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Genetic studies of body mass index yield new insights for obesity biology

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Abstract

Obesity is heritable and predisposes to many diseases. To understand the genetic basis of obesity better, here we conduct a genome-wide association study and Metabochip meta-analysis of body mass index (BMI), a measure commonly used to define obesity and assess adiposity, in up to 339,224 individuals. This analysis identifies 97 BMI-associated loci ($P < 5 \times 10^{-8}$), 56 of which are novel. Five loci demonstrate clear evidence of several independent association signals, and many loci have significant effects on other metabolic phenotypes. The 97 loci account for ~2.7% of BMI variation, and genome-wide estimates suggest that common variation accounts for >20% of BMI variation. Pathway analyses provide strong support for a role of the central nervous system in obesity susceptibility and implicate new genes and pathways, including those related to synaptic function, glutamate signalling, insulin secretion/action, energy metabolism, lipid biology and adipogenesis.

Obesity is a worldwide epidemic associated with increased morbidity and mortality that imposes an enormous burden on individual and public health. Around 40–70% of inter-individual variability in BMI, commonly used to assess obesity, has been attributed to genetic factors[1–3]. At least 77 loci have previously been associated with an obesity measure[4], 32 loci from our previous meta-analysis of BMI genome-wide association studies (GWAS)[5]. Nevertheless, most of the genetic variability in BMI remains unexplained. Moreover, although analyses of previous genetic association results have suggested intriguing biological processes underlying obesity susceptibility, few specific genes supported these pathways[5,6]. For the vast majority of loci, the probable causal gene(s) and pathways remain unknown.

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To expand the catalogue of BMI susceptibility loci and gain a better understanding of the genes and biological pathways influencing obesity, we performed the largest GWAS meta-analysis for BMI so far. This work doubles the number of individuals contributing GWAS results, incorporates results from >100,000 individuals genotyped with Metabochip[7], and nearly doubles the number of BMI-associated loci. Comprehensive assessment of meta-analysis results provides several lines of evidence supporting candidate genes at many loci and highlights pathways that reinforce and expand our understanding of biological processes underlying obesity.

Identification of 97 genome-wide significant loci

This BMI meta-analysis included association results for up to 339,224 individuals from 125 studies, 82 with GWAS results (n = 236,231) and 43 with results from Metabochip (n = 103,047; Extended Data Table 1 and Supplementary Tables 1–3). After regression on age and sex and inverse normal transformation of the residuals, we carried out association analyses with genotypes or imputed genotype dosages. GWAS were meta-analysed together, as were Metabochip studies, followed by a combined GWAS plus Metabochip meta-analysis. In total, we analysed data from 322,154 individuals of European descent and 17,072 individuals of non-European descent (Extended Data Fig. 1).

Our primary meta-analysis of European-descent individuals from GWAS and Metabochip studies (n = 322,154) identified 77 loci reaching genome-wide significance (GWS) and separated by at least 500 kilo-bases (kb) (Table 1, Extended Data Table 2 and Supplementary Figs 1 and 2). We carried out additional analyses to explore the effects of power and heterogeneity. The inclusion of 17,072 non-European-descent individuals (total n = 339,224) identified ten more loci, while secondary analyses identified another ten GWS loci (Table 2, Supplementary Tables 4–8 and Supplementary Figs 3–9). Of the 97 BMI-associated loci, 41 have previously been associated with one or more obesity measure[5,8–12]. Thus, our current analyses identified 56 novel loci associated with BMI (Tables 1 and 2 and Extended Data Table 2).

Effects of associated loci on BMI

Newly identified loci generally have lower minor allele frequency and/or smaller effect size estimates than previously known loci (Extended Data Fig. 2a, b). On the basis of effect estimates in the discovery data set, which may be inflated owing to winner's curse, the 97 loci account for 2.7% of BMI phenotypic variance (Supplementary Table 4 and Extended Data Fig. 2a, b). We conservatively used only GWS single nucleotide polymorphisms (SNPs) after strict double genomic control correction, which probably over-corrects association statistics given the lack of evidence for population stratification in family-based analyses[13] (Extended Data Fig. 3 and Extended Data Table 1). Polygene analyses suggest that SNPs with P values well below GWS add significantly to the phenotypic variance explained. For example, 2,346 SNPs selected from conditional and joint multiple-SNP analysis with $P < 5 \times 10^{-3}$ explained 6.6 ± 1.1% (mean ± s.e.m.) of variance, compared to 21.6 ± 2.2% explained by all HapMap3 SNPs (31–54% of heritability; Fig. 1a). Furthermore, of 1,909 independent SNPs (pairwise distance >500 kb and $r^2 < 0.1$) included

on Metabochip for replication of suggestive BMI associations, 1,458 (76.4%) have directionally consistent effects with our previous GWAS meta-analysis[5] and the non-overlapping samples in the current meta-analysis (Extended Data Fig. 2c). On the basis of the significant excess of these directionally consistent observations (sign test $P = 2.5 \times 10^{-123}$), we estimate ~1,007 of the 1,909 SNPs represent true BMI associations.

We compared the effects of our 97 BMI-associated SNPs between the sexes, between ethnicities, and across several cross-sections of our data (Supplementary Tables 4–11 and Extended Data Fig. 4). Two previously identified loci, near *SEC16B* ($P = 5.2 \times 10^{-5}$) and *ZFP64* ($P = 9.1 \times 10^{-5}$), showed evidence of heterogeneity between men and women. Both have stronger effects in women (Supplementary Table 10). Two SNPs, near *NEGR1* ($P = 9.1 \times 10^{-5}$) and *PRKD1* ($P = 1.9 \times 10^{-5}$), exhibited significant evidence for heterogeneity of effect between European- and African-descent samples, and one SNP, near *GBE1* ($P = 1.3 \times 10^{-4}$), exhibited evidence for heterogeneity between European and east Asian individuals (Supplementary Table 9). These findings may reflect true heterogeneity at these loci, but are most likely due to linkage disequilibrium (LD) differences across ancestries. Effect estimates for 79% of BMI-associated SNPs in African-descent samples ($P = 9.2 \times 10^{-9}$) and 91% in east Asian samples ($P = 1.8 \times 10^{-15}$) showed directional consistency with our European-only analyses. These results suggest that common BMI-associated SNPs have comparable effects across ancestries and between sexes. In additional heterogeneity analyses, we detected an influence of ascertainment at *TCF7L2* (stronger effects in type 2 diabetes case/control studies than in population-based studies); however, we saw no evidence of systematic ascertainment bias at other loci owing to inclusion of case/control studies (Supplementary Tables 10 and 11).

We also took advantage of LD differences across populations to fine-map association signals using Bayesian methods[14,15]. At 10 of 27 loci fine-mapped for BMI on Metabochip, the addition of non-European individuals into the meta-analysis either narrowed the genomic region containing the 99% credible set, or decreased the number of SNPs in the credible set (Supplementary Table 12 and Supplementary Fig. 10). At the *SEC16B* and *FTO* loci, the all ancestries credible set includes a single SNP, although the SNP we highlight at *FTO* (rs1558902) differs from that identified by a recent fine-mapping effort in African-American cohorts[16]. Fine-mapping efforts using larger, more diverse study samples and more complete catalogues of variants will help to further narrow association signals.

We examined the combined effects of lead SNPs at the 97 loci in an independent sample of 8,164 European-descent individuals from the Health and Retirement Study[17]. We observed an average increase of 0.1 BMI units (kg per m^2) per BMI-increasing allele, equivalent to 260–320 g for an individual 160–180 cm in height. There was a 1.8 kg per m^2 difference in mean BMI between the 145 individuals (1.78%) carrying the most BMI-increasing alleles (>104) and those carrying the mean number of BMI-increasing alleles in the sample (91; Extended Data Fig. 2d), corresponding to a difference of 4.6–5.8 kg for an individual 160–180 cm in height, and a 1.5 kg m^{-2} difference (3.8–4.9 kg difference) in mean BMI between the 95 individuals (1.16%) carrying the least BMI-increasing alleles (<78) and those carrying the mean number. Such differences are medically significant in predisposing to development of metabolic disease[18]. For predicting obesity (BMI ≥ 30 kg per m^2), adding

genetic risk score to a model including age, age squared, sex and four genotype-based principal components slightly, but significantly increases the area under the receiver-operating characteristic curve from 0.576 to 0.601.

Additional associated variants at BMI loci

To identify additional SNPs with independent BMI associations at the 97 established loci, we used genome-wide complex trait analysis (GCTA)[19] to perform approximate joint and conditional association analysis[20] using summary statistics from European sex-combined meta-analysis after removing family-based validation studies (TwinGene and QIMR). GCTA confirmed two signals at *MC4R* previously identified using exact conditional analyses[5], and identified five loci with evidence of independent associations (Table 3): second signals near *LINC01122, NLRC3-ADCY9, GPRC5B-GP2* and *BDNF*, and a third signal near *MC4R* (rs9944545, Fig. 1b). Joint conditional analyses at two genomic regions separated by >500 kb (the *AGBL4-ELAVL4* regions on chr. 1, and the *ATP2A1-SBK1* regions on chr. 16), indicate that these pairs of signals may not be independent owing to extended LD.

Effects of BMI variants on other traits

We tested for associations between our 97 BMI-associated index SNPs and other metabolic phenotypes (Supplementary Tables 13–15 and Extended Data Figs 5 and 6). Thirteen of the twenty-three phenotypes tested had significantly more SNPs with effects in the anticipated direction than expected by chance (Supplementary Table 16). These results corroborate the epidemiological relationships of BMI with metabolic traits. Whether this reflects a common genetic aetiology or a causal relationship of BMI on these traits requires further investigation.

Interestingly, some loci showed significant association with traits in the opposite direction than expected based on their phenotypic correlation with BMI (Extended Data Fig. 5). For example, at *HHIP*, the BMI-increasing allele is associated with decreased type 2 diabetes risk and higher high-density lipoprotein cholesterol (HDL). At *LOC646736* and *IRS1*, the BMI-increasing allele is associated with reduced risk of coronary artery disease (CAD) and diabetic nephropathy, decreased triglyceride levels, increased HDL, higher adiponectin, and lower fasting insulin. This may be due to increased subcutaneous fat and possible production of metabolic mediators protective against the development of metabolic disease despite increased adiposity[8]. These unexpected associations may help us to understand better the complex pathophysiology underlying these traits, and may indicate benefits or side effects if these regions contain targets of therapeutic intervention. Furthermore, of our 97 GWS loci, 35 (binomial $P = 0.0019$) were in high LD ($r^2 > 0.7$) with one or more GWS SNPs in the National Human Genome Research Institute (NHGRI) GWAS catalogue ($P < 5 \times 10^{-8}$), even after removing anthropometric trait-associated SNPs. These SNPs were associated not only with cardiometabolic traits, but also with schizophrenia, smoking behaviour, irritable bowel syndrome, and Alzheimer's disease (Supplementary Table 17a, b).

BMI tissues, biological pathways and gene sets

We anticipated the expanded sample size would not only identify additional BMI-associated variants, but also more clearly highlight the biology implicated by genetic studies of BMI. By applying multiple complementary methods, we identified biologically relevant tissues, pathways and gene sets, and highlighted potentially causal genes at associated loci. These approaches included systematic methods incorporating diverse data types, including the novel approach, Data-driven Expression Prioritized Integration for Complex Traits (DEPICT)[21], and extensive manual review of the literature.

DEPICT used 37,427 human gene expression microarray samples to identify tissues and cell types in which genes near BMI-associated SNPs are highly expressed, and then tested for enrichment of specific tissues by comparing results with randomly selected loci matched for gene density. In total, 27 out of 31 significantly enriched tissues were in the central nervous system (CNS) (out of 209 tested; Fig. 2a and Supplementary Table 18). Current results are not sufficient to isolate specific brain regions important in regulating BMI. However, we observe enrichment not only in the hypothalamus and pituitary gland—key sites of central appetite regulation—but even more strongly in the hippocampus and limbic system, tissues that have a role in learning, cognition, emotion and memory.

As a complementary approach, we examined overlap of associated variants at the 97 loci ($r^2 > 0.7$ with the lead SNP) with five regulatory marks found in most of the 14 selected cell types from brain, blood, liver, pancreatic islet and adipose tissue from the ENCODE Consortium[22] and Roadmap Epigenomics Project[23] (Supplementary Table 19a–c). We found evidence of enrichment ($P < 1.2 \times 10^{-3}$) in 24 out of 41 data sets examined. The strongest enrichment was observed with promoter (histone 3 Lys 4 trimethylation (H3K4me3), histone 3 Lys 9 acetylation (H3K9ac)) and enhancer (H3K4me1, HeK27ac) marks detected in mid-frontal lobe, anterior caudate, astrocytes and substantia nigra, supporting neuronal tissues in BMI regulation.

To identify pathways or gene sets implicated by the BMI-associated loci, we first used Meta-Analysis Gene-set Enrichment of varia NT Associations (MAGENTA)[24], which takes as input pre-annotated gene sets, and then tests for overrepresentation of gene set genes at BMI-associated loci. We found enrichment (false discovery rate (FDR) < 0.05) of seven gene sets, including neurotrophin signalling. Other highlighted gene sets related to general growth and patterning: basal cell carcinoma, acute myeloid leukaemia, and hedgehog signalling (Supplementary Table 20a, b).

Second, we used DEPICT, that uses predefined gene sets reconstituted using coexpression data, to perform gene set enrichment analysis. After merging highly correlated gene sets, nearly 500 gene sets were significantly enriched (FDR < 0.05) for genes in BMI-associated loci (Fig. 2b and Supplementary Table 21a, b). The most strongly enriched gene sets highlight potentially novel pathways in the CNS. These include gene sets related to synaptic function, long-term potentiation and neurotransmitter signalling (glutamate signalling in particular, but also noradrenaline, dopamine and serotonin release cycles, and GABA (γ-aminobutyric acid) receptor activity; Fig. 2c). Potentially relevant mouse behavioural

phenotypes, such as physical activity and impaired coordination were also highly enriched (Fig. 2b and Supplementary Table 21a). Several gene sets previously linked to obesity, such as integration of energy metabolism, polyphagia, secretion and action of insulin and related hormones (for example, 'regulation of insulin secretion by glucagon-like peptide 1′ and 'glucagon signalling in metabolic regulation'), mTOR signalling (which affects cell growth in response to nutrient intake via insulin and growth factors[25]), and gene sets overlapping the neurotrophin signalling pathway identified by MAGENTA were also enriched, although not as significantly as other CNS processes (Fig. 2d). DEPICT also identified significant enrichment for additional cellular components and processes: calcium channels, MAP kinase activity, chromatin organization and modification, and ubiquitin ligases.

Third, we manually reviewed literature related to all 405 genes within 500 kb and $r^2 > 0.2$ of the 97 index SNPs. We classified these genes into one or more biological categories, and observed 25 categories containing three or more genes (Supplementary Table 22). The largest category comprised genes involved in neuronal processes, including monogenic obesity genes involved in hypothalamic function and energy homeostasis, and genes involved in neuronal transmission and development. Other processes highlighted by the manual literature review included glucose and lipid homeostasis and limb development, which were less notable in the above methods, but may still be related to the underlying biology of BMI.

To identify specific genes that may account for BMI association, we considered each of the following to represent supportive evidence for a gene within a locus: (1) the gene nearest the index SNP[26]; (2) genes containing missense, nonsense or copy number variants, or a *cis*-expression quantitative trait locus (eQTL) in LD with the index SNP; (3) genes prioritized by integrative methods implemented in DEPICT; (4) genes prioritized by connections in published abstracts by GRAIL (Gene Relationships Across Implicated Loci)[27]; or (5) genes biologically related to obesity, related metabolic disease, or energy expenditure based on manual literature review (Tables 1 and 2, Extended Data Tables 2–4 and Supplementary Tables 23–25). We first focused on the 64 genes in associated loci with more than one consistent line of supporting evidence. As expected, many of these genes overlap with CNS processes, including synaptic function, cell–cell adhesion, and glutamate signalling (*ELAVL4*, *GRID1*, *CADM2*, *NRXN3*, *NEGR1* and *SCG3*), cause monogenic obesity syndromes (*MC4R*, *BDNF*, *BBS4* and *POMC*), or function in extreme/early onset obesity in humans and mouse models (*SH2B1* and *NEGR1*)[6,28,29]. Other genes with several lines of supporting evidence are related to insulin secretion and action, energy metabolism, lipid biology, and/or adipogenesis (TCF7L2, GIPR, IRS1, FOXO3, ASB4, RPTOR, NPC1, CREB1, FAM57B, APOBR and *HSD17B12*), encode RNA binding/processing proteins (*PTBP2*, *ELAVL4*, *CELF1* and possibly *RALYL*), are in the MAP kinase signalling pathway (*MAP2K5* and *MAPK3*), or regulate cell proliferation or cell survival (*FAIM2*, *PARK2* and *OLFM4*). Although we cannot be certain that any individual gene is related to the association at a given locus, the strong enrichment of pathways among genes within associated loci argues for a causal role for these pathways, prioritizes specific genes for follow-up experiments, and provides the strongest genetic evidence so far for a role of particular biological and CNS processes in the regulation of human body mass.

Discussion

Our meta-analysis of nearly 340,000 individuals identified 97 GWS loci associated with BMI, 56 of which are novel. These loci account for 2.7% of the variation in BMI, and suggest that as much as 21% of BMI variation can be accounted for by common genetic variation. Our analyses provide robust evidence to implicate particular genes and pathways affecting BMI, including synaptic plasticity and glutamate receptor activity—pathways that respond to changes in feeding and fasting, are regulated by key obesity-related molecules such as BDNF and MC4R, and impinge on key hypothalamic circuits[30–32]. These pathways also overlap with one of the several proposed mechanisms of action of topiramate, a component of one of two weight-loss drugs approved by the US Food and Drug Administration[33,34]. This observation suggests that the relevant site of action for this drug may be glutamate receptor activity, supporting the idea that these genes and pathways could reveal more targets for weight-loss therapies. BMI-associated loci also overlap with genes and pathways implicated in neurodevelopment (Supplementary Tables 21 and 22). Finally, consistent with previous work and findings from monogenic obesity syndromes, we confirm a role for the CNS—particularly genes expressed in the hypothalamus—in the regulation of body mass.

Examining the genes at BMI-associated loci in the context of gene expression, molecular pathways, eQTL results, mutational evidence and genomic location provides several complementary avenues through which to prioritize genes for relevance in BMI biology. Genes such as *NPC1* and *ELAVL4* are implicated by many lines of evidence (literature, mutational, eQTL and DEPICT) and become strong candidate genes in their respective locations. It is important to recognize that pathway methods and literature reviews are limited by current data sets and knowledge, and thus provide only a working model of obesity biology. For example, little is known about host genetic factors that regulate the microbiome. Variation in immune-related genes such as *TLR4* could presumably exert an influence on obesity through the microbiome[35]. Together, our results underscore the heterogeneous aetiology of obesity and its links with several related metabolic diseases and processes.

BMI variants are generally associated with related cardiometabolic traits in accord with established epidemiological relationships. This could be due to shared genetic effects or to other causes of cross-phenotypic correlations. However, some BMI-associated variants have effects on related traits counter to epidemiological expectations. Once better understood, these mechanisms may not only help to explain why not all obese individuals develop related metabolic diseases, but also suggest possible mechanisms to prevent development of metabolic disease in those who are already obese.

Larger studies of common genetic variation, studies of rare variation (including those based on imputation, exome chips and sequencing), and improved computational tools will continue to identify genetic variants associated with BMI and help to further refine the biology of obesity. The 97 loci identified here represent an important step in understanding the physiological mechanisms leading to obesity. These findings strengthen the connection between obesity and other metabolic diseases, enhance our appreciation of the tissues,

physiological processes, and molecular pathways that contribute to obesity, and will guide future research aimed at unravelling the complex biology of obesity.

METHODS

Study design

We conducted a two-stage meta-analysis to identify BMI-associated loci in European adults (Extended Data Fig. 1 and Extended Data Table 1). In stage 1 we performed meta-analysis of 80 GWAS (n = 234,069); and stage 2 incorporated data from 34 additional studies (n = 88,137) genotyped using Metabochip[7] (Supplementary Tables 1–3). Secondary meta-analyses were also conducted for: (1) all ancestries, (2) European men, (3) European women, and (4) European population-based studies. The total number of subjects and SNPs included in each stage for all analyses is shown in Extended Data Table 1. No statistical methods were used to predetermine sample size.

Phenotype

BMI, measured or self-reported weight in kg per height in metres squared (Supplementary Tables 1 and 3) was adjusted for age, age squared, and any necessary study-specific covariates (for example, genotype-derived principal components) in a linear regression model. The resulting residuals were transformed to approximate normality using inverse normal scores. For studies with no known related individuals, residuals were calculated separately by sex and case/control status. For family-based studies, residuals were calculated with men and women together, adding sex as an additional covariate in the linear regression model. Relatedness was accounted for in a study-specific manner (Supplementary Table 2).

Sample quality control, imputation and association

Following study-specific quality control measures (Supplementary Table 2), all contributing GWAS common SNPs were imputed using the HapMap phase II CEU reference panel for European-descent studies[37], and CEU+YRI+CHB+JPT HapMap release 22 for the African-American and Hispanic GWAS. Directly genotyped (GWAS and Metabochip) and imputed variants (GWAS only) were then tested for association with the inverse normally transformed BMI residuals using linear regression assuming an additive genetic model. Quality control following study level analyses was conducted following procedures outlined elsewhere[38].

Meta-analysis

Fixed effects meta-analyses were conducted using the inverse variance-weighted method implemented in METAL[39]. Study-specific GWAS results as well as GWAS meta-analysis results were corrected for genomic control using all SNPs[40]. Study-specific Metabochip results as well as Metabochip meta-analysis results were genomic-control-corrected using 4,425 SNPs included on Metabochip for replication of associations with QT-interval, a phenotype not correlated with BMI, after pruning of SNPs within 500 kb of an anthropometry replication SNP. The final meta-analysis combined the genomic-control-corrected GWAS and Metabochip meta-analysis results.

Identification of novel loci

We used a distance criterion of ±500 kb surrounding each GWS peak ($P < 5 \times 10^{-8}$) to define independent loci and to place our results in the context of previous studies, including our previous GIANT meta-analyses. Of several locus models tested, this definition most closely reflected the loci defined by approximate conditional analysis using GCTA (Tables 1 and 2, respectively). Current index SNPs falling within 500 kb of a SNP previously associated with BMI, weight, extreme obesity or body fat percentage[5,8–11] were considered previously identified.

Characterization of BMI-associated SNP effects

To investigate potential sources of heterogeneity between groups we compared the effect estimates of our 97 GWS SNPs for men versus women of European ancestry and Europeans versus non-Europeans. To address the effects of studies ascertained on a specific disease or phenotype on our results we also compare the effect estimates of European ancestry studies of population-based studies with the following European-descent subsets of studies: (1) non-population-based studies (that is, those ascertained on a specific disease or phenotype); (2) type 2 diabetes cases; (3) type 2 diabetes controls; (4) combined type 2 diabetes cases and controls; (5) CAD cases; (6) CAD controls; and (7) combined CAD cases and controls (Supplementary Tables 10 and 11). We also tested for heterogeneity of effect estimates between our European sex-combined meta-analysis and results from recent GWAS meta-analyses for BMI in individuals of African or east Asian ancestry[10,41] (Supplementary Table 9). Heterogeneity was assessed as described previously[42]. A Bonferroni-corrected $P < 5 \times 10^{-4}$ (corrected for 97 tests) was used to assess significance. For heterogeneity tests assessing effects of ascertainment, we also used a 5% FDR threshold to assess significance of heterogeneity statistics (Supplementary Table 11).

Fine-mapping

We compared the meta-analysis results and credible sets of SNPs likely to contain the causal variant, based on the method described previously[14], across the European-only, non-European, and all ancestries sex-combined meta-analyses. For each index SNP falling within a Metabochip fine-mapping region (27 for BMI), all SNPs available within 500 kb on either side of the index SNP were selected. Effect size estimates and standard errors for each SNP were converted to approximate Bayes' factors according to the method described previously[15]. All approximate Bayes' factors were then summed across the 1-megabase (Mb) region and the proportion of the posterior odds of being the causal variant was calculated for each variant (approximate Bayes' factor for SNP_i/sum of approximate Bayes' factors for the region). The set of SNPs that accounts for 99% of posterior odds of association in the region denotes the set most likely to contain the causal variant for that association region (Supplementary Table 12).

Cumulative effects, risk prediction and variance explained

We assessed the cumulative effects of the 97 GWS loci on mean BMI and on their ability to predict obesity (BMI ≥ 30 kg m^{-2}) using the c statistic from logistic regression models in the Health and Retirement Study[17], a longitudinal study of 26,000 European Americans 50

years or older. The variance explained (VarExp) by each SNP was calculated using the effect allele frequency (f) and beta (β) from the meta-analyses using the formula VarExp = $\beta^2(1 - f)2f$.

For polygene analyses, the approximate conditional analysis from GCTA[19,20], was used to select SNPs using a range of P value thresholds (that is, 5×10^{-8}, 5×10^{-7}, …, 5×10^{-3}) based on summary data from the European sex-combined meta-analysis excluding TwinGene and QIMR studies. We performed a within-family prediction analysis using full-sib pairs selected from independent families (1,622 pairs from the QIMR cohort and 2,758 pairs from the TwinGene cohort) and then SNPs at each threshold were used to calculate the percentage of phenotypic variance explained and predict risk (Extended Data Figs 2 and 3). We then confirmed the results from population-based prediction and estimation analyses in an independent sample of unrelated individuals from the TwinGene (n = 5,668) and QIMR (n = 3,953) studies (Extended Data Fig. 3 and Fig. 1c). The SNP-derived predictor was calculated using the profile scoring approach implemented in PLINK and estimation analyses were performed using the all-SNP estimation approach implemented in GCTA.

Enrichment analysis of Metabochip SNPs selected for replication

The 5,055 SNPs that were included for BMI replication on Metabochip included 1,909 independent SNPs ($r^2 < 0.1$ and > 500 kb apart), of which 1,458 displayed directionally consistent effect estimates with those reported previously[5]. To estimate the number of Metabochip SNPs truly associated with BMI, we counted the number of SNPs with directional consistency (DC) between ref. 5 and a meta-analysis of non-overlapping samples for these 1,909 SNPs. We then calculated DC in the presence of a mixture of associated and non-associated SNPs assuming P(DC | associated) = 1 and P(*DC* | not associated) = 0.5. In this formulation, DC = $R/2 + S$, meaning that $S = 2DC - T$, in which T equals the total number of SNPs, R equals the number of SNPs not associated with BMI, and S equals the number of SNPs associated with BMI. With DC = 1,458 and T = 1,909, we estimate S to be $2DC - T = 2 \times 1{,}458 - 1{,}909 = 1{,}007$.

Joint and conditional multiple SNP association analysis

To identify additional signals in regions of association, we used GCTA[19], an approach that uses meta-analysis summary statistics and an LD matrix derived from a reference sample, to perform approximate joint and conditional SNP association analysis. We used 6,654 unrelated individuals of European ancestry from the ARIC cohort as the reference sample to approximate conditional P values.

Manual gene annotation and biological description

All genes within 500 kb of an index SNP were annotated for molecular function, cellular function, and for evidence of association with BMI-related traits in human or animal model experiments (Supplementary Table 22). We used several avenues for annotation, including Spotter (http://csg.sph.umich.edu/boehnke/spotter/), SNIPPER (http://csg.sph.umich.edu/boehnke/snipper/), PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), OMIM (http:/www.omim.org) and UNIPROT (http://www.uniprot.org/). When no genes mapped to this interval the nearest gene on each side of the index SNP was annotated. In examining

possible functions of genes in the region, we excluded any references to GWAS or other genetic association studies. We analysed 405 genes in the 97 GWS loci and manually curated them into 25 biological categories containing more than three genes.

Functional variants

All variants within 500 kb (HapMap release 22/1000 Genomes CEU) and in LD ($r^2 > 0.7$) with an index SNP were annotated for functional effects based on RefSeq transcripts using Annovar[43] (http://www.openbioinformatics.org/annovar/). PhastCon, Grantham, GERP, and PolyPhen[44] predictions were accessed via the Exome Variant Server[45] (http://evs.gs.washington.edu/EVS), and from SIFT[46] (http://sift.jcvi.org/) (Extended Data Table 4).

Copy number variations correlated with BMI index SNPs

To study common copy number variations, we used a list of copy number variations well-tagged by SNPs in high LD ($r^2 > 0.8$) with deletions in European populations from phase 1 release of the 1000 Genomes Project[47] (Supplementary Table 25).

eQTLs

We examined the *cis* associations between the 97 GWS SNPs and expression of nearby genes in whole blood, lymphocytes, skin, liver, omental fat, subcutaneous fat and brain tissue[48–55] (Supplementary Table 23). Conditional analyses were performed by including both the BMI-associated SNP and the most significant *cis*-associated SNP for the given transcript. Conditional analyses were conducted for all data sets, except the brain tissue data set due to limited power. To minimize the potential for false-positives, only cis associations below a study-specific FDR of 5% (or 1% for some data sets), in LD with the peak SNP ($r^2 > 0.7$) for the transcript, and with conditional $P > 0.05$ for the peak SNP, are reported (Extended Data Table 2).

MAGENTA

We used the MAGENTA method to test predefined gene sets for enrichment at BMI-associated loci[24]. We used the GWAS + Metabochip data as input and applied default settings.

GRAIL

We used GRAIL[27] to identify genes near BMI-associated loci having similarities in the published scientific text using PubMed abstracts as of December 2006. The BMI loci were queried against HapMap release 22 for the European panel, and we controlled for gene size.

DEPICT

We used DEPICT to identify the most likely causal gene at a given associated locus, reconstituted gene sets enriched for BMI associations, and tissues and cell types in which genes from associated loci are highly expressed[21]. To accomplish this, the method relies on publicly available gene sets (including molecular pathways) and uses gene expression data from 77,840 gene expression arrays[75] to predict which other genes are likely to be part of

these gene sets, thus combining known annotations with predicted annotations. For details and negative control analyses please see Supplementary Methods.

We first clumped the European-only GWAS-based meta-analysis summary statistics using 500 kb flanking regions, LD $r^2 > 0.1$ and excluded SNPs with $P \geq 5 \times 10^{-4}$; which resulted in a list of 590 independent SNPs. HapMap phase II CEU genotype data[37] was used to compute LD and genomic coordinates were defined by genome build GRCh38. Because the GWAS meta-analysis was based on both GWAS and Metabochip studies, there were discrepancies in the index SNPs that are referenced in Table 1 of the paper and the ones used in DEPICT, which was run on the GWAS data only. Therefore we forced in GWS index SNPs from the GWAS plus Metabochip GWA meta-analysis into the DEPICT GWAS-only based analysis. This enabled a more straightforward comparison of genes in DEPICT loci and genes in GWS loci highlighted by manual lookups, and did not lead to any significant bias towards SNPs on Metabochip (data not shown). We forced in 62 of the GWS loci in Table 1, so all of the 97 SNPs were among the 590 SNPs. The 590 SNPs were further merged into 511 non-overlapping regions (FDR < 0.05) used in DEPICT analysis. For additional information on the analysis please refer to Supplementary Methods.

Cross-trait analyses

To explore the relationship between BMI and an array of cardiometabolic traits and diseases, association results for the 97 BMI index SNPs were requested from 13 GWAS meta-analysis consortia: DIAGRAM (type 2 diabetes)[56], CARDIoGRAM-C4D (CAD)[57], ICBP (systolic and diastolic blood pressure (SBP, DBP))[58], GIANT (waist-to-hip ratio, hip circumference, and waist circumference, each unadjusted and adjusted for BMI)[13,59], GLGC (HDL, low density lipoprotein cholesterol, triglycerides, and total cholesterol)[60], MAGIC (fasting glucose, fasting insulin, fasting insulin adjusted for BMI, and two-hour glucose)[61–63], ADIPOGen (BMI-adjusted adiponectin)[64], CKDgen (urine albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate, and overall CKD)[65,66], ReproGen (age at menarche, age at menopause)[67,68], GENIE (diabetic nephropathy)[69,70]. Proxies ($r^2 > 0.8$ in CEU) were used when an index SNP was unavailable.

Enrichment of concordant effects

We compared the effects for the 97 BMI index SNP across these related traits using a one-sided binomial test of the number of concordant effects versus a null expectation of $P = 0.5$. Concordant and nominally significant ($P < 0.05$) SNP effects were similarly tested using a one-sided binomial test with a null expectation of $P = 0.05$. We evaluated significance in either test with a Bonferroni-corrected threshold of $P = 0.002$ (0.05/23 traits tested).

Joint effects of cross-trait associations

To determine the joint effect of all 97 BMI loci on other cardiometabolic phenotypes, we used the meta-regression technique from ref. 64 to correlate the effect estimates of the BMI-increasing alleles with effect estimates from meta-analyses for each of the metabolic traits from other consortia (DIAGRAM, MAGIC, ICBP, GLGC, ADIPOGen, ReproGen and CARDIoGRAM).

Cross-traits heatmap

To explore observed concordance in effects of BMI loci on other cardiometabolic and anthropometric traits, we converted the effect estimates and standard errors (or *P* values) from meta-analysis to *Z*-scores oriented with respect to the BMI-increasing allele, for each of the 97 BMI index SNPs in the twenty-three traits. We then classified each *Z*-score as follows to generate a vector of the *Z*-score of each trait at each locus: 0 (not significant) if $-2 \leq Z \leq 2$; 1 (significant positive) if $Z > 2$; −1 (significant negative) if $Z < -2$.

Extended Data Fig. 5 displays these locus-trait relationships in a heatmap using Euclidean distance and complete linkage clustering to order both loci and traits.

Cross-traits bubble plot

We also represent the genetic overlap between other cardiometabolic traits and BMI susceptibility loci with a bubble plot in which the size of each bubble is proportional to the fraction of BMI-associated loci for which there was a significant association ($P < 5 \times 10^{-4}$). Each pair of bubbles is connected by a line proportional to the number of significant BMI-increasing loci overlapping between the traits.

NHGRI GWAS catalogue lookups

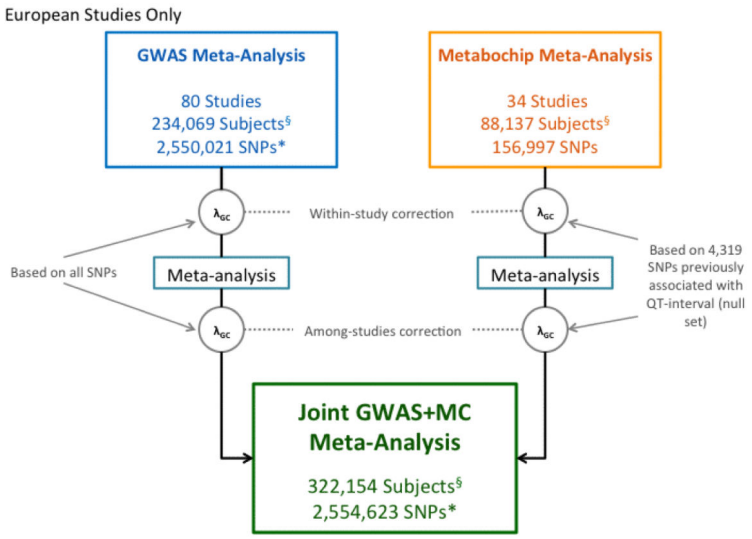
We extracted previously reported GWAS association within 500 kb of and $r^2 > 0.7$ with any BMI-index SNP from the NHGRI GWAS catalogue[71] (http://www.genome.gov/gwastudies; Supplementary Table 17a, b). For studies reporting greater than 30 significant hits, additional SNP-trait associations were pulled from the literature and compared to BMI index SNPs the same as with other GWAS catalogue studies.

ENCODE/Roadmap

To identify global enrichment of data sets at the BMI-associated loci we performed permutation-based tests in a subset of 41 open chromatin (DNase-seq), histone modification (H3K27ac, H3K4me1, H3K4me3 and H3K9ac), and transcription factor binding data sets from the ENCODE Consortium[22], Roadmap Epigenomics Project[23] and when available the ENCODE Integrative Analysis[60,72] (Supplementary Table 19). We processed Roadmap Epigenomics sequencing data with multiple biological replicates using MACS2 (ref. 73) and then applied same Irreproducible Discovery Rate pipeline used in the ENCODE Integrative Analysis[60,72]. Roadmap Epigenomics data with only a single replicate were analysed using MACS2 alone. We examined variants in LD with 97 BMI index SNPs based on $r^2 > 0.7$ from the 1000 Genomes phase 1 version 2 EUR samples[74]. We matched the index SNP at each locus with 500 variants having no evidence of association ($P > 0.5$, ~1.2 million total variants) with a similar distance to the nearest gene (± 11,655 bp), number of variants in LD (±8 variants), and minor allele frequency. Using these pools, we created 10,000 sets of control variants for each of the 97 loci and identified variants in LD ($r^2 > 0.7$) and within 1 Mb. For each SNP set, we calculated the number of loci with at least one variant located in a regulatory region under the assumption that one regulatory variant is responsible for each association signal. We estimated the *P* value assuming a sum of binomial distributions to represent the number of index SNPs (or their LD proxies; $r^2 > 0.7$) that overlap a regulatory

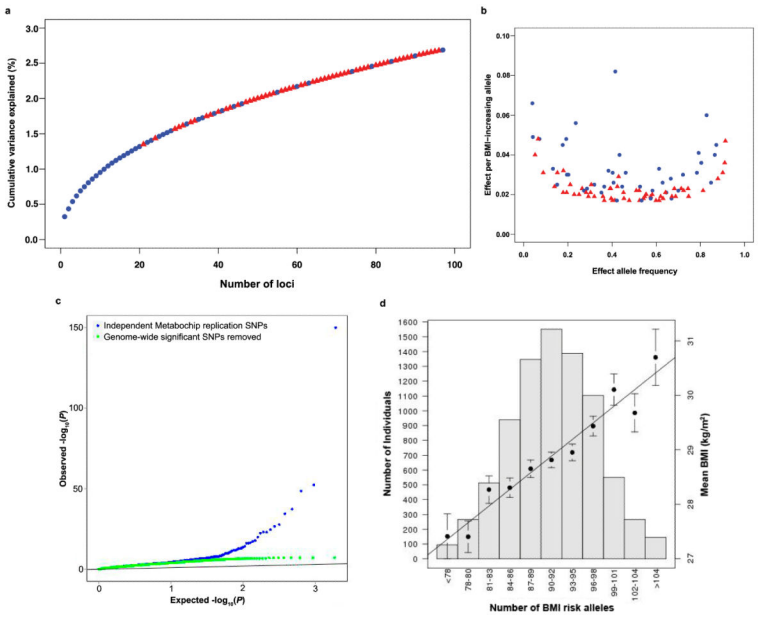
data set compared to the expectation observed in the 500 matched control sets. Data sets were considered significantly enriched if the *P* value was below a Bonferroni-corrected threshold of 1.2×10^{-3}, adjusting for 41 tests.

Extended Data



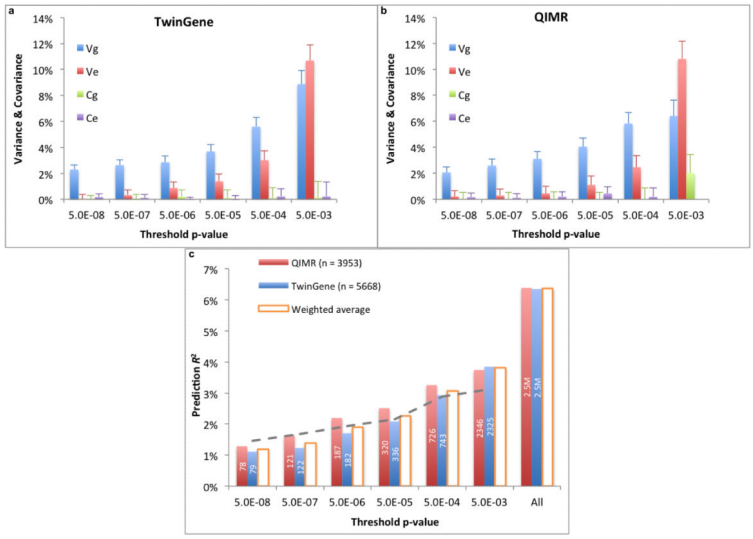
Extended Data Figure 1. Study design

*The SNP counts reflect sample size filter of $n \geq 50{,}000$. §Counts represent the primary European sex-combined analysis. Please see Extended Data Table 1 for counts for secondary analyses.



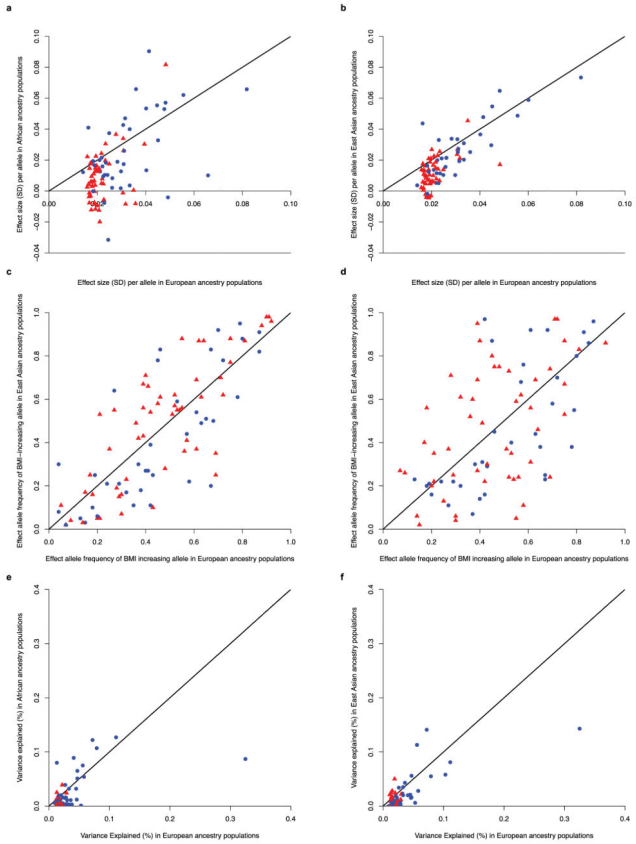
Extended Data Figure 2. Genetic characterization of BMI-associated variants

a, Plot of the cumulative phenotypic variance explained by each locus ordered by decreasing effect size. **b,** The relationship between effect size and allele frequency. Previously identified loci are blue circles and novel loci are red triangles. **c,** Quantile–quantile (Q–Q) plot of meta-analysis *P* values for all 1,909 BMI-replication SNPs (blue) and after removing SNPs near the 97 associated loci (green). **d,** Histogram of cumulative effect of BMI risk alleles. Mean BMI for each bin is shown by the black dots (with standard deviation) and corresponds to the right-hand *y* axis.



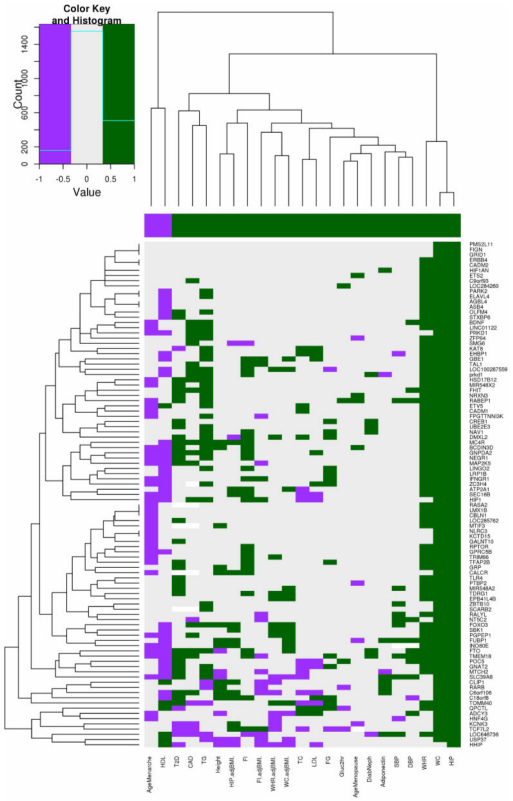
Extended Data Figure 3. Partitioning the variance in and risk prediction from SNP-derived predictor

a, b, The analyses were performed using 2,758 full sibling pairs from the TwinGene cohort (**a**) and 1,622 pairs from the QIMR cohort (**b**). The SNP-based predictor was adjusted for the first 20 principal components. The variance of the SNP-based predictor can be partitioned into four components (V_g, V_e, C_g and C_e) using the within-family prediction analysis, in which V_g is the variance explained by real SNP effects, C_g is the covariance between predictors attributed to the real effects of SNPs that are not in LD but correlated due to population stratification, V_e is the accumulated variance due to the errors in estimating SNP effects, and C_e is the covariance between predictors attributed to errors in estimating the effects of SNPs that are correlated due to population stratification. Error bars reflect s.e.m. of estimates. **c,** The prediction R^2 shown on the *y* axis is the squared correlation between phenotype and SNP-based genetic predictor in unrelated individuals from the TwinGene (n = 5,668) and QIMR (n = 3,953) studies. The number shown in each column is the number of SNPs selected from the GCTA joint and conditional analysis at a range of *P*-value thresholds. In each case, the predictor was adjusted by the first 20 principal components. The column in orange is the average prediction R^2 weighted by sample size over the two cohorts. The dashed grey line is the value inferred from the within-family prediction analyses using this equation $R^2 = (V_g + C_g)^2/(V_g + V_e + C_g + C_e)$.



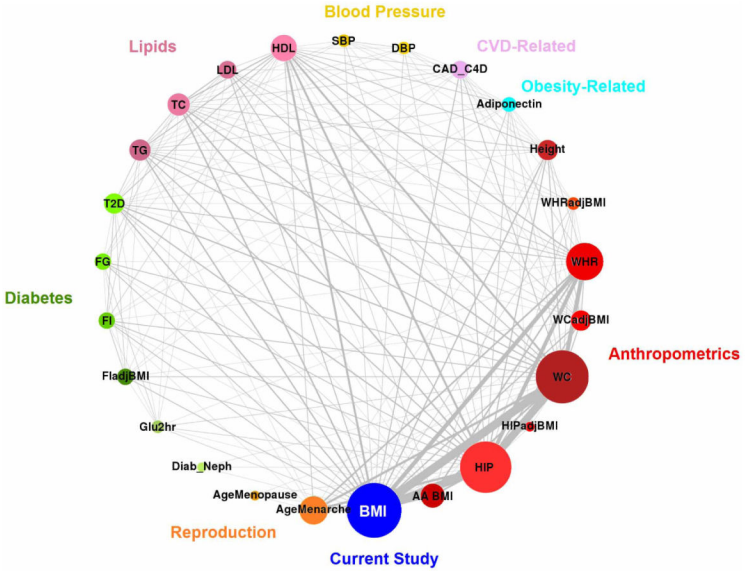
Extended Data Figure 4. Comparison of BMI-associated index SNPs across ethnicities

a, b, BMI effects observed in European ancestry individuals (*x* axes) compared to African ancestry (**a**) or Asian ancestry (**b**) individuals (*y* axes). **c, d,** Allele frequencies between ancestry groups, as in **a** and **b. e, f,** Comparison of the estimates of explained variance. In all plots, novel loci are in red and previously identified loci are in blue.



Extended Data Figure 5. Effects of BMI-associated loci on related metabolic traits

Unsupervised hierarchical clustering of the 97 BMI-associated loci (*y* axis) on 23 related metabolic traits (*x* axis). The top row shows the a priori expected relationship with BMI (green is concordant effect direction, purple is opposite). Loci with statistically significant concordant direction of effect are highlighted in green, and significant but opposing effects are in purple. Grey indicates a non-significant relationship and those with no information are in white. The key in the top left corner also shows the count of gene–phenotype pairs in each category (cyan bars).



Extended Data Figure 6. Bubble chart representing the genetic overlap across traits at BMI susceptibility loci

Each bubble represents a trait for which association results were requested for the 97 GWS BMI loci. The size of the bubble is proportional to the number of BMI-increasing loci with a significant association. A line connects each pair of bubbles with thickness proportional to the number of significant loci shared between the traits. Traits tested include the current study BMI SNPs, African-American BMI (AA BMI), hip circumference (HIP), HIP adjusted for BMI (HIPadjBMI), waist circumference (WC), waist circumference adjusted for BMI (WCadjBMI), waist-to-hip ratio (WHR), waist-to-hip ratio adjusted for BMI (WHRadjBMI), height, adiponectin, coronary artery disease (CAD), diastolic blood pressure (DBP), systolic blood pressure (SBP), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), triglycerides (TG), type 2 diabetes (T2D), fasting glucose (FG), fasting insulin (FI), fasting insulin adjusted for BMI (FIadjBMI), two-hour glucose (Glu2hr), diabetic nephropathy (Diab_Neph), age at menopause (AgeMenopause), and age at menarche (AgeMenarche).

Extended Data Table 1

Descriptive characteristics of meta-analyses

Meta-analysis	Total number of studies	Maximum number of subjects	Number of SNPs*	λ_{GC}
European sex-combined				
GWAS	80	234,069	2,550,021	1.526
Metabochip	34	88,137	156,997	1.25
Joint GWAS+Metabochip	114	322,154	2,554,623	1.084
European men				
GWAS	72	104,666	2,473,152	1.279
Metabochip	34	48,274	152,326	1.121
Joint GWAS+Metabochip	106	152,893	2,477,617	1.006

Meta-analysis	Total number of studies	Maximum number of subjects	Number of SNPs*	λ_{GC}
European women				
GWAS	74	132,115	2,491,697	1.336
Metabochip	33	39,864	153,086	1.029
Joint GWAS+Metabochip	107	171,977	2,494,571	1.002
European population-based				
GWAS	49	162,262	2,502,573	1.385
Metabochip	20	46,263	155,617	1.034
Joint GWAS+Metabochip	69	209,521	2,506,448	1.003
All ancestries				
GWAS	82	236,231	2,550,614	1.451
Metabochip	43	103,047	181,718	1.25
Joint GWAS+Metabochip	125	339,224	2,555,496	1.004

* For the GWAS and joint GWAS+Metabochip analyses, SNP count reflects $n \geq 50{,}000$.

Extended Data Table 2

Previously known GWS BMI loci in European meta-analysis

SNP	Chr:Position	*Notable gene(s)	Alleles	EAF	β	SE	*P* value
rs1558902	16:52,361,075	*FTO*(B,N)	A/T	0.415	0.082	0.003	7.51E-153
rs6567160	18:55,980,115	*MC4R*(B,N)	C/T	0.236	0.056	0.004	3.93E-53
rs13021737	2:622,348	*TMEM18*(N)	G/A	0.828	0.06	0.004	1.11E-50
rs10938397	4:44,877,284	*GNPDA2*(N); *GABRG1*(B)	G/A	0.434	0.04	0.003	3.21E-38
rs543874	1:176,156,103	*SEC16B*(N)	G/A	0.193	0.048	0.004	2.62E-35
rs2207139	6:50,953,449	*TFAP2B*(B,N)	G/A	0.177	0.045	0.004	4.13E-29
rs11030104	11:27,641,093	*BDAF*(B,M,N)	A/G	0.792	0.041	0.004	5.56E-28
rs3101336	1:72,523,773	N*EGR1*(B,C,D,N)	C/T	0.613	0.033	0.003	2.66E-26
rs7138803	12:48,533,735	*BCDIN3D*(N); *FAIM2*(D)	A/G	0.384	0.032	0.003	8.15E-24
rs10182181	2:25,003,800	*ADCY3*(B,M,N,Q); *POMC*(B,G); *NCOA1*(B) *SH2B1*(B,M,Q); *APOBR*(M,Q);	G/A	0.462	0.031	0.003	8.78E-24
rs3888190	16:28,796,987	*ATXN2L*(Q); *SBK1*(Q,D); *SULT1A2*(Q); *TUFM*(Q)	A/C	0.403	0.031	0.003	3.14E-23
rs1516725	3:187,306,698	*E7V5*(N)	C/T	0.872	0.045	0.005	1.89E-22
rs12446632	16:19,842,890	*GPRC5B*(C,N); *IQCK*(Q)	G/A	0.865	0.04	0.005	1.48E-18
rs2287019	19:50,894,012	*QPCTL*(N); *GIPR*(B,M)	C/T	0.804	0.036	0.004	4.59E-18
rs16951275	15:65,864,222	*M4P2K5*(B,D,N); *LBXCOR1*(M)	T/C	0.784	0.031	0.004	1.91E-17
rs3817334	11:47,607,569	*MTCH2*(M,Q); *C1QTNF4*(Q,I); *SPI1*(Q); *CELF1*(D)	T/C	0.407	0.026	0.003	5.15E-17
rs2112347	5:75,050,998	*POC5*(M); *HMGCR*(B); *COL4A3BP*(B)	T/G	0.629	0.026	0.003	6.19E-17
rs12566985	1:74,774,781	*FPGT-TNNI3K*(N)	G/A	0.446	0.024	0.003	3.28E-15
rs3810291	19:52,260,843	*ZC3H4*(D,N,Q)	A/G	0.666	0.028	0.004	4.81E-15
rs7141420	14:78,969,207	*NRXN3*(D,N)	T/C	0.527	0.024	0.003	1.23E-14
rs13078960	3:85,890,280	*CADM2*(D,N)	G/T	0.196	0.03	0.004	1.74E-14
rs10968576	9:28,404,339	*LINGO2*(D,N)	G/A	0.32	0.025	0.003	6.61E-14

SNP	Chr:Position	*Notable gene(s)	Alleles	EAF	β	SE	*P* value
rs17024393	1:109,956,211	*GNAT2*(N); *AMPD2*(D)	C/T	0.04	0.066	0.009	7.03E-14
rs12429545	13:53,000,207	*OLFM4*(B,N)	A/G	0.133	0.033	0.005	1.09E-12
rs13107325	4:103,407,732	*SLC39A8*(M,N,Q)	T/C	0.072	0.048	0.007	1.83E-12
rs11165643	1:96,696,685	*PTBP2*(D,N)	T/C	0.583	0.022	0.003	2.07E-12
rs17405819	8:76,969,139	*HNF4G*(B,N)	T/C	0.7	0.022	0.003	2.07E-11
rs1016287	2:59,159,129	*LINC01122*(N)	T/C	0.287	0.023	0.003	2.25E-11
rs4256980	11:8,630,515	*TRIM66*(D,M,N); *TUB*(B)	G/C	0.646	0.021	0.003	2.90E-11
rs12401738	1:78,219,349	*FUBP1*(N); *USP33*(D)	A/G	0.352	0.021	0.003	1.15E-10
rs205262	6:34,671,142	*C6orf106*(N); *SNRPC*(Q)	G/A	0.273	0.022	0.004	1.75E-10
rs12016871	13:26,915,782	*MTIF3*(N); *GTF3A(Q)*	T/C	0.203	0.03	0.005	2.29E-10
rs12940622	17:76,230,166	*RPTOR*(B,N)	G/A	0.575	0.018	0.003	2.49E-09
rs11847697	14:29,584,863	*PRKD1*(N)	T/C	0.042	0.049	0.008	3.99E-09
rs2075650	19:50,087,459	*TOMM40*(B,N); *APOE*(B); *APOC1*(B)	A/G	0.848	0.026	0.005	1.25E-08
rs2121279	2:142,759,755	*LRP1B*(N)	T/C	0.152	0.025	0.004	2.31E-08
rs29941	19:39,001,372	*KCTD15*(N)	G/A	0.669	0.018	0.003	2.41E-08
rs1808579	18:19,358,886	*NPC1*(B,G,M,Q); *C18orf8*(N,Q)	C/T	0.534	0.017	0.003	4.17E-08

SNP positions are reported according to Build 36 and their alleles are coded based on the positive strand. Effect alleles, allele frequencies, betas (β), s.e.m., sample sizes (*n*), and *P* values are based on the meta-analysis of GWAS I + II + Metabochip association data from the European sex-combined data set.

* Notable genes from biological relevance to obesity (B); GRAIL results (G); BMI-associated variant is in strong LD ($r^2 \geq 0.7$) with a missense variant in the indicated gene (M); gene nearest to Index SNP (N); association and eQTL data converge to affect gene expression (Q); DEPICT analyses (D); copy number variation (C).

Extended Data Table 3

Association of the GWS SNPs for BMI with *cis*-gene expression (*cis*-eQTLs)

SNP	Chr.	BMI increasing allele	Tissue	Gene	β for Giant SNP	*P* for GIANT SNP	P_{adj} for GIANT SNP	PeakSNP	r^2	*P* for peak SNP	P_{adj} for peak SNP	Reference
Novel loci												
rs11583200	1	c	Subcutaneous	*ELAVL4*	−0.066	1.90E-12	0.44	rs6588374	0.78	1.07E-12	0.36	Zhong et al.
rs492400	2	c	Liver	*PLCD4*	−0.054	4.64E-40	0.98	rs10187066	1.00	4.49E-40	0.98	Zhong et al.
rs492400	2	c	Lymphocyte	*RQCD1*	0.392	7.11E-22	0.94	rs526134	1.00	4.06E-22	0.21	Dixon et al.
rs492400	2	c	PBMC	*RQCD1*	−0.102	2.43E-06	0.98	rs526134	0.95	2.21E-06	0.96	PBMC meta-analysis
rs492400	2	c	Omental	*TTLL4*	0.018	1.33E-10	0.82	rs12987009	0.73	2.82E-13	0.07	Zhong et al.
rs492400	2	c	Lymphocyte	*TTLL4*	0.158	9.02E-06	1	rs492400	1.00	9.02E-06	1	Dixon et al.
rs17001654	4	G	Lymphocyte	*SCARB2*	0.248	5.57E-09	0.59	rs6835324	0.94	3.42E-09	0.25	Dixon et al.
rs9400239	6	C	Subcutaneous	*HSS00296402*	0.034	9.51E-22	0.97	rs2153960	0.94	1.93E-23	0.48	Zhong et al.
rs9400239	6	C	Omental	*HSS00296402*	0.015	1.34E-13	0.50	rs2153960	0.93	4.64E-17	0.22	Zhong et al.
rs1167827	7	G	Blood	*PMS2P3*	−0.595	4.20E-32	0.66	rs6963105	0.93	3.00E-32	0.39	Emilsson et al.
rs1167827	7	G	Omental	*PMS2P3*	−0.027	1.57E-11	0.95	rs6963105	0.98	6.94E-12	0.86	Zhong et al.
rs1167827	7	G	Subcutaneous	*PMS2P3*	−0.030	1.30E-10	0.71	rs1167796	0.73	1.04E-12	0.10	Zhong et al.
rs1167827	7	G	Adipose	*PMS2P3*	−0.346	3.40E-09	1	rs1167827	1.00	3.40E-09	1	Emilsson et al.
rs1167827	7	G	Blood	*PMS2P5*	−0.367	1.20E-11	0.47	rs6963105	0.93	5.00E-12	0.14	Emilsson et al.
rs1167827	7	G	Subcutaneous	*WBSCR16*	0.025	1.44E-10	1	rs1167827	1.00	1.44E-10	1	Zhong et al.
rs1167827	7	G	Omental	*WBSCR16*	0.017	1.75E-06	1	rs1167827	1.00	1.75E-06	1	Zhong et al.
rs9641123	7	C	Abdominal SAT	*hsa-miR-653*	−0.344	1.54E-04	0.23	rs16868443	0.71	1.38E-04	0.20	Parts et al.
rs11191560	10	C	Gluteal SAT	*SFXN2*	0.153	1.72E-05	0.20	rs71496550	NA	4.42E-06	0.41	Min et al.
rs11191560	10	C	Abdominal SAT	*SFXN2*	0.628	1.44E-04	0.02	rs71496550	NA	9.13E-05	0.94	Min et al.
rs7164727	15	T	Lymphocyte	*BBS4*	−0.163	3.14E-05	1	rs7164727	1.00	3.14E-05	1	Dixon et al.
rs9925964	16	A	Liver	*VKORC1*	0.122	4.41E-37	0.84	rs2303223	0.88	3.62E-44	0.05	Zhong et al.
rs9925964	16	A	Subcutaneous	*ZNF646*	0.017	2.55E-06	1	rs9925964	1.00	2.55E-06	1	Zhong et al.
rs9925964	16	A	Blood	*ZNF668*	−0.382	1.70E-12	0.48	rs10871454	0.93	1.10E-12	0.26	Emilsson et al.
rs9914578	17	G	Subcutaneous	*C17orf13*	−0.010	3.01E-06	0.99	rs7225843	0.99	2.86E-06	0.97	Zhong et al.
rs1808579	18	C	SKIN	*C18orf8*	−0.073	5.74E-10	0.86	rs1788781	0.90	1.67E-10	0.13	Grundberg et al.
rs1808579	18	C	Subcutaneous	*C18orf8*	−0.014	8.41E-08	1	rs1808579	1.00	8.41E-08	1	Zhong et al.

SNP	Chr.	BMI increasing allele	Tissue	Gene	β for Giant SNP	*P* for GIANT SNP	P_{adj} for GIANT SNP	PeakSNP	r^2	*P* for peak SNP	P_{adj} for peak SNP	Reference
rs17724992	19	A	Blood	*PGPEP1*	−0.825	1.60E-40	1	rs17724992	1.00	1.60E-40	1	Emilsson et al.
Previously reported loci												
rs10182181	2	G	Subcutaneous	*ADCY3*	0.022	7.57E-06	0.69	rs11684619	0.72	8.70E-09	0.05	Zhong et al.
rs2176040	2	A	Omental	*IRS1*	−0.036	3.74E-09	0.97	rs908252	0.87	3.98E-10	0.47	Zhong et al.
rs13107325	4	T	Liver	*SLC39A8*	−0.101	1.29E-17	1	rs13107325	1.00	1.29E-17	1	Zhong et al.
rs205262	6	G	Blood	*SNRPC*	−0.462	9.60E-15	0.58	rs6457792	0.96	9.40E-15	0.55	Emilsson et al.
rs205262	6	G	PBMC	*SNRPC*	−0.127	3.40E-09	0.03	rs2744943	0.73	3.15E-11	0.12	PBMC meta-analysis
rs205262	6	G	Omental	*SNRPC*	−0.012	6.64E-06	0.81	rs2814984	0.75	8.03E-07	0.30	Zhong et al.
rs3817334	11	T	SKIN	*C1QTNF4*	−0.051	1.34E-09	0.82	rs7124681	1.00	9.42E-10	0.34	Grundberg et al.
rs3817334	11	T	Subcutaneous	*MTCH2*	0.044	7.64E-13	0.76	rs12794570	0.76	2.54E-15	0.10	Zhong et al.
rs3817334	11	T	Brain	*MTCH2*	28.255	7.51E-08	NA	NA	NA	NA	NA	Myers et al.
rs3817334	11	T	FAT	*SPI1*	−0.090	9.90E-07	0.90	rs10769262	0.70	1.15E-08	1	Grundberg et al.
rs12016871	13	T	PBMC	*GTF3A*	−0.258	6.68E-34	0.90	rs7988412	0.81	1.81E-36	0.29	PBMC meta-analysis
rs12016871	13	T	Lymphocyte	*GTF3A*	−0.375	3.89E-15	0.32	rs7988412	0.86	1.32E-15	0.06	Dixon et al.
rs12446632	16	G	Omental	*IQCK*	0.028	2.27E-10	0.83	rs11865578	0.83	4.14E-13	0.14	Zhong et al.
rs12446632	16	G	Liver	*IQCK*	0.031	5.39E-06	0.74	rs9921401	0.70	3.82E-07	0.20	Zhong et al.
rs3888190	16	A	Blood	*APOBR*	0.303	2.10E-08	0.68	rs2411453	0.83	1.10E-08	0.25	Emilsson et al.
rs3888190	16	A	PBMC	*ATXN2L*	0.084	1.04E-04	0.99	rs8049439	0.99	8.59E-05	0.88	PBMC meta-analysis
rs3888190	16	A	SKIN	*SBK1*	−0.063	1.63E-06	0.41	rs4788084	0.82	2.87E-07	0.10	Grundberg et al.
rs3888190	16	A	Adipose	*SH2B1*	−0.407	4.10E-13	0.67	rs12928404	0.92	2.40E-13	0.30	Emilsson et al.
rs3888190	16	A	Omental	*SH2B1*	−0.014	5.29E-07	0.87	rs12928404	0.93	4.65 E-07	0.83	Zhong et al.
rs3888190	16	A	Subcutaneous	*SULT1A2*	0.067	3.36E-21	0.52	rs1074631	0.80	3.93E-23	0.14	Zhong et al.
rs3888190	16	A	PBMC	*TUFM*	0.694	9.81E-198	0.94	rs8049439	0.99	9.81E-198	0.12	PBMC meta-analysis
rs1808579	18	C	Subcutaneous	*NPC1*	−0.027	2.52E-10	0.83	rs1805081	0.78	7.86E-14	0.06	Zhong et al.
rs3888190	16	A	SKIN	*TUFM*	0.074	7.90E-10	0.46	rs2411453	0.76	1.91E-10	0.09	Grundberg et al.
rs3810291	19	A	Adipose	*ZC3H4*	−0.386	3.70E-09	1	rs3810291	1.00	3.70E-09	1	Emilsson et al.

Extended Data Table 4

Putative coding variants in LD ($r^2 \geq 0.7$) with GWS BMI loci

BMI SNP	Chr.	Source	Putative Coding Variant	r^2	Gene	Protein Alteration	PhastCon Score	GERP Score	Grantham Score	PolyPhen	SIFT Prediction	SIFT Score
Novel genome-wide significant loci												
rs492400	2	1000G	rs3770213	0.89	*ZNF142*	L956H	0	−1.6	99	possibly damaging	Damaging	0
rs492400	2	1000G	rs3770214	0.89	*ZNF142*	S751G	0.2	1.4	56	benign	Tolerated	0.08
rs492400	2	1000G	rs2230115	0.963	*ZNF142*	A541S	0.5	5.1	99	benign	Tolerated	0.044
rs492400	2	1000G	rs1344642	0.963	*STK36*	R583Q	0	2.4	43	possibly damaging	Damaging	0
rs492400	2	1000G	rs1863704	0.89	*STK36*	G1003D	0	2	94	possibly damaging	Tolerated	0.41
rs492400	2	1000G	rs1863704	0.89	*STK36*	G982D	0	2	94	possibly damaging	-	-
rs492400	2	1000G	rs3731877	0.792	*TLL4*	E34Q	1	5.5	29	probably damaging	Unknown	Not scored
rs17001654	4	1000G	rs61750814	1	*NUP54*	N250S	1	5.5	46	benign	Damaging	0.05
rs4740619	9	1000G	rs4741510	0.901	*CCDC171*	S121T	1	2	58	benign	Damaging	0.05
rs4740619	9	1000G	rs1539172	0.74	*CCDC171*	K1069R	1	4.1	26	benign	Tolerated	1
rs2176598	11	1000G	rs11555762	0.774	*HSD17B12*	S280L	0	0.4	145	benign	Tolerated	0.74
rs3849570	3	1000G	rs2229519	0.771	*GBE1*	R190G	1	4.8	125	benign	Damaging	0.04
rs3736485	15	1000G	rs12102203	0.966	*DMXL2*	S1288P	0.7	1.7	74	benign	Tolerated	0.32
rs7164727	15	1000G	rs2277598	0.839	*BBS4*	I182T	0	−4.4	89	benign	Tolerated	0.47
rs9925964	16	1000G	rs749670	0.869	*ZNF646*	E327G	1	4.2	98	benign	Tolerated	0.44
Previously identified genome-wide significant loci												
rs10182181	2	HapMap	rs11676272	0.967	*ADCY3*	S107P	0	2.9	74	benign	Tolerated	0.28
rs13107325	4	1000G	rs13107325	1	*SLC39A8*	A324T	1	4.4	5.8	benign	Tolerated	0.09
rs13107325	4	1000G	rs13107325	1	*SLC39A8*	A391T	1	4.4	5.8	benign	Tolerated	0.09
rs2112347	5	1000G	rs2307111	0.862	*POC5*	H11R	0.9	5.8	29	benign	Unknown	Not scored
rs2112347	5	1000G	rs2307111	0.862	*POC5*	H36R	0.9	5.8	29	benign	Unknown	Not scored
rs4256980	11	HapMap	rs7935453	0.729	*TRIM66*	L630V	-	-	-	-	Tolerated	1
rs4256980	11	1000G	rs11042022	0.876	*TRIM66*	H466R	-	-	-	-	Tolerated	0.38
rs4256980	11	1000G	rs11042023	0.959	*TRIM66*	H324R	1	5.1	29	probably damaging	Damaging	0.03
rs11030104	11	1000G	rs6265	0.817	*BDNF*	V148M	1	5.2	21	probably damaging	Damaging	0
rs11030104	11	1000G	rs6265	0.817	*BDNF*	V66M	1	5.2	21	probably damaging	Damaging	0

BMI SNP	Chr.	Source	Putative Coding Variant	r^2	Gene	Protein Alteration	PhastCon Score	GERP Score	Grantham Score	PolyPhen	SIFT Prediction	SIFT Score
rs11030104	11	1000G	rs6265	0.817	*BDNF*	V74M	1	5.2	21	probably damaging	Damaging	0
rs11030104	11	1000G	rs6265	0.817	*BDNF*	V81M	1	5.2	21	probably damaging	Damaging	0
rs11030104	11	1000G	rs6265	0.817	*BDNF*	V95M	1	5.2	21	probably damaging	Damaging	0
rs3817334	11	1000G	rs1064608	0.809	*MTCH2*	P290A	1	5.1	27	probably damaging	Tolerated	0.12
rs3888190	16	1000G	rs180743	0.789	*APOBR*	P428A	0.1	0.5	27	benign	Unknown	Not scored
rs3888190	16	1000G	rs7498665	1	*SH2B1*	T484A	1	3.1	58	benign	Tolerated	0.25
rs16951275	15	1000G	rs7170185	1	*LBXCOR1*	W200R	-	-	-	-	-	-
rs1808579	18	1000G	rs1805082	0.935	*NPC1*	I858V	1	6.1	29	benign	Tolerated	0.24
rs1808579	18	1000G	rs1805081	0.905	*NPC1*	H215R	0	−1.1	29	benign	Tolerated	0.59
rs2287019	19	1000G	rs1800437	0.714	*GIPR*	E354Q	1	3.1	29	probably damaging	Tolerated	0.09

r^2 is the LD between the BMI index SNP and the putative coding variant.

Supplementary Material

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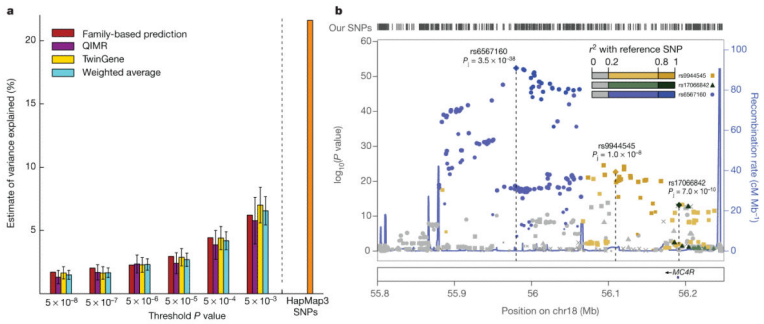

Figure 1. Cumulative variance explained and example of secondary signals

a, The estimated variance in BMI explained by SNPs selected at a range of *P* values using unrelated individuals from the QIMR (*n* = 3,924; purple) and TwinGene (*n* = 5,668; gold), their weighted average (cyan), inferred from within-family prediction (red; Extended Data Fig. 2), and by all HapMap phase III SNPs in 16,275 unrelated individuals from the QIMR, TwinGene and ARIC studies (orange). **b,** Plot of the region surrounding *MC4R* (ref. 36). SNP associations from the European sex-combined meta-analysis are plotted with joint conditional *P* values (P_j) indicated for the three conditionally significant signals. SNPs are shaded and shaped based on the index SNP with which they are in strongest LD (rs6567160 in blue, rs994545 in yellow and rs17066842 in green).

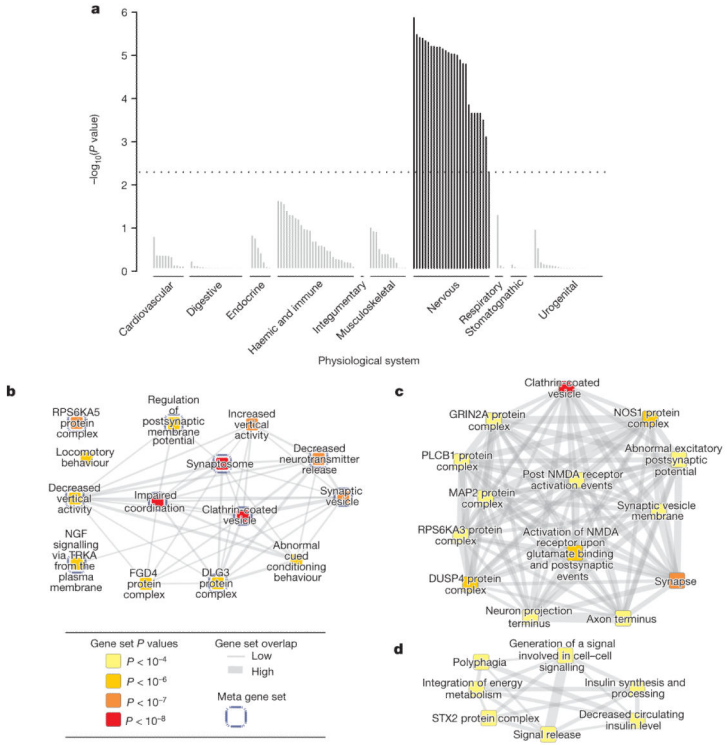

Figure 2. Tissues and reconstituted gene sets significantly enriched for genes within BMI-associated loci

a, DEPICT predicts genes within BMI-associated loci ($P < 5 \times 10^{-4}$) are enriched for expression in the brain and central nervous system. Tissues are sorted by physiological system and significantly enriched tissues are in black; the dotted line represents statistically significant enrichment. **b,** The gene sets most significantly enriched for BMI-associated loci by DEPICT ($P < 10^{-6}$, FDR $< 4 \times 10^{-4}$). Nodes represent reconstituted gene sets and are colour-coded by *P* value. Edge thickness between nodes is proportional to degree of gene overlap as measured by the Jaccard index. Nodes with gene overlap greater than 25% were collapsed into a single 'meta-node' (blue border). **c,** The nodes contained within the most enriched meta-node, 'clathrin-coated vesicle', which shares genes with other gene sets relevant to glutamate signalling and synapse biology. **d,** The 'generation of a signal involved in cell–cell signalling' meta-node represents several overlapping gene sets relevant to obesity and energy metabolism (gene sets with $P < 4 \times 10^{-3}$, FDR < 0.05 shown). For the complete list of enriched gene sets refer to Supplementary Table 21a.

Table 1

Novel GWS BMI loci In European meta-analysis

SNP	Chr:position	Notable gene(s)*	Alleles	EAF	β	s.e.m.	*P* value
rs657452	1:49,362,434	*AGBL4*(N)	A/G	0.394	0.023	0.003	5.48×10^{-13}
rs12286929	11:114,527,614	*CADM1*(N)	G/A	0.523	0.022	0.003	1.31×10^{-12}
rs7903146	10:114,748,339	*TCF7L2*(B,N)	C/T	0.713	0.023	0.003	1.11×10^{-11}
rs10132280	14:24,998,019	*STXBP6*(N)	C/A	0.682	0.023	0.003	1.14×10^{-11}
rs17094222	10:102,385,430	*HIF1AN*(N)	C/T	0.211	0.025	0.004	5.94×10^{-11}
rs7599312	2:213,121,476	*ERBB4*(D,N)	G/A	0.724	0.022	0.003	1.17×10^{-10}
rs2365389	3:61,211,502	*FHIT*(N)	C/T	0.582	0.020	0.003	1.63×10^{-10}
rs2820292	1:200,050,910	*NAV1*(N)	C/A	0.555	0.020	0.003	1.83×10^{-10}
rs12885454	14:28,806,589	*PRKD1*(N)	C/A	0.642	0.021	0.003	1.94×10^{-10}
rs16851483	3:142,758,126	*RASA2*(N)	T/G	0.066	0.048	0.008	3.55×10^{-10}
rs1167827	7:75,001,105	*HIP1*(B,N); *PMS2L3*(B,Q); *PMS2P5*(Q); *WBSCR16*(Q)	G/A	0.553	0.020	0.003	6.33×10^{-10}
rs758747	16:3,567,359	*NLRC3*(N)	T/C	0.265	0.023	0.004	7.47×10^{-10}
rs1928295	9:119,418,304	*TLR4*(B,N)	T/C	0.548	0.019	0.003	7.91×10^{-10}
rs9925964	16:31,037,396	*KAT8*(N);*ZNF646*(M,Q); *VKORC1*(Q); *ZNF668*(Q); *STX1B*(D); *FBXL19*(D)	A/G	0.620	0.019	0.003	8.11×10^{-10}
rs11126666	2:26,782,315	*KCNK3*(D,N)	A/G	0.283	0.021	0.003	1.33×10^{-9}
rs2650492	16:28,240,912	*SBK1*(D,N); *APOBR*(B)	A/G	0.303	0.021	0.004	1.92×10^{-9}
rs6804842	3:25,081,441	*RARB*(B)	G/A	0.575	0.019	0.003	2.48×10^{-9}
rs4740619	9:15,624,326	*C9orf93*(C,M,N)	T/C	0.542	0.018	0.003	4.56×10^{-9}
rs13191362	6:162,953,340	*PARK2*(B,D,N)	A/G	0.879	0.028	0.005	7.34×10^{-9}
rs3736485	15:49,535,902	*SCG3*(B,D); *DMXL2*(M,N)	A/G	0.454	0.018	0.003	7.41×10^{-9}
rs17001654	4:77,348,592	*NUP54*(M); *SCARB2*(Q,N)	G/C	0.153	0.031	0.005	7.76×10^{-9}
rs11191560	10:104,859,028	*NT5C2*(N); *CYP17A1*(B); *SFXN2*(Q)	C/T	0.089	0.031	0.005	8.45×10^{-9}
rs1528435	2:181,259,207	*UBE2E3*(N)	T/C	0.631	0.018	0.003	1.20×10^{-8}
rs1000940	17:5,223,976	*RABEP1*(N)	G/A	0.320	0.019	0.003	1.28×10^{-8}
rs2033529	6:40,456,631	*TDRG1*(N); *LRFN2*(D)	G/A	0.293	0.019	0.003	1.39×10^{-8}
rs11583200	1:50,332,407	*ELAVL4*(B,D,N,Q)	C/T	0.396	0.018	0.003	1.48×10^{-8}
rs9400239	6:109,084,356	*FOXO3*(B,N); *HSS00296402*(Q)	C/T	0.688	0.019	0.003	1.61×10^{-8}
rs10733682	9:128,500,735	*LMX1B*(B,N)	A/G	0.478	0.017	0.003	1.83×10^{-8}
rs11688816	2:62,906,552	*EHBP1*(B,N)	G/A	0.525	0.017	0.003	1.89×10^{-8}
rs11057405	12:121,347,850	*CLIP1*(N)	G/A	0.901	0.031	0.006	2.02×10^{-8}
rs11727676	4:145,878,514	*HHIP*(B,N)	T/C	0.910	0.036	0.006	2.55×10^{-8}
rs3849570	3:81,874,802	*GBE1*(B,M,N)	A/C	0.359	0.019	0.003	2.60×10^{-8}
rs6477694	9:110,972,163	*EPB41L4B*(N); *C9orf4*(D)	C/T	0.365	0.017	0.003	2.67×10^{-8}
rs7899106	10:87,400,884	*GRID1*(B,N)	G/A	0.052	0.040	0.007	2.96×10^{-8}
rs2176598	11:43,820,854	*HSD17B12*(B,M,N)	T/C	0.251	0.020	0.004	2.97×10^{-8}
rs2245368	7:76,446,079	*PMS2L11*(N)	C/T	0.180	0.032	0.006	3.19×10^{-8}

SNP	Chr:position	Notable gene(s)*	Alleles	EAF	β	s.e.m.	*P* value
rs17724992	19:18,315,825	*GDF15*(B); *PGPEP1*(Q,N)	A/G	0.746	0.019	0.004	3.42×10^{-8}
rs7243357	18:55,034,299	*GRP*(B,G,N)	T/G	0.812	0.022	0.004	3.86×10^{-8}
rs2033732	8:85,242,264	*RALYL*(D,N)	C/T	0.747	0.019	0.004	4.89×10^{-8}

GWS isdefinedas $P < 5 \times 10^{-8}$. SNP positions are reported according to Build 36 and their alleles are coded based on the positive strand. Alleles (effect/other), effect allele frequency (EAF), beta (β), standard error of the mean (s.e.m.) and *P* values are based on the meta-analysis of GWAS I + II + Metabochip association data from the European sex-combined data set.

*Notable genes from biological relevance to obesity (B); copy number variation (C); DEPICT analyses (D); GRAIL results (G); BMI-associated variantis in strong LD ($r^2 \geq 0.7$) with a missens evariant in the indicated gene (M); gene nearest to index SNP (N); association and eQTL data converge to affect gene expression (Q).

Table 2

GWS BMI loci from secondary analyses

SNP	Chr:position	Notable gene(s)*	Alleles	EAF	β	s.e.m.	*P* value	Analysis
Novel loci								
rs9641123	7:93,035,668	*CALCR*(B,N); *hsa-miR*-653(Q)	C/G	0.430	0.029	0.005	2.08×10^{-10}	EPB
rs7164727	15:70,881,044	*LOC100287559*(N), *BBS4*(B,M,Q)	T/C	0.671	0.019	0.003	3.92×10^{-9}	All
rs492400	2:219,057,996	*PLCD4*(B,Q); *CYP27A1*(B); USP37(N); *TTLL4*(M,Q); *STK36*(B,M); *ZNF142*(M); *RQCD1*(Q)	C/T	0.424	0.024	0.004	6.78×10^{-9}	Men
rs2080454	16:47,620,091	*CBLN1*(N)	C/A	0.413	0.017	0.003	8.60×10^{-9}	All
rs7239883	18:38,401,669	*LOC284260*(N); *RIT2*(B,D)	G/A	0.391	0.023	0.004	1.51×10^{-8}	Women
rs2836754	21:39,213,610	*ETS2*(N)	C/T	0.599	0.017	0.003	1.61×10^{-8}	All
rs9914578	17:1,951,886	*SMG6*(D,N); *N29617*(Q)	G/C	0.229	0.020	0.004	2.07×10^{-8}	All
rs977747	1:47,457,264	*TAL1*(N)	T/G	0.403	0.017	0.003	2.18×10^{-8}	All
rs9374842	6:120,227,364	*LOC285762*(N);	T/C	0.744	0.023	0.004	2.67×10^{-8}	EPB
rs4787491	16:29,922,838	*MAPK3*(D); *KCTD13*(D); *INO80E*(N); *TAOK2*(D); *YPEL3*(D); *DOC2A*(D); *FAM57B*(D)	G/A	0.510	0.022	0.004	2.70×10^{-8}	EPB
rs1441264	13:78,478,920	*MIR548A2*(N)	A/G	0.613	0.017	0.003	2.96×10^{-8}	All
rs17203016	2:207,963,763	*CREB1*(B,N); *KLF7*(B)	G/A	0.195	0.021	0.004	3.41×10^{-8}	All
rs16907751	8:81,538,012	*ZBTB10*(N)	C/T	0.913	0.047	0.009	3.89×10^{-8}	Men
rs13201877	6:137,717,234	*IFNGR1*(N); *OLIG3*(G)	G/A	0.140	0.024	0.004	4.29×10^{-8}	All
rs9540493	13:65,103,705	*MIR548X2*(N); *PCDH9*(D)	A/G	0.452	0.021	0.004	4.97×10^{-8}	EPB
rs1460676	2:164,275,935	*FIGN*(N)	C/T	0.179	0.021	0.004	4.98×10^{-8}	All
rs6465468	7:95,007,450	*ASB4*(B,N)	T/G	0.306	0.025	0.005	4.98×10^{-8}	Women
Previously identified loci								
rs6091540	20:50,521,269	*ZFP64*(N)	C/T	0.721	0.030	0.004	2.15×10^{-11}	Women
rs7715256	5:153,518,086	*GALNT10*(N)	G/T	0.422	0.017	0.003	8.85×10^{-9}	All
rs2176040	2:226,801,046	*LOC646736*(N); *IRS1*(B,Q)	A/G	0.365	0.024	0.004	9.99×10^{-9}	Men

SNP positions are reported according to Build 36 and their alleles are coded based on the positive strand. Alleles (effect/other), EAF, beta (β), s.e.m. and *P* values are based on the meta-analysis of GWAS I + II+ Metabochip association data from the data set shown in the 'Analysis' column. EPB denotes European population-based studies, 'All' denotes all ancestries.

*Notable genes from biological relevance to obesity (B); copy number variation (C); DEPICT analyses (D); GRAIL results (G); BMI-associated variant is in strong LD ($r^2 \geq 0.7$) with a missense variant in the indicated gene (M); gene nearest to the index SNP (N); association and eQTL data converge to affect gene expression (Q).

Table 3

Secondary signals reaching GWS by conditional analysis

SNP	Chr: position	Nearest gene	Alleles	EAF	β	s.e.m.	Variance explained	*P* value
rs1016287	2:59159129	*LINC01122*	T/C	0.294	0.023	0.003	0.021%	2.62×10^{-11}
rs4671328	2:58788786	*LINC01122*	T/G	0.457	0.021	0.004	0.021%	2.73×10^{-8}
rs758747	16:3567359	*NLRC3*	T/C	0.241	0.022	0.004	0.018%	2.00×10^{-9}
rs879620	16:3955730	*ADCY9*	T/C	0.620	0.024	0.004	0.027%	2.17×10^{-9}
rs12446632	16:19842890	*GPRC5B*	G/A	0.860	0.036	0.005	0.031%	1.06×10^{-14}
rs11074446	16:20162624	*GP2*	T/C	0.867	0.029	0.005	0.019%	1.71×10^{-10}
rs6567160	18:55980115	*MC4R*	C/T	0.233	0.048	0.004	0.084%	3.52×10^{-38}
rs17066842	18:56191604	*MC4R*	G/A	0.960	0.051	0.008	0.020%	6.99×10^{-10}
rs9944545	18:56109224	*MC4R*	T/C	0.296	0.020	0.004	0.017%	1.01×10^{-8}
rs11030104	11:27641093	*BDNF*	A/G	0.791	0.051	0.004	0.087%	1.26×10^{-34}
rs10835210	11:27652486	*BDNF*	C/A	0.570	0.020	0.004	0.020%	1.25×10^{-8}

SNP positions are reported according to Build 36 and their alleles are coded based on the positive strand. Alleles (effect/other), EAF, estimated beta (β), s.e.m., explained variance, and *P* values from GCTA. First row at each locus represents lead signal, other row(s) represent secondary signals.