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

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Abstract

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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 (up to 77,167 participants), following up 16 loci in an additional 29 studies (up to 113,636 subjects). We identified 13 novel loci in or near *RSPO3, VEGFA, TBX15-WARS2, NFE2L3, GRB14, DNM3-PIGC, ITPR2-SSPN, LY86, HOXC13, ADAMTS9, ZNRF3-KREMEN1, NISCH-STAB1*, and *CPEB4* (P 1.9×10^{-9} to 1.8×10^{-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 1.2×10^{-13}). These findings provide evidence for multiple loci that modulate body fat distribution, independent of overall adiposity, and reveal powerful gene-by-sex interactions.

Keywords

Central obesity and body fat distribution, as measured by waist circumference (WC) and waist-hip-ratio (WHR), are associated with individual risk of type 2 diabetes (T2D)[1,2] and coronary heart disease[3], and with all-cause mortality[4]. 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, since it integrates the adverse metabolic risk associated with increasing WC 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 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 BMI[13], providing proof-of-principle for the genetic control of body fat distribution, distinct from that of overall adiposity.

Within the GIANT (Genetic Investigation of Anthropometric Traits) consortium, we performed a large-scale meta-analysis of genome-wide association (GWA) studies informative for WHR, using adjustment for BMI to focus discovery towards 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 single nucleotide polymorphisms (SNPs) were examined in 32 GWA studies 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 study and in the meta-analysis, these analyses revealed a substantial excess of low p-values (Figure 1 a, b).

We selected SNPs representing the top 16 independent (> 1 Mb distance) regions of association (discovery $P < 1.4 \times 10^{-6}$, Table 1) and evaluated them in 29 additional, independent studies (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 showed strong directionally-consistent evidence for replication ($P < 1.0 \times 10^{-3}$) and ten 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 (P 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*, see 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 CEU) with the previously reported WHR-associated variant (rs2605100) near the *LYPLAL1* gene[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* (Figure 2). These 14 loci explain 1.03% of the variance in WHR (after adjustment for BMI, age, and sex), with each locus contributing from 0.02% (*ZNRF3-KREMEN1*) to 0.14% (*RSPO3*) 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 evidence from variance decomposition studies that this reflects sex-specific genetic effects[17], we performed sex-specific meta-analyses for the 14 WHR associated SNPs. These analyses included up to 108,979 women (42,735 discovery, 66,244 follow-up) or 82,483 men (34,601 discovery, 47,882 follow-up). In joint analysis of discovery and follow-up data, 12 of the 14 SNPs reached genome-wide significance in women, but only 3 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 beta-coefficients (P ranging from 1.9×10^{-3} to 1.2×10^{-13}). All loci displayed consistent patterns of sex-specific differences in both 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% 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 10 loci identified shown to be associated with BMI in previous genome-wide association studies [14,15,18], only two showed nominally significant ($P < 0.05$) associations for BMI-adjusted WHR in the discovery analysis (*FTO:* rs805013614, $P = 0.03$, N = 77,074; *TMEM18*: rs654823815, $P = 3.0 \times 10^{-3}$, 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 association). Of the 14 WHR loci, four (near *TBX15-WARS2, CPEB4, LYPLAL1* and *GRB14*) also showed evidence of association with BMI (4.1×10^{-3} P 3.2×10^{-6}) with the WHR-increasing allele associated with decreased BMI (Supplementary Table 3). When adding an interaction term of SNP and 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 the obese compared to the non-obese (see Supplementary Note).

To determine whether the WHR-associated signals exert their effects primarily through an effect on waist (WC) or hip circumference (HIP), we performed meta-analyses for these specific phenotypes in the discovery and follow-up studies (Supplementary Table 1 and 3). Overall, we observed stronger associations for HIP than for WC. Effect-size estimates were numerically greater for HIP than for WC at eleven of the 14 loci, and there were nominal associations ($P < 0.05$) with HIP for twelve of the WHR-associated loci but only four associations with WC. In both sexes, the WHR-associated loci displaying nominal association with HIP always featured the WHR-increasing allele associated with reduced HIP. In contrast, we observed sexual dimorphism in the pattern of WC associations. In women, the WHR-increasing allele at all 14 loci was associated with increased WC, whereas this was only true for 6 of these loci in men (Figure 3). At *GRB14*, for example, the WHR-increasing allele was associated with increased WC in women ($P = 3.6 \times 10^{-4}$) but decreased WC in men ($P = 6.8 \times 10^{-3}$). These differences in the relationships between WC, HIP 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 GWA data provided by trait-specific consortia[19–21] as well as our *de novo* genotyped follow-up studies. As expected, given the sample overlap between this GWA data with our WHR GWA data as well as 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, LDL-cholesterol, fasting insulin, and HOMA-derived measures of insulin resistance (binomial P from 3.2×10^{-4} to 1.8×10^{-8}; Table 3 and Supplementary Table 5a). For example, the WHR-increasing allele at *GRB14* shows 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 14 WHR-associated loci showed directionally consistent associations with T2D, three of these (*ADAMTS9, NISCH-STAB1*, and *ITPR2-SSPN*) reaching nominal significance ($P < 0.05$) (Table 3 and Supplementary Table 5a,b). Because the association signals for correlated traits in this

analysis are vulnerable to overestimation given the overlap in GWAS samples examined, we repeated these analyses restricted to our *de novo* genotyped follow-up studies. Although this also resulted in lower sample size, similar patterns of enrichment were still observed (Supplementary Table 5c).

Pathway analysis of the WHR-associated loci and potential biological role

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 a $P < 1.0 \times 10^{-5}$ in the WHR discovery studies.

First, we performed a survey of the published literature using GRAIL[22], to search for connectivity between the genes and specific keywords that describe these functional connections (see Online Methods). Although there was no evidence, after correcting for multiple testing, that the connectivity between these genes was greater than chance, we identified 8 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 database[23] 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 retained nominal significance after adjustment for bias (e.g. due to non-random SNP coverage in relation to genes) and the number of biological processes tested (Supplementary Note, 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 other analyses described in this paper. These uncovered possible roles in adipocyte development (*TBX15*), pattern formation during embryonic development (*HOXC13*), angiogenesis (*VEGFA, RSPO3, STAB1*), Wnt/beta-catenin signaling (*RSPO3, KREMEN1*), insulin signaling (*ADAMTS9, GRB14, NISCH*), lipase activity (*LYPLAL1*), lipid biosynthesis (*PIGC*) and intracellular calcium signaling (*ITPR2*) (see Supplementary Note for details).

Evaluation of copy number variants (CNVs) and nonsynonymous changes

Both common and rare 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 GWA discovery meta-analysis, using a set of 6,018 CNV-tagging SNPs, which collectively capture >40% of common CNVs >1 kb [26,27] (Online Methods, Supplementary Note).

One CNV-tagging SNP (rs1294421, *LY86*) was observed amongst 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 ($r^2>0.7$) 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* (Val441Leu, Arg1285Trp and Arg3809Cys) and *GLYCTK* (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.

Evaluation of effect of the WHR associations on expression in relevant tissues

Expression-QTL (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, 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 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, HapMap CEU) with the SNP with the strongest effect on *PIGC* expression (rs991790), and this *cis*-eQTL association is 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 are driven through altered expression of *PIGC, TBX15*, AA553656, *GRB1, ZNRF3* and *STAB1*.

Differential RNA expression of gluteal compared to 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 (*RSPO3, TBX15, ITPR2, WARS2* and *STAB1*) were differentially expressed between the two tissues (F-test, corrected for false discovery rate across the 15 expressed genes, $P < 0.05$;

Supplementary Table 7). This supported 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 emerge from this study display no overlap with those shown to be associated with BMI, either in previous reports[14,15,16] or in the expanded meta-analysis recently completed by the GIANT consortium[32].

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 hormones[33]. Consistent with our findings, variance decomposition studies have shown that the genetic contribution to the overall variance in WHR, waist or hip circumference is greater in women[17]. While there is some evidence for loci with differential sex effects influencing lipids[34], uric acid levels[35] and risk of schizophrenia[36], we are unaware of prior reports indicating such strong enrichment of female-specific associations for any other phenotype, including BMI[32].

The primary objective of genetic discovery efforts is to characterize the specific mechanisms involved in the regulation of the trait of interest. Despite the considerable challenges associated with moving from common variant association signals to definition of the 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 HDL-cholesterol [37]. These inferences about the role of *GRB14* are supported by evidence that *Grb14*-deficient mice exhibit improved glucose homeostasis despite lower circulating insulin levels, and enhanced insulin signaling in liver and skeletal muscle[38]. The signal near *ADAMTS9* overlaps a previously-reported T2D locus[39], and the lead SNP for WHR in our study is identical to the SNP displaying the strongest T2D association in an expanded T2D meta-analysis[40]. Given evidence that *ADAMTS9* T2D-risk alleles are associated with insulin resistance in peripheral tissues[41], 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 adipogenesis[42] 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 overrepresentation of developmental processes. Developmental genes have been implicated in fat accumulation and distribution[45,46], and recent evidence supports a link between developmental genes and body fat distribution, including HOXC13[47] and TBX15[45,48]. Developmental genes may in part determine the adipocyte-specific expression patterns that have been observed in different fat depots[45]. 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 body mass index and overall adiposity[49].

By providing novel 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 characterise the causal relationships between body fat distribution and related metabolic and cardiovascular traits, and to explore ethnic 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.

Supplementary Material

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Abbreviations

BMI   Body-mass-index

WC   waist circumference

WHR   waist-hip ratio

HIP   hip circumference

GWA   genome-wide association

SNP   single-nucleotide polymorphism

LD   linkage disequilibrium

eQTL   Expression Quantitative Trait Loci

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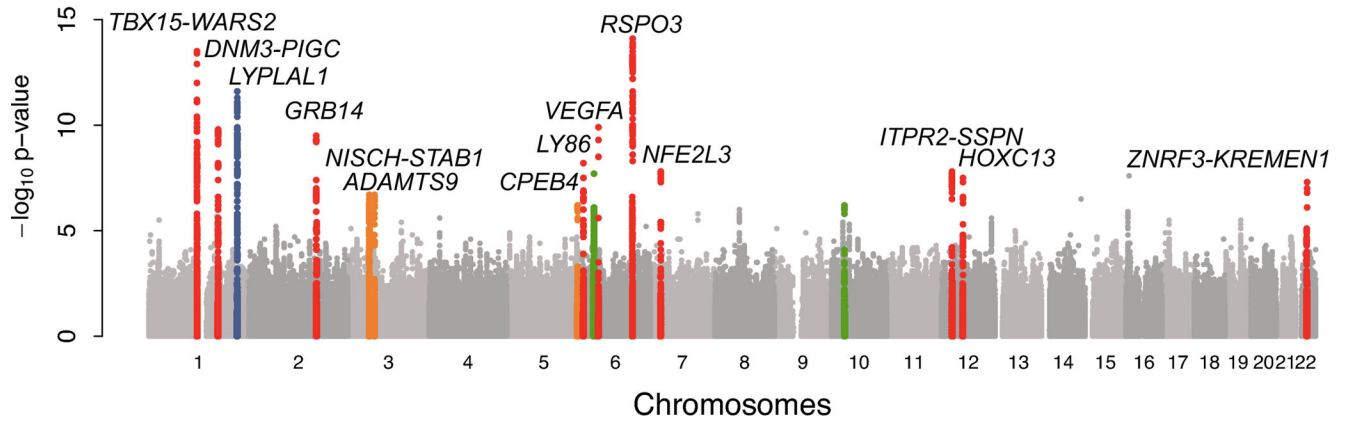
Figure 1. Genome-wide association analyses for WHR in discovery studies
A. Manhattan plot shows results of the WHR association meta-analysis in discovery studies
(P on the y-axis and SNP genomic position on the x-axis). Colored genomic loci indicate
significant association ($P < 5 \times 10^{-8}$) detected previously (blue)13, in our GWA stage (red),
and after the meta-analysis combining GWA and follow-up studies (orange). Two loci tested
in the follow-up stage did not achieve genome-wide significance (green).
B. Quantile-quantile (QQ) 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 grey area represents the 95% confidence interval
around the test statistic under the null distribution.
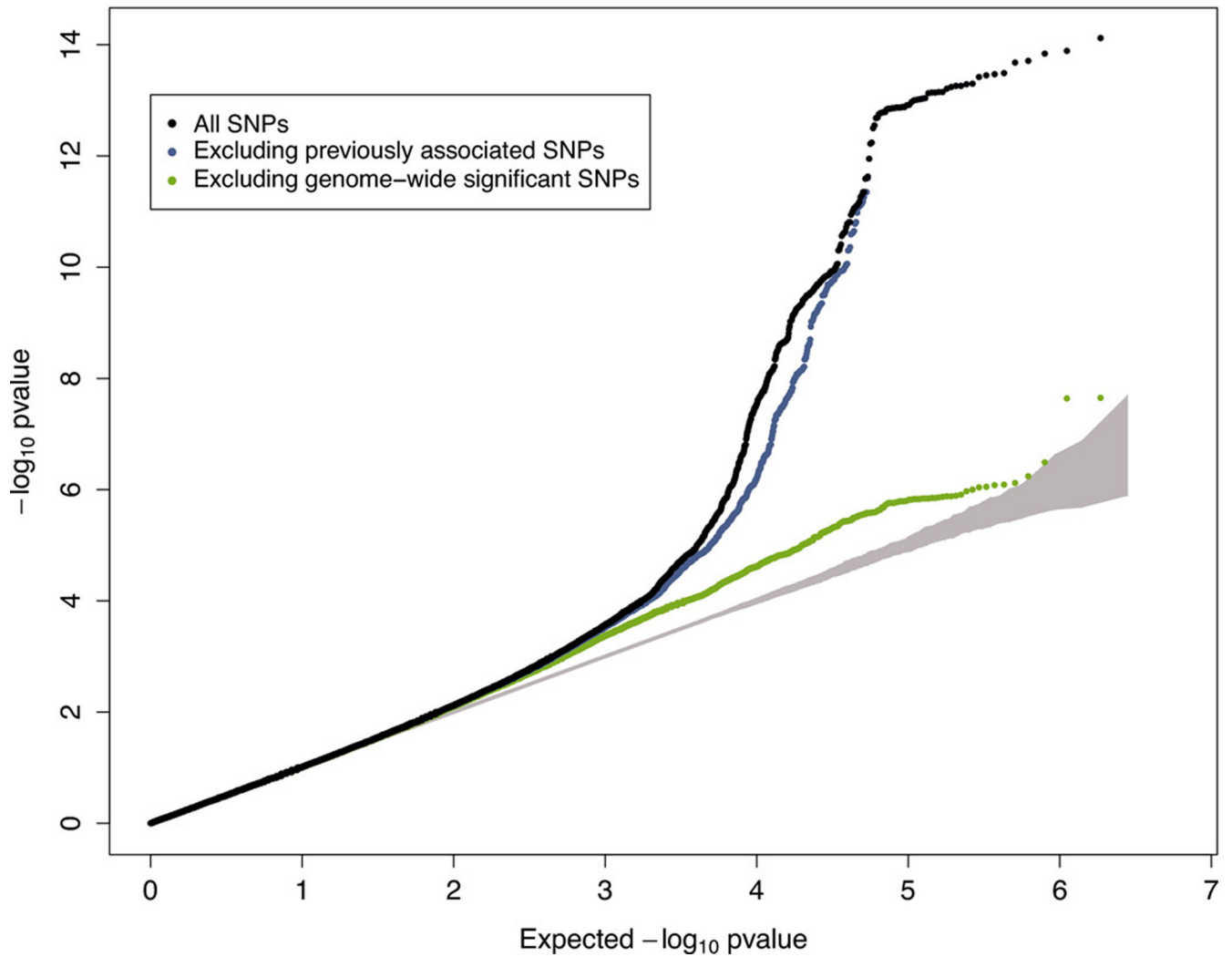
Figure 2. Regional plots of 14 loci with genome-wide significant association

SNP association with WHR in meta-analysis of discovery studies for 14 loci ($-\log_{10} P$ on the y-axis and 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 (pair-wise r^2 values from HapMap CEU). Gene and microRNA annotations are from the UCSC genome browser.
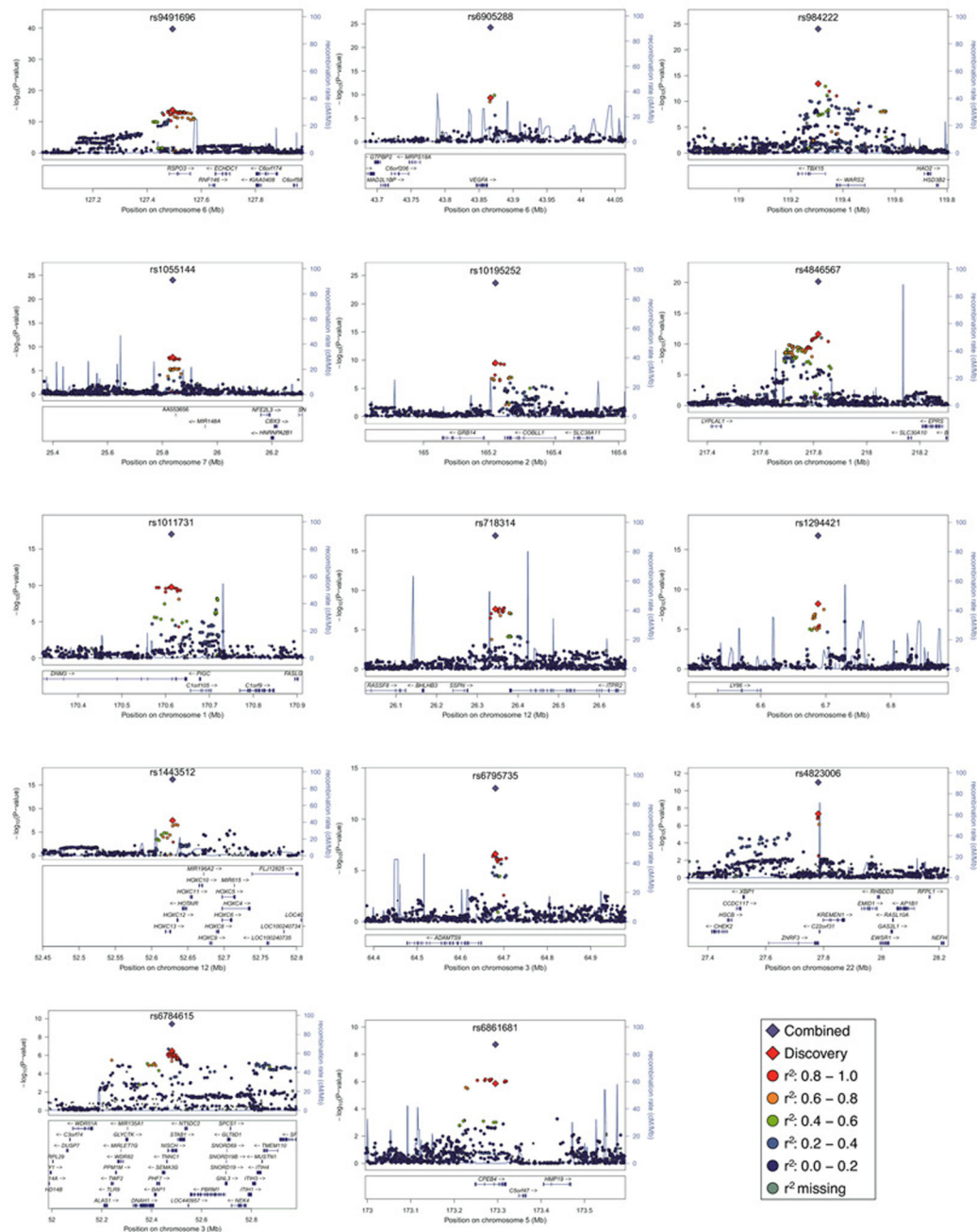
Figure 3. Association of the 14 WHR loci with waist and hip circumference
Beta-coefficients for waist circumference (WC, x-axis) and hip circumference (HIP, y-axis) in women and men derived from the joint discovery and follow-up analysis. *P* for WC and HIP are represented by color. In men, grey gene labels refer to those SNPs that were not significant in the male-specific WHR analysis. More details can be found in Supplementary Table 3.
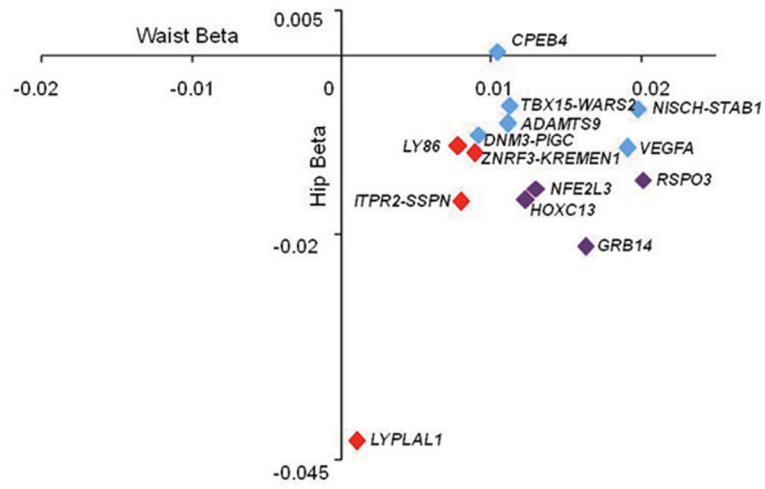
Figure 4.

Table 1

Fourteen SNPs associated with WHR at genome-wide significance levels

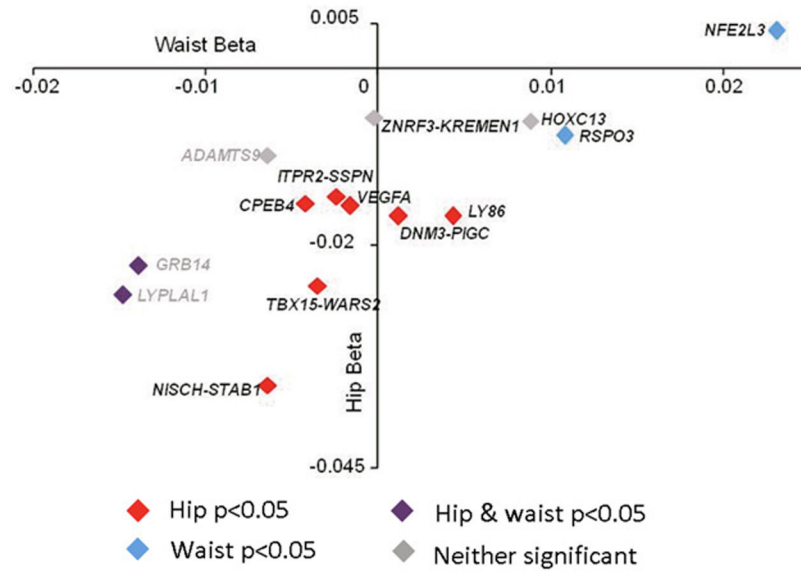| SNP	Chr	Position (b36)	Nearby genes	EA[a]	EAF[b]	Discovery			Follow-up			Combined	
						P	Beta	N	P	Beta	N	P	Beta
SNPs evaluated in follow-up achieving genome-wide significance													
rs9491696	6	127,494,332	RSPO3	G	0.520	2.10E-14	0.037	77,164	3.27E-28	0.045	113,582	1.84E-40	0.042
rs6905288	6	43,866,851	VEGFA	A	0.562	4.72E-10	0.033	77,129	1.18E-16	0.039	95,430	5.88E-25	0.036
rs984222	1	119,305,366	TBX15-WARS2	G	0.365	3.81E-14	0.037	77,167	1.56E-12	0.031	109,623	8.69E-25	0.034
rs1055144	7	25,837,634	NFE2L3	T	0.210	1.49E-08	0.034	77,145	3.26E-18	0.043	113,636	9.97E-25	0.040
rs10195252	2	165,221,337	GRB14	T	0.599	3.23E-10	0.031	77,119	3.18E-16	0.036	102,449	2.09E-24	0.033
rs4846567	1	217,817,340	LYPLAL1	G	0.283	2.37E-12	0.037	77,167	3.15E-10	0.032	91,820	6.89E-21	0.034
rs1011731	1	170,613,171	DNM3-PIGC	G	0.572	1.72E-10	0.031	77,094	7.47E-09	0.026	92,018	9.51E-18	0.028
rs718314	12	26,344,550	ITPR2-SSPN	G	0.741	2.41E-08	0.031	77,167	1.49E-10	0.030	107,503	1.14E-17	0.030
rs1294421	6	6,688,148	LY86	G	0.387	6.31E-09	0.029	77,154	2.69E-10	0.028	102,189	1.75E-17	0.028
rs1443512	12	52,628,951	HOXC13	A	0.239	3.33E-08	0.031	77,165	2.92E-10	0.030	112,353	6.38E-17	0.031
rs6795735	3	64,680,405	ADAMTS9	C	0.406	2.47E-07	0.025	77,162	6.75E-08	0.026	84,480	9.79E-14	0.025
rs4823006	22	27,781,671	ZNRF3-KREMEN1	A	0.569	4.47E-08	0.027	77,086	2.41E-05	0.019	93,911	1.10E-11	0.023
rs6784615	3	52,481,466	NISCH-STAB1	T	0.941	3.18E-07	0.052	76,859	1.56E-04	0.036	109,028	3.84E-10	0.043
rs6861681	5	173,295,064	CPEB4	A	0.340	1.40E-06	0.026	77,164	2.13E-04	0.019	85,722	1.91E-09	0.022
Further SNPs evaluated in follow-up but not achieving genome-wide significant in the combined analysis													
rs2076529	6	32,471,933	BTNL2	C	0.570	2.22E-08	0.041	34,532	0.012	0.011	92,778	3.71E-07	0.020
rs7081678	10	32,030,629	ZEB1	A	0.085	5.76E-07	0.045	76,270	0.094	0.013	100,527	5.57E-06	0.027

P-values and beta-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), follow-up studies (up to 113,636 subjects), and both combined (up to 190,781 subjects). Fourteen of the 16 SNPs put forward to follow-up show genome-wide significant results ($P < 5 \times 10^{-8}$) in the combined analysis. P-values in the discovery were genomic control corrected per study and in the meta-analysis. Details on between-study heterogeneity in Supplementary Table 1c.

[a] Effect Allele: WHR increasing allele on the forward strand;

[b] Effect allele frequency

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
		P	Beta	P	Beta	P	Beta	P	Beta	P	Beta	P	Beta	P
rs9491696	RSPO3	1.68E-04	0.026	6.97E-09	0.036	1.05E-11	0.031	1.62E-12	0.047	8.84E-22	0.053	1.93E-32	0.050	1.94E-03
rs6905288	VEGFA	0.066	0.013	2.09E-04	0.025	7.38E-05	0.020	7.72E-13	0.052	3.14E-15	0.051	2.27E-26	0.052	5.20E-06
rs984222	TBX15-WARS2	3.32E-09	0.041	2.43E-05	0.029	9.41E-13	0.035	1.21E-07	0.036	1.33E-08	0.033	1.02E-14	0.034	0.951
rs1055144	NFE2L3	6.00E-04	0.029	5.67E-08	0.040	2.52E-10	0.035	2.34E-06	0.040	7.13E-12	0.046	1.41E-16	0.044	0.270
rs10195252	GRB14	0.201	0.009	0.114	0.011	0.043	0.010	6.33E-15	0.053	4.95E-21	0.054	3.84E-34	0.054	1.41E-11
rs4846567	LYPLAL1	0.191	0.010	0.982	0.000	0.358	0.005	4.84E-18	0.064	8.12E-17	0.055	4.95E-33	0.059	1.18E-13
rs1011731	DNM3-PIGC	4.88E-07	0.034	1.95E-03	0.022	7.81E-09	0.028	2.13E-05	0.028	7.03E-07	0.030	6.90E-11	0.029	0.855
rs718314	ITPR2-SSPN	0.177	0.010	2.02E-03	0.022	1.41E-03	0.017	8.29E-10	0.047	4.21E-09	0.038	2.41E-17	0.042	4.67E-04
rs1294421	LY86	4.18E-03	0.020	7.00E-06	0.030	1.63E-07	0.025	3.44E-08	0.038	7.32E-06	0.026	2.40E-12	0.031	0.357
rs1443512	HOXC13	0.184	0.011	9.74E-04	0.024	9.45E-04	0.018	1.43E-09	0.048	3.09E-08	0.035	6.38E-16	0.040	2.23E-03
rs6795735	ADAMTS9	0.011	0.017	0.614	0.004	0.027	0.011	7.85E-07	0.033	2.95E-11	0.042	1.92E-16	0.038	8.50E-05
rs4823006	ZNRF3-KREMEN1	6.87E-03	0.019	0.094	0.012	1.94E-03	0.015	6.86E-08	0.037	3.81E-05	0.024	3.24E-11	0.030	0.032
rs6784615	NISCH-STAB1	1.51E-03	0.045	0.033	0.032	1.68E-04	0.039	6.23E-05	0.057	1.72E-03	0.039	6.01E-07	0.047	0.574
rs6861681	CPEB4	1.88E-03	0.023	0.045	0.015	3.03E-04	0.019	2.14E-04	0.027	1.58E-06	0.021	1.55E-06	0.024	0.555

P-values and beta-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, 42,735 women), the follow-up (up to 47,882 men, 65,780 women) and the combined meta-analysis (up to 81,301 men, 107,429 women). Also given are the P-values for testing for difference between sex-specific beta-coefficients in the combined meta-analysis; SNPs with P for sex difference $< 3.6\text{E-}03$ ($=0.05/14$) were considered to show significant sex difference.

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 $P<.05$[c]	
		# SNPs	P	# SNPs	P
Triglycerides	43,826	14	6.10E-5	7	1.79E-8
HDL-C	45,561	13	9.16E-4	4	3.20E-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	9.16E-4	5	1.62E-5
HOMA-IR	53,625	13	9.16E-4	6	6.17E-7
2-hr glucose	27,011	7	0.605	0	1.000
Type 2 diabetes	10,128[f]	11	0.029	3	4.62E-3

The 14 WHR SNPs were tested for association with other traits by meta-analysis of GWA data from previous reports19–21,39 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-hr glucose, glucose levels 2 h after an oral glucose challenge.

[a] Maximum number of subjects available for any of the 14 SNPs

[b] Number of the 14 SNPs for which the WHR increasing allele is associated with the trait in the concordant direction (i.e. increased levels except for HDL-C) and corresponding binomial P-value to test whether this number is greater than by chance not accounting for the correlation between the traits.

[c] Number of SNPs in concordant direction that show $P<0.05$ for the association with the trait and corresponding binomial P-value as in[b].

[f] 4,549 cases, 5579 controls

Table 4

Expression quantitative trait locus analysis for 11 out of the 14 WHR signals.

WHR SNP	Tissue	Gene	Effect[a]	WHR SNP association with transcript (P)		Transcript peak SNP[b]	r²[c]	Peak SNP association with transcript (P)	
				Unadj.	Adj. for peak SNP			Unadj.	Adj. for WHR SNP
rs9491696	SAT-D	*RSPO3*	+	1.10E-07	0.03	rs1936795	0.26	2.20E-13	7.40E-08
rs984222	**Omental**	***TBX15***	+	**7.90E-10**	**1.00**	**rs984222**	**1.00**	**7.90E-10**	**1.00**
	Omental	*WARS2*	+	5.11E-36	0.03	rs10802075	0.27	1.31E-163	1.33E-88
	Subcutaneous fat	*WARS2*	+	1.67E-25	0.01	rs10802075	0.22	3.88E-110	1.01E-63
	Lymph.	*WARS2*	–	4.30E-18	5.47E-05	rs2645305	0.27	5.57E-40	6.88E-26
	Liver	*WARS2*	+	2.57E-17	0.07	rs1057990	0.26	6.69E-59	1.97E-32
	SAT-D	*WARS2*	+	1.10E-18	0.51	rs1057990	0.26	5.80E-130	5.80E-100
	Blood	*WARS2*	+	6.10E-17	0.11	rs1057990	0.26	6.30E-75	1.10E-54
rs1055144	**SAT-D**	**AA553656[d]**	–	**1.20E-11**	**0.96**	**rs7798002**	**0.95**	**7.20E-12**	**0.32**
	SAT-M	AA553656[d]	–	2.46E-07	0.65	rs1451385	0.77	5.93E-08	0.38
rs10195252	**SAT-D**	***GRB14***	+	**4.40E-11**	**1.00**	**rs10195252**	**1.00**	**4.40E-11**	**1.00**
	SAT-M	***GRB14***	+	**5.51E-06**	**1.00**	**rs10184004**	**1.00**	**5.51E-06**	**1.00**
	Omental	***GRB14***	+	**1.02E-13**	**1.00**	**rs10195252**	**1.00**	**1.02E-13**	**1.00**
	SAT-M	*SLC38A11*	–	3.93E-06	0.66	rs10184126	0.18	7.76E-44	8.57E-34
	SAT-D	*SLC38A11*	–	3.70E-09	0.35	rs10184126	0.18	2.40E-94	7.40E-82
rs1011731	Blood	*C1orf105*	+	3.80E-16	0.20	rs2157451	0.28	1.30E-33	8.20E-18
	Lymph.	***PIGC***	–	**5.87E-10**	**1.00**	**rs991790**	**1.00**	**5.65E-10**	**1.00**
rs718314	Lymph.	*ITPR2*	+	1.79E-09	0.98	rs7976877	0.45	2.21E-18	1.91E-06
	Blood	*ITPR2*	–	2.40E-09	0.20	rs2570	0.41	2.40E-37	1.80E-28
rs1294421	SAT-M	*BC039678*	–	2.43E-07	0.38	rs1294404	0.64	1.89E-16	3.42E-04
	Omental	*BC039678*	–	1.09E-06	0.33	rs912056	0.71	8.28E-17	4.26E-05
rs6795735	SAT-D	*ADAMTS9*	–	1.50E-06	0.04	rs7372321	0.11	1.10E-09	2.30E-05
	Omental	*AK022320*	–	7.99E-15	0.64	rs4521216	0.02	5.15E-42	1.49E-19
	SAT-D	*AK022320*	–	2.24E-10	0.98	rs4521216	0.02	9.62E-37	7.58E-19
rs4823006	**SAT-D**	***ZNRF3***	–	**2.40E-08**	**0.63**	**rs3178915**	**0.81**	**6.70E-11**	**8.90E-04**

WHR SNP	Tissue	Gene	Effect[a]	WHR SNP association with transcript (P)		Transcript peak SNP[b]	r^{2c}	Peak SNP association with transcript (P)	
				Unadj.	Adj. for peak SNP			Unadj.	Adj. for WHR SNP
	SAT-M	*ZNRF3*	–	**1.08E-18**	0.93	**rs6005975**	0.79	**1.59E-19**	**0.50**
	Omental	*ZNRF3*	–	**9.13E-18**	0.98	**rs6005975**	0.79	**6.07E-21**	**0.27**
rs6784615	**Blood**	*STAB1*	+	**2.80E-09**	0.32	**rs9846089**	0.83	**9.40E-10**	**0.08**
rs6861681	Lymph.	*CPEB4*	+	3.79E-22	0.89	rs7705502	0.87	4.95E-29	2.00E-03
	Blood	*HMP19*	+	1.60E-16	0.97	rs10516107	0.83	1.10E-21	4.30E-06

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 (see Supplementary Note): results are given if the unadjusted WHR SNP association showed $P < 1.00E-05$. 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 (i.e. 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.

[a] Effect direction for the WHR increasing allele.

[b] SNP with the strongest association with the transcript in the region (transcript peak SNP).

[c] Correlation (Hapmap CEU, B36) between the WHR SNP and transcript peak SNP.

[d] The transcript labeled AA553656 was detected as Contig27623_RC and corresponds to chr7: 25,854,143-25,854,203 (B36)