

Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution

Waist-hip ratio (WHR) is a measure of body fat distribution and a predictor of metabolic consequences independent of overall adiposity. WHR is heritable, but few genetic variants influencing this trait have been identified. We conducted a meta-analysis of 32 genome-wide association studies for WHR adjusted for body mass index (comprising up to 77,167 participants), following up 16 loci in an additional 29 studies (comprising up to 113,636 subjects). We identified 13 new loci in or near *RSPO3*, *VEGFA*, *TBX15-WARS2*, *NFE2L3*, *GRB14*, *DNM3-PIGC*, *ITPR2-SSPN*, *LY86*, *HOXC13*, *ADAMTS9*, *ZNRF3-KREMEN1*, *NISCH-STAB1* and *CPEB4* ($P = 1.9 \times 10^{-9}$ to $P = 1.8 \times 10^{-40}$) and the known signal at *LYPLAL1*. Seven of these loci exhibited marked sexual dimorphism, all with a stronger effect on WHR in women than men (P for sex difference = 1.9×10^{-3} to $P = 1.2 \times 10^{-13}$). These findings provide evidence for multiple loci that modulate body fat distribution independent of overall adiposity and reveal strong gene-by-sex interactions.

Central obesity and body fat distribution, as measured by waist circumference and WHR, are associated with individual risk of type 2 diabetes (T2D)^{1,2} and coronary heart disease³ and with mortality from all causes⁴. These effects are independent of overall adiposity as measured by body mass index (BMI). WHR is of particular interest as a measure of body fat distribution because it integrates the adverse metabolic risk associated with increasing waist circumference with the more protective role of gluteal fat deposition with respect to diabetes, hypertension and dyslipidemia^{5,6}.

There is abundant evidence that body fat distribution is influenced by genetic loci distinct from those regulating BMI and overall adiposity. First, even after accounting for BMI, individual variation in WHR is heritable^{7,8}, with heritability estimates ranging from 22%–61%^{7–10}. Second, the striking abnormalities of regional fat deposition associated with lipodystrophic syndromes demonstrate that genetic variation can have dramatic effects on the development and maintenance of specific fat depots^{11,12}. Third, in a previous genome-wide association analysis, we identified a locus near *LYPLAL1* strongly associated with WHR independent of any effects on BMI¹³, providing proof of principle for the genetic control of body fat distribution distinct from that of overall adiposity.

Within the Genetic Investigation of Anthropometric Traits (GIANT) consortium, we performed a large-scale meta-analysis of genome-wide association studies (GWAS) informative for WHR using adjustment for BMI to focus discovery toward genetic loci associated with body fat distribution rather than overall adiposity^{14–16}.

RESULTS

Genome-wide significant association of WHR with 14 SNPs

We conducted a two-stage study among individuals of European descent (Supplementary Table 1 and Online Methods). In the

discovery stage, up to 2,850,269 imputed and genotyped SNPs were examined in 32 GWAS comprising up to 77,167 participants informative for anthropometric measures of body fat distribution. We performed a fixed-effects meta-analysis of WHR, employing study-specific linear regression adjusted for BMI and age, stratified by gender, and using an additive genetic model. After genomic control adjustment per each individual study and in the meta-analysis, these analyses revealed a substantial excess of low P values (Fig. 1a,b).

We selected SNPs representing the top 16 independent (defined as being located >1 Mb apart) regions of association (discovery $P < 1.4 \times 10^{-6}$; Table 1) and evaluated them in 29 additional, independent studies (comprising up to 113,636 individuals) using a mixture of *in silico* data and *de novo* genotyping. In these follow-up studies, 14 of the 16 SNPs analyzed showed strong directionally consistent evidence for replication ($P < 1.0 \times 10^{-3}$) and ten SNPs reached genome-wide significance ($P < 5.0 \times 10^{-8}$). Joint analysis of the discovery and follow-up results revealed genome-wide significant associations for 14 signals (with P values between 1.9×10^{-9} and 1.8×10^{-40} ; Table 1). Between-study heterogeneity was low ($I^2 < 30\%$) for all but two signals (*GRB14* and *LYPLAL1*; Supplementary Note), and all 14 associations remained genome-wide significant in a random-effects meta-analysis (Supplementary Table 2).

One of these SNPs, rs4846567, is in linkage disequilibrium (LD) ($r^2 = 0.64$, $D' = 0.84$; HapMap European CEU population) with the previously reported WHR-associated variant near *LYPLAL1* (rs2605100)¹³. The remaining 13 loci were in or near genes not previously associated with WHR or other measures of adiposity: *RSPO3*, *VEGFA*, *TBX15-WARS2*, *NFE2L3*, *GRB14*, *DNM3-PIGC*, *ITPR2-SSPN*, *LY86*, *HOXC13*, *ADAMTS9*, *ZNRF3-KREMEN1*, *NISCH-STAB1* and *CPEB4* (Fig. 2). These 14 loci explain 1.03% of the variance in WHR (after adjustment for BMI, age and sex), with each locus contributing

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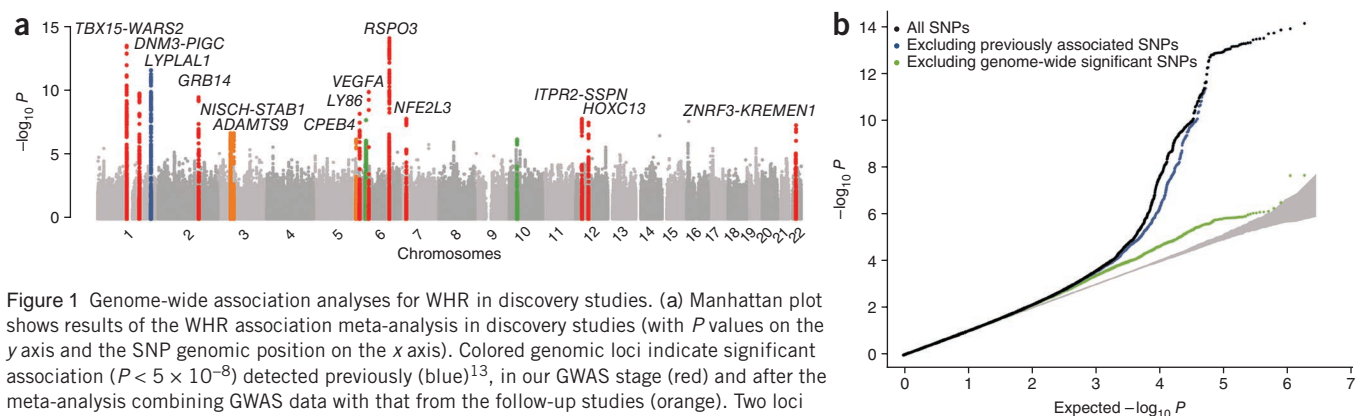


Figure 1 Genome-wide association analyses for WHR in discovery studies. (a) Manhattan plot shows results of the WHR association meta-analysis in discovery studies (with P values on the y axis and the SNP genomic position on the x axis). Colored genomic loci indicate significant association ($P < 5 \times 10^{-8}$) detected previously (blue)¹³, in our GWAS stage (red) and after the meta-analysis combining GWAS data with that from the follow-up studies (orange). Two loci tested in the follow-up stage did not achieve genome-wide significance (green). (b) Quantile-quantile plot of SNPs for the discovery meta-analysis of WHR (black) and after removing SNPs within 1 Mb of either the recently reported *LYPLAL1* signal (blue) or the 14 significant associations (green). The gray area represents the 95% CI around the test statistic under the null distribution.

from 0.02% (*ZNRF3-KREMEN1*) to 0.14% (*RSPO3*) of the variance based on effect estimates in the follow-up stage.

Sexual dimorphism at several of the WHR loci

Given the known sexual dimorphism of WHR and the evidence from variance decomposition studies that this reflects sex-specific genetic effects¹⁷, we performed sex-specific meta-analyses for the 14 WHR-associated SNPs. These analyses included up to 108,979 women (42,735 in the discovery stage and 66,244 in the follow up) and 82,483 men (34,601 in the discovery and 47,882 in the follow up). In a joint analysis of discovery and follow-up data, 12 of the 14 SNPs reached genome-wide significance in women, but only three SNPs reached genome-wide significance in men (**Table 2**). At all but one locus (*TBX15-WARS2*), effect-size estimates were numerically greater in women. At seven of the loci (those near *RSPO3*, *VEGFA*, *GRB14*, *LYPLAL1*, *HOXC13*, *ITPR2-SSPN* and *ADAMTS9*), there were marked differences in sex-specific β coefficients (with P values ranging from 1.9×10^{-3} to 1.2×10^{-13}).

All loci displayed consistent patterns of sex-specific differences in both the discovery and follow-up studies (**Table 2**). These 14 loci explain 1.34% of the variance in WHR (after adjustment for BMI and age) in women but only 0.46% of the variance in WHR in men.

Association with other anthropometric measures

By focusing on WHR after adjustment for BMI, our goal was to detect effects on body fat distribution independent of those influencing overall adiposity. As expected, we found very little evidence that known BMI-associated variants were detected in our WHR analysis. Of the ten loci shown to be associated with BMI in previous GWAS^{14,15,18}, only two showed nominally significant ($P < 0.05$) associations for BMI-adjusted WHR in the discovery analysis (*FTO*, rs8050136, $P = 0.03$, $n = 77,074$; *TMEM18*, rs6548238, $P = 3.0 \times 10^{-3}$, $n = 77,016$).

We also tested the 14 WHR-associated SNPs for their effect on BMI using data from up to 242,530 participants available from the GIANT consortium (including most of the studies available for WHR

Table 1 Fourteen SNPs associated with WHR at genome-wide significant levels

SNP	Chr.	Position (b36)	Nearby genes	EA ^a	EAF ^b	Discovery			Follow-up			Combined	
						P	β	n	P	β	n	P	β
SNPs evaluated in follow up achieving genome-wide significance													
rs9491696	6	127,494,332	<i>RSPO3</i>	G	0.480	2.10×10^{-14}	0.037	77,164	3.27×10^{-28}	0.045	113,582	1.84×10^{-40}	0.042
rs6905288	6	43,866,851	<i>VEGFA</i>	A	0.562	4.72×10^{-10}	0.033	77,129	1.18×10^{-16}	0.039	95,430	5.88×10^{-25}	0.036
rs984222	1	119,305,366	<i>TBX15-WARS2</i>	G	0.635	3.81×10^{-14}	0.037	77,167	1.56×10^{-12}	0.031	109,623	8.69×10^{-25}	0.034
rs1055144	7	25,837,634	<i>NFE2L3</i>	T	0.210	1.49×10^{-8}	0.034	77,145	3.26×10^{-18}	0.043	113,636	9.97×10^{-25}	0.040
rs10195252	2	165,221,337	<i>GRB14</i>	T	0.599	3.23×10^{-10}	0.031	77,119	3.18×10^{-16}	0.036	102,449	2.09×10^{-24}	0.033
rs4846567	1	217,817,340	<i>LYPLAL1</i>	G	0.717	2.37×10^{-12}	0.037	77,167	3.15×10^{-10}	0.032	91,820	6.89×10^{-21}	0.034
rs1011731	1	170,613,171	<i>DNM3-PIGC</i>	G	0.428	1.72×10^{-10}	0.031	77,094	7.47×10^{-9}	0.026	92,018	9.51×10^{-18}	0.028
rs718314	12	26,344,550	<i>ITPR2-SSPN</i>	G	0.259	2.41×10^{-8}	0.031	77,167	1.49×10^{-10}	0.030	107,503	1.14×10^{-17}	0.030
rs1294421	6	6,688,148	<i>LY86</i>	G	0.613	6.31×10^{-9}	0.029	77,154	2.69×10^{-10}	0.028	102,189	1.75×10^{-17}	0.028
rs1443512	12	52,628,951	<i>HOXC13</i>	A	0.239	3.33×10^{-8}	0.031	77,165	2.92×10^{-10}	0.030	112,353	6.38×10^{-17}	0.031
rs6795735	3	64,680,405	<i>ADAMTS9</i>	C	0.594	2.47×10^{-7}	0.025	77,162	6.75×10^{-8}	0.026	84,480	9.79×10^{-14}	0.025
rs4823006	22	27,781,671	<i>ZNRF3-KREMEN1</i>	A	0.569	4.47×10^{-8}	0.027	77,086	2.41×10^{-5}	0.019	93,911	1.10×10^{-11}	0.023
rs6784615	3	52,481,466	<i>NISCH-STAB1</i>	T	0.941	3.18×10^{-7}	0.052	76,859	1.56×10^{-4}	0.036	109,028	3.84×10^{-10}	0.043
rs6861681	5	173,295,064	<i>CPEB4</i>	A	0.340	1.40×10^{-6}	0.026	77,164	2.13×10^{-4}	0.019	85,722	1.91×10^{-9}	0.022
Further SNPs evaluated in follow up but not achieving genome-wide significance in the combined analysis													
rs2076529	6	32,471,933	<i>BTNL2</i>	C	0.430	2.22×10^{-8}	0.041	34,532	0.012	0.011	92,778	3.71×10^{-7}	0.020
rs7081678	10	32,030,629	<i>ZEB1</i>	A	0.085	5.76×10^{-7}	0.045	76,270	0.094	0.013	100,527	5.57×10^{-6}	0.027

P values and β coefficients (per change of WHR-increasing allele) for the association with WHR on the inverse normal transformed ranked scale in the meta-analyses of discovery studies (up to 77,167 subjects), follow-up studies (up to 113,636 subjects) and both combined (up to 190,781 subjects). Fourteen of the sixteen SNPs examined in the follow-up samples showed genome-wide significant results ($P < 5 \times 10^{-8}$) in the combined analysis. P values in the discovery stage were genomic control corrected per study and in the meta-analysis. Details on between-study heterogeneity are given in **Supplementary Table 1c**.

^aEA, effect allele (WHR-increasing allele on the forward strand). ^bEAF, effect allele frequency. Chr., chromosome.

association). Of the 14 WHR loci, four (near *TBX15*-*WARS2*, *CPEB4*, *LYPLAL1* and *GRB14*) also showed evidence of association with BMI ($4.1 \times 10^{-3} \leq P \leq 3.2 \times 10^{-6}$), with the WHR-increasing allele associated with decreased BMI (Supplementary Table 3). After adding

an interaction term of SNP with BMI into the model, we observed that BMI modified the WHR association at the *LY86* locus (P for interaction = 9.5×10^{-5}), with a larger WHR effect among obese individuals compared to non-obese individuals (Supplementary Note).

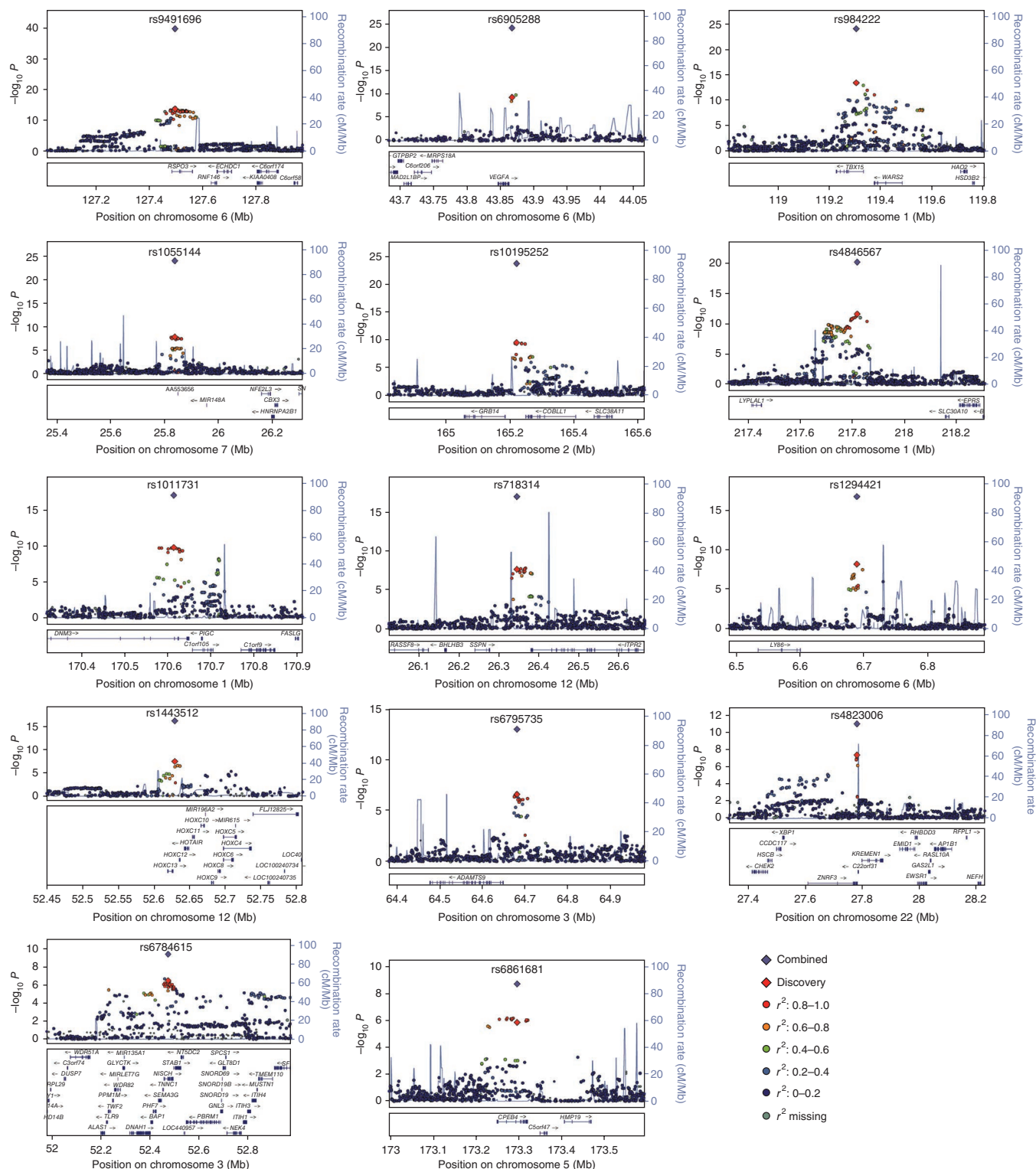


Figure 2 Regional plots of 14 loci with genome-wide significant association. Shown is the SNP association with WHR in the meta-analysis of discovery studies for 14 loci (with $-\log_{10} P$ values on the y axis and the SNP genomic position on the x axis). In each panel, an index SNP is denoted with a purple diamond and plotted using the P attained across discovery and follow-up data (Table 1). Estimated recombination rates are plotted in blue. SNPs are colored to reflect LD with the index SNP (pairwise r^2 values from HapMap CEU). Gene and microRNA annotations are from the UCSC genome browser.

Table 2 Evidence of sex-differences in the WHR association at seven of the 14 associated loci

SNP	Nearby genes	Men						Women						Sex difference
		Discovery		Follow up		Combined		Discovery		Follow up		Combined		Combined
		<i>P</i>	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>	β	
rs9491696	<i>RSPO3</i>	1.68×10^{-4}	0.026	6.97×10^{-9}	0.036	1.05×10^{-11}	0.031	1.62×10^{-12}	0.047	8.84×10^{-22}	0.053	1.93×10^{-32}	0.050	1.94×10^{-3}
rs6905288	<i>VEGFA</i>	0.066	0.013	2.09×10^{-4}	0.025	7.38×10^{-5}	0.020	7.72×10^{-13}	0.052	3.14×10^{-15}	0.051	2.27×10^{-26}	0.052	5.20×10^{-6}
rs984222	<i>TBX15-WARS2</i>	3.32×10^{-9}	0.041	2.43×10^{-5}	0.029	9.41×10^{-13}	0.035	1.21×10^{-7}	0.036	1.33×10^{-8}	0.033	1.02×10^{-14}	0.034	0.951
rs1055144	<i>NFE2L3</i>	6.00×10^{-4}	0.029	5.67×10^{-8}	0.040	2.52×10^{-10}	0.035	2.34×10^{-6}	0.040	7.13×10^{-12}	0.046	1.41×10^{-16}	0.044	0.270
rs10195252	<i>GRB14</i>	0.201	0.009	0.114	0.011	0.043	0.010	6.33×10^{-15}	0.053	4.95×10^{-21}	0.054	3.84×10^{-34}	0.054	1.41×10^{-11}
rs4846567	<i>LYPLAL1</i>	0.191	0.010	0.982	0.000	0.358	0.005	4.84×10^{-18}	0.064	8.12×10^{-17}	0.055	4.95×10^{-33}	0.059	1.18×10^{-13}
rs1011731	<i>DNM3-PIGC</i>	4.88×10^{-7}	0.034	1.95×10^{-3}	0.022	7.81×10^{-9}	0.028	2.13×10^{-5}	0.028	7.03×10^{-7}	0.030	6.90×10^{-11}	0.029	0.855
rs718314	<i>ITPR2-SSPN</i>	0.177	0.010	2.02×10^{-3}	0.022	1.41×10^{-3}	0.017	8.29×10^{-10}	0.047	4.21×10^{-9}	0.038	2.41×10^{-17}	0.042	4.67×10^{-4}
rs1294421	<i>LY86</i>	4.18×10^{-3}	0.020	7.00×10^{-6}	0.030	1.63×10^{-7}	0.025	3.44×10^{-8}	0.038	7.32×10^{-6}	0.026	2.40×10^{-12}	0.031	0.357
rs1443512	<i>HOXC13</i>	0.184	0.011	9.74×10^{-4}	0.024	9.45×10^{-4}	0.018	1.43×10^{-9}	0.048	3.09×10^{-8}	0.035	6.38×10^{-16}	0.040	2.23×10^{-3}
rs6795735	<i>AD-AMTS9</i>	0.011	0.017	0.614	0.004	0.027	0.011	7.85×10^{-7}	0.033	2.95×10^{-11}	0.042	1.92×10^{-16}	0.038	8.50×10^{-5}
rs4823006	<i>ZNRF3-KREMEN1</i>	6.87×10^{-3}	0.019	0.094	0.012	1.94×10^{-3}	0.015	6.86×10^{-8}	0.037	3.81×10^{-5}	0.024	3.24×10^{-11}	0.030	0.032
rs6784615	<i>NISCH-STAB1</i>	1.51×10^{-3}	0.045	0.033	0.032	1.68×10^{-4}	0.039	6.23×10^{-5}	0.057	1.72×10^{-3}	0.039	6.01×10^{-7}	0.047	0.574
rs6861681	<i>CPEB4</i>	1.88×10^{-3}	0.023	0.045	0.015	3.03×10^{-4}	0.019	2.14×10^{-4}	0.027	1.58×10^{-3}	0.021	1.55×10^{-6}	0.024	0.555

P values and β coefficients (per change of WHR-increasing allele in the sex-combined analysis as in Table 1) for the WHR association are given for the discovery (up to 34,601 men and 42,735 women), the follow-up (up to 47,882 men and 65,780 women) and the combined meta-analysis (up to 81,301 men and 107,429 women). Also given are the *P* values for testing for difference between sex-specific β coefficients in the combined meta-analysis; SNPs with *P* for sex difference $< 3.6 \times 10^{-3}$ (0.05/14) were considered to show a significant sex difference.

To determine whether the WHR-associated signals exert their effects primarily through an effect on waist or hip circumference, we performed meta-analyses for these specific phenotypes in the discovery and follow-up studies (Supplementary Tables 1 and 3). Overall, we observed stronger associations for hip circumference than for waist circumference. Effect-size estimates were numerically greater for hip circumference than for waist circumference at 11 of the 14 loci, and there were nominal associations ($P < 0.05$) with hip circumference for 12 of the WHR-associated loci but there were only four associations with waist circumference. In both sexes, the WHR-associated loci displaying nominal association with hip circumference always featured the WHR-increasing allele associated with reduced hip circumference. In contrast, we observed sexual dimorphism in the pattern of waist

circumference associations. In women, the WHR-increasing allele at all 14 loci was associated with increased waist circumference, whereas this was only true for six of these loci in men (Fig. 3). At *GRB14*, for example, the WHR-increasing allele was associated with increased waist circumference in women ($P = 3.6 \times 10^{-4}$) but with decreased waist circumference in men ($P = 6.8 \times 10^{-3}$). These differences in the relationships between waist circumference, hip circumference and WHR underlie some of the sexual dimorphism in the patterns of WHR association.

Enrichment of association with metabolic traits

We evaluated the 14 WHR-associated loci for their relationships with related metabolic traits using GWAS data provided by trait-specific

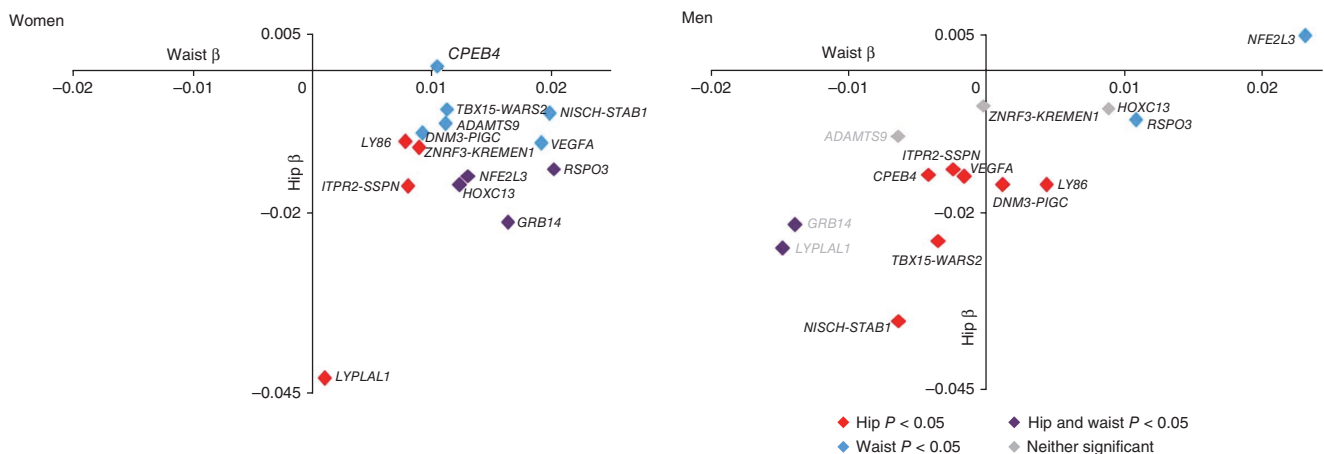


Figure 3 Association of the 14 WHR loci with waist and hip circumference. β coefficients for waist circumference (WC, x axis) and hip circumference (HIP, y axis) in women and men derived from the joint discovery and follow-up analysis. *P* for WC and HIP are represented by color. In men, gray gene labels refer to those SNPs that were not significant in the male-specific WHR analysis. More details can be found in Supplementary Table 3.

Table 3 WHR signals show enrichment of association with other traits related to metabolic disorders

Trait	Sample size ^a	SNPs in concordant direction ^b		SNPs in concordant direction with $P < 0.05^c$	
		<i>n</i>	<i>P</i>	<i>n</i>	<i>P</i>
Triglycerides	43,826	14	6.10×10^{-5}	7	1.79×10^{-8}
HDL-C	45,561	13	9.16×10^{-4}	4	3.20×10^{-4}
LDL-C	43,889	10	0.090	1	0.298
Fasting glucose	63,849	10	0.090	1	0.298
Fasting insulin	54,883	13	9.16×10^{-4}	5	1.62×10^{-5}
HOMA-IR	53,625	13	9.16×10^{-4}	6	6.17×10^{-7}
2 h glucose	27,011	7	0.605	0	1.000
Type 2 diabetes	10,128 ^d	11	0.029	3	4.62×10^{-3}

The 14 WHR SNPs were tested for association with other traits by meta-analysis of GWAS data from previous reports^{19–21,39} together with our non-overlapping *de novo* genotyped follow-up studies. HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HOMA-IR, index of insulin resistance; 2 h glucose, glucose levels 2 h after an oral glucose challenge.

^aMaximum number of subjects available for any of the 14 SNPs. ^bNumber of the 14 SNPs for which the WHR-increasing allele is associated with the trait in the concordant direction (that is, increased levels, except for HDL-C) and corresponding binomial *P* value to test whether this number is greater than that expected by chance and not accounting for the correlation between the traits. ^cNumber of SNPs in concordant direction that show $P < 0.05$ for the association with the trait and the corresponding binomial *P* value as in ^b. ^d4,549 cases, 5579 controls.

consortia^{19–21} as well as our *de novo* genotyped follow-up studies. As expected given the sample overlap between this GWAS data and our WHR GWAS data as well as information on known trait correlations (**Supplementary Table 4**), we observed directionally consistent enrichment of associations ($P < 0.05$) between the 14 WHR-associated alleles and increased triglycerides, low-density lipoprotein (LDL) cholesterol, fasting insulin and homeostasis model assessment (HOMA)-derived measures of insulin resistance (binomial *P* from 3.2×10^{-4} to 1.8×10^{-8} ; **Table 3** and **Supplementary Table 5**). For example, the WHR-increasing allele at *GRB14* showed strong associations with increased triglycerides ($P = 7.4 \times 10^{-9}$), fasting insulin levels ($P = 5.0 \times 10^{-6}$) and insulin resistance ($P = 1.9 \times 10^{-6}$). Eleven of the 14 WHR-associated loci showed directionally consistent associations with T2D, with three of these loci (at *ADAMTS9*, *NISCH-STAB1* and *ITPR2-SSPN*) reaching nominal significance ($P < 0.05$) (**Table 3** and **Supplementary Table 5**). Because the association signals for correlated traits in this analysis were vulnerable to overestimation given the overlap in the GWAS samples examined, we repeated these analyses and restricted the samples included to those from our *de novo* genotyped follow-up studies. Although this also resulted in a lower sample size, similar patterns of enrichment were still observed (**Supplementary Table 5**).

Pathway analysis and potential biological roles

To identify potential functional connections and pathway relationships between genes mapping at the WHR-associated loci, we focused on the 95 genes located in a 2-Mb interval centered around each of the 48 independent SNPs that attained $P < 1.0 \times 10^{-5}$ in the WHR discovery studies.

First, we performed a survey of the published literature using GRAIL²² to search for connectivity between the genes and specific keywords that describe these functional connections (Online Methods). Although there was no evidence after correcting for multiple testing that the connectivity between these genes was greater than chance, we identified eight genes with nominal significance ($P < 0.05$) for potential functional connectivity (*PLXND*, *HOXC10*, *TBX15*, *RSPO3*, *HOXC4*, *HOXC6*, *KREMEN1* and *HOXC11*). The keywords associated

with these connections included ‘vegf’, ‘homeobox’, ‘patterning’, ‘mesenchyme’, ‘embryonic’, ‘development’ and ‘angiogenesis’.

Additionally, we performed pathway analyses using the PANTHER database²³ based on the same set of 95 genes (Online Methods and **Supplementary Note**). This analysis generated some evidence for over-representation of ‘developmental processes’ ($P = 5.8 \times 10^{-8}$) and ‘mRNA transcription regulation’ ($P = 2.7 \times 10^{-6}$) but neither of these factors retained nominal significance after adjustment for bias (for example, due to non-random SNP coverage in relation to genes) and the number of biological processes tested (**Supplementary Note** and **Supplementary Table 6**).

Finally, we examined the described functional roles of some of the most compelling candidates based on either proximity to the signal or the other analyses described in this paper. These analyses uncovered possible genetic roles in adipocyte development (*TBX15*), pattern formation during embryonic development (*HOXC13*), angiogenesis (*VEGFA*, *RSPO3* and *STAB1*), Wnt and β -catenin signaling (*RSPO3* and *KREMEN1*), insulin signaling (*ADAMTS9*, *GRB14* and *NISCH*), lipase activity (*LYPLAL1*), lipid biosynthesis (*PIGC*) and intracellular calcium signaling (*ITPR2*) (**Supplementary Note**).

Evaluation of copy number variants and non-synonymous changes

Both common and rare copy number variants (CNVs) have been reported to be associated with overall adiposity^{14,15,24,25}, but the impact of CNVs on fat distribution has not been evaluated previously. To examine the potential contribution of common CNVs to variation in WHR, we looked for evidence of association in our genome-wide association discovery meta-analysis using a set of 6,018 CNV-tagging SNPs which collectively capture >40% of common CNVs that are greater than 1 kb in length^{26,27} (Online Methods and **Supplementary Note**).

One CNV-tagging SNP (rs1294421 in *LY86*) was observed among our 14 WHR-associated loci. This SNP is in strong LD ($r^2 = 0.98$) with a 2,832-bp duplication variant (CNVR2760.1)²⁷ located 12 kb from an expressed sequence tag (BC039678) and 87 kb from *LY86* such that the duplication allele is associated with reduced WHR. The duplicated region consists entirely of noncoding sequence but includes part of a predicted enhancer sequence (E.5552.1)²⁸.

To identify other putatively causal variants in our associated regions, we searched for non-synonymous coding SNPs in strong LD (defined as $r^2 > 0.7$) with the most strongly associated SNPs at each locus using data from the HapMap (Build 21) and 1000 Genomes Project (April and August 2009 releases). In this search, one lead SNP (rs6784615, at the *NISCH-STAB1* locus) was correlated with non-synonymous changes in two nearby genes, *DNAH1* (p.Val441Leu, p.Arg1285Trp and p.Arg3809Cys) and *GLYCTK* (p.Leu170Val). Fine-mapping and functional studies will be required to determine whether the *DNAH1* or *GLYCTK* SNPs or the *LY86* CNV are causal for the WHR associations at these loci.

Effect of WHR associations on expression in relevant tissues

Expression quantitative trait locus (eQTL) data can implicate regional transcripts that mediate trait associations, and we therefore examined the 14 WHR-associated loci using eQTL data from human subcutaneous adipose tissue (SAT)²⁹ (two separate sample sets, $n = 610$ and $n = 603$), omental fat³⁰ ($n = 740$), liver³⁰ ($n = 518$), blood²⁹ ($n = 745$) and lymphocytes³¹ ($n = 830$) (Online Methods and **Supplementary Note**).

At six of the loci, the WHR-associated SNP was either the strongest SNP associated with significant ($P < 1.0 \times 10^{-5}$) expression of a local (within 1 Mb) gene transcript or explained the majority of the association between the most significant eQTL SNP and the gene transcript

Table 4 Expression quantitative trait locus analysis for 11 of the 14 WHR signals

WHR SNP	Tissue	Gene	Effect ^a	WHR SNP association with transcript (P)			LD (r ²) ^c	Peak SNP association with transcript (P)	
				Unadj.	Adj. for peak SNP	Transcript peak SNP ^b		Unadj.	Adj. for WHR SNP
rs9491696	SAT-D	<i>RSPO3</i>	+	1.10 × 10 ⁻⁷	0.03	rs1936795	0.26	2.20 × 10 ⁻¹³	7.40 × 10 ⁻⁸
rs984222	Omental	<i>TBX15</i>	+	7.90 × 10 ⁻¹⁰	1.00	rs984222	1.00	7.90 × 10 ⁻¹⁰	1.00
	Omental	<i>WARS2</i>	+	5.11 × 10 ⁻³⁶	0.03	rs10802075	0.27	1.31 × 10 ⁻¹⁶³	1.33 × 10 ⁻⁸⁸
	Subcutaneous fat	<i>WARS2</i>	+	1.67 × 10 ⁻²⁵	0.01	rs10802075	0.22	3.88 × 10 ⁻¹¹⁰	1.01 × 10 ⁻⁶³
	Lymphocytes	<i>WARS2</i>	-	4.30 × 10 ⁻¹⁸	5.47 × 10 ⁻⁵	rs2645305	0.27	5.57 × 10 ⁻⁴⁰	6.88 × 10 ⁻²⁶
	Liver	<i>WARS2</i>	+	2.57 × 10 ⁻¹⁷	0.07	rs1057990	0.26	6.69 × 10 ⁻⁵⁹	1.97 × 10 ⁻³²
	SAT-D	<i>WARS2</i>	+	1.10 × 10 ⁻¹⁸	0.51	rs1057990	0.26	5.80 × 10 ⁻¹³⁰	5.80 × 10 ⁻¹⁰⁰
	Blood	<i>WARS2</i>	+	6.10 × 10 ⁻¹⁷	0.11	rs1057990	0.26	6.30 × 10 ⁻⁷⁵	1.10 × 10 ⁻⁵⁴
rs1055144	SAT-D	AA553656 ^d		1.20 × 10 ⁻¹¹	0.96	rs7798002	0.95	7.20 × 10 ⁻¹²	0.32
	SAT-M	AA553656 ^d		2.46 × 10 ⁻⁷	0.65	rs1451385	0.77	5.93 × 10 ⁻⁸	0.38
rs10195252	SAT-D	<i>GRB14</i>	+	4.40 × 10 ⁻¹¹	1.00	rs10195252	1.00	4.40 × 10 ⁻¹¹	1.00
	SAT-M	<i>GRB14</i>	+	5.51 × 10 ⁻⁶	1.00	rs10184004	1.00	5.51 × 10 ⁻⁶	1.00
	Omental	<i>GRB14</i>	+	1.02 × 10 ⁻¹³	1.00	rs10195252	1.00	1.02 × 10 ⁻¹³	1.00
	SAT-M	<i>SLC38A11</i>	-	3.93 × 10 ⁻⁶	0.66	rs10184126	0.18	7.76 × 10 ⁻⁴⁴	8.57 × 10 ⁻³⁴
	SAT-D	<i>SLC38A11</i>	-	3.70 × 10 ⁻⁹	0.35	rs10184126	0.18	2.40 × 10 ⁻⁹⁴	7.40 × 10 ⁻⁸²
rs1011731	Blood	<i>C1orf105</i>	+	3.80 × 10 ⁻¹⁶	0.20	rs2157451	0.28	1.30 × 10 ⁻³³	8.20 × 10 ⁻¹⁸
	Lymphocytes	<i>PIGC</i>		5.87 × 10 ⁻¹⁰	1.00	rs991790	1.00	5.65 × 10 ⁻¹⁰	1.00
rs718314	Lymphocytes	<i>ITPR2</i>	+	1.79 × 10 ⁻⁹	0.98	rs7976877	0.45	2.21 × 10 ⁻¹⁸	1.91 × 10 ⁻⁶
	Blood	<i>ITPR2</i>	-	2.40 × 10 ⁻⁹	0.20	rs2570	0.41	2.40 × 10 ⁻³⁷	1.80 × 10 ⁻²⁸
rs1294421	SAT-M	<i>BC039678</i>	-	2.43 × 10 ⁻⁷	0.38	rs1294404	0.64	1.89 × 10 ⁻¹⁶	3.42 × 10 ⁻⁴
	Omental	<i>BC039678</i>	-	1.09 × 10 ⁻⁶	0.33	rs912056	0.71	8.28 × 10 ⁻¹⁷	4.26 × 10 ⁻⁵
rs6795735	SAT-D	<i>ADAMTS9</i>	-	1.50 × 10 ⁻⁶	0.04	rs7372321	0.11	1.10 × 10 ⁻⁹	2.30 × 10 ⁻⁵
	Omental	<i>AK022320</i>	-	7.99 × 10 ⁻¹⁵	0.64	rs4521216	0.02	5.15 × 10 ⁻⁴²	1.49 × 10 ⁻¹⁹
	SAT-D	<i>AK022320</i>	-	2.24 × 10 ⁻¹⁰	0.98	rs4521216	0.02	9.62 × 10 ⁻³⁷	7.58 × 10 ⁻¹⁹
rs4823006	SAT-D	<i>ZNRF3</i>		2.40 × 10 ⁻⁸	0.63	rs3178915	0.81	6.70 × 10 ⁻¹¹	8.90 × 10 ⁻⁴
	SAT-M	<i>ZNRF3</i>		1.08 × 10 ⁻¹⁸	0.93	rs6005975	0.79	1.59 × 10 ⁻¹⁹	0.50
	Omental	<i>ZNRF3</i>		9.13 × 10 ⁻¹⁸	0.98	rs6005975	0.79	6.07 × 10 ⁻²¹	0.27
rs6784615	Blood	<i>STAB1</i>	+	2.80 × 10 ⁻⁹	0.32	rs9846089	0.83	9.40 × 10 ⁻¹⁰	0.08
rs6861681	Lymphocytes	<i>CPEB4</i>	+	3.79 × 10 ⁻²²	0.89	rs7705502	0.87	4.95 × 10 ⁻²⁹	2.00 × 10 ⁻³
	Blood	<i>HMP19</i>	+	1.60 × 10 ⁻¹⁶	0.97	rs10516107	0.83	1.10 × 10 ⁻²¹	4.30 × 10 ⁻⁶

Association between the 14 WHR SNPs and expression of transcripts located within 1 Mb of the WHR SNP in two sets of abdominal subcutaneous adipose tissue (SAT-D from deCODE and SAT-M from Massachusetts General Hospital), omental fat, liver, lymphocytes and blood (Supplementary Note). Results are given if the unadjusted WHR SNP association showed $P < 1.00 \times 10^{-5}$. Findings are highlighted in bold font where the WHR SNP was the transcript peak SNP or where the WHR signal and the *cis* eQTL signal were considered coincident (that is, the transcript peak SNP was highly correlated with the WHR SNP, $r^2 > 0.7$ and the transcript peak association disappeared by adjusting on the WHR SNP, $P > 0.05$); see also Online Methods. Unadj., unadjusted; Adj., adjusted.

^aEffect direction for the WHR-increasing allele. ^bSNP with the strongest association with the transcript in the region (transcript peak SNP). ^cCorrelation (HapMap CEU, build 36) between the WHR SNP and the transcript peak SNP. ^dThe transcript labeled AA553656 was detected as Contig27623_RC and corresponds to chromosome 7 locations 25,854,143–25,854,203 (HapMap build 36).

in conditional analyses (adjusted $P > 0.05$; Table 4). For example, the WHR-associated SNP rs1011731 (near *DNM3-PIGC*) was strongly associated with expression of *PIGC* in lymphocytes ($P = 5.9 \times 10^{-10}$); furthermore, rs1011731 is in high LD ($r^2 = 1.00$, $D' = 1.00$ from the HapMap CEU population) with the SNP with the strongest effect on *PIGC* expression (rs991790), and this *cis* eQTL association was abolished by conditioning on rs1011731. These analyses therefore indicate that these two signals are coincident and that *PIGC* is a strong candidate for mediating the WHR association at rs1011731. We found similar evidence for coincidence of the WHR signal with expression for rs984222 (*TBX15* in omental fat), rs1055144 (expressed sequence tag AA553656 in SAT), rs10195252 (*GRB14* in SAT), rs4823006 (*ZNRF3* in SAT and omental fat) and rs6784615 (*STAB1* in blood) (Table 4). Taken together, the overlap between trait association and gene expression at these loci suggests that the WHR associations may be driven through altered expression of *PIGC*, *TBX15*, AA553656, *GRB1*, *ZNRF3* and *STAB1*.

RNA expression of gluteal and abdominal fat tissue

To determine whether genes within the WHR-associated loci showed evidence of differential transcription in distinct fat depots, we

compared expression levels in gluteal or abdominal SAT in 49 individuals. We focused on the 15 genes with the strongest credentials for causal involvement (on the basis of proximity to the lead SNP and/or other biological or functional data; Table 1) for which expression data were available. Five of these genes (*RSPO3*, *TBX15*, *ITPR2*, *WARS2* and *STAB1*) were differentially expressed between the two tissues (using an *F* test, corrected for false discovery rate across the 15 expressed genes, $P < 0.05$; Supplementary Table 7). This supports the hypothesis that, at some loci at least, the association with WHR reflects depot-specific differences in expression patterns.

DISCUSSION

Overall, our findings demonstrate that the genetic regulation of body fat distribution involves loci and processes that are largely distinct from those that influence BMI and risk of obesity. This finding is consistent with the evidence that WHR displays substantial heritability even after adjustment for BMI. The loci that emerged from this study display no overlap with those shown to be associated with BMI either in previous reports^{14–16} or in the expanded meta-analysis recently completed by the GIANT consortium³².

Another point of distinction between our findings and those for BMI relates to the evidence for sexual dimorphism that we observed at several of the WHR-associated loci. Sex differences in the regulation of body fat distribution have long been acknowledged without a clear understanding of the underlying molecular mechanisms. These differences become apparent during puberty and are generally attributed to the influence of sex hormones³³. Consistent with our findings, variance decomposition studies have shown that the genetic contribution to the overall variance in WHR, waist and hip circumference is greater in women¹⁷. Although there is some evidence for loci with differential sex effects influencing lipids³⁴, uric acid levels³⁵ and risk of schizophrenia³⁶, we are unaware of prior reports indicating such strong enrichment of female-specific associations for any other phenotype, including BMI³².

The primary objective of genetic discovery efforts is to characterize the specific mechanisms involved in regulating the trait of interest. Despite the considerable challenges associated with moving from common variant association signals to defining causal alleles and pathways, we have identified strong candidates at several of the loci. For example, the *cis* eQTL data implicate *GRB14* as a compelling candidate for the WHR association on chromosome 2, and we were able to show that the same *GRB14* variants are also associated with triglyceride and insulin levels, consistent with previous association of this locus with high-density lipoprotein (HDL) cholesterol³⁷. These inferences about the role of *GRB14* are supported by evidence that *Grb14*-deficient mice exhibit improved glucose homeostasis despite lower circulating insulin levels, as well as enhanced insulin signaling in liver and skeletal muscle³⁸. The signal near *ADAMTS9* overlaps a previously-reported T2D locus³⁹, and the lead SNP for WHR in our study is identical to the SNP displaying the strongest T2D association in a previous expanded T2D meta-analysis⁴⁰. Given evidence that *ADAMTS9* T2D risk alleles are associated with insulin resistance in peripheral tissues⁴¹, these findings are consistent with a primary effect of *ADAMTS9* variants on body fat distribution. At the chromosome 6 locus, *VEGFA* is the most apparent biological candidate given the presumed role of *VEGFA* as a mediator of adipogenesis⁴² and evidence that serum levels of *VEGFA* are correlated with obesity^{43,44}. Finally, at the *TBX15*-*WARS2* locus, *TBX15* emerges as the strongest candidate based on the *cis* eQTL data in omental fat, marked depot-specific differences in adipose tissue expression in mice and humans and associations between *TBX15* expression in visceral fat and WHR^{45,46}.

Our efforts to use pathway- and literature-mining approaches to look for functional enrichment of the genes mapping to associated regions met with only limited success but did provide some support for over-representation of developmental processes. Developmental genes have been implicated in fat accumulation and distribution^{45,46}, and recent evidence supports a link between developmental genes, including *HOXC13* (ref. 47) and *TBX15* (refs. 45,48), and body fat distribution. Developmental genes may in part determine the adipocyte-specific expression patterns that have been observed in different fat depots⁴⁵. Taken together, our findings point to a set of genes influencing body fat distribution that have their principal effects in adipose tissue. This is in contrast to the predominantly central (hypothalamic) processes that are involved in the regulation of BMI and overall adiposity⁴⁹.

By providing new insights into the regulation of body fat distribution, the present study raises a number of issues for future investigation. From the genetic perspective, re-sequencing, dense-array genotyping and fine-mapping approaches will be required to characterize causal variants at the loci we have identified and to support further discoveries that may account for the substantial

proportion of genetic variance unexplained by our findings. From the clinical perspective, it will be important to explore the relationship of these variants to more refined measures of body fat distribution derived from detailed imaging studies, to use the variants identified to characterize the causal relationships between body fat distribution and related metabolic and cardiovascular traits and to explore population differences in patterns of body fat distribution. Efforts to tackle overall obesity through therapeutic or lifestyle-based modulation of overall energy balance have proved extremely challenging to implement, and the manipulation of processes associated with more beneficial patterns of fat distribution offers an alternative perspective for future drug discovery.

URLs. LocusZoom, <http://csg.sph.umich.edu/locuszoom/>.

METHODS

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

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

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ONLINE METHODS

Phenotype definition. Our main phenotype was waist-hip ratio (WHR), a widely available surrogate for body fat distribution⁵⁰. For each cohort, we computed age-adjusted residuals for men and women separately with BMI adjustment (RAW phenotype) and transformed these by the inverse standard normal function (UNIFORM phenotype) to ensure comparability across studies, between men and women and also with other phenotypes. Cohorts with related males and females also provided sex-combined phenotypes. For each cohort, we also computed the same UNIFORM transformations for the other anthropometric measures of waist circumference, hip circumference and BMI.

When adjusted for BMI, WHR was associated with android to gynoid ratio, visceral abdominal fat (VAT) and, to a lesser degree, subcutaneous abdominal fat (**Supplementary Table 4**). We also observed correlations between WHR adjusted for BMI and HDL, triglycerides and fasting insulin of similar magnitude to correlations previously published between these traits and VAT⁵¹, BMI^{52,53} or percent body fat^{52,53}. The phenotype used for this investigation was therefore WHR adjusted for BMI.

Contributing studies. This GWAS on WHR adjusted for BMI involved 32 discovery studies with up to 77,167 individuals (34,601 men and 42,735 women) to identify potentially interesting SNPs for central obesity. Our total sample size in the discovery stage reached 80% power to detect SNP associations that explained as small as 0.025% of trait variance. We included 11 studies with *in silico* genotype information and 18 studies with *de novo* genotyping for the follow-up SNP set to provide up to 113,636 individuals (up to 47,882 men and 66,244 women) for the follow-up stage. Specific sample sizes varied slightly per SNP. Sample sizes, design, sample quality control and descriptive statistics for all studies are given in **Supplementary Tables 1** and **8**. All studies were conducted according to the declaration of Helsinki, informed consent was obtained from all participants and the studies were approved by the ethics committees of all participating institutions.

Genotypes. Each discovery study and *in silico* follow-up study used genotypes from a genome-wide SNP chip to impute up to 2.85 million SNPs using HapMap CEU (build 21) as reference. The *de novo* genotyped follow-up studies used genotypes for the SNPs selected for follow-up or their proxies. Study-specific details on genotyping platforms, imputation methods and SNP quality control are given in **Supplementary Table 9**.

Standardized association analysis on the study level. In each discovery study, SNP associations for WHR adjusted for BMI were computed by linear regression on the UNIFORM phenotype separately for men and women. Where appropriate, sex-combined analyses were also performed to account for the relatedness between men and women. For comparison with the other anthropometric measures, the same statistical models without adjustment for BMI were used to compute SNP associations with BMI, waist circumference and hip circumference. All analyses accounted for the uncertainty introduced by the genotype imputation by using the expected allele dosage as an independent variable in the regression model. For the follow-up studies, the same models were computed as for the discovery studies, complemented by linear regression on the RAW phenotype to yield effect sizes on the original phenotype scale. Details on the software used for study-specific association analyses are given in **Supplementary Table 9**.

Quality control on the study level. All study-specific files underwent extensive and standardized quality control procedures before meta-analysis. All files were checked for completeness and plausible descriptive statistics on all variables. Particularly, the ranges of β estimates were checked for potential issues in phenotype transformation. Allele frequencies and compliance with HapMap alleles were checked. In addition to the study-specific quality control filters, we included SNP results of a study in our meta-analysis only if (i) the SNP imputation quality score was above 0.3 for MACH imputation or BimBam or was above 0.4 for other methods (for example, IMPUTE) and (ii) MAF times the number of subjects for a SNP in one study was greater than 3 to ensure low genotype imputation error and robust study-specific statistics^{54–56}.

Meta-analyses of WHR association. Meta-analyses of WHR discovery studies for the UNIFORM phenotype (see above) used (i) men- and women-specific

results for studies where men and women were unrelated or the sex-combined results where men and women were related, (ii) men-only results or (iii) women-only results. We applied the inverse variance weighted fixed effect model to pool β estimates⁵⁷. For discovery studies, P values and standard errors of each study were genomic control corrected and a second GC correction was applied on the meta-analyzed results to avoid inflation of the test statistics due to population stratification⁵⁸. The overall inflation factor (λ) of the meta-analyzed results was 1.09 for our WHR analysis. Plots of association were generated using LocusZoom (see URLs).

From the list of SNPs with $P < 5.0 \times 10^{-6}$ in a preliminary version of our discovery meta-analysis, we generated a list of 16 independent SNPs for follow up by starting with the SNP with the smallest P value and adding SNPs located >1 Mb to either side of any already selected SNP. All SNPs with $P < 1.0 \times 10^{-5}$ in the WHR discovery analysis beyond those already in **Table 1** are given in **Supplementary Table 10**.

We performed a meta-analysis of WHR follow-up studies for the selected SNPs using the same models as for the discovery study without GC correction. Additionally, we performed a meta-analysis for the RAW phenotype (see above). For the joint meta-analysis, results of discovery and follow-up meta-analyses on the UNIFORM phenotype were combined using a fixed effect model.

To check for potential β -scaling inconsistencies, we also applied the sample-size weighted z score method, which pools the P values^{59,60}. No inconsistencies were found. We also tested for between-study heterogeneity using the Q statistics and the I^2 measure and computed random effect model estimates for comparison with fixed effect model estimates. Results are reported for the fixed effect model throughout this paper if not stated otherwise.

The men-specific pooled β estimates were compared to women-specific pooled β estimates using t statistics (**Supplementary Note**).

The percentage of the variance of the analyzed trait, WHR, that was explained by one SNP was computed by comparing the meta-analyzed estimated SNP effect (using the RAW phenotype) with the phenotypic variance of one population-based example study and taking the genotypic variance using the average allele frequency into account (**Supplementary Note**).

Meta-analysis for other anthropometric measures. We also performed meta-analyses for BMI, waist circumference and hip circumference associations using the same models as for WHR.

Evidence of association with other metabolic traits. We obtained the association results for the 14 SNPs reaching genome-wide significance for metabolic traits (HDL cholesterol, LDL cholesterol, triglycerides, fasting glucose, fasting insulin, homeostasis model assessment-insulin resistance (HOMA-IR) and 2-h glucose levels) and T2D from other GWAS consortia with published data^{19–21,39}. For all traits except T2D, we meta-analyzed the consortia results with several of our *de novo* genotyped follow-up studies. To assess whether the observed concordance between effect directions was more than expected by chance, we tested the overall number of concordant SNPs compared to a binomial draw with a null expectation of $P = 0.5$. To investigate whether the observed number of nominally significant concordant associations with effects in the same direction was due to chance, we performed the same test on SNPs with $P < 0.05$ using a one-sided test and a null expectation of $P = 0.05$. These binomial P values do not take into account that WHR is correlated with the metabolic traits, and therefore, concordance found also reflects the correlation of trait values. The enrichment was considered significant if the binomial P was less than 0.05. As there was some overlap between this consortium data on metabolic traits with our GIANT discovery, we repeated the analyses and restricted the data to our *de novo* genotyped follow-up studies.

Pathway analyses. We investigated potential functional connections and pathway relationships between genes mapping at the WHR-associated loci. We selected 48 independent SNPs from the discovery WHR meta-analysis with $P < 1 \times 10^{-5}$ and derived 95 neighboring genes (**Supplementary Note**). From these 95 genes, 94 were available to be tested for connectivity patterns using GRAIL²² (hg18 assembly of the human genome, HapMap build 21 and PubMed queries from March 2009), which uses literature-mining techniques to rank the best gene based on its relatedness to other listed genes, applying

corrections for multiple hypothesis testing and gene density within regions. Furthermore, 89 of the 95 genes were available in the PANTHER database of 25,431 genes and were tested for correlation with 240 biological processes classified in the database (**Supplementary Note**)²³.

Copy number variation (CNV) analyses. We examined SNPs known to provide robust tags with high LD for CNVs in European-descent studies by using 6,018 CNV-tag SNPs for which we had WHR discovery meta-analysis results (**Supplementary Fig. 1, Supplementary Table 11 and Supplementary Note**).

eQTL analyses. We examined the association between the 14 identified WHR SNPs and expression transcripts of nearby genes in five different tissues: lymphocytes, SAT, omental fat, liver and blood (details on methodology and tissue samples in the **Supplementary Note**). We used conditional analyses and r^2 measures to identify the subset of significant *cis* eQTL signals that were likely to be coincident with WHR association signals.

Differences in gene expression between subcutaneous and gluteal fat. We analyzed differences in expression in subcutaneous gluteal fat tissue as compared to subcutaneous abdominal fat tissue from 49 individuals available from the MoLOBB study. The *P* values from the *F* test fitting a linear mixed model were adjusted for multiple testing for the 15 expressed genes using the false discovery rate⁶¹ and considered significant if this *P* was greater than 0.05 (**Supplementary Note**).

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