New genetic loci link adipose and insulin biology to body fat distribution

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173. Membership to this consortium is provided below.
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ABSTRACT

To increase our understanding of the genetic basis of body fat distribution and its molecular links to cardiometabolic traits, we conducted genome-wide association meta-analyses of waist- and hip-circumference related traits in up to 224,459 individuals. We identified 49 loci (33 new) associated with waist-to-hip ratio adjusted for body mass index (WHRadjBMI) and an additional 19 loci newly associated with related waist and hip circumference measures (all $P < 5 \times 10^{-8}$). Twenty of the 49 lead WHRadjBMI variants exhibited differential effect size estimates in men and women. The 49 loci were enriched for genes expressed in adipose tissue and for putative regulatory elements in adipocytes. Pathway analyses implicated adipogenesis, angiogenesis, transcriptional regulation, and insulin resistance as processes affecting fat distribution.

INTRODUCTION

Depot-specific accumulation of fat, particularly central abdominal fat, confers an elevated risk of metabolic and cardiovascular diseases and mortality[1]. An easily accessible measure of body fat distribution is waist-to-hip ratio (WHR), a relative comparison of waist and hip circumferences. A larger WHR indicates more intra-abdominal fat deposition and is associated with higher risk for type 2 diabetes (T2D) and cardiovascular disease[2-4]. Conversely, a smaller WHR indicates greater gluteal fat accumulation and is associated with lower risk for T2D, hypertension, dyslipidemia, and mortality[5-8]. Our previous genome-wide association study (GWAS) meta-analyses identified loci for WHR after adjusting for body mass index (WHRadjBMI)[9,10]. These loci are enriched for association with other metabolic traits[9,10] and showed that different fat distribution patterns can have distinct genetic underpinnings[11,12].

To further elucidate the genetic architecture of fat distribution and to increase our understanding of molecular connections between fat distribution and cardiometabolic traits, we performed a meta-analysis of WHRadjBMI in 142,762 individuals with GWAS data, combined with up to 81,697 individuals genotyped with the Metabochip[13], all from the Genetic Investigation of ANthropometric Traits (GIANT) Consortium (see URLs). Given the marked sexual dimorphism previously observed among established WHRadjBMI loci[9,10], we performed analyses in men and women both separately and together. In secondary analyses to more fully characterize the genetic determinants of specific aspects of body fat distribution, we also examined unadjusted WHR, as well as BMI-adjusted and unadjusted waist (WCadjBMI and WC) and hip circumferences (HIPadjBMI and HIP). We evaluated the associated loci in greater detail to understand their contributions to variation in fat distribution, metabolism, and adipose tissue biology, and their links to cardiometabolic traits on the molecular level.

RESULTS

New loci associated with WHRadjBMI

We performed meta-analyses of GWAS of WHRadjBMI in up to 142,762 individuals of European ancestry from 57 new or previously described GWAS[9], and separately in up to an additional 67,326 European ancestry individuals from 44 Metabochip studies (**Supplementary Fig. 1**; **Supplementary Tables 1-3**). The further meta-analysis of these GWAS and Metabochip meta-analyses included up to 2,542,447 autosomal SNPs in up to 210,088 European ancestry individuals (Online Methods). We defined new loci based on thresholds of genome-wide significant association ($P < 5 \times 10^{-8}$ after genomic control correction at both the study-specific and meta-analytic levels) and initially, based on distance (>500 kb) from previously established loci[9,10].

Across all meta-analyses of European ancestry individuals, we identified 48 loci for WHRadjBMI, 32 novel and 16 previously described[9,10]. Of the 48 loci, 39 were identified in the sex-combined analysis, 24 of which were novel (**Table 1**, **Supplementary Table 4**, and **Supplementary Figs. 2-4**)[9,10]. The sex-specific analyses confirmed a 16th established locus (*TNFAIP8-HSD17B4*)[10] and identified eight additional new WHRadjBMI loci significant in women but not in men (all $P > 0.05$; **Table 1**, **Supplementary Fig. 5**). When we included Metabochip data from eight studies of 14,371 individuals of non-European ancestry (**Supplementary Tables 1-3**), we identified a 49th WHRadjBMI locus in women (rs1534696, near *SNX10*, $P_{women} = 2.1 \times 10^{-8}$, $P_{men} = 0.26$, **Table 1**), with no evidence of heterogeneity across ancestries ($P_{het} = 0.86$, **Supplementary Note**).

Genetic architecture of WHRadjBMI

To evaluate sexual dimorphism, we compared sex-specific effect size estimates of the 49 genome-wide significant WHRadjBMI lead SNPs. The effect estimates were significantly different ($P_{difference}$ < 0.05/49 = 0.001) at 20 SNPs, 19 of which showed larger effects in women (**Table 1, Supplementary Fig. 6**), similar to previous findings[9,10]. The only SNP that showed a larger effect in men mapped near *GDF5* (rs224333, β_{men} = 0.036 and $P = 9.00 \times 10^{-12}$, β_{women} = 0.009 and P = 0.074, $P_{difference}$= 6.42 x 10^{-5}), a locus shown previously to be associated with height (rs6060369, r^2 = 0.96 and rs143384, r^2 = 0.96) without significant differences between sexes[14,15]. Consistent with the larger number of loci identified in women, however, variance component analyses demonstrated a significantly larger heritability of WHRadjBMI in women than men in the Framingham Heart (h^2_{women} = 0.46, h^2_{men} = 0.19, $P_{difference}$ = 0.0037) and TwinGene studies (h^2_{women} = 0.56, h^2_{men} = 0.32, $P_{difference}$ = 0.001, **Supplementary Table 5**, **Supplementary Fig. 7**, Online Methods).

To identify additionally associated variants, we performed approximate conditional analyses of the sex-combined and sex-specific data using GCTA[16,17], allowing signals within 500 kb of each other to be identified (Online Methods, **Supplementary Note**). Additional significant association signals ($P < 5 \times 10^{-8}$) were identified at nine loci (**Table 2**). Fitting SNPs jointly identified different SNPs in the sex-specific and sex-combined analyses at some loci. For example, the *MAP3K1-ANKRD55* locus showed two independent SNPs 54 kb apart (r^2 < 0.06) that were significant only in women (rs3936510) or in men (rs459193, **Table 2, Supplementary Table 4**). Other signals are more complex. The *TBX15-WARS2* locus showed different lead SNPs in men and women near *WARS2* (r^2 = 0.43), an independent signal near *TBX15,* and a distant independent signal near *SPAG17* (**Fig. 1, Table 2**). At the *HOXC* gene cluster, conditional analyses identified SNPs ~80 kb apart near *HOXC12-HOXC13-HOTAIR* and near *HOXC4-HOXC5-HOXC6,* which exhibit low pairwise linkage disequilibrium (LD) (r^2 < 0.01, **Fig. 1, Table 2**). These data identify

additional, independent signals that might suggest different possible underlying genes and show that these independent SNPs could be specific to one sex.

We assessed the aggregate effects of the 49 lead WHRadjBMI variants using a genetic risk score in the KORA study (n = 3,440 individuals) by calculating sex-combined and sex-specific risk scores including genome-wide significant SNPs (Online Methods). The risk scores were significantly associated with WHRadjBMI in a linear regression model, with substantially stronger effect in women than in men (overall effect per allele $\beta = 0.001$, $P = 6.7 \times 10^{-4}$, women $\beta = 0.002$, $P = 1.0 \times 10^{-11}$, men $\beta = 7.0 \times 10^{-4}$, $P = 0.02$, **Supplementary Fig. 8, Supplementary Note**). The 49 SNPs combined explained 1.4% of the variance in WHRadjBMI overall, more in women (2.4%) than in men (0.8%) (**Supplementary Table 6;** Online Methods). When compared to the 16 previously reported loci[9,10], the new loci approximately doubled the explained variance in women and tripled the explained variance in men. Sex-combined analyses demonstrating an excess of directionally consistent effects between GWAS and Metabochip meta-analyses suggest that additional common WHRadjBMI variants may be found to be reproducible with larger samples ($P_{binomial} = 3.9 \times 10^{-12}$**, Supplementary Note**).

At 17 loci with high-density coverage on the Metabochip[18], we used association summary statistics to define credible sets of variants with a high probability of containing a likely functional variant (Online Methods). The 99% credible sets at seven WHRadjBMI loci spanned <20 kb, and at *HOXC13* included only a single SNP (**Supplementary Table 7, Supplementary Fig. 9**). Although these analyses do not test all SNPs and thus do not necessarily pinpoint the causal variants, they help prioritize variants for further investigation.

Association of WHRadjBMI variants with other anthropometric and cardiometabolic traits

Given the epidemiological associations between central obesity and other anthropometric and cardiometabolic traits and diseases, we evaluated lead WHRadjBMI variants in association data from GWAS consortia for 22 traits (Online Methods). The 49 variants were associated ($P < 5 \times 10^{-8}$) with high-density lipoprotein cholesterol (HDL-C; $n = 7$ SNPs), triglycerides ($n = 5$), low-density lipoprotein cholesterol (LDL-C; $n = 2$), adiponectin ($n = 3$), fasting insulin adjusted for BMI ($n = 2$), T2D ($n = 1$), and height ($n = 7$) (**Supplementary Tables 8-9**). WHRadjBMI SNPs showed enrichment for directionally consistent (as expected from phenotypic correlations) and nominally significant ($P < 0.05$) associations with these traits and also with 2-hour glucose, coronary artery disease, and endometriosis ($P_{binomial} < 0.05/23 = 0.0022$, **Supplementary Table 10**); these results were generally supported by meta-regression analysis of the beta-estimates (**Supplementary Table 11**). Further, our WHRadjBMI loci overlap with associations reported in the NHGRI GWAS Catalog (**Supplementary Table 12**)[19], the strongest of which is the locus near *LEKR1,* which is associated ($P = 2.0 \times 10^{-35}$) with birth weight[20]. These data extend knowledge about genetic links between WHRadjBMI and metabolic, insulin resistance-related traits; whether this reflects underlying causal relations between WHRadjBMI and these traits, or pleiotropic loci, cannot be inferred from our data.

To evaluate whether these cross-trait SNP associations segregate into subsets of WHRadjBMI loci with shared biological effects, we performed unsupervised hierarchical clustering of the corresponding matrix of association *Z*-scores (**Fig. 2**). The WHRadjBMI-increasing alleles at the 49 lead SNPs segregate into three major clusters comprised of alleles that associate with: 1) larger WCadjBMI and smaller HIPadjBMI (30 SNPs); 2) taller stature and larger WCadjBMI (8 SNPs); and 3) shorter stature and smaller HIPadjBMI (11 SNPs). The three visually identified SNP clusters could be statistically distinguished with >90% confidence[21]. Alleles of the first cluster were predominantly associated with lower HDL-C, and with higher triglycerides and

720 fasting insulin adjusted for BMI, suggesting that the genes at these loci may play a role in
721 regulating metabolic traits. Our data cannot distinguish whether these effects are independent of
722 or mediated by WHR.
723
724 **Potential functional variants at new WHRadjBMI loci**
725 We next examined variants in strong LD with the WHRadjBMI lead SNPs (r^2 > 0.70, 1000
726 Genomes Phase 1) for predicted effects on protein sequence, copy number, or *cis*-regulatory
727 effects on expression (**Table 3,** Online Methods). New loci did not contain any known copy
728 number variants (**Supplementary Table 13, Supplementary Note).** We identified one
729 nonsynonymous substitution (*GDF5* S276A; **Supplementary Table 14**) and 25 variants (at 12
730 loci) within 500 bp of a transcription start site (**Supplementary Table 15**). At 11 of the new loci,
731 the SNP associated with WHRadjBMI was either the strongest SNP associated ($P < 10^{-5}$) in *cis*
732 with expression of a transcript in subcutaneous adipose tissue, omental adipose tissue, liver, or
733 blood cell types, or it explained a substantial portion of the variance in transcript levels when
734 conditional analyses were performed (adjusted $P > 0.05$; **Table 3, Supplementary Table 16**).
735 There was no convincing evidence of sexual dimorphism in the expression quantitative trait
736 locus (eQTL) associations, perhaps reflecting limited power (**Supplementary Table 17)**.
737
738 At the 11 WHRadjBMI loci harboring eQTLs, we compared the location of the candidate variants
739 to regions of open chromatin (DNase I hypersensitivity and FAIRE[22] peaks) and histone
740 modification enrichment (H3K4me1, H3K4me2, H3K4me3, H3K27ac, and H3K9ac peaks) in
741 adipose, liver, skeletal muscle, bone, brain, blood, and pancreatic islet tissues or cell lines
742 (**Supplementary Table 18**). At seven of these 11 loci, at least one variant was located in a
743 putative regulatory element in two or more datasets from the same tissue as the eQTL,
744 suggesting that these elements may influence transcriptional activity (**Supplementary Table**

745 **19**). For example, at *LEKR1*, five variants in LD with our WHRadjBMI lead SNP are located in a
746 1.1 kb region with evidence of active enhancer activity (H3K4me1 and H3K27ac) in adipose
747 tissue (**Supplementary Fig. 10**).
748
749 We also examined whether any variants overlapped with open chromatin or histone
750 modifications from only one of the tested tissues, possibly reflecting tissue-specific regulatory
751 elements (**Supplementary Table 19**). For example, five variants in a 2.2 kb region located 77
752 kb upstream from the first *CALCRL* transcription start site overlapped with peaks in at least five
753 datasets in endothelial cells (**Supplementary Fig. 10**), suggesting that one or more of these
754 variants may influence transcriptional activity. In line with this, *CALCRL*, which is highly
755 expressed in endothelial cells, is required for lipid absorption in the small intestine, and
756 influences body weight in mice[23]. Other variants located in apparently tissue-specific regulatory
757 elements were detected at *NMU* for endothelial cells, at *KLF13* and *MEIS1* for liver, and at
758 *GORAB* and *MSC* for bone (**Supplementary Table 19**).
759
760 **Biological mechanisms identified by the genes underlying the WHRadjBMI variants**
761 To identify potential functional connections between genes mapping at the 49 WHRadjBMI-
762 associated loci, we used three partly complementary approaches that rely on published
763 literature, predefined gene sets, or expression data-based gene sets (**Supplementary Note**). A
764 survey of published literature using GRAIL[24] identified 24 genes with nominal significance ($P <$
765 0.05) for potential functional connectivity, and key words describing these connections include
766 'development', 'VEGF' (vascular endothelial growth factor), 'mesenchyme' and 'transcription'
767 (**Supplementary Table 20**). To identify potential predefined gene set relationships across loci
768 we used MAGENTA[25], which prioritizes gene sets. MAGENTA highlighted VEGF and PTEN
769 (phosphatase and tensin homolog) signaling (**Supplementary Table 21**); VEGF signaling plays

770 a central, complex role in angiogenesis, insulin resistance, and obesity[26], and PTEN signaling
771 promotes insulin resistance[27]. In parallel, we employed DEPICT, which facilitates prioritization of
772 genes at associated loci, analyses of tissue specificity, and enrichment of gene sets through
773 integration of association results with expression data, protein-protein interactions, phenotypic
774 data from gene knockout screens in mice, and predefined gene sets (Online Methods). To avoid
775 biasing the identification of genes and pathways covered by SNPs on the Metabochip, analyses
776 were restricted to GWAS cohort data and included 226 WHRadjBMI SNPs in 78 non-
777 overlapping loci with sex-combined $P < 10^{-5}$. DEPICT identified at least one significantly
778 prioritized gene (false discovery rate (FDR) < 5%) at 28 of the 78 loci (8 of the 49 new loci)
779 (**Table 3**, **Supplementary Table 22**). DEPICT also identified 234 gene sets (161 after pruning
780 of overlapping gene sets) enriched for genes at WHRadjBMI loci, including gene sets involved
781 in body fat regulation (including adiponectin signaling, insulin sensitivity, and regulation of
782 glucose levels), skeletal growth, transcriptional regulation, and development (**Fig. 3,**
783 **Supplementary Table 23**). These gene sets include sets specific for abundance or
784 development of metabolically active tissues including adipose, heart, liver, and muscle. Specific
785 genes at the associated loci were also significantly enriched (FDR < 5%) for expression in
786 adipocyte-related tissues, including abdominal subcutaneous fat (**Fig. 4**, **Supplementary Table**
787 **24**). Together, these analyses identified processes related to insulin and adipose biology and
788 highlight mesenchymal tissues, especially adipose tissue.
789
790 We also tested variants at the 49 WHRadjBMI loci for overlap with elements from 60 selected
791 regulatory datasets from the ENCODE and Epigenomic RoadMap data[28] and found evidence of
792 enrichment in 12 datasets ($P < 0.05/60 = 8.3 \times 10^{-4}$, **Supplementary Table 25**). The strongest
793 enrichments were detected for datasets typically attributed to enhancer activity (H3K4me1 and
794 H3K27ac) in adipose, muscle, endothelial cells, and bone, suggesting that variants at

795 WHRadjBMI loci may regulate transcription in these tissues and cells. These analyses point to
796 mechanisms linking WHRadjBMI loci to regulation of gene expression in tissues highly relevant
797 for adipocyte metabolism and insulin resistance.
798
799 We subsequently evaluated reported functions in the literature of candidate genes located near
800 new and previously identified WHRadjBMI loci[9,10], identifying numerous genes involved in
801 adipogenesis, angiogenesis, and transcriptional regulation (**Table 3,** literature review in the
802 **Supplementary Note**). Adipogenesis candidate genes include *CEBPA*, *PPARG, BMP2,*
803 *HOXC/miR196, SPRY1, TBX15,* and *PEMT*. Of these, *CEBPA* and *PPARG* are essential for
804 white adipose tissue differentiation[29], *BMP2* induces differentiation of mesenchymal stem cells
805 toward adipogenesis or osteogenesis[30], and *HOXC8* is a repressor of brown adipogenesis in
806 mice that is regulated by miR-196a[31], also located within the *HOXC* candidate gene region (**Fig.**
807 **1**). Angiogenesis genes may influence expansion and loss of adipose tissue[32]; they include
808 *VEGFA, VEGFB, RSPO3, STAB1, WARS2, PLXND1, MEIS1, FGF2, SMAD6,* and *CALCRL*.
809 *VEGFB* is involved in endothelial targeting of lipids to peripheral tissues[33], and *PLXND1* limits
810 blood vessel branching, antagonizes VEGF signalling, and affects adipose tissue
811 inflammation[34,35]. Transcriptional regulators at WHR loci include *CEBPA*, *PPARG*, *MSC,*
812 *SMAD6, HOXA*, and *HOXC* genes*, ZBTB7B, JUND, KLF13, MEIS1, RFX7, NKX2-6*, and
813 *HMGA1*. Other candidate genes include *NMU*, *FGFR4*, and *HMGA1*, for which mice deficient for
814 the corresponding genes exhibit obesity, glucose intolerance, and/or insulin resistance[36-38].
815
816 **New loci associated with five additional central obesity traits and their biology**
817 To determine whether the WHRadjBMI variants exert their effects primarily through an effect on
818 WC or HIP and to identify loci that are not reported for WHRadjBMI, BMI, or height[39,40], we
819 performed association analyses in GWAS and Metabochip data for five additional traits:

WCadjBMI, HIPadjBMI, WHR, WC, and HIP. Based on phenotypic data alone, WC and HIP are highly correlated with BMI (r = 0.59–0.92), and WHR is highly correlated with WHRadjBMI (r = 0.82–0.95), while WCadjBMI, HIPadjBMI are moderately correlated with height (r = 0.24–0.63) (**Supplementary Table 26)**. Analyses of genetic correlations showed that, in contrast to WHRadjBMI, which has almost no genetic correlation with height (r_G < 0.04, Online Methods, **Supplementary Table 27**), WCadjBMI and HIPadjBMI have moderate genetic correlations with height (r_G = 0.42 and 0.82, respectively), suggesting that some, but not all, WCadjBMI and HIPadjBMI loci would be associated with height. For all five traits, sex-combined and sex-specific analyses were performed in European ancestry individuals and in individuals of all ancestries. Association loci were defined as novel based on distance and LD thresholds (>500 kb and r^2 < 0.1) compared to loci previously or currently reported for WHRadjBMI, BMI, or height[39,40].

Sex-combined and sex-specific association meta-analyses identified an additional 19 loci associated with traits other than WHRadjBMI ($P < 5 \times 10^{-8}$), nine of which showed significantly larger effects ($P_{difference}$ < 0.05/19 = 0.003) in one sex (**Table 4**, **Supplementary Figs. 2-5, Supplementary Tables 28-29**). Three of the four new loci with larger effects in women were associated with HIPadjBMI, the strongest of which mapped near *KLF14* ($P = 9.89 \times 10^{-14}$), a locus previously associated with multiple metabolic traits[41-44] (**Supplementary Table 12**). Three of the five new loci with larger effects in men were associated with WCadjBMI, one of which mapped near *ARL15,* a locus at which other variants (r^2 < 0.7) have been associated with adiponectin and lipid levels[43,45]. The locus near *PDXDC1* associated with HIP was previously associated with phospholipid levels, fatty acid metabolism, and bone mineral density[46-48] (**Supplementary Table 12**). Of the 19 loci identified for these additional traits, most showed some evidence of association with WHRadjBMI in sex-combined, women-specific or men-

specific analyses, but four loci showed no association (P > 0.01) with WHRadjBMI, BMI, or height (**Supplementary Tables 8G, 8H and 30**).

We next asked whether the genes and pathways influencing these additional aspects of body fat distribution are shared with WHRadjBMI or are distinct. Candidate genes were identified based on association with other metabolic traits, eQTLs, GRAIL pathway analysis, and literature review (**Supplementary Tables 8, 12, 14, 16, 20, 28**). Coding variants were identified (r^2 > 0.7) in *NTAN1* and *HMGXB4*, and six loci showed significant eQTLs in subcutaneous adipose tissue. Based on the literature, several likely candidate genes are involved in adipogenesis and insulin resistance. For example, delayed induction of preadipocyte transcription factor *ZNF423* in fibroblasts results in delayed adipogenesis[49], *NLRP3* is part of inflammasome and pro-inflammatory T-cell populations in adipose tissue that contribute to inflammation and insulin resistance[50], and *FABP6* is involved in fatty acid uptake, transport, and metabolism[51]. GRAIL analyses for the five traits identified connections that partially overlap with those identified for WHRadjBMI. The largest overlap was observed for WHR and HIPadjBMI (~50–55% overlap), following by WCadjBMI and HIP (~35–40%); common key words describing the connections included ‘expression’, ‘growth’, ‘signaling’ and ‘transcription’ (**Supplementary Table 20**). Based on these collected analyses, the additional loci appear to function in processes similar to the WHRadjBMI loci. The identification of loci that are more strongly associated with WCadjBMI or HIPadjBMI than the other anthropometric traits suggests that these traits characterize aspects of central obesity and fat distribution that are not captured by WHRadjBMI or BMI alone.

DISCUSSION

These extensive meta-analyses of GWAS and Metabochip data in up to 224,459 individuals identified 33 new and 16 known loci associated with WHRadjBMI, including nine loci that

harbored two or more signals. Our analyses identified 19 additional loci associated with waist and hip circumference measures that had not been reported previously for anthropometric traits. Collectively, these observations help elucidate the role of common genetic variation in body fat distribution that is distinct from BMI and height, and provide new insights into its molecular basis and connections with cardiometabolic traits.

Our results emphasize the strong sexual dimorphism in the genetic regulation of fat distribution traits, a characteristic not observed for overall obesity as assessed by BMI[39,52,53]. Of the 49 WHRadjBMI loci, 19 show stronger effects in women compared to one with stronger effects in men, and we report larger heritability of WHRadjBMI in women. Nine of the 19 loci associated with WCadjBMI, HIPadjBMI, and WHR not adjusted for BMI also showed clear evidence of sexual dimorphism. WCadjBMI loci usually had stronger effects in men and HIPadjBMI loci in women.

Annotation of the loci associated with body fat distribution based on functional relationships with respect to tissue expression and biological pathways, other metabolic traits, eQTLs, and epigenomic data emphasized an important role for mesenchymally-derived tissues, especially adipose tissue, in fat distribution and central obesity. The development and regulation of adipose tissue deposition is closely associated with angiogenesis, a process highlighted by prioritized candidate genes at several WHRadjBMI loci. Explant cultures of adipose tissue trigger the formation of blood vessels through production and secretion of proangiogenic factors, such as VEGFA and VEGFB; in parallel, adipose endothelial cells stimulate preadipocyte differentiation[54]. These peripheral tissues are implicated in insulin resistance, consistent with the enrichment of shared GWAS signals with lipids, diabetes, and glycemic traits. The identification of skeletal growth processes suggests that the underlying genes affect early development

and/or differentiation of adipocytes from mesenchymal stem cells. The processes observed here are also consistent with those in monogenic disorders, such as partial lipodystrophies, which affect development and/or maintenance of specific regional fat depots[55].

Together, these data demonstrate that the genetic regulation of fat distribution involves genes and processes largely distinct from those that influence overall obesity, as assessed by BMI. BMI has a significant neuronal component, involving processes such as appetite regulation[39,52,53], in contrast to the central role of adipocyte biology and insulin resistance suggested here for the fat distribution traits. Further, BMI has significant enrichment of expression in neuronal tissues (see accompanying GIANT paper) while WHRadjBMI shows enrichment of adipose tissue only (**Fig. 4**). We thus provide a foundation for future biological research in the regulation of body fat distribution and its connections with cardiometabolic traits, and offer potential target mechanisms for ultimate interventions in the risks associated with abdominal fat accumulation.

FIGURE LEGENDS

Figure 1 - Regional SNP association plots illustrating the complex genetic architecture at two loci related to WHRadjBMI. Sex-combined meta-analysis SNP associations in European individuals were plotted with $-\log_{10}$ *P* values (left *y*-axis) and estimated local recombination rate in blue (right *y*-axis). Regional SNP coverage is shown in rows above each panel. Three SNPs near *HOXC6-HOXC13* (**A–C**) and four near *TBX15-WARS2-SPAG17* (**D–G**) were identified at these loci through approximate conditional analyses of sex-combined or sex-specific associations (values shown as $P_{conditional} < 5 \times 10^{-8}$, see Methods). On each plot, the signals are distinguished by both color and shape, and linkage disequilibrium (r^2) of nearby SNPs is shown by a color intensity gradient.

Figure 2 - Heat map of unsupervised hierarchical clustering of the effects of 49 WHRadjBMI SNPs on 24 anthropometric and metabolic traits and diseases. The matrix of *Z*-scores representing the set of associations was scaled by row (locus name) and by column (trait) to range from –3 to 3. Negative values (blue) indicate that the WHRadjBMI-increasing allele was associated with decreased values of the trait and positive values (red) indicate that this allele was associated with increased values of the trait. Dendrograms indicating the clustering relationships are shown to the left and above the heat map. WCadjBMI, waist circumference adjusted for BMI; HIPadjBMI, hip circumference adjusted for BMI; HDL, high-density lipoprotein cholesterol; eGFRcrea, estimated glomerular filtration rate based on creatinine; LDL, low-density lipoprotein cholesterol; FIadjBMI, fasting insulin adjusted for BMI; UACR, urine albumin-to-creatinine ratio; BMD, bone mineral density.

Figure 3 - Significant gene sets from the DEPICT gene set enrichment analysis. Among genes at loci associated with WHRadjBMI ($P < 10^{-5}$), gene sets found to be significantly

935 enriched by DEPICT are represented as nodes. Their degree of pairwise overlap with other
936 gene sets, as measured by the Jaccard Index, is denoted by the width of the line connecting
937 nodes. Gene sets were collapsed into meta-nodes if the proportion of overlapping genes was
938 greater than 25%. All gene sets with FDR < 5% are shown and are color-coded according to
939 their empirical enrichment *P* value (dark blue gene sets as most significant). The inset shows in
940 greater detail the 'Decreased Liver Weight' meta-node, which consisted of 12 overlapping gene
941 sets, several of which are relevant to WHRadjBMI, including adiponectin signaling and insulin
942 sensitivity.
943
944 **Figure 4 - Genes at WHRadjBMI-associated loci are significantly enriched for expression**
945 **in adipocytes and adipose tissues.** Based on expression patterns in 37,427 human
946 microarray samples, DEPICT identified that genes at WHRadjBMI loci ($P < 10^{-5}$) were
947 significantly enriched for expression in adipocytes and adipose tissues (FDR < 5%).
948 Enrichments are grouped according to cell- and tissue-type annotations and significance
949
950
951 **URLs**
952 Summary results for GIANT Consortium studies are available at
953 http://www.broadinstitute.org/collaboration/giant/
954 NHGRI GWAS Catalog, http://www.genome.gov/gwastudies
955 GENCODE, http://www.gencodegenes.org/
956 ANNOVAR, http://www.openbioinformatics/annovar/

Table 1 - WHRadjBMI loci achieving genome-wide significance ($P < 5 \times 10^{-8}$) in sex-combined and/or sex-specific meta-analyses

					Sex-combined			Women			Men			Sex difference
SNP	**Chr**	**Position**	**Locus**	**EA[a]**	**EAF**	**β**	***P***	***N***	**β**	***P***	***N***	**β**	***P***	***N***	***P*[b]**
Novel loci achieving genome-wide significance in European-ancestry meta-analyses															
rs905938	1	153,258,013	*DCST2*	T	0.74	0.025	7.3E-10	207,867	0.034	**4.9E-10**	115,536	0.015	1.10E-02	92,461	1.6E-02
rs10919388	1	168,639,127	*GORAB*	C	0.72	0.024	3.2E-09	181,049	0.033	**4.8E-10**	102,446	0.013	2.98E-02	78,738	9.8E-03
rs1385167	2	66,054,152	*MEIS1*	G	0.15	0.029	**1.9E-09**	206,619	0.023	4.0E-04	114,668	0.036	2.32E-07	92,085	1.6E-01
rs1569135	2	187,823,643	*CALCRL*	A	0.53	0.021	**5.6E-10**	209,906	0.023	6.9E-07	116,642	0.019	1.48E-04	93,398	5.8E-01
rs10804591	3	130,816,923	*PLXND1*	A	0.79	0.025	6.6E-09	209,921	0.040	**6.1E-13**	116,667	0.004	5.28E-01	93,387	**5.7E-06**
rs17451107	3	158,280,303	*LEKR1*	T	0.61	0.026	**1.1E-12**	207,795	0.023	1.0E-06	115,735	0.030	1.42E-08	92,194	3.5E-01
rs3805389	4	56,177,507	*NMU*	A	0.28	0.012	1.5E-03	209,218	0.027	**4.6E-08**	116,226	-0.007	2.09E-01	93,125	**1.6E-06**
rs9991328	4	89,932,144	*FAM13A*	T	0.49	0.019	4.5E-08	209,925	0.028	**3.4E-10**	116,652	0.007	1.69E-01	93,407	**8.5E-04**
rs303084	4	124,286,398	*SPATA5-FGF2*	A	0.80	0.023	**3.9E-08**	209,941	0.029	3.4E-07	116,662	0.016	9.91E-03	93,412	1.1E-01
rs9687846	5	55,897,651	*MAP3K1*	A	0.19	0.024	7.1E-08	208,181	0.041	**3.8E-12**	115,897	0.000	9.69E-01	92,417	**1.3E-06**
rs6556301	5	176,460,183	*FGFR4*	T	0.36	0.022	**2.6E-08**	178,874	0.018	7.1E-04	101,638	0.029	1.00E-06	77,370	1.4E-01
rs7759742	6	32,489,714	*BTNL2*	A	0.51	0.023	**4.4E-11**	208,263	0.024	1.7E-07	115,648	0.023	5.49E-06	92,749	8.6E-01
rs1776897	6	34,302,989	*HMGA1*	G	0.08	0.030	1.1E-05	177,879	0.052	**6.8E-09**	100,516	0.003	7.42E-01	77,497	**1.8E-04**
rs7801581	7	27,190,296	*HOXA11*	T	0.24	0.027	**3.7E-10**	195,215	0.025	7.7E-06	108,866	0.029	2.39E-06	86,483	6.9E-01
rs7830933	8	23,659,269	*NKX2-6*	A	0.77	0.022	7.4E-08	209,766	0.037	**1.2E-12**	116,567	0.001	8.35E-01	93,333	**1.4E-06**
rs12679556	8	72,676,782	*MSC*	G	0.25	0.027	**2.1E-11**	203,826	0.033	2.1E-10	114,369	0.017	4.15E-03	89,591	2.8E-02
rs10991437	9	106,775,741	*ABCA1*	A	0.11	0.031	**1.0E-08**	209,941	0.040	2.8E-08	116,644	0.022	6.13E-03	93,430	7.2E-02
rs7917772	10	104,477,433	*SFXN2*	A	0.62	0.014	5.6E-05	209,642	0.027	**5.5E-09**	116,514	-0.001	8.57E-01	93,263	**2.3E-05**
rs11231693	11	63,619,188	*MACROD1-VEGFB*	A	0.06	0.041	4.5E-08	198,072	0.068	**2.7E-11**	110,164	0.009	4.20E-01	88,043	**2.5E-05**
rs4765219	12	123,006,063	*CCDC92*	C	0.67	0.028	**1.6E-15**	209,807	0.037	1.0E-14	116,592	0.018	5.32E-04	93,350	5.7E-03
rs8042543	15	29,495,555	*KLF13*	C	0.78	0.026	**1.2E-09**	208,255	0.023	6.7E-05	115,760	0.030	1.01E-06	92,629	3.6E-01
rs8030605	15	54,291,890	*RFX7*	A	0.14	0.030	**8.8E-09**	208,374	0.031	1.0E-05	115,864	0.031	5.91E-05	92,644	9.9E-01
rs1440372	15	64,820,205	*SMAD6*	C	0.71	0.024	**1.1E-10**	207,447	0.022	1.1E-05	115,201	0.027	1.39E-06	92,380	5.2E-01
rs2925979	16	80,092,291	*CMIP*	T	0.31	0.018	1.2E-06	207,828	0.032	**3.4E-11**	115,431	-0.002	7.86E-01	92,531	**1.2E-06**
rs4646404	17	17,360,924	*PEMT*	G	0.67	0.027	**1.4E-11**	198,196	0.034	5.3E-11	115,337	0.017	2.45E-03	87,857	2.6E-02
rs8066985	17	65,964,940	*KCNJ2*	A	0.50	0.018	1.4E-07	209,977	0.026	**4.0E-09**	116,683	0.007	1.89E-01	93,428	1.8E-03
rs12454712	18	58,996,864	*BCL2*	T	0.61	0.016	1.0E-04	169,793	0.035	**1.1E-09**	96,182	-0.007	2.45E-01	73,576	**1.6E-07**
rs12608504	19	18,250,135	*JUND*	A	0.36	0.022	**8.8E-10**	209,990	0.017	2.6E-04	116,689	0.028	1.05E-07	93,435	1.2E-01
rs4081724	19	38,516,786	*CEBPA*	G	0.85	0.035	**7.4E-12**	207,418	0.033	9.2E-07	115,322	0.039	1.41E-07	92,230	5.0E-01
rs979012	20	6,571,374	*BMP2*	T	0.34	0.027	**3.3E-14**	209,941	0.026	1.0E-07	116,668	0.028	6.59E-08	93,407	6.7E-01
rs224333	20	33,487,376	*GDF5*	G	0.62	0.020	2.6E-08	208,025	0.009	7.4E-02	115,803	0.036	**9.00E-12**	92,356	**6.4E-05**
rs6090583	20	44,992,238	*EYA2*	A	0.48	0.022	**6.2E-11**	209,435	0.029	2.8E-10	116,382	0.015	2.37E-03	93,187	3.2E-02
Novel loci achieving genome-wide significance in all-ancestry meta-analyses															
rs1534696	7	26,363,764	*SNX10*	C	0.43	0.011	1.3E-03	212,501	0.027	**2.1E-08**	118,187	-0.006	2.64E-01	92,243	**2.1E-06**
Previously reported loci achieving genome-wide significance in European-ancestry meta-analyses															
rs2645294	1	119,376,110	*TBX15-WARS2*	T	0.58	0.031	**1.7E-19**	209,808	0.035	1.5E-14	116,596	0.027	1.46E-07	93,346	2.0E-01
rs714515	1	170,619,613	*DNM3-PIGC*	G	0.43	0.027	**4.4E-15**	203,401	0.029	1.8E-10	113,939	0.025	8.54E-07	89,596	5.1E-01
rs2820443	1	217,820,132	*LYPLAL1*	T	0.72	0.035	5.3E-21	209,975	0.062	**5.7E-35**	116,672	0.002	6.91E-01	93,437	**2.6E-17**
rs10195252	2	165,221,337	*GRB14-COBLL1*	T	0.59	0.027	5.9E-15	209,395	0.052	**4.7E-30**	116,329	-0.003	5.33E-01	93,199	**2.4E-17**
rs17819328	3	12,464,342	*PPARG*	G	0.43	0.021	2.4E-09	208,809	0.035	**4.6E-14**	116,072	0.005	3.26E-01	92,871	**5.1E-06**
rs2276824	3	52,612,526	*PBRM1*[c]	C	0.43	0.024	**3.2E-11**	208,901	0.028	3.7E-09	116,128	0.020	1.35E-04	92,907	2.0E-01
rs2371767	3	64,693,298	*ADAMTS9*	G	0.72	0.036	1.6E-20	194,506	0.056	**1.2E-26**	108,624	0.012	3.49E-02	86,016	**3.6E-09**
rs1045241	5	118,757,185	*TNFAIP8-HSD17B4*	C	0.71	0.019	4.4E-07	209,710	0.035	**6.6E-12**	116,560	-0.001	9.29E-01	93,284	**8.3E-07**
rs7705502	5	173,253,421	*CPEB4*	A	0.33	0.027	**4.7E-14**	209,827	0.027	1.9E-08	116,609	0.027	2.30E-07	93,352	1.0E+00
rs1294410	6	6,683,751	*LY86*	C	0.63	0.031	**2.0E-18**	209,830	0.037	1.6E-15	116,624	0.025	1.37E-06	93,340	6.3E-02
rs1358980	6	43,872,529	*VEGFA*	T	0.47	0.039	3.1E-27	206,862	0.060	**3.7E-34**	115,047	0.015	4.02E-03	91,949	**3.7E-11**
rs1936805	6	127,493,809	*RSPO3*	T	0.51	0.043	**3.6E-35**	209,859	0.052	3.7E-30	116,602	0.031	3.08E-10	93,392	**1.0E-03**
rs10245353	7	25,825,139	*NFE2L3*	A	0.20	0.035	**8.4E-16**	210,008	0.041	7.9E-13	116,704	0.027	1.43E-05	93,438	7.2E-02
rs10842707	12	26,362,631	*ITPR2-SSPN*	T	0.23	0.032	**4.4E-16**	210,023	0.041	6.1E-15	116,704	0.022	1.44E-04	93,453	1.1E-02
rs1443512	12	52,628,951	*HOXC13*	A	0.24	0.028	6.9E-13	209,980	0.040	**1.1E-14**	116,688	0.013	2.77E-02	93,425	**1.6E-04**
rs2294239	22	27,779,477	*ZNRF3-KREMEN1*	A	0.59	0.025	**7.2E-13**	209,454	0.028	6.9E-10	116,414	0.024	2.31E-06	93,173	5.0E-01

P values and β coefficients (per change of the effect allele) for the association with WHRadjBMI on the inverse normal transformed ranked scale in the meta-analyses of combined GWAS and Metabochip studies. The smallest *P*-value for each SNP is shown in bold. Positions are reported in base pairs (NCBI Build 36). [a]The effect allele is the WHRadjBMI-increasing allele in the sex-combined analysis. [b]Test for sex difference; values significant at the table-wise Bonferroni threshold of $0.05/49 = 1.02 \times 10^{-3}$ are marked in bold. [c]Locus previously named *NISCH-STAB1.* Chr, chromosome; EA, effect allele; EAF, effect allele frequency. Details of GWAS and metabochip analyses are provided in **Supplementary Table 4**, and between-study heterogeneity is provided in **Supplementary Table 31**.

Table 2 - WHRadjBMI loci with multiple association signals in the sex-combined and/or sex-specific approximate conditional meta-analyses

							Sex-combined			Women			Men			Sex	CEU r^2
Locus[a]	SNP	Chr	Position	Nearest gene(s)	EA[b]	EAF	β	*P*	*N*	β	*P*	*N*	β	*P*	*N*	difference *P*[c]	with lead SNP
TBX15-WARS2	rs2645294	1	119,376,110	*WARS2*	T	0.58	**0.031**	**7.6E-19**	**209,808**	**0.035**	**1.5E-14**	**116,596**	0.014	2.2E-02	93,346	4.9E-03	Same SNP
	rs1106529	1	119,333,020	*TBX15*	A	0.75	0.016	1.4E-03	209,930	0.021	1.1E-03	116,663	**0.034**	**4.8E-09**	**93,401**	1.1E-01	0.43
	rs12143789	1	119,298,677	*TBX15*	C	0.21	**0.026**	**1.0E-09**	**209,874**	0.022	1.3E-04	116,640	0.019	2.3E-03	93,369	7.1E-01	0.06
	rs12731372	1	118,654,498	*SPAG17*	C	0.76	**0.024**	**1.3E-09**	**209,856**	0.020	1.1E-04	116,636	0.028	3.4E-06	93,354	2.8E-01	>500 kb
GRB14-COBLL1	rs1128249[e]	2	165,236,870	*COBLL1*	G	0.60	**0.062**	**8.6E-19**	**209,414**	**0.093**	**1.0E-24**	**116,348**	-0.002	7.1E-01	93,200	**8.6E-22**	0.93
	rs12692737	2	165,262,555	*COBLL1*	A	0.31	**0.043**	**1.6E-08**	**203,265**	**0.134**	**2.7E-26**	**112,317**	0.003	5.7E-01	91,082	**2.8E-21**	0.71
	rs12692738	2	165,266,498	*COBLL1*	T	0.76	0.021	5.9E-05	209,551	**0.092**	**3.8E-20**	**116,474**	-0.005	4.1E-01	93,211	**4.7E-18**	0.30
	rs17185198	2	165,268,482	*COBLL1*	A	0.83	0.002	7.4E-01	207,702	**0.072**	**8.5E-13**	**115,657**	-0.004	5.8E-01	92,179	**8.0E-11**	0.15
PRBM1	rs13083798	3	52,624,788	*PRBM1*	A	0.49	**0.023**	**4.1E-11**	**209,128**	0.013	1.2E-01	115,974	0.016	1.1E-03	93,288	7.4E-01	0.88
	rs12489828	3	52,542,054	*NT5DC2*	T	0.55	0.011	6.5E-02	204,485	**0.029**	**2.6E-10**	**112,633**	-0.015	2.9E-03	91,986	**7.2E-11**	0.57
MAP3K1	rs3936510	5	55,896,623	*MAP3K1*	T	0.18	0.022	1.5E-06	207,896	**0.042**	**6.0E-12**	**115,645**	-0.002	8.2E-01	92,386	**5.9E-07**	0.88
	rs459193	5	55,842,508	*ANKRD55*	A	0.26	**0.026**	**1.6E-11**	**209,952**	0.016	1.9E-03	116,677	**0.033**	**6.7E-09**	**93,410**	2.3E-02	0.06
VEGFA	rs998584[d]	6	43,865,874	*VEGFA*	A	0.48	**0.043**	**1.1E-29**	**189,620**	**0.065**	**1.0E-35**	**106,771**	0.018	8.2E-04	82,983	**3.1E-10**	0.84
	rs4714699	6	43,910,541	*VEGFA*	C	0.38	0.019	3.5E-07	193,327	**0.028**	**1.0E-08**	**107,987**	0.007	1.9E-01	85,475	4.9E-03	0.01
RSPO3	rs1936805[d]	6	127,493,809	*RSPO3*	T	0.51	**0.038**	**2.0E-28**	**209,859**	**0.071**	**6.4E-37**	**116,602**	**0.031**	**3.3E-10**	**93,392**	**8.4E-08**	Same SNP
	rs11961815	6	127,477,288	*RSPO3*	A	0.75	0.022	5.0E-06	209,679	**0.037**	**6.5E-09**	**116,503**	0.021	3.6E-03	93,310	6.9E-02	0.32
	rs72959041[e]	6	127,496,586	*RSPO3*	A	0.06	**0.101**	**8.7E-15**	**72,472**	-	-	-	-	-	-	-	0.05
NFE2L3, SNX10[f]	rs1534696	7	26,363,764	*SNX10*	C	0.44	0.011	2.0E-03	198,194	**0.028**	**2.0E-08**	**111,643**	-0.007	1.9E-01	86,685	**2.2E-07**	Same SNP
	rs10245353	7	25,825,139	*NFE2L3*	A	0.20	**0.035**	**8.4E-16**	**210,008**	0.016	1.3E-01	116,704	0.027	1.4E-05	93,438	3.6E-01	Same SNP
	rs3902751	7	25,828,164	*NFE2L3*	A	0.25	0.009	2.0E-01	209,969	**0.039**	**4.2E-14**	**116,676**	0.019	8.4E-04	93,427	7.4E-03	0.608[f]
HOXC13	rs1443512	12	52,628,951	*HOXC13*	A	0.24	0.016	2.7E-03	209,980	0.040	1.1E-14	116,688	0.012	3.0E-02	93,425	**1.8E-04**	Same SNP
	rs10783615	12	52,636,040	*HOXC12*	G	0.14	**0.037**	**6.7E-14**	**209,368**	0.023	8.5E-03	116,356	0.022	1.8E-03	93,146	9.3E-01	0.59
	rs2071449[d]	12	52,714,278	*HOXC4/5/6*	A	0.37	**0.028**	**5.0E-15**	**206,953**	**0.026**	**4.6E-08**	**114,259**	**0.029**	**3.4E-08**	**92,829**	6.6E-01	0.00
CCDC92	rs4765219	12	123,006,063	*CCDC92*	C	0.67	**0.025**	**6.9E-12**	**209,807**	**0.032**	**2.5E-11**	**116,592**	0.018	5.3E-04	93,350	3.8E-02	Same SNP
	rs863750	12	123,071,397	*ZNF664*	T	0.59	**0.022**	**3.9E-10**	**209,371**	**0.031**	**1.6E-11**	**116,367**	0.015	4.0E-03	93,138	1.8E-02	0.02

P values and β coefficients (per change of the effect allele) for the association with WHRadjBMI on the inverse normal transformed ranked scale from the joint model in the approximate conditional analysis of combined GWAS and Metabochip studies. SNPs selected by conditional analyses as independently associated with WHRadjBMI in a meta-analysis (sex-combined, women- or men-specific) have their respective summary statistics for these analyses marked in black and bold. SNPs not selected by a particular conditional analysis as independently associated are marked in gray and show the association analysis results for the SNP conditioned on the locus SNPs selected by GCTA. Positions are reported in base pairs (NCBI Build 36) and sample sizes are from the unconditioned meta-analysis. [a]Locus and lead SNPs are defined by **Table 1**. [b]The effect allele is the WHRadjBMI-increasing allele in the sex-combined analysis. [c]Test for sex difference in conditional analysis based on the effect correlation estimate from primary analyses; values significant at the table-wise Bonferroni threshold of 0.05 / 25 = 2×10^{-3} are marked in bold. [d]SNPs selected by conditional analysis in the sex-combined analysis; proxies were selected by joint conditional analysis in the women- and/or men-specific analyses. [e]SNP not present in the sex-specific meta-analyses due to sample size filter requiring $N \geq 50{,}000$; sample size from GCTA. [f]At *NFE2L3-SNX10*, different lead SNPs were identified in the European and all-ancestry analyses but LD is reported with respect to rs10245353. Chr, chromosome; EA, effect allele; EAF, effect allele frequency.

Table 3 - Candidate genes at new WHRadjBMI loci

SNP	Locus	Expression quantitative trait locus genes ($P < 10^{-5}$)[a]	Pathway genes in GRAIL ($P < 0.05$)[b]	Lead genes in DEPICT (FDR < 0.05)[c]	Candidate genes based on literature review[d]	Genes at current or previous GWAS signals[e]
rs905938	*DCST2*	*ZBTB7B* (PBMC, Blood)	-	-	-	-
rs10919388	*GORAB*	-	-	-	-	-
rs1385167	*MEIS1*	-	-	-	*MEIS1*	-
rs1569135	*CALCRL*	-	*TFPI*	-	*CALCRL*	-
rs10804591	*PLXND1*	-	*PLXND1*	-	*PLXND1*	-
rs17451107	*LEKR1*	*TIPARP* (SAT, Omental), *LEKR1* (SAT)	*VEPH1*	-	-	Birthweight: *CCNL1, LEKR1*
rs3805389	*NMU*	-	-	-	*NMU*	-
rs9991328	*FAM13A*	*FAM13A* (SAT)	*FAM13A*	*FAM13A*	-	Fasting insulin adjusted for BMI: *FAM13A*
rs303084	*SPATA5-FGF2*	-	*FGF2*	-	*FGF2, NUDT6, SPRY1*	-
rs9687846	*MAP3K1*	-	*ANKRD55, MAP3K1*	-	*MAP3K1*	Fasting insulin adjusted for BMI, Triglycerides: *ANKRD55, MAP3K1*
rs6556301	*FGFR4*	-	*MXD3*	-	*FGFR4*	Height
rs7759742	*BTNL2*	*HLA-DRA* (SAT), *KLHL31* (SAT)	-	(not analyzed)	-	-
rs1776897	*HMGA1*	-	-	(not analyzed)	*HMGA1*	Height: *HMGA1, C6orf106, LBH*
rs1534696	*SNX10*	*SNX10* (SAT), *CBX3* (SAT)	-	-	*SNX10*	-
rs7801581	*HOXA11*	-	*HOXA11*	*HOXA11*	*HOXA11*	-
rs7830933	*NKX2-6*	*STC1* (SAT)	-	-	*NKX2-6, STC1*	-
rs12679556	*MSC*	-	*EYA1*	-	*MSC, EYA1*	-
rs10991437	*ABCA1*	-	*ABCA1*	-	*ABCA1*	-
rs7917772	*SFXN2*	-	-	-	*SFXN2*	Height
rs11231693	*MACROD1-VEGFB*	-	*VEGFB*	*MACROD1*	*MACROD1, VEGFB*	-
rs4765219	*CCDC92*	*CCDC92* (Omental, SAT, Liver), *ZNF664* (SAT, Omental)	*FAM101A*	-	-	Adiponectin levels, Fasting insulin adjusted for BMI, HDL cholesterol, Triglycerides: *CCDC92, ZNF664*
rs8042543	*KLF13*	-	*KLF13*	-	*KLF13*	-
rs8030605	*RFX7*	-	*TEX9*	-	-	-
rs1440372	*SMAD6*	*SMAD6* (Blood)	*SMAD6*	*SMAD6*	*SMAD6*	Height
rs2925979	*CMIP*	*CMIP* (SAT)	-	-	*CMIP, PLCG2*	Adiponectin levels, Fasting insulin adjusted for BMI, HDL-cholesterol: *CMIP*
rs4646404	*PEMT*	-	*RAI1*	*PEMT*	*PEMT*	-
rs8066985	*KCNJ2*	-	*KCNJ2*	-	*KCNJ2*	-
rs12454712	*BCL2*	-	-	-	*BCL2*	-
rs12608504	*JUND*	*KIAA1683* (PBMC, Omental), *JUND* (LCL)	*JUND*	-	*JUND*	-
rs4081724	*CEBPA*	-	*CEBPA, PEPD*	-	*CEBPA, CEBPG*	-
rs979012	*BMP2*	-	*BMP2*	*BMP2*	*BMP2*	Height: *BMP2*
rs224333	*GDF5*	*CEP250* (Omental, SAT), *UQCC* (Blood, Omental, SAT, Liver, LCL)	*GDF5*	*GDF5*	*GDF5*	Height: *GDF5, UQCC*
rs6090583	*EYA2*	-	*EYA2*	*EYA2*	*EYA2*	-

Candidate genes based on secondary analyses or literature review. Further details are provided in **Supplementary Tables 8-9, 12-14, 16, 20, 22** and the **Supplementary Note**. Loci are shown in order of chromosome and position. [a]Gene transcript levels associated with the SNP in the indicated tissue(s). [b]Genes in pathways identified as enriched by GRAIL analysis; [c]Significant pathway genes derived by DEPICT. [d]Strongest candidate genes identified based on manual literature review. [e]Traits associated at $P < 5 \times 10^{-8}$ in GWAS lookups or in the GWAS catalog using the index SNP or a proxy in LD ($r^2 > 0.7$), and the genes(s) named in those reports. The only nonsynonymous variant in high LD with index SNP based on 1000 Genomes CEU reference panel was *GDF5* S276A. No copy number variants were identified

Table 4 - New loci achieving genome-wide evidence of association ($P < 5 \times 10^{-8}$) with additional waist and hip circumference traits

							Sex-combined			Women			Men			Sex diff.
SNP	**Trait**	**Chr**	**Position**	**Locus**	**EA[a]**	**EAF**	**β**	***P***	***N***	**β**	***P***	***N***	**β**	***P***	***N***	***P*[b]**
Loci achieving genome-wide significance in European-ancestry meta-analyses																
rs10925060	WCadjBMI	1	245,717,763	*OR2W5-NLRP3*	T	0.03	0.017	2.2E-05	140,515	0.002	6.8E-01	85,186	0.045	**9.1E-13**	55,522	**1.7E-08**
rs10929925	HIP	2	6,073,008	*SOX11*	C	0.55	0.020	**4.5E-08**	207,648	0.021	9.0E-06	115,428	0.018	3.2E-04	92,499	6.1E-01
rs2124969	WCadjBMI	2	160,697,732	*ITGB6*	C	0.42	0.020	**7.1E-09**	231,284	0.016	3.5E-04	127,437	0.025	2.3E-07	104,039	1.4E-01
rs17472426	WCadjBMI	5	159,626,935	*CCNJL*	T	0.92	0.014	3.1E-02	217,564	-0.014	1.0E-01	119,804	0.052	**4.3E-08**	97,954	**3.9E-08**
rs7739232	HIPadjBMI	6	53,648,294	*KLHL31*	A	0.07	0.037	5.4E-05	131,877	0.063	**1.0E-08**	80,475	-0.004	7.5E-01	51,589	**2.9E-05**
rs13241538	HIPadjBMI	7	130,090,402	*KLF14*	C	0.48	0.017	1.6E-06	210,935	0.033	**9.9E-14**	117,210	-0.003	5.0E-01	93,911	**2.0E-09**
rs7044106	HIPadjBMI	9	122,533,883	*C5*	C	0.24	0.023	4.1E-05	143,412	0.039	**5.7E-09**	86,733	-0.003	6.9E-01	56,865	**1.3E-05**
rs11607976	HIP	11	68,988,292	*MYEOV*	C	0.70	0.022	**4.2E-08**	212,815	0.019	1.9E-04	118,391	0.024	7.7E-06	94,701	4.4E-01
rs1784203	WCadjBMI	11	93,089,782	*KIAA1731*	A	0.01	0.031	1.3E-08	63,892	0.000	9.9E-01	35,539	0.075	**1.0E-19**	28,353	1.2E-01
rs1394461	WHR	11	98,727,559	*CNTN5*	C	0.25	0.017	4.7E-04	144,349	0.035	**3.6E-08**	87,441	-0.011	1.6E-01	57,094	**1.1E-06**
rs319564	WHR	13	92,630,880	*GPC6*	C	0.45	0.014	3.4E-05	212,137	0.003	5.3E-01	117,970	0.027	**1.6E-08**	94,350	**6.0E-05**
rs2047937	WCadjBMI	16	48,422,292	*ZNF423*	C	0.50	0.019	**4.7E-08**	231,009	0.022	5.5E-07	127,288	0.014	3.6E-03	103,914	2.0E-01
rs2034088	HIPadjBMI	17	369,801	*VPS53*	T	0.53	0.021	4.8E-09	210,737	0.028	**9.6E-10**	117,142	0.014	6.5E-03	93,781	2.5E-02
rs1053593	HIPadjBMI	22	33,990,875	*HMGXB4*	T	0.65	0.021	3.9E-08	202,070	0.029	**1.8E-09**	114,347	0.011	5.1E-02	87,908	6.2E-03
Loci achieving genome-wide significance in all-ancestry meta-analyses																
rs1664789	WCadjBMI	5	53,318,406	*ARL15*	C	0.41	0.014	2.6E-05	244,110	0.005	2.8E-01	133,052	0.026	**3.6E-08**	109,025	**4.4E-04**
rs722585	HIPadjBMI	6	1,720,862	*GMDS*	G	0.68	0.015	2.1E-04	205,815	-0.001	8.8E-01	113,965	0.032	**9.2E-09**	89,831	**4.3E-06**
rs1144	WCadjBMI	7	104,543,591	*SRPK2*	C	0.34	0.019	**3.1E-08**	239,342	0.020	1.2E-05	131,398	0.018	4.1E-04	105,911	7.8E-01
rs2398893	WHR	9	95,798,163	*PTPDC1*	A	0.71	0.020	**4.0E-08**	226,572	0.019	5.1E-05	124,577	0.019	2.7E-04	99,968	9.5E-01
rs4985155[c]	HIP	16	15,036,960	*PDXDC1*	A	0.66	0.018	4.5E-07	227,296	0.011	1.6E-02	125,048	0.029	**9.7E-09**	100,313	6.3E-03

P values and β coefficients (per change of the effect allele) for the association with the trait indicated on the inverse normal transformed ranked scale in the meta-analysis of combined GWAS and Metabochip studies. The smallest *P*-value for each SNP is shown in bold. Positions are reported in base pairs (NCBI Build 36). [a]The effect allele is the trait-increasing allele in the sex-combined analysis. [b]Test for sex difference; values significant at the table-wise Bonferroni threshold of 0.05 / 19 = 2.63×10^{-3} are marked in bold. [c]$P = 7.3 \times 10^{-6}$ with height in Okada *et al*.[56] (index SNP rs1136001; $r^2 = 0.790$, distance = 2,515 bp). Chr, chromosome; EA, effect allele; EAF, effect allele frequency.

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ONLINE METHODS

Study overview. Our study included 224,459 individuals of European, East Asian, South Asian, and African American ancestry. The European ancestry arm of the study included 142,762 individuals from 57 cohorts genotyped with genome-wide SNP arrays and 67,326 individuals from 44 cohorts genotyped with the Metabochip[18] (**Supplementary Fig. 1**, **Supplementary Table 1**). The non-European ancestry arm comprised ~1,700 individuals from one cohort of East Asian ancestry, ~3,400 individuals from one cohort of South Asian ancestry, and ~9,200 individuals from six cohorts of African American ancestry, all genotyped with the Metabochip.

Phenotype definition. Our primary phenotype was WHRadjBMI, the ratio of waist and hip circumferences adjusted for age, age², study-specific covariates if necessary, and BMI. For each cohort, age- and BMI-adjusted residuals were calculated for men and women separately. These residuals were then transformed by the inverse standard normal function to ensure comparability across cohorts and between sexes. Cohorts with related men and women provided inverse standard normal transformed sex-combined residuals. For each cohort, the same transformations were applied to other related phenotypes: (i) WHR without adjustment for BMI (WHR); (ii) waist circumference with (WCadjBMI) and without (WC) adjustment for BMI; and (iii) hip circumference with (HIPadjBMI) and without (HIP) adjustment for BMI.

European ancestry meta-analysis for genome-wide SNP array data. Sample and SNP quality control (QC) were undertaken within each cohort (**Supplementary Table 3**). The GWAS scaffold in each cohort was imputed using CEU data from HapMap resulting in ~2.5 million SNPs. Each directly typed and imputed SNP passing QC was tested for association with WHRadjBMI and additional phenotypes under an additive model using linear regression (**Supplementary Table 1**). All analyses took account of uncertainty in imputation in a “missing

data" likelihood framework, or by computing expected dosages over the genotype probability distribution (**Supplementary Table 3**). For each cohort, sex-specific association summary statistics for WHRadjBMI and additional phenotypes were corrected for residual population structure using the genomic control inflation factor[57] (median λ_{GC} = 1.01, range = 0.99 – 1.08). SNPs were removed prior to meta-analysis if they had a minor allele count ≤ 3, Hardy-Weinberg equilibrium $P < 10^{-6}$, directly genotyped SNP call rate < 95%, or low imputation quality (below 0.3 for MACH, 0.4 for IMPUTE, and 0.8 for PLINK imputed data). Association summary statistics for WHRadjBMI and additional phenotypes were then combined via inverse-variance weighted fixed-effects meta-analysis, and corrected for a second round of genomic control to account for structure between cohorts (**Supplementary Fig. 2**).

European ancestry meta-analysis for Metabochip data. Sample and SNP QC analyses were undertaken in each cohort (**Supplementary Table 3**). Each SNP passing QC was tested for association with WHRadjBMI and additional phenotypes under an additive model using linear regression (**Supplementary Table 1**). Inflation of the number of statistically significant association signals for WHRadjBMI and additional phenotypes across the content of the Metabochip would be anticipated, even in the absence of latent population substructure, because the array is enriched, by design, for loci associated with anthropometric and cardiometabolic traits. Thus, we based our correction on a subset of 4,425 SNPs selected for inclusion on Metabochip[18] based on suggestive associations with QT-interval that were not expected to be associated with anthropometric traits (>500 kb from variants on Metabochip[18] for these traits). These study-specific inflation factors had a median λ_{GC} of 1.01 (range 0.93 – 1.11), with only one study exceeding 1.10. After further removing SNPs for QC as described in the previous section, association summary statistics for WHRadjBMI and additional phenotypes were combined via inverse-variance weighted fixed-effects meta-analysis, and corrected for a

second round of genomic control on the basis of QT-interval SNPs to account for structure between cohorts.

European ancestry sex-combined meta-analysis. Association summary statistics from the two parts of the European ancestry arm were combined via inverse-variance weighted fixed-effects meta-analysis using METAL[58]. No further genomic control correction was performed. Results were reported for SNPs with a sex-combined sample size ≥ 50,000.

European ancestry sex-stratified meta-analyses. The genome-wide, Metabochip, and combined meta-analyses were repeated for men and women separately, for WHRadjBMI and the additional phenotypes. Analyses were corrected for population structure within each sex. The meta-analysis of WHRadjBMI in men included up to 93,480 individuals, and in women up to 116,742 individuals. Tests for differences in allelic effects between men-specific and women-specific beta estimates were performed using a t statistic as described previously[10].

Meta-analyses of studies of all ancestries. Sample and SNP QC analyses were undertaken in each cohort of non-European ancestry, all of which were genotyped on the Metabochip (**Supplementary Table 3**). Each SNP passing QC was tested for association with WHRadjBMI and additional phenotypes, under an additive model using linear regression (**Supplementary Table 1**). For each cohort, association summary statistics for WHRadjBMI and additional phenotypes were corrected for latent population substructure using the genomic control inflation factor obtained from QT-interval SNPs (median λ_{GC} = 1.01, range = 0.90 – 1.17), with only one study exceeding 1.10. Association summary statistics were combined via inverse-variance weighted fixed-effects meta-analysis, corrected for a second round of genomic control on the basis of QT-interval SNPs. Sex-combined and sex-specific meta-analyses were undertaken. Association summary statistics from the European ancestry and non-European ancestry meta-

analyses were finally combined via inverse-variance weighted fixed-effects meta-analysis without further genomic control correction.

Heterogeneity. For each lead SNP, we tested for sex differences based on the sex-specific beta estimates and standard errors, while accounting for potential correlation between the sex-specific estimates[10]. We tested for potential differences in effects between European and non-European samples in a similar manner, comparing the effects from GWAS+Metabochip data for Europeans and Metabochip data for non-Europeans. Between-study heterogeneity in all meta-analyses was assessed using I^2 statistics[59].

Heritability, and genetic and phenotypic correlations of waist traits. We calculated the heritability and genetic correlations of several central obesity traits using variance component models[60,61] in the Framingham Heart Study (FHS) and TWINGENE study. In this approach, the phenotypic variance is decomposed into additive genetic, non-additive genetic, and environmental sources of variation (including model error), and for sets of traits, the covariances between traits. We report narrow sense heritability (h^2), the ratio of the additive genetic variance to the total phenotypic variance. Sex-specific inverse normal trait residuals, adjusted for age (and cohort in FHS), were used to estimate heritability separately in men and women, using variance components analysis in SOLAR version 4.2.7 [62] (FHS) or Mx 1.703[63] (TWINGENE). Additionally, the sex-specific residuals were used to conduct bivariate quantitative variance component genetic analyses that calculate genetic and environmental correlations between traits. The genetic correlations obtained are estimates of the additive effects of shared genes, and a genetic correlation significantly different from zero suggests a direct influence of the same genes on more than one trait. Similarly, significant environmental correlations suggest shared environmental effects.

1103 We estimated sex-stratified correlations between all waist traits, as well as BMI, height, and
1104 weight in TWINGENE, FHS, KORA, and EGCUT. In TWINGENE and FHS, age-adjusted
1105 Pearson correlations were used; in EGCUT and KORA, correlations were adjusted for age and
1106 age^2.
1107
1108 **European ancestry approximate conditional analyses.** To evaluate the evidence for multiple
1109 association signals within identified WHRadjBMI loci, we performed approximate conditional
1110 analyses of sex-combined, women-specific, and men-specific data as implemented in the GCTA
1111 software[16,17]. This approach makes use of association summary statistics from the combined
1112 European ancestry meta-analysis and a reference dataset of individual-level genotype data to
1113 estimate linkage disequilibrium (LD) between variants and hence also the approximate
1114 correlation between allelic effect estimates in a joint association model. Although it is expected
1115 that the set of SNPs selected by GCTA and their effect estimates will depend on the reference
1116 dataset, the results should be fairly robust when the reference dataset LD pattern represents
1117 well the population considered and when the reference dataset offers good coverage of the
1118 SNPs in the meta-analysis.
1119
1120 To evaluate robustness of the GCTA results, we performed analyses using two reference
1121 datasets that contributed to the combined European ancestry meta-analysis with Metabochip
1122 and/or GWAS genotype data: Prospective Investigation of the Vasculature in Uppsala Seniors
1123 (PIVUS) consisting of 949 individuals from Uppsala County, Sweden, with both GWAS (imputed
1124 using CEU haplotypes from Phase II of the International HapMap Project)[64] and Metabochip
1125 genotype data; and Atherosclerosis Risk in Communities (ARIC) consisting of 6,654 individuals
1126 of European descent from four communities in the USA with GWAS data also imputed using
1127 data from Phase II of the International HapMap Project[64]. Results shown use the PIVUS
1128 reference dataset because Metabochip genotypes are available (see a comparison in the

Supplementary Note. Assuming that the LD correlations between SNPs more than 10 Mb away or on different chromosomes are zero, and using each of the reference datasets in turn, we performed a genome-wide stepwise selection procedure to select associated SNPs one-by-one at a *P* value < 5×10^{-8}. **Table 2** shows the loci for which GCTA identifies multiple association signals in the sex-combined, women-, and/or men-specific data. For each locus, the SNPs selected by GCTA as independently associated with WHRadjBMI in any of the three meta-analyses are reported, with the SNP identified in the sex-combined analysis taken by default when proxies are identified in the women- and/or men-specific analyses. For SNPs not selected by a particular joint conditional analysis, but identified by either of the other two analyses, summary statistics were calculated for association analysis of the SNP conditioned on the GCTA-selected SNP(s).

Genetic risk score. We calculated a genetic risk score for each individual in the population-based KORA study (3,440 individuals: 1,670 men and 1,750 women) using the 49 identified variants, weighted by the allelic effect from the European ancestry meta-analyses of WHRadjBMI. Sex-combined scores were computed on the basis of the sex-combined meta-analysis. Sex-stratified scores were calculated on the basis of men- and women-specific meta-analyses, where SNPs not achieving nominal significance in the respective sex (*P* ≥ 0.05) were excluded (resulting in 48 SNPs in the women-specific score and 33 SNPs in the men-specific score). For each individual, the sex-combined and sex-stratified risk scores were rounded to the nearest integer for plotting. Risk scores were then tested for association with WHRadjBMI using linear regression.

Explained variance. We calculated the variance explained by a single SNP as:

$$2 \cdot \mathrm{MAF} \cdot (1 - \mathrm{MAF}) \cdot \beta^2 / \mathrm{Var(Y)}$$

where MAF is the minor allele frequency, β the SNP effect estimate computed by meta-analysis,

and *Var(Y)* being the variance of the phenotype Y as it went into the study-specific association testing. To derive the total variance explained by a set of independent SNPs, we computed the sum of single-SNP explained variances under the assumption of independent contributions.

Fine-mapping analyses. We considered each identified locus, defined as 500 kb upstream and downstream of the lead SNP, and computed 95% credible intervals using a Bayesian approach. On the basis of association summary statistics from the European ancestry, non-European ancestry, or all ancestries sex-combined meta-analyses, we calculated an approximate Bayes' factor[65] in favor of association, given by:

$$BF_j = \frac{\sqrt{1 - R_j}}{\exp\left(-\frac{R_j \beta_j^2}{2\sigma_j^2}\right)}$$

where β_j is the allelic effect of the j^{th} SNP, with corresponding standard error σ_j, and R_j = $0.04/(\sigma_j^2+0.04)$, which incorporates a $N(0,0.2^2)$ prior for β_j. This prior gives high probability to small effect sizes, and only small probability to large effect sizes. We then calculated the posterior probability that the *j*th SNP is causal by:

$$\varphi_j = \frac{BF_j}{\sum_k BF_k}$$

where the summation in the denominator is over all SNPs passing QC across the locus. We compared the meta-analysis results and credible sets of SNPs likely to contain the causal variant as described[66]. Assuming a single causal variant at each locus, a 95% credible set of variants was then constructed by: (i) ranking all SNPs according to their BF; and (ii) combining ranked SNPs until their cumulative posterior probability exceeded 0.95. For each locus, we calculated the number of SNPs contained within the 95% credible sets, and the length of the genomic interval covered by these SNPs.

Comparison of loci across traits

To determine whether the identified loci were also associated with any of 22 cardio-metabolic traits, we obtained association data from meta-analysis consortia DIAGRAM (T2D)[67], CARDIoGRAM-C4D (CAD)[68], ICBP (systolic and diastolic blood pressure (SBP, DBP))[69], GIANT (BMI, height)[39,40], GLGC (high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), and triglycerides (TG))[70], MAGIC (fasting glucose, fasting insulin, fasting insulin adjusted for BMI, and two-hour glucose)[71-73], ADIPOGen (BMI-adjusted adiponectin)[74], CKDgen (urine albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), and overall CKD)[75,76], ReproGen (age at menarche, age at menopause)[77,78], and GEFOS (bone mineral density)[48]; others provided association data for IgA nephropathy[79] (also Kiryluk K, Choi M, Lifton RP, Gharavi AG, unpublished data) and for endometriosis[80]. Proxies ($r^2 > 0.80$ in CEU) were used when an index SNP was unavailable.

We also searched the National Human Genome Research Institute (NHGRI) GWAS Catalog for previous SNP-trait associations near our lead SNPs[81]. We supplemented the catalog with additional genome-wide significant SNP-trait associations from the literature[15,48,82-88]. We used PLINK to identify SNPs within 500 kb of lead SNPs using 1000 Genomes Project Pilot I genotype data, which includes the majority of the Metabochip SNPs; LD (r^2) values were from CEU[89,90]. All SNPs within the specified regions were compared with the NHGRI GWAS Catalog[19] for overlap. For rs7759742, 1000 Genomes Project data were unavailable and HapMap release 22 CEU data [89,91] were used for r^2 and distance calculations.

Enrichment of concordant cross-trait associations and effects. To evaluate whether the alleles associated with increased WHRadjBMI at the 49 identified SNPs convey effects for any of the 22 cardiometabolic traits, we conducted meta-regression analyses of the beta-estimates on these metabolic outcomes from other consortia with the beta-estimates for WHRadjBMI in our data[74].

Based on the association data across traits, we generated a matrix of *Z*-scores by dividing the association betas for each of the 49 WHRadjBMI SNPs for each of 22 traits by their respective standard errors. These traits did not include WHRadjBMI itself or nephropathy in Chinese subjects, but did include HIPadjBMI and WCadjBMI. Each *Z*-score was made positive if the original trait-increasing allele also increased the look-up trait and negative if not. Eleven missing associations with endometriosis, nephropathy in Italians, and CAD were assigned a value of zero, treating these unknowns as null associations. We performed unsupervised hierarchical clustering of the *Z* score matrix in R using the default settings of the "heatplot" function from the made4 library (version 1.20.0), agglomerating clusters using average linkage and Pearson correlation metric distance. The rows and columns of matrix values were each automatically scaled to range from 3 to −3. Confidence in the hierarchical clustering was assessed by bootstrap analysis (10,000 resamplings) using the R package "pvclust"[21].

Identification of candidate functional variants. The 1000 Genomes CEU pilot data were queried for SNPs within 500 kb and in LD ($r^2 > 0.7$) with any index SNP. All identified variants were then annotated based on RefSeq transcripts using Annovar to identify potential nonsynonymous variants near identified association signals. The distance between each variant and the nearest transcription start site were calculated using gene annotations from GENCODE (version 12).

To investigate whether SNPs in LD with index SNPs are also in LD with common copy number variants (CNVs), we extracted waist trait association results for a list of SNP proxies that are in high LD ($r^2 > 0.8$, CEU) with CNVs in European populations as described previously[9]. Altogether 6,200 CNV-tagging SNPs were used, which are estimated collectively to capture > 40% of CNVs > 1 kb in size.

Expression quantitative trait loci (eQTLs). We examined our lead SNPs (**Tables 1, 2 and4**) in multiple tissues in a collection of eQTL datasets from several sources (**Supplementary Note**) for *cis* effects significant at $P < 10^{-5}$. We then checked if the trait-associated SNP also had the strongest association with the expression level of its corresponding transcript. If not, we identified a nearby SNP that had a stronger association with expression (peak transcript SNP) of that transcript. To check whether effects of the peak transcript SNP and waist trait-associated SNP overlapped, we conducted conditional analyses to estimate associations between the waist-associated SNP and transcript level when the peak transcript-associated SNP was also included in the model, and vice versa. In these conditional tests, where the association for the expression-associated SNP was not significant ($P > 0.05$) when conditioned on the waist-associated SNP, we concluded that the waist-associated SNP is likely to explain a substantial proportion of the variance in gene transcript levels in the region and that the two SNP signals most probably coincide. Additionally, for SNPs that passed these criteria in either women or men eQTL datasets from the deCODE dataset, we investigated sex heterogeneity in gene transcript levels for whole blood in 312 men and 435 women and for subcutaneous adipose tissue in 252 men and 351 women based on the sex-specific beta estimates and standard errors, while accounting for potential correlation between the sex-specific associations[10].

Epigenomic regulatory element overlap with individual variants. We examined overlap of regulatory elements with the 49 WHRadjBMI-associated variants, the 19 secondary signals, and variants in LD with them ($r^2 > 0.7$, 1000 Genomes Phase 1 version 2 EUR[92]), totaling 1,547 variants. We obtained regulatory element data sets from the ENCODE Consortium[28] and Roadmap Epigenomics Project[93] corresponding to eight tissues selected based on a current understanding of WHRadjBMI pathways. The 226 regulatory element datasets included experimentally-identified regions of open chromatin (DNase-seq, FAIRE-seq), histone

modification (H3K4me1, H3K27ac, H3K4me3, H3K9ac, and H3K4me2), and transcription factor binding (**Supplementary Table 18**). When available, we downloaded data processed during the ENCODE Integrative Analysis[28]. We processed Roadmap Epigenomics sequencing data with multiple biological replicates using MACS2[94] and the same Irreproducible Discovery Rate pipeline used in the ENCODE Integrative Analysis. Roadmap Epigenomics data with only a single replicate was processed using MACS2 alone.

Global enrichment of WHRadjBMI-associated loci in epigenomic datasets. We performed permutation-based tests in a subset of 60 open chromatin (DNase-seq) and histone modification (H3K27ac, H3K4me1, H3K4me3, H3K9ac) datasets to identify global enrichment of the WHRadjBMI-associated loci. We matched the index SNP at each locus with 500 variants having no evidence of association ($P > 0.5$, ~1.2 million total variants) with a similar distance to the nearest gene (± 11,655 bp), number of variants in LD (±8 variants), and minor allele frequency. Using these pools, we created 10,000 sets of control variants for each of the 49 loci and identified variants in LD ($r^2 > 0.7$) and within 1 Mb. For each SNP set, we calculated the number of loci with at least one variant located in a regulatory region under the assumption that one regulatory variant is responsible for each association signal. We initially calculated an enrichment *P* value by finding the proportion of control sets for which as many or more loci overlap a regulatory element than the set of associated loci. For increased *P* value accuracy, we estimated the *P* value assuming a sum of binomial distributions to represent the number of index SNPs (or their LD proxies; $r^2 > 0.7$) that overlap a regulatory dataset compared the expectation observed in the 500 matched control sets.

GRAIL. Genes from independently identified trait regions that share more text in the scientific literature than expected by chance are more likely to be functionally related and therefore more likely to truly contribute towards the trait variation. Using a text-based definition of relatedness,

Gene Relationships Among Implicated Loci (GRAIL)[24] is a text-mining algorithm that evaluates the degree of relatedness among genes within trait regions. Using PubMed abstracts, a subset of genes enriched for relatedness and a set of keywords that suggest putative pathways are identified. To avoid potential bias caused by selecting papers focused on the investigation of candidate genes stimulated by GWAS, we restricted our search to PubMed abstracts prior to 2006. We tested for enrichment of connectivity in the list of independent SNPs that were statistically significant in our study ($P < 10^{-5}$).

MAGENTA. To investigate if pathways including predefined sets of genes were enriched in the lower part of the gene *P* value distribution for WHRadjBMI, we performed a pathway analysis using Magenta 2.4.[25] All SNPs included in both the Metabochip and in the GWAS meta-analyses were included in these analyses. SNPs were assigned to a gene if within 110 kb upstream or 40 kb downstream of the transcript's most extreme boundaries, based on chromosome and position. The most significant SNP *P* value within this interval of a gene was adjusted for putative confounders (gene size, number of SNPs in a gene, LD pattern) using stepwise linear regression, creating a gene association score. If the same top SNP was assigned to multiple genes, only the gene with the lowest gene score was kept. The *HLA* region was removed from further analyses due to its high LD structure and gene density. Each gene was then assigned one or several pathway terms using multiple annotation databases (GO, PANTHER, Ingenuity, KEGG)[95-98]. Finally, the genes were ranked based on their gene association score, and a modified gene-set enrichment analysis (GSEA) using MAGENTA was performed; the purpose of this analysis was to test for enrichment of gene association score ranks above a given rank cutoff (including 5% of all genes) in a gene-set belonging to a predefined pathway term, compared to multiple, equally sized gene-sets that were randomly sampled from all genes in the genome. A minimum of 10,000 gene-set permutations were performed, and up to 1,000,000 for GSEA $P < 10^{-4}$.

Data-driven Enrichment-Prioritized Integration for Complex Traits (DEPICT). This method is described in detail in the accompanying manuscript[39] and Pers *et al.*, in preparation. Briefly, DEPICT uses gene expression data derived from a panel of 77,840 expression arrays[99], 169,810 high-confidence experimentally-derived protein-protein interactions[100], 211,882 gene-phenotype pairs from the Mouse Genetics Initiative[101], 737 Reactome pathways[102], 184 KEGG pathways[103], and 5,083 Gene Ontology terms[24]. DEPICT uses the expression data to reconstitute the protein-protein interaction gene sets, mouse phenotype gene sets, Reactome pathway gene sets, KEGG pathway gene sets, and Gene Ontology term gene sets. We used DEPICT to map genes to associated WHRadjBMI regions, which then allowed us to (1) systematically identify the most likely causal gene(s) in a given associated region, (2) identify reconstituted gene sets that were enriched in genes from associated regions, and (3) identify tissue and cell type annotations in which genes from associated regions were highly expressed. All loci with WHRadjBMI association P values < 10^{-5} were included in the DEPICT analysis. Associated regions were defined by all genes residing within LD (r^2 > 0.5) distance of the WHRadjBMI-associated index SNPs. Overlapping regions were merged, and we excluded two SNPs (rs7759742 and rs1776897) that mapped near to or within the HLA region (chromosome 6, base pairs: 20,000–40,000). The 93 WHRadjBMI SNPs with P < 10^{-5} (HapMap release 27 CEU data based LD (r^2) threshold for clumping = 0.01, physical (kb) threshold for clumping = 500) resulted in 78 non-overlapping regions.

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NEW GWAS

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PREVIOUS GWAS

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Our SNPs

rs1443512 (*A*)
Women-Only $P_{cond.} = 1.1 \times 10^{-14}$
rs10783615 (*B*)
Sex-Combined $P_{cond.} = 6.7 \times 10^{-14}$
rs2071449 (*C*)
Sex-Combined $P_{cond.} = 5.0 \times 10^{-15}$
Women-Only $P_{cond.} = 4.6 \times 10^{-8}$
Men-Only $P_{cond.} = 3.4 \times 10^{-8}$

r^2 with reference SNP
0 0.2 0.8 1

A B C

$-\log_{10}$(*P* value)
15
10
5
0

Recombination rate (cM/Mb)
100
80
60
40
20
0

HOXC13→ ←HOTAIR HOXC10→ HOXC8→ MIR615→ FLJ12825→
HOXC12→ HOXC11→ MIR196A2→ HOXC6→
HOXC9→ HOXC5→
HOXC4→

52.6 52.62 52.64 52.66 52.68 52.7 52.72 52.74
Position on chr12 (Mb)

Our SNPs

r^2 with reference SNP
0 0.2 0.8 1

rs12731372 (*D*)
Sex-Combined $P_{cond.} = 1.3 \times 10^{-9}$
rs12143789 (*E*)
Sex-Combined $P_{cond.} = 1.0 \times 10^{-9}$
rs1106529 (*F*)
Men-Only $P_{cond.} = 4.8 \times 10^{-9}$
rs2645294 (*G*)
Sex-Combined $P_{cond.} = 7.6 \times 10^{-19}$
Women-Only $P_{cond.} = 1.5 \times 10^{-14}$

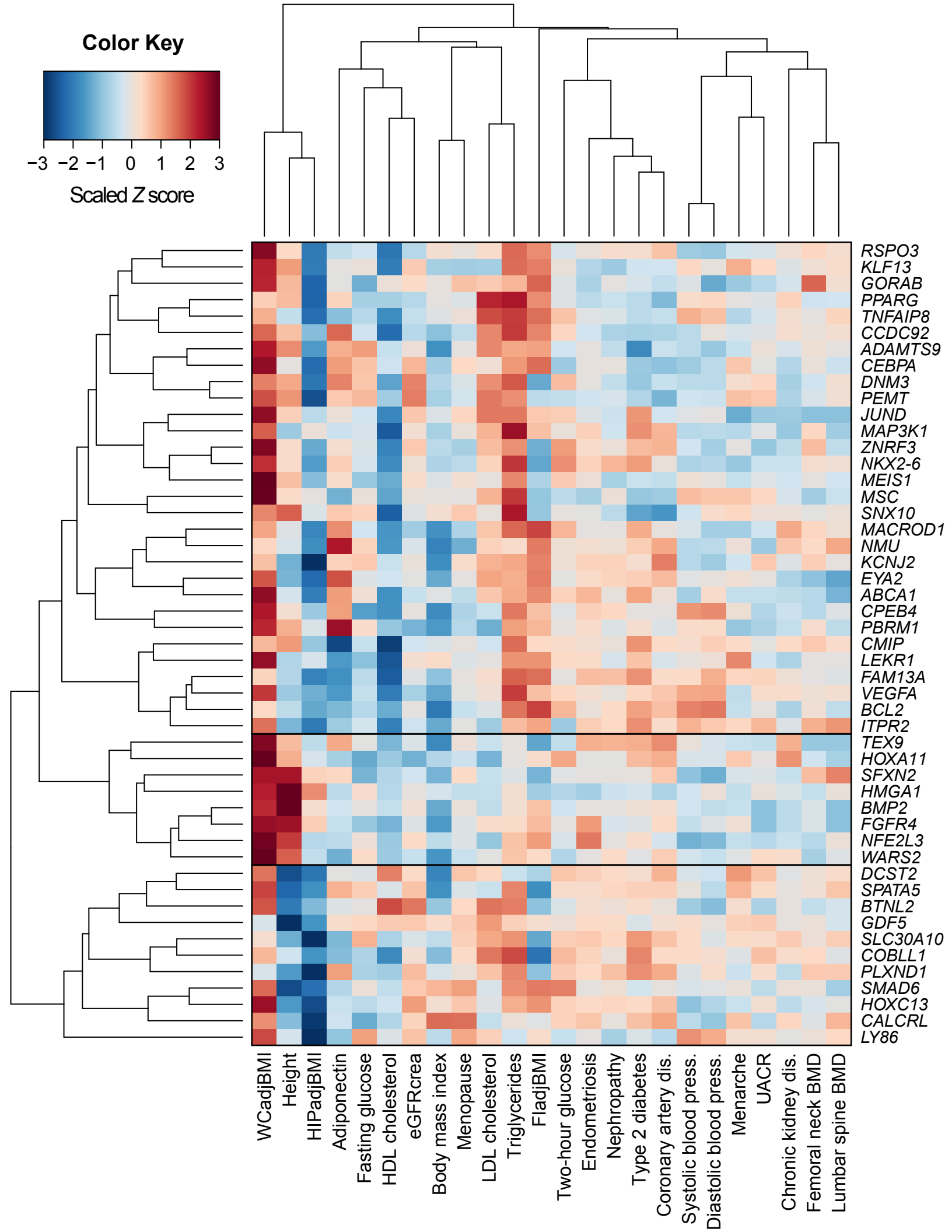
D E F G

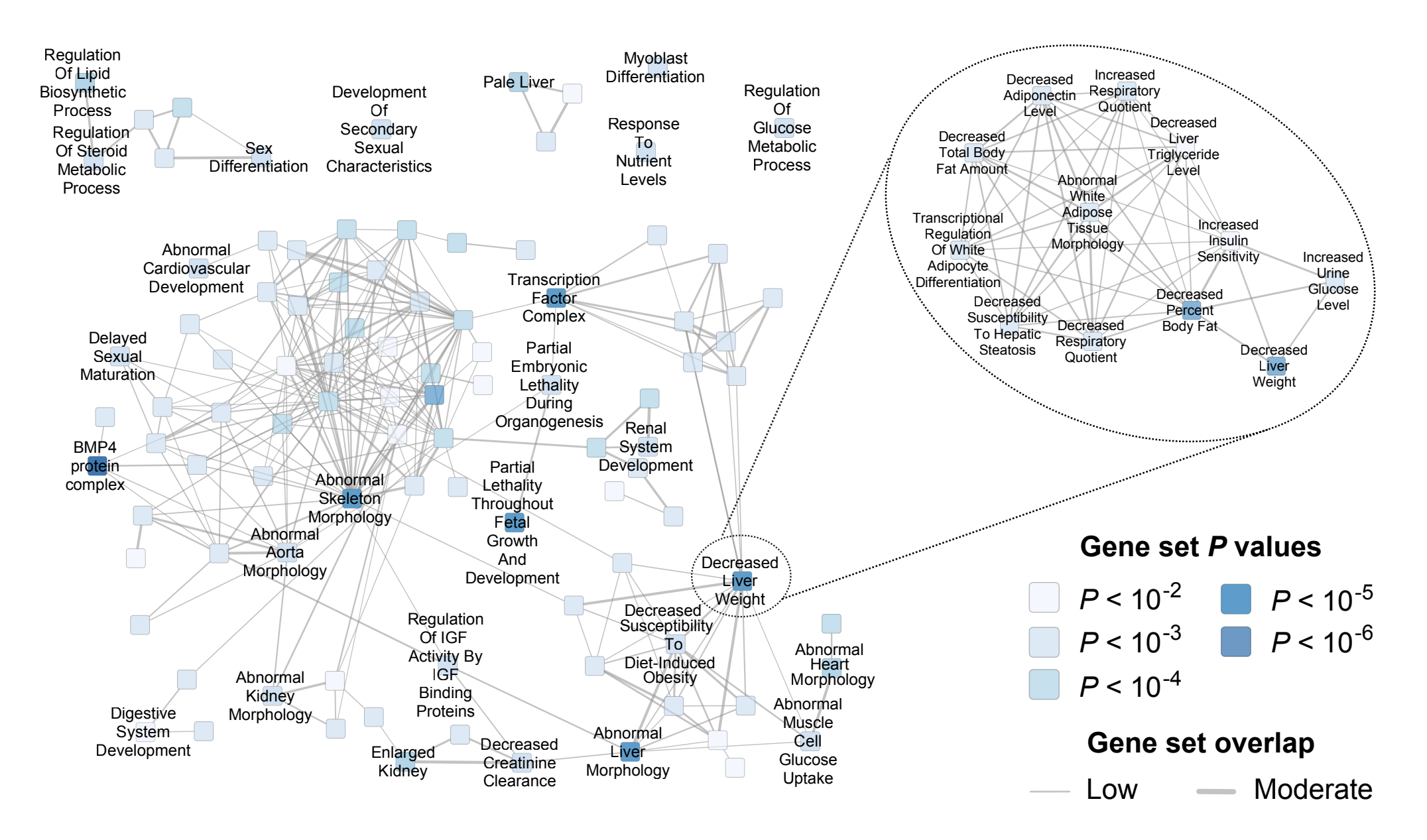
$-\log_{10}$(*P* value)
20
15
10
5
0

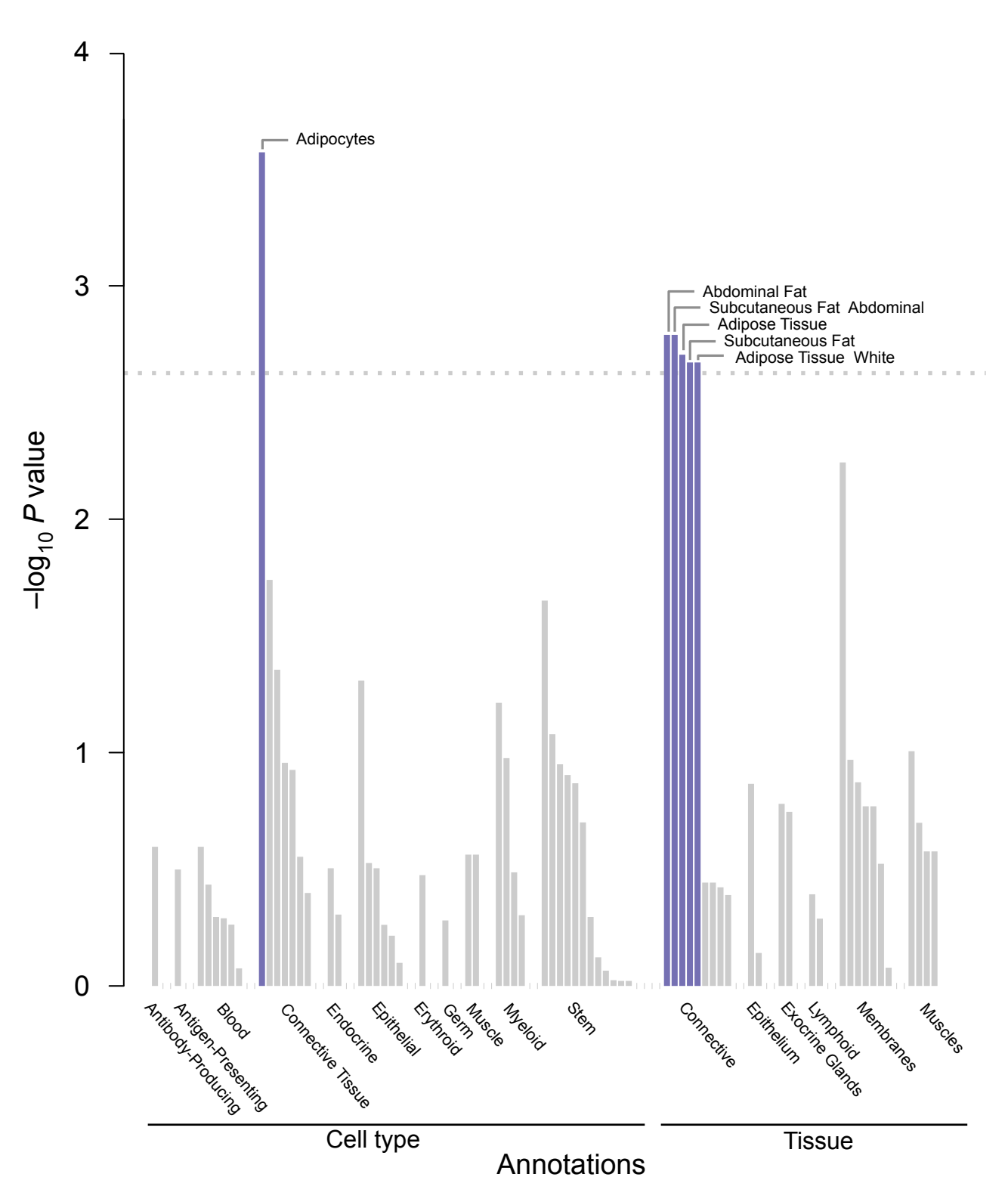
Recombination rate (cM/Mb)
100
80
60
40
20
0

←SPAG17 ←TBX15 ←WARS2

118.6 118.8 119 119.2 119.4
Position on chr1 (Mb)


Color Key
−3 −2 −1 0 1 2 3
Scaled Z score
RSPO3
KLF13
GORAB
PPARG
TNFAIP8
CCDC92
ADAMTS9
CEBPA
DNM3
PEMT
JUND
MAP3K1
ZNRF3
NKX2-6
MEIS1
MSC
SNX10
MACROD1
NMU
KCNJ2
EYA2
ABCA1
CPEB4
PBRM1
CMIP
LEKR1
FAM13A
VEGFA
BCL2
ITPR2
TEX9
HOXA11
SFXN2
HMGA1
BMP2
FGFR4
NFE2L3
WARS2
DCST2
SPATA5
BTNL2
GDF5
SLC30A10
COBLL1
PLXND1
SMAD6
HOXC13
CALCRL
LY86
WCadjBMI
Height
HIPadjBMI
Adiponectin
Fasting glucose
HDL cholesterol
eGFRcrea
Body mass index
Menopause
LDL cholesterol
Triglycerides
FladjBMI
Two-hour glucose
Endometriosis
Nephropathy
Type 2 diabetes
Coronary artery dis.
Systolic blood press.
Diastolic blood press.
Menarche
UACR
Chronic kidney dis.
Femoral neck BMD
Lumbar spine BMD


Regulation Of Lipid Biosynthetic Process
Regulation Of Steroid Metabolic Process
Sex Differentiation
Development Of Secondary Sexual Characteristics
Pale Liver
Myoblast Differentiation
Response To Nutrient Levels
Regulation Of Glucose Metabolic Process
Abnormal Cardiovascular Development
Transcription Factor Complex
Delayed Sexual Maturation
Partial Embryonic Lethality During Organogenesis
BMP4 protein complex
Renal System Development
Abnormal Skeleton Morphology
Partial Lethality Throughout Fetal Growth And Development
Abnormal Aorta Morphology
Decreased Liver Weight
Regulation Of IGF Activity By IGF Binding Proteins
Decreased Susceptibility To Diet-Induced Obesity
Abnormal Heart Morphology
Abnormal Kidney Morphology
Digestive System Development
Abnormal Muscle Cell Glucose Uptake
Enlarged Kidney
Decreased Creatinine Clearance
Abnormal Liver Morphology
Decreased Adiponectin Level
Increased Respiratory Quotient
Decreased Liver Triglyceride Level
Decreased Total Body Fat Amount
Abnormal White Adipose Tissue Morphology
Transcriptional Regulation Of White Adipocyte Differentiation
Increased Insulin Sensitivity
Increased Urine Glucose Level
Decreased Susceptibility To Hepatic Steatosis
Decreased Respiratory Quotient
Decreased Percent Body Fat
Decreased Liver Weight
Gene set P values
P < 10-2
P < 10-3
P < 10-4
P < 10-5
P < 10-6
Gene set overlap
Low
Moderate


4
3
2
1
0
–log10 P value
Adipocytes
Abdominal Fat
Subcutaneous Fat Abdominal
Adipose Tissue
Subcutaneous Fat
Adipose Tissue White
Antibody-Producing
Antigen-Presenting
Blood
Connective Tissue
Endocrine
Epithelial
Erythroid
Germ
Muscle
Myeloid
Stem
Connective
Epithelium
Exocrine Glands
Lymphoid
Membranes
Muscles
Cell type
Tissue
Annotations