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Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index

Obesity is globally prevalent and highly heritable, but its underlying genetic factors remain largely elusive. To identify genetic loci for obesity susceptibility, we examined associations between body mass index and ~2.8 million SNPs in up to 123,865 individuals with targeted follow up of 42 SNPs in up to 125,931 additional individuals. We confirmed 14 known obesity susceptibility loci and identified 18 new loci associated with body mass index ($P < 5 \times 10^{-8}$), one of which includes a copy number variant near *GPRC5B*. Some loci (at *MC4R*, *POMC*, *SH2B1* and *BDNF*) map near key hypothalamic regulators of energy balance, and one of these loci is near *GIPR*, an incretin receptor. Furthermore, genes in other newly associated loci may provide new insights into human body weight regulation.

Obesity is a major and increasingly prevalent risk factor for multiple disorders, including type 2 diabetes and cardiovascular disease[1,2]. Although lifestyle changes have driven its prevalence to epidemic proportions, heritability studies provide evidence for a substantial genetic contribution (with heritability estimates (h^2) of ~40%–70%) to obesity risk[3,4]. BMI is an inexpensive, non-invasive measure of obesity that predicts the risk of related complications[5]. Identifying genetic determinants of BMI could lead to a better understanding of the biological basis of obesity.

Genome-wide association studies (GWAS) of BMI have previously identified ten loci with genome-wide significant ($P < 5 \times 10^{-8}$) associations[6–10] in or near *FTO*, *MC4R*, *TMEM18*, *GNPDA2*, *BDNF*, *NEGR1*, *SH2B1*, *ETV5*, *MTCH2* and *KCTD15*. Many of these genes are expressed or known to act in the central nervous system, highlighting a likely neuronal component in the predisposition to obesity[9]. This pattern is consistent with results in animal models and studies of monogenic human obesity in which neuronal genes, particularly those expressed in the hypothalamus and involved in regulation of appetite or energy balance, are known to play a major role in susceptibility to obesity[11–13].

The ten previously identified loci account for only a small fraction of the variation in BMI. Furthermore, power calculations based on the effect sizes of established variants have suggested that increasing the sample size would likely lead to the discovery of additional variants[9]. To identify additional loci associated with BMI, we expanded the Genetic Investigation of Anthropometric Traits (GIANT) Consortium genome-wide association meta-analysis to include a total of 249,796 individuals of European ancestry.

RESULTS

Stage 1 GWAS identifies new loci associated with BMI

We first conducted a meta-analysis of GWAS of BMI and ~2.8 million imputed or genotyped SNPs using data from 46 studies including up to 123,865 individuals (Online Methods, **Supplementary Fig. 1** and **Supplementary Note**). This stage 1 analysis revealed 19 loci associated with BMI at $P < 5 \times 10^{-8}$ (**Table 1**, **Fig. 1a** and **Supplementary Table 1**). These 19 loci included all ten loci from previous GWAS of BMI[6–10], two loci previously associated with body weight[10] (at *FAIM2* and *SEC16B*) and one locus previously associated with waist circumference[14] (near *TFAP2B*). The remaining six loci, near *GPRC5B*, *MAP2K5-LBXCOR1*, *TNNI3K*, *LRRN6C*, *FLJ35779-HMGCR* and *PRKD1*, have not previously been associated with BMI or other obesity-related traits.

Stage 2 follow up identifies additional new loci for BMI

To identify additional BMI-associated loci and to validate the loci that reached genome-wide significance in the stage 1 analyses, we examined SNPs representing 42 independent loci (including the 19 genome-wide significant loci) having a stage 1 $P < 5 \times 10^{-6}$. Variants were considered to be independent if the pair-wise linkage disequilibrium (LD, r^2) was less than 0.1 and if they were separated by at least 1 Mb. In stage 2, we examined these 42 SNPs in up to 125,931 additional individuals (79,561 newly genotyped individuals from 16 different studies and 46,370 individuals from 18 additional studies for which genome-wide association data were available; **Table 1**, **Supplementary Note** and Online Methods). In a joint analysis of stage 1 and stage 2 results, 32 of the 42 SNPs reached $P < 5 \times 10^{-8}$ (**Table 1**, **Supplementary Table 1** and **Supplementary Figs. 1** and **2**). Even after excluding SNPs within the 32 confirmed BMI loci, we still observed an excess of small *P* values compared to the distribution expected under the null hypothesis (**Fig. 1b** and **Supplementary Fig. 3**), suggesting that more BMI loci remain to be uncovered.

The 32 confirmed associations included all 19 loci with $P < 5 \times 10^{-8}$ at stage 1, 12 additional new loci near *RBJ-ADCY3-POMC*, *QPCTL-GIPR*, *SLC39A8*, *TMEM160*, *FANCL*, *CADM2*, *LRP1B*, *PTBP2*, *MTIF3-GTF3A*, *ZNF608*, *RPL27A-TUB* and *NUDT3-HMGA1* and one locus (in *NRXN3*) previously associated with waist circumference[15] (**Table 1**, **Supplementary Table 1** and **Supplementary Figs. 1** and **2**). In all, our study increased the number of loci robustly associated with BMI from 10 to 32. Four of the 22 new loci were previously associated

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with body weight[10] or waist circumference[14,15], whereas 18 new loci had not previously associated with any obesity-related trait in the general population. Although we confirmed all loci previously established by large-scale GWAS for BMI[6–10] and waist circumference[14,15], four loci previously identified in GWAS for early-onset or adult morbid obesity[16,17] (at *NPC1*, rs1805081, $P = 0.0025$; *MAF*, rs1424233, $P = 0.25$; *PTER*, rs10508503, $P = 0.64$; and *TNKS-MSRA*, rs473034, $P = 0.23$) showed limited or no evidence of association with BMI in our study.

Table 1 Stage 1 and stage 2 results of the 32 SNPs that were associated with BMI at genome-wide significant ($P < 5 \times 10^{-8}$) levels

SNP	Nearest gene	Other nearby genes[a]	Chr.	Position[b] (bp)	Alleles[b] Effect	Alleles[b] Other	Frequency effect allele	Per allele change in BMI β (s.e.m.)[c]	Explained variance (%)	Stage 1 *P*	Stage 2 *P*	Stage 1 + 2 *n*	Stage 1 + 2 *P*
Previously identified BMI loci													
rs1558902	*FTO*		16	52,361,075	A	T	0.42	0.39 (0.02)	0.34%	2.05×10^{-62}	1.01×10^{-60}	192,344	4.8×10^{-120}
rs2867125	*TMEM18*		2	612,827	C	T	0.83	0.31 (0.03)	0.15%	2.42×10^{-22}	4.42×10^{-30}	197,806	2.77×10^{-49}
rs571312	*MC4R* (B)		18	55,990,749	A	C	0.24	0.23 (0.03)	0.10%	1.82×10^{-22}	3.19×10^{-21}	203,600	6.43×10^{-42}
rs10938397	*GNPDA2*		4	44,877,284	G	A	0.43	0.18 (0.02)	0.08%	4.35×10^{-17}	1.45×10^{-15}	197,008	3.78×10^{-31}
rs10767664	*BDNF* (B,M)		11	27,682,562	A	T	0.78	0.19 (0.03)	0.07%	5.53×10^{-13}	1.17×10^{-14}	204,158	4.69×10^{-26}
rs2815752	*NEGR1* (C,Q)		1	72,585,028	A	G	0.61	0.13 (0.02)	0.04%	1.17×10^{-14}	2.29×10^{-9}	198,380	1.61×10^{-22}
rs7359397	*SH2B1* (Q,B,M)	*APOB48R* (Q,M), *SULT1A2* (Q,M), *AC138894.2* (M), *ATXN2L* (M), *TUFM* (Q)	16	28,793,160	T	C	0.40	0.15 (0.02)	0.05%	1.75×10^{-10}	7.89×10^{-12}	204,309	1.88×10^{-20}
rs9816226	*ETV5*		3	187,317,193	T	A	0.82	0.14 (0.03)	0.03%	7.61×10^{-14}	1.15×10^{-6}	196,221	1.69×10^{-18}
rs3817334	*MTCH2* (Q,M)	*NDUFS3* (Q), *CUGBP1* (Q)	11	47,607,569	T	C	0.41	0.06 (0.02)	0.01%	4.79×10^{-11}	1.10×10^{-3}	191,943	1.59×10^{-12}
rs29941	*KCTD15*		19	39,001,372	G	A	0.67	0.06 (0.02)	0.00%	1.31×10^{-9}	2.40×10^{-2}	192,872	3.01×10^{-9}
Previously identified waist and weight loci													
rs543874	*SEC16B*		1	176,156,103	G	A	0.19	0.22 (0.03)	0.07%	1.66×10^{-13}	2.41×10^{-11}	179,414	3.56×10^{-23}
rs987237	*TFAP2B*		6	50,911,009	G	A	0.18	0.13 (0.03)	0.03%	5.97×10^{-16}	2.40×10^{-6}	195,776	2.90×10^{-20}
rs7138803	*FAIM2*		12	48,533,735	A	G	0.38	0.12 (0.02)	0.04%	3.96×10^{-11}	7.82×10^{-8}	200,064	1.82×10^{-17}
rs10150332	*NRXN3*		14	79,006,717	C	T	0.21	0.13 (0.03)	0.02%	2.03×10^{-7}	2.86×10^{-5}	183,022	2.75×10^{-11}
Newly identified BMI loci													
rs713586	*RBJ*	*ADCY3* (Q, M), *POMC* (Q,B)	2	25,011,512	C	T	0.47	0.14 (0.02)	0.06%	1.80×10^{-7}	1.44×10^{-16}	230,748	6.17×10^{-22}
rs12444979	*GPRC5B* (C,Q)	*IQCK* (Q)	16	19,841,101	C	T	0.87	0.17 (0.03)	0.04%	4.20×10^{-11}	8.13×10^{-12}	239,715	2.91×10^{-21}
rs2241423	*MAP2K5*	*LBXCOR1* (M)	15	65,873,892	G	A	0.78	0.13 (0.02)	0.03%	1.15×10^{-10}	1.59×10^{-9}	227,950	1.19×10^{-18}
rs2287019	*QPCTL*	*GIPR* (B,M)	19	50,894,012	C	T	0.80	0.15 (0.03)	0.04%	3.18×10^{-7}	1.40×10^{-10}	194,564	1.88×10^{-16}
rs1514175	*TNNI3K*		1	74,764,232	A	G	0.43	0.07 (0.02)	0.02%	1.36×10^{-9}	7.04×10^{-6}	227,900	8.16×10^{-14}
rs13107325	*SLC39A8* (Q,M)		4	103,407,732	T	C	0.07	0.19 (0.04)	0.03%	1.37×10^{-7}	1.93×10^{-7}	245,378	1.50×10^{-13}
rs2112347	*FLJ35779* (M)	*HMGCR* (B)	5	75,050,998	T	G	0.63	0.10 (0.02)	0.02%	4.76×10^{-8}	8.29×10^{-7}	231,729	2.17×10^{-13}
rs10968576	*LRRN6C*		9	28,404,339	G	A	0.31	0.11 (0.02)	0.02%	1.88×10^{-8}	3.19×10^{-6}	216,916	2.65×10^{-13}
rs3810291	*TMEM160* (Q)	*ZC3H4* (Q)	19	52,260,843	A	G	0.67	0.09 (0.02)	0.02%	1.04×10^{-7}	1.59×10^{-6}	233,512	1.64×10^{-12}
rs887912	*FANCL*		2	59,156,381	T	C	0.29	0.10 (0.02)	0.03%	2.69×10^{-6}	1.72×10^{-7}	242,807	1.79×10^{-12}
rs13078807	*CADM2*		3	85,966,840	G	A	0.20	0.10 (0.02)	0.02%	9.81×10^{-8}	5.32×10^{-5}	237,404	3.94×10^{-11}
rs11847697	*PRKD1*		14	29,584,863	T	C	0.04	0.17 (0.05)	0.01%	1.11×10^{-8}	2.25×10^{-4}	241,667	5.76×10^{-11}
rs2890652	*LRP1B*		2	142,676,401	C	T	0.18	0.09 (0.03)	0.02%	2.38×10^{-7}	9.47×10^{-5}	209,068	1.35×10^{-10}
rs1555543	*PTBP2*		1	96,717,385	C	A	0.59	0.06 (0.02)	0.01%	7.65×10^{-7}	4.48×10^{-5}	243,013	3.68×10^{-10}
rs4771122	*MTIF3*	*GTF3A* (Q)	13	26,918,180	G	A	0.24	0.09 (0.03)	0.02%	1.20×10^{-7}	8.24×10^{-4}	198,577	9.48×10^{-10}
rs4836133	*ZNF608*		5	124,360,002	A	C	0.48	0.07 (0.02)	0.01%	7.04×10^{-7}	1.88×10^{-4}	241,999	1.97×10^{-9}
rs4929949	*RPL27A*	*TUB* (B)	11	8,561,169	C	T	0.52	0.06 (0.02)	0.01%	7.57×10^{-8}	1.00×10^{-3}	249,791	2.80×10^{-9}
rs206936	*NUDT3*	*HMGA1* (B)	6	34,410,847	G	A	0.21	0.06 (0.02)	0.01%	2.81×10^{-6}	7.39×10^{-4}	249,777	3.02×10^{-8}

Chr., chromosome; Q, association and eQTL data converge to affect gene expression; B, biological candidate; M, BMI-associated variant is in strong LD ($r^2 \geq 0.75$) with a missense variant in the indicated gene; C, CNV.
[a]Genes within ± 500 kb of the lead SNP. [b]Positions according to Build 36 and allele coding based on the positive strand. [c]Effect sizes in kg/m^2 obtained from stage 2 cohorts only.

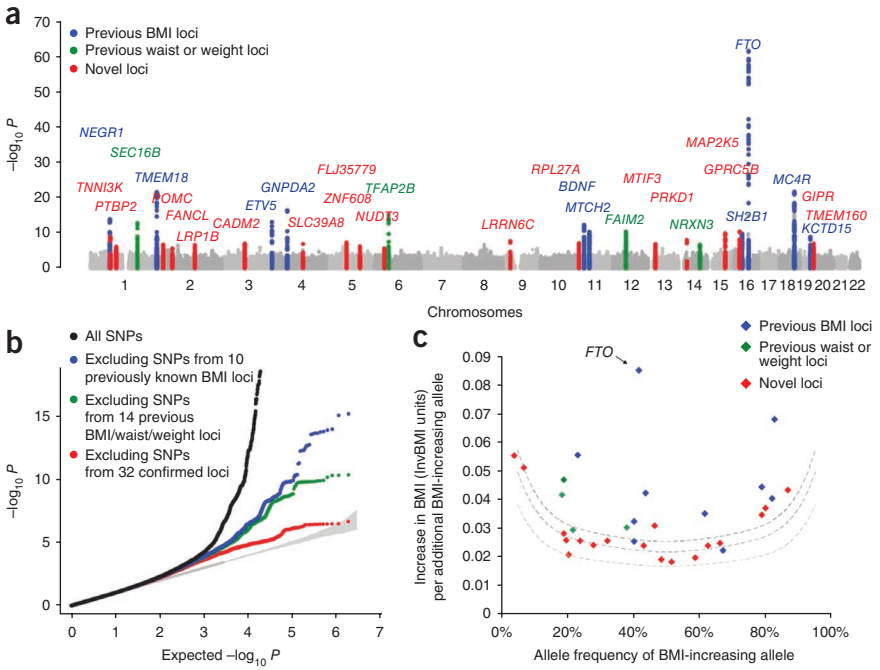

Figure 1 Genome-wide association results for the BMI meta-analysis. (**a**) Manhattan plot showing the significance of association between all SNPs and BMI in the stage 1 meta-analysis, highlighting SNPs previously reported to show genome-wide significant association with BMI (blue), weight or waist circumference (green) and the 18 new regions described here (red). The 19 SNPs that reached genome-wide significance in stage 1 (13 previously reported and 6 new SNPs) are listed in **Table 1**. (**b**) Quantile-quantile plot of SNPs in the stage 1 meta-analysis (black) and after removing any SNPs within 1 Mb of the ten previously reported genome-wide significant hits for BMI (blue), after additionally excluding SNPs from the four loci for waist or weight (green), and after excluding SNPs from all 32 confirmed loci (red). The plot is abridged at the *y* axis (at $P < 10^{-20}$) to better visualize the excess of small *P* values after excluding the 32 confirmed loci (**Supplementary Fig. 3** shows the full-scale quantile-quantile plot). The shaded region is the 95% concentration band. (**c**) Plot of effect size (in inverse-normally transformed units (invBMI)) versus effect-allele frequency of newly identified and previously identified BMI variants after stage 1 and stage 2 meta-analysis, including the 10 previously identified BMI loci (blue), the 4 previously identified waist and weight loci (green) and the 18 newly identified BMI loci (blue). The dotted lines represent the minimum effect sizes that could be identified for a given effect-allele frequency with 80% (upper line), 50% (middle line) and 10% (lower line) power, assuming a sample size of 123,000 individuals and an α level of 5×10^{-8}.

As could be expected, the effect sizes of the 18 newly discovered loci are slightly smaller, for a given minor allele frequency, than those of the previously identified variants (**Table 1** and **Fig. 1c**). The increased sample size used here also brought out more signals with low minor allele frequency. The BMI-increasing allele frequencies for the 18 newly identified variants ranged from 4% to 87%, covering more of the allele frequency spectrum than previous, smaller GWAS of BMI (24%–83%)[9,10] (**Table 1** and **Fig. 1c**).

We tested for evidence of non-additive (dominant or recessive) effects, SNP × SNP interaction effects and heterogeneity by sex or study among the 32 BMI-associated SNPs (Online Methods). We found no evidence for any such effects (all $P > 0.001$ and no significant results were seen after correcting for multiple testing) (**Supplementary Table 1** and **Supplementary Note**).

Impact of the 32 confirmed loci on BMI, obesity, body size and other metabolic traits

Together, the 32 confirmed BMI loci explained 1.45% of the inter-individual variation in BMI in the stage 2 samples, with the *FTO* SNP accounting for the largest proportion of the variance (0.34%) (**Table 1**). To estimate the cumulative effect of the 32 variants on BMI, we constructed a genetic susceptibility score that summed the number of BMI-increasing alleles weighted by the overall stage 2 effect sizes in the Atherosclerosis Risk in Communities (ARIC) study (n = 8,120), one of our largest population-based studies (Online Methods). For each unit increase in the genetic-susceptibility score, which is approximately equivalent to having one additional risk allele, BMI increased by 0.17 kg/m^2, the equivalent of a 435–551 g gain in body weight in adults of 160–180 cm in height. The difference in average BMI between individuals with a high genetic-susceptibility score (defined as having ≥38 BMI-increasing alleles, comprising 1.5% (n = 124) of the ARIC sample) and those with a low genetic-susceptibility score (defined as having ≤21 BMI-increasing alleles, comprising 2.2% (n = 175) of the ARIC sample) was 2.73 kg/m^2, equivalent to a 6.99–8.85 kg body weight difference in adults of 160–180 cm in height (**Fig. 2a**). Still, we note that the predictive value for obesity risk and BMI of the 32 variants combined was modest, although it was statistically significant (**Fig. 2b** and **Supplementary Fig. 4**). The area under the receiver-operating characteristic (ROC) curve for prediction of risk of obesity (BMI ≥ 30 kg/m^2) using a model including age, age^2 and sex only was 0.515 (P = 0.023 compared to the area under the curve (AUC) of 0.50), which increased to 0.575 ($P < 10^{-5}$) when the 32 confirmed SNPs were also included in the model (**Fig. 2b**). The area under the ROC curve for the model including the 32 SNPs only was 0.574 ($P < 10^{-5}$).

All 32 confirmed BMI-increasing alleles showed directionally consistent effects on the risk of being overweight (BMI ≥ 25 kg/m^2) or obese (BMI ≥ 30 kg/m^2) in the stage 2 samples, with 30 of 32 variants achieving at least nominally significant associations. The BMI-increasing alleles increased the odds of being overweight by 1.013- to 1.138-fold and the odds of being obese by 1.016- to 1.203-fold (**Supplementary Table 2**). In addition, 30 of the 32 loci also showed directionally consistent effects on the risk of extreme and early-onset obesity in a meta-analysis of seven case-control studies of adults and children (binomial sign test $P = 1.3 \times 10^{-7}$) (**Supplementary Table 3**). The BMI-increasing allele observed in adults also increased the BMI in children and adolescents with directionally consistent effects observed for 23 of the 32 SNPs (binomial sign test P = 0.01). Furthermore, in family-based studies, the BMI-increasing allele was over-transmitted to the obese offspring for 24 of the 32 SNPs (binomial sign test P = 0.004) (**Supplementary Table 3**). As these studies in extreme obesity cases, children and families were relatively small (with n ranging from 354 to 15,251 individuals) compared to the overall meta-analyses, their power was likely insufficient to confirm association for all 32 loci. Nevertheless, these results show that the effects are unlikely to reflect population stratification and that they extend to BMI differences throughout the life course.

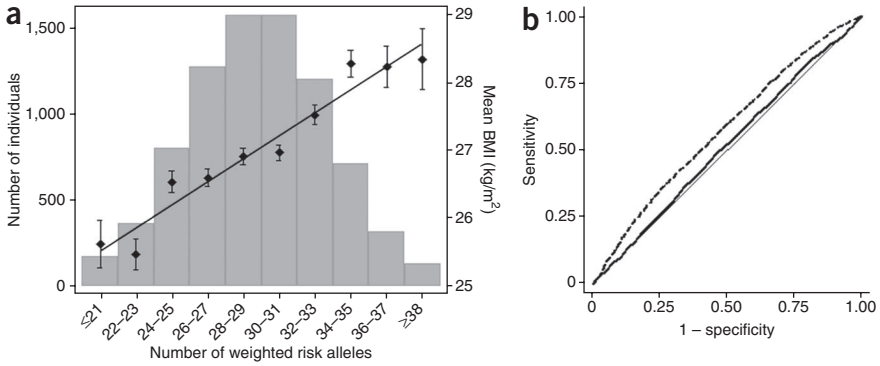

Figure 2 Combined impact of risk alleles on BMI and obesity. (**a**) Combined effect of risk alleles on average BMI in the population-based ARIC study ($n = 8,120$ individuals of European descent). For each individual, the number of 'best guess' replicated ($n = 32$) risk alleles from imputed data (0, 1 or 2) per SNP was weighted for its relative effect size estimated from the stage 2 data. Weighted risk alleles were summed for each individual, and the overall individual sum was rounded to the nearest integer to represent the individual's risk allele score (ranging from 16 to 44). Along the *x* axis, individuals in each risk allele category are shown (grouped as having ≤21 risk alleles and ≥38 risk alleles at the extremes), and the mean BMI (± s.e.m.) is plotted (*y* axis on right), with the line representing the regression of the mean BMI values across the risk-allele scores. The histogram (*y* axis on left) represents the number of individuals in each risk-score category. (**b**) The area under the ROC curve (AUC) of two different models predicting the risk of obesity (BMI ≥ 30 kg/m^2) in the 8,120 genotyped individuals of European descent in the ARIC study. Model 1, represented by the solid line, includes age, age^2 and sex (AUC = 0.515, $P = 0.023$ for difference from the null AUC = 0.50). Model 2, represented by the dashed line, includes age, age^2, sex and the 32 confirmed BMI SNPs (AUC = 0.575, $P < 10^{-5}$ for difference from the null AUC = 0.50). The difference between both AUCs is significant ($P < 10^{-4}$).

All BMI-increasing alleles were associated with increased body weight, as could be expected from the correlation between BMI and body weight (**Supplementary Table 2**). To confirm an effect of the loci on adiposity rather than general body size, we tested for association with body fat percentage, for which data was available in a subset of the stage 2 replication samples ($n = 5,359$ to $n = 28,425$) (**Supplementary Table 2**). The BMI-increasing allele showed directionally consistent effects on body fat percentage at 31 of the 32 confirmed loci (binomial sign test $P = 1.54 \times 10^{-8}$) (**Supplementary Table 2**).

We also examined the association of the BMI loci with metabolic traits (type 2 diabetes[18], fasting glucose, fasting insulin, indices of β-cell function (HOMA-B) and insulin resistance (HOMA-IR)[19], and blood lipid levels[20]) and with height (**Supplementary Tables 2** and **4**). Although many nominal associations were expected because of known correlations between BMI and most of these traits, and because of overlap in samples, several associations stood out as possible examples of pleiotropic effects of the BMI-associated variants. Particularly interesting is the variant in the *GIPR* locus, where the BMI-increasing allele is also associated with increased fasting glucose levels and lower 2-h glucose levels (**Supplementary Table 4**)[19,21]. The direction of the effect is opposite to what would be expected due to the correlation between obesity and glucose intolerance but is consistent with the suggested roles of *GIPR* in glucose and energy metabolism (see below)[22]. Three loci showed strong associations ($P < 10^{-4}$) with height (at *MC4R*, *RBJ-ADCY3-POMC* and *MTCH2-NDUFS3*). Because BMI is weakly correlated with height (and indeed, the BMI-associated variants as a group show no consistent effect on height), these associations are also suggestive of pleiotropy. Notably, analogous to the effects of severe mutations in *POMC* and *MC4R* on height and weight[23,24], the BMI-increasing alleles of the variants near these genes were associated with decreased (*POMC*) and increased (*MC4R*) height, respectively (**Supplementary Table 2**).

Potential functional roles and pathway analyses

Although associated variants typically implicate genomic regions rather than individual genes, we note that some of the 32 loci include candidate genes with established connections to obesity. Several of the ten previously identified loci are located in or near genes that encode neuronal regulators of appetite or energy balance, including *MC4R*[12,25], *BDNF*[26] and *SH2B1*[11,27]. Each of these genes has been tied to obesity, not only in animal models, but also by rare human variants that disrupt each of these genes and lead to severe obesity[24,28,29]. Using the automated literature search program Snipper (Online Methods), we identified various genes within the newly discovered loci with potential biological links to obesity susceptibility (**Supplementary Note**). Among the new loci, the location of rs713586 near *POMC* provides further support for a role of neuroendocrine circuits that regulate energy balance in susceptibility to obesity. *POMC* encodes several polypeptides, including α-MSH, a ligand of the *MC4R* gene product[30], and rare mutations in *POMC* also cause obesity in humans[23,29,31].

In contrast, the locus near *GIPR*, which encodes a receptor of gastric inhibitory polypeptide (GIP), suggests a role for peripheral biology in obesity. GIP, which is expressed in the K cell of the duodenum and intestine, is an incretin hormone that mediates incremental insulin secretion in response to oral intake of glucose. The variant associated with BMI is in strong LD ($r^2 = 0.83$) with a missense SNP in *GIPR* (rs1800437, p.Glu354Gln) that has recently been shown to influence glucose and insulin response to an oral glucose challenge[21]. Although no human phenotype is known to be caused by mutations in *GIPR*, mice with disruption of *Gipr* are resistant to diet-induced obesity[32]. The association of a variant in *GIPR* with BMI suggests that there may be a link between incretins, insulin secretion and body weight regulation in humans as well.

To systematically identify biological connections among the genes located near the 32 confirmed SNPs and to potentially identify new pathways associated with BMI, we performed pathway-based analyses using MAGENTA[33]. Specifically, we tested for enrichment of genetic associations to BMI in biological processes or molecular functions that contain at least one gene from the 32 confirmed BMI loci (Online Methods). Using annotations from the Kyoto Encyclopedia of Genes and Genomes (KEGG), Ingenuity, Protein Analysis Through Evolutionary Relationships (PANTHER) and Gene Ontology databases, we found evidence of enrichment for pathways involved in platelet-derived growth factor (PDGF) signaling (PANTHER, $P = 0.0008$, false discovery rate (FDR) = 0.0061), translation elongation (PANTHER, $P = 0.0008$, FDR = 0.0066), hormone or nuclear-hormone receptor binding (Gene Ontology, $P < 0.0005$, FDR < 0.0085), homeobox transcription (PANTHER, $P = 0.0001$, FDR = 0.011), regulation of cellular metabolism (Gene Ontology, $P = 0.0002$, FDR = 0.031), neurogenesis and neuron differentiation (Gene Ontology, $P < 0.0002$, FDR < 0.034), protein phosphorylation (PANTHER, $P = 0.0001$, FDR = 0.045)

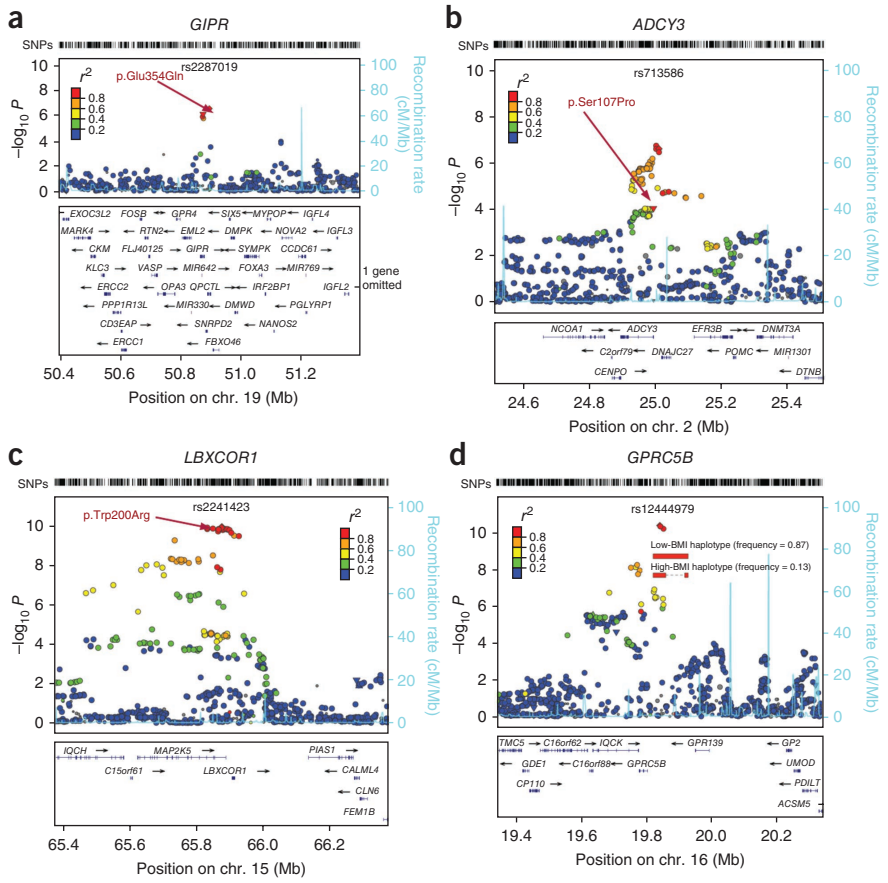

Figure 3 Regional plots of selected replicating BMI loci with missense and CNV variants. SNPs are plotted by position on the chromosome against association with BMI ($-\log_{10} P$). The SNP name shown on the plot was the most significant SNP after the stage 1 meta-analysis. Estimated recombination rates (from HapMap) are plotted in cyan to reflect the local LD structure. The SNPs surrounding the most significant SNP are color coded to reflect their LD with this SNP (taken from pairwise r^2 values from the HapMap CEU data). Genes, the position of exons and the direction of transcription from the UCSC genome browser are noted. Hashmarks represent SNP positions available in the meta-analysis. (**a**–**c**) Missense variants noted with their amino acid change for the gene listed above the plot. (**d**) Structural haplotypes and the BMI association signal in the *GPRC5B* region. A 21-kb deletion polymorphism was associated with four SNPs ($r^2 = 1.0$) that comprise the best haplogroup associating with BMI. Plots were generated using LocusZoom (see URLs).

and numerous other pathways related to growth, metabolism, immune and neuronal processes (Gene Ontology, $P < 0.002$, FDR < 0.046) (**Supplementary Table 5**).

Identifying possible functional variants

We used data from the 1000 Genomes Project and the HapMap Consortium to explore whether the 32 confirmed BMI SNPs were in LD ($r^2 \geq 0.75$) with common missense SNPs or copy number variants (CNVs) (Online Methods). Non-synonymous variants in LD with our signals were present in *BDNF*, *SLC39A8*, *FLJ35779-HMGCR*, *QPCTL-GIPR*, *MTCH2*, *ADCY3* and *LBXCOR1*. In addition, the rs7359397 signal was in LD with coding variants in several genes including *SH2B1*, *ATNX2L*, *APOB48R*, *SULT1A2* and *AC138894.2* (**Table 1**, **Fig. 3**, **Supplementary Table 6** and **Supplementary Fig. 2**). Furthermore, two SNPs tagged common CNVs. The first CNV has been previously identified[9] and is a 45-kb deletion near *NEGR1*. The second CNV is a 21-kb deletion that lies 50 kb upstream of *GPRC5B*; the deletion allele is tagged by the T allele of rs12444979 ($r^2 = 1$) (**Fig. 3**). Although the correlations with potentially functional variants do not prove that these variants are indeed causal, they provide first clues as to which genes and variants at these loci might be prioritized for fine mapping and functional follow up.

Because many of the 32 BMI loci harbor multiple genes, we examined whether gene expression quantitative trait loci (eQTL) analyses could also direct us to positional candidates. Gene expression data were available for human brain, lymphocyte, blood, subcutaneous and visceral adipose tissue, and liver[34–36] (Online Methods, **Table 1** and **Supplementary Table 7**). Significant *cis* associations, defined at the tissue-specific level, were observed between 14 BMI-associated alleles and expression levels (**Table 1** and **Supplementary Table 7**). In several instances, the BMI-associated SNP was the most significant SNP or explained a substantial proportion of the association with the most significant SNP for the gene transcript in conditional analyses (adjusted $P > 0.05$). These significant associations included *NEGR1*, *ZC3H4*, *TMEM160*, *MTCH2*, *NDUFS3*, *GTF3A*, *ADCY3*, *APOB48R*, *SH2B1*, *TUFM*, *GPRC5B*, *IQCK*, *SLC39A8*, *SULT1A1* and *SULT1A2* (**Table 1** and **Supplementary Table 7**), making these genes higher priority candidates within the associated loci. However, we note that some BMI-associated variants were correlated with the expression of multiple nearby genes, making it difficult to determine the most relevant gene.

Evidence for the existence of additional associated variants

Because the variants identified by this large study explain only 1.45% of the variance in BMI (2%–4% of genetic variance based on an estimated heritability of 40%–70%), we considered how much the explained phenotypic variance could be increased by including more SNPs at various degrees of significance in a polygene model using an independent validation set (Online Methods)[37]. We found that including SNPs associated with BMI at lower significance levels (up to $P > 0.05$) increased the explained phenotypic variance in BMI to 2.5%, or 4%–6% of the genetic variance (**Fig. 4a**). In a separate analysis, we estimated the total number of independent BMI-associated variants that are likely to exist with similar effect sizes as the 32 confirmed here (Online Methods)[38]. Based on the effect size and allele frequencies of the 32 replicated loci observed in stage 2 and the power to detect association in stage 1 and stage 2 combined, we estimated that there are 284 (95% CI 132–510) loci with similar effect sizes as those currently observed, which together would account for 4.5% (95% CI 3.1%–6.8%) of the phenotypic variation or 6%–11% of the genetic variation in BMI (based on an estimated heritability of 40%–70%) (**Supplementary Table 8**). In order to detect 95% of these loci, a sample size of approximately 730,000 subjects would be needed (**Fig. 4b**). This method does not account for the potential of loci of smaller effect than those identified here to explain even more of the variance and thus provides an estimated lower bound of explained variance. These two analyses strongly suggest that larger GWAS will

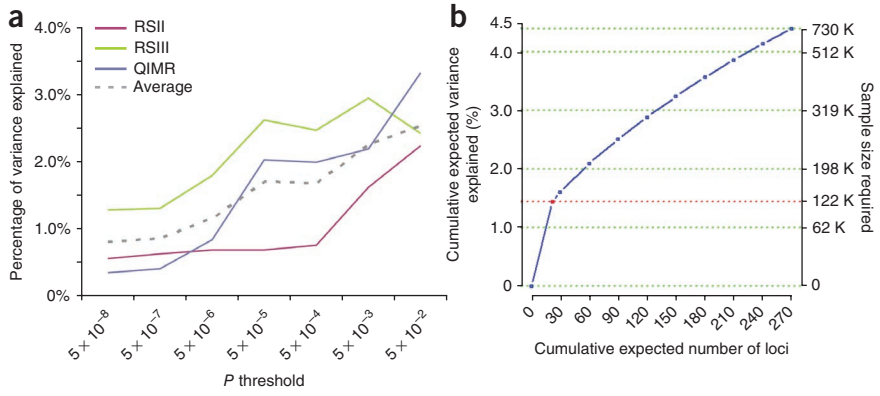

Figure 4 Phenotypic variance explained by common variants. (**a**) The variance explained is higher when SNPs not reaching genome-wide significance are included in the prediction model. The *y* axis represents the proportion of variance explained at different *P* value thresholds from the stage 1 meta-analysis. Results are given for three studies (Rotterdam Study II (RSII), Rotterdam Study III (RSIII), Queens Institute of Medical Research (QIMR)) which were not included in the meta-analysis, after exclusion of all samples from The Netherlands (for RSII and RSIII) and the United Kingdom (for QIMR) from the discovery analysis for this sub-analysis. The dotted line represents the weighted average of the explained variance of three validation sets. (**b**) Cumulative number of susceptibility loci expected to be discovered, including those we have already identified and others that have yet to be detected, by the expected percentage of phenotypic variation explained and the sample size required for a one-stage GWAS assuming a genomic control correction is used. The projections are based on loci that achieved a significance level of $P < 5 \times 10^{-8}$ in the joint analysis of stage 1 and stage 2 and the distribution of their effect sizes in stage 2. The dotted red line corresponds to the expected phenotypic variance explained by the 22 loci that are expected to be discovered in a one-stage GWAS using the sample size of stage 1 of this study.

continue to identify additional new associated loci but also indicate that even extremely large studies focusing on variants with allele frequencies above 5% will not account for a large fraction of the genetic contribution to BMI.

We examined whether selecting only a single variant from each locus for follow up led us to underestimate the fraction of phenotypic variation explained by the associated loci. To search for additional independent loci at each of the 32 associated BMI loci, we repeated our genome-wide association meta-analysis conditioning on the 32 confirmed SNPs. Using a significance threshold of $P = 5 \times 10^{-6}$ for SNPs at known loci, we identified one apparently independent signal at the *MC4R* locus; rs7227255 was associated with BMI ($P = 6.56 \times 10^{-7}$) even after conditioning for the most strongly associated variant near *MC4R* (rs571312) (**Fig. 5**). Notably, rs7227255 is in perfect LD ($r^2 = 1$) with a relatively rare *MC4R* missense variant (rs2229616, p.Val103Ile, minor allele frequency = 1.7%) that has been associated with BMI in two independent meta-analyses[39,40]. Furthermore, mutations at the *MC4R* locus are known to influence early-onset obesity[24,41], supporting the notion that allelic heterogeneity may be a frequent phenomenon in the genetic architecture of obesity.

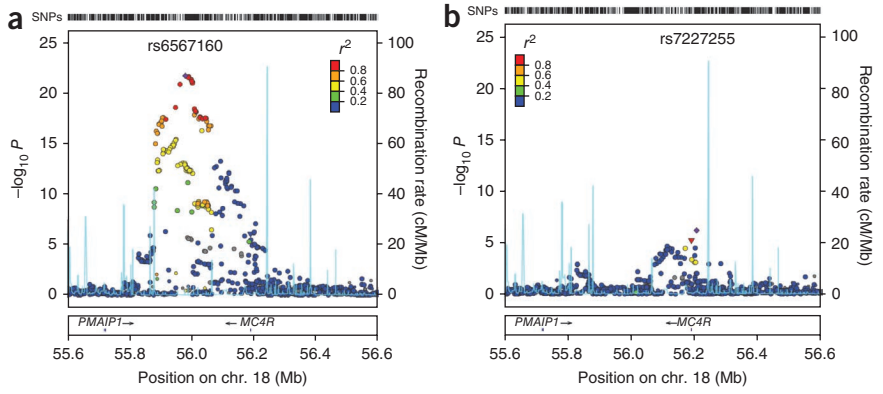

Figure 5 A second signal at the *MC4R* locus contributing to BMI. SNPs are plotted by position in a 1-Mb window of chromosome 18 against association with BMI ($-\log_{10} P$). (**a**) Plot highlighting the most significant SNP in the stage 1 meta-analysis. (**b**) Plot highlighting the most significant SNP after conditional analysis, where the model included the most strongly associated SNP as a covariate. Estimated recombination rates (from HapMap) are plotted in cyan to reflect the local LD structure. The SNPs surrounding the most significant SNP are color coded to reflect their LD with this SNP (taken from pairwise r^2 values from the HapMap CEU database). Genes, exons and the direction of transcription from the UCSC genome browser are noted. Hashmarks at the top of the figure represent the positions of SNPs in the meta-analysis. Regional plots were generated using LocusZoom.

DISCUSSION

Using a two-stage genome-wide association meta-analysis of up to 249,796 individuals of European descent, we identified 18 additional loci that are associated with BMI at genome-wide significance, bringing the total number of such loci to 32. We estimate that more than 250 common variant loci (that is, 284 predicted loci minus 32 confirmed loci) with effects on BMI similar to those described here remain to be discovered and that even larger numbers of loci with smaller effects remain to be identified. A substantial proportion of these loci should be identifiable through larger GWAS and/or by targeted follow up of the top signals selected from our stage 1 analysis. The latter approach is already being implemented through large-scale genotyping of samples informative for BMI using a custom array (the Metabochip) designed to support follow up of thousands of promising variants in hundreds of thousands of individuals.

The combined effect on BMI of the associated variants at the 32 loci is modest, and even when we try to account for as yet undiscovered variants with similar properties, we estimate that these common variant signals account for only 6%–11% of the genetic variation in BMI. There is a strong expectation that additional variance and biology will be explained using complementary approaches that capture variants not examined in the current study, such as lower frequency variants and short insertion-deletion polymorphisms. There is good reason to believe (based on our findings at *MC4R* and other loci, such as those at *POMC*, *BDNF* and *SH2B1*, which feature both common and rare variant associations) that a proportion of such low-frequency and rare causal variation will map to the loci already identified by GWAS.

A primary goal of human genetic discovery is to improve understanding of the biology

of conditions such as obesity[42]. One particularly noteworthy finding in this regard is the association between BMI and common variants near *GIPR*, which may indicate a causal contribution of variation in postprandial insulin secretion in the development of obesity. In most instances, the loci identified by the present study harbor few, if any, annotated genes with clear connections to the biology of weight regulation. This reflects our still limited understanding of the biology of BMI and obesity-related traits and is in striking contrast with the results from equivalent studies of certain other traits (such as autoimmune diseases or lipid levels). Thus, these results suggest that much of the biology that underlies obesity remains to be uncovered and that GWAS may provide an important entry point for investigation. In particular, further examination of the associated loci through a combination of resequencing and fine mapping to find causal variants and genomic and experimental studies designed to assign function could uncover new insights into the biology of obesity.

In conclusion, we performed GWAS in large samples to identify numerous genetic loci associated with variation in BMI, a common measure of obesity. Because current lifestyle interventions are largely ineffective in addressing the challenges of growing obesity[43,44], new insights into the biology of obesity are critically needed to guide the development and application of future therapies and interventions.

URLs. LocusZoom, http://csg.sph.umich.edu/locuszoom; METAL, http://www.sph.umich.edu/csg/abecasis/Metal/.

METHODS

Methods and any associated references are available in the online version of the paper at http://www.nature.com/naturegenetics/.

Note: Supplementary information is available on the Nature Genetics website.

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A full list of author contributions appears in the **Supplementary Note**.

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The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturegenetics/.

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ONLINE METHODS

Study design. We designed a multistage study (**Supplementary Fig. 1**) comprising a genome-wide association meta-analysis (stage 1) of data on up to 123,865 genotyped individuals from 46 studies and selected 42 SNPs with $P < 5 \times 10^{-6}$ for follow up in stage 2. Stage 2 comprised up to 125,931 additional genotyped individuals from 42 studies. Meta-analysis of stage 1 and stage 2 summary statistics identified 32 SNPs that reached genome-wide significance ($P < 5 \times 10^{-8}$).

Stage 1 genome-wide association meta-analysis. *Samples and genotyping.* The GIANT consortium currently encompasses 46 studies with up to 123,865 genotyped adult individuals of European ancestry with data on BMI (**Supplementary Note**). The samples from 46 studies, including between 276 and 26,799 individuals each, were genotyped using Affymetrix and Illumina whole genome genotyping arrays (**Supplementary Note**). To allow for meta-analysis across different marker sets, imputation of polymorphic HapMap European CEU SNPs (**Supplementary Note**) was performed using MACH[45], IMPUTE[46] or BimBam[47].

Association analysis with BMI. Each study performed single marker association analyses with BMI using an additive genetic model implemented in MACH2QTL (Y. Li, C.J.W., P.S. Ding and G.R.A., unpublished data), Merlin[48], SNPTEST[46], ProbAbel[49], GenABEL[50], LME in R or PLINK[51]. BMI was adjusted for age, age^2 and other appropriate covariates (for example, principal components) and inverse normally transformed to a mean of 0 and a standard deviation of 1. Analyses were stratified by sex and case status (for samples ascertained for other diseases) (**Supplementary Note**). To allow for relatedness in the SardiNIA, Framingham Heart, Amish HAPI Heart and Family Heart studies, regression coefficients were estimated in the context of a variance component model that modeled relatedness in men and women combined with sex as a covariate. Before meta-analyzing the genome-wide association data for the 46 studies, SNPs with poor imputation quality scores (r^2.hat < 0.3 in MACH, observed/expected dosage variance < 0.3 in BimBam or proper_info < 0.4 in IMPUTE) and those with a minor allele count (MAC = $2 \times N \times$ minor allele frequency) of < 6 in each sex- and case-specific stratum were excluded for each study. All individual GWAS were genomic control corrected before meta-analysis. Individual study-specific genomic control values ranged from 0.983 to 1.104 (**Supplementary Note**).

Meta-analysis of stage 1 association results. Next, we performed the stage 1 meta-analysis using the inverse variance method, which is based on β values and standard errors from each individual GWAS. To ensure consistency of results, we also performed the stage 1 meta-analysis using the weighted *z*-score method, which is based on the direction of association and *P* values of each of the individual studies. Both meta-analyses were performed using METAL (see URLs), and the correlation between the resulting $-\log_{10} P$ values was high ($r >$ 0.99). For the discovery of replicating variants, the results of the inverse variance meta-analysis were used followed by a final genomic control correction of the meta-analyzed results. The genomic control value for the meta-analyzed results before genomic control correction was 1.318.

Selection of SNPs for follow up. Forty-two lead SNPs, representing the forty-two most significant ($P < 5 \times 10^{-6}$) independent loci, were selected for replication analyses (stage 2) (**Supplementary Table 1**). Loci were considered independent when separated by at least 1 Mb. For some loci, the SNP with the strongest association could not be genotyped for technical reasons and was substituted by a proxy SNP that was in high LD with it ($r^2 > 0.8$) according to the HapMap CEU data (**Supplementary Table 1**). We tested the association of these 42 SNPs in 16 *de novo* and 18 *in silico* replication studies in stage 2.

Stage 2 follow up. *Samples and genotyping.* Directly genotyped data for the 42 SNPs was available from a total of 79,561 adults of European ancestry from 16 studies using Sequenom iPLEX or TaqMan assays (**Supplementary Note**). Samples and SNPs that did not meet the quality control criteria defined by each individual study were excluded. Minimum genotyping quality control criteria were defined as Hardy-Weinberg Equilibrium $P > 10^{-6}$, call rate > 90% and concordance > 99% in duplicate samples in each of the follow-up studies. Association results were also obtained for the 42 most significant SNPs from 46,370 individuals of European ancestry from 18 GWAS that had not been included in the stage 1 analyses (**Supplementary Note**). Studies included between 345 and 22,888 individuals and were genotyped using Affymetrix and Illumina genome-wide genotyping arrays. Autosomal HapMap SNPs were imputed using either MACH[45] or IMPUTE[46]. SNPs with poor imputation quality scores from the *in silico* studies (r^2.hat < 0.3 in MACH or proper_info < 0.4 in IMPUTE), and SNPs with a MAC < 6 in each sex- and case-specific stratum were excluded.

Association analyses and meta-analysis. We tested the association between the 42 SNPs and BMI in each *in silico* and *de novo* stage 2 study separately as described for the stage 1 studies. We subsequently meta-analyzed β values and standard errors from the stage 2 studies using the inverse-variance method. The meta-analysis using a weighted *z*-score method was similar (the *r* between *P* values was >0.99) and included up to 249,796 individuals. Data was available for at least 179,000 individuals for 41 of the 42 SNPs. For one SNP (rs6955651 in *KIAA1505*), data was only available for 125,672 individuals due to technical challenges relating to the genotyping and imputation of this SNP. Next, we meta-analyzed the summary statistics of the stage 1 and stage 2 meta-analyses using the inverse-variance method in METAL.

Assessment of population stratification. To assess for possible inflation of test statistics by population stratification, we performed a family-based analysis, which is immune to stratification, in 5,507 individuals with pedigree information from the Framingham Heart Study using that the QFAM–within procedure in PLINK. Effect sizes and directions in the Framingham Heart Study data are the β statistics reported by PLINK from the within-family analysis, and the *P* values are empirical and are based on permutation testing. For imputed SNPs, only those with r^2.hat > 0.3 in MACH were analyzed using the best-guess genotypes from dosages reported by MACH. For the 32 loci in general and the 18 new loci in particular, the estimated effect sizes on BMI were essentially identical in the overall meta-analysis and in the Framingham Heart Study sample (**Supplementary Note**), and, as expected in the absence of substantial stratification, about half of the loci (18 out of 32 loci total and 10 out of 18 new loci) had a larger effect size in the family-based sample. These results indicate that the genome-wide significant associations in our meta-analysis are not substantially confounded by stratification.

In addition, we estimated the fixation index (Fst) for all SNPs to test whether the 32 confirmed BMI SNPs might be false-positive results due to population stratification. We selected five diverse European populations with relatively large sample sizes (Northern Finland Birth Cohort (NFBC), British 1958 Birth Cohort, SardiNIA, CoLaus and DeCODE) for this analysis. The mean Fst value for the 32 confirmed BMI SNPs was not significantly different from the mean Fst for 2.1 million non-BMI associated SNPs (*t* test $P = 0.28$), suggesting that the SNPs that are associated with BMI do not appear to have strong allele frequency differences across the European samples examined.

Follow-up analyses. Subsequently, we performed an extensive series of follow-up analyses to estimate the impact of the 32 confirmed BMI loci in adults and children and to explore their potential functional roles. These follow-up analyses are described in detail in the **Supplementary Note**.

In brief, we estimated the cumulative effect of the 32 loci combined on BMI and assessed their predictive ability in obesity and BMI in the ARIC study. Association between the 32 confirmed BMI variants and overweight or obese status was assessed in stage 2 samples, and association with BMI in children and adolescents was examined in four population-based studies. Furthermore, we tested for association between the 32 SNPs and extreme or early-onset obesity in seven case-control studies of extremely obese adults and extremely obese children or adolescents. Data on the association between the 32 SNPs and height and weight were obtained from the stage 2 replication samples, and data on the association with related traits were extracted from previously reported genome-wide association meta-analyses for type 2 diabetes (Diabetes Genetics Replication and Meta-analysis (DIAGRAM) Consortium[18]), lipid levels (the Global Lipids

Genetics Consortium[20]) and glycemic traits (Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC)[19,21]).

To discover potentially new pathways associated with BMI, we tested whether predefined biological processes or molecular functions that contain at least one gene within 300 kb of the 32 confirmed BMI SNPs were enriched for multiple modest BMI associations using MAGENTA[33]. We identified SNPs having $r^2 \geq 0.75$ with the lead SNP that were likely non-synonymous, nonsense or which occurred within 5 bp of the exon-intron boundary and also evaluated whether any of the 32 confirmed BMI SNPs tagged common CNVs. We examined the *cis* associations between each of the 32 confirmed BMI SNPs and expression of nearby genes in adipose tissue[34,52], whole blood[34], lymphocytes[36,52] and brain[35].

We evaluated the amount of phenotypic variance explained by the 32 BMI loci using a method proposed by the International Schizophrenia Consortium[37] and estimated the number of susceptibility loci that are likely to exist using a new method[38] based on the distribution of effect sizes and minor allele frequencies observed for the established BMI loci and the power to detect those effects in the combined stage 1 and stage 2 analysis.

We performed a conditional genome-wide association analysis to examine whether any of the 32 confirmed BMI loci harbored additional independent signals, and we also examined gene-by-gene and gene-by-sex interactions among the BMI loci. Dominant and recessive analyses were performed for the 32 confirmed BMI SNPs to test for non-additive effects.

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