**Supplemental Data**

# Genetic Regulation of Adipose Gene Expression

and Cardio-Metabolic Traits

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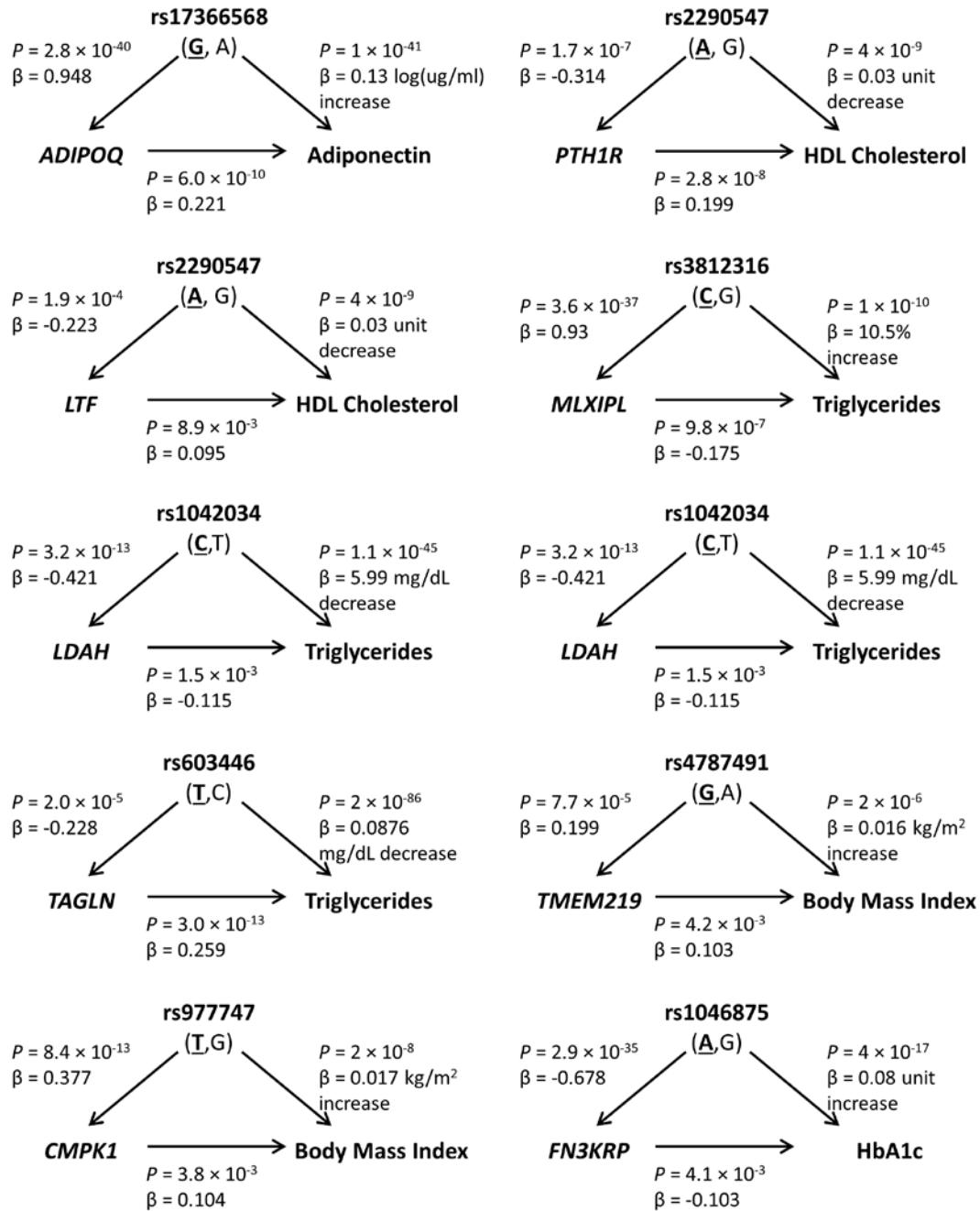
SUPPLEMENTAL FIGURES
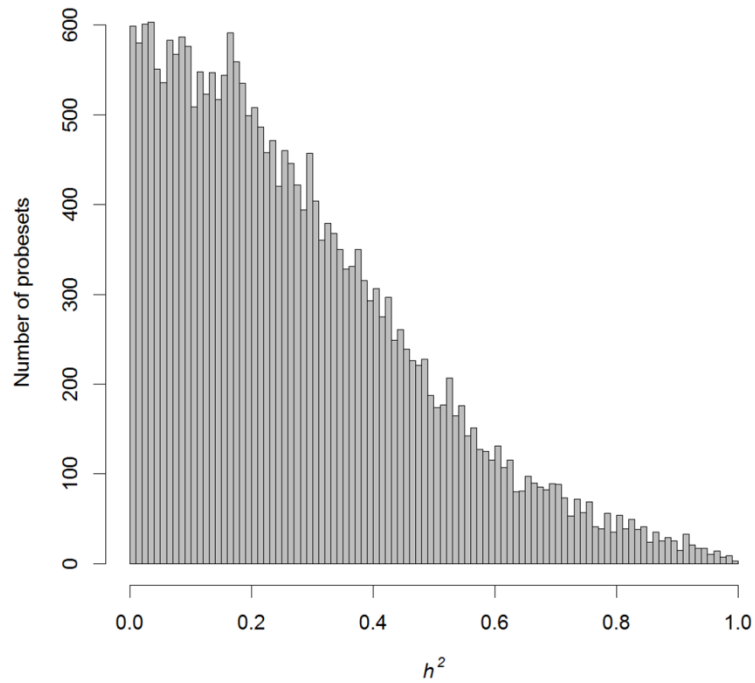
**Figure S1**: Narrow sense heritability (h^2) for transcript expression probes. h^2 for each probeset was calculated from the PEER residuals using a variance component method as implemented in the Genome-wide Complex Trait Analysis (GCTA) software[5]. The mean narrow-sense heritability, h^2, of the 59.8% of probesets with a non-zero estimate was 0.27 (range 1.4×10^{-5} to 0.99, mean standard error = 0.27).

A.

B.

+/- 250 kb
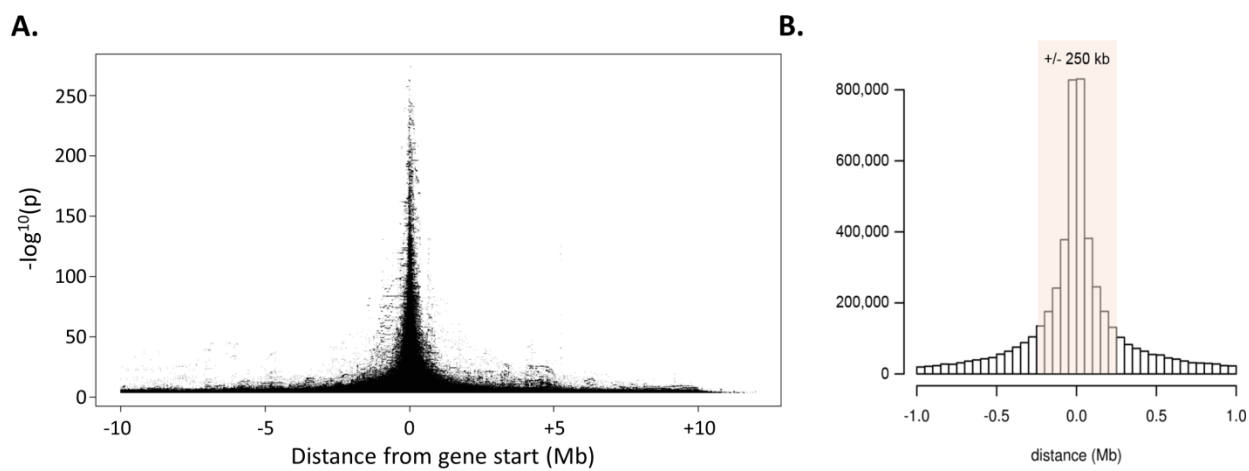
Figure S2: Characteristics of *cis*-eQTL associations located up to 10 Mb from transcription start sites. **(A)** Association *P*-values within 10 Mb of the transcript **(B)** Numbers of variants with *cis*-eQTL $P < 2.46 \times 10^{-4}$ in 50 kb bins within 1 Mb of the transcript. The pink shading indicates *cis*-eQTL variants located within 250 kb of the transcript.

rs17366568
(<u>G</u>, A)

$P = 2.8 \times 10^{-40}$
$\beta = 0.948$

$P = 1 \times 10^{-41}$
$\beta = 0.13$ log(ug/ml) increase

ADIPOQ → **Adiponectin**

$P = 6.0 \times 10^{-10}$
$\beta = 0.221$

rs2290547
(<u>A</u>, G)

$P = 1.7 \times 10^{-7}$
$\beta = -0.314$

$P = 4 \times 10^{-9}$
$\beta = 0.03$ unit decrease

PTH1R → **HDL Cholesterol**

$P = 2.8 \times 10^{-8}$
$\beta = 0.199$

rs2290547
(<u>A</u>, G)

$P = 1.9 \times 10^{-4}$
$\beta = -0.223$

$P = 4 \times 10^{-9}$
$\beta = 0.03$ unit decrease

LTF → **HDL Cholesterol**

$P = 8.9 \times 10^{-3}$
$\beta = 0.095$

rs3812316
(<u>C</u>,G)

$P = 3.6 \times 10^{-37}$
$\beta = 0.93$

$P = 1 \times 10^{-10}$
$\beta = 10.5\%$ increase

MLXIPL → **Triglycerides**

$P = 9.8 \times 10^{-7}$
$\beta = -0.175$

rs1042034
(<u>C</u>,T)

$P = 3.2 \times 10^{-13}$
$\beta = -0.421$

$P = 1.1 \times 10^{-45}$
$\beta = 5.99$ mg/dL decrease

LDAH → **Triglycerides**

$P = 1.5 \times 10^{-3}$
$\beta = -0.115$

rs1042034
(<u>C</u>,T)

$P = 3.2 \times 10^{-13}$
$\beta = -0.421$

$P = 1.1 \times 10^{-45}$
$\beta = 5.99$ mg/dL decrease

LDAH → **Triglycerides**

$P = 1.5 \times 10^{-3}$
$\beta = -0.115$

rs603446
(<u>T</u>,C)

$P = 2.0 \times 10^{-5}$
$\beta = -0.228$

$P = 2 \times 10^{-86}$
$\beta = 0.0876$ mg/dL decrease

TAGLN → **Triglycerides**

$P = 3.0 \times 10^{-13}$
$\beta = 0.259$

rs4787491
(<u>G</u>,A)

$P = 7.7 \times 10^{-5}$
$\beta = 0.199$

$P = 2 \times 10^{-6}$
$\beta = 0.016$ kg/m² increase

TMEM219 → **Body Mass Index**

$P = 4.2 \times 10^{-3}$
$\beta = 0.103$

rs977747
(<u>T</u>,G)

$P = 8.4 \times 10^{-13}$
$\beta = 0.377$

$P = 2 \times 10^{-8}$
$\beta = 0.017$ kg/m² increase

CMPK1 → **Body Mass Index**

$P = 3.8 \times 10^{-3}$
$\beta = 0.104$

rs1046875
(<u>A</u>,G)

$P = 2.9 \times 10^{-35}$
$\beta = -0.678$

$P = 4 \times 10^{-17}$
$\beta = 0.08$ unit increase

**FN3KRP** → **HbA1c**

$P = 4.1 \times 10^{-3}$
$\beta = -0.103$

Figure S3: Candidate causal genes at select GWAS loci. Associations between the GWAS SNP, gene expression, and trait for which the causal inference test showed evidence of mediation ($P_{CIT} < 0.05$) are shown. Results of the causal inference test are detailed in supplementary file 4. Direction of effect size is based on the underlined allele.
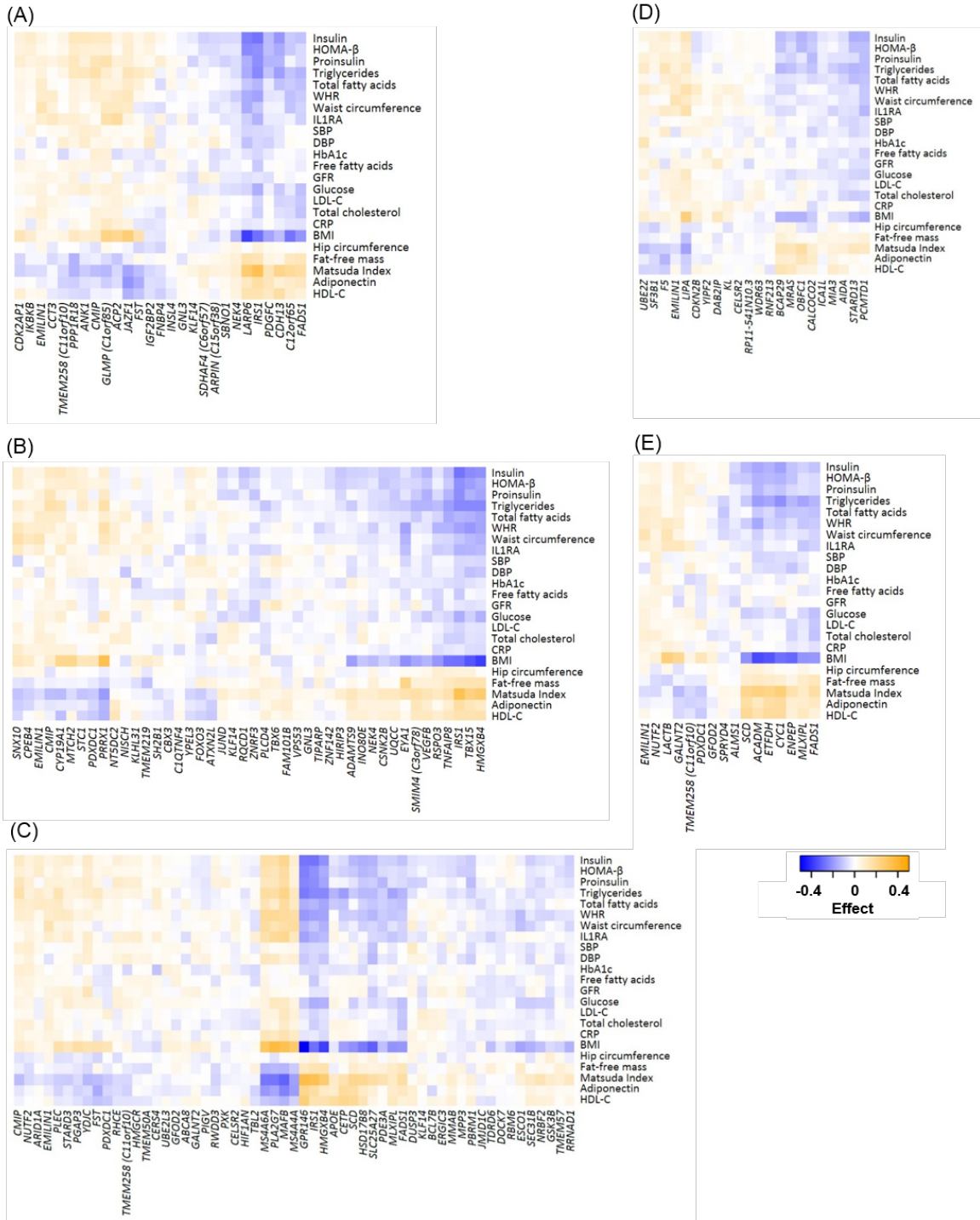
Figure S4: Effects of the association between cardiometabolic traits and genes for which the eQTL was coincident with the GWAS signals. Trait association with eQTL genes at GWAS loci for **(A)** diabetes and glycemic traits, **(B)** obesity and related traits, **(C)** lipids, **(D)** CVD/CHD, and **(E)** MetS. Orange: positive association; blue: negative association. The effect size scale is the same as that shown in main Figure 2 and 3.
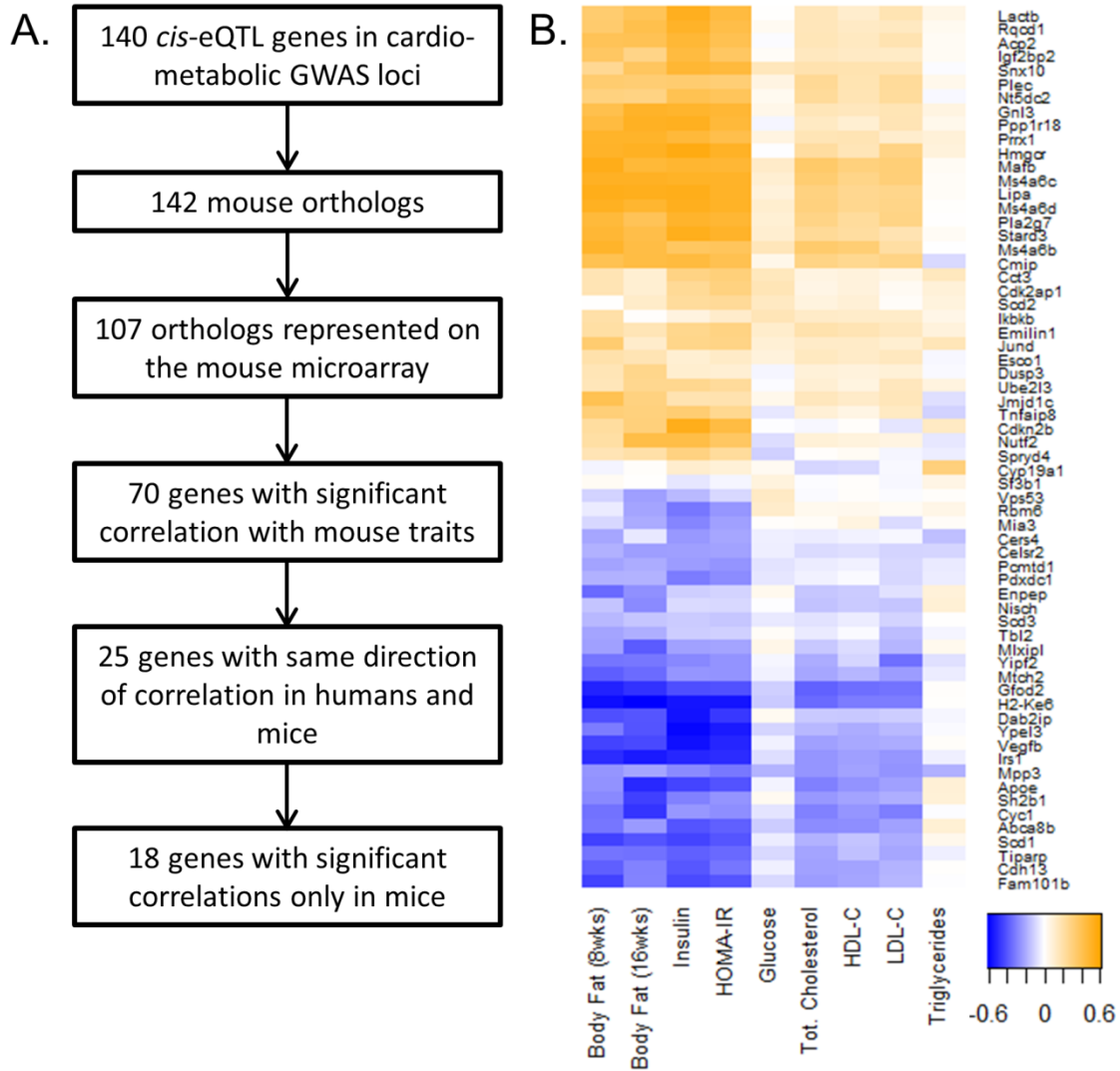
Figure S5: Correlation between cardio-metabolic traits and genes in 120 strains from the Hybrid Mouse Diversity Panel. **(A)** Flowchart showing the identification of the overlap of the trait-expression correlations in humans and mice. **(B)** Mouse orthologs are shown for the human *cis*-eQTL genes coincident with GWAS loci. Correlation strength is shown between selected cardio-metabolic traits and adipose tissue expression in males. Expression and phenotype data from Parks *et al*[6; 7].
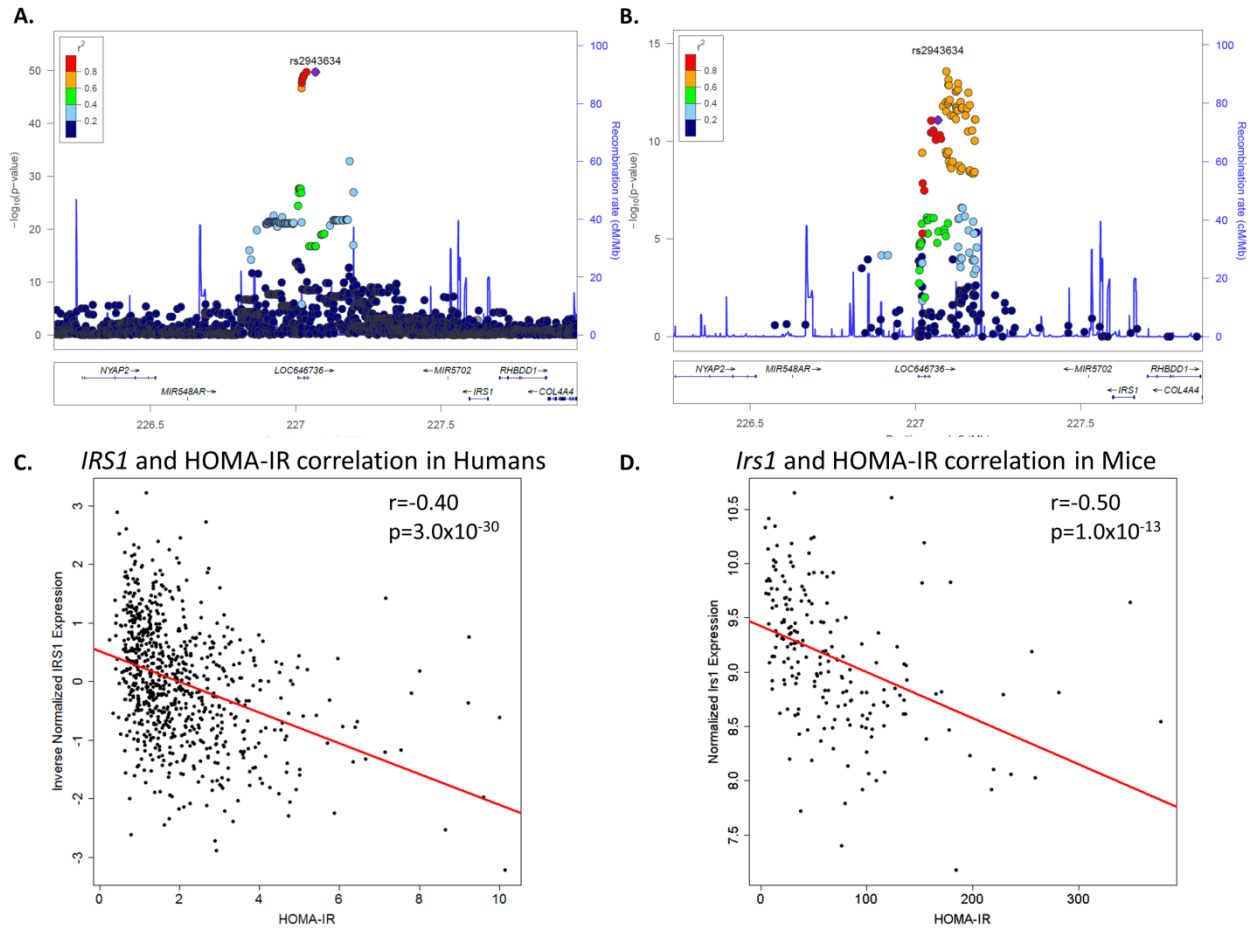
Figure S6: Association of variants at chr2q36.3 with *IRS1* expression and insulin resistance in humans and mice. **(A)** Variants associated with *IRS1* expression in the METSIM study. Variants are colored based on LD with the lead eSNP rs2943634 (purple dot) in METSIM. **(B)** Variants associated with type 2 diabetes susceptibility from the DIAGRAM consortium[8]. Variants are colored based on LD with rs2943634. **(C)** Correlation of *IRS1* with a homeostatic model of insulin resistance (HOMA-IR) in humans from the METSIM study. **(D)** Correlation of *Irs1* with HOMA-IR in mice from the HMDP.
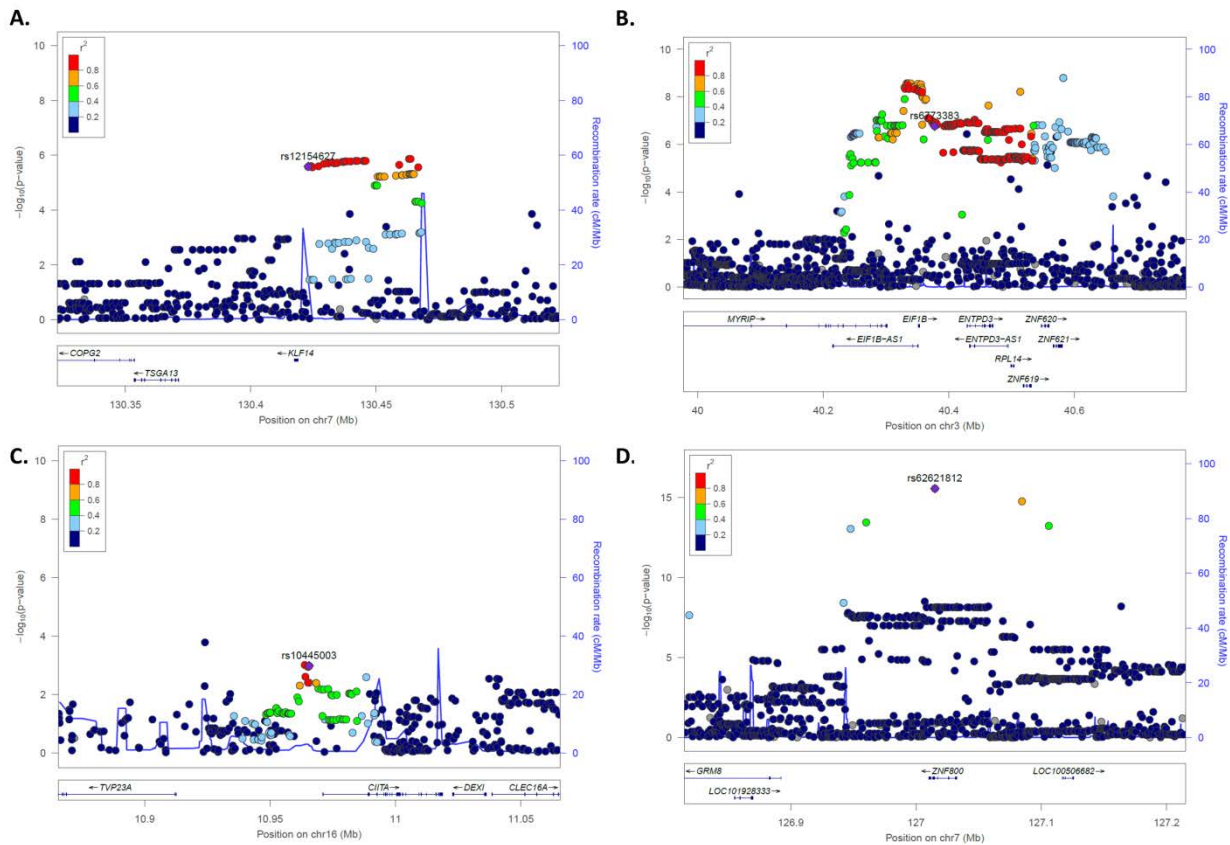
Figure S7: *cis*-regulated genes at the *trans*-eQTL hotspot loci. Variants associated with (A) *KLF14*, (B) *SLC25A38* (transcript located at chr3: 39.7 Mb), (C) *CIITA*, (D) *ZNF800* expression in the METSIM study. Variants are colored based on LD with the peak *trans*-eQTL variant, which is colored in purple.
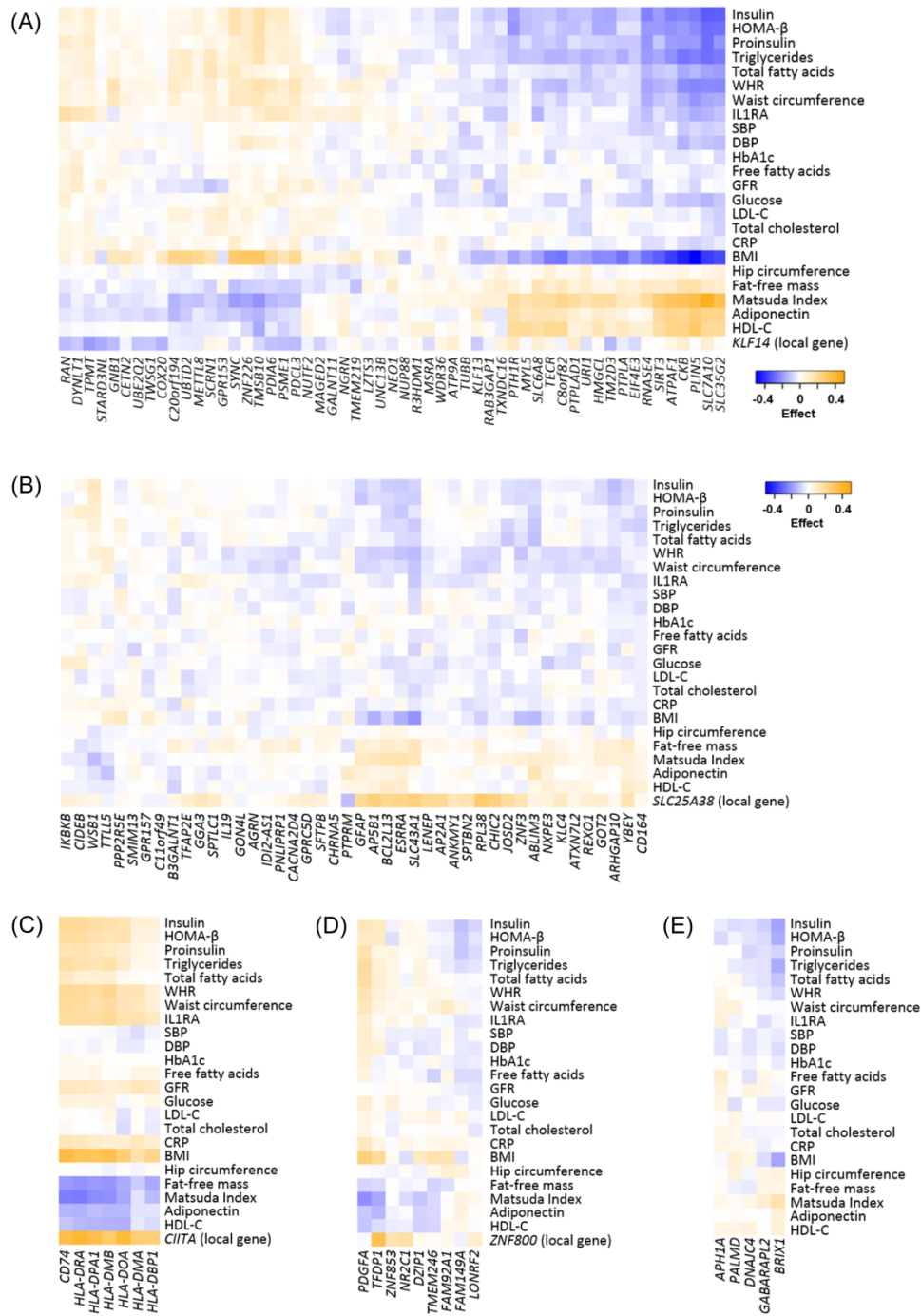
Figure S8: Heat map of effect sizes for associations (*P* < 0.05) between the expression of target genes at *trans*-eQTL hotspots and cardio-metabolic trait levels. (A) *KLF14* locus, (B) *SLC25A38* locus, (C) *CIITA* locus (D) *ZNF800* locus, (E) and *HBB* locus. Rows show 23 selected cardio-metabolic traits and columns show the eQTL genes (and reported GWAS trait at the coincident locus). Negative values (blue) indicate that increased gene expression level was associated with decreased trait level, while positive values (orange) indicate that increased gene expression level was associated with increased trait level.

SUPPLEMENTAL TABLES

Table S1: Characteristics of the 770 METSIM study participants

Abbreviation	Metabolic trait	Mean ± standard deviation	Median (25th, 75th percentile)
Age	Age (years)	54.8 ± 5.1	54.0 (51.0, 59.0)
BMI	Body mass index (kg/m^2)	26.6 ± 3.5	26.2 (24.4, 28.4)
WHR	Waist-to-hip ratio	0.96 ± 0.06	0.96 (0.92, 1.00)
WC	Waist circumference (cm)	96.6 ± 9.5	95.0 (90.0, 102.0)
HIP	Hip circumference (cm)	100.5 ± 6.2	100.0 (97.0, 104.0)
FFMASS	Fat-free mass (%)	78.8 ± 5.1	79.4 (76.3, 82.0)
TotFA	Total fatty acids (mmol/l)	11.9 ± 3.1	11.3 (9.9, 13.2)
FFA	Fasting plasma free fatty acid (mmol/l)	0.36 ± 0.14	0.34 (0.25, 0.43)
TG	Total triglycerides (mmol/l)	1.41 ± 0.95	1.19 (0.87, 1.64)
CHOL	Total cholesterol (mmol/l)	5.50 ± 0.88	5.42 (4.87, 6.10)
LDL-C	LDL cholesterol (mmol/l)	3.48 ± 0.77	3.40 (2.90, 3.97)
HDL-C	HDL cholesterol (mmol/l)	1.49 ± 0.39	1.44 (1.21, 1.69)
Adiponectin	Plasma adiponectin (ug/ml)	7.5 ± 3.5	6.7 (4.2, 9.6)
Matsuda	Matsuda composite insulin sensitivity index (mg/dl, mU/l)	7.3 ± 4.3	6.4 (4.2, 9.6)
HOMA-B	Insulin resistance index based on homeostasis model assessment	68.1 ± 41.3	57.1 (40.8, 82.2)
Glucose	Fasting plasma glucose (mmol/l)	5.8 ± 0.6	5.7 (5.4, 6.0)
Insulin	Fasting plasma insulin (mU/l)	45.9 ± 29.3	37.2 (25.8, 58.8)
Proinsulin	Fasting plasma proinsulin (pmol/l)	13.2 ± 6.3	11.9 (9.3, 15.3)
HbA1c	Blood glycated HbA1c (%)	5.6 ± 0.4	5.6 (5.4, 5.8)
SBP	Systolic blood pressure (mm Hg)	134.7 ± 14.4	133.3 (124.0, 142.0)
DBP	Diastolic blood pressure (mm Hg)	87.4 ± 8.8	87.3 (80.7, 92.7)
CRP	High sensitivity C-reactive protein (mg/l)	1.8 ± 3.1	1.0 (0.5, 2.1)
IL1RA	Interleukin-1 receptor antagonist (pg/ml)	200.0 ± 124.8	170.4 (128.2, 235.9)
GFR	Glomerular filtration rate	0.09 ± 0.01	0.09 (0.08, 0.10)
		YES	**NO**
T2D	Type 2 diabetes	27	743
IGT	Impaired glucose tolerance	61	682

Table S2: Discovery of *cis*- and *trans*-eQTL genes on chromosome 7 with different numbers of PEER factors

Number of PEER factors (Nk)	Number of *cis*-eQTL genes on chr7 (FDR < 1%)	Number of *trans*-eQTL genes associated with *KLF14* variant rs4731702 ($P < 5\times10^{-8}$)
10	572	28
15	593	36
20	605	41
25	608	43
30	610	51
35	612	50
40	616	45
45	613	32
50	610	27

To optimize the discovery of both *cis*- and *trans*-eQTLs, we compared the number of *cis*- and *trans*-eQTL genes on chromosome 7 from the association analysis for PEER-processed residuals of transcript levels by setting the number of inferred PEER factors (Nk) at 10, 15, 20, 25, 30, 35, 40, 45, and 50. *Cis*-eQTLs were defined as the distance between the variant and associated genes < 1 Mb and FDR < 1%. The number of *trans*-eQTL genes was only counted for associated genes ($P < 5\times10^{-8}$) located > 5 Mb away or on a different chromosome from the *KLF14* locus on chromosome 7[1]. Association tests for this set of pilot eQTL analyses were performed using Matrix-eQTL.

Table S3: Discovery of *cis*- and *trans*-eQTLs in METSIM adipose tissue

	cis associations	*trans* associations
Number of variant-probeset pairs	5,006,029	11,053
Number of variant-gene pairs	3,265,851	10,294
Number of variants associated with ≥ 1 gene	710,325	4,082
Number of associated probe sets	24,375	121
Number of associated genes	12,400	90

cis- and *trans*-eQTLs were defined based on the distance between the gene boundary and the significantly associated variant location. Variants with minor allele frequency (MAF) ≥ 0.01 associated with the transcript level of a gene at FDR < 1% were considered. The *P*-value corresponding to a 1% FDR for *cis* associations is 2.46×10^{-4}. *Trans* associations were determined at the Bonferroni-corrected *P*-value of 1.51×10^{-13}.

Table S4: List of cardio-metabolic diseases and related quantitative traits for which GWAS loci were examined

Trait group	Trait from the GWAS catalog
diabetes	Type 2 diabetes
diabetes	Diabetes (gestational)
diabetes	Type 2 diabetes and other traits
glycemic	Adiponectin levels
glycemic	Fasting glucose-related traits
glycemic	Fasting glucose-related traits (interaction with BMI)
glycemic	Fasting insulin-related traits
glycemic	Fasting insulin-related traits (interaction with BMI)
glycemic	Fasting plasma glucose
glycemic	Glycated hemoglobin levels
glycemic	Glycemic traits
glycemic	Insulin-related traits
glycemic	Proinsulin levels
glycemic	Two-hour glucose challenge
obesity	Adiposity
obesity	BMI
obesity	Body mass index
obesity	Body mass (lean)
obesity	HIP
obesity	HIPadjBMI
obesity	Obesity
obesity	Obesity (early onset extreme)
obesity	Obesity (extreme)
obesity	Obesity-related traits
obesity	Visceral adipose tissue/subcutaneous adipose tissue ratio
obesity	Visceral fat
obesity	Waist circumference
obesity	Waist circumference and related phenotypes
obesity	Waist Circumference - Triglycerides (WC-TG)
obesity	Waist-hip ratio
obesity	WCadjBMI
obesity	Weight
obesity	WHR

obesity	WHRadjBMI
lipids	Apolipoprotein Levels
lipids	Cholesterol
lipids	Cholesterol total
lipids	HDL cholesterol
lipids	HDL Cholesterol - Triglycerides (HDLC-TG)
lipids	Hypertriglyceridemia
lipids	LDL cholesterol
lipids	LDL (oxidized)
lipids	Lipid metabolism phenotypes
lipids	Lipid traits
lipids	Lipoprotein-associated phospholipase A2 activity and mass
lipids	Lipoprotein-associated phospholipase A2 activity change in response to statin therapy
lipids	Oleic acid (18:1n-9) plasma levels
lipids	Palmitic acid (16:0) plasma levels
lipids	Palmitoleic acid (16:1n-7) plasma levels
lipids	Phospholipid levels (plasma)
lipids	Phytosterol levels
lipids	Plasminogen activator inhibitor type 1 levels (PAI-1)
lipids	Resistin levels
lipids	Sphingolipid levels
lipids	Stearic acid (18:0) plasma levels
lipids	Triglycerides
lipids	Triglycerides-Blood Pressure (TG-BP)
MetS	Metabolic syndrome
MetS	Metabolic syndrome (bivariate traits)
MetS	Metabolic traits
CVD/CHD	Abdominal aortic aneurysm
CVD/CHD	Ankle-brachial index
CVD/CHD	Aortic root size
CVD/CHD	Aortic stiffness
CVD/CHD	Aortic-valve calcification
CVD/CHD	Arterial stiffness
CVD/CHD	Cardiac hypertrophy
CVD/CHD	Cardiac structure and function

CVD/CHD	Cardiac Troponin-T levels
CVD/CHD	Cardiovascular disease risk factors
CVD/CHD	Cardiovascular heart disease in diabetics
CVD/CHD	Carotid atherosclerosis in HIV infection
CVD/CHD	Carotid intima media thickness
CVD/CHD	Coronary arterial lesions in patients with Kawasaki disease
CVD/CHD	Coronary artery calcification
CVD/CHD	Coronary heart disease
CVD/CHD	Hypertension
CVD/CHD	Hypertension risk in short sleep duration
CVD/CHD	Intracranial aneurysm
CVD/CHD	Lp(a) levels
CVD/CHD	Moyamoya disease
CVD/CHD	Myocardial infarction
CVD/CHD	Myocardial infarction (early onset)
CVD/CHD	Pulmonary arterial hypertension (without BMPR2 mutations)
CVD/CHD	Stroke
CVD/CHD	Stroke (ischemic)
CVD/CHD	Thiazide-induced adverse metabolic effects in hypertensive patients
CVD/CHD	Thoracic aortic aneurysms and dissections
CVD/CHD	Vascular dementia
CVD/CHD	Venous thromboembolism
CVD/CHD	Venous thromboembolism (gene x gene interaction)

Table S5: GWAS summary results used in the summary-data-based Mendelian randomization method analysis

Table S5 is an online Excel file (Table S5.xlsx)

Table S6 Comparison of previous adipose eQTL studies to the METSIM study

Study	deCODE	MGH	MuTHER	METSIM
Number of participants	585	701	855 twins	770
Sex ratio (Female:Male)	60:40	75:25	100:00	0:100
Genotyping platform	Illumina	Illumina 650Y chip	Illumina HumanHap300, HumanHap610Q, 1M-Duo and 1.2MDuo 1M chips	Illumina OmniExpress chip
Imputation	NA	HapMap2	HapMap2	Haplotype Reference Consortium
Number of variants tested	1,732 microsatellite markers	2,529,766 variants	2,029,988 variants	7,677,356 variants
Minor allele frequency threshold	NA	NA	5%	1%
Association method	score statistic for a Gaussian variance component model	Kruskal-Wallis test with correction for covariates	two-step mixed model–based score test	linear mixed model
Software	SOLAR 2.0	Matlab	GenABEL/ProbABEL	FaST-LMM and EPACTS
Expression array	Agilent custom array	Agilent custom array	Illumina HT12 v3.0	Affymetrix U219
Number of transcripts	20,877	39,303	23,423	43,145
Number of genes	NA	NA	NA	18,155
Expression heterogeneity removal	removal of known covariates	19 principal components identified from control probes	none	Probabilistic estimation of expression residuals (k=35)
cis-eQTL P-value threshold	5% FDR	10% FDR	5×10^{-5} (1% FDR)	2.46×10^{-4} (1% FDR)
trans-eQTL P-value threshold	5% FDR	10% FDR	5×10^{-8} (10% FDR)	1.51×10^{-13}
Number of transcripts with eQTLs	820 cis; 25 trans	15,241 cis and trans	3,523 cis; 595 trans	24,375 cis; 121 trans
Number of genes with eQTLs	NA	9,931 cis and trans	NA	12,400 cis; 90 trans
Citation	Emilsson et al (2008)[2]	Greenawalt et al (2011)[3]	Grundberg et al (2012)[4]	current study

Table S7: Comparison of adipose eQTLs identified in the METSIM and MuTHER cohorts

Discovery Study	Comparison study	Number of eQTLs in the discovery study	Number of these eQTLs available in the comparison study	P-value threshold				
				5×10^{-2}	5×10^{-3}	5×10^{-4}	5×10^{-5}	5×10^{-6}
				Number of *cis*-eQTLs observed (%)				
METSIM	MuTHER	12,400	5,162	4,421 (85.6%)	3,186 (61.7%)	2,378 (46.1%)	1,922 (37.2%)	1,550 (30.0%)
MuTHER	METSIM	3,142	2,279	2,128 (93.0%)	2042 (89.6%)	1,939 (85.1%)	1,870 (82.0%)	1,802 (79.1%)
				Number of *trans*-eQTLs observed (%)				
METSIM	MuTHER	90	41	18 (43.9%)	14 (34.1%)	12 (29.3%)	11 (26.8%)	5 (12.2%)
MuTHER	METSIM	639	517	63 (12.2%)	14 (2.7%)	0 (0%)	0 (0%)	0 (0%)

The total number of eQTLs is the number identified in the discovery study at FDR<1%. Of these, the eQTLs available are those for which the replication study data included a probeset for the same gene and had the same variant available. The *P*-value threshold columns report the discovery study eQTLs observed in the replication study at or exceeding that significance threshold and in the same observed direction of effect.

Table S8: Adipose eQTLs identified at GWAS loci for cardiometabolic dieseases and traits

Table S8 is an online Excel file (Table S8.xlsx)

Table S9: Results of the summary-data-based Mendelian randomization (SMR) analysis. Source of the GWAS summary results are given in Table S5

Table S9 is an online Excel file (Table S9.xlsx)

Table S10: Results of the causal inference test (CIT). CIT was performed for the GWAS index SNP, expression of the *cis*-eQTL gene, and inverse-normalized traits measured in the METSIM population

Table S10 is an online Excel file (Table S10.xlsx)

Table S11: Association of gene expression and cardio-metabolic traits

Table S11 is an online Excel file (Table S11.xlsx)

Table S12: Number of probesets and genes associated with each of the 23 cardiometabolic-related traits.

Traits	Number of associated probesets	Number of associated genes
Body mass index (BMI)	10,819	6,064
Matsuda insulin sensitivity index	6,640	3,940
Insulin	4,933	3,039
Triglycerides	4,103	2,553
HOMA-β	3,340	2,126
Adiponectin	3,003	1,894
Wasit-to-hip ratio (WHR)	2,880	1,790
HDL cholesterol (HDL-C)	2,574	1,660
Proinsulin	2,487	1,618
IL1 receptor antagonist (IL1RA)	1,882	1,250
Fat free mass (FFM)	1,641	1,103
Waist circumference (WC)	1,387	892
Total fatty acids (TotFA)	1,181	784
Glucose	386	312
Diastolic blood pressure (DBP)	364	275
Glomerular filtration rate (GFR)	272	234
C-reactive protein (CRP)	164	121
Systolic blood pressure (SBP)	98	81
Free fatty acids (FFA)	67	54
Total cholesterol	52	46
HbA1c	40	36
Hip circumference	27	25
LDL cholesterol (LDL-C)	25	23
Total	**48,365**	**29,920**

Table S13: METSIM *cis*-eQTLs in GWAS loci for which adipose expression is correlated with similar metabolic traits in the hybrid mouse diversity panel (HMDP)

	METSIM				HMDP				
Locus	***cis*-eQTL gene**	**Trait**	**Association *P*-value**	**Direction of correlation**	**Mouse gene**	**Trait**	**Correlation *P*-value**	**Correlation**	**Diet**
IRS1	*IRS1*	Matsuda	1.4×10^{-21}	+	*Irs1*	HOMA-IR	1.0×10^{-13}	-0.50	HF
		WHR	5.1×10^{-7}	-		BFP	1.9×10^{-18}	-0.54	HF
		TG	9.0×10^{-11}	-					
		Adipo	8.8×10^{-7}	+					
		HDL-C	1.7×10^{-5}	+					
MLXIPL	*MLXIPL*	TG	9.8×10^{-7}	-	*Mlxipl*	SqFP	2.6×10^{-11}	-0.42	HF
		HDL-C	7.2×10^{-4}	+					
GORAB	*PRRX1*	WHR	4.5×10^{-6}	+	*Prrx1*	BFP	6.6×10^{-22}	0.58	HF
LACTB	*LACTB*	Waist	5.8×10^{-5}	+	*Lactb*	SqFP	2.5×10^{-12}	0.44	HF
ENPEP	*ENPEP*	Matsuda	1.0×10^{-5}	+	*Enpep*	BFP	6.2×10^{-8}	-0.35	HF
		TG	1.0×10^{-4}	-					
SNX10	*SNX10*	WHR	3.0×10^{-4}	+	*Snx10*	BFP	4.9×10^{-9}	0.38	HF
MAFB	*MAFB*	LDL-C	6.1×10^{-4}	+	*Mafb*	LDL-C	1.7×10^{-6}	0.33	HF
INO80E	*TMEM219*	BMI	4.2×10^{-3}	+	*Tmem219*	BFP	5.2×10^{-6}	0.45	Chow
CMIP	*CMIP*	WHR	9.3×10^{-3}	+	*Cmip*	BFP	1.9×10^{-17}	0.52	HF
AIF1	*CSNK2B*	BMI	1.3×10^{-2}	-	*Csnk2b*	BFP	4.1×10^{-11}	-0.62	Chow
MPHOSPH9	*CDK2AP1*	Matsuda	1.6×10^{-2}	-	*Cdk2ap1*	HOMA-IR	1.5×10^{-10}	0.44	HF
NT5DC2	*NT5DC2*	WHR	1.8×10^{-2}	+	*Nt5dc2*	SqFP	4.4×10^{-7}	0.33	HF
LEKR1	*TIPARP*	WHR	2.6×10^{-2}	-	*Tiparp*	SqFP	1.4×10^{-8}	-0.37	HF
MADD	*ACP2*	P_ins	3.7×10^{-2}	+	*Acp2*	Ins	8.4×10^{-16}	0.53	HF
GCKR	*EMILIN1*	P_ins	5.1×10^{-2}	+	*Emilin1*	HOMA-IR	7.4×10^{-8}	0.37	HF
		Gluc	6.5×10^{-2}	+					
		Ins	1.2×10^{-1}	+					
MACROD1	*VEGFB*	WHR	1.5×10^{-1}	-	*Vegfb*	SqFP	1.8×10^{-14}	-0.48	HF
MPP3	*MPP3*	TG	2.1×10^{-1}	-	*Mpp3*	HOMA-IR	5.8×10^{-6}	-0.32	HF
VPS53	*FAM101B*	Hip	2.2×10^{-1}	-	*Fam101b*	BFP	2.5×10^{-12}	-0.44	HF
JUND	*JUND*	WHR	2.3×10^{-1}	+	*Jund*	BFP	2.6×10^{-7}	0.33	HF
USP37	*RQCD1*	BMI	4.9×10^{-1}	+	*Rqcd1*	SqFP	2.6×10^{-11}	0.42	HF
B3GALT4	*HSD17B8*	LDL-C	5.8×10^{-1}	-	*H2-Ke6*	TC	4.8×10^{-7}	-0.35	HF
LCAT	*GFOD2*	HDL-C	6.7×10^{-1}	-	*Gfod2*	HDL-C	9.5×10^{-7}	-0.34	HF
C1orf85-CCT3-TMEM79	*CCT3*	HbA1c	6.8×10^{-1}	+	*Cct3*	HOMA-IR	1.6×10^{-7}	0.36	HF
INO80E	*YPEL3*	BMI	8.4×10^{-1}	-	*Ypel3*	BFP	2.9×10^{-10}	-0.4	HF
GNL3	*GNL3*	WHR	9.2×10^{-1}	+	*Gnl3*	SqFP	2.8×10^{-13}	0.46	HF

Of 140 METSIM eQTLs coincident with GWAS loci, 107 mouse homologs were available in the HMDP. The table shows the genes for which mouse adipose tissue expression was correlated ($P < 5.2 \times 10^{-5}$) with a similar metabolic trait in the same direction. Matsuda, Matsuda index; WHR, waist-to-hip ratio; TG, triglycerides; Adipo,

adiponectin; HDL-C, high density lipoprotein cholesterol; Waist, waist circumference; LDL-C, low density lipoprotein cholesterol; BMI, body mass index; P_ins, proinsulin; Gluc, glucose; Ins, insulin; Hip, hip circumference; HbA1c, glycated hemoglobin; BFP, body fat percentage; SqFP, subcutaneous fat percentage; TC, total cholesterol; HF, high fat diet

Table S14: Trans-eQTL hotspots identified in METSIM adipose tissue and their look ups in the MuTHER cohort (red color indicates cis regulated gene in the locus)

Table S14 is an online Excel file (Table S14.xlsx)

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