New loci for body fat percentage reveal link between adiposity and cardiometabolic disease risk

Yingchang Lu et al.

To increase our understanding of the genetic basis of adiposity and its links to cardiometabolic disease risk, we conducted a genome-wide association meta-analysis of body fat percentage (BF%) in up to 100,716 individuals. Twelve loci reached genome-wide significance \((P<5 \times 10^{-8})\), of which eight were previously associated with increased overall adiposity (BMI, BF%) and four (in or near \(COBLL1/GRB14, IGF2BP1, PLA2G6, CRTCI\)) were novel associations with BF%. Seven loci showed a larger effect on BF% than on BMI, suggestive of a primary association with adiposity, while five loci showed larger effects on BMI than on BF%, suggesting association with both fat and lean mass. In particular, the loci more strongly associated with BF% showed distinct cross-phenotype association signatures with a range of cardiometabolic traits revealing new insights in the link between adiposity and disease risk.
large-scale meta-analyses of genome-wide association studies (GWAS) for adiposity traits and obesity risk have identified at least 160 loci that contribute to body weight and fat distribution in adults and children of diverse ancestry. Studies of overall adiposity, assessed by body mass index (BMI), have mainly implicated genes that provide support for a role of the central nervous system (CNS) in obesity susceptibility, whereas genetic loci associated with body fat distribution, assessed by waist-to-hip ratio (WHR), seem enriched for genes involved in adipocyte metabolism. Although these commonly studied adiposity traits are easily collected in large populations and thus allow statistically well-powered meta-analyses, they represent heterogeneous phenotypes, for example, people with the same BMI or WHR may vary in BF%, translating in differences in cardiometabolic risk.

To assess the genetic contribution to adiposity, we previously performed the first GWAS for BF% in nearly 40,000 individuals and identified two new loci (near IRS1 and SPRY2), not identified in earlier large-scale GWAS for BMI. Follow-up analyses of these loci provided strong evidence for IRS1 to be involved in tissue-specific body fat storage and subsequent effects on cardiometabolic disease, such as type 2 diabetes (T2D) and coronary artery disease (CAD). While little is known about SPRY2, the Spry1 homolog in mice has been implicated in adipose tissue differentiation. Taken together, these loci for BF% pointed towards new mechanisms involved in adipocyte metabolism that differ from the BMI-associated loci that suggested a role for the CNS.

Here, we have extended our study to include more than 100,000 individuals and continue to discover novel genetic loci associated with BF% that have not been identified before for any of the commonly studied adiposity traits. Through an in-depth integrative characterization, including cross-trait association analyses, expression quantitative trait loci (eQTL), pathway and network analyses, regulome analyses and transgenic drophila models, we show that these loci provide new insights into the biology that underlies adiposity and related cardiometabolic health, by specifically highlighting peripheral physiological mechanisms.

**Results**

Analyses in >100,000 individuals identify 12 loci for BF%.

In our primary meta-analysis, we combined results of genetic associations with BF% for up to 100,716 individuals from 43 GWAS (n up to 76,137) and 13 MetaboChip studies (n up to 24,582), predominantly of European ancestry (n up to 89,297), but also of non-European ancestry (n up to 11,419) populations (Supplementary Table 1 and Supplementary Fig. 1). As women have on average a higher BF% than men, we also stratified meta-analyses by sex (n\textsubscript{men} up to 52,416; n\textsubscript{women} up to 48,956). In secondary meta-analyses, we combined data from European-ancestry populations only (n up to 89,297; n\textsubscript{men} up to 44,429; n\textsubscript{women} up to 45,525) to reduce genotypic and phenotypic heterogeneity that may have been introduced in the overall analyses by combining diverse ancestries.

In our primary meta-analysis of men and women combined, single-nucleotide polymorphisms (SNPs) in 10 independent loci reached genome-wide significance (GWS, P < 5 × 10\textsuperscript{-8}; Table 1 and Supplementary Fig. 2), including the three loci that we identified before. Two additional loci, near PLA2G6 and in CRTC1, were identified in men-specific and women-specific analyses, respectively (Table 1 and Supplementary Fig. 3). The European-ancestry-only analyses revealed the same loci, but no additional ones (Supplementary Tables 4–6, Supplementary Figs 4 and 5). We did not identify evidence of secondary signals at any of the 12 loci.

Two (near IRS1 and SPRY2) of the 12 loci had been first identified in our previous genome-wide screen for BF% (ref. 13), and six loci (in/near FTO, MC4R, TMEM18, TOMM40/APOE, TUFM/SH2B1 and SEC16B) had been first reported for association with BMI\textsubscript{13–19}. Four of the 12 loci, in or near COBLL1/GRB14, IGE2BP1, PLA2G6 and CRTC1, have not been associated with an overall adiposity trait (such as BMI, BF%, obesity risk) before (Fig. 1 and Supplementary Fig. 6). Of note, the COBLL1/GRB14 locus was previously established as a locus for body fat distribution independent of overall adiposity, assessed by WHR\textsubscript{adjBMI}, and the CRTC1 locus has been first reported for its association with age at menarche (Table 2, Supplementary Table 7, See also ‘Cross-phenotype association’ section).

**Effect sizes and explained variance.** Index SNPs in the 12 established loci increase BF% by 0.024 to 0.051 s.d. per allele (equivalent to 0.16 to 0.33% in BF%, Table 1, Fig. 2). Given the high correlation between BF% and BMI, the BF% increasing effect sizes and explained variance of the 12 loci are associated with BMI and, the BF% increasing alleles of each of the 12 loci are associated with increased BF%.

### Table 1 | Loci reaching genome-wide significance (P < 5 × 10\textsuperscript{-8}) for body fat percentage in all ancestry analyses, sorted according to significance in the overall analysis.

| SNP          | Chr. | Position (bp) | Nearest gene | Other nearby genes of interest | Fat% increasing allele | Fat% increasing allele frequency | Other allele | Other allele frequency | All ancestry | All ancestry-m | All ancestry-w |
|--------------|------|---------------|--------------|--------------------------------|-----------------------|--------------------------------|--------------|-----------------------|--------------|---------------|---------------|
| rs543874      | 1    | 176,156,103    | SEC16B       |                                | G                     | 0.078                          | T            | 0.022                 | 0.229        | 0.196         | 0.164         |
| rs6755502     | 2    | 625,721       | TMEM18       |                                | G                     | 0.024                          | T            | 0.076                 | 0.251        | 0.127         | 0.112         |
| rs677131      | 2    | 625,721       | TMEM18       |                                | G                     | 0.024                          | T            | 0.076                 | 0.251        | 0.127         | 0.112         |
| rs693839      | 3    | 79,654,284    | SPRY2        |                                | C                     | 0.018                          | T            | 0.082                 | 0.260        | 0.133         | 0.119         |
| rs757318      | 19   | 18,681,308     | IRS1         |                                | C                     | 0.028                          | T            | 0.072                 | 0.254        | 0.130         | 0.107         |
| rs757318      | 19   | 18,681,308     | IRS1         |                                | C                     | 0.028                          | T            | 0.072                 | 0.254        | 0.130         | 0.107         |
| rs757318      | 19   | 18,681,308     | IRS1         |                                | C                     | 0.028                          | T            | 0.072                 | 0.254        | 0.130         | 0.107         |
| rs757318      | 19   | 18,681,308     | IRS1         |                                | C                     | 0.028                          | T            | 0.072                 | 0.254        | 0.130         | 0.107         |

**Cchr.: chromosome; pos.: position (bp) according to Build 36; and allele coding on the positive strand.**

*Based on all-ancestry sex-combined analyses.

1Evaluates the SORC, ATACH, and GTEX

All loci identified in sex-specific or all-ancestry analyses.

2Cchr.: chromosome; pos.: position (bp) according to Build 36; and allele coding on the positive strand.

*Based on all-ancestry sex-combined analyses.

1Evaluates the SORC, ATACH, and GTEX

All loci identified in sex-specific or all-ancestry analyses.

Effect sizes and explained variance. Index SNPs in the 12 established loci increase BF% by 0.024 to 0.051 s.d. per allele (equivalent to 0.16 to 0.33% in BF%, Table 1, Fig. 2). Given the high correlation between BF% and BMI, the BF% increasing alleles of each of the 12 loci are associated with increased BF%.
GWAS catalogues SNPs with 'X' symbol for SNPs located in mcs44placental region and circle for SNPs with no annotation information. SNPs with rates are also estimated from International HapMap Project data, and gene annotations are obtained from the UCSC Genome Browser.

Figure 1 | Regional plots of the four newly identified loci that reached genome-wide significant association with body fat percentage. Regional plots of the four newly identified loci that reached genome-wide significant association with body fat percentage in all-ancestry analyses, in men and women combined for the COBLL1/GRB14 and IGF2BP1 loci (a,b), and separately for the CRTC1 and PLA2G6 (c,d). Each symbol represents the significance (P value on a − log10 scale) of a SNP with BF% as a function of the SNP's genomic position (NCBI Build 36). For each locus, the index SNP is represented in the purple colour. The colour of all other SNPs indicates LD with the index SNP (estimated by CEU $r^2$ from the HapMap Project data Phase II CEU). Recombination rates are also estimated from International HapMap Project data, and gene annotations are obtained from the UCSC Genome Browser. GWAS catalogues SNPs with P value $<5 \times 10^{-8}$ are shown in the middle panel. Different shapes denote the different categories of the SNPs: up-triangle for framestop or splice SNPs, down-triangle for nonsynonymous SNPs, square for coding or untranslated region (UTR) SNPs; star for SNPs in tfscons region, square filled with 'X' symbol for SNPs located in mcs44placental region and circle for SNPs with no annotation information.
other were first identified for BF% (green). Six loci had first been identified for BMI (blue), whereas six loci were derived, respectively, from the men- and women-based T2D (INV) GIANT (Genetic Investigation of ANthropometric Traits) consortium6, odds ratio; SAT-VAT, subcutaneous adipose tissue (SAT) visceral adipose tissue (VAT) consortium; WHRadjBMI, waist-to-hip ratio adjusted by BMI; Z, z-score transformation (mean of 0, s.d. of 1); LEPgen, circulating leptin consortium (Kilpeläinen et al., in preparation); Ln, natural logarithm-transformation; MAGIC, the Meta-Analyses of Glucose and Insulin-related traits Consortium; O/E, odds ratio; SAT-VAT, subcutaneous adipose tissue (SAT) visceral adipose tissue (VAT) consortium; WHRadjBMI, waist-to-hip ratio adjusted by BMI; Z, z-score transformation (mean of 0, s.d. of 1). The fat percentage (Fat%) increasing allele frequency was based on all-ancestry sex-combined analysis. The * / -- in effect stands for increasing or decreasing phenotypes. The threshold for a statistically significant association with Bonferroni correction for 13 traits is P = 0.00385 (0.05/13). Colour coding of cells: BF%-increasing shows risk-increasing association with respective cardiometabolic traits at nominal (red) or multiple-testing corrected (solid red) significance. BF%-increasing shows risk-reducing association with respective cardiometabolic traits at nominal (faded green) or multiple-testing corrected (solid green) significance.

Results of men and women are combined in Supplementary Table 8.

Table 2 | Cross-phenotype associations: associations signatures of 12 established body fat percentage loci for anthropometric and cardiometabolic traits through look-ups in large-scale genetics consortia.

| Gene     | Sex | Effect | Effect | Effect size | Effect | Effect size | Effect | Effect size | Effect | Effect size | Effect | Effect size | Effect | Effect size | Effect | Effect size | Effect | Effect size |
|----------|-----|--------|--------|-----------|--------|-----------|--------|-----------|--------|-----------|--------|-----------|--------|-----------|--------|-----------|--------|-----------|
| NA        |     |        |        |           |        |           |        |           |        |           |        |           |        |           |        |           |        |           |
| FTO       |     |        |        |           |        |           |        |           |        |           |        |           |        |           |        |           |        |           |
| SEC16B    |     |        |        |           |        |           |        |           |        |           |        |           |        |           |        |           |        |           |
| TMEM18    |     |        |        |           |        |           |        |           |        |           |        |           |        |           |        |           |        |           |
| PLA2G6    |     |        |        |           |        |           |        |           |        |           |        |           |        |           |        |           |        |           |
| GIANT     |     |        |        |           |        |           |        |           |        |           |        |           |        |           |        |           |        |           |
| COBLL1    |     |        |        |           |        |           |        |           |        |           |        |           |        |           |        |           |        |           |
| GRB14     |     |        |        |           |        |           |        |           |        |           |        |           |        |           |        |           |        |           |
| LEPgen    |     |        |        |           |        |           |        |           |        |           |        |           |        |           |        |           |        |           |
| MAGIC     |     |        |        |           |        |           |        |           |        |           |        |           |        |           |        |           |        |           |

Figure 2 | Comparison of effects of the 12 loci on body fat percentage (x axis) and on BMI (y axis). Both outcomes (BMI and BF%) were inverse normally transformed (mean of 0, s.d. of 1) such that effect sizes are at the same scales and directly comparable. Effect sizes for BMI were obtained from Locke et al.19. The allele effects for the PLA2G6 (square) and CRTC1 (round) loci were derived, respectively, from the men- and women-based meta-analyses. Six loci had first been identified for BMI (blue), whereas six others were first identified for BF% (green).

BMI (Fig. 2, Table 2, and Supplementary Table 7). However, loci that had been previously identified for BMI, have larger effects (expressed in s.d. per allele) on BMI than on BF% except the TOMM40/APOE locus, together with the loci previously (IRSI and SPRY2) and newly (COBLL1/GRB14, IGF2BP1, PLA2G6 and CRTC1) identified for BF% all have larger effects on BF% than on BMI (Fig. 2). This division based on effect sizes, illustrated in Fig. 2, suggests that IRS1, SPRY2, COBLL1/GRB14, TOMM40/APOE, IGF2BP1, PLA2G6 and CRTC1 affect adiposity in particular, which is not fully captured by BMI (which represents both lean and fat mass).

Of the 12 loci, four showed significant sex-specific effects. For the loci near IRS1 and PLA2G6, the effect in men was twice as large as in women, whereas for the TMEM18 and CRTC1 loci the effect was two- to threefold larger in women than in men (Table 1). As the European-ancestry-only populations represent the vast majority (90%) of the total sample, effect sizes from European only and all-ancestry analyses were similar (Supplementary Tables 5 and 8).

In aggregate, the 12 loci explained 0.58% of the variance in BF% in men and women combined. Because of the sex-specific effects of four loci, the explained variance was slightly higher, when estimated in men (0.62%) and women (0.61%) separately. Individually, the FTO locus explained the most variance of all identified loci (0.12%) (Table 1).

Cross-phenotype association with cardiometabolic traits. To gain insight in how the BF% loci affect anthropometric and cardiometabolic traits and comorbidities, we performed look-ups in the most recent large-scale GWAS meta-analyses from the GIANT (Genetic Investigation of ANthropometric Traits) consortium (WHRadjBMI and height)20,26, the SAT-VAT consortium (abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT))22, the LEPgen consortium (circulating leptin), the GLGC (high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG))28, the MAGIC (fasting glucose and fasting insulin)29, DIAGRAM (T2D)30 and CARDIoGRAMplusC4D (CAD)31. To account for multiple testing, associations were considered statistically significant if P values were < 5.2 × 10⁻⁴ (Bonferroni-corrected P = 0.05/96 (12 SNP * eight trait groups)).

Associations with anthropometric and adiposity traits. The BF% increasing alleles for 11 of the 12 loci were associated with
increased circulating leptin levels ($P_{\text{binomial}} = 0.006$), of which four reached statistical significance and another four were nominally significant (Table 2, Supplementary Table 7). These results are consistent with the notion that leptin is secreted by adipocytes proportional to adipose tissue mass.

The BF% increasing alleles of all 12 loci were associated with increased SAT and VAT ($P_{\text{binomial}} = 0.0005$), two (FTO and TMEM18) of which reached significance for association with SAT, and two (FTO and TOMM40/APOE) with VAT. The BF% increasing allele of the locus near IRS1 was associated with a lower VAT/SAT ratio, indicative of a proportionally greater subcutaneous than visceral fat storage, as we have shown previously\(^{13}\) (Table 2, Supplementary Table 7).

As expected, most of the identified BF% loci showed no association with WHRadjBMI, as this trait, because of the adjustment for BMI, does not correlate with overall adiposity. Nevertheless, associations with WHRadjBMI for two loci (COBLL1/GRB14 and TOMM40/APOE) did reach statistical significance. The COBLL1/GRB14 locus was previously identified as a WHRadjBMI locus\(^{11}\). We show that it is the BF% increasing allele that is associated with lower WHRadjBMI, suggestive of a preferential gluteal rather than abdominal fat storage. Although the COBLL1/GRB14 association with WHRadjBMI is five times stronger in women than in men\(^{11}\), we observed no sex difference for association with BF% (Table 1). For the TOMM40/APOE locus, it is the BF% increasing allele that is also associated with increased WHRadjBMI, suggesting that the TOMM40/APOE locus increases abdominal and overall fat accumulation, at least in part, in an additive and independent manner. Furthermore, the BF% increasing allele was also significantly associated with increased VAT (Table 2, Supplementary Table 7) and liver fat storage ($P = 3.4 \times 10^{-4}$, $n = 5,550$, Methods section).

SNPs in three loci (MC4R, PLA2G6 and IGF2BP1) showed significant association with height, two of which (PLA2G6 and IGF2BP1) have not been reported in large GWAS studies before. Similar to the MC4R locus, the BF% increasing allele of the PLA2G6 (rs3761445) was associated with greater adult height ($P = 6.7 \times 10^{-5}$; Table 2, Supplementary Table 7). Following up this variant in data from the Early Growth Genetics Consortium, we found that the BF% increasing allele was associated with higher birth weight ($P = 0.003$, $n$ up to 26,836; ref. 32) and greater prepubertal height ($P = 0.007$, $n = 13,948$; ref. 33), yet not with growth during or timing of puberty (Supplementary Table 10)\(^{33}\). In contrast, the BF% increasing allele in IGF2BP1 (rs9906944) was associated with shorter height (Table 2, Supplementary Table 7), a cross-phenotype association pattern that is consistent with the effects of the GH/IGF1 axis\(^{34}\). SNPs in IGF2BP1, in linkage disequilibrium (LD) with rs9906944 ($r^2_{\text{EUR}} = 0.47$), have been previously implicated with primary tooth development in infancy\(^{35}\). Consistently, the BF% increasing allele of IGF2BP1 (rs9906944) showed association with a later eruption of the first tooth ($\beta = 0.16$ months per allele; $P = 3.1 \times 10^{-8}$) and reduced number of teeth at 1 year ($\beta = -0.14$ number of teeth at age 1 year per allele; $P = 1.1 \times 10^{-7}$; ref. 35). Even though this suggests a role in maturation, we found no evidence for association with pre-pubertal height or pubertal growth and timing (Supplementary Table 10)\(^{33}\) or age at menarche ($\beta = 0.01$ age of menarche (years) per allele; $P = 0.11$; ref. 24). Although this locus harbours a number of genes, data in rodents suggest that IGF2BP1 might be a potential candidate gene driving the associations observed here, as Igf2bp1 knockout mice demonstrate fetal and postnatal growth retardation\(^{36}\).

Taken together, alleles of each of the 12 loci are associated with increased BF%, yet their associations with other anthropometric traits differ, which in turn might result in varying impacts on cardiometabolic health.

**Associations with cardiometabolic traits.** Although phenotypic correlations observed in epidemiological studies have shown that increased adiposity is associated with increased cardiometabolic risk, the BF% increasing alleles of identified loci do not always associate with poorer health outcomes (Table 2 and Supplementary Table 11). For some loci, the BF% increasing allele may even have significant protective effects, as we have shown previously for the locus near IRS1 (ref. 13).

For the loci in near FTO, MC4R, TMEM18, TUFM/SH2B1 and SEC16B, which were all five previously established for BMI, the observed cross-phenotype associations with cardiometabolic traits are generally directionally consistent with the phenotypic correlations. Specifically, their BF% increasing allele is typically associated with an unfavourable lipid profile and increased insulin resistance (Table 2, Supplementary Tables 12 and 13). These cross-phenotype associations translate in increased risk of
T2D and CAD and higher CRP levels, at least for the FTO, TMEM18 and MC4R loci (Fig. 2, Table 2, Supplementary Tables 9,12 and 13).

For the remaining seven loci, which all have a larger effect on BF% than on BMI (Fig. 2), the cross-phenotype associations are not always consistent with the phenotypic correlation between BF% and cardiometabolic traits. For example, the COBLL1/GRB14 locus was previously identified for its association with fasting insulin29, TG37, HDL-C37-and, T2D risk30 (Table 2, Supplementary Tables 12 and 13). However, we show for the first time that it is the BF% increasing allele that is associated with a protective effect on cardiometabolic health; that is, with significantly lower TG levels and higher HDL-C levels, and a reduced risk of T2D (Table 2, Supplementary Tables 12 and 13). This association signature of the COBLL1/GRB14 locus is consistent with the observation that its BF% increasing allele is associated with a lower WHRadjBMI, corresponding to a locus that was previously identified for its association with Alzheimer’s disease, slower cognitive decline and increased longevity.

Although we do not observe association of IGF2BP1-rs9906944 with circulating lipid levels or glycemic traits, interestingly, the BF% increasing allele is significantly associated with increased risk of T2D and CAD, and with higher CRP levels (Table 2, Supplementary Tables 9,12 and 13).

The sex-specific effect of PICK1/PLA2G6-rs37614455 does not translate in sex dimorphic associations with other traits (Table 2, Supplementary Tables 12 and 13). Interestingly, the BF% increasing allele is associated with a favourable lipid profile; in particular with lower TG levels (P = 8.1 × 10−15) and higher HDL-C levels (P = 3.9 × 10−6, Supplementary Table 12), but no association with CAD risk was observed (Supplementary Table 12). The PICK1/PLA2G6-rs37614455 is in moderate LD with SNPs identified before for nevus count (rs2284063, rEUR = 0.67, DEUR = 0.90; ref. 42) and melanoma risk (rs738322, rEUR = 0.77, DEUR = 0.98; refs 42,43). Consistently, the rs3761445 BF% increasing allele is associated with a lower number of cutaneous nevi (−0.067 nevi/allele, P = 9.4 × 10−6, ref. 43) and reduced melanoma risk (OR = 0.86 per allele, P = 5.3 × 10−10, ref. 44).

The BF% increasing allele of CRTCI-rs757318, which showed a significantly stronger association in women than men, was not associated with any of the cardiometabolic traits in either sex-stratified or sex-combined results. Rs757318 is in moderate LD (rEUR = 0.57, DEUR = 1) with another CRTCI SNP (rs10423674) that was previously established for age at menarche24 and, consistently, also the rs757318 BF% increasing allele was significantly associated with earlier age at menarche (β = −0.03 years per allele; P = 2.4 × 10−10; ref. 24).

Functional annotation of genome-wide significant loci. The causal genes and/or variants underlying most of the BF% associated loci remain unknown. For the 12 genome-wide significant loci, and also for putative loci (P < 1 × 10−5), we used multiple complementary approaches to prioritize candidate genes and/or variants and to elucidate the mechanisms involved in body fat regulation. These approaches include identification of nearby coding variants or copy-number variants (CNVs), cis-eQTL analysis, epigenetic marker and functional regulatory genomic element analysis, pathway and tissue enrichment analysis, and a transgenic Drosophila model.

Coding variants and CNV analysis. Among the 12 index SNPs, only rs4788099 near SH2B1 was in high LD with seven coding variants (rEUR > 0.7) in nearby genes (APOBR, SH2B1 and ATP2A1; Supplementary Table 15, Methods section). Two of these seven variants were non-synonymous, of which, one, Thr484Ala (rs7498665) in SH2B1, was in perfect LD with our index SNP. Thr484Ala shows a high degree of conservation, but was predicted to be functionally benign by PolyPhen and tolerated by SIFT. None of the other 11 index SNPs were in high LD with coding or CNVs.

eQTL analysis. We examined cis-associations between each index SNP and gene expression of transcripts within 1 Mb-region flanking the respective SNP (Supplementary Tables 16 and 17, Methods section). As shown previously13, the BF% increasing allele of rs2943652 near IRS1 is associated with increased IRS1 expression in omental and subcutaneous fat. SNPs within the same locus (LD rEUR > 0.95) have also been shown to be associated with increased IRS1 expression in skeletal muscle45. We also identified significant (P < 1 × 10−5 or 5% FDR) eQTLs for other BF% associated loci, even after conditioning for the most significant SNP-transcript association in the regions. The BF% increasing allele of COBLL1/GRB14-rs6738627 is associated with lower expression of GRB14, whereas there is no evidence of association with COBLL1 expression. The BF% increasing allele
for PLA2G6/MAFF: rs3761445 is associated with lower expression of MAFF and TMEM184B in omental and subcutaneous fat. TUFM/SH2B1: rs4788099 is associated with the expression of a number of genes, such as TUFM (blood), APOB (blood), SBIK (blood), SULT1A2 (omental and subcutaneous fat) and SH2B1 (omental fat).

**Epigenetic marker and functional regulatory genomic element analysis.** We examined the overlap of 746 variants in LD ($r^2_{\text{CEU}} > 0.70$) with the 12 index SNPs with regulatory elements in brain, blood, liver, adipose and pancreatic islets from the ENCODE Consortium and Roadmap Epigenomic Projects (Supplementary Table 18). Across loci, 179 (24%) variants showed evidence of being located in a regulatory element as defined by overlapping variants in two or more data sets from the same tissue (Supplementary Table 19). Promoter variants, located within 2 kb of a transcription start site, overlapped with an average of 22 regulatory elements, while more distal variants (> 2 kb) overlapped with an average of nine elements.

Two of the distal variants with the greatest amount of regulatory overlap were rs4808844 and rs4808845 (43 and 41 elements, respectively; Supplementary Table 19). These variants are located 58 bp apart in intron 1 of CRTC1 and overlap evidence of open chromatin, histone marks that are characteristic of active transcription regulation and Pol2 binding (Fig. 3a). We found that rs4808844 was significantly associated ($P = 0.036$) with Pol2 binding signal strength (Fig. 3b). In addition, DNaseI hypersensitivity signal in this region has been shown to negatively correlate with CRTC1 and CRLF1 transcription levels across many cell types. These data suggest that rs4808844 and rs4808845, both in high LD ($r^2_{\text{CEU}} = 0.76$ and 0.79, respectively) with our index SNP (rs757318), may influence the transcription of these and/or other nearby genes.

We further characterized variants overlapping with regulatory elements at each of the 12 loci using RegulomeDB, and two loci stood out. In the TUFM-SH2B1 region, three variants (rs4788084, rs1074631 and rs149299) in LD ($r^2_{\text{CEU}} = 0.82, 0.76$ and 0.75, respectively) with rs4788099 are located in an EBF1-binding protein ChIP-seq signal in lymphoblastoid cells. In addition, rs4788084 is located within an EBF1-binding motif. EBF1 is involved in the thalamic axon projection into the neocortex and the genetic variants around rs4788099 might affect the regulation of EBF1 of the nearby SH2B1 (ref. 47). In the PLAG26/PICK1 region, rs4384 in LD with rs3761445 ($r^2_{\text{EUR}} = 0.73$) overlapped with more elements (50 elements in four tissues, Supplementary Table 19) than any other distal variant. This variant is located in a HEN1-binding motif with evidence of a DNase footprint in multiple cell types. HEN1 is a transcription factor potentially involved in the CNS development.

**Pathway, network and tissue-enrichment analysis.** To test for enrichment and define pathways and networks between the genes harboured by the 12 GW–significant loci and 31 loci with putative evidence ($P < 1 \times 10^{-5}$) of association with BF%, we applied a number of approaches (see Methods section). Neither DEPICT (data-driven enrichment prioritized integration for complex traits) nor Ingenuity IPA identified pathways, tissues or networks that were significantly enriched among the genes across the 43 loci (Supplementary Tables 20–22). Also, GRAIL (Gene Relationships Among Implicated Loci), which searches the published literature to identify relationships between genes, and DAPPLE (Disease Association Protein–protein Link Evaluator), which tests for protein–protein interactions, did not identify significant connection between any of the genes in the identified loci. Their limited power may be due to the relatively small number of loci identified in this meta-analyses or to limited knowledge related to adipogenesis.

**Experimental follow-up of candidate genes in Drosophila.** We used Drosophila as a fast and inexpensive model to help prioritize which genes within the identified loci are the most likely candidates to underlie the observed associations.

To gain first insights in the potential candidacy of the genes located within the 12 BF% associated loci, we performed a look-up in data from a genome-wide transgenic RNAi screen for fat content in adult Drosophila. In that screen, whole-body TG, also in Drosophila the major lipid storage form, were used as a direct measure of fly adiposity upon activation of a heat shock-inducible Hsp70-GAL4 system. As such, transgenic fly lines were made to test the adiposity regulating potential of 10,489 of the ~14,000 annotated Drosophila protein coding genes. Of the 80 genes located within a 1 Mb-window of each of the 12 index SNPs, 44 Drosophila orthologues were available, yet, 12 of these 44 transgenic RNAi fly lines were too weak to be screened. Of the remaining 32 fly lines, 15 fly lines had substantially lower (> 2 s.d. less) whole-body TG than the wild-type flies, whereas five fly lines showed higher TG (> 2 s.d. more) (Supplementary Table 23). Next, we selected one to three candidate genes within each of the 12 loci based on their potential role in adipocyte metabolism. We knocked down their corresponding orthologues in Drosophila that were subsequently exposed to a high-sugar diet (Supplementary Table 24), as described before. Both Drosophila experiments pinpoint the SPRY2 (or sty) as the potential causal gene within the locus; that is, knockdown flies for sty have significantly lower whole-body TG levels than wild-type flies. While the genome-wide transgenic RNAi screen pointed towards the CRTC1 gene in the CRTC1 locus, we could not confirm a role for CRTC1 in the knockdown experiment.

**Established loci and body fat percentage.** The most recent GWAS meta-analysis for BMI, including nearly 340,000 individuals, identified 97 loci that reached GWS. Each of the 97 BMI-associated SNPs showed directionally consistent association with BF% ($P_{\text{binomial}} < 1 \times 10^{-4}$), 71 of which also reached nominal statistical significance (Supplementary Table 25). One of the reasons for the non-significance for the remaining loci might be insufficient power as the current final meta-analysis sample size for BF% was only one-third of that for BMI.

Of the 12 loci previously identified through GWAS for extreme and early-onset obesity, 7,12,54,55,11 showed directionally consistent association with BF% ($P_{\text{binomial}} < 0.006$), of which five also reached nominal statistical significance (Supplementary Table 25).

**Discussion**

Our meta-analysis of data from more than 100,000 individuals identified 12 loci significantly associated with BF%. While a recent GWAS including more than 340,000 individuals reported nearly 100 loci associated with BMI, a commonly used proxy measure for overall adiposity, four (SPRY2, IGF2BP1, PLA2G6 and CRTC1) of the 12 BF% associated loci did not reach GWS for BMI, despite the enormous sample size. This observation most likely reflects the heterogeneity of BMI as a marker of overall adiposity and emphasizes the increased statistical power of more precisely measured phenotypes.

The 12 BF% associated loci divide into two distinct groups. The first group comprises the five loci (FTO, MC4R, TMEM18, SEC16B and SH2B1) of which the association is stronger with BMI than with BF%, suggesting that they affect both fat mass and lean mass. All five loci have been identified and described in detail before in relation with BMI. Their associations with cardiometabolic outcomes are predictable, reflecting the phenotypic correlations with BF%; that is, their BF% increasing...
alleles are associated with an unfavourable glycemic and lipid profile and with an increased risk of T2D and CVD.

The second group, comprising the remaining seven loci (IRS1, SPRY2, TOMM40/APOE, CRCT1, PLA2G6, IGBP2BP1 and COBLL1/GRB14), all show a more pronounced effect on BF% than on BMI, suggesting a specific effect on adiposity rather than on overall body mass. Most notably, the association patterns with cardiometabolic traits of this group of loci, as opposed to the first group, often do not reflect the phenotypic correlations. For example, as we have described before, the BF% increasing allele of the index SNP 500 kb upstream of IRS1, which affects IRS1 expression, is associated with a favourable cardiometabolic risk profile, including a reduced risk of T2D and CVD13. We showed that this association signature, which goes against the phenotypic correlations, could be explained by an effect on fat distribution, as the BF% increasing allele was associated with increased subcutaneous, but not with the metabolically more harmful visceral fat13. The locus between GRB14 and COBLL1 shows a similar association signature. In fact, this locus was first described for its association with a lower WHR(ABM1) and reduced risk of T2D10. Here, we show that the same allele associated with increased BF%, suggesting that the association with WHR(ABM1) likely reflects a proportionally greater fat accumulation at hips and thighs rather than at the waist. Although this locus requires further experimental follow-up, current observations point towards GRB14 as the candidate gene in this locus. GRB14 encodes a protein that binds directly to the insulin receptor (IR), and the BF% increasing allele of the index SNP is associated with reduced GRB14 expression in adipose tissue. This is consistent with previous observations showing that Grb14/Grb14 expression is increased in adipose tissue of insulin-resistant rodents and in obese patients with T2D36. Furthermore, Grb14-deficient mice show improved glucose homeostasis and enhanced insulin action through increased IR-mediated IRS1 phosphorylation in the liver and skeletal muscle67. The similar cross-phenotype association signatures of the IRS1 and GRB14/COBLL1 loci might be a reflection of the close interaction between IRS1 and GRB14 in the IR-signalling pathway.

The BF% increasing allele of the PLA2G6 locus is associated with lower insulin and TG levels and reduced T2D risk, particularly in men. PLA2G6 is the nearest gene and encodes a calcium-independent phospholipase A2 involved in the hydrolysis of phospholipids. However, this locus harbours a number of other genes that would make plausible candidates for driving the cross-phenotype associations, including PICK1, which is membrane sculpting BAR domain protein. PICK1-deficient mice and flies display marked growth retardation, which at least in mice, might be due to impaired storage and secretion of growth hormone from the pituitary and possibly insulin from the pancreas58. PICK1-deficient mice, despite their smaller size, demonstrate increased body fat and reduced lean mass, reduced TG levels and impaired insulin secretion, which was compensated by increased insulin sensitivity58. Given the locus’ association with nevus count, SOX10, which encodes a member of the SOX (SRY-related HMG-box) family of transcription factors, is another candidate gene in this locus. SOX genes are involved in the regulation of embryonic development and SOX10 in particular is important for the development of neural crest and peripheral nervous system. Mutations in SOX10 have been implicated in uveal melanoma and Waardenburg syndrome, which presents with pigmentation abnormalities and hearing loss, and Kallmann syndrome, which presents with failure to start or complete puberty and hypogonadotropic hypogonadism (short stature, absence of puberty and sex hormones, among others) and absence of smell59,60. The phenotype similarity of these syndromes and the association signature may suggest that SOX10 could be driving the associations observed for the PLA2G6 locus.

The TOMM40/APOE locus is another locus with an intriguing association signature; while the BF% increasing allele has an unfavourable effect on glycemic traits and T2D risk, it is associated with a favourable lipid profile and reduced risk of CVD. The high LD in this region poses a major challenge to elucidate whether the association with lipid traits is due to a ‘spillover’ effect from nearby lipid-associated loci in APOE. Using conditional analyses, we provide evidence suggesting that at least the association with lower TG and high HDL-C levels might be distinct from previously reported loci. Of interest is that the BF% increasing allele seems to be associated with markers of increased longevity61.

The CRCT1 locus is another gene-rich locus, but given the epigenetic marks in this gene and data from animal models, CRCT1 poses to be a good candidate gene. CRCT1 is primarily expressed in the brain, and it may affect leptin anorexic effect in the hypothalamus61. CRCTC knockout mice demonstrated hyperphagia, increased white adipose tissue and infertility61.

Our meta-analysis was limited by the fact that participating studies all had imputed HapMap reference panels for autosomal chromosomes and that the analysis model assumed additive effects. Future discovery efforts based on genome-wide imputation of 1000 Genomes reference panels, that include X- and Y-chromosomes and that also test recessive and dominant inheritance, will allow for the discovery of more and lower-frequency variants and for refining association signatures of already established BF%–associated loci.

Taken together, our expanded genome-wide meta-analyses of BF% has identified a number of loci with distinct cross-phenotype association signature that, together with our functional follow-up analyses, facilitated the identification of strong positional candidates. Particularly striking is that two of the 12 loci harbour genes (IRS1, GRB14) that influence insulin receptor signalling, and two other loci contain genes (IGF2BP1, PICK1) that are involved in the GH/IGF1 pathway, that in turn also relates to insulin receptor signalling.

**Methods**

**Discovery of new loci.** Study design. A two-stage meta-analysis was performed to identify loci associated with BF%. In Stage 1, we conducted two parallel meta-analyses: one meta-analysis combined summary statistics from 43 GWAS, totalling up to 76,137 adult individuals (65,831 European ancestry, 7,557 South Asian ancestry, 2,333 East Asian ancestry and 416 African Americans), and the other meta-analysis combined summary statistics from 13 additional studies genotyped using the Metabochip, totalling up to 24,582 individuals (23,469 Europeans and 1,113 African Americans). In Stage 2, we combined the GWAS meta-analysis results and Metabochip meta-analysis results from Stage 1 (Supplementary Table 1 and Supplementary Figs 1 and 2) in one final meta-analysis, including 100,716 individuals from 56 studies. All the studies were approved by their local institutional review boards and written consent was obtained from all the study participants.

Through our primary analysis, described above, combined all the data available to us, in the secondary analyses, we conducted stratified analyses for (1) all-ancestry men-only, (2) all-ancestry women-only, (3) European ancestry, (4) European ancestry men-only and (5) European ancestry women-only (Supplementary Tables 4–6 and Supplementary Figs 2–5).

**Phenotype.** BF% in each cohort was measured either with bioimpedance analysis (BIA) or dual energy X-ray absorptiometry (DEXA) as described in detail before13. For each study, BF% was adjusted for age, age2 and study-specific covariates (for example, genotype-based principle components, study centre and others), if necessary. For studies of unrelated individuals, the residuals were calculated separately in men and in women, and in cases and controls. For studies of family-based design, the residuals were calculated in men and women together, and sex was additionally adjusted in the model. The residuals were then inverse normally transformed for association testing. For studies of family-based design, the family relatedness was additionally adjusted in the association testing.

**Sample quality control, imputation and association.** Each study did the study-specific quality control (QC) (Supplementary Table 2). The GWAS common SNPs were imputed in each study using the respective HapMap Phase II (Release 22)
are the effect size estimates, se1 and se2 are the corresponding standard errors and reference panels (EUR for studies of European-ancestry populations, CHB for studies of East Asian ancestry populations, and CEU + YRI + CHB + JPT for studies of Indian Asian ancestry populations and African American populations). Individual SNPs were associated with inverse normally transformed BF% residuals using linear regression with an additive model. All the SNPs with low information scores (MACH r2 < 0.3, IMPUTE proper info < 0.1 or PLINK info < 0.8) and a minor allele frequency < 0.5 were removed for detailed Qc of study level analyses and meta-level analysis, as described elsewhere.10

Meta-analysis. Meta-analyses were performed using inverse variance-weighted fixed-effect method in METAL. Inflation before genomic control (GC)-correction was generally low in all-ancestry (κall-ancestry = 1.13; κmen = 1.07; κwomen = 1.09) and European-only (κall-ancestry = 1.13; κmen = 1.07; κwomen = 1.10) analyses. To reduce the inflation of the test statistics from potential population structure, individual GWAS results and GWAS meta-analysis results were corrected for GC using all SNPs. Individual Metabochip results and Metabochip meta-analysis results were GC-corrected using 4,423 SNPs, which are derived from pruning on QT implanted GWAS (Supplementary Table 1). 500 SNPs with 500 non-redundant SNPs were randomly selected from 500 SNPs identified through Qc procedures. The GC-corrected Metabochip and Metabochip meta-analysis results were finally meta-analysed (Supplementary Fig. 1).

Using the LD score regression method in the European-only meta-analyses suggests that the observed inflation is not due to population substructure.10

Identification of novel loci. Using a threshold of p < 5 × 10−8 for the GWS-index loci, we identified 776 variants and annotated each of the 12 GWS-index SNPs and the most significant cis-associated SNP for the given transcript in the model to examine whether associations were driven by our GWS-index SNPs or by other nearby variants. Conditional analyses were conducted for all tissues except the brain tissue.

Analyses of eQTLs. The cis-associations between 12 GWS-index SNPs and expression of nearby genes (±500 kb of the index SNP) were examined in the Ensembl annotation79. To identify cis-eQTLs, we performed approach joint and conditional SNP association analysis. Although our primary analyses were based on all ancestry populations, the 12 GWS-index SNPs were strongly associated with BF% in European populations, 6 of them reaching the GWS (Supplementary Table 5).

The estimated LD matrix based on 6,654 unrelated individuals of European ancestry in ARIC cohort was used in the analysis.

Heterogeneity among studies. The potential heterogeneity in the effect estimates for our GWS-index SNPs were investigated between men and women in all-ancestry populations and in European populations, and between individuals of European ancestry and individuals of all ancestry. We also tested for heterogeneity between results from studies that used BIA for BF% assessment and that used DEXA. Heterogeneity was assessed using a t-statistic, which is calculated as:

\[ t = \frac{(β_1 - β_2)/(se_1 + se_2)^{-1/2}}{2 - r_{se_1,se_2}} \]

where \( β_1 \) and \( β_2 \) are the effect size estimates, se1 and se2 are the corresponding standard errors and r is Spearman’s correlation coefficient of beta values between men and women or between European ancestry and all ancestry.

Variance explained. The variance explained by each GWS-index SNP was calculated using the effect allele frequency (f) and \( β \) from the respective meta-analyses using the formula of Explained variance = \( 2β(1 - f^2) \).

Cross-trait association lookups. Cardiometabolic consortia. To explore the relationship between BF% and an array of cardiometabolic traits and diseases, the associations between 12 GWS-index SNPs and primary cardiometabolic genetic consortia: the LEIPen consortium (circulating leptin, Kippen et al., in preparation), VATGen consortium27, GIANT (BMI, height and WHRadjusted)33,42,43, GLGC (HDL-C, LDL-C, TG, TC)38,42, MAGIC, DIAGRAM (T2D)36 and CARDioGRAMplusCHD (CAD)36. On the basis of known traits associations among these cardiometabolic traits, we considered circulating leptin levels, adipose tissue storage, height, WHRwithin, plasma lipid levels, plasma glycemic traits, T2D and CAD as eight independent trait groups. In addition, the associations for these 12 SNPs were also looked up in four consortia that examined phenotypes more distantly related to BF%: ADIPOGen (BMI-adjusted adiponectin)43,44, ReproGen (age at menarche)34, liver enzyme meta-analysis46 and CRP meta-analysis38. For certain GWS-index SNPs, we also did specific lookups: rs6857 association in liver fat storage, rs3761445 associations in cutaneous nevi and melanoma risk meta-analysis42,43, early growth genetics (birth weight2 and pubertal height3), insulin-like growth factor 1 meta-analysis (Gaensler et al., in preparation) and CHARGE and CHARGE-alliance meta-analysis and eBioinfo0049 associations in tooth development meta-analysis33 and Early Growth Genetics Consortium (birth weight2 and pubertal height3).

Coding variants and CNVs. To determine whether any of our 12 GWS-index SNPs might be tagging potentially functional variants, we identified all variants between 500 kb and in LD (r2 > 0.7, HapMap release 22/1000 Genomes Pilot1 EUR) with our GWS-index SNPs. As such, we identified 776 variants and annotated each of them using AnnoVar (http://www.openbioinformatics.org/annovar/). The predicted functional impacts for coding variants were accessed via the Exome Variant Server (https://evs.gs.washington.edu/ EVS/) for PhanGoRM, Grantham, Gphan and PolyPhen, and were also from SIFT (http://sift.jcvi.org/). To determine whether any of the 12 GWS-index SNPs tagged (r2 > 0.7) CNVs, all genetic variants (SNV, Indel and SVS) were included from a GWAS index SNP from the 1000 Genomes Project EUR population (Phase 1) were downloaded. The LD indexes were calculated between each of the 12 GWS-index SNPs and any nearby CNV variants.

Regulatory analysis using ENCODE and Roadmap. Regulatory element overlap. We identified variants in LD (r2 > 0.7, 1000 Genomes Project Pilot, EUR) with each of the 12 GWS-index SNPs and tested for overlap between these variants and elements from regulatory datasets. In total, 746 variants at the 12 GWS-index loci were examined for overlap with regulatory elements in 181 data sets (Supplementary Tables 18 and 19) from five tissues (blood, brain, liver, adipose tissue and pancreatic islets). These data sets, downloaded from the ENCODE Consortium and Roadmap Epigenomics Projects, identify regions of open chromatin (DNase-seq, FAIRE-seq), histone modification signal enrichment (H3K4me1, H3K27ac, H3K4me3, H3K9ac and H3K4me2), and transcription factor binding in cell lines and tissues believed to influence BF%. When available, we downloaded data processed as a part of the ENCODE Integrative Analysis. Roadmap Epigenomics sequencing data were processed with MACS2 and the same irreproducible discovery rate pipeline used in the ENCODE Integrative analysis when multiple data sets were available, or MACS2 alone when only a single replicate was available.

Pol2 binding. We tested for correlation between Pol2 binding strength and genotype in lymphoblastoid cell lines at two SNPs, rs480884 and rs4808844 that were moderated by sex. We conducted GWS-index SNP and the most significant cis-associated SNP for the given transcript in the model to examine whether associations were driven by our GWS-index SNPs or by other nearby variants. Conditional analyses were conducted for all tissues except the brain tissue.

Pathway, network and tissue-enrichment analysis. To define pathways, networks and tissue enrichment, we extended the list of genome-wide significant loci to also include loci that showed putative (p < 1 × 10−3) association with BF% (using the same criteria described above to define independent loci). As such loci, we identified 43 index SNPs that were considered for gene prioritization, pathway enrichment (DEPICT), Ingenuity Pathways Analysis, gene relationship analysis (GRAIL) and protein–protein interaction analyses (DAPPLE).

Data-driven enrichment prioritized integration for complex traits. Details of this method are provided in Pers et al.35 DEPICT is designed to systematically identify the most likely causal gene at a locus, to test gene sets for enrichment for genetic associations, and to identify tissues and cell types in which genes from associated loci are highly expressed.

NHGRI GWAS catalogue lookups. We manually curated and searched the National Human Genome Research Institute (NHGRI) GWAS Catalogue (www.genome.gov/gwastudies) for previously reported associations for SNPs within 500 kb and r2 > 0.7 (1000 Genomes Pilot1 EUR population based on Snapshot: http://www.broadinstitute.org/mpg/snap/ldsearch.php) with each of the 12 GWS-index SNPs. All previously reported associations that reached p < 5 × 10−8 were retained (Supplementary Table 11).
DEPICT assigned genes to the 43 associated loci if the genes resided within the associated LD region \((r^2 > 0.5)\) of a given associated SNP. After merging overlapping regions and discarding regions that mapped within the extended major histocompatibility complex locus, we were left with 42 non-overlapping regions that covered a total of 82 genes. We then used DEPICT to test enrichment at these loci for a total of 14,461 reconstituted gene sets, and for 209 tissue and cell type annotations.

Ingenuity pathway analyses. We used HaploReg v2 (http://www.broadinstitute.org/mammals/haploreg/haploreg.php) and adopted a stringent \(L^2 (r^2 > 0.8)\) in 1000 Genome phase 1 EUR) to extract all the nearby genes (88 genes in total) of the index SNPs based on both GENCODE and RefSeq. For 65 out of them, they were successively mapped into the Ingenuity Knowledge Base, and those unmapped genes are mainly lincRNA, miRNA, antisense or processed transcript genes derived from GENCODE. The 65 genes were incorporated into Ingenuity Canonical pathway enrichment analysis. The \(P\) values are calculated based on Fisher’s right-tailed exact test. The default settings were used for Ingenuity Interaction network analysis.

Gene relationships among implicated loci. The GRAIL was used to examine relationships between genes. For each query and seed SNP, we adopted the default methods implemented in GRAIL to extract the genes around each index SNP: that is, (1) we first identified neighboring SNPs in the 3’ and 5’ direction in LD \((r^2 > 0.3, \text{CEU HapMap})\), proceeding outwards in each direction to the nearest combination hotspots to define an interval region, and extracted all the genes in this interval; (2) if there are no genes in that interval region, the interval is extended an additional 250 kb in either direction. The 12 GWS-index SNP regions were input as seed regions, and the regions for the remaining 31 SNPs were input as query regions. Connections between genes were inferred from textual relationships based on published scientific text using PubMed abstracts as of December 2006. The significant gene similarity was declared based on \(P_{\text{GRAIL}} < 0.01\).

Disease association protein–protein link evaluator. The DAPPLE package was used to examine the potential encoded protein–protein interaction evidence for the genes located in the 43 associated loci. Genes from 32 of the 43 loci were annotated in the high-confidence pair-wise interaction InWeb database. Both the direct and indirect interactions were considered. The running settings were 1,000 permutation, common interaction binding degree \(= 2\), and 110 kb upstream and 40 kb downstream to define a gene’s residence.

**Drosophila knockdown experiments.** Genome-wide screen. We first identified all genes within \(\pm 500\) kb of the 12 GWS-index SNPs, and subsequently identified the corresponding Drosophila orthologues available in the ensemble orthologue database (www.ensembl.org, Supplementary Table 23). Drosophila triglyceride content values were mined from a publicly available genome-wide obesity screen dataset\(^1\). Estimated values represent fractional changes in triglyceride content in adult male flies. Data are from male progeny resulting from crosses of male UAS-RNAi flies and respective fly RNAi stocks for each orthologue were acquired from the Vienna Drosophila Resource Center, as well as genetic background controls w1118 (for GD lines, VDRC #60000); tub-GAL4/TM6 and w; tub-GAL80ts/TM6 is available from the Bloomington Drosophila Stock Center. For fly triglyceride assay in the adult, male RNAi flies were crossed with w; tub-GAL4/tub-GAL80ts/TM6 virgins. Progeny were kept in 16°C until eclosion. Adults were transferred to 25°C for 2 weeks. Whole-animal triglycerides were measured as previously described\(^2\). Briefly, triglycerides were measured using the Infinity Triglycerides Reagent kit (Thermo Fisher #TR232321) on whole-animal homogenates of groups of three animals. Proteins from the same homogenates were measured using the Pierce BCA protein Assay kit (Thermo Scientific #23227). Triglycerides were normalized by proteins. Data were average of three experiments. The fractional changes in triglyceride content in adult male flies between knockdown group and the control groups were compared using the two-tailed t-tests in SAS version 9.2 software (SAS Institute, Cary, NC).

**References**

1. Frayling, T. M. et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 316, 889–894 (2007).
2. Seguret, S. et al. Genome-wide association scan reveals genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet. 3, e115 (2007).
3. Loos, R. J. et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat. Genet. 40, 768–775 (2008).
4. Chambers, J. C. et al. Common genetic variation near MC4R is associated with waist circumference and insulin resistance. Nat. Genet. 40, 716–718 (2008).
5. Willer, C. J. et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat. Genet. 41, 25–34 (2009).
6. Thorleifsson, G. et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nat. Genet. 41, 18–24 (2009).
7. Meyre, D. et al. Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. Nat. Genet. 41, 157–159 (2009).
8. Lindgren, C. M. et al. Genome-wide association scan meta-analysis identifies three loci influencing adiposity and fat distribution. PLoS Genet. 5, e1000508 (2009).
9. Heard-Costa, N. L. et al. NRXN3 is a novel locus for waist circumference: a genome-wide association study from the CHARGE Consortium. PLoS Genet. 5, e1000339 (2009).
10. Speliotes, E. K. et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat. Genet. 42, 937–948 (2010).
11. Heid, I. M. et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat. Genet. 42, 949–960 (2010).
12. Scherag, A. et al. Two new loci for body-weight regulation identified in a joint analysis of genome-wide association studies for early-onset extreme obesity in French and German study groups. PLoS Genet. 6, e1000916 (2010).
13. Kilpelainen, T. O. et al. Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. Nat. Genet. 43, 753–760 (2011).
14. Wen, W. et al. Meta-analysis identifies common variants associated with body mass index in east Asian populations. Nat. Genet. 43, 302–306 (2012).
15. Okada, Y. et al. Common variants at CDKAL1 and KLF9 are associated with body mass index in East Asian populations. Nat. Genet. 44, 507–512 (2012).
16. Bradford, J. P. et al. A genome-wide association meta-analysis identifies new childhood obesity loci. Nat. Genet. 44, 526–531 (2012).
17. Monda, K. L. et al. A meta-analysis identifies new loci associated with body mass index in individuals of African ancestry. Nat. Genet. 45, 690–696 (2013).
18. Falchi, M. et al. Low copy number of the salivary amylase gene predisposes to obesity. Nat. Genet. 46, 492–497 (2014).
19. Locke, A. E. et al. Genetic studies of body mass index yield new insights for obesity biology. Nature 518, 197–206 (2015).
20. Shungin, D. et al. New genetic loci link adipose and insulin biology to body fat distribution. Nature 518, 190–199 (2015).
21. Heo, M., Faith, M. S., Pietrobelli, A. & Heymsfield, S. B. Percentage of body fat cuto...
36. Hansen, T. V. et al. Dwarfism and impaired gut development in insulin-like growth factor II mRNA-binding protein 1-deficient mice. Mol. Cell. Biol. 24, 4492–4503 (2004).
37. Teslovich, T. M. et al. Biological, clinical and population relevance of 95 loci for blood lipids. Nature 466, 707–713 (2010).
38. Dehghan, A. et al. Meta-analysis of genome-wide association studies in >80 000 subjects identifies multiple loci for C-reactive protein levels. Circulation 123, 731–738 (2011).
39. Jun, G. et al. Comprehensive search for Alzheimer disease susceptibility loci in the ARKNeo population. Arch. Neurol. 69, 1270–1279 (2012).
40. Davies, G. et al. A genome-wide association study implicates the APOE locus in nonpathological cognitive ageing. Mol. Psychiatry 19, 76–87 (2014).
41. Deelen, J. et al. Genome-wide association study identifies a single major locus contributing to survival into old age; the APOE locus revisited. Aging Cell 10, 686–696 (2011).
42. Falchi, M. et al. Genome-wide association study identifies variants at 2q21 and 22q13 associated with development of cutaneous nevi. Nat. Genet. 41, 915–919 (2009).
43. Nan, H. et al. Genome-wide association study identifies naidogen 1 (NID1) as a susceptibility locus to cutaneous nevi and melanoma risk. Hum. Mol. Genet. 20, 2673–2679 (2011).
44. Barrett, J. H. et al. Genome-wide association study identifies three new melanoma susceptibility loci. Nat. Genet. 43, 1108–1113 (2011).
45. Rung, J. et al. Genetic variant near IRS1 is associated with type 2 diabetes, insulin resistance and hyperinsulinemia. Nat. Genet. 41, 1110–1115 (2009).
46. Sheffield, N. C. et al. Patterns of regulatory activity across diverse human cell types predict gene activity, transcription factor binding, and long-range interactions. Genome Res. 23, 777–788 (2013).
47. Garel, S., Yun, K., Grosschedl, R. & Rubenstein, J. L. The early topography of thalamocortical projections is shifted in Ebf1 and Dlx1/2 mutant mice. Development 129, 5621–5634 (2002).
48. Ren, D., Li, M., Duan, C. & Rui, L. Identification of SH2-B as a key regulator of leptin sensitivity, energy balance, and body weight in mice. Cell Metab. 2, 95–105 (2005).
49. Brown, L. & Baer, R. HEN1 encodes a 20-kilodalton phosphoprotein that binds an extended E-box motif as a homodimer. Mol. Cell. Biol. 14, 1245–1255 (1994).
50. Pers, T. H. et al. Biological interpretation of genome-wide association studies using predicted gene functions. Nat. Commun. 6, 5890 (2015).
51. Rosen, E. D. & Spiegelman, B. M. What we talk about when we talk about fat. Mol. Endocrinol. 45, 501–512 (2013).
52. Pospisil, J. A. et al. Drosophila genome-wide obesity screen reveals hedgehog as a determinant of brown versus white adipose cell fate. Cell 140, 148–160 (2010).
53. Musselman, L. P. et al. A high-sugar diet produces obesity and insulin resistance in wild-type Drosophila. Dis. Model. Mech. 4, 842–849 (2011).
54. Wheeler, E. et al. Genome-wide SNP and CNV analysis identifies common and low-frequency variants associated with severe early-onset obesity. Nat. Genet. 45, 513–517 (2013).
55. Burd, C. S. et al. KDIGO and KDQIC consensus. Am. J. Kidney Dis. 69, 609–638 (2017).
56. Meier, K. et al. Genomic and epigenetic diversity in renal fibrosis. Kidney Int. 84, 1155–1166 (2013).
57. Nissenson, A. R. et al. The association of chronic kidney disease with mortality and cardiovascular disease: A meta-analysis. Clin. J. Am. Soc. Nephrol. 7, 1113–1123 (2012).
58. Buik-Bakker, J. L. et al. Genome-wide association study and pathway analysis of gene expression for genome-wide association studies (GWAS). PLoS Genet. 8, e1002607 (2012).
59. Chambers, J. C. et al. Genome-wide association study identifies loci influencing concentrations of liver enzymes in plasma. Nat. Genet. 43, 1131–1138 (2011).
60. Ohlsson, C. et al. Genetic determinants of serum testosterone concentrations in 1953 men: evidence from the Stockholm male/twin study. PLoS Genet. 7, e1001313 (2011).
61. Fehrmann, R. S. N. et al. Trans-eQTLs reveal that independent genetic variants associated with a complex phenotype converge on intermediate genes, with a major role for the HLA. PLoS Genet. 7, e1001977 (2011).
62. Zheng, H., Yang, X., Kaplan, L. M., Molony, C. & Schadt, E. E. Integrating pathway analysis and genetics of gene expression for genome-wide association studies (GWAS). Nat. Genet. 41, 591–598 (2010).
63. Min, J. et al. Coexpression network analysis in abdominal and gluteal adipose tissue reveals regulatory genetic loci for metabolic syndrome and related phenotypes. PLoS Genet. 8, e1002505 (2012).
64. Myers, A. J. et al. A survey of genetic human cortical gene expression. Nat. Genet. 39, 1494–1499 (2007).
Franckophone du 358 Diabète); Siemens Healthcare; Signe and Anne Gyllenberg Foundation; Sigrid Jusélius Foundation; Social Insurance Institution of Finland (KELA); State of Bavaria; Stroke Association, UK; Swedish Diabetes Foundation; Swedish Foundation for Strategic Research; Swedish Heart–Lung Foundation; Swedish Research Council; Swedish Research Council for Infrastructures; Swiss National Science Foundation; Sylvia & Charles Viertel Charitable Foundation; Tampere Tubercolous Foundation; Timber Merchant Vilhelm Bangs Foundation; Topcon; Torsten and Ragnar Söderberg’s Foundation; Translational Genomics Research Institute; Unilever UK; University Cancer Research Fund at UNC Chapel Hill; University of Eastern Finland; University of Maryland General Clinical Research Center; Uppsala University; Uppsala University Hospital; USDA National Institute of Food and Agriculture; VA Clinical Science Research and Development; Velux Foundation; VU University Medical Center; Wageningen University; Wellcome Trust.

Author contributions
R.J.F.L. oversaw all aspects of this study and chaired the writing group that consisted of Y.L., F.R.D., S.G., M.L.B., J.N., K.L.M., M.C.Z., J.A.P., C.L. and T.O.K.. Data cleaning and preparations were performed by F.R.D., S.G., R.J.F.L., Y.L. and R.W.W.; and meta-analyses were performed by F.R.D., S.G. and Y.L. A full list of author contributions can be found in the Supplementary Notes.

Additional information
Supplementary Information accompanies this paper at http://www.nature.com/naturecommunications

Competing financial interests: R.E. received honoraria for lectures from the following companies (within the past 2 years): MSD Sharp&Dohme and Pfizer. J.M.I. disclosed Trinity Partners, Inc., Osteoarthritis Research Society International, Chronic Osteoarthritis Management Initiative of US Bone and Joint Initiative, Samumed, Interleukin Genetics, Inc. and Algonomics, Inc. K.S. is a full-time employee of GlaxoSmithKline. D.S. received honoraria for lectures from the following companies (within the past 2 years): MSD Sharp&Dohme. E.S.-T. received honoraria for lectures, research grants and consultancy fees from the following companies (within the past 2 years): Aegerion, Fresenius, MSD Sharp&Dohme, Pfizer and Sanofi. Peter Vollenweider received an unrestricted grant from GSK to build the CoLaus study.

Reprints and permission information is available online at http://npg.nature.com/reprintsandpermissions/

How to cite this article: Lu, Y. et al. New loci for body fat percentage reveal link between adiposity and cardiometabolic disease risk. Nat. Commun. 7:10495 doi: 10.1038/ncomms10495 (2016).

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/
Jeffrey R. O’Connell129, Ben A. Oostra118, Alan R. Shuldiner129,130, Kijoung Song131, Liesbeth Vandeput132, Cornelia M. van Duijn91,118,133, Peter Vollenweider134, Charles C. White30, Michael Boehnke29, Yvonne Boettcher135,136, Richard S. Cooper137, Nita G. Forouhi3, Christian Gieger116,120,125, Harald Graller120,125,138, Aroon Hingorani139, Torben Jørgensen140,141,142, Pekka Jou丝丝lahti56, Mika Kivimaki143, Meena Kamar143, Markku Laasko12,113,114, Claudia Langenberg3,143, Allan Linneberg143, Amy Luke137, Colin A. Mckenzie111, Aarno Palotie10,26,145, Oluf Pedersen31, Annette Peters120,125, Konstantin Strauch116,146, Bamidele O. Tayo137, Nicholas J. Wareham3, David A. Bennett57, Lars Bertram147,148, John Blangero61, Matthias Blüher135,136, Claude Bouchard99, Harry Campbell97, Nam H. Cho149, Steven R. Cummings66, Stefan A. Czerwinski59, Ilja Demuth102,150, Rahel Eckardt102, Johan G. Eriksson56,67,81, Luigi Ferrucci109, Oscar H. Franco91,92, Philippe Froguel53,54,55, Ron T. Gansevoort51, Torben Hansen31,151, Tamara B. Harris72, Nicholas Haste175, Markku Heliövaara56, Albert Hofman91,92, Joanne M. Jordaan87, Antti Jula56, Mika Kähönen152,153, Eero Kajantie56,154,155, Paul B. Knek56, Seppo Koskinen56, Peter Kovacs135, Terho Lehtimäki89,90, Lars Lind56, Yongmei Liu157, Eric S. Orwol95, Clive Osmond158, Markus Perola10,13,15,6, Louis Pérousse159,160, Olli T. Raitakari161,162, Tuomo Rankinen99, D.C. Rao20,104,163, Treva K. Rice104,163, Fernando Rivadeneira65,91,92, Igor Rudan97, Veikko Salomaa56, Thorkild I.A. Sørensen18,31,164, Michael Stumvoll135,136, Anke Tönjes136, Bradford Towne59, Gregory J. Tronah66, Angelo Tremblay159, André G. Uitterlinden65,91,92, Pim van der Harst77,165,166, Erkki Vartiainen56, Jorma S. Viikari167, Veronique Vitart75, Marie-Claude Vohl160,168, Henry Völzke41,169,170, Mark Walker44,171, Henri Wallachofski21,169, Sarah Wild172, James F. Wilson75,97, Loïc Yengo53,54,55, D. Timothy Bishop23, Ingrid B. Borecki20,173, John C. Chambers36,37,147, L. Adrienne Cupples30,175, Abbas Dehghan176, Panos Deloukas25,26,177, Ghazaleh Fatemifar18, Caroline Fox53,175, Terrence S. Furey6,178, Lude Franke77,166, Jiali Han179, David J. Hunter14,28,180,181, Juha Karjalainen166, Fredrik Karpe27,182, Robert C. Kaplan34, Jaspal S. Kooner37,174,183, Mark I. McCarthy12,27,182, Joanne M. Murabito184,185, Andrew P. Morris12,186, Julia A.N. Bishop23, Kari E. North187, Claes Ohlsson132, Ken K. Ong3,188,189, Inga Prokopenko12,19,27, J. Brent Richards11,190,191,192, Eric E. Schadt193,194, Tim D. Spector9, Elisabeth Widén10, Cristen J. Willer35,195,196, M. Carola Zillikens65,91, Cecilia Lindgren12,14,199, Tuomas Oskari Kilpeläinen3,31 & Ruth J.F. Loos1,2,3,200,201

1 The Charles Bronfman Institute for Personalized Medicine, The Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. 2 The Department of Preventive Medicine, The Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. 3 MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, University of Cambridge, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK. 4 Science for Life Laboratory, Uppsala University, 750 85 Uppsala, Sweden. 5 Department of Medical Sciences, Molecular Epidemiology, Uppsala University, 751 85 Uppsala, Sweden. 6 Department of Genetics, University of North Carolina, Chapel Hill, North Carolina 27599, USA. 7 Department of Developmental and Regenerative Biology, The Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. 8 West Herts NHS Trust, Hertfordshire HP2 4AD, UK. 9 Department of Twin Research and Genetic Epidemiology, King’s College London, London SE1 7EH, UK. 10 Institute for Molecular Medicine OX3 7BN, UK. 11 Estonian Genome Center, University of Tartu, Tartu, 51010, Estonia. 12 Broad Institute of the Massachusetts Institute of Technology and Uppsala University, 751 85 Uppsala, Sweden. 13 Department of Preventive Medicine, The Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. 14 The Charles Bronfman Institute for Personalized Medicine, The Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. 15 Divisions of Endocrinology and Genetics and Center for Basic and Translational Obesity Research, Boston Children’s Hospital, Boston, Massachusetts 02115, USA. 16 Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA. 17 University of Queensland Diamantina Institute, Translational Research Institute, Brisbane, Queensland 4102, Australia. 18 MRC Integrative Epidemiology Unit, School of Social and Community Medicine, University of Bristol, Bristol BS82BN, UK. 19 Department of Genomics of Common Disease, School of Public Health, Imperial College London, London W12 ONN, UK. 20 Division of Statistical Genomics, Department of Genetics, Washington University School of Medicine, St Louis, Missouri 63108, USA. 21 Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, 17475 Greifswald, Germany. 22 European University of Applied Sciences, Faculty of Applied Public Health, 18055 Rostock, Germany. 23 Leeds Institute of Cancer and Pathology, Cancer Research UK Leeds Centre, University of Leeds, Leeds LS9 7TF, UK. 24 Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, USA. 25 William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ, UK. 26 Wellcome Trust Sanger Institute, Human Genetics, Hinxton, Cambridge CB10 1SA, UK. 27 Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Churchill Hospital, Oxford OX3 7LJ, UK. 28 Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115, USA. 29 Center for Statistical Genetics, Department of Biostatistics, University of Michigan, Ann Arbor, Michigan 48109, USA. 30 Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts 02118, USA. 31 Novo Nordisk Foundation Center for Basic Metabolic Research, Section of Metabolic Genetics, Faculty of Health and Medical Sciences, University of Copenhagen,
2100 Copenhagen, Denmark. 32 Medical and Population Genetics Program, Broad Institute of MIT and Harvard, Cambridge 02142, USA. 33 Department of Epidemiology Research, Statens Serum Institut, 2100 Copenhagen, Denmark. 34 Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York 10461, USA. 35 Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, Michigan 48109, USA. 36 Department of Epidemiology and Biostatistics, Imperial College London, London W2 1PG, UK. 37 Ealing Hospital NHS Trust, Middex U1 3HW, UK. 38 Lund University Diabetes Centre, Department of Clinical Science, Genetic and Molecular Epidemiology Unit, Skåne University Hospital, 205 02 Malmö, Sweden. 39 Department of Public Health and Clinical Medicine, Unit of Medicine, Umeå University, 901 87 Umeå, Sweden. 40 Department of Odontology, Umeå University, 901 85 Umeå, Sweden. 41 Institute for Community Medicine, University Medicine Greifswald, 17475 Greifswald, Germany. 42 Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, 17475 Greifswald, Germany. 43 Queensland Brain Institute, The University of Queensland, Brisbane 4072, Australia. 44 Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts 02142, USA. 45 Division of Genomics and Rheumatology, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts 02446, USA. 46 Partners Center for Personalized Genetic Medicine, Boston, Massachusetts 02446, USA. 47 Department of Dermatology, Brigham and Women’s Hospital, Boston, Massachusetts 02115, USA. 48 Copenhagen Prospective Studies on Asthma in Childhood, Faculty of Health and Medical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark. 49 Danish Pediatric Asthma Center, Gentofte Hospital, The Capital Region, 2200 Copenhagen, Denmark. 50 Steno Diabetes Center A/S, DK-2820 Gentofte, Denmark. 51 University of Groningen, University Medicine Groningen Center, Department of Medicine, 9700 RB Groningen, The Netherlands. 52 Department of Genetics, Texas Biomedical Research Institute, San Antonio, Texas 78245, USA. 53 CNRS UMR 8199, F-59019 Lille, France. 54 European Genomic Institute for Diabetics, 59000 Lille, France. 55 Université de Lille 2, 59000 Lille, France. 56 National Institute for Health and Welfare, FI-00271 Helsinki, Finland. 57 Rush Alzheimer’s Disease Center, Rush University Medical Center, Chicago, Illinois 60612, USA. 58 Department of Public Health and Caring Sciences, Clinical Nutrition and Metabolism, Uppsala University, 751 85 Uppsala, Sweden. 59 Lifespan Health Research Center, Wright State University Boonshoft School of Medicine, Dayton, Ohio 45420, USA. 60 Department of Anatomy, Seoul National University College of Medicine, Seoul 03080, Korea. 61 South Texas Diabetes and Obesity Institute, University of Texas Rio Grande Valley, Brownsville, Texas 78520, USA. 62 Department of Human Nutrition, Wageningen University, Wageningen, The Netherlands. 63 Umeå University School of Veterinary Medicine, Umeå, Sweden. 64 Partners Translational Psychiatric Neurogenetics, Department of Neurology, Brigham and Women’s Hospital, Boston, Massachusetts 02115, USA. 65 Department of Internal Medicine, Erasmus Medical Center, 3015GT Rotterdam, The Netherlands. 66 California Pacific Medical Center Research Institute, San Francisco, California 94107, USA. 67 Department of General Practice and Primary Health Care, University of Helsinki, FI-00014 Helsinki, Finland. 68 INSERM, UMR_S 1138, Centre de Recherche des Cordeliers, F-75006 Paris, France. 69 Sorbonne Universités, UPMC Univ Paris 06, UMR_S 1138, Centre de Recherche des Cordeliers, F-75006 Paris, France. 70 Université Paris Diderot, Sorbonne Paris Cité, UMR_S 1138, Centre de Recherche des Cordeliers, F-75006 Paris, France. 71 Univ Paris Descartes, Sorbonne Paris Cité, UMR_S 1138, Centre de Recherche des Cordeliers, F-75006 Paris, France. 72 Laboratory of Epidemiology and Population Sciences, National Institute on Aging, Bethesda, Maryland 20892, USA. 73 Department of Medicine A, University Medicine Greifswald, 17475 Greifswald, Germany. 74 Center for Genome Science, National Institute of Health, Osong Health Technology Administration Complex, Chungcheongbuk-do 370914, Korea. 75 MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh EH4 2XU, UK. 76 Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland 20892, USA. 77 University of Groningen, University Medicine Groningen Center, Department of Cardiology, 9700 RB Groningen, The Netherlands. 78 Department of Public Health, Faculty of Medicine, University of Split, Split 21000, Croatia. 79 Hospital District of North Karelia, FI-80210 Joensuu, Finland. 80 Institute of Public Health and Clinical Medicine, University of Eastern Finland, FI-70211 Kuopio, Finland. 81 Folkhälsoforskning Clef, Sweden. 82 Department of Medicine, Oregon Health and Science University, Portland, Oregon 97239, USA. 83 Department of Behavioural Sciences, University of Helsinki, FI-00014 Helsinki, Finland. 84 Research Service, Veterans Affairs Medical Center, Portland, Oregon 97239, USA. 85 Max Planck Institute for Molecular Genetics, Department of Vertebrate Genomics, 14195 Berlin, Germany. 86 Max Planck Institute for Human Development, 14194 Berlin, Germany. 87 Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7280, USA. 88 Translational Laboratory in Genetic Medicine (TIGM), Agency for Science, Technology and Research (A*STAR), 8A Biomedical Grove, Immunos, Level 5, Singapore 138648, Singapore. 89 Department of Clinical Chemistry, University of Tampere School of Medicine, FI-33014 Tampere, Finland. 90 Department of Clinical Chemistry, Fimalab Laboratories and School of Medicine, University of Tampere, FI-33520 Tampere, Finland. 91 Netherlands Genomics Initiative (NGI)-sponsored Netherlands Consortium for Healthy Aging (NCHA), Rotterdam The Netherlands. 92 Department of Epidemiology, Erasmus Medical Center, 3015GT Rotterdam, The Netherlands. 93 Department of Surgical Sciences, Orthopaedics, Uppsala University, 751 85 Uppsala, Sweden. 94 School of Public Health, Oregon Health & Science University, Portland, Oregon 97239, USA. 95 Bone & Mineral Unit, Oregon Health & Science University, Portland, Oregon 97239, USA. 96 Institute of Cell & Molecular Biosciences, New England, Newcastle NE1 7RU, UK. 97 Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG, UK. 98 Hjelt Institute, University of Helsinki, FI-00014 Helsinki, Finland. 99 Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, Louisiana 70808, USA. 100 Department of Internal Medicine, Seoul National University College of Medicine, Seoul 03080, Korea. 101 Institute for Anthropological Research, Zagreb 10000, Croatia. 102 The Berlin Aging Study II; Research Group on Geriatrics; Charité—Universitätsmedizin Berlin, 13347 Berlin, Germany. 103 Lipid Clinic at the Interdisciplinary Metabolism Center, Charité-Universitätsmedizin Berlin, 13353 Berlin, Germany. 104 Division of Biostatistics, Washington University School of Medicine, St Louis, Missouri 63110, USA. 105 EMGO Institute for Health and Care Research, VU University Medical Center, 1081 BT Amsterdam, The Netherlands. 106 VUMC, Department of Epidemiology and Biostatistics, 1081 BT Amsterdam, The Netherlands. 107 Department of Pediatrics, University of Oulu, FI-90014 Oulu, Finland. 108 Department of Pediatrics, Vaasa Central Hospital, FI-65100 Vaasa, Finland. 109 Translational Gerontology Branch, National Institute on Aging, Baltimore, Maryland 21225, USA. 110 Department of Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA. 111 Translational Research Institute of the West Indies, Mona JMAAW15, Jamaica. 112 Faculty of Health Sciences, Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland, 70210 Kuopio, Finland. 113 Department of Medicine, University of Eastern Finland and Kuopio University Hospital, 70210 Kuopio, Finland. 114 Kuopio University Hospital, 70029 Kuopio, Finland. 115 Institute of Human Genetics, Helmholtz Zentrum München—German Research Center for Environmental Health, 85764 Neuherberg, Germany. 116 Institute of Genetic Epidemiology, Helmholtz Zentrum München—German Research Center for Environmental Health, 85764 Neuherberg, Germany. 117 Department of Medicine, University of Eastern Finland and Kuopio University Hospital, 70210 Kuopio, Finland. 118 Genetic Epidemiology Unit, Department of Epidemiology, Erasmus University Medical Center, 3015GT Rotterdam, The Netherlands. 119 Institute of Epidemiology I, Helmholtz Zentrum München—German Research Center for Environmental Health, 85764 Neuherberg, Germany. 120 Institute of Epidemiology II, Helmholtz Zentrum München—German Research Center for Environmental Health, 85764 Neuherberg, Germany. 121 Icelandic Heart Association, Kopavogur 201, Iceland. 122 University of Iceland, Faculty of Medicine, Reykjavík 101, Iceland. 123 Department of Medicine Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts 02115, USA. 124 Institute for Aging Research Hebrew Senior Life, Boston, Massachusetts 02131, USA. 125 Research Unit of Molecular Epidemiology, Helmholtz Zentrum München—German Research Center for Environmental Health, 85764 Neuherberg, Germany. 126 Cardiovascular Health Research Unit, University of Washington, Seattle, Washington 98101, USA. 127 Program in Biostatistics and Biomathematics, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington 98109, USA. 128 Department of Biostatistics, University of Washington, Seattle, Washington 98195, USA. 129 Program for Personalized and Genomic Medicine, Division of Endocrinology, Diabetes and Nutrition,
Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA. 130 Geriatric Research and Education Clinical Center, Vettrans Medical Administration Medical Center, Baltimore, Maryland 21042, USA. 131 Genetics, Projects Clinical Platforms and Sciences, GlaxoSmithKline, Philadelphia, Pennsylvania 19112, USA. 132 Center for Bone and Arthritis Research, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, 413 45 Gothenburg, Sweden. 133 Center for Medical Systems Biology, 2300 Leiden, The Netherlands. 134 Department of Internal Medicine, Hospital Lausanne (CHUV) and University of Lausanne, 1011 Lausanne, Switzerland. 135 University of Leipzig, IFF Adiposity Diseases, 04103 Leipzig, Germany. 136 University of Leipzig, Department of Medicine, 04103 Leipzig, Germany. 137 Department of Public Health Sciences, Stritch School of Medicine, Loyola University Chicago, Maywood, Illinois 61053, USA. 138 German Center for Diabetes Research (DZD), 85764 Neuherberg, Germany. 139 Institute of Cardiovascular Science, University College London, London WC1E 6BT, UK. 140 Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark. 141 Faculty of Medicine, University of Aalborg, 9220 Aalborg, Denmark. 142 Research Centre for Prevention and Health, DK2600 Capital Region of Denmark, Denmark. 143 Department of Epidemiology and Public Health, UCL, London WC1E 6BT, UK. 144 Research Centre for Prevention and Health, Glostrup Hospital, 2600 Glostrup, Denmark. 145 Massachusetts General Hospital, Center for Human Genetic Research, Psychiatric and Neurodevelopmental Genetics Unit, Boston, Massachusetts 02114, USA. 146 Institute of Medical Informatics, Biometry and Epidemiology, Chair of Genetic Epidemiology, Ludwig-Maximilians-Universität, 81377 Munich, Germany. 147 School of Public Health, Faculty of Medicine, Imperial College London, London W6 8RP, UK. 148 Lübeck Interdisciplinary Platform for Genome Analytics, Institutes of Neurogenetics and Integrative and Experimental Genomics, University of Lübeck, 23562 Lübeck, Germany. 149 Ajou University School of Medicine, Department of Preventive Medicine, Suwon Kyong-gi 443-721, Korea. 150 Institute of Medical and Human Genetics, Charité—Universitätsmedizin Berlin, 13353 Berlin, Germany. 151 Faculty of Health Sciences, University of Southern Denmark, 5000 Odense, Denmark. 152 Department of Clinical Physiology, Tampere University Hospital, FI-33014 Tampere, Finland. 153 Department of Clinical Physiology, University of Tampere School of Medicine, FI-33001 Tampere, Finland. 154 Children's Hospital, Helsinki University Hospital and University of Helsinki, FI-00029 Helsinki, Finland. 155 Department of Obstetrics and Gynecology, MRC Oulu, Oulu University Hospital and University of Oulu, FI-90029 Oulu, Finland. 156 Department of Medical Sciences, Uppsala University, 751 85 Uppsala, Sweden. 157 Center for Human Genetics, Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina 27157, USA. 158 MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, UK. 159 Department of Kinesiology, Lausanne University, Quebec City, Quebec, Canada G1V OA6. 160 Institute of Nutrition and Functional Foods, Lausanne University, Quebec City, Quebec, Canada G1V OA6. 161 Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, FI-20521 Turku, Finland. 162 Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, FI-20520 Turku, Finland. 163 Department of Psychiatry, Washington University School of Medicine, St Louis, Missouri 63110, USA. 164 Institute of Preventive Medicine, Bispebjerg and Frederiksborg Hospital, The Capital Region, 2000 Frederiksborg, Denmark. 165 Durrer Center for Cardiogenetic Research, Interuniversity Cardiology Institute Netherlands-Netherlands Heart Institute, 3501 DG Utrecht, The Netherlands. 166 Department of Genetics, University Medicine Center Groningen, University of Groningen, 9700 RB Groningen, The Netherlands. 167 Department of Medicine, University of Turku, FI-20521 Turku, Finland. 168 School of Nutrition, Laval University, Quebec City, Quebec, Canada G1V OA6. 169 DZH-K (German Centre for Cardiovascular Research), partner site Greifswald, 17475 Greifswald, Germany. 170 DZD (German Centre for Diabetes Research), partner site Greifswald, 17475 Greifswald, Germany. 171 Institute of Cellular Medicine, Newcastle University, Newcastle NE2 4HH, UK. 172 Centre for Population Health Sciences, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh EH8 9AG, UK. 173 Analytical Genetics Group, Regeneron Genetics Center, Regeneron Pharmaceuticals, Inc., Tarrytown, New York 10591, USA. 174 Imperial College Healthcare NHS Trust, London W12 OHS, UK. 175 National Heart, Lung, and Blood Institute, the Framingham Heart Study, Framingham, Massachusetts 01702, USA. 176 Department of Epidemiology, Erasmus Medical Center, 3000CA Rotterdam/Zuidholland, The Netherlands. 177 Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah 21589, Saudi Arabia. 178 Department of Biology, University of North Carolina, Chapel Hill, North Carolina 27599, USA. 179 Department of Epidemiology, Richard M. Fairbanks School of Public Health, Melvin and Bren Simon Cancer Center, Indianapolis, Indiana 46202, USA. 180 Channing Division of Network Medicine, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA. 181 Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts 02115, USA. 182 Oxford NIHR Biomedical Research Centre, Oxford OX3 7LI, UK. 183 National Heart and Lung Institute, Imperial College London, London W12 ONN, UK. 184 Boston University School of Medicine, Department of Medicine, Section of General Internal Medicine, Boston, Massachusetts 02118, USA. 185 NHLBI’s and Boston University’s Framingham Heart Study, Framingham, Massachusetts 01702, USA. 186 Department of Biostatistics, University of Liverpool, Liverpool L69 3GA, UK. 187 Carolina Center for Genome Sciences and Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7400, USA. 188 MRC Unit for Lifelong Health and Ageing at UCL, London WC1B 5JU, UK. 189 Department of Paediatrics, University of Cambridge, Cambridge CB2 OQK, UK. 190 Department of Medicine, Lady Davis Institute, Jewish General Hospital, McGill University, Montréal, Québec, Canada H3T1E2. 191 Department of Twin Research, King’s College London, London SE1 1E7, UK. 192 Division of Endocrinology, Lady Davis Institute, Jewish General Hospital, McGill University, Montréal, Québec, Canada H3T1E2. 193 Icahn Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. 194 Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. 195 Department of Human Genetics, University of Michigan, Ann Arbor, Michigan 48109, USA. 196 Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan 48109, USA. 197 Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California 94305, USA. 198 Department of Epigenetics, Max Planck Institute for Immunobiology and Epigenetics, D-76108 Freiburg, Germany. 199 The Big Data Institute, University of Oxford, Oxford OX3 7LI, UK. 200 The Genetics of Obesity and Related Metabolic Traits Program, The Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. 201 The Mindich Child Health and Development Institute, The Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA.