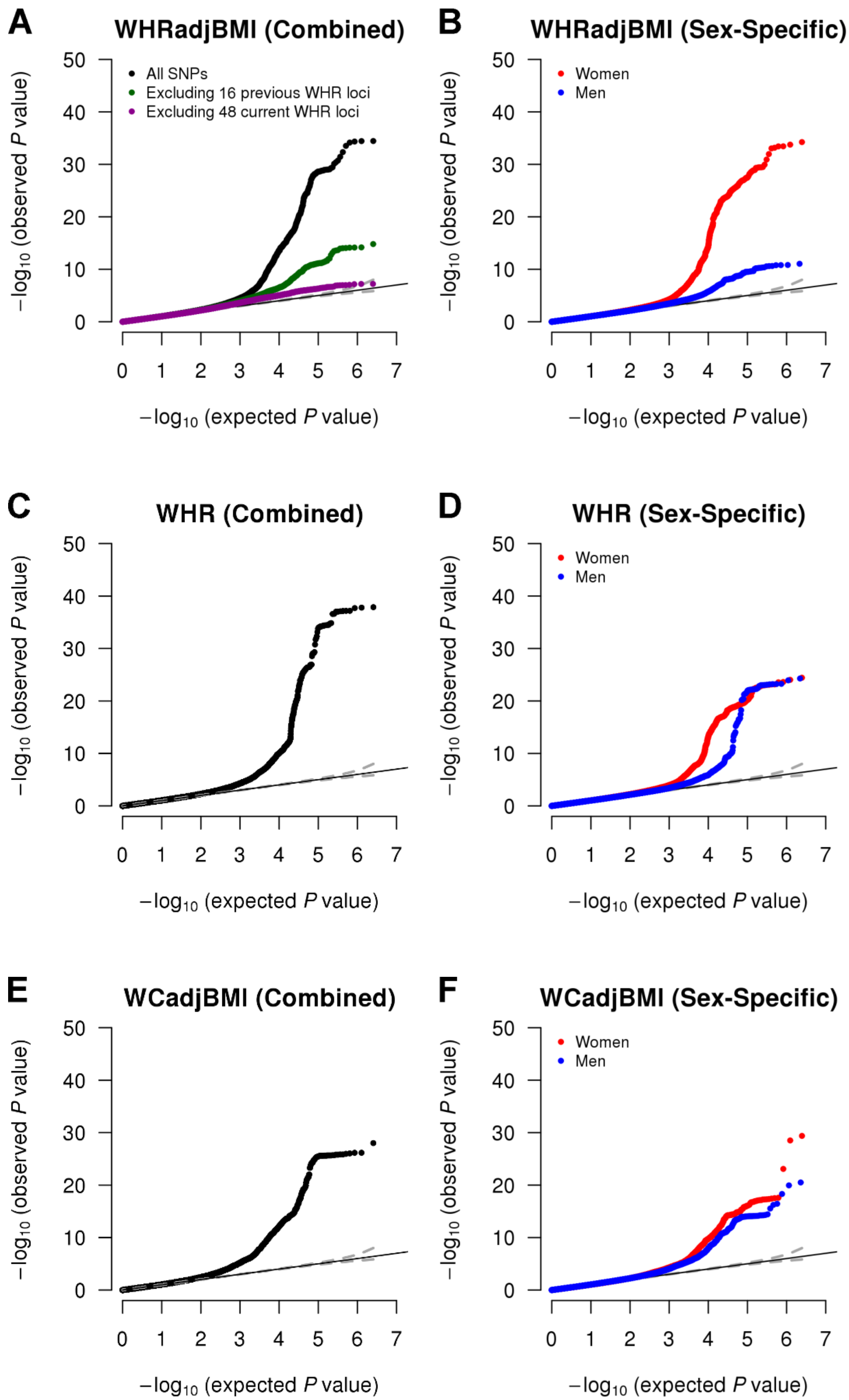
Contents

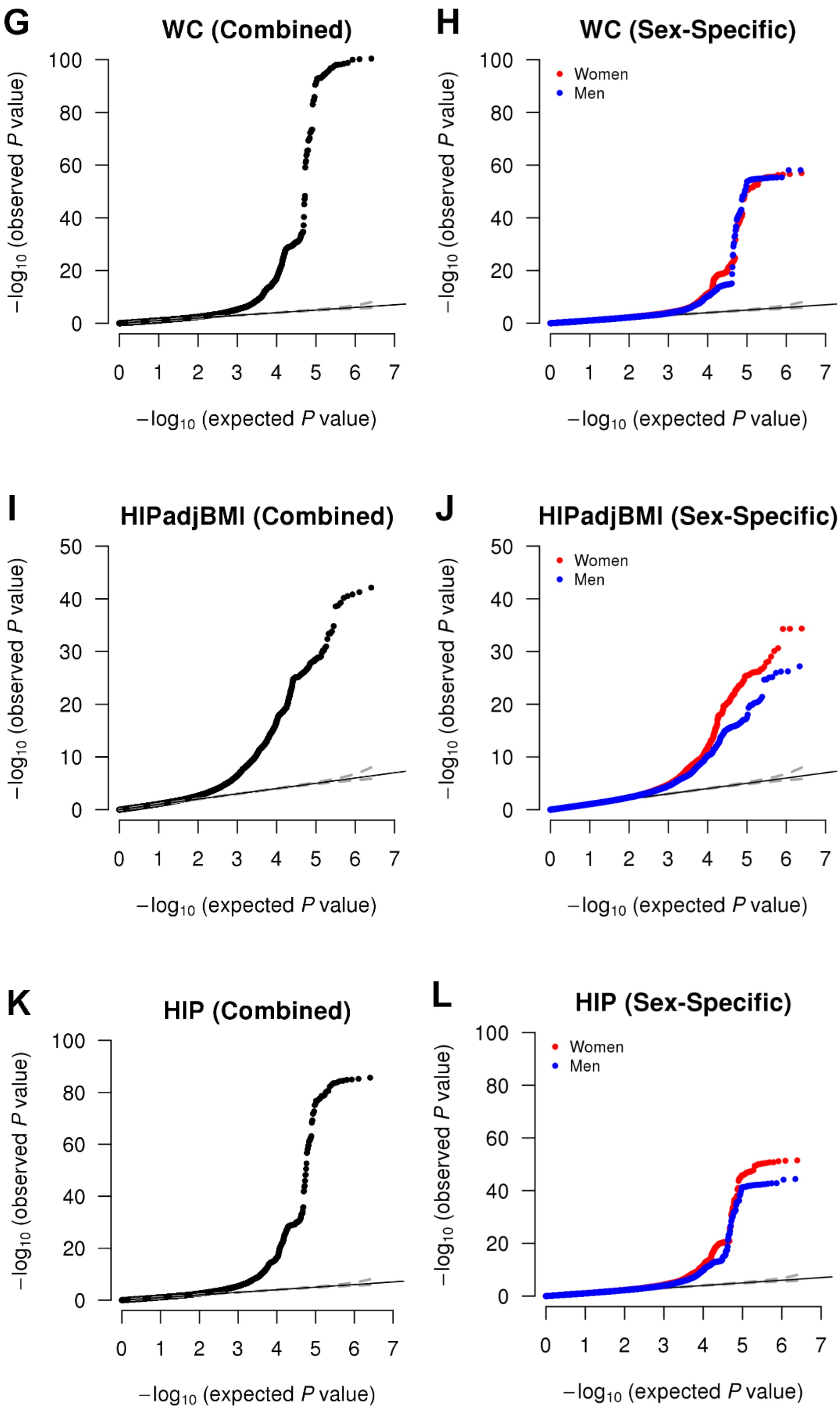
Supplementary Figures

This document contains **Supplementary Figures 1, 2, 3, 4,** and **5**.

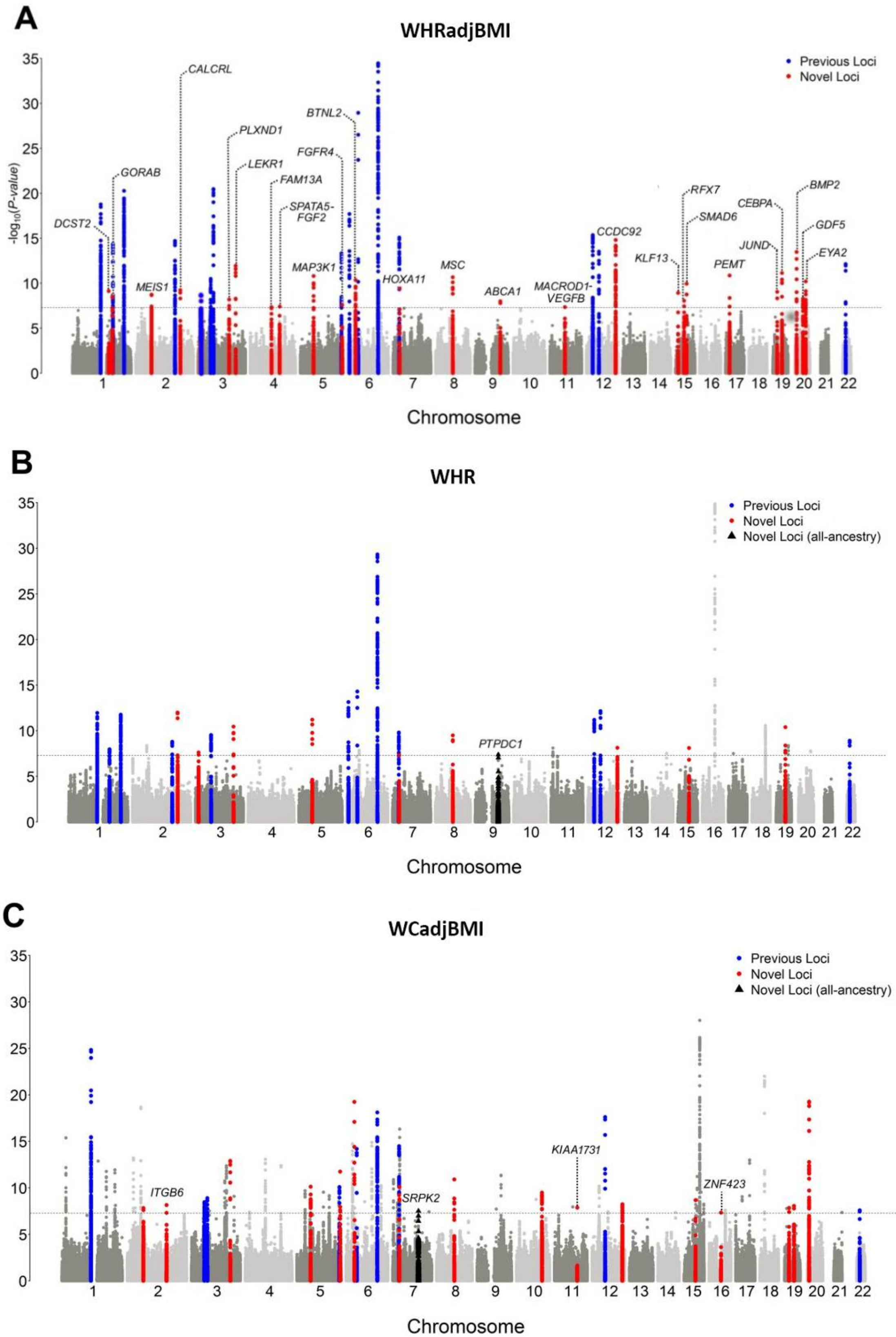
Supplementary Figure 1 | Quantile-quantile plots of sex-combined and sex-specific SNP associations with six waist-related traits. Sex-combined (***A***, ***C***, ***E***, ***G***, ***I***, ***K***) and sex-specific (***B***, ***D***, ***F***, ***H***, ***J***, ***L***) SNP associations are shown for six waist-related traits (waist-hip ratio (WHR), waist circumference (WC), and hip circumference (HIP), adjusted and not adjusted for body mass index (BMI)). Only SNPs with *N* ≥ 50,000 samples are shown. In the panels containing sex-combined data, SNPs are marked in black. In the WHR data (**A**), after removing all SNPs within 500 kb of the 16 previously reported WHR loci the remaining SNPs are colored green and after removing all SNPs within 500 kb of the 48 WHR loci reported in **Table 1** the remaining SNPs are colored purple. In the panels containing sex-specific data, the SNPs are colored red for female-specific associations and blue for male-specific associations. In each panel, the uniform null distribution is marked with a solid black line and the related 95% confidence interval is marked with dashed gray lines. While the substantial departure from the null distribution suggests an excess of strongly associated SNPs in each panel, the corresponding genomic control values do not suggest strong evidence of systematic association inflation (λ_{GC} = 1.01–1.05).



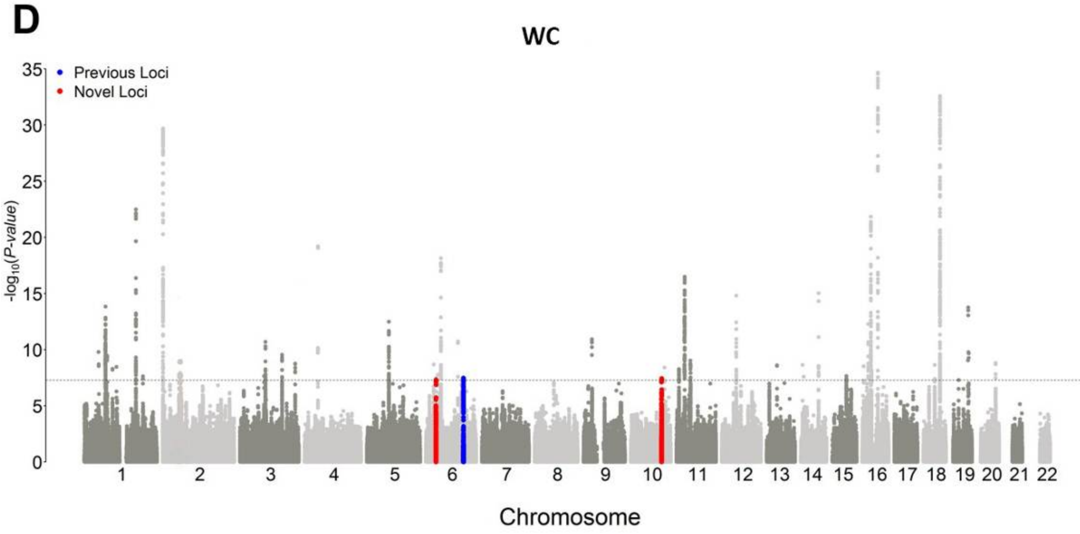
A
WHRadjBMI (Combined)
All SNPs
Excluding 16 previous WHR loci
Excluding 48 current WHR loci
B
WHRadjBMI (Sex-Specific)
Women
Men
C
WHR (Combined)
D
WHR (Sex-Specific)
Women
Men
E
WCadjBMI (Combined)
F
WCadjBMI (Sex-Specific)
Women
Men
$-\log_{10}$ (observed P value)
$-\log_{10}$ (expected P value)


G
WC (Combined)
H
WC (Sex-Specific)
I
HIPadjBMI (Combined)
J
HIPadjBMI (Sex-Specific)
K
HIP (Combined)
L
HIP (Sex-Specific)
Women
Men
−log10 (observed P value)
−log10 (expected P value)
0
1
2
3
4
5
6
7
10
20
30
40
50
60
80
100

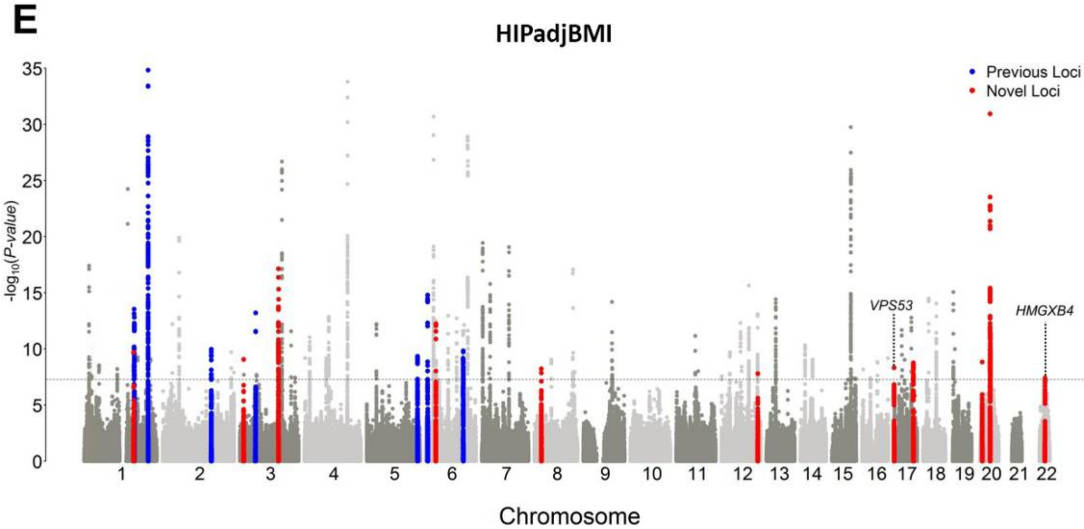
Supplementary Figure 2 | Manhattan plots of sex-combined SNP associations for six waist-related traits. The traits are waist-hip ratio (WHR), waist circumference (WC), and hip circumference (HIP), with and without adjustment for body mass index (BMI)). Only SNP results with N > 50,000 samples are shown. Dashed gray lines mark statistical significance at the genome-wide level ($P = 5 \times 10^{-8}$). Novel loci achieving genome-wide significance in sex-combined WHR association analysis in Europeans are highlighted in red on all figures (***A***–***F***) and annotated in panel ***A***. Novel loci achieving genome-wide significance in Europeans in other waist-related traits (***B***–***F***) are highlighted in red and annotated only on the relevant figure. Previously established loci are highlighted in blue (***A***–***F***). Additional novel loci achieving genome-wide significance when all ancestries were analyzed are marked as black triangles and annotated. SNP association signals that achieve genome-wide significance and are previously established height or BMI loci are shown in light or dark grey. Detailed information about the loci is presented in **Tables 1 and 3** and **Supplementary Tables 4 and 25**.


A
WHRadjBMI
Previous Loci
Novel Loci
-log10(P-value)
DCST2
GORAB
MEIS1
CALCRL
PLXND1
LEKR1
FAM13A
SPATA5-
FGF2
MAP3K1
FGFR4
BTNL2
HOXA11
MSC
ABCA1
MACROD1-
VEGFB
CCDC92
KLF13
RFX7
SMAD6
PEMT
CEBPA
JUND
BMP2
GDF5
EYA2
Chromosome
B
WHR
Previous Loci
Novel Loci
Novel Loci (all-ancestry)
PTPDC1
Chromosome
C
WCadjBMI
Previous Loci
Novel Loci
Novel Loci (all-ancestry)
ITGB6
SRPK2
KIAA1731
ZNF423
Chromosome

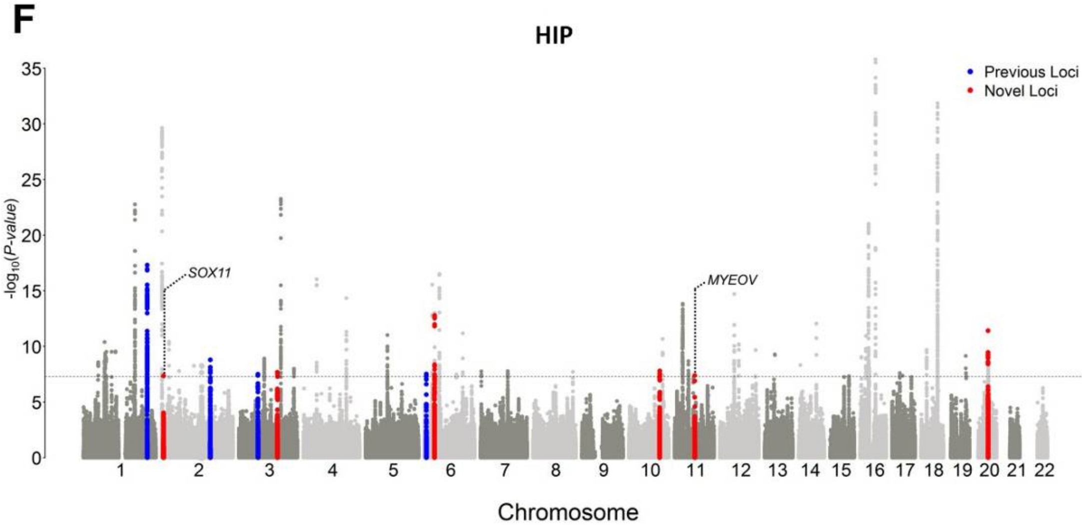
D


WC
Previous Loci
Novel Loci
-log10(P-value)
Chromosome

E

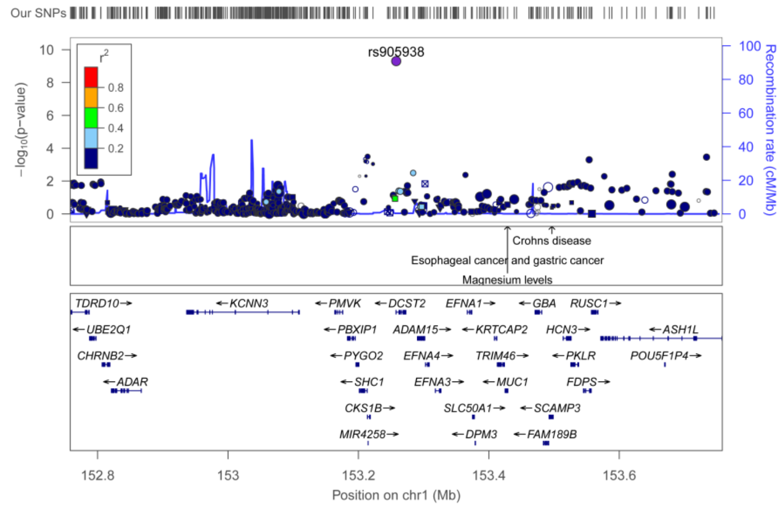

HIPadjBMI
Previous Loci
Novel Loci
VPS53
HMGXB4
-log10(P-value)
Chromosome

F

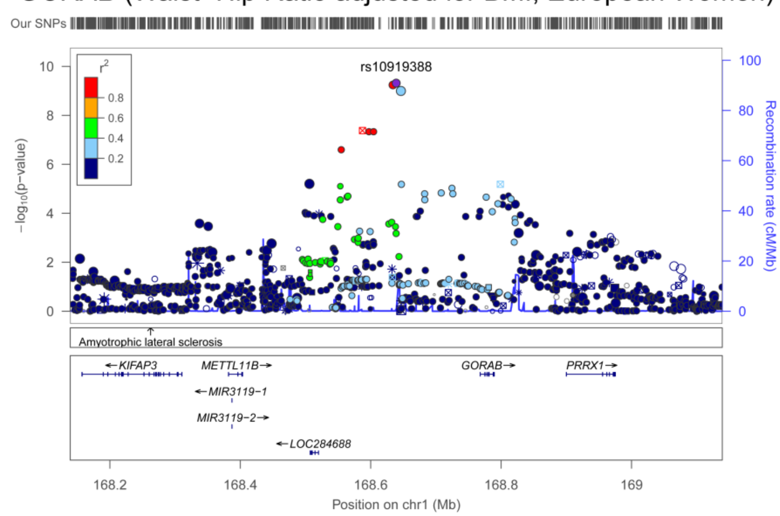

HIP
Previous Loci
Novel Loci
SOX11
MYEOV
-log10(P-value)
Chromosome

Supplementary Figure 3 | Regional association plots for 68 novel loci achieving genome-wide evidence of association with six waist-related traits. The signals shown for waist-hip ratio (WHR), waist circumference, and hip circumference, adjusted and not adjusted for body mass index (BMI) do not overlap with association signals with height or BMI. Plots are arranged in the same order as **Tables 1** and **3**. In the plot of the *HOXA11* locus, the eponymous gene was automatically omitted by LocusZoom for space; it is located just to the left of *HOXA13* (upstream with respect to the genome).

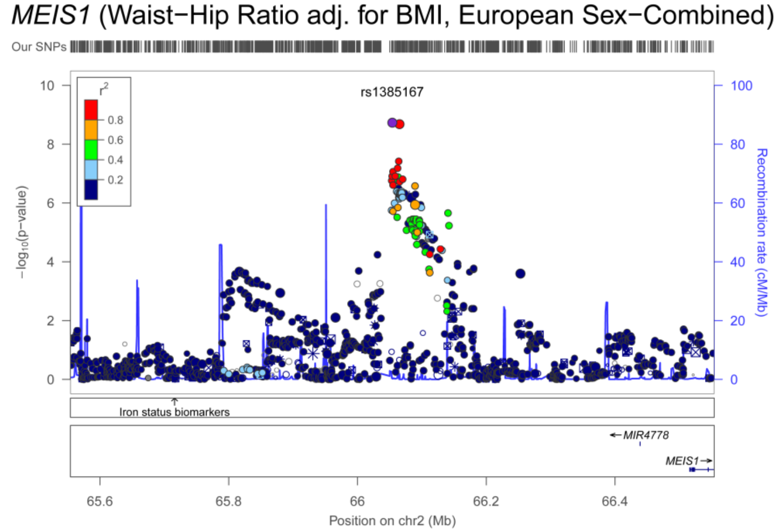
DCST2 (Waist−Hip Ratio adjusted for BMI, European Women)



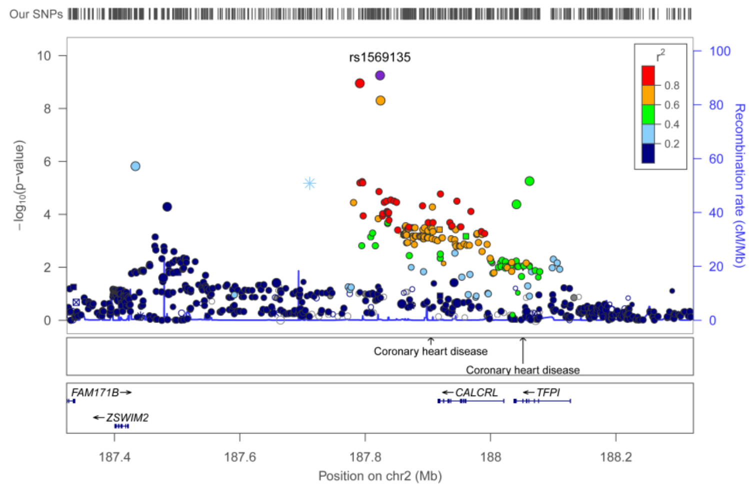
GORAB (Waist−Hip Ratio adjusted for BMI, European Women)



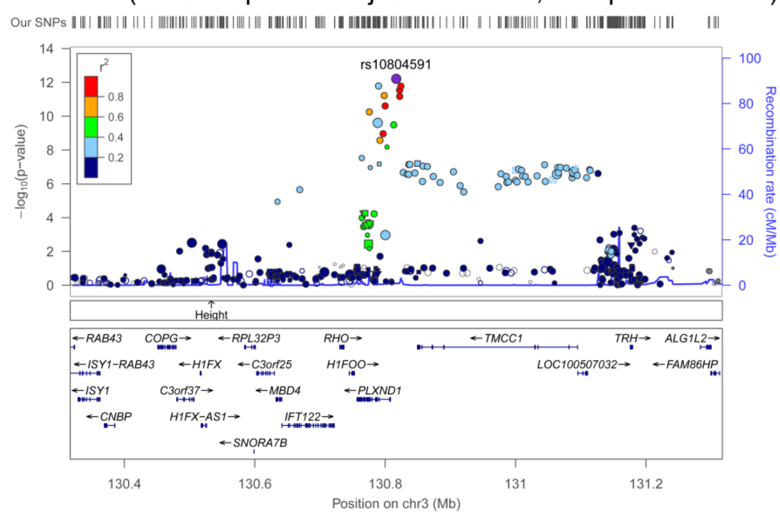
MEIS1 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



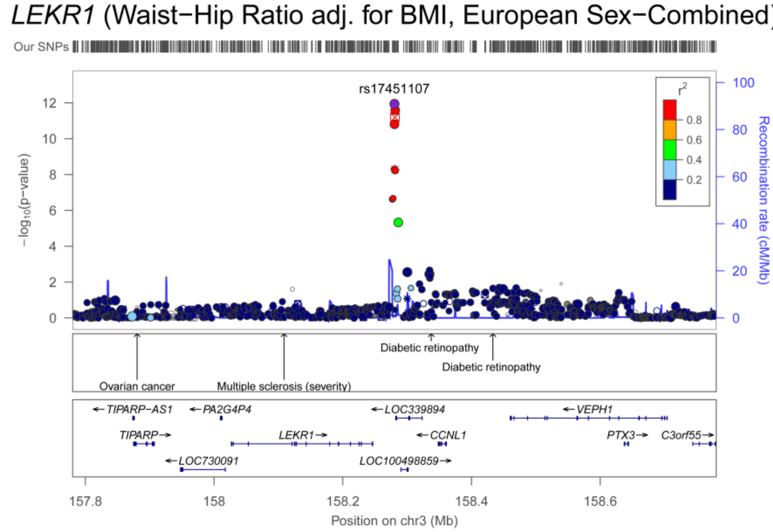
CALCRL (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



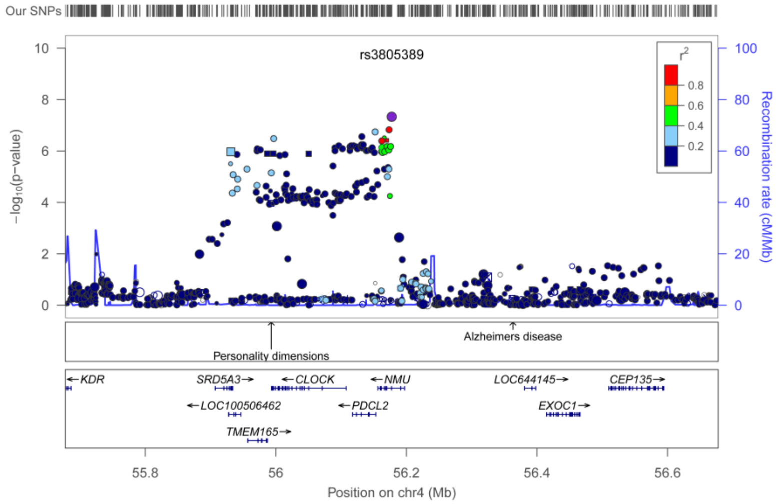
PLXND1 (Waist−Hip Ratio adjusted for BMI, European Women)



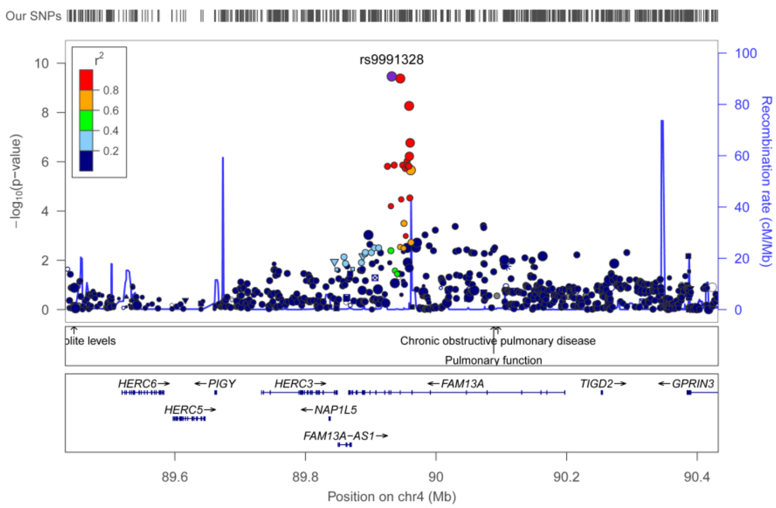
LEKR1 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



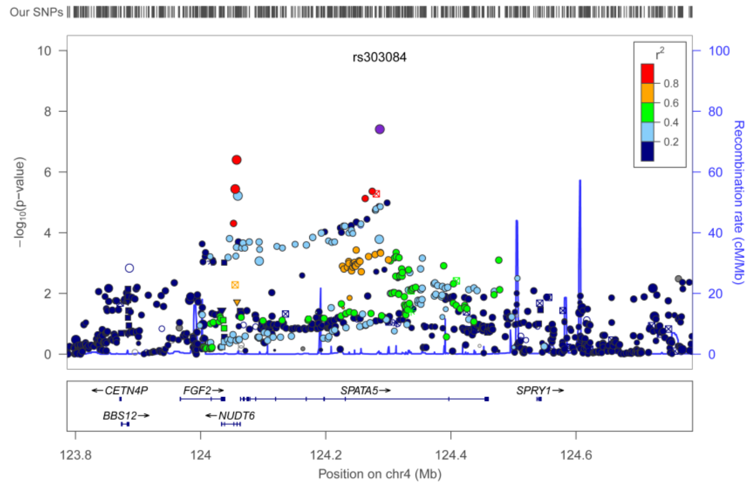
NMU (Waist−Hip Ratio adjusted for BMI, European Women)



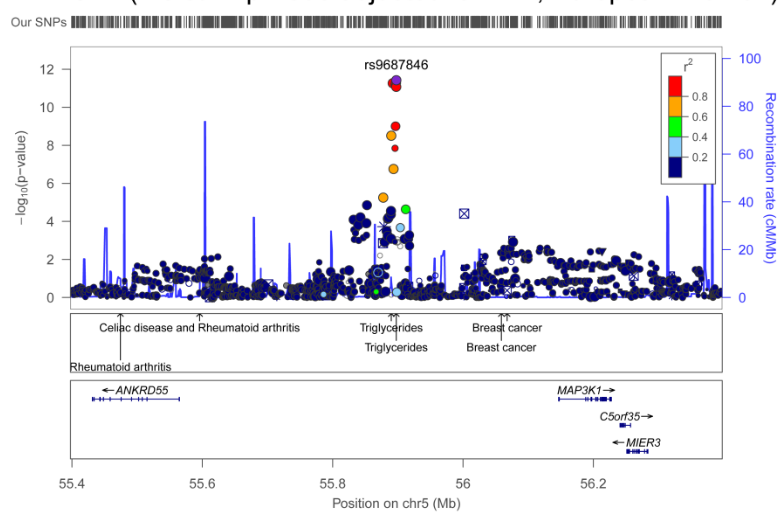
FAM13A (Waist−Hip Ratio adjusted for BMI, European Women)



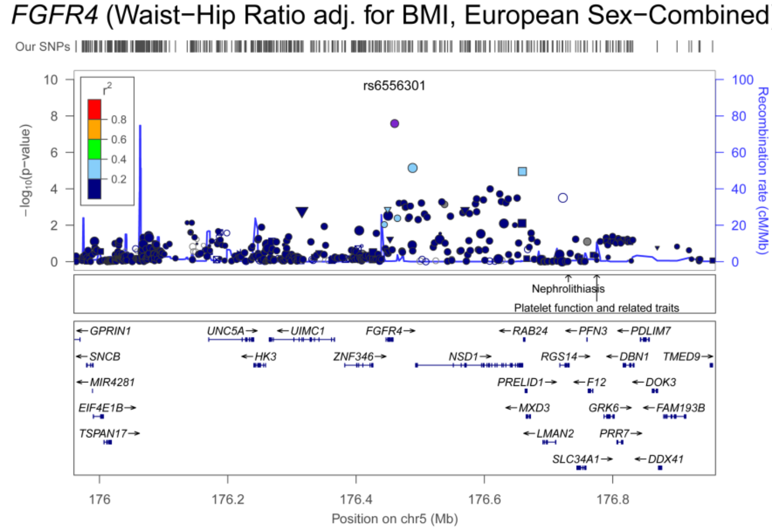
SPATA5−FGF2 (WHR adjusted for BMI, European Sex−Combined)



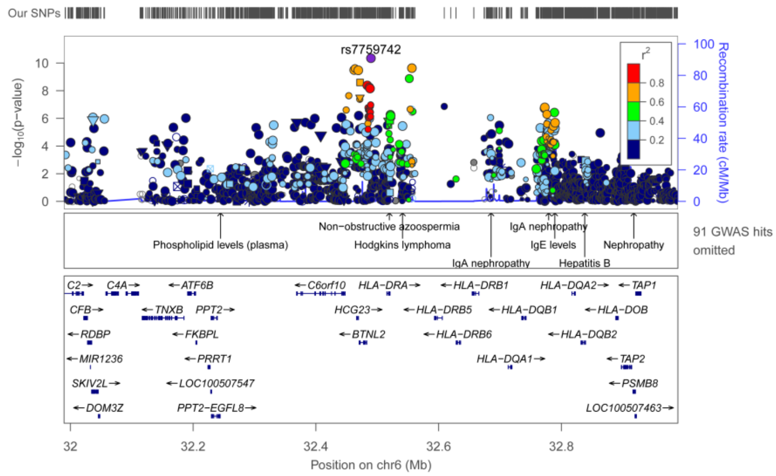
MAP3K1 (Waist−Hip Ratio adjusted for BMI, European Women)



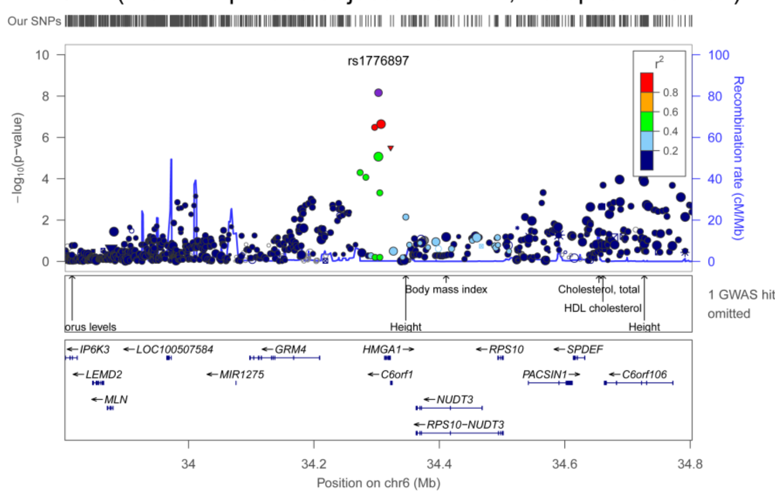
FGFR4 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



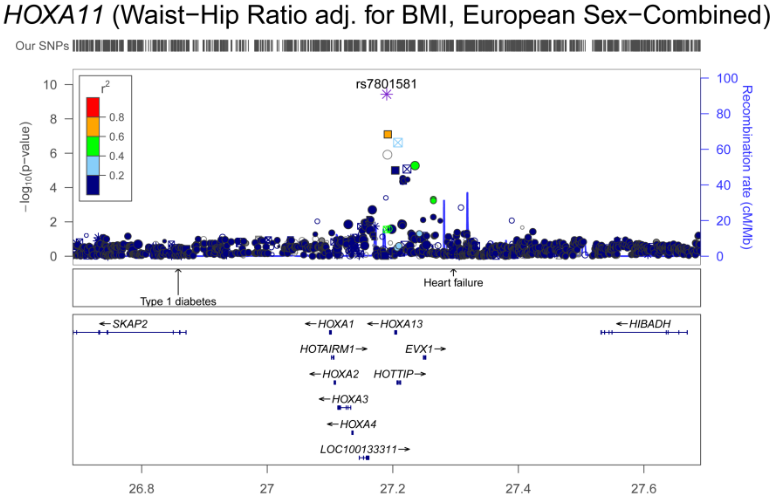
BTNL2 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



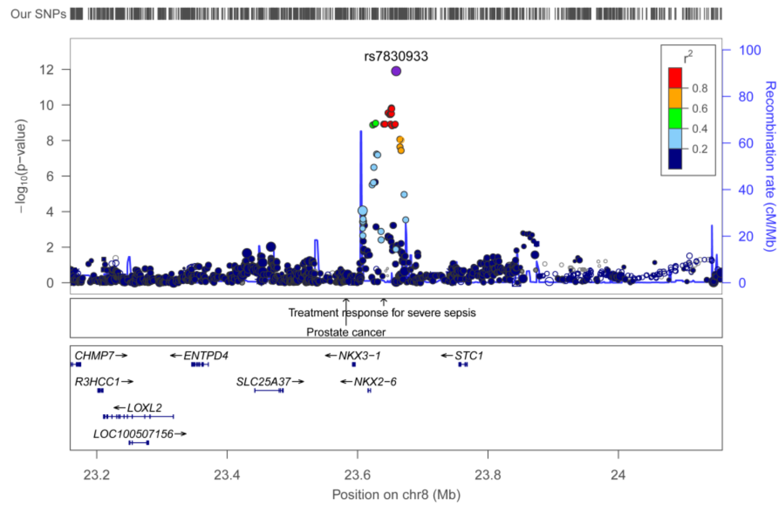
HMGA1 (Waist−Hip Ratio adjusted for BMI, European Women)



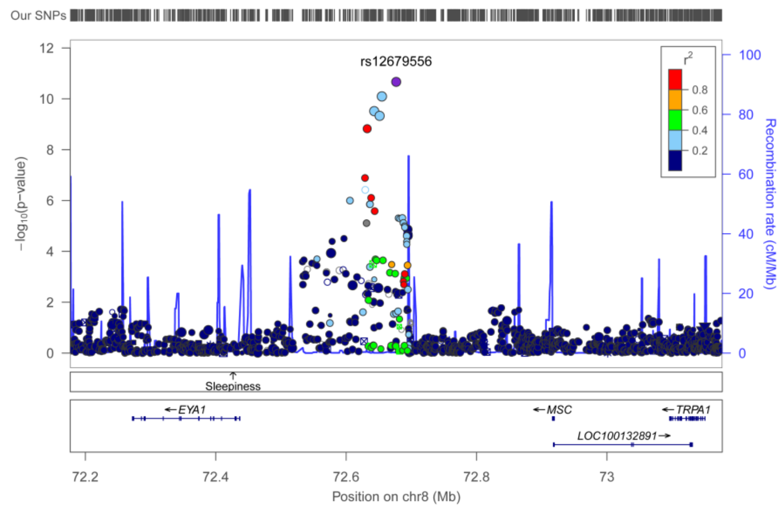
HOXA11 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



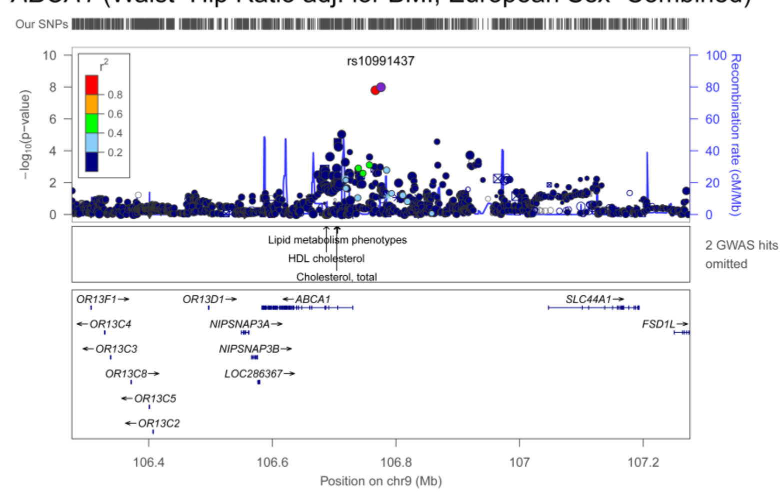
NKX2−6 (Waist−Hip Ratio adjusted for BMI, European Women)



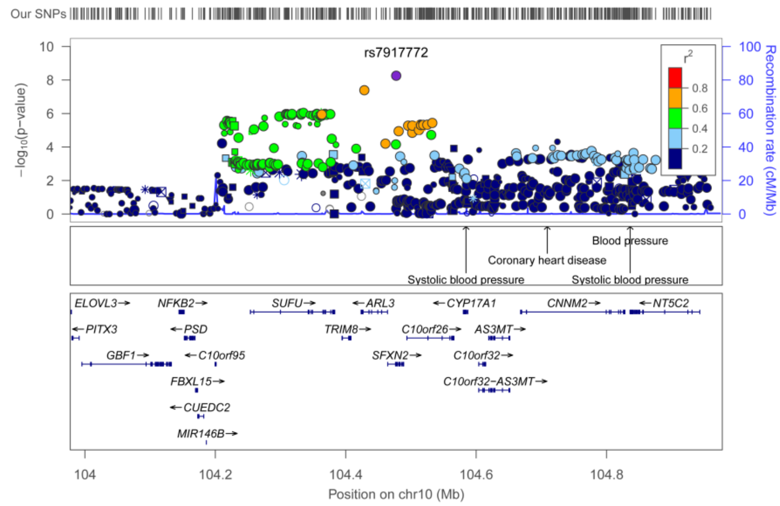
MSC (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



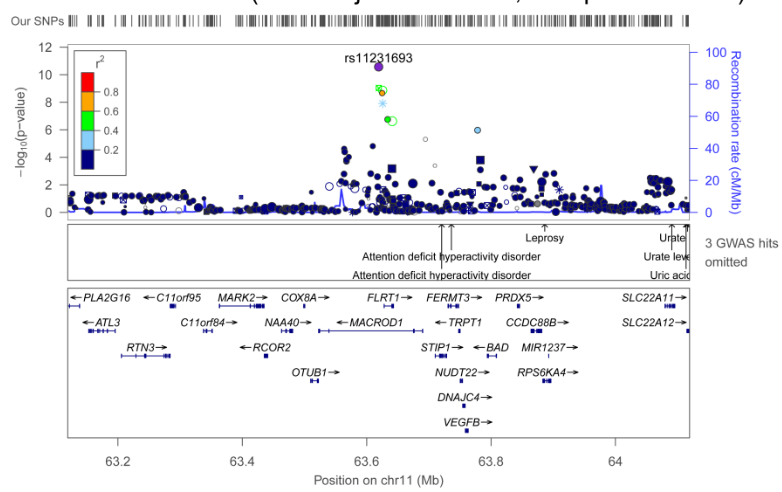
ABCA1 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



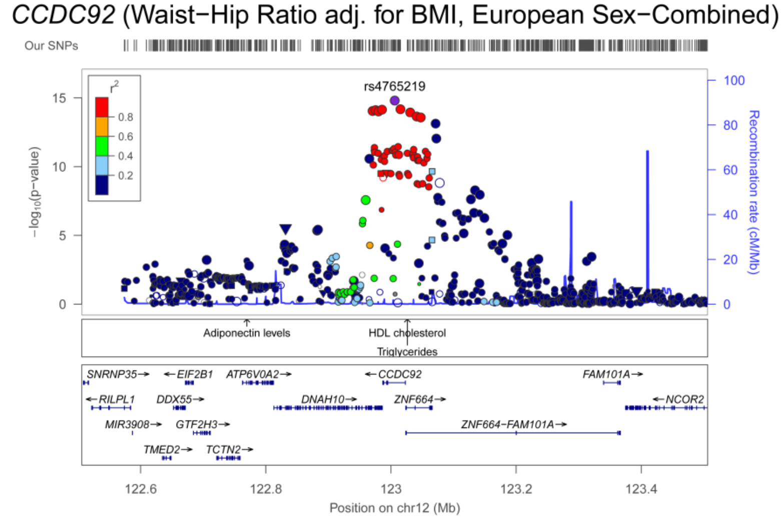
SFXN2 (Waist−Hip Ratio adjusted for BMI, European Women)

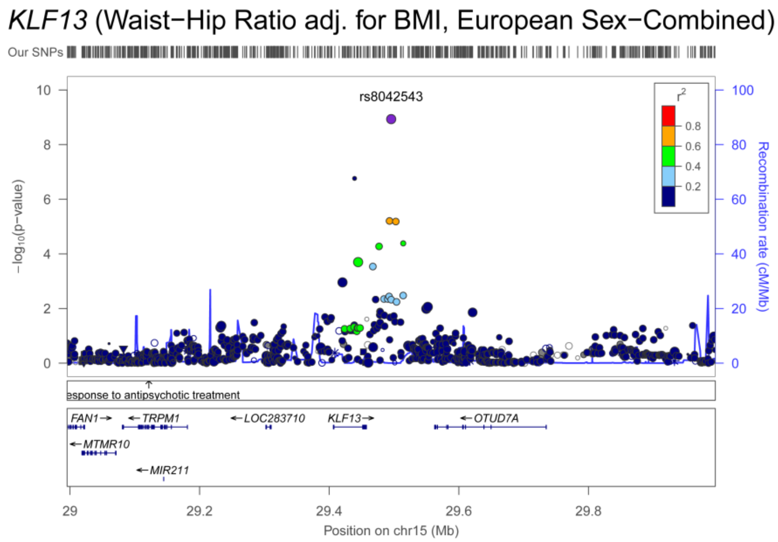


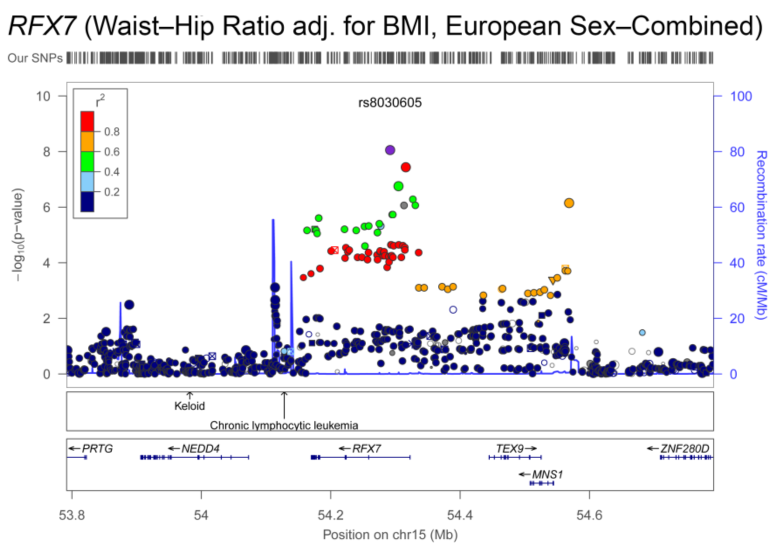
MACROD1−VEGFB (WHR adjusted for BMI, European Women)

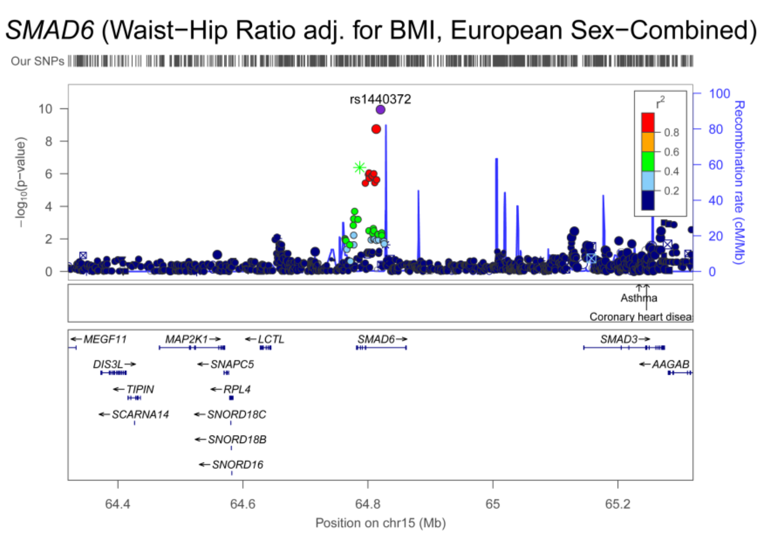


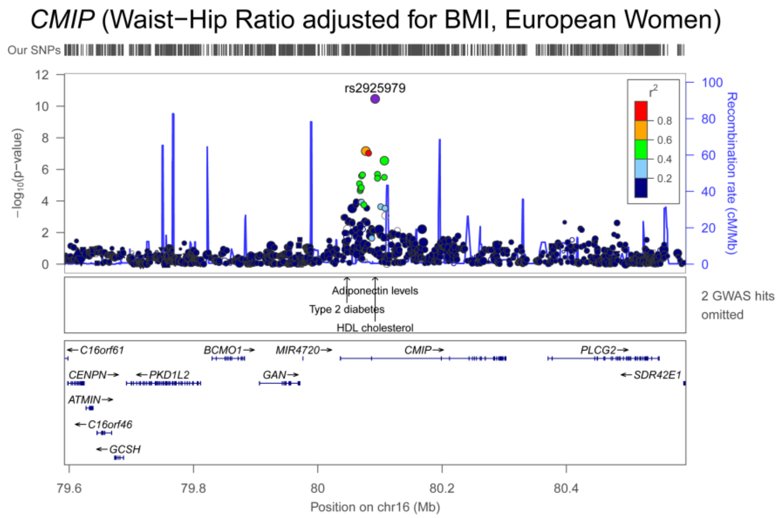
CCDC92 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)

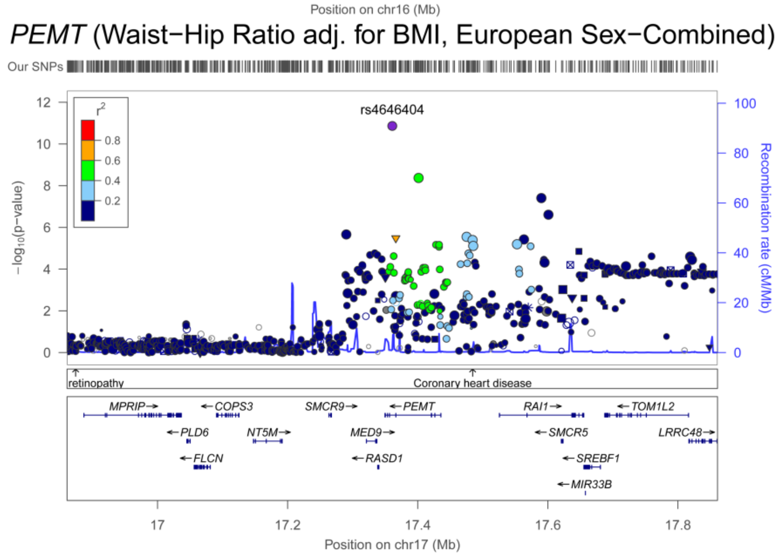


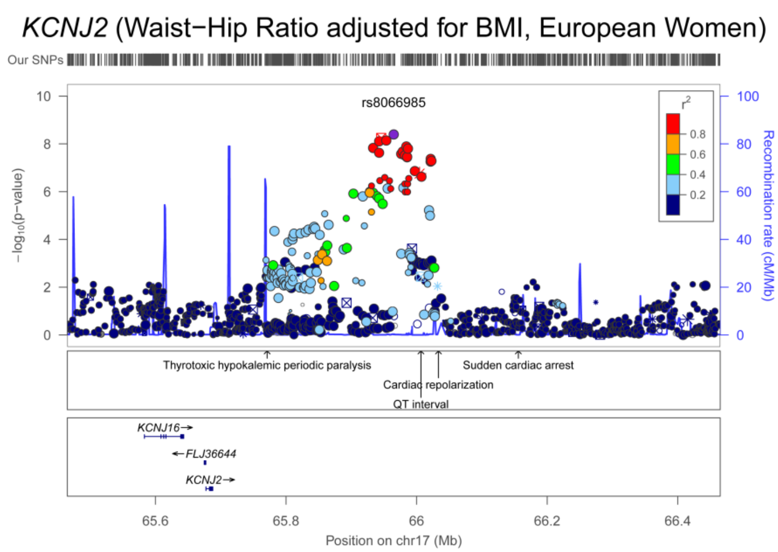

KLF13 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)
Our SNPs
rs8042543
−log10(p−value)
Recombination rate (cM/Mb)
r2
response to antipsychotic treatment
FAN1
TRPM1
LOC283710
KLF13
OTUD7A
MTMR10
MIR211
Position on chr15 (Mb)


RFX7 (Waist–Hip Ratio adj. for BMI, European Sex–Combined)
Our SNPs
rs8030605
−log10(p−value)
Recombination rate (cM/Mb)
r2
Keloid
Chronic lymphocytic leukemia
PRTG
NEDD4
RFX7
TEX9
ZNF280D
MNS1
Position on chr15 (Mb)

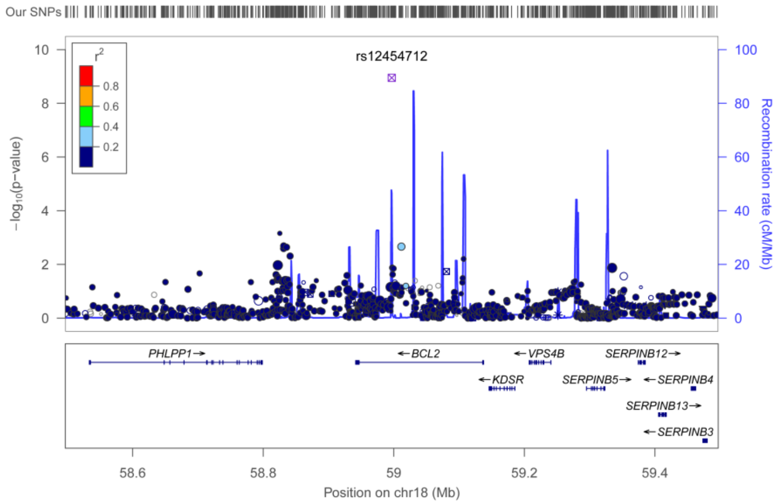

SMAD6 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)
Our SNPs
rs1440372
−log10(p−value)
Recombination rate (cM/Mb)
r2
Asthma
Coronary heart disea
MEGF11
MAP2K1
LCTL
SMAD6
SMAD3
DIS3L
SNAPC5
AAGAB
TIPIN
RPL4
SCARNA14
SNORD18C
SNORD18B
SNORD16
Position on chr15 (Mb)


CMIP (Waist−Hip Ratio adjusted for BMI, European Women)
Our SNPs
rs2925979
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
Adiponectin levels
Type 2 diabetes
HDL cholesterol
2 GWAS hits omitted
C16orf61
BCMO1
MIR4720
CMIP
PLCG2
CENPN
PKD1L2
GAN
SDR42E1
ATMIN
C16orf46
GCSH
Position on chr16 (Mb)

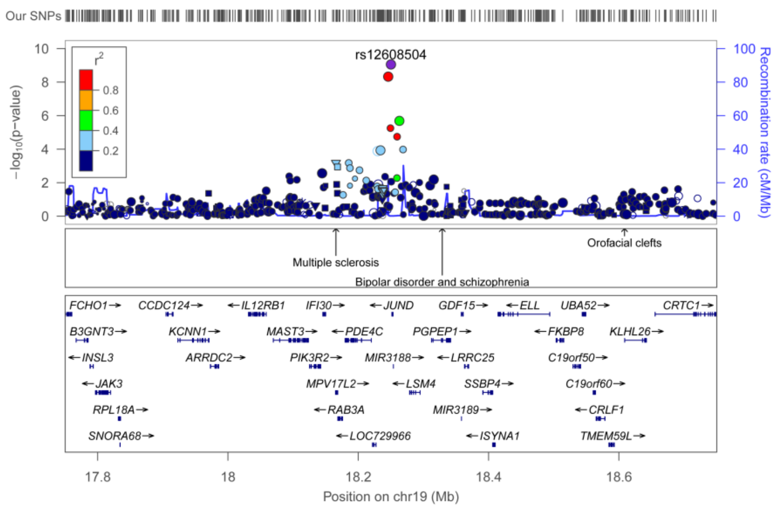

PEMT (Waist−Hip Ratio adj. for BMI, European Sex−Combined)
Our SNPs
rs4646404
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
retinopathy
Coronary heart disease
MPRIP
COPS3
SMCR9
PEMT
RAI1
TOM1L2
PLD6
NT5M
MED9
SMCR5
LRRC48
FLCN
RASD1
SREBF1
MIR33B
Position on chr17 (Mb)


KCNJ2 (Waist−Hip Ratio adjusted for BMI, European Women)
Our SNPs
rs8066985
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
Thyrotoxic hypokalemic periodic paralysis
Sudden cardiac arrest
Cardiac repolarization
QT interval
KCNJ16
FLJ36644
KCNJ2
Position on chr17 (Mb)

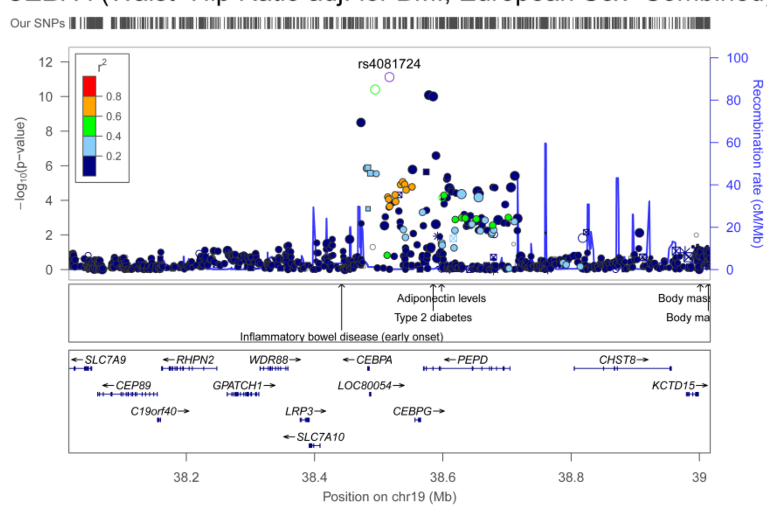
BCL2 (Waist−Hip Ratio adjusted for BMI, European Women)



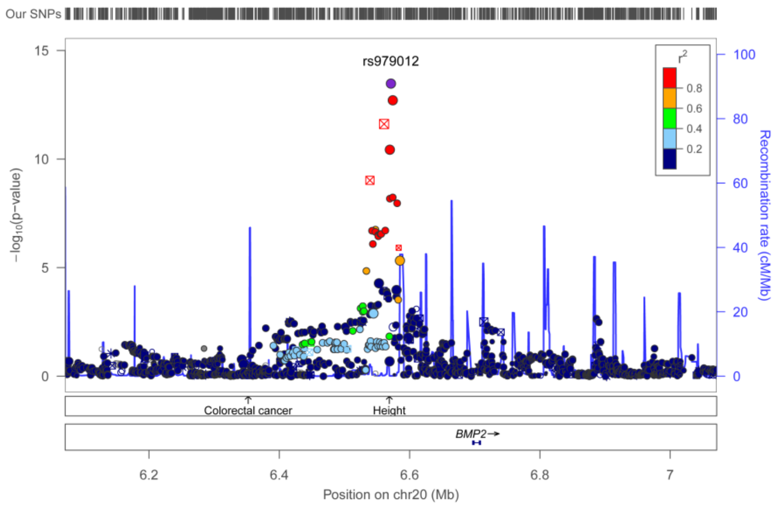
JUND (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



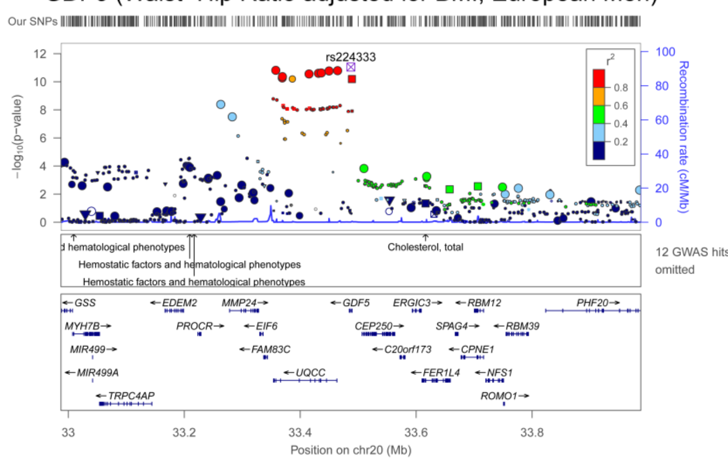
CEBPA (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



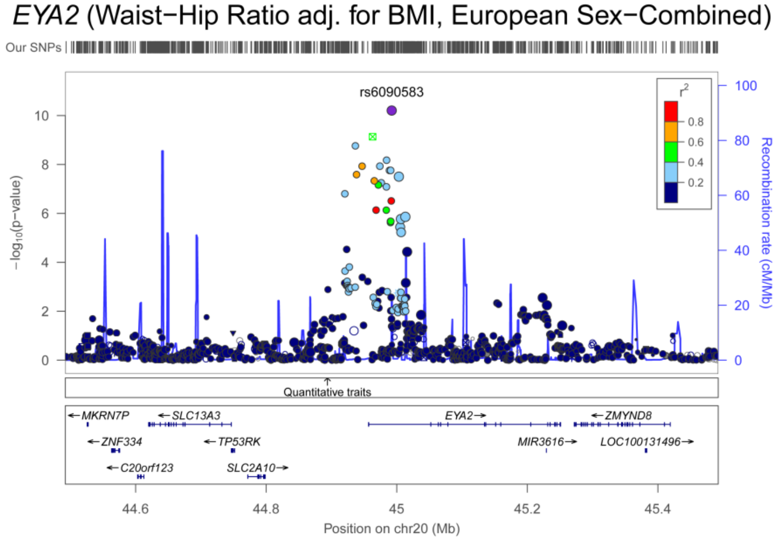
BMP2 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



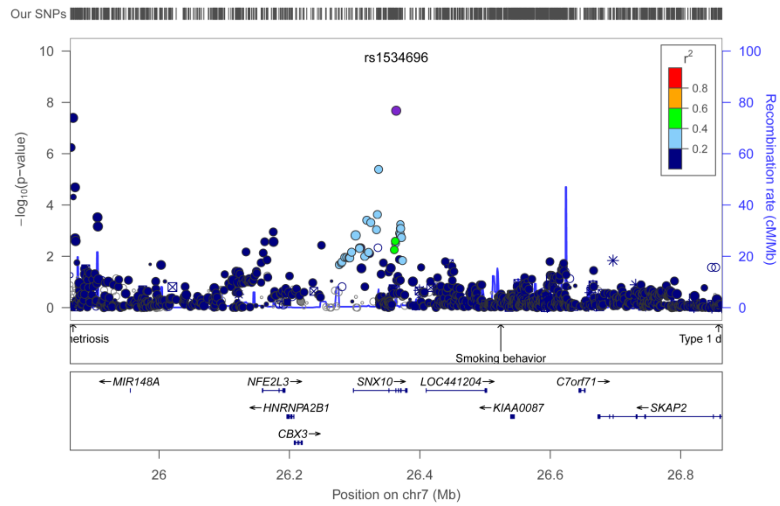
GDF5 (Waist−Hip Ratio adjusted for BMI, European Men)



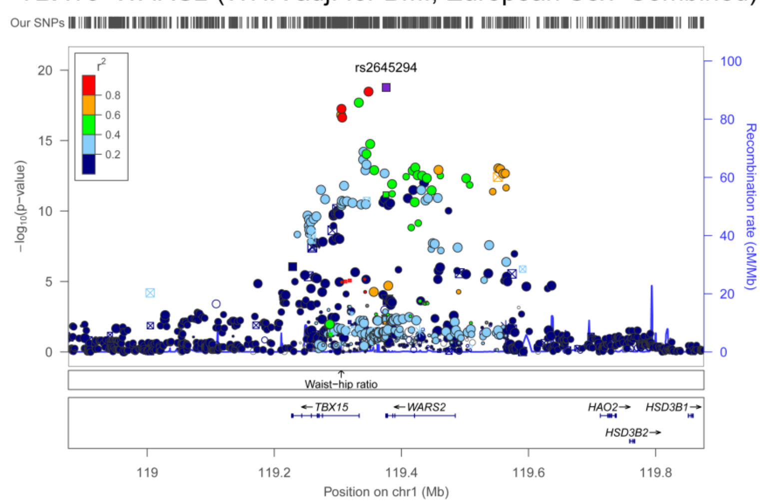
EYA2 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



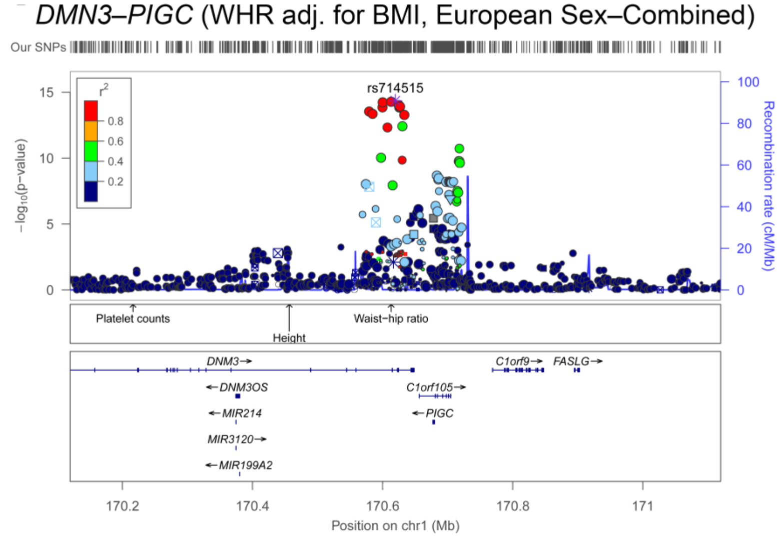
SNX10 (Waist−Hip Ratio adj. for BMI, All Ancestries Women)



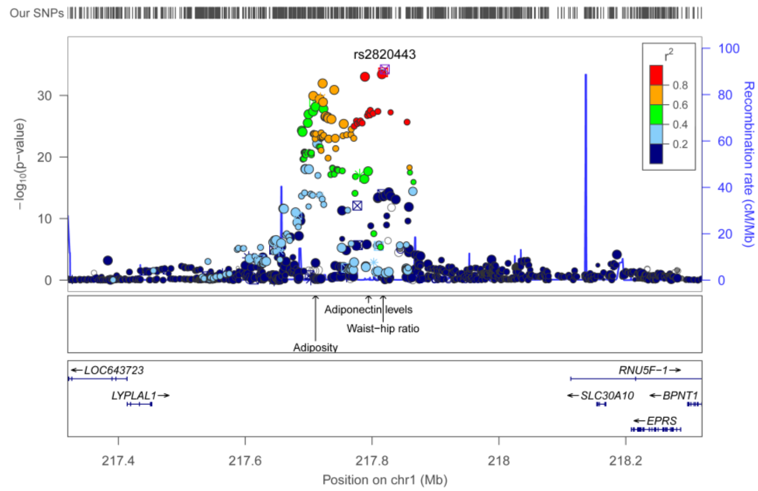
TBX15–WARS2 (WHR adj. for BMI, European Sex–Combined)



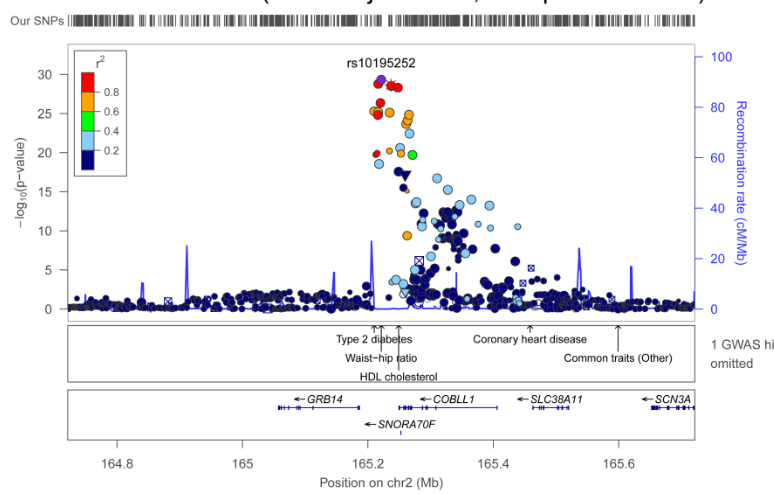
DMN3–PIGC (WHR adj. for BMI, European Sex–Combined)



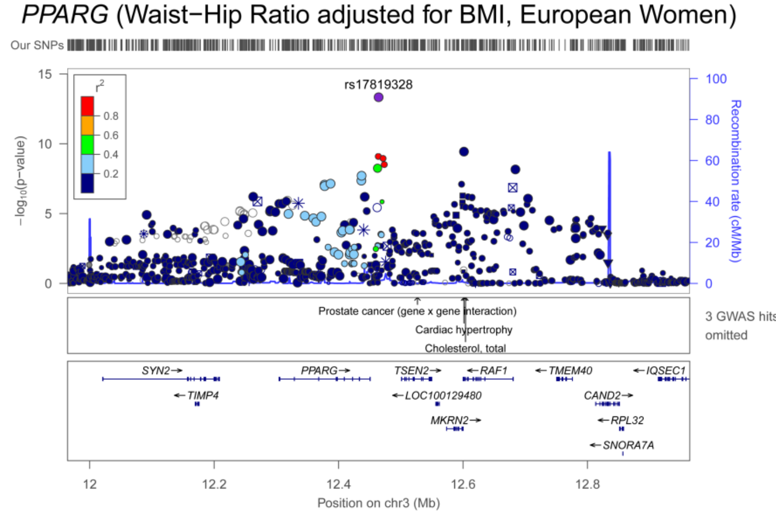
LYPLAL1 (Waist–Hip Ratio adj. for BMI, European Women)



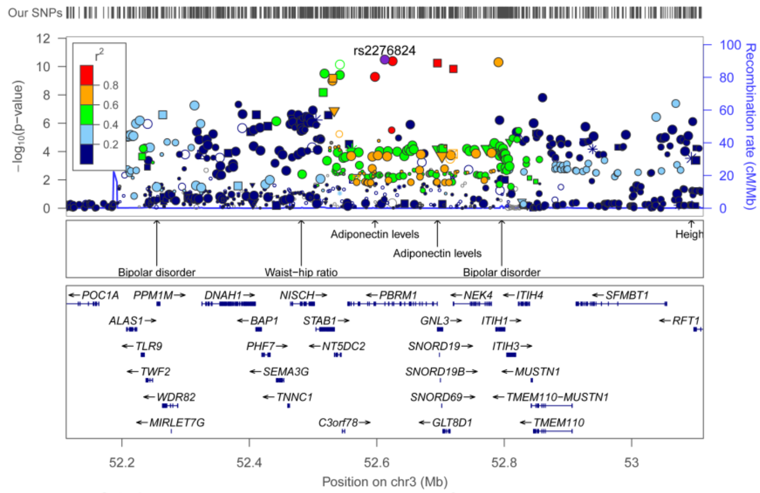
GRB14–COBLL1 (WHR adj. for BMI, European Women)



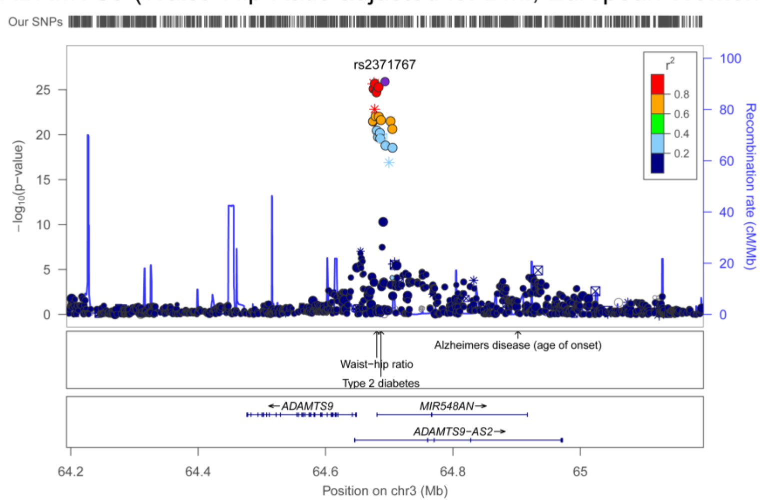
PPARG (Waist−Hip Ratio adjusted for BMI, European Women)



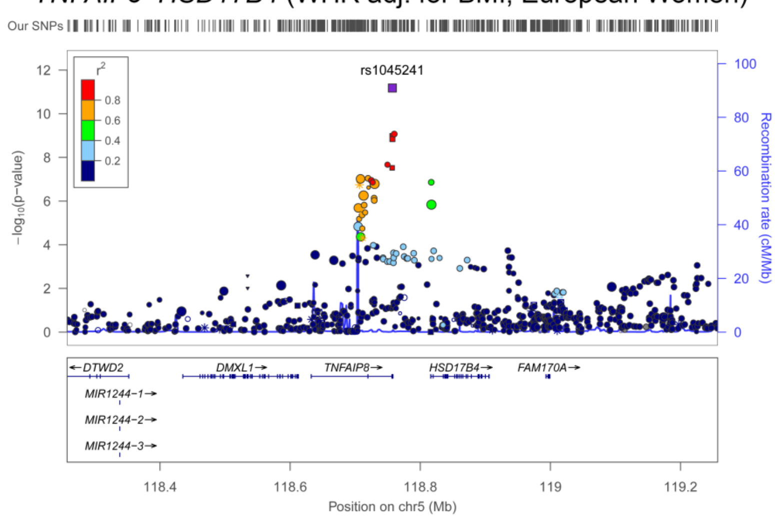
PBRM1 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



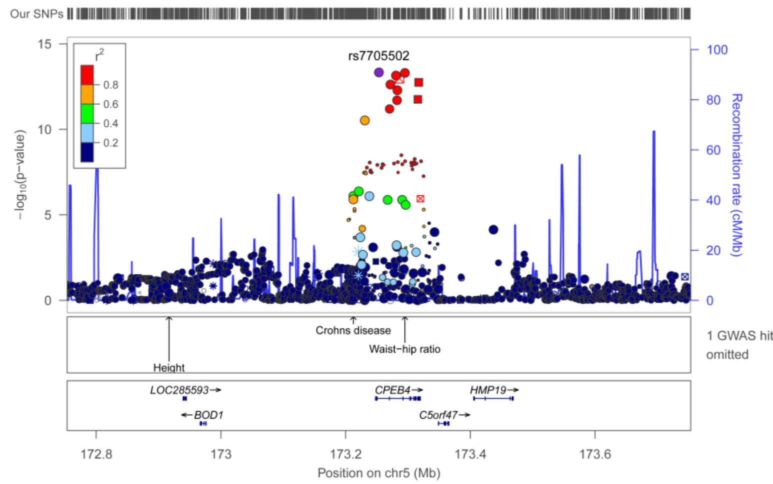
ADAMTS9 (Waist−Hip Ratio adjusted for BMI, European Women)



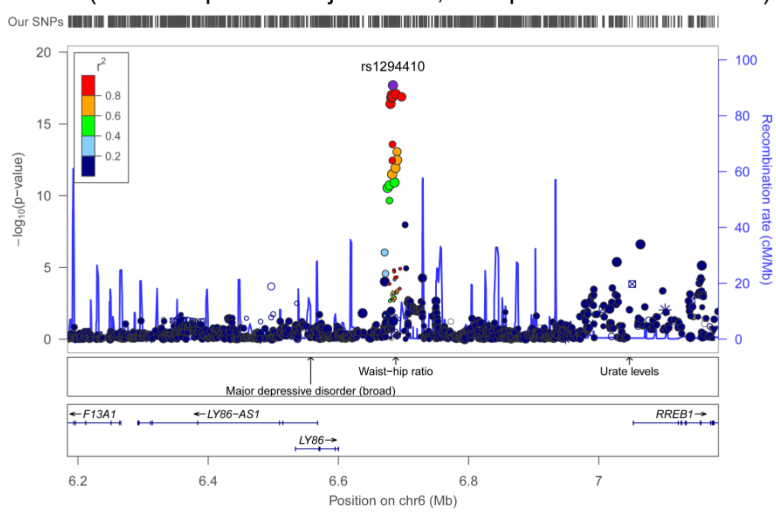
TNFAIP3–HSD17B4 (WHR adj. for BMI, European Women)



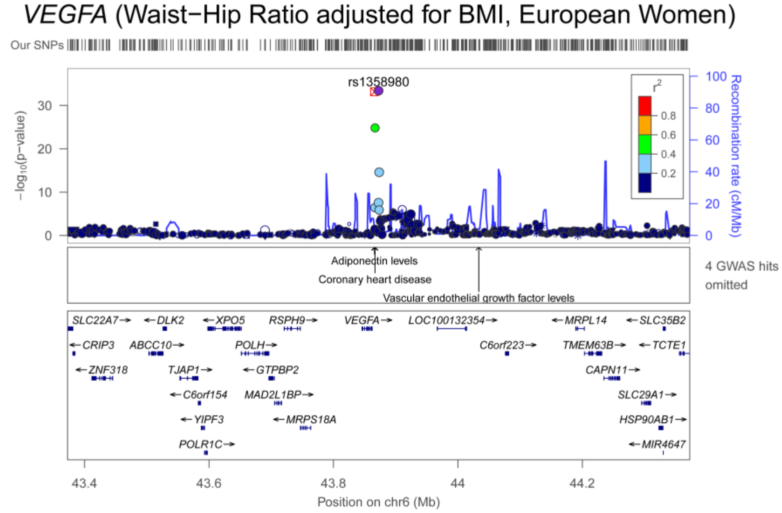
CPEB4 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



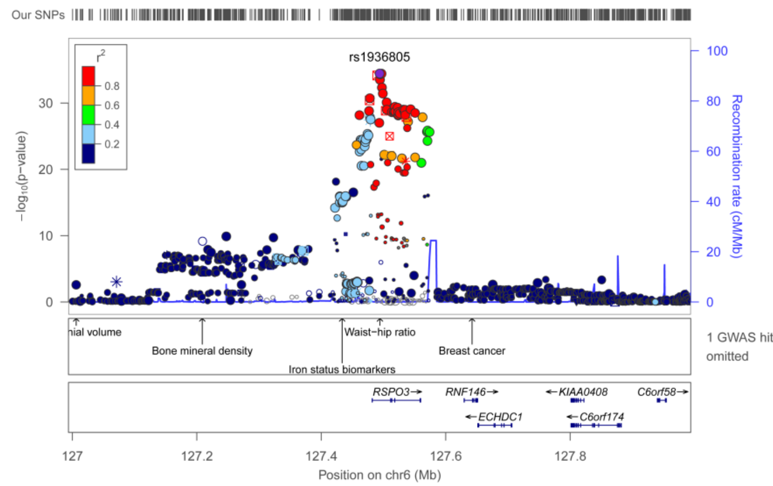
LY86 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



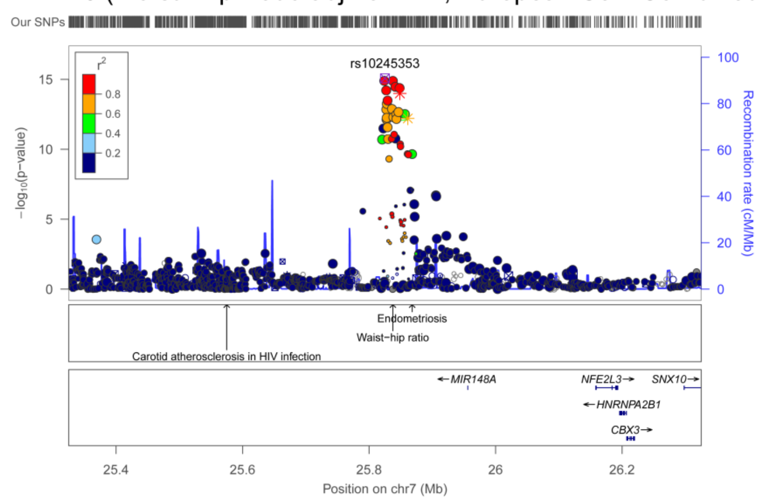
VEGFA (Waist−Hip Ratio adjusted for BMI, European Women)



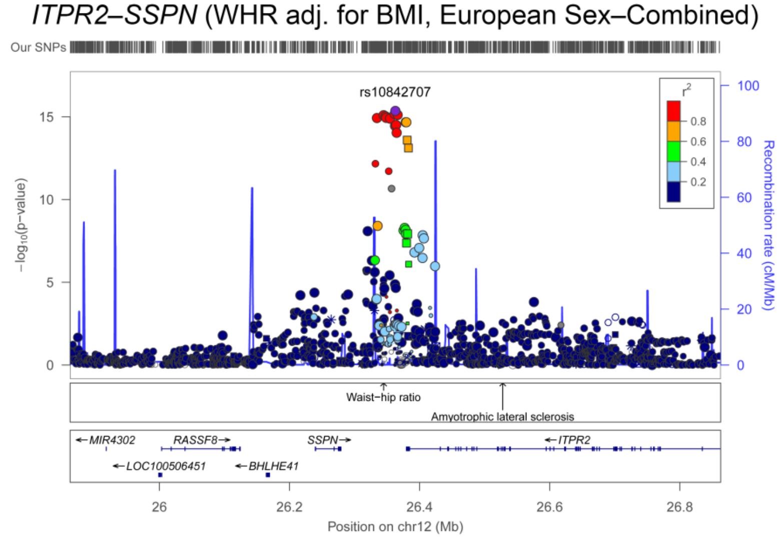
RSPO3 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



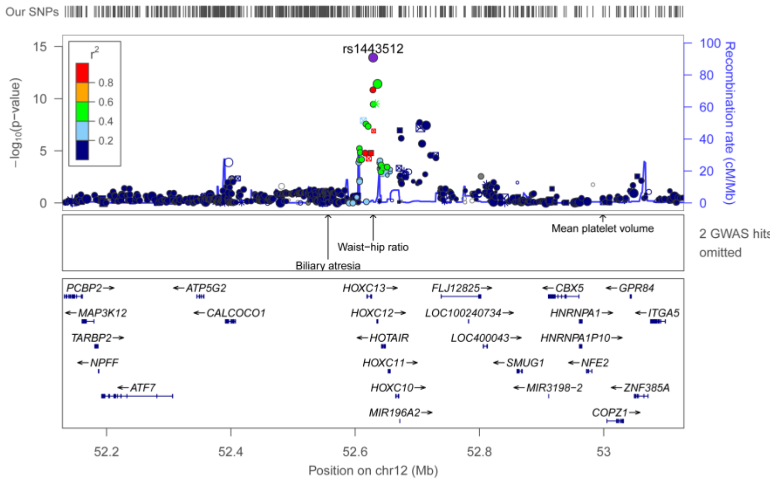
NFE2L3 (Waist−Hip Ratio adj. for BMI, European Sex−Combined)



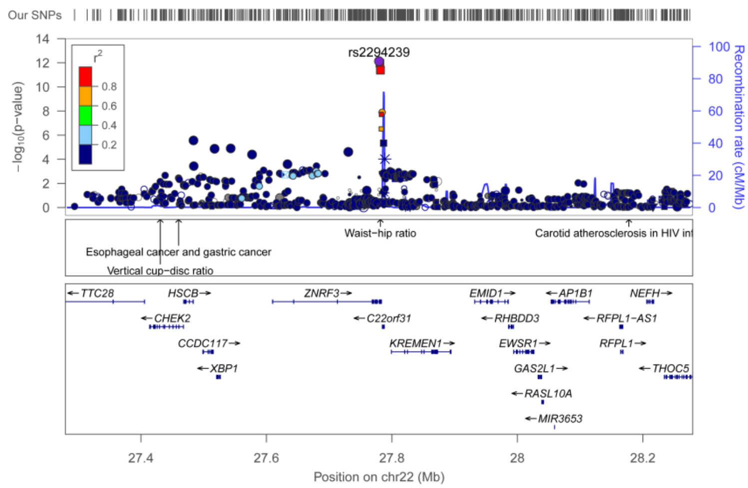
ITPR2–SSPN (WHR adj. for BMI, European Sex–Combined)



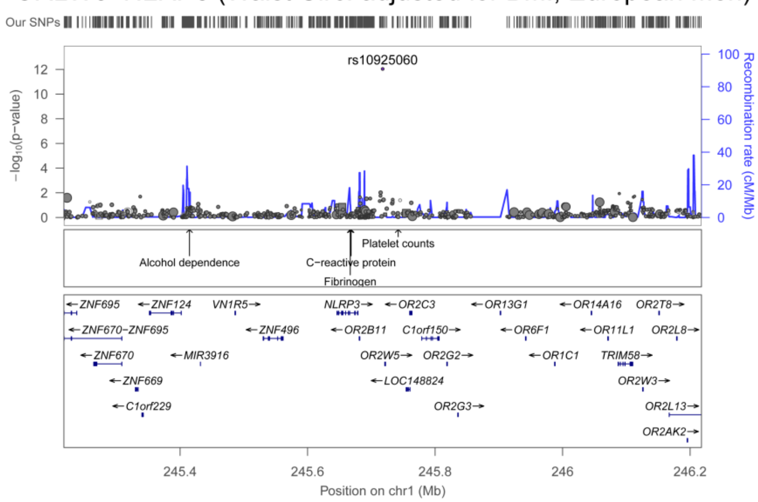
HOXC13 (Waist−Hip Ratio adjusted for BMI, European Women)



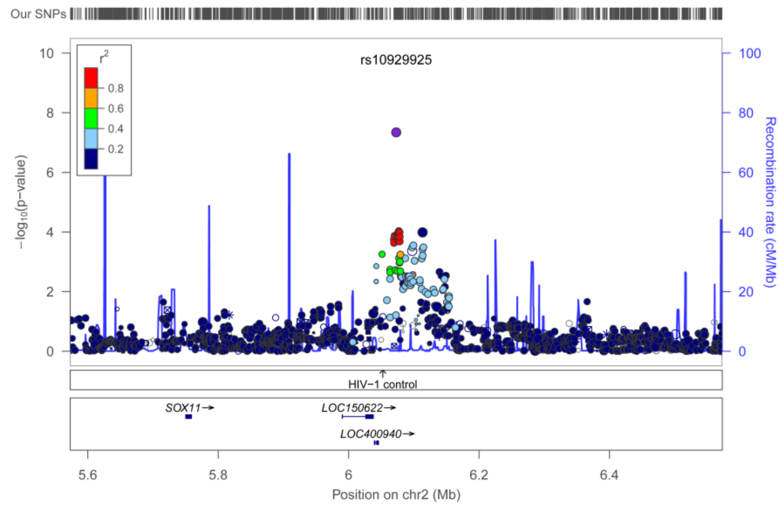
ZNFR3–KREMEN1 (WHR adj. for BMI, European Sex–Combined)



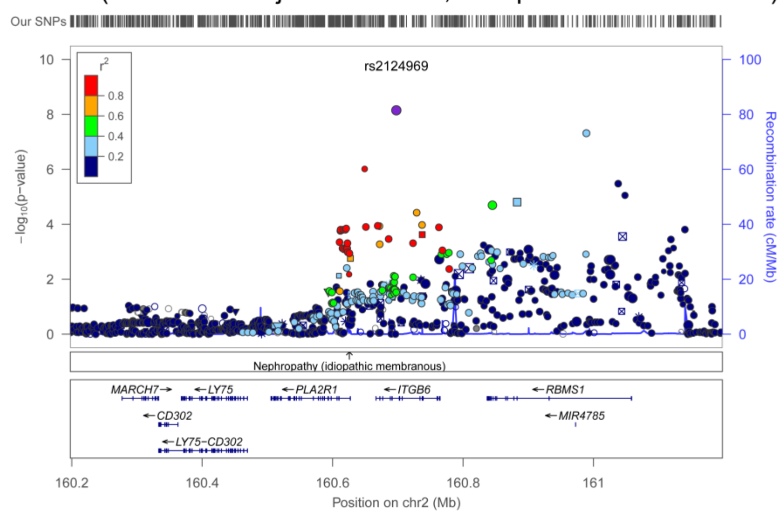
OR2W5−NLRP3 (Waist Circ. adjusted for BMI, European Men)



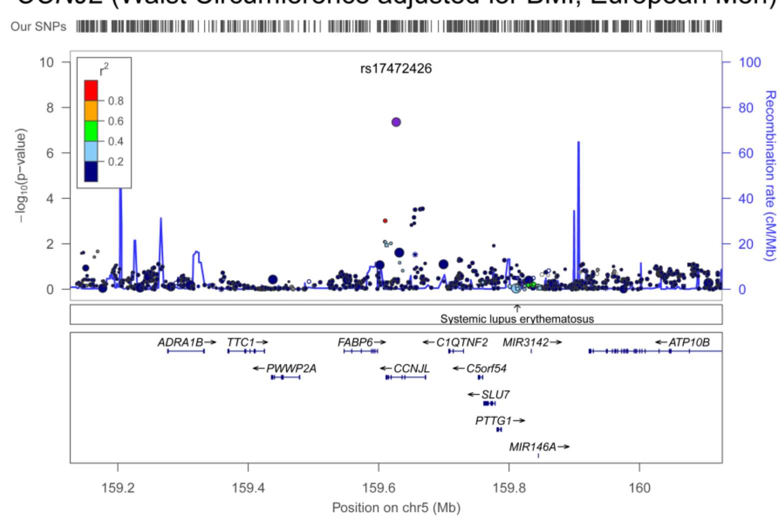
SOX11 (Hip Circumference, European Sex−Combined)



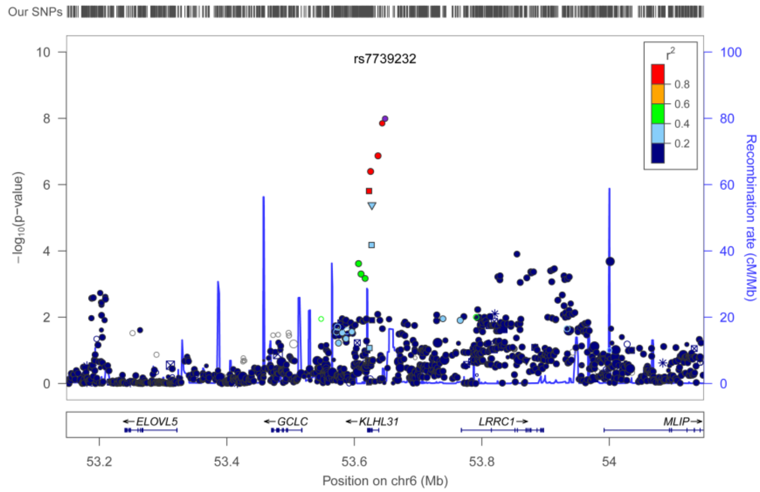
ITGB6 (Waist Circ. adjusted for BMI, European Sex−Combined)



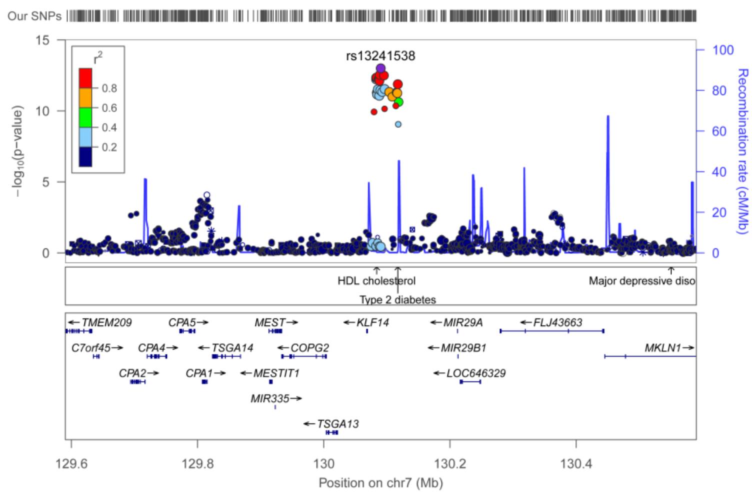
CCNJL (Waist Circumference adjusted for BMI, European Men)



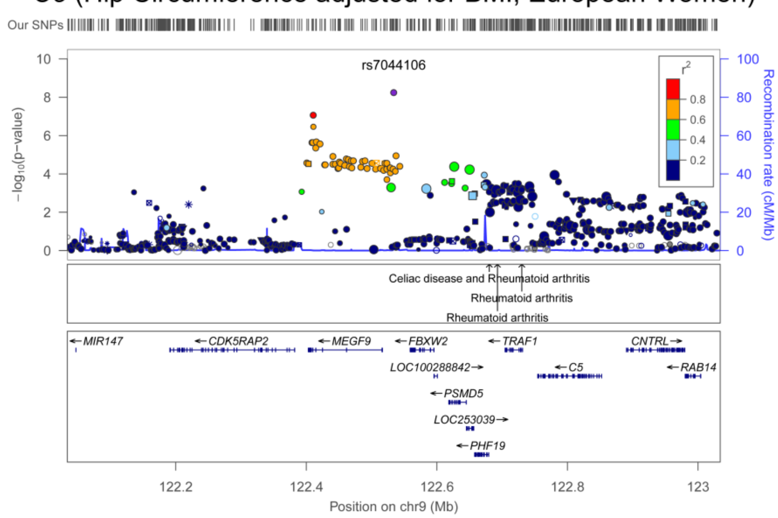
KLHL31 (Hip Circumference adjusted for BMI, European Women)

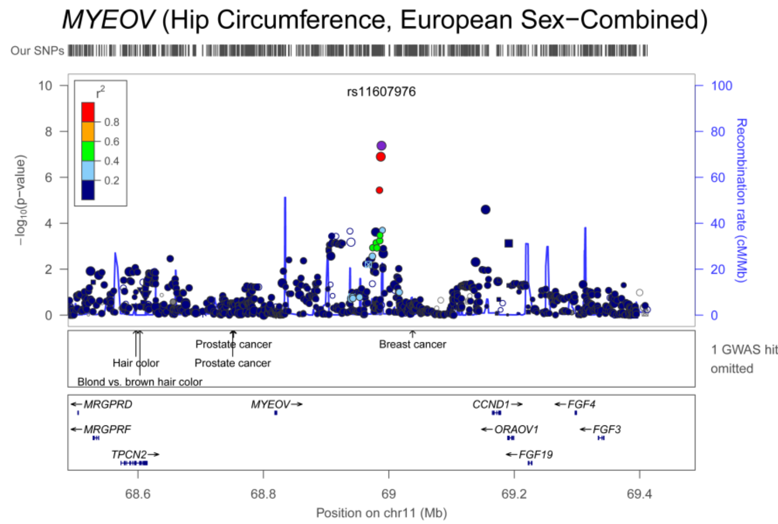


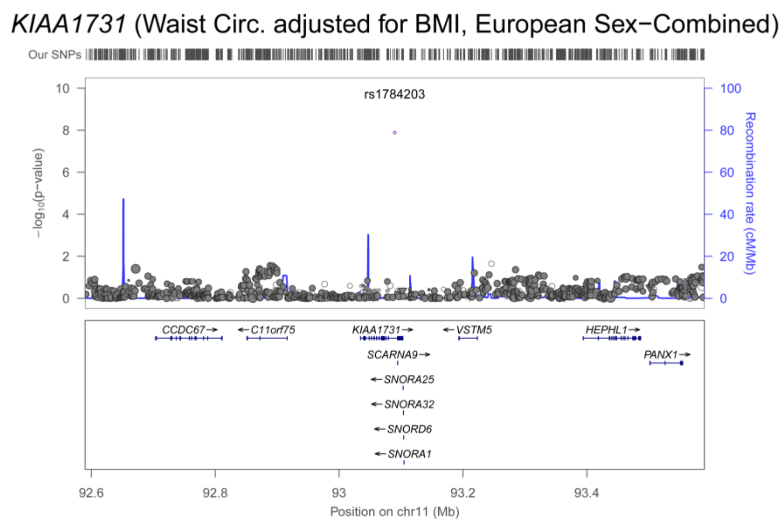
KLF14 (Hip Circumference adjusted for BMI, European Women)

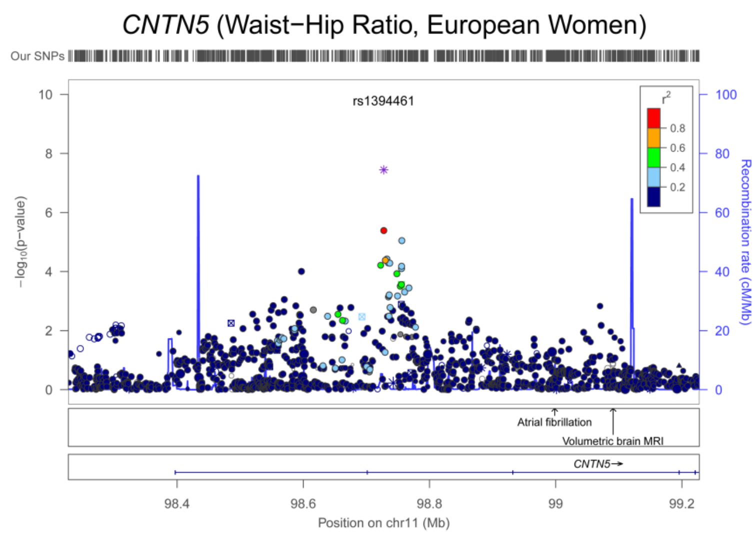


C5 (Hip Circumference adjusted for BMI, European Women)

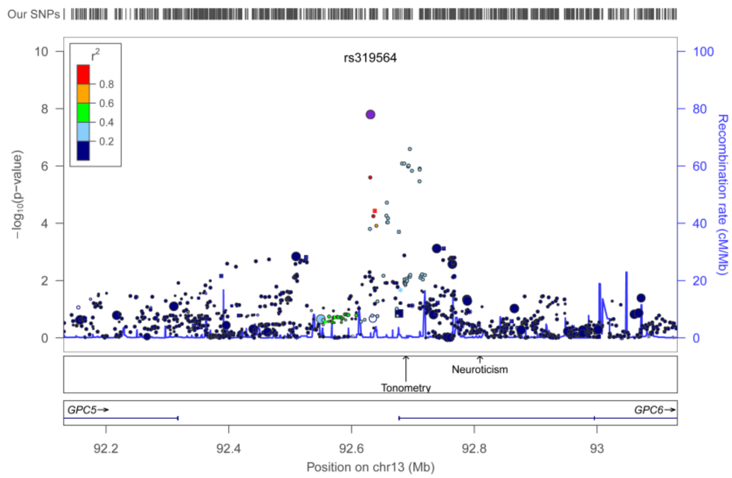



MYEOV (Hip Circumference, European Sex−Combined)
Our SNPs
rs11607976
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
Hair color
Blond vs. brown hair color
Prostate cancer
Prostate cancer
Breast cancer
1 GWAS hit omitted
MRGPRD
MRGPRF
TPCN2
MYEOV
CCND1
ORAOV1
FGF19
FGF4
FGF3
Position on chr11 (Mb)

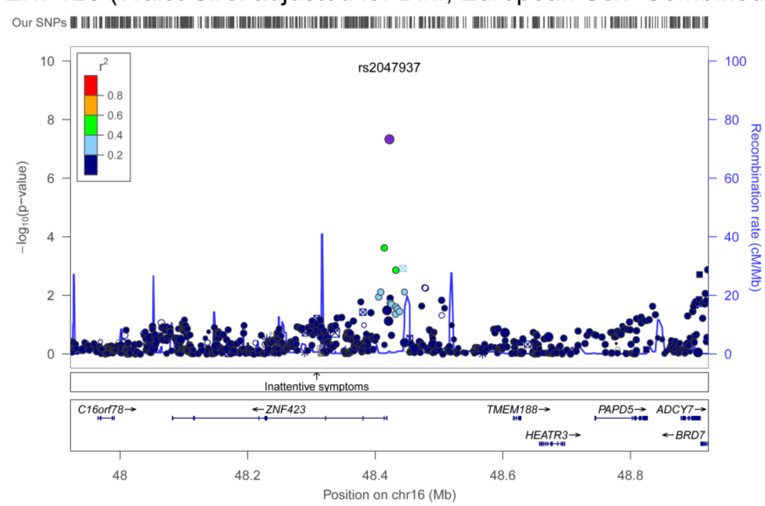

KIAA1731 (Waist Circ. adjusted for BMI, European Sex−Combined)
Our SNPs
rs1784203
−log10(p−value)
Recombination rate (cM/Mb)
CCDC67
C11orf75
KIAA1731
SCARNA9
SNORA25
SNORA32
SNORD6
SNORA1
VSTM5
HEPHL1
PANX1
Position on chr11 (Mb)


CNTN5 (Waist−Hip Ratio, European Women)
Our SNPs
rs1394461
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
Atrial fibrillation
Volumetric brain MRI
CNTN5
Position on chr11 (Mb)

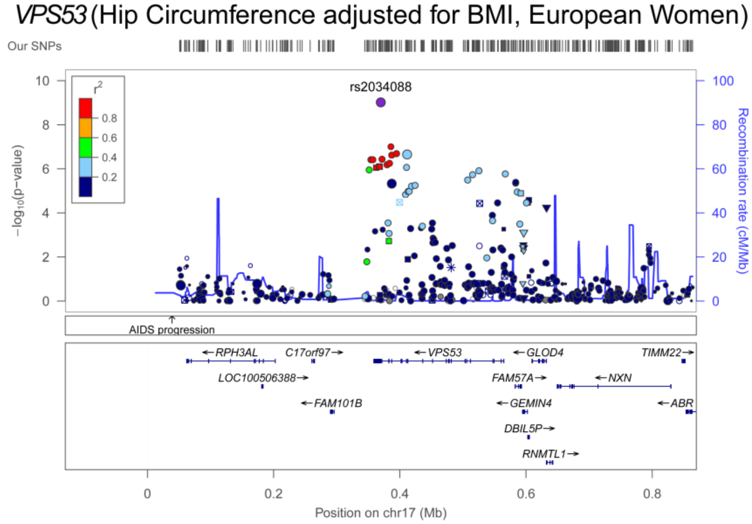
GPC6 (Waist−Hip Ratio, European Men)



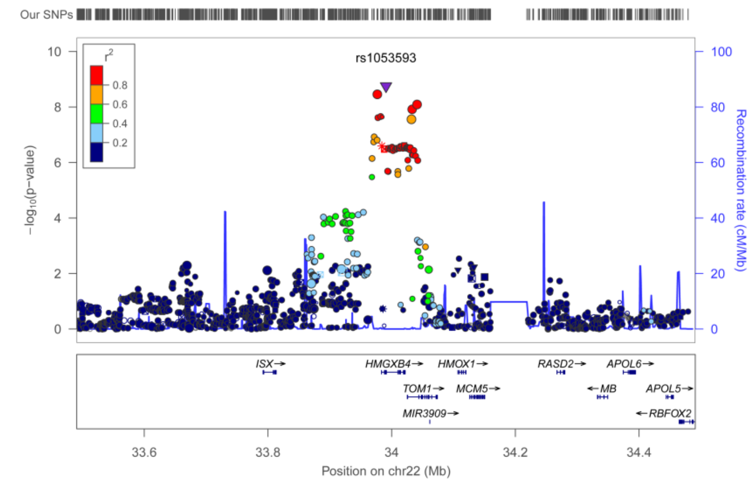
ZNF423 (Waist Circ. adjusted for BMI, European Sex−Combined)



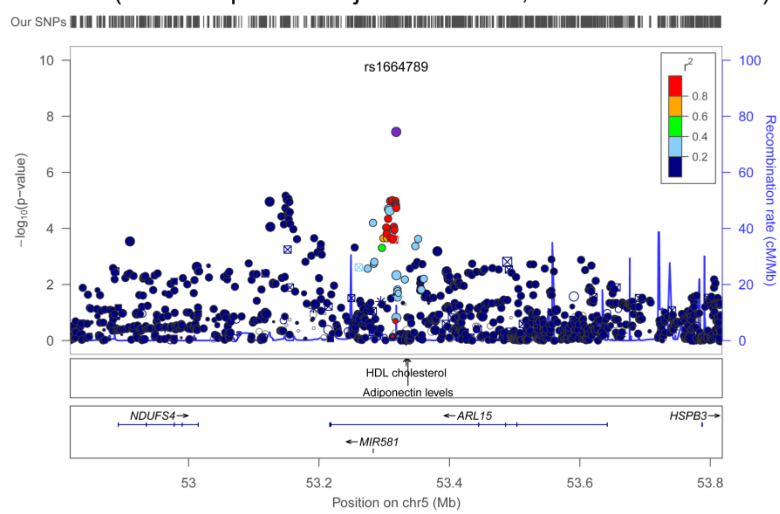
VPS53 (Hip Circumference adjusted for BMI, European Women)



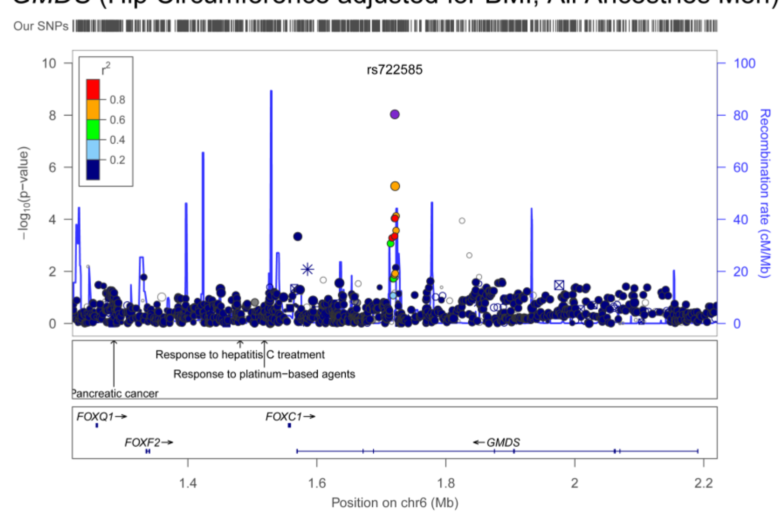
HMGXB4 (Hip Circumference adjusted for BMI, European Women)



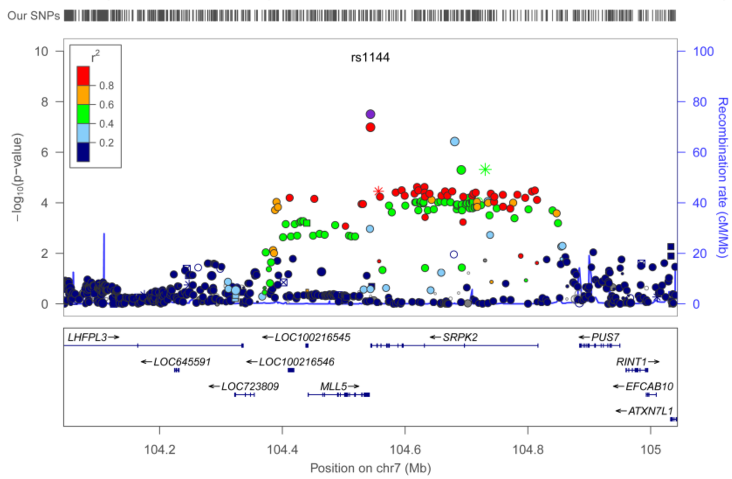
ARL15 (Waist−Hip Ratio adjusted for BMI, All Ancestries Men)



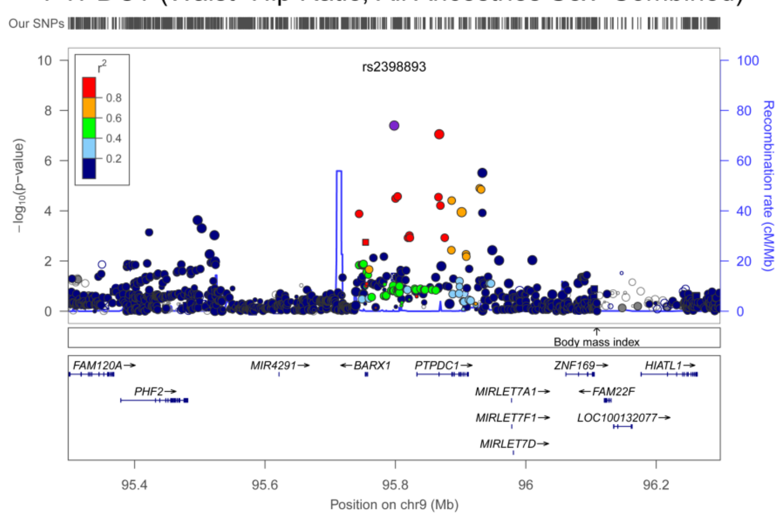
GMDS (Hip Circumference adjusted for BMI, All Ancestries Men)



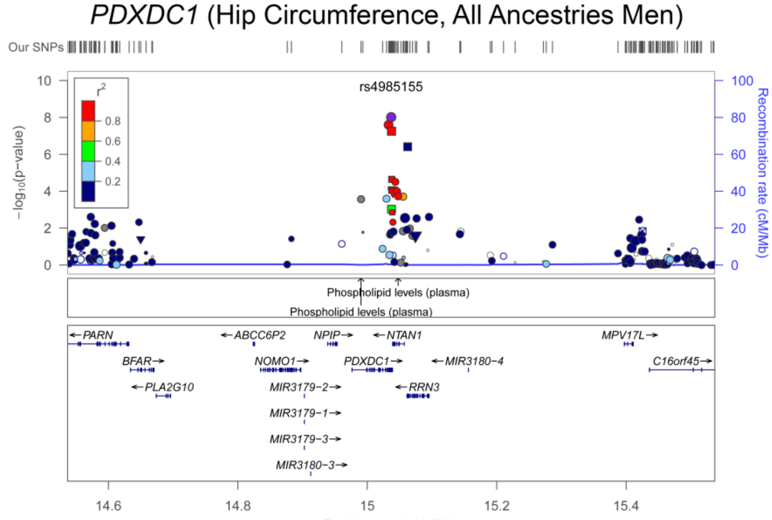
SRPK2 (Waist Circ. adj. for BMI, All Ancestries Sex−Combined)



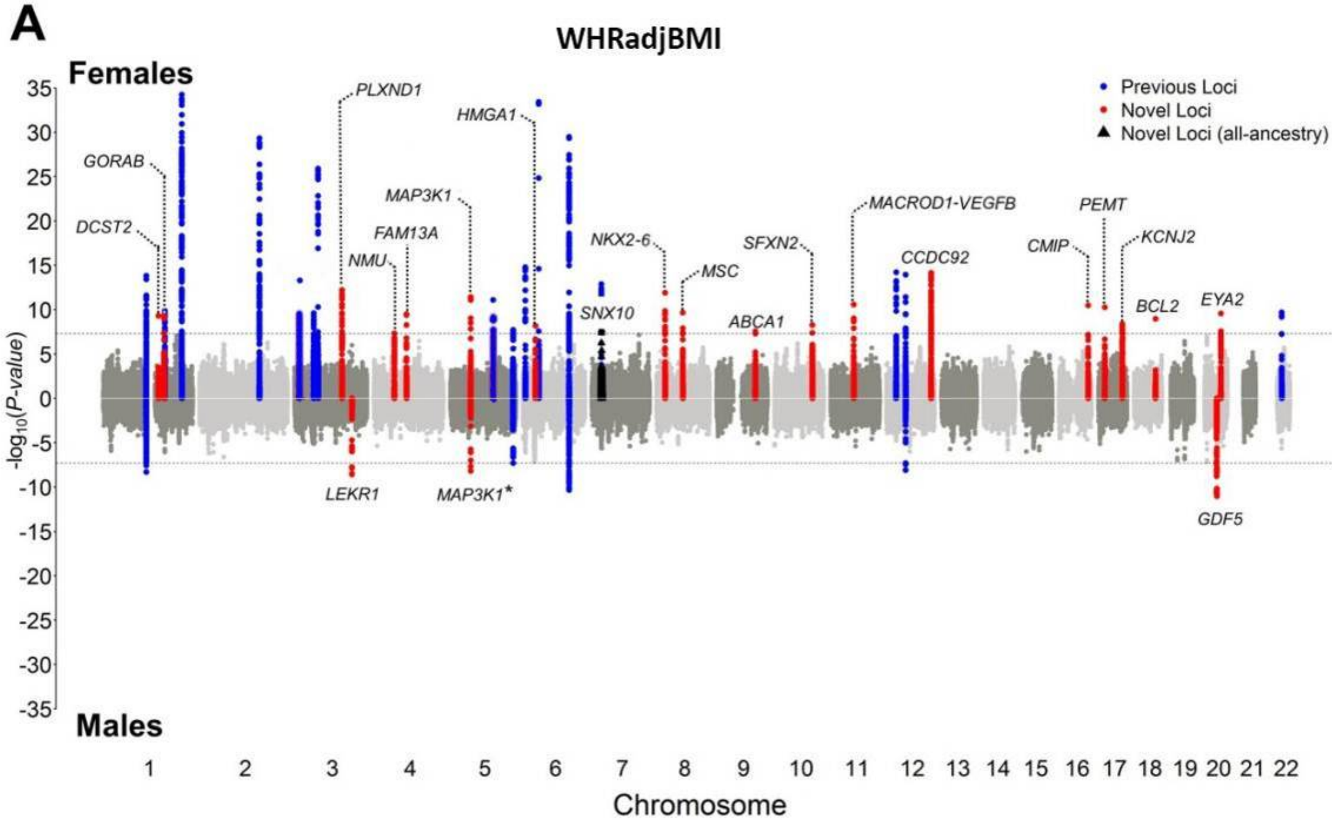
PTPDC1 (Waist−Hip Ratio, All Ancestries Sex−Combined)

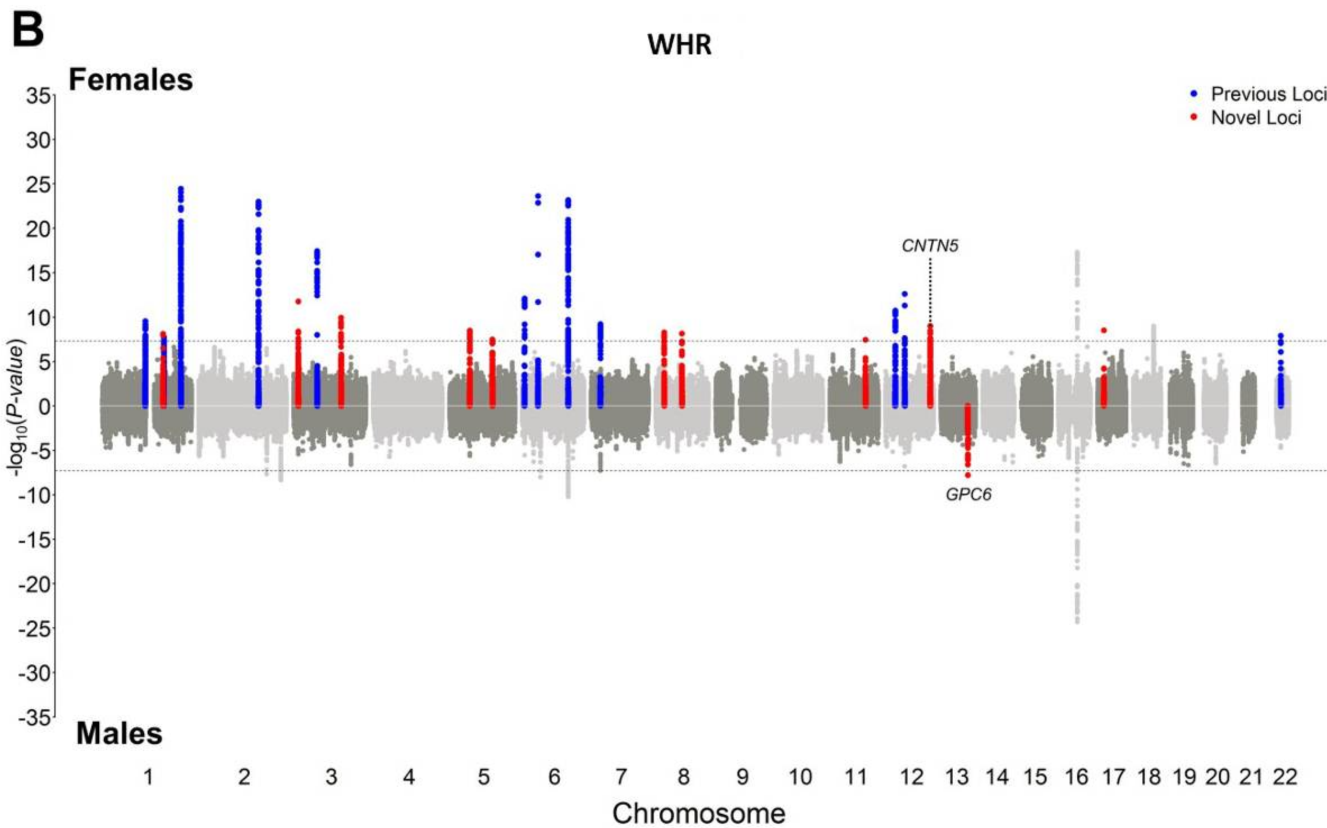


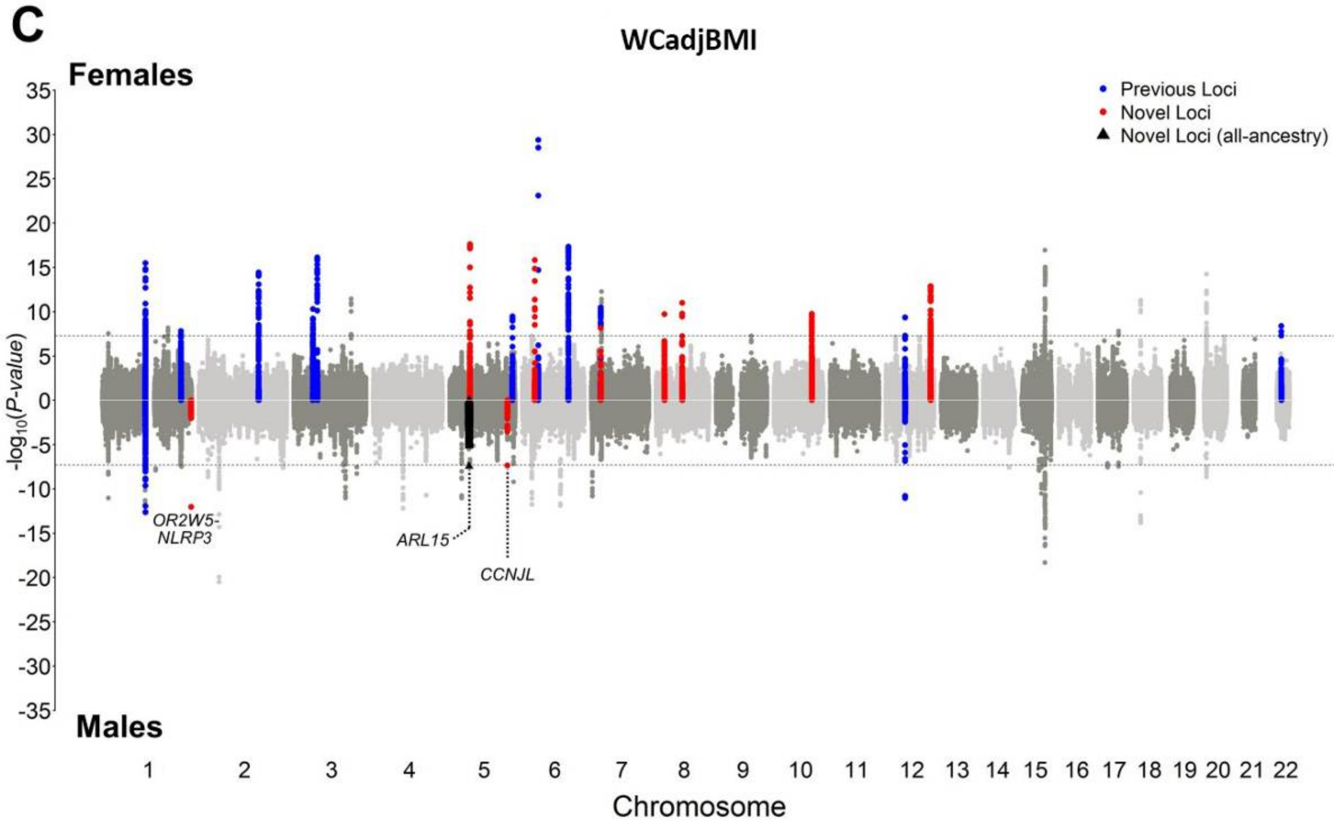
PDXDC1 (Hip Circumference, All Ancestries Men)

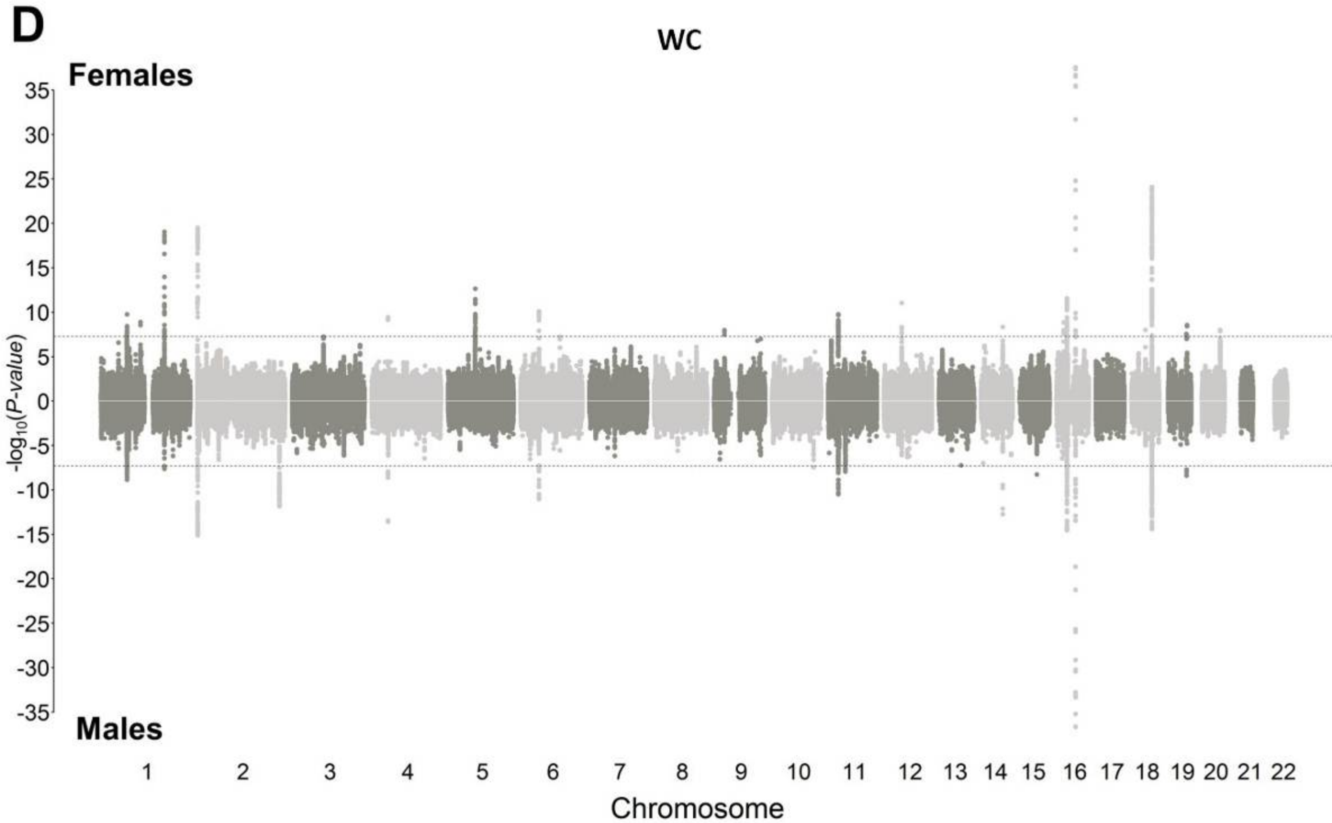


Supplementary Figure 4 | Chicago plots of sex-specific SNP associations for six waist-related traits. Sex-specific SNP associations are shown for waist-hip ratio (WHR), waist circumference (WC), and hip circumference (HIP), with and without adjustment for body mass index (adjBMI). Associations in women are shown above the *x*-axis as $-\log_{10}(P$ values), and associations in men are shown below as $\log_{10}(P$ values). Only SNP results with $N > 50{,}000$ samples are shown. Dashed gray lines mark statistical significance at the genome-wide level ($P = 5 \times 10^{-8}$). Novel loci achieving genome-wide significance in sex-stratified WHR association analysis in Europeans are highlighted in red on all figures (***A***–***F***) and annotated on figure ***A***. One additional novel locus achieving genome-wide significance when all ancestries were analyzed is marked as black triangles and annotated on figure ***A***. Novel loci achieving genome-wide significance in Europeans in other waist-related traits (***B***–***F***) are highlighted in red and annotated only on the relevant figure. Previously established loci are highlighted in blue (***A***–***F***). Additional novel loci achieving genome-wide significance when all ancestries were analyzed in other waist-related traits (***B***–***F***) are marked as black triangles and annotated. SNP association signals that achieve genome-wide significance and are previously established height or BMI loci are shown in light or dark grey. In figure ***A***, the asterisk indicates that different lead SNPs were identified in women and men. Detailed information about the loci is presented in **Tables 1** and **3** and **Supplementary Tables 4** and **25.**

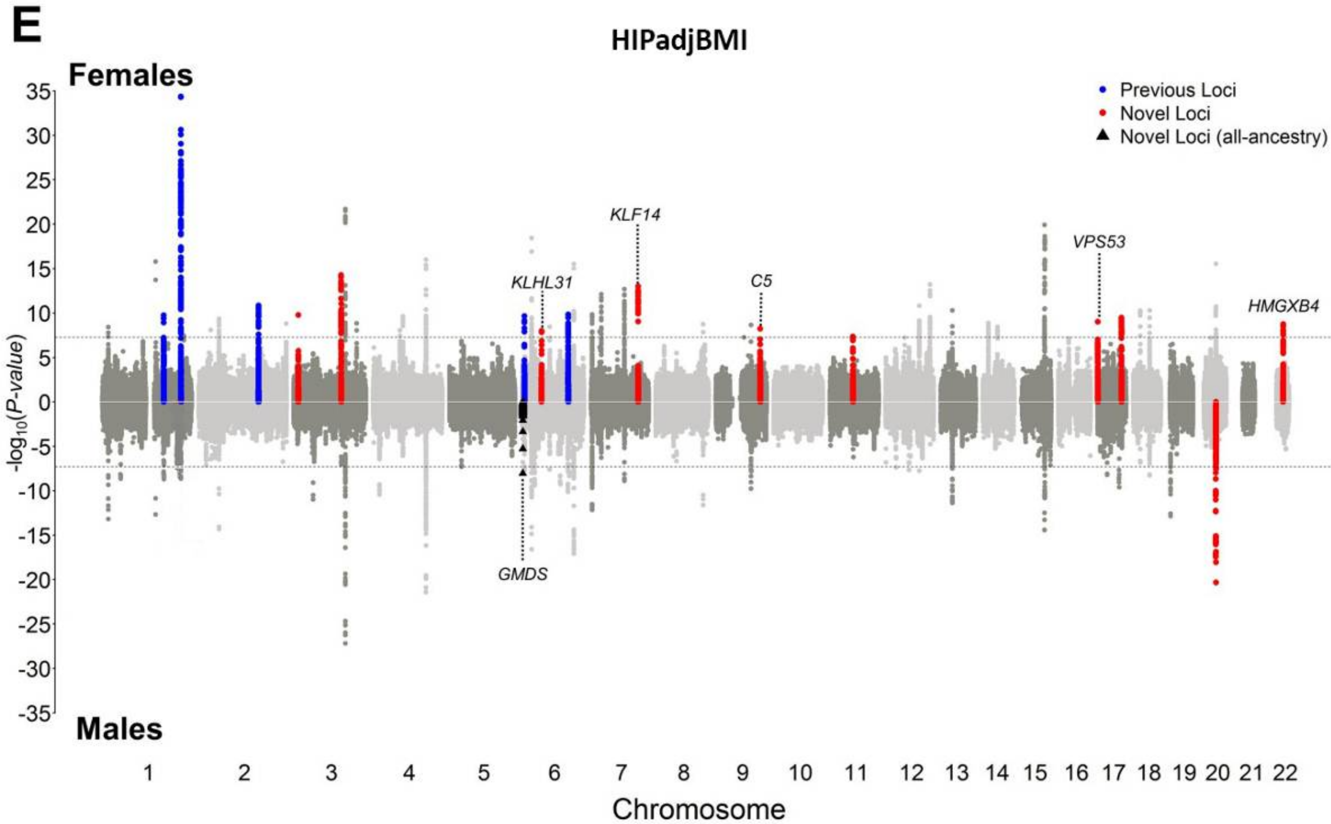

A
WHRadjBMI
Females
Males
Previous Loci
Novel Loci
Novel Loci (all-ancestry)
-log10(P-value)
Chromosome
GORAB
DCST2
PLXND1
HMGA1
MAP3K1
FAM13A
NMU
LEKR1
MAP3K1*
SNX10
NKX2-6
MSC
SFXN2
ABCA1
MACROD1-VEGFB
CCDC92
CMIP
PEMT
KCNJ2
BCL2
EYA2
GDF5

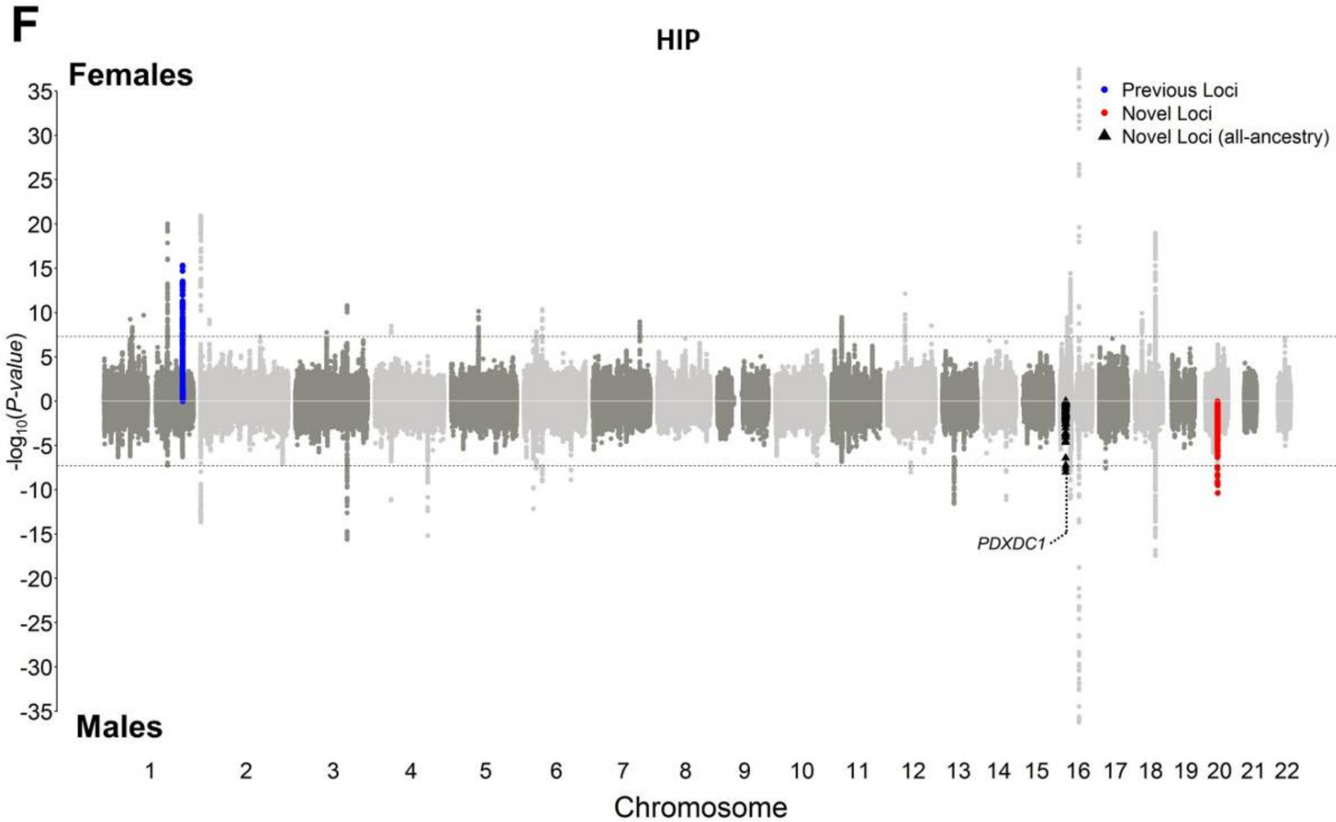

B
WHR
Females
Males
Previous Loci
Novel Loci
CNTN5
GPC6
-log10(P-value)
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome


C
WCadjBMI
Females
Males
Previous Loci
Novel Loci
Novel Loci (all-ancestry)
-log10(P-value)
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
OR2W5-NLRP3
ARL15
CCNJL
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Chromosome

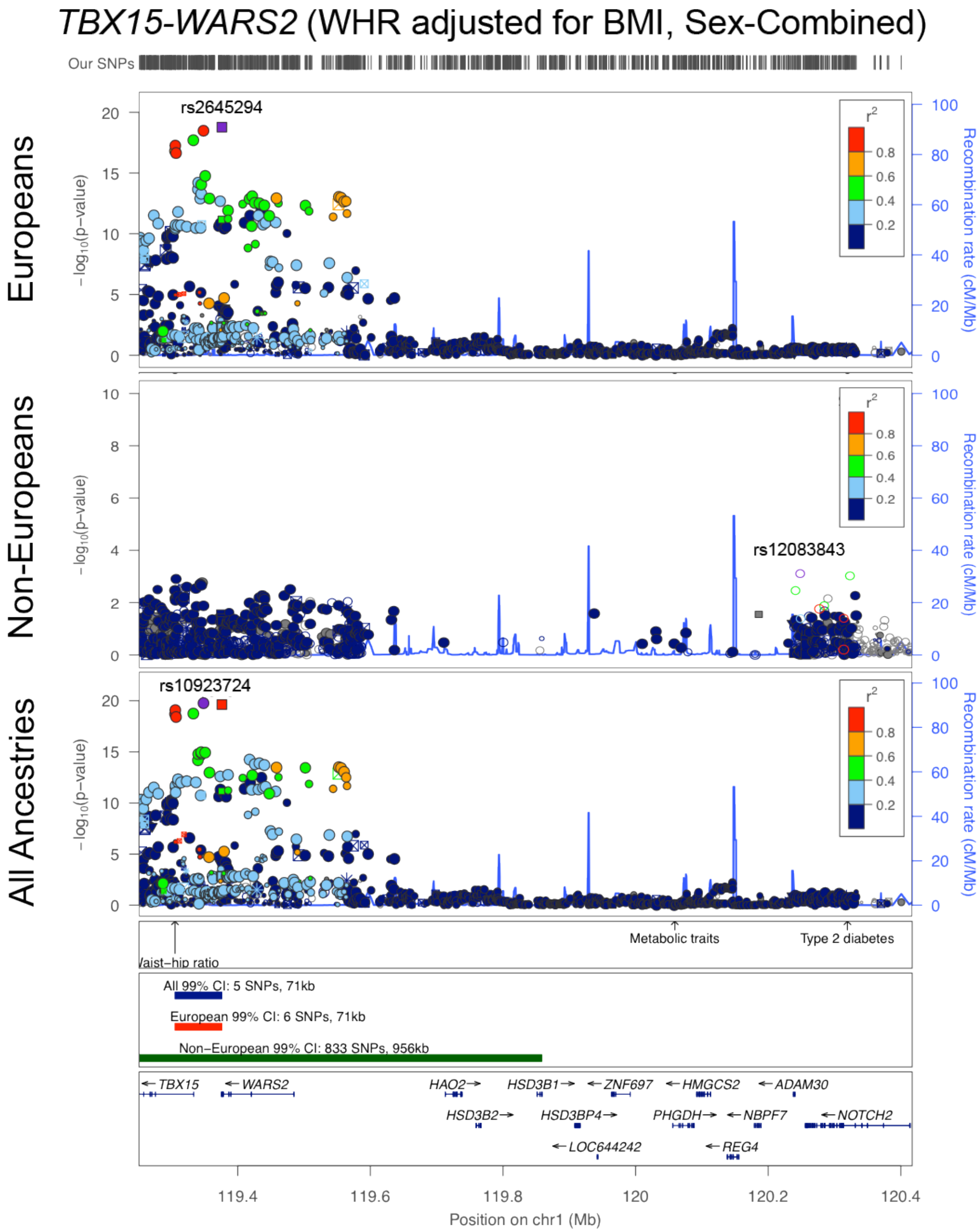


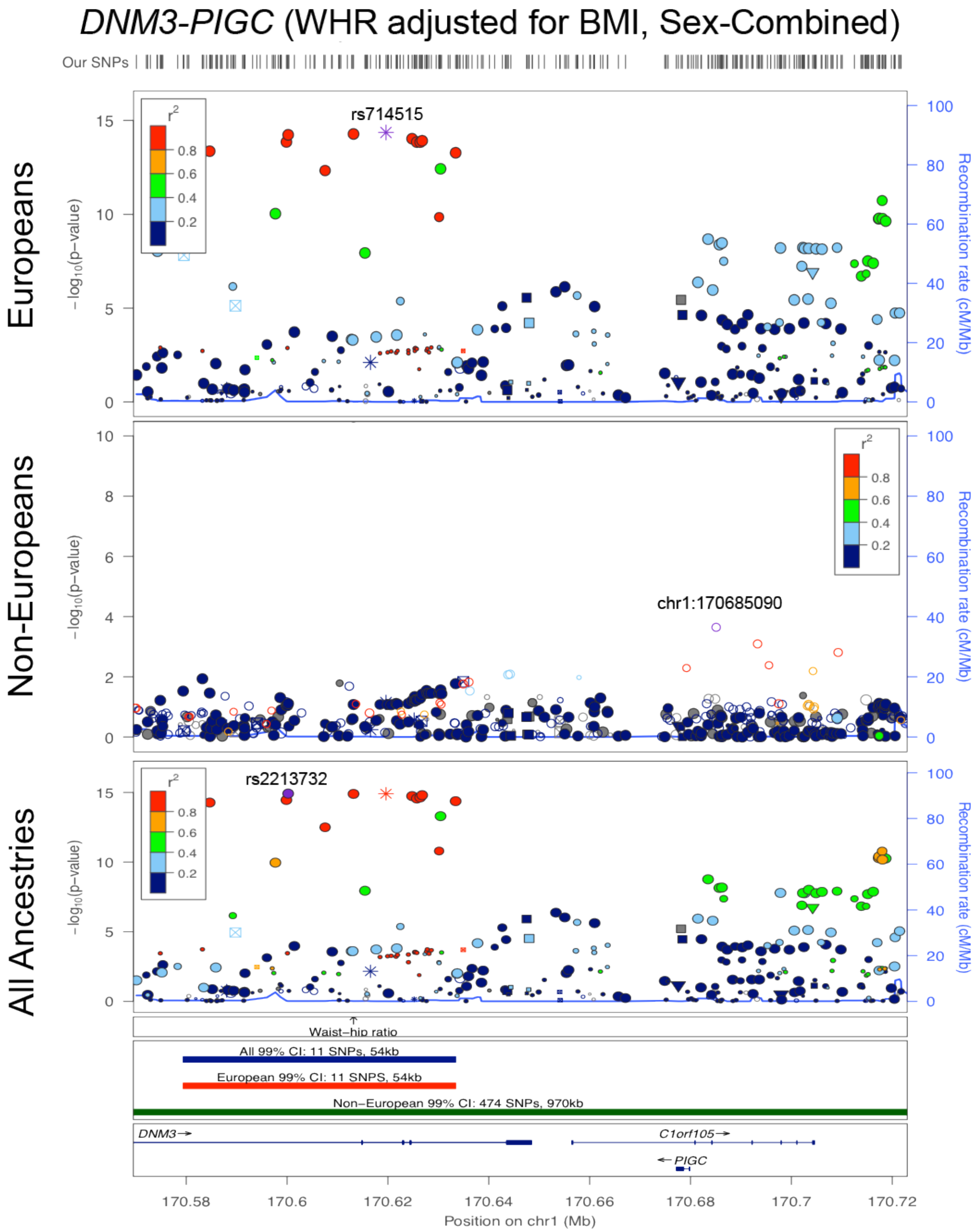
D
WC
Females
Males
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-log10(P-value)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome

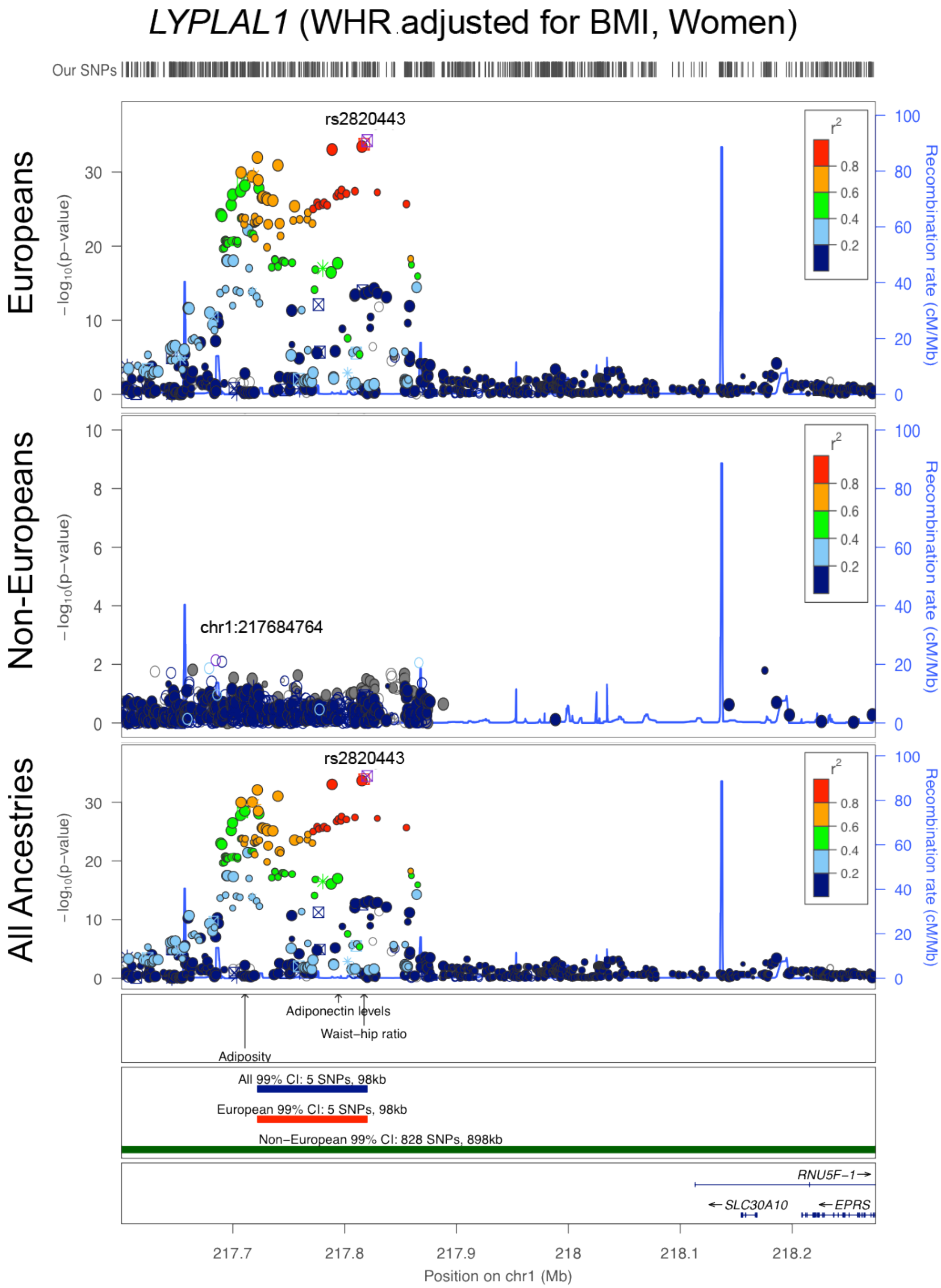

E
HIPadjBMI
Females
Males
Previous Loci
Novel Loci
Novel Loci (all-ancestry)
KLF14
VPS53
KLHL31
C5
HMGXB4
GMDS
-log10(P-value)
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome


F
HIP
Females
Males
Previous Loci
Novel Loci
Novel Loci (all-ancestry)
-log10(P-value)
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
PDXDC1
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome

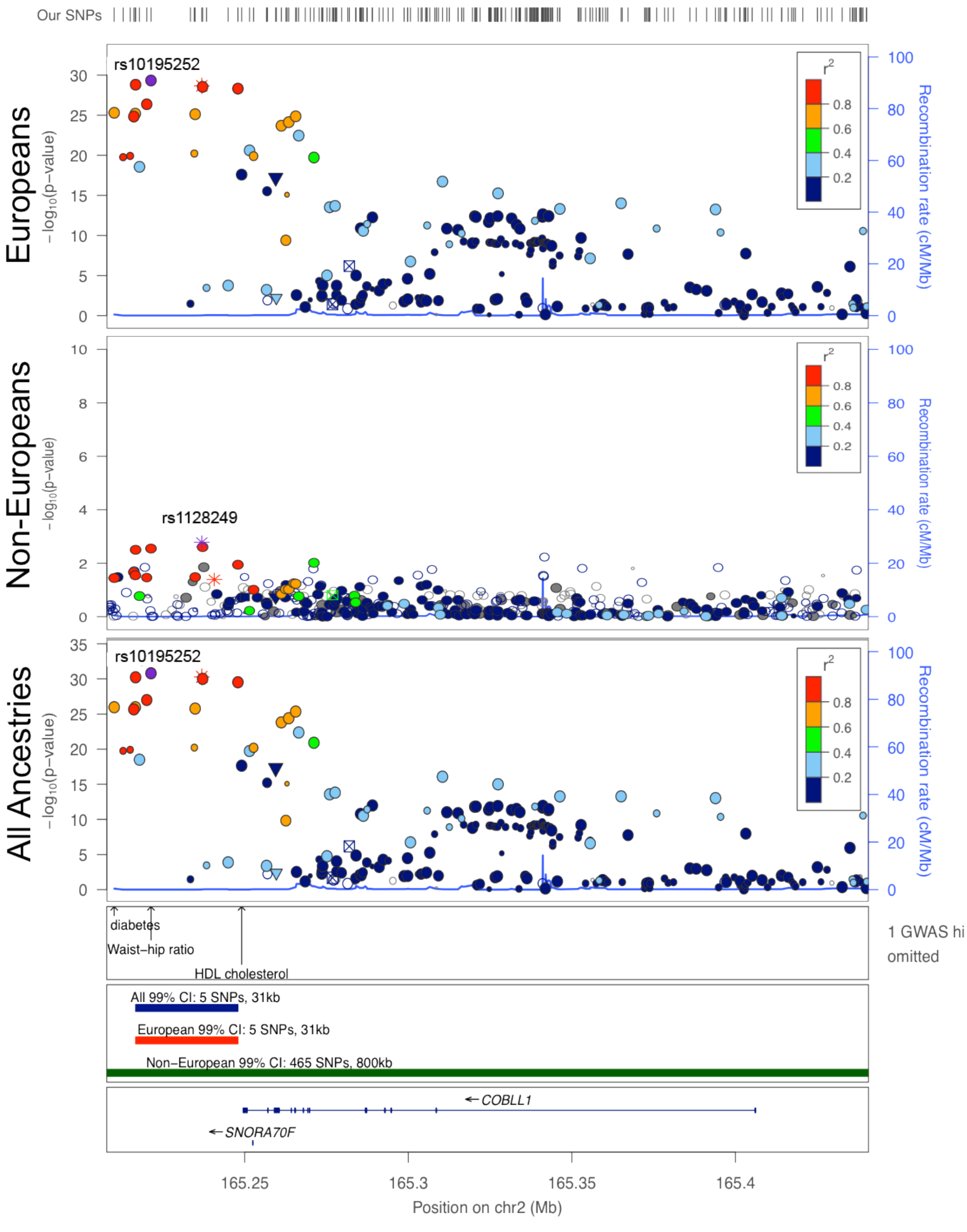
Supplementary Figure 5 | Regional association plots of WHRadjBMI signals covered with fine-mapping density on the Metabochip. Plots of 17 waist-hip ratio adjusted for body mass index (WHRadjBMI) signals from **Table 1** are arranged in chromosomal order.


TBX15-WARS2 (WHR adjusted for BMI, Sex-Combined)
Our SNPs
Europeans
Non-Europeans
All Ancestries
rs2645294
rs12083843
rs10923724
-log10(p-value)
Recombination rate (cM/Mb)
r2
Waist-hip ratio
Metabolic traits
Type 2 diabetes
All 99% CI: 5 SNPs, 71kb
European 99% CI: 6 SNPs, 71kb
Non-European 99% CI: 833 SNPs, 956kb
TBX15
WARS2
HAO2
HSD3B1
ZNF697
HMGCS2
ADAM30
HSD3B2
HSD3BP4
PHGDH
NBPF7
NOTCH2
LOC644242
REG4
Position on chr1 (Mb)

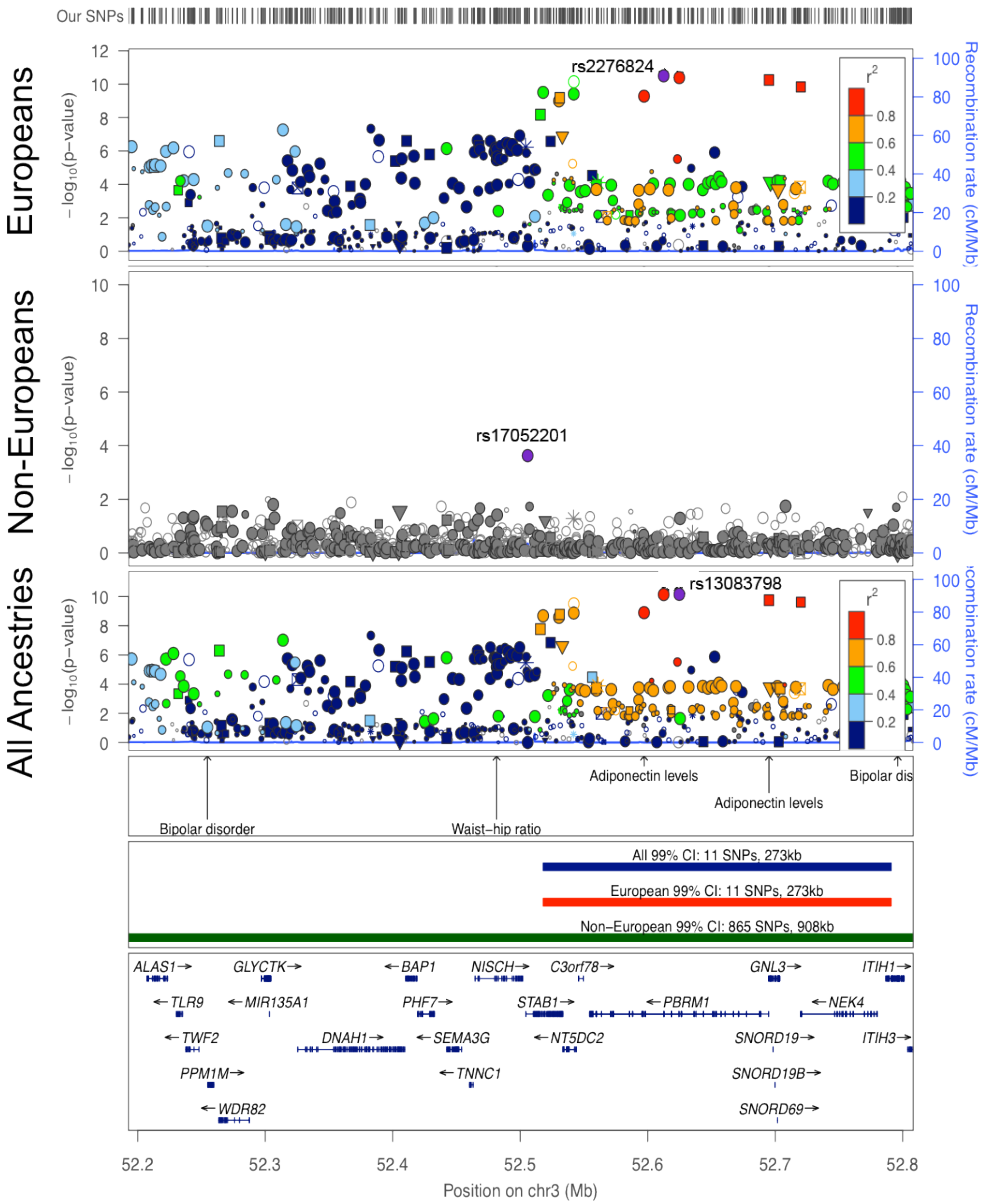

DNM3-PIGC (WHR adjusted for BMI, Sex-Combined)
Our SNPs
Europeans
Non-Europeans
All Ancestries
rs714515
chr1:170685090
rs2213732
−log10(p−value)
Recombination rate (cM/Mb)
Waist−hip ratio
All 99% CI: 11 SNPs, 54kb
European 99% CI: 11 SNPS, 54kb
Non−European 99% CI: 474 SNPs, 970kb
DNM3
C1orf105
PIGC
Position on chr1 (Mb)

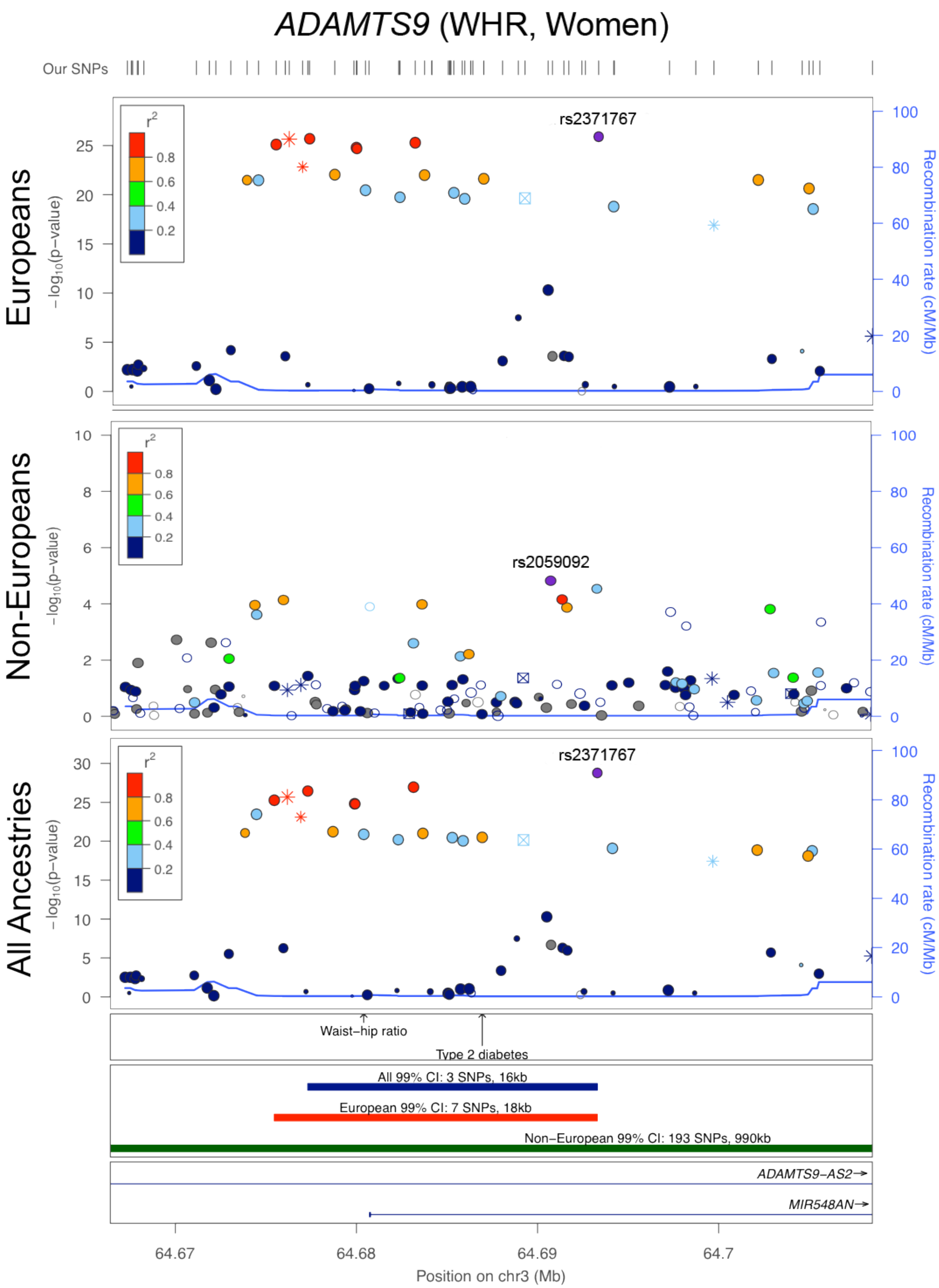

LYPLAL1 (WHR adjusted for BMI, Women)
Our SNPs
Europeans
rs2820443
Non-Europeans
chr1:217684764
All Ancestries
rs2820443
−log10(p-value)
Recombination rate (cM/Mb)
r2
Adiponectin levels
Waist−hip ratio
Adiposity
All 99% CI: 5 SNPs, 98kb
European 99% CI: 5 SNPs, 98kb
Non−European 99% CI: 828 SNPs, 898kb
RNU5F−1
SLC30A10
EPRS
Position on chr1 (Mb)

GRB14-COBLL1 (WHR adjusted for BMI, Women)

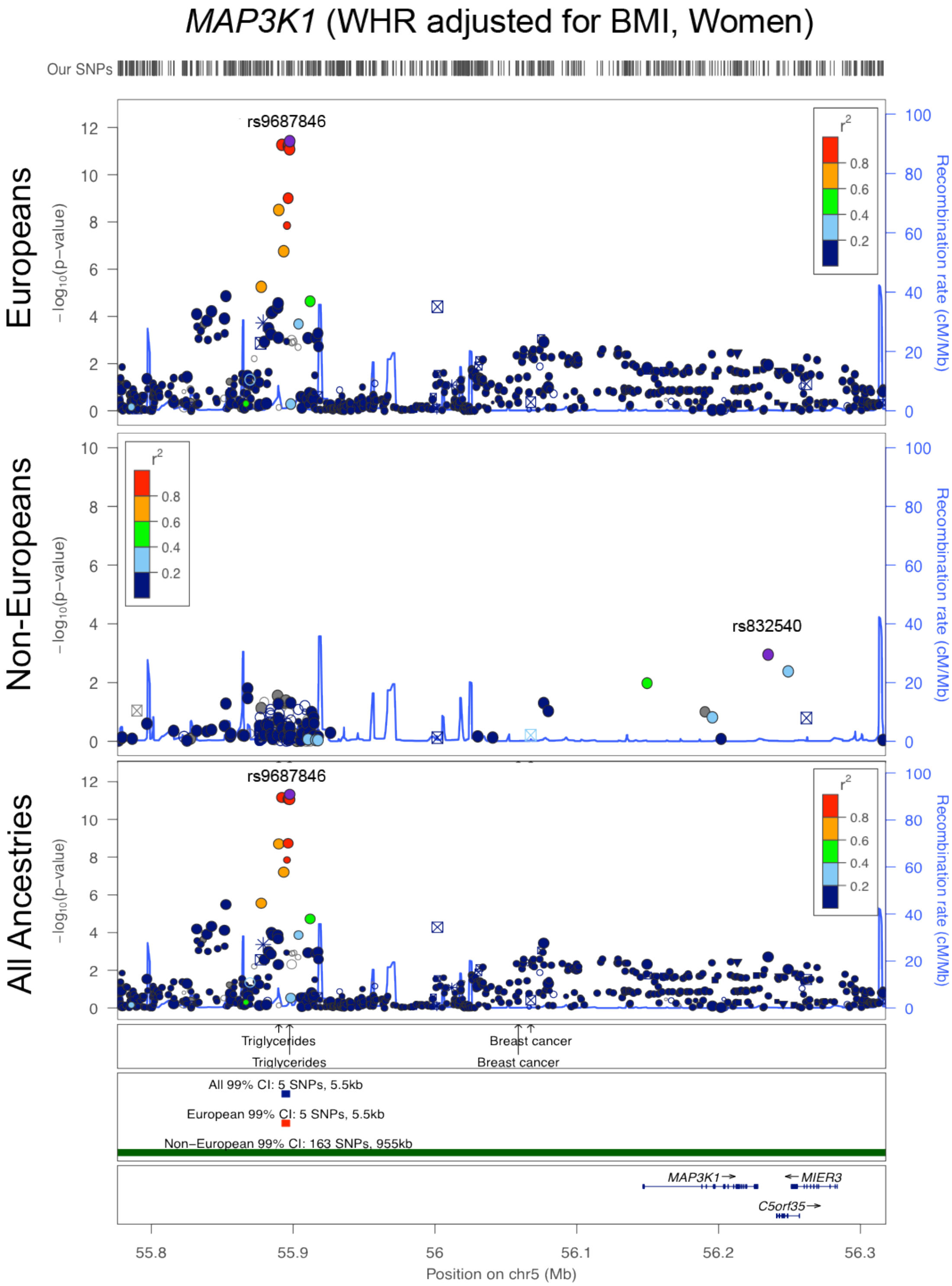


PBRM1 (WHR adjusted for BMI, Sex-Combined)

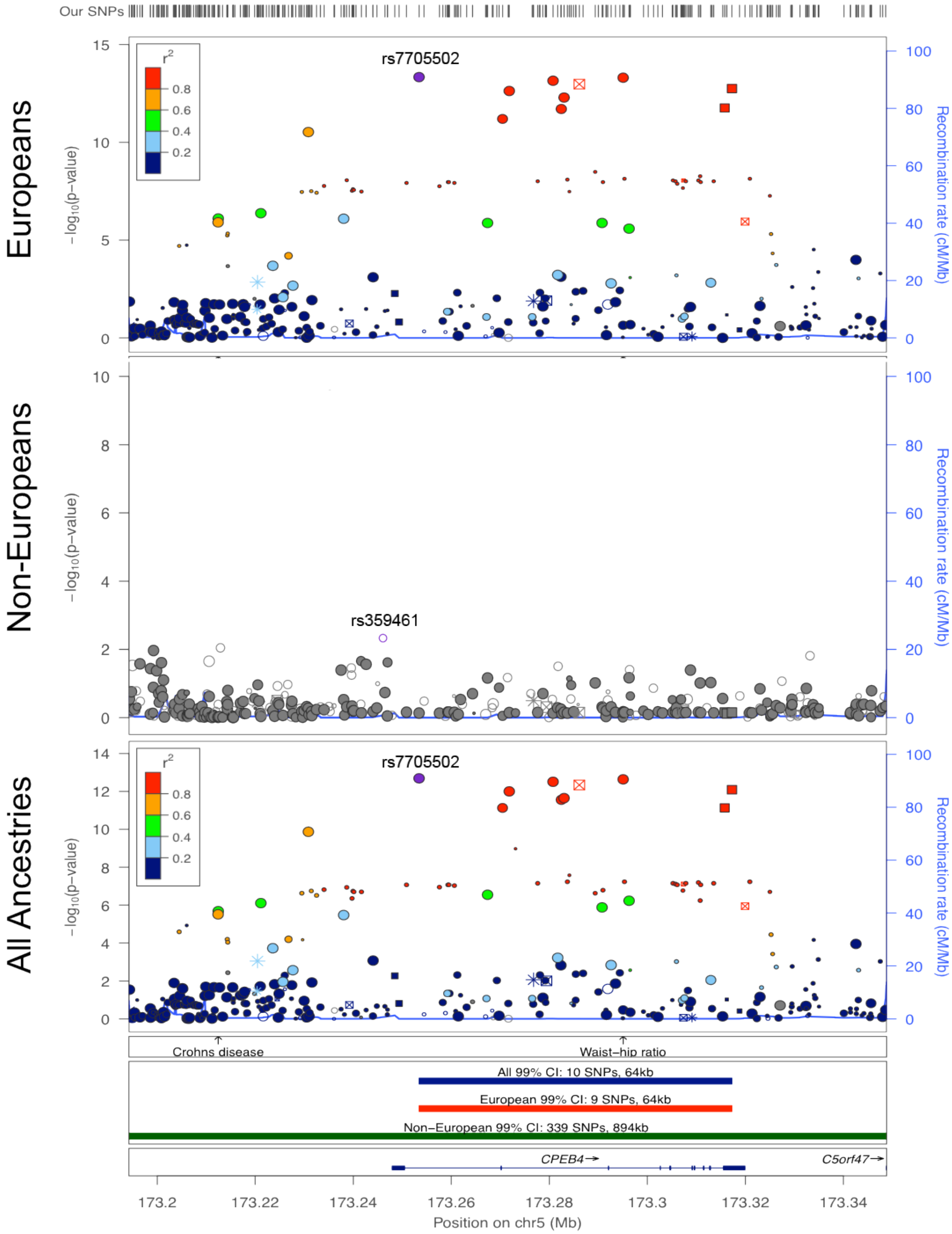


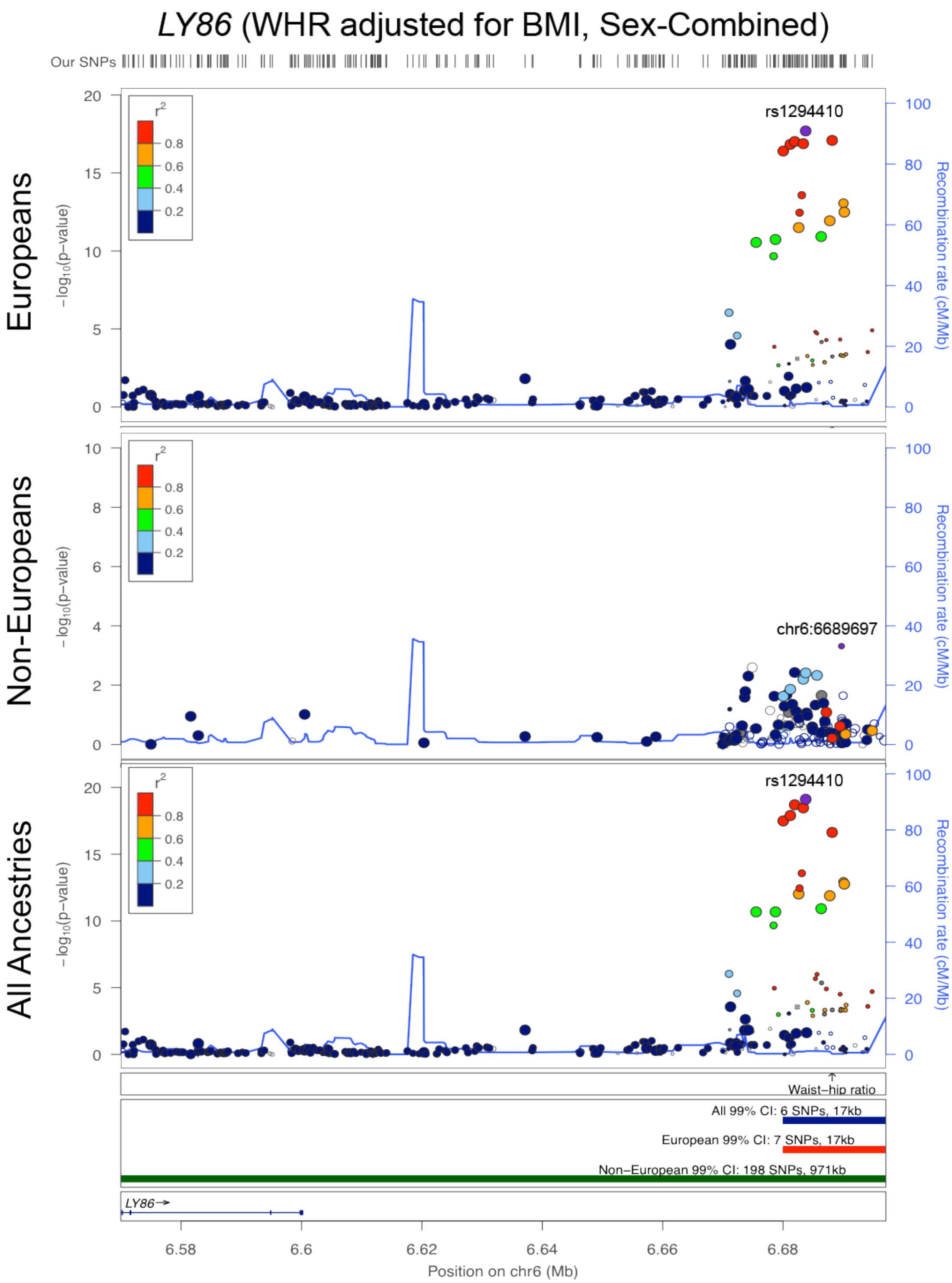


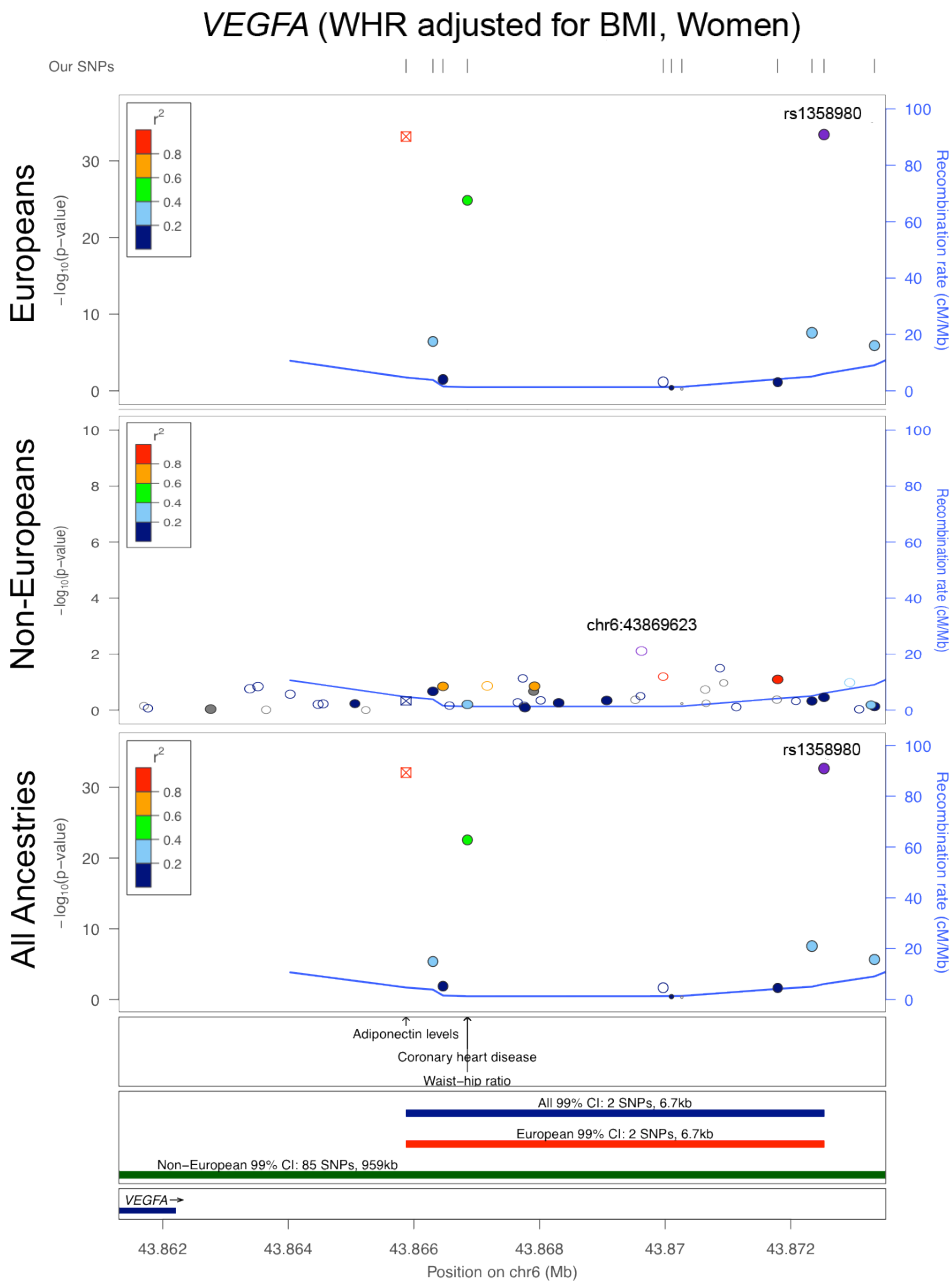
ADAMTS9 (WHR, Women)
Our SNPs
Europeans
Non-Europeans
All Ancestries
rs2371767
rs2059092
rs2371767
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
Waist−hip ratio
Type 2 diabetes
All 99% CI: 3 SNPs, 16kb
European 99% CI: 7 SNPs, 18kb
Non−European 99% CI: 193 SNPs, 990kb
ADAMTS9−AS2→
MIR548AN→
64.67
64.68
64.69
64.7
Position on chr3 (Mb)


MAP3K1 (WHR adjusted for BMI, Women)
Our SNPs
Europeans
rs9687846
−log10(p−value)
Recombination rate (cM/Mb)
Non-Europeans
rs832540
All Ancestries
rs9687846
Triglycerides
Triglycerides
Breast cancer
Breast cancer
All 99% CI: 5 SNPs, 5.5kb
European 99% CI: 5 SNPs, 5.5kb
Non−European 99% CI: 163 SNPs, 955kb
MAP3K1
MIER3
C5orf35
Position on chr5 (Mb)

CPEB4 (WHR adjusted for BMI, Sex-Combined)

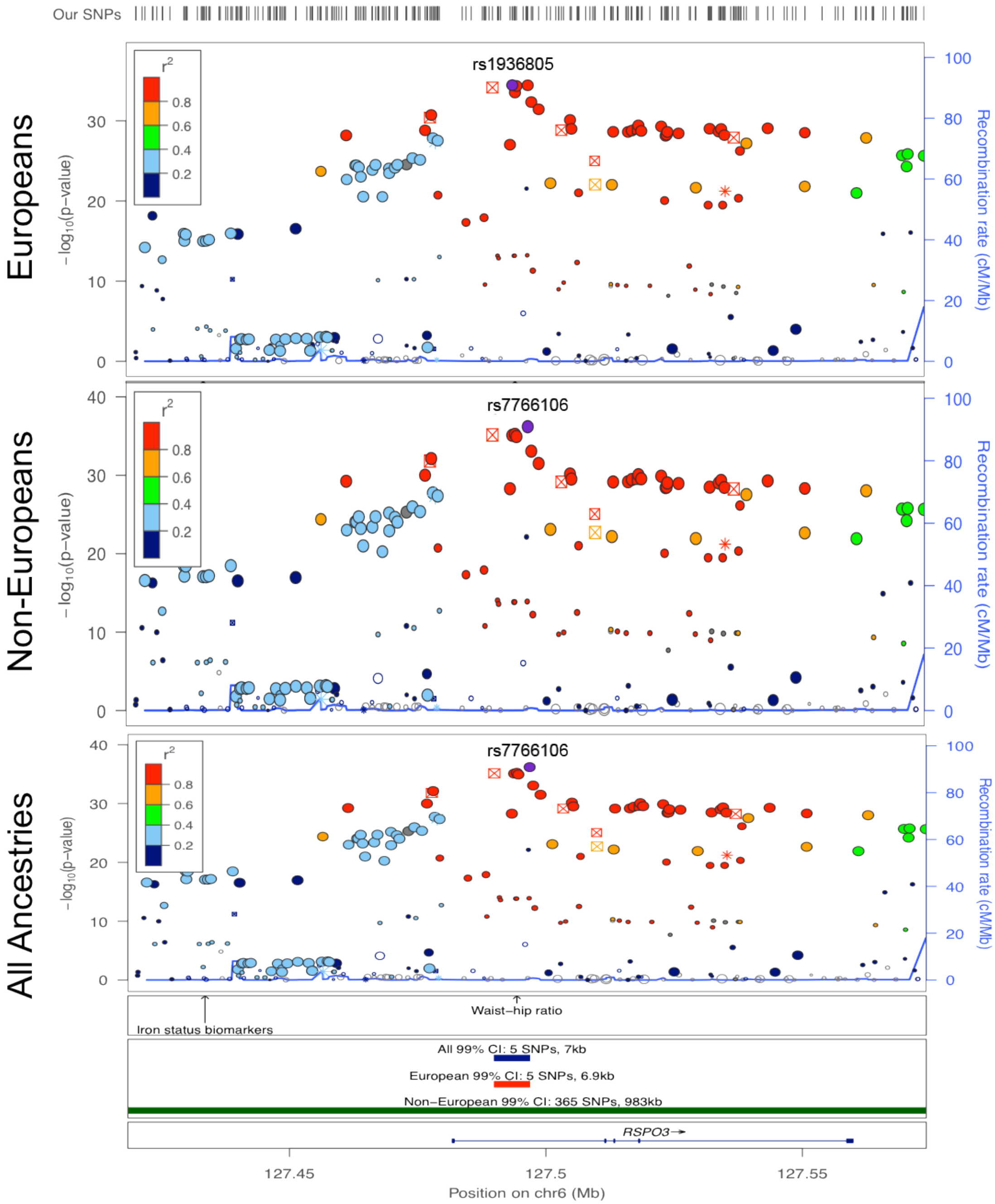


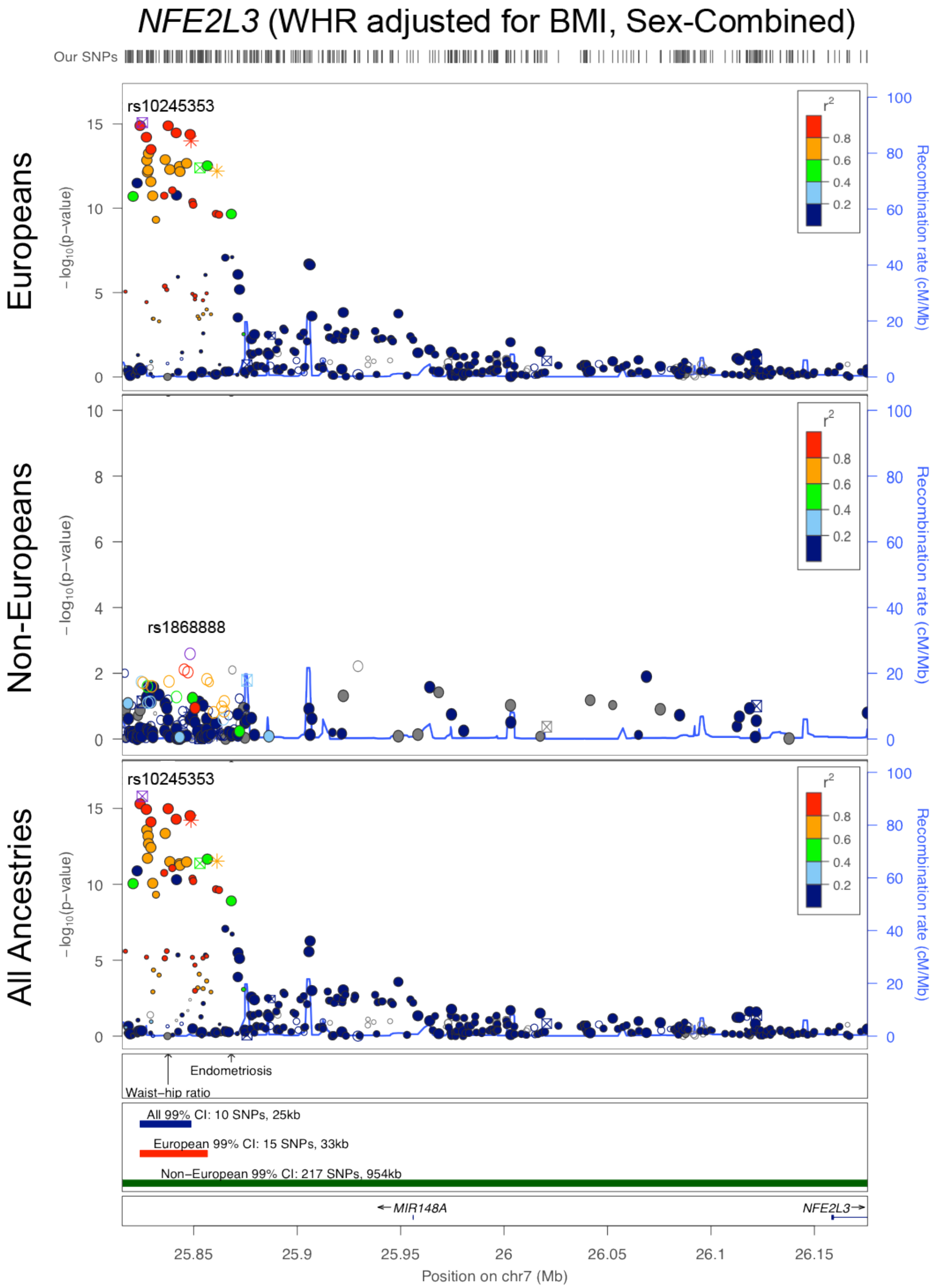

LY86 (WHR adjusted for BMI, Sex-Combined)
Our SNPs
Europeans
Non-Europeans
All Ancestries
−log10(p−value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
rs1294410
chr6:6689697
Waist−hip ratio
All 99% CI: 6 SNPs, 17kb
European 99% CI: 7 SNPs, 17kb
Non−European 99% CI: 198 SNPs, 971kb
LY86
6.58
6.6
6.62
6.64
6.66
6.68
Position on chr6 (Mb)

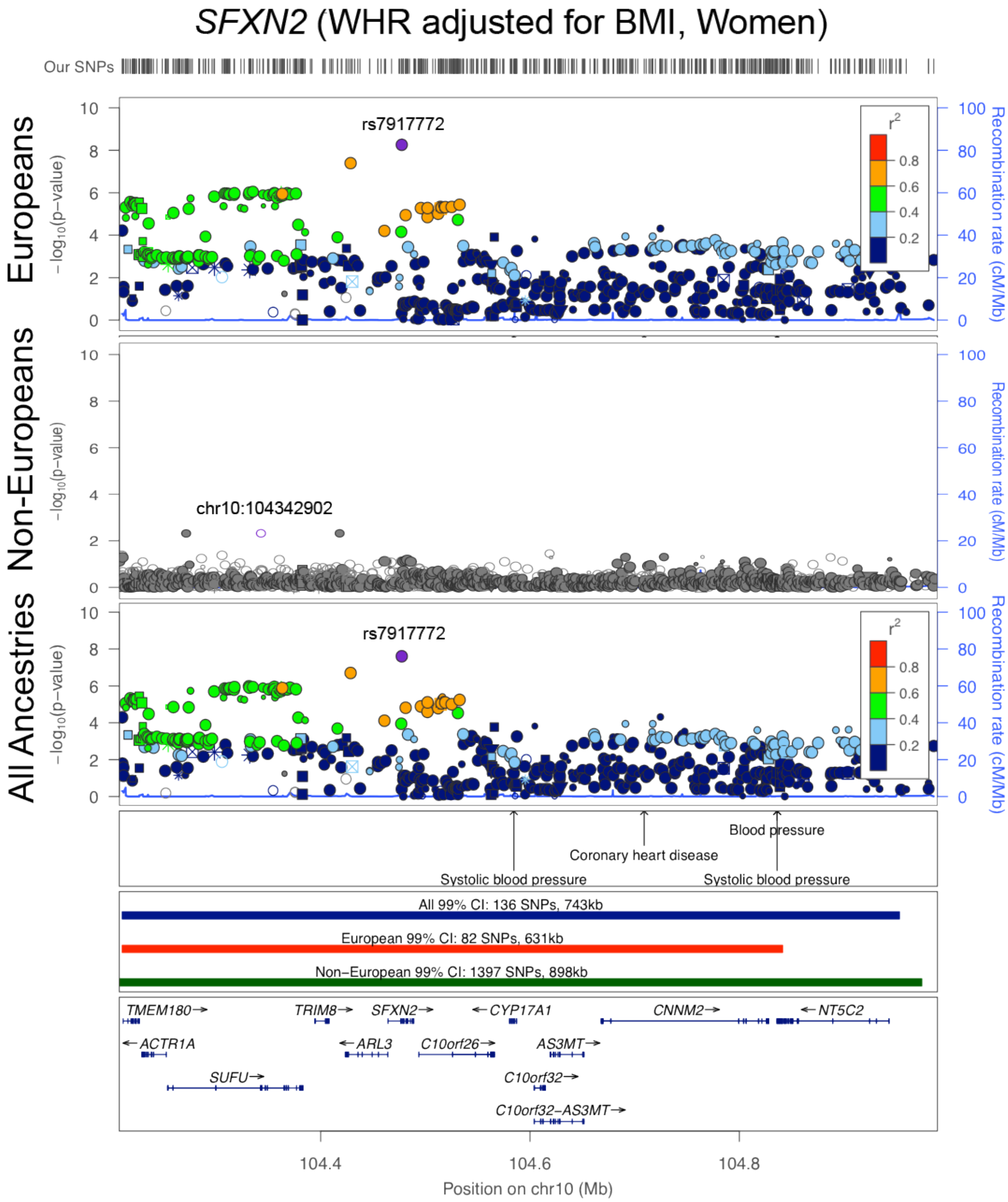


VEGFA (WHR adjusted for BMI, Women)
Our SNPs
Europeans
Non-Europeans
All Ancestries
−log10(p−value)
Recombination rate (cM/Mb)
rs1358980
chr6:43869623
r2
0.8
0.6
0.4
0.2
Adiponectin levels
Coronary heart disease
Waist−hip ratio
All 99% CI: 2 SNPs, 6.7kb
European 99% CI: 2 SNPs, 6.7kb
Non−European 99% CI: 85 SNPs, 959kb
VEGFA
43.862
43.864
43.866
43.868
43.87
43.872
Position on chr6 (Mb)

RSPO3 (WHR adjusted for BMI, Sex-Combined)

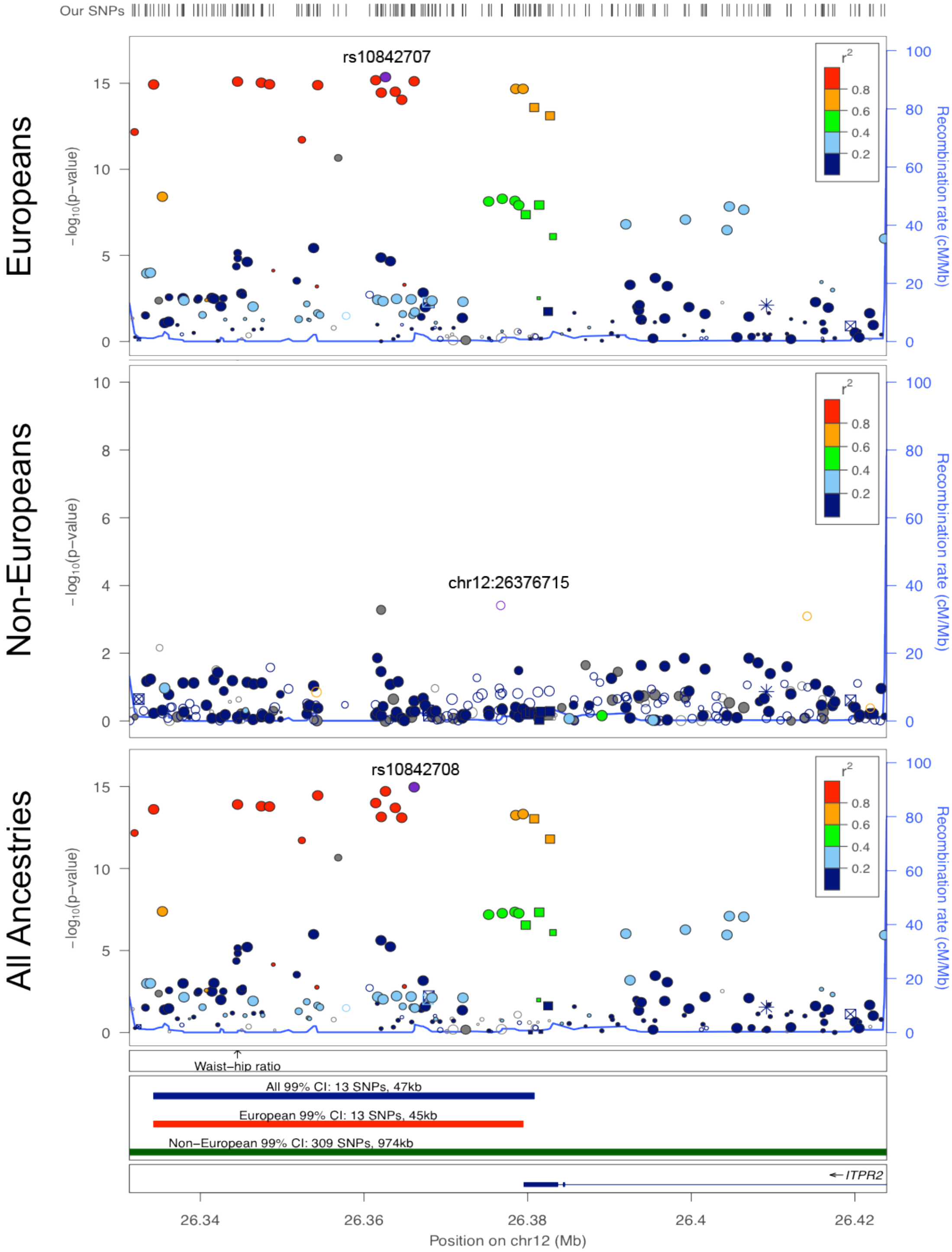


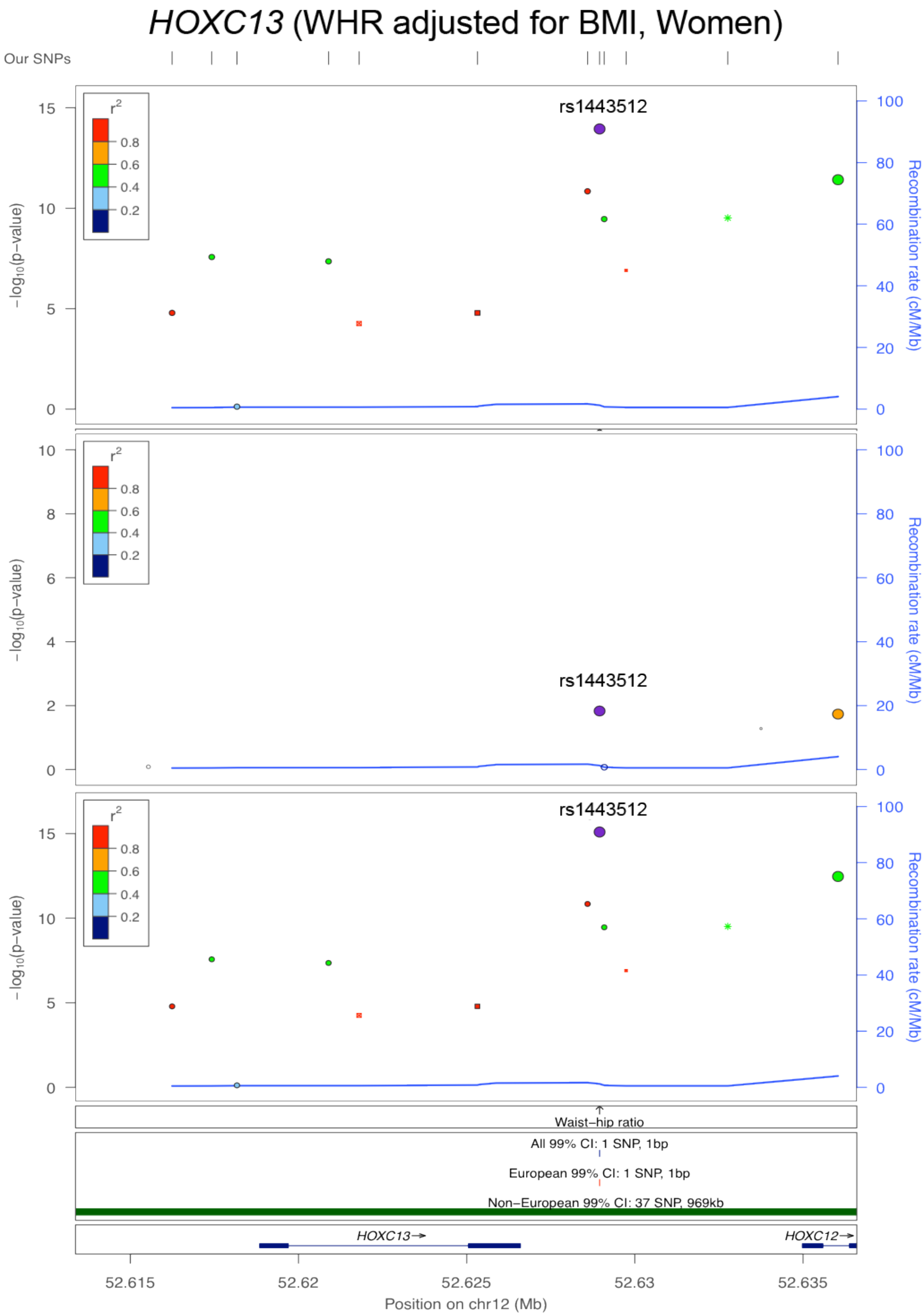

NFE2L3 (WHR adjusted for BMI, Sex-Combined)
Our SNPs
Europeans
Non-Europeans
All Ancestries
rs10245353
rs1868888
−log10(p−value)
Recombination rate (cM/Mb)
r2
Endometriosis
Waist−hip ratio
All 99% CI: 10 SNPs, 25kb
European 99% CI: 15 SNPs, 33kb
Non−European 99% CI: 217 SNPs, 954kb
MIR148A
NFE2L3
Position on chr7 (Mb)

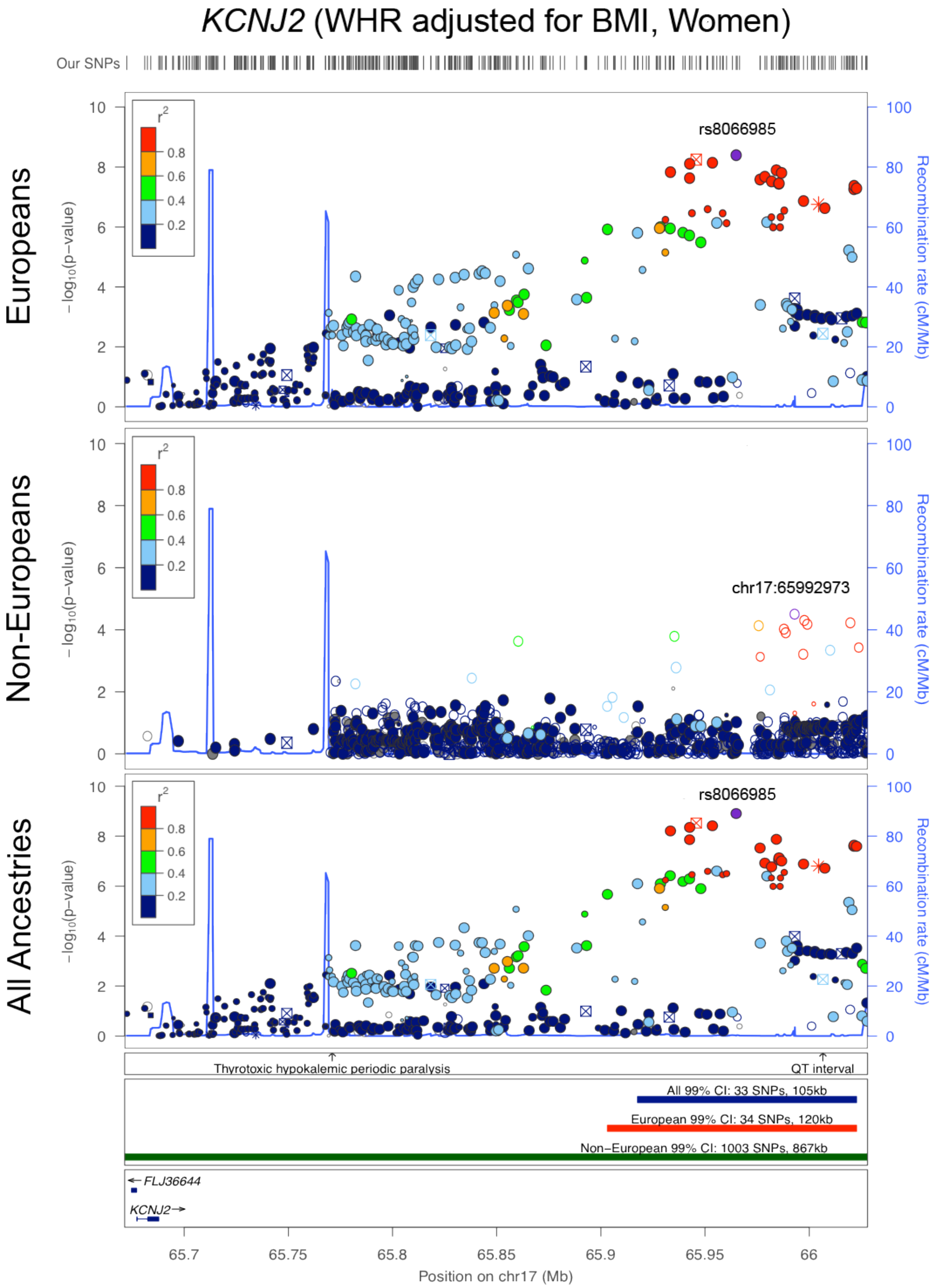


SFXN2 (WHR adjusted for BMI, Women)
Our SNPs
Europeans
Non-Europeans
All Ancestries
−log10(p−value)
Recombination rate (cM/Mb)
rs7917772
chr10:104342902
r2
Blood pressure
Coronary heart disease
Systolic blood pressure
Systolic blood pressure
All 99% CI: 136 SNPs, 743kb
European 99% CI: 82 SNPs, 631kb
Non−European 99% CI: 1397 SNPs, 898kb
TMEM180
TRIM8
SFXN2
CYP17A1
CNNM2
NT5C2
ACTR1A
ARL3
C10orf26
AS3MT
SUFU
C10orf32
C10orf32−AS3MT
Position on chr10 (Mb)

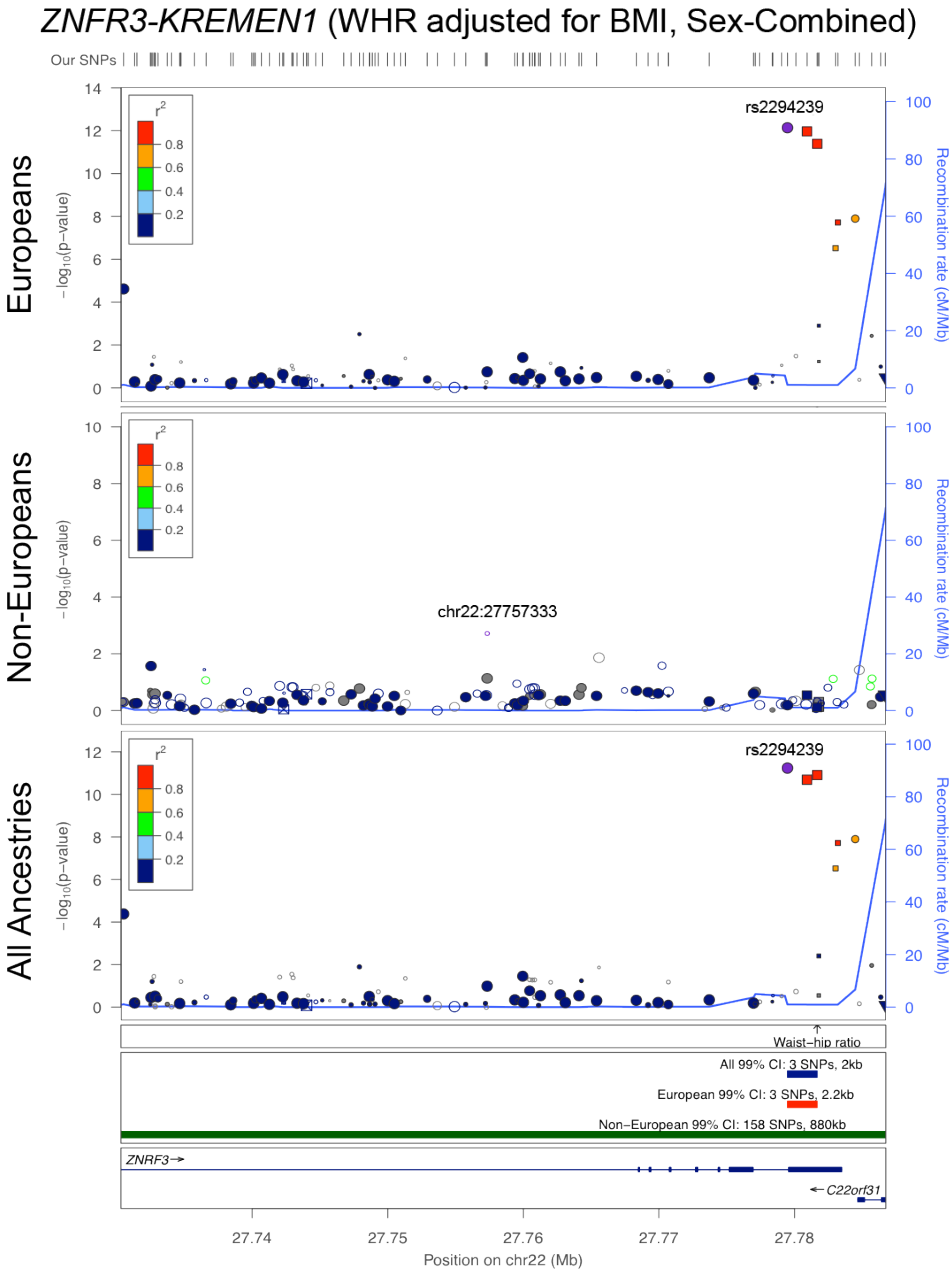
ITPR2-SSPN (WHR adjusted for BMI, Sex-Combined)




HOXC13 (WHR adjusted for BMI, Women)
Our SNPs
rs1443512
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
Waist−hip ratio
All 99% CI: 1 SNP, 1bp
European 99% CI: 1 SNP, 1bp
Non−European 99% CI: 37 SNP, 969kb
HOXC13→
HOXC12→
52.615
52.62
52.625
52.63
52.635
Position on chr12 (Mb)



KCNJ2 (WHR adjusted for BMI, Women)
Our SNPs
Europeans
Non-Europeans
All Ancestries
−log10(p−value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
rs8066985
chr17:65992973
Thyrotoxic hypokalemic periodic paralysis
QT interval
All 99% CI: 33 SNPs, 105kb
European 99% CI: 34 SNPs, 120kb
Non−European 99% CI: 1003 SNPs, 867kb
FLJ36644
KCNJ2
65.7
65.75
65.8
65.85
65.9
65.95
66
Position on chr17 (Mb)



ZNFR3-KREMEN1 (WHR adjusted for BMI, Sex-Combined)
Our SNPs
Europeans
Non-Europeans
All Ancestries
−log10(p-value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
rs2294239
chr22:27757333
rs2294239
Waist−hip ratio
All 99% CI: 3 SNPs, 2kb
European 99% CI: 3 SNPs, 2.2kb
Non−European 99% CI: 158 SNPs, 880kb
ZNRF3→
←C22orf31
27.74
27.75
27.76
27.77
27.78
Position on chr22 (Mb)

Supplementary Tables

This document contains **Supplementary Tables 5, 6, 7, 9, 10, 12, 13, 14, 17, 20,** and **24**.

Supplementary Table 5 | Estimated narrow-sense age-adjusted heritability (h^2) for waist-related traits, height, weight, and body mass index

	Women						Men						Sex Difference *P*	
	Framingham Heart Study			TWINGENE			Framingham Heart Study			TWINGENE			FHS	TWINGENE
Traits	*n*	h^2 (SE)	*P*	*n*	h^2 (95% CI)	*P*	*n*	h^2 (SE)	*P*	*n*	h^2 (95% CI)	*P*	*P*	*P* value
WHRadjBMI	1,595	0.463 (0.10)	6.00E-07	6,471	0.558 (0.441, 0.595)	1.46E-14	1,446	0.188 (0.12)	5.11E-02	5,362	0.317 (0.145, 0.381)	8.23E-04	3.67E-03	1.04E-03
WHR	1,599	0.388 (0.10)	4.39E-05	6,704	0.577 (0.488, 0.612)	3.15E-18	1,452	0.315 (0.11)	1.22E-03	5,541	0.473 (0.289, 0.524)	5.10E-07	1.87E-01	4.30E-02
BMI	4,177	0.492 (0.04)	8.50E-47	6,515	0.702 (0.576, 0.730)	2.83E-93	3,528	0.586 (0.04)	1.56E-48	5,446	0.662 (0.595, 0.701)	4.65E-32	3.88E-01	4.28E-01
Height	4,181	0.999 (0.03)	1.25E-193	6,515	0.908 (0.811, 0.921)	2.31E-105	3,528	0.965 (0.03)	3.11E-136	5,446	0.885 (0.610, 0.901)	2.11E-57	3.23E-03	7.00E-03
Weight	4,177	0.550 (0.04)	9.56E-60	6,515	0.718 (0.688, 0.745)	3.14E-169	3,528	0.596 (0.04)	3.81E-51	5,446	0.711 (0.674, 0.744)	1.99E-118	5.64E-02	5.68E-01
WC	3,615	0.473 (0.04)	2.36E-38	6,738	0.661 (0.627, 0.693)	3.56E-28	3,233	0.549 (0.05)	8.62E-40	5,608	0.651 (0.601, 0.690)	4.60E-23	6.95E-02	6.79E-01
WCadjBMI	3,610	0.505 (0.04)	5.20E-43	6,496	0.595 (0.363, 0.633)	5.45E-13	3,227	0.572 (0.05)	3.39E-41	5,420	0.359 (0.195, 0.419)	5.59E-05	3.86E-02	1.82E-10
HIP	1,601	0.447 (0.09)	3.00E-07	6,718	0.675 (0.595, 0.706)	3.50E-32	1,455	0.416 (0.10)	1.10E-05	5,553	0.602 (0.521, 0.645)	2.60E-18	1.20E-02	8.49E-03
HIPadjBMI	1,597	0.495 (0.09)	6.37E-09	6,476	0.592 (0.519, 0.631)	2.61E-20	1,449	0.528 (0.10)	2.52E-08	5,369	0.451 (0.251, 0.505)	1.36E-06	9.05E-01	6.71E-05

Narrow-sense heritability estimated separately from the Framingham Heart Study and the TWINGENE study. SE, standard error; CI, confidence interval; WHR, waist-to-hip ratio; WC, waist circumference; HIP, hip circumference; adjBMI, adjusted for body mass index.

Supplementary Table 6 | Variance in WHRadjBMI explained by all current loci compared to only previously established loci

Loci Source	Sex-combined R^2	Male-specific R^2	Female-specific R^2	Data set	Phenotype Transformation
14 Heid *et al.* loci	1.03%[a]	0.46%[a]	1.34%[a]	Heid *et al.* (Follow-up studies)	Raw
14 Heid *et al.* loci	0.60%[b]	0.31%[b]	1.03%[b]	Heid *et al.* (Follow-up studies)	Inverse-normalized
2 Randall *et al.* loci (additional to Heid *et al.*)	0.05%[c]	0.02%[c]	0.12%[c]	Randall *et al.* (Follow-up studies)	Inverse-normalized
16 previously reported loci (14 Heid *et al.* + 2 Randall *et al.*)	0.66%[d]	0.28%[d]	1.27%[d]	This paper; all studies	Inverse-normalized
49 current loci	1.36%[e]	0.82%[e]	2.40%[e]	This paper; all studies	Inverse-normalized

The variance explained by all waist-hip ratio adjusted for body mass index (WHRadjBMI) loci reported in this paper compared to WHRadjBMI loci in two previous reports. [a]The 14 previously reported loci from Heid *et al.* [PMID: 20935629] as presented there based on meta-analyzed beta-estimates of follow-up studies (*N* > 110,000) using "raw" WHRadjBMI (i.e., residuals of WHR adjusted for BMI, age, age^2, and study-specific covariates, stratified by sex but not inverse normal transformed) using a model variance of that trait as observed in the population-based cross-sectional study KORA S3 (*N* = 3,996). [b]The 14 previously reported loci from Heid *et al.* [PMID: 20935629] using the same data as in (a) using the meta-analyzed beta estimates of the inverse normal transformed values of WHRadjBMI (thus Var(Y)=1). [c]The two additional reported loci from Randall *et al.* [PMID:23754948] (*PPARG* and *HSD17B4*) based on meta-analyzed beta-estimates of follow-up studies (*N* > 105,000) using inverse normal transformed values of WHRadjBMI (thus Var(Y)=1). [d]The 16 previously reported loci using the here presented data (*N* > 210,000) based on meta-analyzed beta-estimates of the inverse normal transformed values of WHRadjBMI (thus Var(Y)=1). [e]The 49 reported loci using the same data as in (c) also on inverse normal transformed values of WHRadjBMI (as in (c)).

Supplementary Table 7 | 99% credible intervals for fine-mapped waist-related loci

Trait	Analysis	Gene	Index SNP	Chr	Position (bp) NCBI build 36	Europeans only # of SNPs	Europeans only Distance (bp)	Non-Europeans # of SNPs	Non-Europeans Distance (bp)	All ancestries # of SNPs	All ancestries Distance (bp)
WHRadjBMI	Overall	***TBX15-WARS2***	rs2645294	1	119,376,110	6	70,745	833	956,454	5	70,745
WHRadjBMI	Overall	***DNM3-PIGC***	rs714515	1	170,619,613	11	54,038	474	969,517	11	54,038
WHRadjBMI	Overall	***PBRM1***	rs2276824	3	52,612,526	11	272,987	865	908,219	11	272,987
WHRadjBMI	Overall	***CPEB4***	rs7705502	5	173,253,421	9	63,849	339	894,027	10	63,849
WHRadjBMI	Overall	***LY86***	rs1294410	6	6,683,751	7	17,038	198	971,095	6	17,038
WHRadjBMI	Overall	***RSPO3***	rs1936805	6	127,493,809	5	6,890	365	982,689	5	6,890
WHRadjBMI	Overall	***NFE2L3***	rs10245353	7	25,825,139	15	32,536	217	954,173	10	24,650
WHRadjBMI	Overall	***ITPR2-SSPN***	rs10842707	12	26,362,631	13	45,153	309	974,009	13	46,515
WHRadjBMI	Overall	***ZNRF3-KREMEN1***	rs2294239	22	27,779,477	3	2,195	158	879,614	3	2,195
WHRadjBMI	Women	***LYPLAL1***	rs2820443	1	217,820,132	5	98,141	828	897,911	5	98,141
WHRadjBMI	Women	***COBLL1***	rs10195252	2	165,221,337	5	31,273	465	800,236	5	31,273
WHRadjBMI	Women	***ADAMTS9***	rs2371767	3	64,693,298	7	17,834	193	989,524	3	15,984
WHRadjBMI	Women	*MAP3K1*	rs9687846	5	55,897,651	5	5,520	163	954,728	5	5,520
WHRadjBMI	Women	***VEGFA***	rs1358980	6	43,872,529	2	6,656	85	959,317	2	6,656
WHRadjBMI	Women	*SFXN2*	rs7917772	10	104,477,433	82	631,096	1397	898,492	136	742,751
WHRadjBMI	Women	***HOXC13***	rs1443512	12	52,628,951	1	1	37	969,387	1	1
WHRadjBMI	Women	*KCNJ2*	rs8066985	17	65,964,940	34	119,579	1003	866,939	33	105,152
HIPadjBMI	Women	*KLF14*	rs13241538	7	130,090,402	22	34,374	130	968,985	22	34,374

Fine-mapping analysis was performed at loci with high-density coverage on the Metabochip, which included 17 waist-hip ratio adjusted for body mass index (WHRadjBMI) loci and one hip circumference adjusted for body mass index (HIPadjBMI) locus. Association summary statistics were used to define credible sets of variants with a high probability of containing the likely functional variant (see Methods). The number of SNPs in the credible sets and the distance in kilobases spanned by those variants are shown. The Metabochip does not include all known SNPs. Previously reported genome-wide associated loci from the Heid *et al.* (2010) paper are marked in bold.

Supplementary Table 9 | Genome-wide significant associations of waist-related SNPs with metabolic and anthropometric traits

Trait	WHRadjBMI SNPs with look-up *P* < 5 × 10^{-8}	Corresponding WHRadjBMI locus names	Other waist and hip trait SNPs with look-up *P* < 5 × 10^{-8}	Corresponding other waist and hip trait locus names
Type 2 diabetes (T2D)	1	*GRB14-COBLL1*	0	-
Fasting glucose (FG)	0	-	0	-
Fasting insulin adjusted for BMI (FIadjBMI)	2	*LYPLAL1,GRB14-COBLL1*	0	-
2-hour glucose (G120)	0	-	0	-
Diastolic blood pressure (DBP)	0	-	0	-
Systolic blood pressure (SBP)	0	-	0	-
Body mass index (BMI)	0	-	0	-
Height	7	*FGFR4, HMGA1, SFXN2, SMAD6, BMP2, GDF5, NFE2L3*	0	-
High-density lipoprotein cholesterol (HDL-C)	7	*FAM13A, MAP3K1, CCDC92, CMIP, GRB14-COBLL1, VEGFA, RSPO3*	1	*KLF14*
Low-density lipoprotein cholesterol (LDL-C)	2	*GRB14-COBLL1, PPARG*	0	-
Triglycerides (TG)	5	*MAP3K1, CCDC92, GRB14-COBLL1, PPARG, VEGFA*	1	*KLF14*
Adiponectin adjusted for BMI	3	*CCDC92, CMIP, PBRM1*	0	-
Nephropathy (in Chinese subjects)	0	-	0	-
Nephropathy (in Italian subjects)	0	-	0	-
Estimated glomerular filtration rate of creatinine (eGFRcrea)	0	-	0	-
Chronic kidney disease (CKD)	0	-	0	-
Urine albumin-to-creatinine ratio (UACR)	0	-	0	-
Endometriosis	0	-	0	-
Coronary artery disease (CAD)	0	-	0	-
Menopause	0	-	0	-
Menarche	0	-	0	-
Femoral neck bone mineral density (FN-BMD)	0	-	0	-

Trait	WHRadjBMI SNPs with look-up $P < 5 \times 10^{-8}$	Corresponding WHRadjBMI locus names	Other waist and hip trait SNPs with look-up $P < 5 \times 10^{-8}$	Corresponding other waist and hip trait locus names
Lumbar spine bone mineral density (LS-BMD)	0	-	0	-

This table summarizes the cross-trait association data as provided by other consortia. Waist-hip ratio adjusted for body mass index (WHRadjBMI) SNPs and locus names refer to SNPs presented on **Table 1.** Other waist and hip trait SNPs refer to the SNPs presented on **Table 3.** *KLF14* is a hip circumference adjusted for body mass index (HIPadjBMI) locus.

Supplementary Table 10 | Joint associations of 39 WHRadjBMI SNPs with metabolic and anthropometric traits

Trait	# of SNPs	β	SE	*P*
Type 2 diabetes (T2D)	39	**0.502**	0.077	**6.3E-11**
Fasting glucose (FG)	39	**0.061**	0.014	**6.1E-06**
Fasting insulin adjusted for BMI (FIadjBMI)	39	**0.226**	0.013	**1.7E-64**
2-hour glucose (G120)	39	0.221	0.079	5.0E-03
Diastolic blood pressure (DBP)	39	**1.450**	0.405	**3.6E-04**
Systolic blood pressure (SBP)	39	**2.470**	0.639	**1.1E-04**
Body mass index (BMI)	39	**-0.217**	0.020	**2.0E-28**
Height	39	-0.010	0.019	0.62
High-density lipoprotein cholesterol (HDL-C)	39	**-0.356**	0.023	**1.1E-55**
Low-density lipoprotein cholesterol (LDL-C)	39	**0.157**	0.024	**1.1E-10**
Total cholesterol	39	**0.131**	0.024	**4.7E-08**
Triglycerides (TG)	39	**0.366**	0.022	**2.7E-65**
Adiponectin	39	**-0.351**	0.029	**1.5E-34**
Endometriosis	36	-0.284	0.291	0.33
Nephropathy (in Chinese subjects)	35	0.192	0.445	0.67
Nephropathy (in Italian subjects)	34	0.264	0.398	0.51
Estimated glomerular filtration rate of creatinine (eGFRcrea)	39	0.010	0.007	0.14
Chronic kidney disease (CKD)	39	-0.122	0.135	0.37
Urine albumin-to-creatinine ratio (UACR)	39	-0.026	0.059	0.67
Menopause	39	0.211	0.193	0.28
Menarche	39	0.030	0.048	0.53
Coronary artery disease (CAD)	38	0.041	0.058	0.48
Femoral neck bone mineral density (FN-BMD)	39	-0.002	0.053	0.98
Lumbar spine bone mineral density (LS-BMD)	39	-0.011	0.057	0.85

This table shows the results of a meta-regression of beta (β) estimates of the 39 waist-hip ratio adjusted for body mass index (WHRadjBMI)-increasing alleles that exhibit genome-wide significant association in the sex-combined analysis with beta estimates of metabolic traits from other consortia (DIAGRAM, MAGIC, ICBP, GLGC, ADIPOgen, IEC, IgAN-Chinese, IgAN-Italian, CKDgen, ReproGEN and CARDIoGRAM). Significant associations ($P < 0.05 / 24$) are marked in bold.

Supplementary Table 12 | Candidate functional nonsynonymous variants

Trait	Index SNP	Proxy SNP	r^2	Effect allele	Non-effect allele	Distance (bp)	Coding impact	Gene	Gene/transcript annotation
WHRadjBMI	rs224333	rs224331	0.96	A	C	1,575	nonsynonymous	*GDF5*	NM_000557p.S276A
HIPadjBMI	rs1053593	rs1053593	-	G	T	0	nonsynonymous	*HMGXB4*	NM_001003681:p.G165V
WCadjBMI	rs1664789	rs1135999	0.89	A	G	2,503	nonsynonymous	*NTAN1*	NM_173474:p.S287P
WCadjBMI	rs1664789	rs1136001	0.89	G	T	2,515	nonsynonymous	*NTAN1*	NM_173474p.H283N

Variants identified in 1000G CEU individuals annotated as nonsynonymous and in linkage disequilibrium (r^2) with index SNPs. WHR, waist-to-hip ratio; WC, waist circumference; HIP, hip circumference; adjBMI, adjusted for body mass index.

Supplementary Table 13 | CNV-tagging variants associated with waist traits in sex-combined European-ancestry meta-analyses

Trait	CNV-tagging SNP	Chr	Position (bp)	Nearby Gene	CNV name	SNP-trait association sex-combined P[a]	Nearest index SNP from waist trait association results	r^2 between CNV tagging SNP and index SNP[b]
WHRadjBMI	rs1294421	6	6,688,148	*LY86*	CNVR2760.1	**8.16E-18**	rs1294410	0.83
WHRadjBMI	rs3733034	3	52,927,473	*SFMBT1*	RR_CNV_269	1.75E-06	rs2276824	0.11
WHRadjBMI	rs1150753	6	32,167,845	*TNXB*	CNVR2843.1	4.45E-06	rs7759742	-
HIPadjBMI	rs1543302	22	33,976,861	*HMGXB4*	CNVR8147.1	1.13E-07	rs1053593	0.86

A total of 6,200 copy number variant (CNV)-tagging SNPs were looked up in sex-combined SNP association results with waist traits. Positions are shown in NCBI build 36. [a]The SNP-trait P value achieving genome-wide significance is shown in **bold** and was described previously in Heid *et al.* (2010). The other P values are significant at $P < 0.05 / 6,200$. [b]Linkage disequilbirium (LD) r^2 values were based on 1000G Pilot1 CEU dataset. CNVs in the *SFMBT1* and *TNXB* gene regions are in low LD with index SNPs from main results and may represent independent or partially independent signals from these regions. Waist-hip ratio adjusted for body mass index (WHRadjBMI); hip circumference adjusted for body mass index (HIPadjBMI).

Supplementary Table 14 | Candidate variants at transcription start sites

SNP	Chr	Position (bp)	Distance to nearest TSS (bp)	Nearest transcript
New WHRadjBMI Loci				
rs62310884	4	56,458,400	-21	*PDCL2*
rs5007262	6	32,379,011	500	*BTNL2*
rs5007261	6	32,379,031	480	*BTNL2*
rs5007260	6	32,379,047	464	*BTNL2*
rs5007259	6	32,379,101	410	*BTNL2*
rs5007258	6	32,379,239	272	*BTNL2*
rs6906730	6	32,379,445	66	*BTNL2*
rs6911383	6	32,379,682	-171	*BTNL2*
rs7801581	7	27,223,771	-365	*HOXA11-AS*
rs17427875	7	27,225,558	406	*HOXA11-AS*
rs1550279	8	23,600,854	-299	*RP11-213G6.2*
rs11680316	2	188,135,298	233	*U6*
rs11057396	12	124,419,062	469	*DNAH10OS*
rs11057397	12	124,419,728	-197	*DNAH10OS*
rs3186071	12	124,429,279	-363	*CCDC92*
rs11835839	12	124,431,049	271	*CCDC92*
rs34180676	12	124,431,519	-199	*CCDC92*
rs7966192	12	124,431,701	-381	*CCDC92*
rs12823740	12	124,458,002	161	*ZNF664*
rs1075403	19	18,384,950	369	*KIAA1683*
rs7247222	19	18,392,873	-441	*JUND*
rs6088816	20	33,982,435	-461	*UQCC*
rs6142379	20	33,999,267	499	*UQCC*
rs143384	20	34,025,756	267	*GDF5*
rs143383	20	34,025,983	40	*GDF5*
Previously Established WHRadjBMI Loci				
rs4846302	1	219,730,586	53	*RP11-95P13.2*
rs4846303	1	219,730,799	266	*RP11-95P13.2*
rs6753142	2	165,544,071	216	*SNORA70F*
rs6738627	2	165,544,450	-163	*SNORA70F*
chr2:165544572	2	165,544,572	-285	*SNORA70F*
chr2:165544573	2	165,544,573	-286	*SNORA70F*
rs10933	3	52,719,816	36	*PBRM1*
rs1108842	3	52,720,080	49	*GNL3*
rs2302417	3	52,814,256	320	*ITIH1*
chr5:173315416	5	173,315,416	134	*CPEB4*
rs55946741	5	173,345,023	-195	*CPEB4*
rs2800709	6	127,439,297	-451	*RSPO3*

SNP	Chr	Position (bp)	Distance to nearest TSS (bp)	Nearest transcript
rs4963979	12	26,468,964	317	*RP11-612B6.1*
rs10842705	12	26,469,016	369	*RP11-612B6.1*
rs7132434	12	26,472,562	91	*RP11-283G6.5*
rs1049380	12	26,489,544	339	*RP11-612B6.2*
chr12:54348554	12	54,348,554	-63	*HOXC12*
rs10876529	12	54,421,810	-331	*HOXC6*
chr12:54422043	12	54,422,043	-98	*HOXC6*
rs2071449	12	54,428,011	278	*MIR615*
Secondary Signals				
rs4282054	3	52,566,065	465	*NT5DC2*
rs7636227	3	52,566,682	-152	*NT5DC2*
rs7614981	3	52,566,914	-384	*NT5DC2*
rs12489828	3	52,567,014	-484	*NT5DC2*
rs66782572	3	52,567,617	176	*NT5DC2*
rs7639267	3	52,568,805	265	*C3orf78*

Variants at novel and previously known waist-hip ratio adjusted for body mass index (WHRadjBMI)-associated loci located within 500 bp of the nearest transcription start (TSS) site are displayed. Negative distance from nearest GENCODE v12 TSS indicates the variant is 5' of the TSS.

Supplementary Table 17 | Sources of data sets used for regulatory annotation

Roadmap Epigenomics Project

Sample	Tissue	DNase	H3K4me1	H3K27ac	H3K4me3	H3K9ac	FAIRE	H3K4me2	TF
Adipose Nuclei	Adipose	-	IDR	MACS2	IDR	IDR	-	-	-
Anterior Caudate	Brain	-	IDR	MACS2	IDR	MACS2	-	-	-
Mid Frontal Lobe	Brain	-	IDR	MACS2	IDR	MACS2	-	-	-
Substantia Nigra	Brain	-	IDR	-	IDR	MACS2	-	-	-
Adult Liver	Liver	-	IDR	-	IDR	IDR	-	-	-
Skeletal Muscle	Muscle	-	IDR	MACS2	IDR	IDR	-	-	-
Pancreatic Islet	Pancreatic Islet	-	MACS2	-	MACS2	MACS2	-	-	-

ENCODE Consortium

Sample	Tissue	DNase	H3K4me1	H3K27ac	H3K4me3	H3K9ac	FAIRE	H3K4me2	TF
GM12878	Blood	Integrative	Integrative	Integrative	Integrative (2)	Integrative	Integrative	Integrative	Integrative (75)
Osteoblasts	Bone	Integrative	Integrative	Integrative	Original	-	-	Integrative	Integrative (1)
Astrocytes	Brain	Integrative	Original	Integrative	Integrative	-	Integrative	-	Integrative (1)
Cerebellum	Brain	Original	-	-	-	-	-	-	-
Cerebrum Frontal	Brain	Original	-	-	-	-	-	-	-
Frontal Cortex	Brain	Original	-	-	-	-	Integrative		-
HUVEC	Endothelial	Integrative	Integrative	Integrative	Integrative (2)	Integrative	Integrative	Integrative	Integrative (11)
HepG2	Liver	Integrative	Integrative	Integrative	Integrative (2)	Integrative	Integrative	Integrative	Integrative (61)
Hepatocytes	Liver	Integrative	-	-	-	-	-	-	-
Huh-7	Liver	Integrative	-	-	-	-	-	-	-
Myocyte	Muscle	Integrative	Integrative	Integrative	Integrative	Integrative	-	Integrative	Integrative (1)
PSOAS Muscle	Muscle	Original	-	-	-	-	-	-	-
Pancreatic Islet	Pancreatic Islet	Integrative	-	-	-	-	Integrative	-	-

Tables indicate the source of regulatory data used to annotate associated SNPs. Peaks were identified in Roadmap Epigenomics data using Irreproducible Discovery Rate methods (IDR; multiple replicates) or MACS2 alone (single replicate). For ENCODE data, peak calls were obtained from the Integrative analysis (when available) or the original analyses. Numbers in parentheses indicate the number of datasets when more than one is available. TF, Transcription Factor Binding; -, Dataset not available.

Supplementary Table 20 | Significant gene sets based on the WHRadjBMI sex-combined GWA analysis results using the MAGENTA gene set enrichment method

Database	Gene set	Effective gene set size	# of expected genes (> 95th percentile cutoff)	# of observed genes (> 95th percentile cutoff)	*P* value	False-discovery rate	Nominally significant genes
Ingenuity	VEGF Signaling	15	1	6	0.0001	0.0006	*SHC1, RAF1, BAD, BCL2, PXN,PTK2B*
Ingenuity	PTEN Signaling	22	1	7	0.0002	0.0008	*SHC1, RAF1, BAD, CDKN1B, PTEN, BCL2, BCL2L11*
Ingenuity	ERK MAPK Signaling	22	1	6	0.0006	0.0076	*SHC1, RAF1, PPARG, BAD, PXN, PTK2B*
Ingenuity	Neuregulin Signaling	25	1	6	0.0007	0.0082	*SHC1, RAF1, ADAM17, BAD, CDKN1B, PTEN*
Ingenuity	BMP Signaling pathway	24	1	6	0.0009	0.0097	*HOXC9, SMAD6, RAF1, ZNF423, SMAD7, NOG*
Ingenuity	PI3K AKT Signaling	27	1	6	0.0015	0.0117	*SHC1, RAF1, BAD, CDKN1B, PTEN, BCL2*
Ingenuity	Ceramide Signaling	15	1	4	0.0051	0.0148	*RAF1, BAD, DIABLO, BCL2, CNKSR1*
Ingenuity	RAR Activation	46	2	8	0.0014	0.0153	*VEGFA, NSD1, IGFBP3, PML, RELA, PTEN, RAC1, PSMC5*
Ingenuity	Insulin Receptor Signaling	31	2	6	0.0035	0.0208	*SHC1, RAF1, BAD, SOCS3, INSR, PTEN*
Ingenuity	PPAR Signaling	17	1	4	0.0082	0.0265	*SHC1, RAF1, PPARG, INSR*
Ingenuity	IGF-1 Signaling	18	1	4	0.0095	0.0275	*SHC1, RAF1, BAD, PXN, NEDD4*
Ingenuity	Tight Junction Signaling	35	2	6	0.0076	0.0314	*CEBPA, RHOA, PTEN, LLGL1, RAC1, VASP, PARD6A*
Ingenuity	Integrin Signaling	37	2	6	0.0087	0.0346	*SHC1, RAF1, MAP3K11, PTEN, PXN, VASP*
Ingenuity	Glucocorticoid Receptor Signaling	92	5	11	0.0048	0.0351	*CEBPA, SHC1, POMC, RAF1, RELA, HMG1L1, SCGB1A1, IL3, CSF2, BCL2, IFNG, RAC1, PBX1*
Ingenuity	TGF-beta Signaling	28	1	5	0.0124	0.0352	*HOXC9, SMAD6, RAF1, ZNF423, SMAD7, AMH*
Ingenuity	Erythropoietin Signaling	13	1	3	0.0213	0.0377	*SHC1, RAF1, SOCS3*
Ingenuity	Chemokine Signaling	21	1	4	0.0181	0.0400	*RAF1, RHOA, ROCK2, PTK2B*
PANTHER Molecular Function	Hydroxylase	17	1	5	0.0006	0.0469	*PH-4, P4HA2, ASPH, DBH, MUS81*

Database	Gene set	Effective gene set size	# of expected genes (> 95th percentile cutoff)	# of observed genes (> 95th percentile cutoff)	*P* value	False-discovery rate	Nominally significant genes
KEGG	Focal Adhesion	179	9	22	0.0001	0.0496	*VEGFA, SHC1, RAF1, LAMB1, COL5A3, VEGFC, BAD, LAMB2, VEGFB, LAMB3, COL6A1, COL6A2, RHOA, PTEN, BCL2, ITGB3, PXN, ROCK2, RAC1, ITGA9, VAV3, ITGB6, VASP, ITGB8, FN1, CDC42*

The table lists waist-hip ratio adjusted for body mass index (WHRadjBMI) gene sets that reached significance (false-discovery rate < 0.05) using MAGENTA and its 95-percentile cutoff model. Using the 75th-percentile cutoff, 'PTEN Signaling' was the only gene set that reached significance ($P = 3.2 \times 10^{-3}$; false-discovery rate = 3.7×10^{-2}). The 'Nominally Significant Genes' column lists genes that were part of a given gene set and exhibited nominally significant MAGENTA gene *P* values.

Supplementary Table 24 | Phenotypic correlations among waist-related traits, height, weight, and body mass index

	BMI	WHR	HEIGHT	WEIGHT	HIP	WC	WHRadjBMI	WCadjBMI	HIPadjBMI
BMI: KORA	-	0.56	-0.07	**0.87**	0.59	**0.88**	0.00	0.00	0.00
EGCUT		0.46	0.00	**0.90**	0.73	**0.82**	NA	NA	NA
TWINGENE		0.41	-0.01	NA	**0.81**	**0.78**	-0.06	0.00	0.22
FRAMINGHAM		0.57	-0.02	**0.88**	**0.83**	**0.88**	0.01	-0.02	-0.03
WHR: KORA	0.44	-	-0.04	0.49	0.18	**0.76**	**0.83**	0.56	-0.19
EGCUT	0.40		0.03	0.43	0.10	0.70	**0.89**	0.56	-0.36
TWINGENE	0.41		0.42	NA	0.14	**0.79**	**0.89**	**0.76**	-0.23
FRAMINGHAM	0.48		-0.04	0.49	0.30	**0.75**	**0.82**	0.52	-0.31
HEIGHT: KORA	-0.13	-0.05	-	0.42	0.35	0.16	0.00	0.48	0.49
EGCUT	-0.06	-0.03		0.42	0.26	0.20	0.04	0.35	0.38
TWINGENE	-0.02	0.42		NA	0.14	0.38	0.47	0.64	0.24
FRAMINGHAM	-0.08	-0.02		0.45	0.34	0.21	-0.04	0.48	0.62
WEIGHT: KORA	**0.92**	0.41	0.28	-	0.71	**0.88**	0.00	0.24	0.24
EGCUT	**0.93**	0.38	0.30		**0.77**	**0.82**	0.02	0.15	0.16
TWINGENE	NA	NA	NA		NA	NA	NA	NA	NA
FRAMINGHAM	**0.94**	0.46	0.26		**0.89**	**0.88**	-0.01	0.21	0.27
HIP: KORA	0.67	0.11	0.21	0.73	-	0.58	-0.18	0.14	**0.81**
EGCUT	**0.82**	0.14	0.16	**0.84**		**0.78**	-0.27	0.31	0.68
TWINGENE	**0.81**	0.14	0.14	NA		0.71	-0.26	0.12	0.75
FRAMINGHAM	**0.92**	0.33	0.12	**0.93**		**0.85**	-0.20	0.25	0.54
WC: KORA	**0.88**	0.72	0.05	**0.87**	0.60	-	0.32	0.47	0.08
EGCUT	**0.83**	0.71	0.09	**0.82**	**0.80**		0.36	0.58	0.26
TWINGENE	**0.78**	**0.79**	0.38	NA	0.71		0.47	0.62	0.29
FRAMINGHAM	**0.89**	**0.75**	0.07	**0.89**	**0.86**		0.31	0.45	0.19
WHRadjBMI:KORA	0.00	**0.90**	0.01	0.01	-0.20	0.37	-	0.68	-0.22
EGCUT	NA	**0.92**	0.00	0.00	-0.21	0.41		0.63	-0.40
TWINGENE	0.10	**0.95**	0.46	NA	-0.13	0.59		**0.84**	-0.37
FRAMINGHAM	0.01	**0.88**	0.02	0.02	-0.12	0.38		0.65	-0.36
WCadjBMI: KORA	0.00	0.70	0.35	0.14	0.03	0.47	**0.78**	-	0.18
EGCUT	NA	0.66	0.25	0.10	0.21	0.56	0.72		0.45
TWINGENE	0.06	**0.79**	0.63	NA	0.17	0.67	**0.83**		0.19
FRAMINGHAM	0.01	0.73	0.31	0.12	0.11	0.47	**0.83**		0.47
HIPadjBMI: KORA	0.00	-0.24	0.39	0.16	0.75	0.02	-0.27	0.05	-
EGCUT	NA	-0.33	0.37	0.13	0.57	0.21	-0.36	0.37	
TWINGENE	-0.14	-0.38	0.25	NA	0.47	0.02	-0.36	0.19	
FRAMINGHAM	0.01	-0.28	0.49	0.17	0.40	0.12	-0.32	0.25	

Phenotypic trait correlations were evaluated in four studies (KORA, EGCUT, TWINGENE and FRAMINGHAM, see Online Methods). Trait correlations in men are listed in the upper triangle and correlations in women are listed in the lower triangle. Correlations > 0.75 are marked in bold. Missing correlations are marked with "NA". BMI, body mass index; WHR, waist-to-hip ratio; HIP, hip circumference; WC, waist circumference; adjBMI, adjusted for body mass index

Supplementary Note and Methods

Candidate genes at new loci for WHRadjBMI achieving genome-wide significance

1. **Chromosome 1q21.3-q22: *DCST2*,** DC-STAMP domain containing 2

   DCST2 encodes dendritic cell-specific transmembrane protein domain containing 2, a multimembrane spanning protein that contains a domain similar to that found in dendritic cells. DC-STAMP proteins have been implicated in skewing hematopoietic differentiation of bone marrow cells toward the myeloid lineage, and in cell fusion during osteoclastogenesis and giant cell formation[97]. A nearby gene is ***ZBTB7B***, zinc finger and BTB domain containing 7B, also known as ThPOK, which encodes a zinc finger transcription factor that is critical to CD4+ T cell development in CD4/CD8 lineage commitment, and suppresses CD8-lineage gene expression[98,99]. ZBTB7B has been shown to function as a transcriptional repressor of fibronectin and alpha1 collagen genes[100].

2. **Chromosome 1q24.2: *GORAB*,** golgin, RAB6-interacting

   GORAB encodes a member of the golgin family, and is a coiled-coil protein localized to the Golgi apparatus. This protein family may play a role in Rab6-regulated membrane-tethering events[101].

3. **Chromosome 2p14: *MEIS1*,** Meis homeobox 1

   The lead WHRadjBMI-associated SNP is located ~500 kb from *MEIS1,* which encodes a transcription factor that is a member of the three-amino-acid loop extension family of homeobox-containing proteins. Meis1 is essential for hematopoiesis and vascular patterning in the mouse embryo[102] and regulates vascular development in zebrafish[103]. Dysregulation of *MEIS1* expression has been linked to a variety of leukemias[104-106]. The lead SNP is also <400 kb from ***miR4778***.

4. **Chromosome 2q32.1: *CALCRL*,** calcitonin receptor-like

   CALCRL encodes calcitonin receptor-like protein receptor, involved in G-protein coupled receptor-like signaling. Calcitonin receptor-like receptor, CRLR, along with receptor activity-modifying protein-2, RAMP2, is a receptor for adrenomedullin. Adrenomedullin and CLRL/RAMP2 levels were increased in epididymal, mesenteric, and retroperitoneal adipose tissue in rats fed a high-fat diet compared to rats fed a normal diet[107]. *CRLR* mRNA levels were decreased in epicardial white adipose tissue compared to subcutaneous white adipose tissue from human biopsies[108]. A nearby gene, *TFPI*, encodes a protease inhibitor that regulates the tissue factor (TF)-dependent pathway of blood coagulation. The encoded protein is predominantly found in the vascular endothelium and plasma in both free forms and in complexes with plasma lipoproteins.

5. **Chromosome 3q22.1: *PLXND1***, plexin D1

PLXND1 encodes plexin D1 protein, a co-receptor for semaphorin proteins[109]. *Plxnd1* is expressed in cells from the central nervous system and vascular endothelium in mouse embryos[110]. Plexin D1 plays a role in vascular patterning; *plxnD1*-deficient zebrafish embryos show defects in segmental artery development such as premature and ectopic sprouting and improper blood vessel branching[111]. Semaphorin-plexinD1 signaling antagonizes the proangiogenic activity of vascular endothelial growth factor, VEGF[34].

6. **Chromosome 3q25.31: *LEKR1,*** leucine, glutamate and lysine rich 1 protein

LEKR1 encodes leucine, glutamate and lysine rich 1 protein with unknown function. The lead WHRadjBMI-associated SNP is also located near ***CCNL1***, encoding cyclin L1, and two uncharacterized noncoding RNAs, LINC00880 and LINC00881. Also nearby, ***TIPARP*** encodes a poly(ADP-ribose) polymerase superfamily member, which catalyzes the transfer of multiple ADP-ribose groups from nicotinamide-adenine dinucleotide (NAD) onto protein targets, and ***VEPH1*** encodes ventricular zone expressed PH domain-containing 1.

7. **Chromosome 4q12: *NMU,*** neuromedin U

NMU encodes neuromedin U, a highly conserved neuropeptide. NMU is found at highest levels in the gastrointestinal tract and pituitary, and has been implicated in the regulation of smooth muscle contraction, blood pressure and local blood flow, ion transport in the gut, stress responses, cancer, gastric acid secretion, and feeding behavior[112]. *Nmu* knockout mice are hyperphagic and obese[36]. Rare coding variants in NMU have been found to be associated with obesity[113].

8. **Chromosome 4q22.1: *FAM13A,*** family with sequence similarity 13, member A

FAM13A has a putative role in signal transduction, however is poorly described. SNPs in this gene region were found to be associated with chronic obstructive pulmonary disease and lung function[114,115]. Other nearby genes include ***HERC3*, *NAP1L5*, *PIGY*** (phosphatidylinositol-glycan biosynthesis class Y protein), and ***TIGD2***.

9. **Chromosome 4q28.1: *SPATA5,*** spermatogenesis associated 5 – ***FGF2***, fibroblast growth factor 2

SPATA5 belongs to the AAA ATPase family and AFG2 subfamily, and may be involved in mitochondrial transformation during spermatogenesis. SNPs at *SPATA5* have been associated with alopecia areata[116]. Other nearby genes include ***FGF2*, *NUDT6***, and ***SPRY1***. FGF2 enhanced vascularization for human adipose tissue engineering[117]. *NUDT6* (nudix-type motif 6) is an antisense gene to *FGF2* that showed associations with fat deposition related traits in pigs[118]. Conditional *Spry1* (sprouty homolog 1) expression in mouse adipose tissue protected against high-fat diet-induced obesity, bone loss, and metabolic dysfunction[119].

10. **Chromosome 5q11.2: *MAP3K1,*** mitogen-activated protein kinase kinase kinase 1, E3 ubiquitin protein ligase

    The lead SNP is located within the intron of an uncharacterized transcript **AC022431**. Located 250 kb away, *MAP3K1*, also known as *MEKK1*, encodes a protein in the MAPK group of serine/threonine protein kinases. The protein contains a PHD plant homeodomain that exhibits E3 ubiquitin ligase activity toward ERK1/2[120]. MAP3K1 also activates the JNK signaling pathway and plays a role in apoptosis[121] and wound healing[122]. Along with IL-1beta, MAP3K1 inhibited basal and membrane depolarization and cAMP-induced transcription of the insulin gene in a hamster beta cell line[123].

11. **Chromosome 5q35.2: *FGFR4,*** fibroblast growth factor receptor 4

    FGFR4 is a member of the receptor tyrosine kinase family[124]. FGFR4 is expressed mainly in lung, kidney, pancreas, spleen and developing muscle[125]. FGFR4-deficient mice on a normal diet displayed increased mass of white adipose tissue, hyperlipidemia, glucose intolerance, insulin resistance and hypercholesterolemia[37].

12. **Chromosome 6p21.32: *BTNL2,*** butyrophilin-like 2 (MHC class II associated)

    Located 30 kb from the HLA cluster, *BTNL2* is an MHC class II gene-linked butyrophilin family member that inhibits T-cell activation[126]. Variants in *BTNL2* are associated with inflammatory diseases[127,128]. Other nearby genes include ***HLA-DRA, HLA-DRB5*, *HLA-DRB1*, *HLA-DRB6*, *HLA-DRB1*, *HLA-DQA1*, *HLA-DQB1***. These HLA genes belong to the HLA class II proteins, which are expressed in antigen presenting cells, such as B lymphocytes, macrophages, and dendritic cells.

13. **Chromosome 6p21.31: *HMGA1,*** high mobility group AT-hook 1

    HMGA1 encodes a protein that binds to the minor groove of stretches of A-T-rich DNA[129]. *HMGA1* is a downstream nuclear target of the insulin receptor signaling pathway[130], and *Hmga1* knockout mice showed decreased insulin receptor expression, impaired insulin signaling and reduced insulin secretion[38].

14. **Chromosome 7p15.2: *HOXA11,*** homeobox A11

    There are 12 *HOXA* genes at this locus, as well as several antisense transcripts. HOX genes encode conserved transcription factors containing a homeodomain that regulate body and axis development and organogenesis[131]. *HOXA11* is necessary for female fertility and regulates embryonic uterine and endometrium development[132,133]. *HOXA11* mutations were found in individuals affected with the blood disease amegakaryocytic thrombocytopenia and the skeletal defect radio-ulnar synostosis[134].

15. **Chromosome 8p21.2: *NKX2-6,*** NK2 homeobox 6

NKX2-6 encodes a homeobox-containing protein that is a homolog of Drosophila tinman[135]. At early stages of mouse embryogenesis, *NKX2-6* is expressed in the pharyngeal endoderm, developing gut endoderm, cardiac progenitors, and heart[136,137]. Nearby ***NKX3-1*** is also a homeobox gene that is involved in prostate epithelium development during embryogenesis[138] and is androgen-regulated[139]. ***STC1*** encodes a secreted, homodimeric glycoprotein that is expressed in a wide variety of tissues and is upregulated by VEGFD. STC1 may play a role in the regulation of renal and intestinal calcium and phosphate transport, cell metabolism, and angiogenesis.

16. **Chromosome 8q13.3: *MSC,*** musculin

MSC encodes a basic helix-loop-helix transcription factor expressed in developing skeletal muscle[140] and mouse embryonic ectoderm[141]. ***EYA1*** encodes eyes absent homolog1, a protein phosphatase and co-activator for the transcription factor SIX1, which regulates skeletal muscle fiber-type and development[142]. Mutations in *EYA1* cause Branchio-oto-renal syndrome and Branchiootic syndrome, which are characterized by hearing loss, branchial arch defects and renal abnormalities[143]. EYA protein phosphatase activity promotes angiogenesis[144].

17. **Chromosome 9q31.1: *ABCA1,*** ATP-binding cassette, sub-family A (ABC1), member 1

This gene encodes an ATP-binding cassette transporter. Mutations in *ABCA1* have been found to be associated with Tangier's disease and familial high-density lipoprotein deficiency[145]. Adipose tissue abundantly expresses *ABCA1*, and adipose tissue *ABCA1*-dependent cholesterol efflux and nascent HDL particle formation contribute to systemic HDL biogenesis[146].

18. **Chromosome 10q24.32: *SFXN2,*** sideroflexin 2

SFXN2 encodes a mitochondrial transmembrane protein that may facilitate transport of pyridoxine or enzyme cofactors involved in heme synthesis into the mitochondria. The gene is widely expressed, and is expressed at particularly high levels in adult kidney and liver[147]. *Sfxn2* was found upregulated in pancreatic islets from streptozotocin-induced diabetic rats compared to normal rats[148].

19. **Chromosome 11q13.1: *MACROD1***, MACRO domain containing 1, ***VEGFB***, vascular endothelial growth factor B

Macrodomains are known to bind ADP-ribose derivatives[149]. Also known as LRP16*,* MACROD1 was found to play a role in estrogen signaling by interacting with estrogen receptor alpha and enhancing the receptor's transcriptional activity[150]. It has also been found to bind to the androgen receptor via its macro domain and amplifies the transactivation of androgen receptor in response to androgen[151]. LRP16 regulated insulin content and glucose-stimulated insulin secretion in MIN6 cells, and overexpression of this gene protected MIN6 cells from fatty acid-induced apoptosis[152]. Diabetic db/db ***Vegfb*** knockout mice had ectopic lipid deposition, increased muscle glucose uptake and maintained normoglycemia, and treatment of db/db mice with a VEGF-B antibody enhanced glucose tolerance, preserved pancreatic islet architecture, improved β-cell function and improved dyslipidemia[153]. The index SNP is located ~6 kb from *FLRT1,* fibronectin leucine rich transmembrane protein 1, involved in cell adhesion and fibroblast growth factor mediated signaling[154].

20. **Chromosome 12q24.31: *CCDC92,*** coiled-coil domain containing 92 protein
    The closest genes to the index variant are not obvious candidate genes. *CCDC92* encodes a protein with unknown function that was found to be upregulated in human B lymphoblastoid cells treated with a polychlorinated biphenyl pollutant[10]. ***DNAH10*** encodes dynein, axonemal, heavy chain 10, which may a play a role in cilia or flagella. ***ZNF664*** encodes zinc finger protein 664; coding variants in ZNF664 have been implicated in myopia[155].

21. **Chromosome 15q13.3: *KLF13,*** Kruppel-like factor 13
    KLF13 encodes Kruppel-like factor 13, which belongs to the Sp1-like family of transcription factors that contain 3 C-terminal zinc finger DNA-binding domains, and bind to GC-rich sequences[156]. KLF13 is a regulator of heart development[157], and was also found to bind and repress the low density lipoprotein receptor promoter[158]. A nearby gene, ***OTUD7A***, belongs to a deubiquitinating enzyme subfamily characterized by an ovarian tumor (OTU) domain. This gene encodes a protease that cleaves ubiquitin linkages.

22. **Chromosome 15q21.3: *RFX7*,** regulatory factor X, 7
    RFX7 encodes a member of the regulatory factor X family of transcription factors. It is a winged-helix transcription factor and contains a well-conserved RFX DNA binding domain. It has high ubiquitous expression, particularly in brain[159]. ***TEX9***, encoding testis-expressed sequence 9, is poorly described. Another nearby gene, ***NEDD4***, encodes neural precursor cell expressed, developmentally down-regulated 4, an E3 ligase. Overexpression of *Nedd4* suppressed BMP-induced osteoblast transdifferentiation process of mouse premyoblast C2C12 cells, and *NEDD4* was also found to be an important modulator of phospho-Smad1 in both BMP-2 and TGF-β1 action[160].

23. **Chromosome 15q22.31: *SMAD6*,** SMAD family member 6
    SMAD6 belongs to the SMAD family of proteins, which are related to *Drosophila* 'mother's against decapentaplegic' and *C elegans* Sma. SMAD proteins are signal transducers of the TGF-β superfamily and are involved in cell growth, morphogenesis, development and immune responses[161]. SMAD6 inhibits the

Bone morphogenetic protein/Smad1 signaling pathway[162]. 3T3-F442A mouse pre-adipocytes overexpressing *Smad6* show increased TGF-β signaling and decreased adipocyte differentiation[163].

24. **Chromosome 16q23.3: *CMIP,*** c-MAF inducing protein

    This gene encodes C-maf inducing protein, which interacts with phosphatidylinositol 3-kinase complex and plays a role in ERK signaling[164]. *CMIP* is expressed in peripheral blood mononuclear cells, kidney, fetal liver, and adult brain and liver[165]. A nearby gene, ***PLCG2,*** encodes phospholipase C, gamma 2 (phosphatidylinositol-specific), which hydrolyzes phosphatidyl inositol 4,5-biphosphate (PIP_2) to inositol-1,4,5-triphosphate (IP_3), resulting in an increase in intracellular calcium levels[166].

25. **Chromosome 17p11.2: *PEMT*,** phosphatidylethanolamine N-methyltransferase

    This gene encodes a liver enzyme that converts phosphatidylethanolamine to the phospholipid phosphatidylcholine by methylation in the liver. The protein localizes to the endoplasmic reticulum and mitochondria-associated membranes. *Pemt* knockout mice on a high fat diet show adipocyte hypotrophy[167]. *Pemt* mRNA and protein increase upon adipocyte differentiation in 3T3-L1 cells[168].

26. **Chromosome 17q24.3: *KCNJ2,*** potassium inwardly-rectifying channel, subfamily J, member 2

    Inwardly rectifying K+ channels control the resting K+ conductance and stabilize the resting potential in many cells[169]. *KCNJ2* was upregulated during myoblast differentiation into skeletal muscle[170] and was expressed in smooth muscle[171] and cardiomyocytes[172].

27. **Chromosome 18q21.33: *BCL2,*** B-cell CLL/lymphoma 2

    B-cell CLL/lymphoma 2 encodes an anti-apoptotic protein that binds the BH3 domain of pro-apoptotic factors and regulates permeabilization of the outer mitochondrial membrane, a critical step in apoptosis[173,174]. *Bcl2* was upregulated and apoptosis was reduced in rat pancreatic beta-cells treated with leptin[175].

28. **Chromosome 19p13.11: *JUND,*** jun D proto-oncogene

    JUND is a component of the Activating protein 1 transcription factor; AP-1 is a dimeric transcription factor with basic leucine zipper domains[176]. JunD dimerizes with DeltaFosB and binds to the *IL-11* gene promoter. Suppression of osteoblast differentiation by aging involved decreased JunD binding to the *IL-11* promoter and reduced *IL-11* transcription[177]. IL-11 inhibits the accumulation of adipose in human long-term bone marrow culture stromal layers[178]. Other nearby genes include ***KIAA1683, LSM4 PIK3R2, PDE4C,*** and ***miR3188***.

29. **Chromosome 19q13.11: *CEBPA,*** CCAAT/enhancer binding protein alpha

C/EBP alpha is a basic leucine zipper transcription factor that is highly expressed in liver and adipose tissue, and is required for differentiation of white adipose tissue[179]. *C/ebp alpha* knockout mice have defects in gluconeogenesis, are hypoglycemic, and die shortly after birth[180]. Additionally, C/EBP alpha also binds to the leptin promoter, a gene that plays an important role in body weight homeostasis[181]. Other nearby genes include ***C/EBPG***, encoding C/EBP gamma, which forms heterodimers with C/EBP beta[182], and ***PEPD***, encoding peptidase D.

30. **Chromosome 20p12.3: *BMP2,*** bone morphogenetic protein 2

BMP2 belongs to the transforming growth factor beta (TGF-β) superfamily of genes[183]. BMPs signal through transmembrane serine/threonine kinase receptors and stimulate Smad, MAPK and Akt signaling pathways[184]. High levels of BMP2 induce chondrogenesis or osteogenesis, while low levels of BMP2 promote adipogenesis[185]. BMP2 stimulates commitment of C3H10T1/2 pluripotent stem cells into adipocytes[186]. BMP2, along with IGF-1, induces differentiation of adipose-derived mesenchymal stem cells into cartilage cells[187].

31. **Chromosome 20q11.22: *GDF5,*** growth differentiation factor 5

GDF5 is a member of the bone morphogenetic protein BMP family and the transforming growth factor-beta superfamily[188]. GDF5 promoted osteogenic differentiation of rat fat-derived stromal cells and may promote angiogenic activity of stromal cells by increasing vascular endothelial growth factor gene expression in vitro[189]. GDF5 also induced chondrogenesis in rat adipose-derived stem cells[190]. Human mesenchymal stem cells that overexpressed GDF5 displayed osteogenic differentiation[191]. ***UQCC*** is a nearby gene, which encodes ubiquinol-cytochrome c reductase complex chaperone, a ZIC-binding protein repressed by basic fibroblast growth factor[192].

32. **Chromosome 20q13.12: *EYA2,*** eyes absent homolog 2

This gene encodes a member of the eyes absent, EYA, family of proteins. EYA2 is a transcriptional co-activator and protein phosphatase. *Eya2* acts synergistically with both *Dach2* and *Six1* to regulate myogenic differentiation and development[193]. Eya2 also prevents adverse cardiac remodeling under pressure overload[194]. Nearby, ***SLC2A10*** encodes solute carrier family 2 (facilitated glucose transporter) member 10.

33. **Chromosome 7p15.2: *SNX10,*** sorting nexin 10

SNX10 encodes a nexin family protein involved in intracellular trafficking. SNX10 has been shown to cause osteopetrosis, a rare disorder resulting from osteoclast dysfunction[195], and to regulate ciliogenesis[196] and endosome homeostasis[197].

Candidate genes at new loci for five additional waist and hip traits

1. **Chromosome 1q44:** ***OR2W5*** olfactory receptor family 2, subfamily W, member 5 and ***NLRP3,*** NLR family, pyrin domain containing 3

   OR2W5 encodes an olfactory receptor. *NLRP3* regulates inflammation, immune response, and apoptosis, and is associated with several inflammatory and autoimmune disorders. Other variants near *NLRP3* are associated with C-reactive protein levels[198]. NLRP3-containing inflammasome and proinflammatory T cell populations in adipose tissue contribute to inflammation and in insulin resistance[42]. Other nearby genes include ***OR2C3***, encoding an olfactory receptor, and ***GCSAML-AS1*** antisense non-coding RNA.

2. **Chromosome 2p25:** ***SOX11,*** SRY (sex determining region Y)-box 11

   This intronless gene encodes a member of the SOX (SRY-related HMG-box) family of transcription factors involved in the regulation of embryonic development and in the determination of the cell fate. SOX11 plays a role in the embryonic development of the central nervous system (CNS) and is expressed in the adult immature neuron. Knockdown of *SOX11* with siRNA decreased the proliferation and osteogenic differentiation potential of mesenchymal stem cells[199]. SOX11 has tumor suppressor function in hematopoietic malignancies[200], and prevents tumorigenesis of glioma initiating cells by inducing neuronal differentiation[201].

3. **Chromosome 2q24.2:** ***ITGB6,*** Integrin, beta 6

   ITGB6 encodes a heterodimeric cell surface receptor, which is absent from the normal epithelium but is expressed in wound-edge keratinocytes during re-epithelialization. ITGB6 is involved in tumor growth and metastasis and may serve a protective role in re-epithelialization of diabetic wounds[202]. Other nearby genes encode ***PLA2R1***, phospholipase A2 receptor, and ***RBMS1***, a protein that binds single-stranded DNA and RNA.

4. **Chromosome 5q11.2:** ***ARL15***, ADP-ribosylation factor-like 15

   ARL15 encodes an ADP-ribosylation factor-like (ARL) protein. ARL proteins are small GTPases that regulate the affinity of ARLs for binding other proteins, lipids, or membranes[203]. *ARL15* is expressed in insulin-responsive tissues, including adipose tissue and skeletal muscle[204]. Other SNPs at *ARL15* have previously been associated with adiponectin levels[65,204], HDL levels[205] and replicated CNVs in childhood obesity[206].

5. **Chromosome 5q33.3: *CCNJL***, cyclin J-like

   This gene encodes a protein that belongs to the cyclin family, cyclin J subfamily, which regulates cyclin dependent kinases[207]. A nearby gene is ***FABP6***, encoding fatty acid binding protein 6, which binds fatty acids and is involved in fatty acid uptake, transport and metabolism[208]. *Fabp6* is necessary for absorption and transport of bile acids in mouse small intestine[209]. Other nearby genes include ***PWWP2A***, encoding PWWP domain containing 2A; and ***C1QTNF2***, encoding C1q and tumor necrosis factor related protein 2.

6. **Chromosome 6p25: *GMDS*,** GDP-mannose 4,6-dehydratase

   GMDS catalyzes the first step of GDP-fucose synthesis from GDP-mannose and can inhibit apoptosis in colon cancers[210]. Other nearby genes include ***FOXC1*** (forkhead box C1), ***FOXQ1*** (forkhead box Q1), ***FOXF2*** (forkhead box F2), all of which are DNA-binding proteins involved in cell growth, apoptosis, migration and differentiation[211]. *FOXQ1* is negatively regulated by Oct4 in adipose tissue stromal cells[212].

7. **Chromosome 6p12.1: *KLHL31,* kelch-like 31**

   KLHL31 regulates transcription in the MAPK/JNK pathway[213]. In chicken, *Klhl31* was found to be highly expressed in the somite myotome, heart, and in differentiated myocardium and skeletal muscle[214]. Nearby gene ***GCLC***, encodes the glutamate-cysteine ligase catalytic subunit, which plays a regulatory role in glutathione synthesis, and may play a role in growth and development[215]. Another nearby gene, ***ELVOL***, encodes fatty acid elongase 5, which is involved in fatty acid synthesis and elongation. Increased expression of *Elvol* has been shown to restore glucose homeostasis and decrease insulin localization in hyperglycemic mice fed a high-fat diet[216].

8. **Chromosome 7q22.3: *SRPK2*,** Serine/arginine-rich splicing factor protein kinase 2

   SRPK2 encodes a non-small nuclear ribonucleoprotein particle that regulates the intracellular storage of splicing factors[217,218]. Knockdown of *SRPK2* by RNAi in HeLa cells demonstrated that this gene essential for cell viability[219]. Nearby genes include ***LHFPL3*** (lipoma HMGIC fusion partner-like 3), ***MLL5*** (myeloid/lymphoid or mixed-lineage leukemia 5), which is suggested to have a role in chromatin remodeling and cellular growth suppression[220], and several non-coding RNAs.

9. **Chromosome 7q32: *KLF14*, Kruppel-like factor 14**

   KLF14 encodes an imprinted developmental transcription factor exhibiting maternal allelic expression induced by TGF-beta. *KLF14* has been shown to be a master trans-regulator affecting multiple metabolic phenotypes[221]. Other nearby genes include ***CPA4*** (carboxypeptidase A4), ***CPA2*** (carboxypeptidase 2), ***MEST*** (mesoderm specific transcript homolog), and ***COPG2*** (coatomer protein complex, subunit gamma 2).

10. **Chromosome 9q22.32: *PTPDC1,* protein tyrosine phosphatase domain containing 1**

PTPDC1 is a member of a protein family known to play roles in molecular signaling in a wide variety of biological processes[222,223]. Mouse *Ptpcd1* was suggested to play a role in centriole duplication and cytokinesis[224] and depletion has been shown to correlate with cilia elongation[225]. Nearby genes include ***BARX1***, encoding BARX homeobox transcription factor, implicated in dentition and cleft lip syndrome[226], and ***ZNF169***, which encodes zinc finger protein 169 transcription factor. A near genome-wide significant association has been found between a nearby SNP (rs10993160, P=5.5×10^{-7}) and BMI in East Asians[47,227].

11. **Chromosome 9q33-q34: *C5,* complement component 5 (also known as *CPAMD4*)**

C5 encodes the fifth component of complement, which plays an important role in host defense and inflammatory processes. Mutations in *C5* cause a propensity for severe recurrent infections. Complement component 5 contributes to poor disease outcome in humans and mice with pneumococcal meningitis[228]. Defects in this gene have also been linked to susceptibility to liver fibrosis and rheumatoid arthritis[229]. Other nearby genes include ***PSMD5***, encoding 26S proteasome non-ATPase regulatory subunit 5, ***FBXW2***, encoding F-box and WD repeat domain containing 2, and ***TRAF1***, TNF receptor-associated factor 1.

12. **Chromosome 11q13: *MYEOV***, myeloma overexpressed

MYEOV, encoding myeloma overexpressed (in a subset of t(11;14) positive multiple myelomas) has been implicated in multiple myeloma, as well as some other cancer types[230]. Nearby are members of the fibroblast growth factor family ***FGF19*****,** ***FGF4*** and ***FGF3***. FGFs play important roles in multiple physiologic functions, including angiogenesis, mitogenesis, pattern formation, cellular differentiation, metabolic regulation, tissue repair, and oncogenesis. *FGF19* has been shown to activate an insulin-independent endocrine pathway that regulates hepatic protein and glycogen metabolism[231]. Other nearby genes include ***CCND1*** (cyclin D1) and ***ORAOV1*** (oral cancer overexpressed 1).

13. **Chromosome 11q21: *KIAA1731***

RNAi analyses suggest that *KIAA1731* encodes a centrosomal protein responsible for centriole formation/stability[232]. Other nearby genes include ***TAF1D*** (TATA box binding protein associated factor, RNA polymerase I)*,* which plays a role in RNA polymerase I transcription[233,234], ***MED17*** (mediator complex subunit 17)*,* ***C11orf54*****,** ***C11orf54*****,** ***SCARNA9*** and ***VSTM5***.

14. **Chromosome 11q22.1**: ***CNTN5,*** contactin 5

CNTN5 is a glycosylphosphatidylinositol (GPI)-anchored neuronal membrane protein that functions as a cell adhesion molecule. CNTN5 may play a role in the formation of axon connections in the developing nervous system[235]. Other nearby genes include ***PGR***, encoding the progesterone receptor, and ***TMEM133***, encoding transmembrane protein 133.

15. **Chromosome 13q31.3, *GPC6,*** glypican 6

GPC6 is a member of a family of glycosylphosphatidylinositol-anchored heparan sulfate proteoglycans that are ubiquitously expressed in most fetal and adult tissues[236]. GPC6 may influence cellular growth control and differentiation during development, and mutations in this gene have been shown to cause the rare skeletal dysplasia autosomal recessive generalized omodysplasia[237].

16. **Chromosome 16p13.11: *PDXDC1,*** pyridoxal-dependent decarboxylase domain containing 1

PDXDC1 has been predicted to belong to the family of group II pyridoxal-dependent decarboxylases, which includes enzymes that decarboxylate glutamate, histidine, tyrosine and tryptophan[238]. Nearby gene ***PLA2G10*** (phospholipase A2, group X), is important for the breakdown of phospholipids and cholesterol into fatty acids[239-242]. Nearby gene ***NTAN1*** (N-terminal asparagine amidase) is an integral part of the N-end rule pathway; disruption of this pathway by knocking out the *Ubr1* gene resulted in mice with decreased body weight due to reduced skeletal muscle and adipose tissue[243].

17. **Chromosome 16q12: *ZNF423,* zinc finger protein 423**

ZNF423 encodes a zinc finger transcription factor that associates with RARalpha/RXRalpha nuclear receptor complex and is critical for retinoic acid-induced differentiation[244]. Delayed induction of preadipocyte transcription factor ZNF423 in fibroblasts resulted in delayed adipogenesis[41]. A nearby gene, ***CNEP1R1***, encoding CTD nuclear envelope phosphatase 1 regulatory subunit 1 is involved in the conversion of phosphatidic acid to diacylglycerols and may indirectly modulate the lipid composition of nuclear and/or endoplasmic reticulum membranes and to regulate the production of lipid droplets and triacylglycerol[245].

18. **Chromosome 17p13.3: *VPS53,*** Vacuolar protein sorting 53 homolog (S. cerevisiae)

The VPS53 protein is a component of the Golgi-associated retrograde protein complex, and is required to maintain the cycling of mannose 6-phosphate receptors between the trans-Golgi network and endosomes[246,247]. Other nearby genes include *FAM101B*, which encodes an actin regulator that stabilizes perinuclear actin filament bundles[248].

19. **Chromosome 22q12.3: *HMGXB4***, high mobility group (HMG) box domain containing 4

HMGXB4 encodes a DNA-binding protein responsible for repression of smooth muscle differentiation[249]. *HMGXB4* was previously named *HMG2L1.* Nearby genes include ***TOM1*** (target of myb1)*,* ***HMOX1*** (heme oxygenase 1)*,* ***ISX*** (intestine-specific homeobox), and ***MCM5*** (minichromosome maintenance complex component 5).

Comparison of ARIC and PIVUS as reference panels for GCTA

To evaluate robustness of the GCTA results, we compared results using reference datasets from PIVUS (949 individuals with GWAS and Metabochip data) and ARIC (6,654 individuals with GWAS data, see **Online Methods**). Although the sets of SNPs selected by GCTA as independently associated with waist-hip ratio adjusted for body mass index (WHRadjBMI) when using either reference dataset were very similar, with the estimated effect sizes in the joint association model highly correlated, a few differences were observed. Given that ARIC includes only GWAS genotype data, while our combined European ancestry meta-analysis includes both GWAS and Metabochip SNPs, any Metabochip SNP in the meta-analysis for which ARIC does not have genotype data was excluded from the GCTA search for independent association signals. These missing reference dataset genotypes explained the majority of the differences observed between the two analyses, including the larger number of loci with multiple association signals identified when estimating the correlation between the variants from PIVUS. In addition, a small number of discrepancies between the two analyses were the result of minor differences between the estimated association p-value for the joint model, with some SNPs reaching the $P < 5 \times 10^{-8}$ threshold when using one dataset as reference, and therefore being selected by GCTA, while they did not reach that threshold when the correlation between SNPs was estimated from the other dataset.

In our particular setting, the choice of the preferable reference dataset is equivalent to the choice to give preference to the larger sample size provided by ARIC or to the larger SNP coverage obtained when using PIVUS. Given the observations, and in this particular case, we believe that we could achieve more insights into the genetic basis of body fat distribution by having a more dense coverage of the SNPs in our meta-analysis as that provided by PIVUS.

Genetic risk score comparison of high versus average genetic susceptibility

We further used the genetic risk score to compare high genetic susceptibility with the average population. We used the linear regression estimates (see Main text) to calculate the difference in WHR units between the 95^{th} percentile and the median of the sex-combined score (median: 46; 95^{th} percentile: 53), the women-specific score (median: 45; 95^{th} percentile: 52) and the men-specific score (median: 31; 95^{th} percentile: 37).

The difference between individuals at the 50^{th} percentile and at the 95^{th} percentile genetic susceptibility risk score groups was 0.007 WHRadjBMI units overall, 0.014 in women and 0.004 in men. These results would imply, for example, that two people from the 50^{th} and 95^{th} percentiles of this risk score distribution and of the same sex, BMI, age, and hip circumference of 100 cm would exhibit a 0.7 cm difference in waist circumference because of differences in their genotypes at these genetic variants (1.4 cm in women and 0.4 cm in men).

Directional consistency of effects in GWAS and Metabochip meta-analyses

To investigate whether additional common variants may contribute to the phenotypic variance of WHRadjBMI, we compared directional consistency in sex-combined allelic effects between GWAS and Metabochip studies in the European-ancestry meta-analysis. We considered the distribution of association *Z*-scores from the Metabochip European ancestry sex-combined meta-analysis for WHRadjBMI, aligned to the trait-increasing allele from the GWA meta-analysis, at a subset of 1,343 independent WHRadjBMI "replication" variants on Metabochip[13] (CEU $r^2 < 0.1$), excluding SNPs within 500 kb of the lead SNPs at identified WHRadjBMI loci. We counted the number of SNPs with the same direction of effect in both GWAs and Metabochip meta-analysis, and performed a one-sided binomial test for enrichment in concordance over that expected by chance (50%). For comparison, we repeated this process by obtaining a subset of 775 independent QT-interval "replication" variants[13] (CEU $r^2 < 0.1$ with each other and >300 kb from any WHRadjBMI "replication" variants) not expected to be associated with anthropometric traits.

Among the 1,343 SNPs included on the Metabochip array based on nominal significance for WHRadjBMI[13], we observed 797 (59%) directionally consistent SNPs compared to 671.5 expected by chance ($P_{binomial} = 3.9 \times 10^{-12}$). The set of 775 SNPs selected for the array on the basis of QT interval[13] did not show such enrichment (372 SNPs, or 48%, compared to 388 expected, $P_{binomial} = 0.87$). These results suggest that additional common WHRadjBMI variants may be found to be reproducible with larger samples.

Copy-number variant analysis

To investigate the associations with copy number variants (CNVs), we used a list of SNPs that are known to be robust tags of CNVs due to high linkage disequilibrium (LD) in European cohorts. Altogether four different CNV-tagging SNPs were genome-wide significant in sex-combined analysis. In **Supplementary Table 13**, all CNV-tagging SNP results are given from the 49 identified loci, which remained significant after multiple testing correction.

In the WHRadjBMI analysis, the marker rs1294421 ($P = 8.2 \times 10^{-18}$), which is in LD with CNVR2760.1 near *LY86* gene, was strongly associated. The same association was described in the previous GIANT analysis[9]. The same CNV tagging SNP was found to be genome-wide significant in the WHR analysis without BMI correction ($P = 6.9 \times 10^{-14}$). Additionally we were able to detect statistically significant results after multiple testing correction at three additional loci: *SFMBT1* (WHRadjBMI: rs3733034 has $P = 1.75 \times 10^{-6}$); *TNXB* (WHRadjBMI: rs1150753 has $P = 4.45 \times 10^{-6}$), and *HMGXB4* (HIPadjBMI: rs1543302 has $P = 1.13 \times 10^{-7}$).

Comparison of results from MAGENTA, DEPICT, and GRAIL analyses

Overlap of gene sets for WHRadjBMI that were significantly prioritized by the MAGENTA and DEPICT pathway methods. The Data-driven Enrichment-Prioritized Integration for Complex Traits (DEPICT) assesses for enrichment of 14,462 reconstituted gene sets, while MAGENTA assesses for enrichment of 3,216 gene sets. Consequently, there may be gene sets with different gene IDs that represent similar molecular functions or pathways (e.g., the BMP.Signaling.pathway in MAGENTA may represent similar biological pathways as the BMP4, BMP6, and BMPR1B protein complexes). To compare overlap of significantly enriched gene sets, we manually identified reconstituted DEPICT gene sets (false discovery rate (FDR) < 0.05) with gene set IDs similar to the enriched MAGENTA gene sets (FDR < 0.05). Among the 19 WHRadjBMI gene sets significantly prioritized by MAGENTA, 9 highly similar gene sets were prioritized by DEPICT (**Supplementary Table 22**).

Overlap of predicted genes for WHRadjBMI identified by both the GRAIL and DEPICT pathway methods. The following 14 genes were significantly predicted by GRAIL (adjusted $P < 0.05$) and DEPICT (FDR < 0.05): *TBX15, EYA2, HOXA11, GDF5, WNT4, BMP2, CITED2, SMAD6, VEGFA, LAMB1, PPARG, RSPO3, DNMT3A,* and *CDC42EP3.*

Evaluation of potential sources of heterogeneity

We tested for heterogeneity of effects to determine if the locus discovered through all ancestries meta-analysis in women (*SNX10*) was the result of increased sample size or due to heterogeneity. We used effect estimates from non-European women (Metabochip meta-analysis) and European descent-only women (GWAS+Metabochip meta-analysis) in the method outlined in Randall et al.[10], and determined there was no evidence for heterogeneity.

To address the effects of study ascertainment for specific diseases or phenotypes, we compared effects in seven subsets of our study sample using population-based studies as described in the Methods. We evaluated significance for heterogeneity tests within each comparison using a Bonferroni-corrected p-value of 0.05/49 = 0.05/49 = 1.02×10^{-3} as well as an FDR threshold of 5%.

Sources of data for expression QTL analyses

Our aim was to discover *cis*-acting expression quantitative trait loci (eQTL) in multiple tissues for our lead SNPs at loci that were associated with waist-related traits (**Tables 1** and **3**). We performed look-ups in previously published eQTL data from multiple biologically-relevant tissues.

In the MuTHER study[250], expression profiling was performed using the Illumina Human HT-12 V3 BeadChips in lymphoblastoid cell lines (LCLs, n = 778), subcutaneous adipose tissue (SAT, n = 776) and skin (n = 667) biopsies from monozygotic and dizygotic female twins from the United Kingdom. Genotyping was done with a combination of Illumina arrays (HumanHap300, HumanHap610Q, 1M-Duo and 1.2MDuo 1M) followed by imputation into HapMap II. Association tests between genotypes and gene expression within 1 Mb windows were performed with the GenABEL/ProbABEL packages using the polygenic linear model incorporating a kinship matrix.

In the MolOBB study, expression profiling in abdominal and gluteal adipose tissue biopsies from 73 individuals (29 with and 44 without metabolic syndrome) were performed with the Affymetrix hgu133plus2 array, as described previously in detail[251]. Genotyping was done with the Illumina 317K array, and *cis* associations between genotypes and expression values were tested using linear regression models assuming additive genetic effects.

Expression data in liver (n = 955), SAT (n = 610), and omental fat tissue (n = 740) from the Massachusetts General Hospital collection[252] was obtained using a custom Agilent 44,000 feature microarray in gastric bypass surgery patients. Genotyping was done using Illumina HumanHap650Y and Affymetrix 500K genotyping arrays followed by imputation into HapMap II. Association analyses within 1 Mb windows were performed using linear regression under an additive genetic model.

For whole blood (n = 743) and SAT biopsies (n = 603) from deCODE, expression profiling of 23,720 transcripts was done using custom arrays, as previously described in detail[253]. *Cis* associations within 1 Mb windows between each SNP (Illumina 317K or 370K chips were used for genotyping followed by imputation to HapMap II) and expression data were tested were tested separately in men and women assuming additive genetic effects using linear regression models accounting for family structure.

Expression data in LCLs from the family asthma study (MRC-A)[254] was obtained with Affymetrix HG-U133 Plus 2.0 chip (n = 405 siblings) and Illumina Human6V1 array (n = 550 siblings). Genotyping was done using Illumina arrays (Human1M and HumanHap300K) and *cis* associations between genotypes and expression values were tested using linear regression models assuming additive genetic effects.

For peripheral blood mononuclear cells (PBMCs), gene expression data was available in the integrated dataset of 1,469 healthy controls and patient samples from the United Kingdom and the Netherlands (Fehrmann-HT12v3 and Fehrmann-H8v2), and 891 individuals from Estonia (EGCUT). In Fehrmann-HT12v3 (*n* =1,240) expression profiling was performed with the Illumina HumanHT-12 array and in Fehrmann-H8v2 (*n*= 229) with the Illumina HumanRef-8 v2 array as described in detail previously[255]. Genotyping was done using the Illumina HumanHap300, HumanHap370 or 610 Quad platform followed by imputation to HapMap II. In EGCUT, expression profiling was performed using Illumina HumanHT12v3 array while genotyping was performed with Illumina Human370CNV-duo chip followed by imputation to HapMap II as described previously[256]. Associations between genotype dosages and gene expression values were tested using linear regression models assuming additive genetic effects within 1 Mb windows. All 2,360 peripheral blood samples from three studies were then meta-analyzed using a z-score method, weighted for the sample size of each dataset.

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