally prompted interest in the normal function of this transcript. In humans, *FTO* encodes a 2-oxoglutarate-dependent nucleic acid demethylase [76] thought to be involved in nucleic acid repair. In vitro studies have suggested a role for *FTO* demethylation in cellular sensing of amino acids [77], which could be relevant to regulation of appetite control in the hypothalamus. Nonetheless, it is clear that we remain some way from a complete description of how these variants influence BMI and obesity risk.

At certain other BMI GWAS loci, the situation is better understood. At four GWAS loci (near *BDNF*, *PCSK1*, *POMC* and *MC4R*) the common variant associations overlap genes in which coding mutations have been shown to be causal for

monogenic or syndromic forms of obesity [20, 36, 78, 79]. In the case of three of these—*PCSK1* (proprotein convertase 1), *POMC* (proopiomelanocortin), and *MC4R* (melanocortin receptor 4)—there are strong mechanistic ties to the hypothalamic leptin–melanocortin signalling pathways that regulate energy balance [80]. *BDNF* encodes a brain derived neurotrophic factor involved in neurogenesis and thought to be involved in food intake [81]. These GWAS signals therefore demonstrate that the neuroendocrine mechanisms documented in monogenic forms of obesity extend to population level variance in BMI and to more common forms of obesity.

At other BMI-associated GWAS, efforts to define the causal transcript are supported by additional sources of genomic data (regulatory annotations [82] or mRNA expression [83]). For example, it can be very useful through integration with mRNA and/or miRNA transcriptomic data [83–88] to demonstrate that the set of BMI-associated variants at a given locus also drives *cis*-expression of one of the regional transcripts. In the most recent GIANT meta-analysis [28], this approach led to positional candidates being identified at almost half the 32 BMI-associated loci.

These candidacy assignments can often be bolstered by other sources of data. Consider for example the association signal mapping close to the *SH2B1* gene, encoding SH2B adapter protein 1. *Cis*-expression data point to *SH2B1* [28], as does the high expression of this transcript in the hypothalamus [30]. The neuronal isoform of *SH2B1* is involved in regulation of energy balance via effects on leptin and insulin signalling, and systemic deletion of the gene in mice results in severe leptin resistance [89].

For some loci, the data seem to point towards peripheral rather than central mechanisms of action. The BMI association on chromosome 19 lies close to the *GIPR* gene, encoding the gastric inhibitory polypeptide receptor, and the lead SNP is in strong LD with a missense SNP in that transcript (though the functional consequences of that mutation are not yet established). GIPR plays an important role in mediating the incretin response, which augments insulin release in response to the ingestion of food. The same locus has also been shown to associate with glucose response and insulin secretion in response to a glucose challenge [90]. Another example, mentioned earlier, is the mechanistic relationship between insulin signalling and obesity implicated by the association between *IRS1* variants and fat percentage [57]. Though both central and peripheral mechanisms may be involved at *IRS1*, the fact that the fat percentage-associated allele is associated with improved insulin sensitivity and a healthy metabolic profile [58, 59] is consistent with enhanced insulin-mediated adipogenesis as the driver of the adiposity.

For several other BMI-associated loci such as *TMEM160-ZC3H4* [28], there are few clues on the biological relevance in obesity, and any one of several transcripts could be responsible. One way of leveraging the combination of genetic and prior biological data to make provisional mechanistic inference in such situations is to perform pathway-based analyses (reviewed in Wang et al. [91]), which test for enrichment of GWAS loci for transcripts that have been mapped to defined biological processes or pathways. Applied to BMI GWAS data, these analyses have tended to support the evidence for broad neuroendocrine involvement, whilst also highlighting processes that are more difficult to assimilate within the current knowledge base (e.g., platelet-derived growth factor signalling) [28].

Fat Distribution

The clinical consequences of adipose tissue excess depend not only on its quantity but also its distribution, with the accumulation of visceral (abdominal) fat leading to particularly adverse metabolic and cardiovascular effects [92, 93]. After accounting for overall obesity (as measured by BMI), fat distribution (commonly measured by WHR) shows substantial residual heritability ($h^2 \sim 0.22–0.61$) consistent with mechanisms of genetic control distinct from those influencing overall energy balance and BMI [9, 10]. The distinct genetic regulation of patterns of fat distribution is also supported by rare monogenic syndromes of selective adipose tissue loss (collectively, the lipodystrophies) [94]. Given the checkered history of efforts to target neuronal pathways related to overall obesity in the search for effective, safe treatments for obesity, there is considerable interest in defining the mechanisms responsible for individual variation in patterns of fat distribution, and in particular, in identifying peripheral (rather than central) targets for therapeutic intervention.

Genome-Wide Association Studies of WHR and WC

Initial efforts to map variants influencing fat distribution focused on the standard clinical traits, WHR and WC. In the first GWAS for WHR, Lindgren et al. discovered an association to a genetic variant on chromosome 1 (close to the *LYPLAL1* gene encoding lysophospholipase-like 1) associated with WHR in women exclusively: this effect was independent of BMI [56]. Studies of WC generated their strongest signals at previously reported BMI loci such as *FTO* and *MC4R*, reflecting the strong correlation between these traits [27, 56, 95, 96]. With the possible exception of the association near *TFAP2B*, at which adjustment with BMI seems to increase the magnitude of the effect on central obesity [97], other WC-associated loci identified by GWAS (*MSRA*, *NRXN3*) are likely to reflect a primary association with BMI [28].

Given these strong trait correlations, more recent fat distribution GWAS efforts have adopted the approach of adjusting WHR (or WC) for BMI before performing the association analyses, thereby seeking to emphasize those signals that influence patterns of relative fat deposition independent of the overall obesity component. In the largest analysis to date, involving data from around 190,000 subjects, Heid et al. [98] used this approach to identify 13 novel loci for BMI-adjusted WHR as well as to replicate the signal near *LYPLAL1*. As might have been expected given the adjustment for BMI, the loci identified by this endeavor were completely distinct from those previously reported to influence overall obesity (Figs. 3.1 and 3.2). In line with the metabolic consequences of visceral fat accumulation, these fat distribution associated variants are also enriched for association with related metabolic traits including fasting insulin, lipids and indices of insulin resistance [98]. The obvious gender dimorphism of WHR prompted efforts to evaluate these signals in terms of their potential for different effects in males and females.

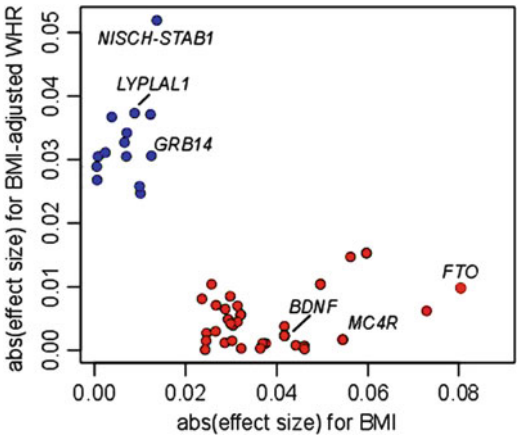

Fig. 3.2 Effect sizes for BMI in GIANT meta-analyses vs. BMI-adjusted WHR in GIANT meta-analyses for genome-wide significant BMI and BMI-adjusted WHR loci. In the *scatterplot*, data for BMI in GIANT meta-analyses [28] are shown on the *X*-axis and data for BMI-adjusted WHR in GIANT meta-analyses [98] on the *Y*-axis. The points are colored according to if they represent loci associated with BMI (*red*) or BMI-adjusted WHR (*blue*)

Half of the 14 loci showed evidence of gender-specific effects: in each case, the effect was stronger in women [98].

In a complementary approach to studies of WHR in population-wide analysis, Berndt et al. restricted analysis to the "tails" of the WHR distribution (upper and lower 5th percentiles) and analyzed WHR in terms of dichotomous "case–control" analyses [51]. This analysis demonstrated a similar pattern of association signals as that of previous population-wide analysis [98], indicating that WHR at the "tails" of the distribution has a similar genetic architecture as that of the full distribution.

Genome-Wide Association Studies of Abdominal Fat Distribution

The use of imprecise, but widely available, clinical measures such as WHR facilitates large meta-analysis, but there is much to be gained by complementary analyses in smaller numbers of more carefully phenotyped subjects. In a recent study, more direct measurements of the extent of abdominal subcutaneous and visceral adiposity were obtained by computed tomography (CT) [60]. This analysis was able to demonstrate that the fat distribution association signal near *LYPLAL1* [51, 56, 98] could also be detected using CT (as the ratio between subcutaneous and visceral fat area). It also highlighted a signal near *THNSL2* that was associated with visceral adiposity in women: this survived adjustment for BMI, and has not previously been associated to obesity traits [60].

Genetic Architecture of Fat Distribution

Combined, the 14 loci for BMI-adjusted WHR uncovered by GWAS account for approximately 1 % of variance in this trait (1.34 % in women; 0.46 % in men) [98]. Using methods analogous to those for BMI described above [65], Vattikuti et al. showed that ~13 % of the overall variance in WHR could be explained by common GWAS SNPs, and thus estimated that 46 % of heritability in WHR may be captured by common variants [99]. A similar range of explanation for the missing genetic variance is possible as for overall obesity [63, 64, 67], and ongoing sequence-based efforts will help to define the extent to which this deficit can be plugged by the contribution of low frequency and rare variants.

From GWAS Associations to Potential Functional Roles in Fat Distribution

As with BMI, progress towards characterization of the mechanisms operating at each of these loci has been patchy. Expression-QTL mapping in adipose tissue, blood, and other tissues has identified promising candidate transcripts at six of the loci (*AA553656*, *GRB14*, *PIGC*, *STAB1*, *TBX15*, and *ZNRF3*) [98].

For several of these transcripts, the genetic data integrates well with the corpus of existing biological data. For example, *GRB14*, encoding a growth factor receptor-binding protein, is known to acts as a negative regulator of insulin receptor signalling [100, 101]. The WHR-associated variant shows directionally consistent associations with triglyceride and insulin levels [98] and other (statistically independent) variants at the same locus influence BMI-adjusted insulin and HDL-cholesterol levels [102, 103]. *TBX15* encodes a mesodermal developmental transcription factor and has been indicated in adipocyte differentiation and triglyceride accumulation [104]. This transcript is also differentially expressed between visceral and subcutaneous adipose tissue, and there is evidence that visceral adipose tissue expression is negatively correlated with BMI [105].

The most consistent signal for fat distribution maps to the *LYPLAL1* locus [51, 56, 60, 98]. As might be expected variants at this locus are associated with a range of related metabolic and anthropometric traits including adiponectin [106], fasting insulin adjusted for BMI [103] and height [107]. So far, there is limited evidence to demonstrate that the signal is mediated through the *LYPLAL1* transcript and the region contains several other potential candidates. However, expression of this gene is induced in subcutaneous fat following obesity [108] and its presumed function as a lysophospholipase is consistent with a causal role.

As with the GWAS loci associated with BMI, pathway enrichment approaches have been applied across the 14 WHR-associated loci. Though the enrichment signals were relatively weak, they highlighted developmental processes and mRNA transcript regulation [98]. The known functions of some of the stronger positional

candidates—such as angiogenesis (*VEGFA*), adipocyte differentiation (*GRB14*) and developmental function (*TBX15*, *HOXC13*)—seem to point towards peripheral mechanisms.

These enrichment patterns, when compared with those seen for BMI, seem consistent with the hypothesis that overall obesity is primarily defined by variation at genes involved in central neuroendocrine regulation, whereas fat distribution is largely influenced by variation at genes, which control peripheral aspects of adipose function and development.

Challenges for the Present and for the Future

Whilst there is no doubt that GWAS studies have accelerated our understanding of the genetics and biology of obesity, there remains much to do. At most of the loci discovered, we have yet to identify the causal variant (or variants) or to define with certainty which regional transcript is responsible for mediating the association effect. The accumulation of transethnic association data [109–111] combined with the growing use of next-generation sequencing to generate reference sets for imputation [112] and to interrogate phenotypically selected individuals (e.g., the morbidly obese) should help to address the former. The latter depends in part on the generation of improved annotations (particularly those from relevant tissues) that connect non-coding variation to transcript regulation, and on the development of appropriate functional assays. As always, the ability to refine the phenotypic consequences of allelic differences at variants of interest in human subjects (for example through imaging of fat tissues) will play a crucial role in defining a mechanistic understanding of these traits.

Missing Genetic Variance

As we have seen the loci identified by GWAS loci explain a surprisingly small proportion of phenotypic variance, far less than appears to be the case for other "similar" quantitative traits, such as height and lipids. Approaches that combine effects across the entire GWAS dataset, rather than considering only those signals reaching genome-wide significance, do a better job of recovering variation (indicating a long "polygenic" tail of common variant susceptibility) but still leave a substantial component of estimated heritability unexplained [65]. To discover further genome-wide significant associations to common genetic variants with increasingly smaller effects would require even larger studies than to date. The latest wave of grand meta-analyses of BMI and BMI-adjusted WHR (involving over 320,000 and 210,000 European samples respectively), currently underway, promise to reveal some of these common variant signals, as do the studies emerging from analyses in a variety of non-European samples.

It has been suggested that rare (MAF < 1 %) or low frequency (MAF 1–5 %) variants beyond the range of the historical GWAS approach, may contribute to this missing genetic variance [24, 64, 113, 114]. The rapidly decreasing cost and increasing accuracy of next-generation sequencing are bringing variants in this class under the microscope for the first time [115].

It is clear that individual risk of obesity reflects the integration of genetic and non-genetic factors including variation in food availability and extent of physical exercise [116]. Indeed, these may directly interact such that variant effects are modulated by these lifestyle factors: under some circumstances these interactions may contribute to the missing "genetic" variance [67]. The detection of such interactions at the genome scale requires massive sample sizes, unless the interaction terms are substantial. Nevertheless, there are several examples now emerging of interaction effects at obesity loci: these include an interaction between *FTO* and exercise [117] as well as sex-specific effects reported for WHR [56, 98] and visceral adiposity [60].

Risk Prediction, Intervention and Medication

One might hope that improved knowledge about the genetics of obesity would help to generate predictive models. These might be used to identify individuals at highest future risk of obesity who could be targeted for early intervention, and/or define genetic markers related to treatment outcome that can be used to guide therapeutic choices. However, the common variants so far identified by GWAS have too weak an effect, even in combination, to have value in this respect. Indeed, genetic risk factors are currently outperformed by traditional risk factors [118] including present BMI (a good predictor of future obesity risk [119]).

Instead, the most valuable translational benefits are likely to accrue from the biological knowledge, which grows from the genetics. Currently, there are few effective pharmaceutical treatments for obesity, and the most successful clinical intervention requires radical (bariatric) surgery. The clinical burden of obesity urgently requires the identification of novel validated therapeutic targets based around a better understanding of underlying mechanisms. The wider behavioral effects of drugs acting on central processes such as appetite may continue to prove problematic in this respect and efforts to target peripheral mechanisms of fat distribution, and thereby ameliorate the adverse metabolic consequences of obesity may prove more productive.

References

1. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ et al (2011) National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 377(9765):557–567

2. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML et al (2011) The global obesity pandemic: shaped by global drivers and local environments. Lancet 378(9793):804–814
3. Stunkard AJ, Foch TT, Hrubec Z (1986) A twin study of human obesity. JAMA 256(1):51–54
4. Stunkard AJ, Harris JR, Pedersen NL, McClearn GE (1990) The body-mass index of twins who have been reared apart. N Engl J Med 322(21):1483–1487
5. Stunkard AJ (1991) Genetic contributions to human obesity. Res Publ Assoc Res Nerv Ment Dis 69:205–218
6. Bouchard C, Tremblay A, Despres JP, Nadeau A, Lupien PJ, Theriault G et al (1990) The response to long-term overfeeding in identical twins. N Engl J Med 322(21):1477–1482
7. Elks CE, den Hoed M, Zhao JH, Sharp SJ, Wareham NJ, Loos RJ et al (2012) Variability in the heritability of body mass index: a systematic review and meta-regression. Front Endocrinol (Lausanne) 3:29
8. Rose KM, Newman B, Mayer-Davis EJ, Selby JV (1998) Genetic and behavioral determinants of waist-hip ratio and waist circumference in women twins. Obes Res 6(6):383–392
9. Mills GW, Avery PJ, McCarthy MI, Hattersley AT, Levy JC, Hitman GA et al (2004) Heritability estimates for beta cell function and features of the insulin resistance syndrome in UK families with an increased susceptibility to type 2 diabetes. Diabetologia 47(4):732–738
10. Souren NY, Paulussen AD, Loos RJ, Gielen M, Beunen G, Fagard R et al (2007) Anthropometry, carbohydrate and lipid metabolism in the East Flanders Prospective Twin Survey: heritabilities. Diabetologia 50(10):2107–2116
11. Zillikens MC, Yazdanpanah M, Pardo LM, Rivadeneira F, Aulchenko YS, Oostra BA et al (2008) Sex-specific genetic effects influence variation in body composition. Diabetologia 51(12):2233–2241
12. Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ et al (1997) Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 387(6636):903–908
13. Echwald SM, Rasmussen SB, Sorensen TIA, Andersen T, TybjaergHansen A, Clausen JO et al (1997) Identification of two novel missense mutations in the human OB gene. Int J Obes Relat Metab Disord 21(4):321–326
14. Oksanen L, Kainulainen K, Heiman M, Mustajoki P, KauppinenMakelin R, Kontula K (1997) Novel polymorphism of the human ob gene promoter in lean and morbidly obese subjects. Int J Obes Relat Metab Disord 21(6):489–494
15. Clement K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D et al (1998) A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 392(6674):398–401
16. Jackson RS, Creemers JWM, Ohagi S, RaffinSanson ML, Sanders L, Montague CT et al (1997) Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene. Nat Genet 16(3):303–306
17. Saunders CL, Chiodini BD, Sham P, Lewis CM, Abkevich V, Adeyemo AA et al (2007) Meta-analysis of genome-wide linkage studies in BMI and obesity. Obesity (Silver Spring) 15(9):2263–2275
18. Botstein D, Risch N (2003) Discovering genotypes underlying human phenotypes: past successes for mendelian disease, future approaches for complex disease. Nat Genet 33(Suppl):228–237
19. Tabor HK, Risch NJ, Myers RM (2002) Candidate-gene approaches for studying complex genetic traits: practical considerations. Nat Rev Genet 3(5):391–397
20. Farooqi IS, Yeo GS, Keogh JM, Aminian S, Jebb SA, Butler G et al (2000) Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. J Clin Invest 106(2):271–279
21. Hinney A, Volckmar AL, Knoll N (2013) Melanocortin-4 receptor in energy homeostasis and obesity pathogenesis. Prog Mol Biol Transl Sci 114:147–191
22. Farooqi S, O'Rahilly S (2006) Genetics of obesity in humans. Endocr Rev 27(7):710–718
23. Hirschhorn JN, Daly MJ (2005) Genome-wide association studies for common diseases and complex traits. Nat Rev Genet 6(2):95–108

24. McCarthy MI, Abecasis GR, Cardon LR, Goldstein DB, Little J, Ioannidis JP et al (2008) Genome-wide association studies for complex traits: consensus, uncertainty and challenges. Nat Rev Genet 9(5):356–369
25. Herbert A, Gerry NP, McQueen MB (2006) A common genetic variant is associated with adult and childhood obesity. Science 312:279–283
26. The International HapMap Consortium (2005) A haplotype map of the human genome. Nature 437(7063):1299–1320
27. Frayling TM, Timpson NJ, Weedon MN (2007) A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 316:889–894
28. Speliotes EK, Willer CJ, Berndt SI (2010) Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet 42:937–948
29. Loos RJ, Lindgren CM, Li S (2008) Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet 40:768–775
30. Willer CJ, Speliotes EK, Loos RJ (2009) Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet 41:25–34
31. Thorleifsson G, Walters GB, Gudbjartsson DF (2009) Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nat Genet 41:18–24
32. Okada Y, Kubo M, Ohmiya H, Takahashi A, Kumasaka N, Hosono N et al (2012) Common variants at CDKAL1 and KLF9 are associated with body mass index in East Asian populations. Nat Genet 44(3):302–306
33. Wen W, Cho YS, Zheng W, Dorajoo R, Kato N, Qi L et al (2012) Meta-analysis identifies common variants associated with body mass index in East Asians. Nat Genet 44(3):307–311
34. Cotsapas C, Speliotes EK, Hatoum IJ (2009) Common body mass index-associated variants confer risk of extreme obesity. Hum Mol Genet 18:3502–3507
35. Park H, Poo MM (2013) Neurotrophin regulation of neural circuit development and function. Nat Rev Neurosci 14(1):7–23
36. Beckers S, Zegers D, Van Gaal LF, Van Hul W (2009) The role of the leptin-melanocortin signalling pathway in the control of food intake. Crit Rev Eukaryot Gene Expr 19(4):267–287
37. Kim YJ, Sano T, Nabetani T, Asano Y, Hirabayashi Y (2012) GPRC5B activates obesity-associated inflammatory signaling in adipocytes. Sci Signal 5(251):ra85
38. Wheeler E, Huang N, Bochukova EG, Keogh JM, Lindsay S, Garg S et al (2013) Genome-wide SNP and CNV analysis identifies common and low-frequency variants associated with severe early-onset obesity. Nat Genet 45:513–517
39. Bochukova EG, Huang N, Keogh J, Henning E, Purmann C, Blaszczyk K et al (2010) Large, rare chromosomal deletions associated with severe early-onset obesity. Nature 463(7281): 666–670
40. Walters RG, Jacquemont S, Valsesia A, de Smith AJ, Martinet D, Andersson J et al (2010) A new highly penetrant form of obesity due to deletions on chromosome 16p11.2. Nature 463(7281):671–675
41. Jacquemont S, Reymond A, Zufferey F, Harewood L, Walters RG, Kutalik Z et al (2011) Mirror extreme BMI phenotypes associated with gene dosage at the chromosome 16p11.2 locus. Nature 478(7367):97–102
42. Hassanein MT, Lyon HN, Nguyen TT, Akylbekova EL, Waters K, Lettre G et al (2010) Fine mapping of the association with obesity at the FTO locus in African-derived populations. Hum Mol Genet 19(14):2907–2916
43. Peters U, North KE, Sethupathy P, Buyske S, Haessler J, Jiao S et al (2013) A systematic mapping approach of 16q12.2/FTO and BMI in more than 20,000 African Americans narrows in on the underlying functional variation: results from the Population Architecture using Genomics and Epidemiology (PAGE) study. PLoS Genet 9(1):e1003171
44. Jackson RS, Creemers JW, Ohagi S, Raffin-Sanson ML, Sanders L, Montague CT et al (1997) Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene. Nat Genet 16(3):303–306

45. Benzinou M, Creemers JW, Choquet H, Lobbens S, Dina C, Durand E et al (2008) Common nonsynonymous variants in PCSK1 confer risk of obesity. Nat Genet 40(8):943–945
46. Arragain S, Handelman SK, Forouhar F, Wei FY, Tomizawa K, Hunt JF et al (2010) Identification of eukaryotic and prokaryotic methylthiotransferase for biosynthesis of 2-methylthio-N6-threonylcarbamoyladenosine in tRNA. J Biol Chem 285(37):28425–28433
47. Steinthorsdottir V, Thorleifsson G, Reynisdottir I, Benediktsson R, Jonsdottir T, Walters GB et al (2007) A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. Nat Genet 39(6):770–775
48. Kamatani Y, Matsuda K, Okada Y, Kubo M, Hosono N, Daigo Y et al (2010) Genome-wide association study of hematological and biochemical traits in a Japanese population. Nat Genet 42(3):210–215
49. Groenewoud MJ, Dekker JM, Fritsche A, Reiling E, Nijpels G, Heine RJ et al (2008) Variants of CDKAL1 and IGF2BP2 affect first-phase insulin secretion during hyperglycaemic clamps. Diabetologia 51(9):1659–1663
50. Kirchhoff K, Machicao F, Haupt A, Schafer SA, Tschritter O, Staiger H et al (2008) Polymorphisms in the TCF7L2, CDKAL1 and SLC30A8 genes are associated with impaired proinsulin conversion. Diabetologia 51(4):597–601
51. Berndt SI, Gustafsson S, Magi R, Ganna A, Wheeler E, Feitosa MF et al (2013) Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. Nat Genet 45:501–512
52. Meyre D, Delplanque J, Chevre JC, Lecoeur C, Lobbens S, Gallina S et al (2009) Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. Nat Genet 41(2):157–159
53. Jiao H, Arner P, Hoffstedt J, Brodin D, Dubern B, Czernichow S et al (2011) Genome wide association study identifies KCNMA1 contributing to human obesity. BMC Med Genomics 4:51
54. Bradfield JP, Taal HR, Timpson NJ, Scherag A, Lecoeur C, Warrington NM et al (2012) A genome-wide association meta-analysis identifies new childhood obesity loci. Nat Genet 44(5):526
55. Scherag A, Dina C, Hinney A, Vatin V, Scherag S, Vogel CIG et al (2010) Two new loci for body-weight regulation identified in a joint analysis of genome-wide association studies for early-onset extreme obesity in French and German study groups. PLoS Genet 6(4):e1000916
56. Lindgren CM, Heid IM, Randall JC, Lamina C, Steinthorsdottir V, Qi L et al (2009) Genome-wide association scan meta-analysis identifies three Loci influencing adiposity and fat distribution. PLoS Genet 5(6):e1000508
57. Kilpelainen TO, Zillikens MC, Stancakova A, Finucane FM, Ried JS, Langenberg C et al (2011) Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. Nat Genet 43(8):753–760
58. Rung J, Cauchi S, Albrechtsen A, Shen L, Rocheleau G, Cavalcanti-Proenca C et al (2009) Genetic variant near IRS1 is associated with type 2 diabetes, insulin resistance and hyperinsulinemia. Nat Genet 41(10):1110–1115
59. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M et al (2010) Biological, clinical and population relevance of 95 loci for blood lipids. Nature 466(7307):707–713
60. Fox CS, Liu Y, White CC, Feitosa M, Smith AV, Heard-Costa N et al (2012) Genome-wide association for abdominal subcutaneous and visceral adipose reveals a novel locus for visceral fat in women. PLoS Genet 8(5):e1002695
61. Shu XO, Long J, Cai Q, Qi L, Xiang YB, Cho YS et al (2010) Identification of new genetic risk variants for type 2 diabetes. PLoS Genet 6(9):e1001127
62. Imamura M, Iwata M, Maegawa H, Watada H, Hirose H, Tanaka Y et al (2011) Genetic variants at CDC123/CAMK1D and SPRY2 are associated with susceptibility to type 2 diabetes in the Japanese population. Diabetologia 54(12):3071–3077
63. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ et al (2009) Finding the missing heritability of complex diseases. Nature 461(7265):747–753

64. Gibson G (2011) Rare and common variants: twenty arguments. Nat Rev Genet 13(2):135–145
65. Yang J, Manolio TA, Pasquale LR, Boerwinkle E, Caporaso N, Cunningham JM et al (2011) Genome partitioning of genetic variation for complex traits using common SNPs. Nat Genet 43(6):519–525
66. Yang J, Benyamin B, McEvoy BP, Gordon S, Henders AK, Nyholt DR et al (2010) Common SNPs explain a large proportion of the heritability for human height. Nat Genet 42(7):565–569
67. Zuk O, Hechter E, Sunyaev SR, Lander ES (2012) The mystery of missing heritability: genetic interactions create phantom heritability. Proc Natl Acad Sci U S A 109(4):1193–1198
68. Visscher PM, Hill WG, Wray NR (2008) Heritability in the genomics era–concepts and misconceptions. Nat Rev Genet 9(4):255–266
69. Bell CG, Finer S, Lindgren CM, Wilson GA, Rakyan VK, Teschendorff AE et al (2010) Integrated genetic and epigenetic analysis identifies haplotype-specific methylation in the FTO type 2 diabetes and obesity susceptibility locus. PLoS One 5(11):e14040
70. Boissel S, Reish O, Proulx K, Kawagoe-Takaki H, Sedgwick B, Yeo GS et al (2009) Loss-of-function mutation in the dioxygenase-encoding FTO gene causes severe growth retardation and multiple malformations. Am J Hum Genet 85(1):106–111
71. Meyre D, Proulx K, Kawagoe-Takaki H, Vatin V, Gutierrez-Aguilar R, Lyon D et al (2010) Prevalence of loss-of-function FTO mutations in lean and obese individuals. Diabetes 59(1):311–318
72. Stratigopoulos G, Padilla SL, LeDuc CA, Watson E, Hattersley AT, McCarthy MI et al (2008) Regulation of Fto/Ftm gene expression in mice and humans. Am J Physiol Regul Integr Comp Physiol 294(4):R1185–R1196
73. Ansley SJ, Badano JL, Blacque OE, Hill J, Hoskins BE, Leitch CC et al (2003) Basal body dysfunction is a likely cause of pleiotropic Bardet-Biedl syndrome. Nature 425(6958): 628–633
74. Church C, Lee S, Bagg EA, McTaggart JS, Deacon R, Gerken T et al (2009) A mouse model for the metabolic effects of the human fat mass and obesity associated FTO gene. PLoS Genet 5(8):e1000599
75. Church C, Moir L, McMurray F, Girard C, Banks GT, Teboul L et al (2010) Overexpression of Fto leads to increased food intake and results in obesity. Nat Genet 42(12):1086–1092
76. Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS et al (2007) The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science 318(5855):1469–1472
77. Gulati P, Cheung MK, Antrobus R, Church CD, Harding HP, Tung YC et al (2013) Role for the obesity-related FTO gene in the cellular sensing of amino acids. Proc Natl Acad Sci U S A 110:2557–2562
78. Hinney A, Schmidt A, Nottebom K, Heibult O, Becker I, Ziegler A et al (1999) Several mutations in the melanocortin-4 receptor gene including a nonsense and a frameshift mutation associated with dominantly inherited obesity in humans. J Clin Endocrinol Metab 84(4):1483–1486
79. Krude H, Gruters A (2000) Implications of proopiomelanocortin (POMC) mutations in humans: the POMC deficiency syndrome. Trends Endocrinol Metab 11(1):15–22
80. Farooqi IS, O'Rahilly S (2008) Mutations in ligands and receptors of the leptin-melanocortin pathway that lead to obesity. Nat Clin Pract Endocrinol Metab 4(10):569–577
81. Vanevski F, Xu B (2013) Molecular and neural bases underlying roles of BDNF in the control of body weight. Front Neurosci 7:37
82. Dunham I, Kundaje A, Aldred SF, Collins PJ, Davis CA, Doyle F et al (2012) An integrated encyclopedia of DNA elements in the human genome. Nature 489(7414):57–74
83. Stranger BE, Forrest MS, Clark AG, Minichiello MJ, Deutsch S, Lyle R et al (2005) Genome-wide associations of gene expression variation in humans. PLoS Genet 1(6):e78
84. Dimas AS, Deutsch S, Stranger BE, Montgomery SB, Borel C, Attar-Cohen H et al (2009) Common regulatory variation impacts gene expression in a cell type-dependent manner. Science 325(5945):1246–1250

85. Borel C, Deutsch S, Letourneau A, Migliavacca E, Montgomery SB, Dimas AS et al (2011) Identification of cis- and trans-regulatory variation modulating microRNA expression levels in human fibroblasts. Genome Res 21(1):68–73
86. Rantalainen M, Herrera BM, Nicholson G, Bowden R, Wills QF, Min JL et al (2011) MicroRNA expression in abdominal and gluteal adipose tissue is associated with mRNA expression levels and partly genetically driven. PLoS One 6(11):e27338
87. Grundberg E, Small KS, Hedman AK, Nica AC, Buil A, Keildson S et al (2012) Mapping cis- and trans-regulatory effects across multiple tissues in twins. Nat Genet 44(10): 1084–1089
88. Parts L, Hedman AK, Keildson S, Knights AJ, Abreu-Goodger C, van de Bunt M et al (2012) Extent, causes, and consequences of small RNA expression variation in human adipose tissue. PLoS Genet 8(5):e1002704
89. Ren D, Zhou Y, Morris D, Li M, Li Z, Rui L (2007) Neuronal SH2B1 is essential for controlling energy and glucose homeostasis. J Clin Invest 117(2):397–406
90. Saxena R, Hivert MF, Langenberg C, Tanaka T, Pankow JS, Vollenweider P et al (2010) Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. Nat Genet 42(2):142–148
91. Wang K, Li M, Hakonarson H (2010) Analysing biological pathways in genome-wide association studies. Nat Rev Genet 11(12):843–854
92. Snijder MB, Dekker JM, Visser M, Bouter LM, Stehouwer CD, Kostense PJ et al (2003) Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study. Am J Clin Nutr 77(5):1192–1197
93. Shao J, Yu L, Shen X, Li D, Wang K (2010) Waist-to-height ratio, an optimal predictor for obesity and metabolic syndrome in Chinese adults. J Nutr Health Aging 14(9):782–785
94. Garg A (2004) Acquired and inherited lipodystrophies. N Engl J Med 350(12):1220–1234
95. Chambers JC, Elliott P, Zabaneh D, Zhang W, Li Y, Froguel P et al (2008) Common genetic variation near MC4R is associated with waist circumference and insulin resistance. Nat Genet 40(6):716–718
96. Heard-Costa NL, Zillikens MC, Monda KL, Johansson A, Harris TB, Fu M et al (2009) NRXN3 is a novel locus for waist circumference: a genome-wide association study from the CHARGE Consortium. PLoS Genet 5(6):e1000539
97. Bille DS, Banasik K, Justesen JM, Sandholt CH, Sandbaek A, Lauritzen T et al (2011) Implications of central obesity-related variants in LYPLAL1, NRXN3, MSRA, and TFAP2B on quantitative metabolic traits in adult Danes. PLoS One 6(6):e20640
98. Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, Steinthorsdottir V et al (2010) Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet 42(11):949–960
99. Vattikuti S, Guo J, Chow CC (2012) Heritability and genetic correlations explained by common SNPs for metabolic syndrome traits. PLoS Genet 8(3):e1002637
100. Holt LJ, Siddle K (2005) Grb10 and Grb14: enigmatic regulators of insulin action–and more? Biochem J 388(Pt 2):393–406
101. Nouaille S, Blanquart C, Zilberfarb V, Boute N, Perdereau D, Roix J et al (2006) Interaction with Grb14 results in site-specific regulation of tyrosine phosphorylation of the insulin receptor. EMBO Rep 7(5):512–518
102. Ridker PM, Pare G, Parker AN, Zee RY, Miletich JP, Chasman DI (2009) Polymorphism in the CETP gene region, HDL cholesterol, and risk of future myocardial infarction: genome-wide analysis among 18 245 initially healthy women from the Women's Genome Health Study. Circ Cardiovasc Genet 2(1):26–33
103. Manning AK, Hivert MF, Scott RA, Grimsby JL, Bouatia-Naji N, Chen H et al (2012) A genome-wide approach accounting for body mass index identifies genetic variants influencing fasting glycemic traits and insulin resistance. Nat Genet 44(6):659–669
104. Gesta S, Bezy O, Mori MA, Macotela Y, Lee KY, Kahn CR (2011) Mesodermal developmental gene Tbx15 impairs adipocyte differentiation and mitochondrial respiration. Proc Natl Acad Sci U S A 108(7):2771–2776

105. Gesta S, Bluher M, Yamamoto Y, Norris AW, Berndt J, Kralisch S et al (2006) Evidence for a role of developmental genes in the origin of obesity and body fat distribution. Proc Natl Acad Sci U S A 103(17):6676–6681
106. Dastani Z, Hivert MF, Timpson N, Perry JR, Yuan X, Scott RA et al (2012) Novel loci for adiponectin levels and their influence on type 2 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals. PLoS Genet 8(3):e1002607
107. Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F et al (2010) Hundreds of variants clustered in genomic loci and biological pathways affect human height. Nature 467(7317):832–838
108. Steinberg GR, Kemp BE, Watt MJ (2007) Adipocyte triglyceride lipase expression in human obesity. Am J Physiol Endocrinol Metab 293(4):E958–E964
109. Zaitlen N, Pasaniuc B, Gur T, Ziv E, Halperin E (2010) Leveraging genetic variability across populations for the identification of causal variants. Am J Hum Genet 86(1):23–33
110. Morris AP (2011) Transethnic meta-analysis of genomewide association studies. Genet Epidemiol 35(8):809–822
111. Franceschini N, van Rooij FJ, Prins BP, Feitosa MF, Karakas M, Eckfeldt JH et al (2012) Discovery and fine mapping of serum protein loci through transethnic meta-analysis. Am J Hum Genet 91(4):744–753
112. Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE et al (2012) An integrated map of genetic variation from 1,092 human genomes. Nature 491(7422):56–65
113. Pritchard JK (2001) Are rare variants responsible for susceptibility to complex diseases? Am J Hum Genet 69(1):124–137
114. Pritchard JK, Cox NJ (2002) The allelic architecture of human disease genes: common disease-common variant…or not? Hum Mol Genet 11(20):2417–2423
115. Cirulli ET, Goldstein DB (2010) Uncovering the roles of rare variants in common disease through whole-genome sequencing. Nat Rev Genet 11(6):415–425
116. Franco M, Bilal U, Ordunez P, Benet M, Morejon A, Caballero B et al (2013) Population-wide weight loss and regain in relation to diabetes burden and cardiovascular mortality in Cuba 1980-2010: repeated cross sectional surveys and ecological comparison of secular trends. BMJ 346:f1515
117. Kilpelainen TO, Qi L, Brage S, Sharp SJ, Sonestedt E, Demerath E et al (2011) Physical activity attenuates the influence of FTO variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. PLoS Med 8(11):e1001116
118. Loos RJ (2012) Genetic determinants of common obesity and their value in prediction. Best Pract Res Clin Endocrinol Metab 26(2):211–226
119. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH (1997) Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med 337(13):869–873
120. Paternoster L, Evans DM, Nohr EA, Holst C, Gaborieau V, Brennan P et al (2011) Genome-wide population-based association study of extremely overweight young adults–the GOYA study. PLoS One 6(9):e24303