ONLINE METHODS

Study design. This study had three stages. Stage I was a meta-analysis of study-specific results on the association between SNPs and BMI from eight GWAS that participated in the consortium and included a total of 27,715 individuals of East Asian ancestry. Each participating study was approved by their local institutional review board. Promising SNPs selected from the stage I meta-analysis were further examined by *in silico* (stage II) and *de novo* (stage III) replication analyses. Supplementary Tables 1 and 2, Supplementary Figure 1, and the Supplementary Note summarize the basic information for all participating studies.

Stage I samples and genotyping. The sample sizes of the eight GWAS in stage I varied between 821 and 8,838, with a total of 27,715 individuals. Two studies used Affymetrix arrays, and six studies used the Illumina platform (detailed information is provided in the Supplementary Note). To allow for combination of the data derived from different genotyping platforms and to improve coverage of the genome, genotype imputation was performed by each participating study using either MACH or IMPUTE.

Stage I statistical analysis. A uniform statistical analysis protocol was followed by each participating study. To calculate BMI, each study collected weight and height measurements. To improve the normality of the BMI distribution and alleviate the impact of outliers, the rank-based inverse normal transformation (INT) was applied to BMI separately for each gender by each study. The INT involves ranking all BMI values, transforming these ranks into quantiles and, finally, converting the resulting quantiles into normal deviates. The association between SNPs and the inverse normal transformed BMI was analyzed with a linear regression model .The association between SNPs and obesity as a dichotomous outcome, which defined obesity as BMI≥27.5[14], was analyzed with a logistic regression model, assuming an underlying additive genetic mode and adjusting for age (continuous), age-squared, gender (if applicable), and ethnicity (if applicable). Stratified analyses by gender and disease status (with or without cancer or type 2 diabetes) were also performed by each study.

Next, we carried out meta-analyses using two methods in parallel for crosschecking, one combining effects weighted by the inverse-variance, another combining *P* values weighted by the square root of the sample size for each study. Both meta-analysis procedures were implemented in the freely available METAL software package. The final *P* values obtained from these two methods were highly congruent (Pearson correlation r=0.98). *P* values derived from the effect-size-based methods are reported herein, as this method is preferred over the *P*-value-based method and also provides combined regression coefficients and their standard errors[26]. The meta-analyses were carried out in all data and also stratified by gender and disease status. The presence of heterogeneity across studies and between-gender heterogeneity were tested with Cochran's Q statistics[27].

To correct each study for residual population stratification or cryptic relatedness, the meta-analyses were performed with genomic control correction[28] by adjusting for the study-specific inflation factor (λ), which ranged from 1.000 to 1.075 in stage I (Supplementary Table 3). After study-specific genomic control adjustment, the estimated inflation factor for the stage I meta-analysis statistic was 1.056, which was further adjusted for when combining stage I results with stage II replication results.

Based on the stage I meta-analysis on the association between SNPs and BMI among all participants, a total of 848 SNPs, which included 798 SNPs with $P<1.0\times10^{-4}$ and 50 SNPs located in previous reported obesity-related loci but with $P>1.0\times10^{-4}$ were taken forward to stage II for replication analysis. The cut-off point of $P<1.0\times10^{-4}$ was chosen, so that the overall P value would reach the genome-wide significance level ($P<5.0\times10^{-8}$), given $P<1.0\times10^{-4}$ and the sample sizes of stages I and II.

Stage II *in silico* replication. These 848 SNPs were investigated in an independent set of 37,691 individuals of East Asian ancestry from seven additional GWAS. The sample sizes of the seven additional studies varied between 901 and 27,284. The RIKEN study was the main source of the replication data and included 27,284 individuals. One study (SCORM) was based on children (aged 9 years). All studies used the Illumina platform except for the GenSalt study, which used the Affymetrix array. Genotype imputation was also performed by each study using either MACH or IMPUTE as for studies included in stage I.

Each study individually conducted a similar analysis of the SNPs selected from stage I, using the same protocol used in stage I. The stage II data were combined using meta-analysis methods with study-specific genomic control adjustment in a manner similar to stage I. Finally,

we used meta-analysis to combine all data from both stages I and II with further adjustment for the estimated inflation factor for the stage I meta-analysis statistic.

Stage III *de novo* replication. Seven SNPs that were associated with BMI according to the analysis of combined stage I and II data, including four SNPs at four newly identified loci and three loci that overlapped with loci reported by the GIANT consortium during the course of our study were further validated in our stage III *de novo* replication studies. These analyses were conducted in data from three study sites (Supplementary Table 1), and the genotyping for the seven SNPs was conducted for a total of 17,642 East Asians. The results from stages I, II, and III were combined and analyzed using meta-analysis methods.

Quality control (QC) procedures. The following QC procedures were recommended for each participating study. The SNPs and/or individuals were excluded either in the primary analysis conducted by each participating study or at the meta-analysis stage (Supplementary Table 3): (1) individuals or SNPs with a call rate < 90%; (2) SNPs with $P<1.0\times10^{-6}$ for the Hardy-Weinberg violation test; (3) SNPs with a MAF<1%; (4) imputed SNPs with low imputation quality (r-hat <0.3 for MACH or proper-info <0.5 for IMPUTE); (5) individuals with first-degree cryptic relationships via an identity-by-descent (IBD) analysis; (6) and samples that were potentially contaminated.

Supplementary Table 3 summarizes the specific QC procedure adopted by each study.

Conditional analysis. To investigate the independent association of SNPs in the same locus, conditional analyses were conducted by including both SNPs in the same locus in the same regression model for mutual adjustment. The normal transformation of BMI and the adjustment of covariates were applied in the same manner as in the stage I analysis. These conditional

analyses were conducted among 57,931 (88.6%) subjects from 11 of the 15 studies in stage I and II.

Estimation of the explained variance. The variation in BMI explained by an individual SNP was estimated using the formula $2\beta^2 f(1-f)$[29], where f is the frequency of the variant and β is its additive effect estimated from the stage II studies. We subsequently estimated the overall fraction of variance that can be explained by all significant SNPs found in the current meta-analyses using the following genetic score:

$$Score_i = \sum_{j=1}^{m} \beta_j \mathrm{A}_{ij}$$

Where m= number of SNPs, β_j =effect of allele at locus j, estimated from the stage II data, A_{ij}=number of reference alleles of individual i at locus j. The measure of variance explained (adjusted R2) was estimated from a linear regression model incorporating the score as the predictor and the covariate-adjusted inverse normal transformed BMI residuals as outcome. We reported the average explained variance weighted by the sample size of each study. These analyses to estimate the explained variance were conducted among 57,931 (88.6%) subjects from 11 of the 15 studies in stage I and II.

Analyses of coding SNPs, eQTLs, and copy number variant (CNV). Variants with potential functional impact were evaluated using the SNP Function Prediction tool, which is part of the SNP Info Web Server http://snpinfo.niehs.nih.gov/guide.htm[30]. This tool identifies SNPs with potential functional consequences, including those resulting in coding changes. The severity of a coding change evaluated by PolyPhen though SNPs reported to result in coding changes of consequence were independently verified using the PolyPhen website [31].

The eQTLs were evaluated using the SCAN database [23] and GeneVar program[25] with the RNA sequencing and genotyping experiments conducted by Montgomery et al[32].

To test for proximity of CNVs with the specific variants of interest, we used the UCSC Genome Browser [33]. While direct access to individual-level SNP genotype information was unavailable to directly test for the presence of CNVs, we used the phased genotypes from HapMap II release 22 data, [34] which shows estimated LD values by for the JPT+CHB HapMap populations (hapmapLdPhChbJpt table) in combination with the UCSC Genome Browser track from the Database of Genomic Variants (dgv table) [35] to identify instances of known CNVs intersecting regions in strong LD with GWAS variants.