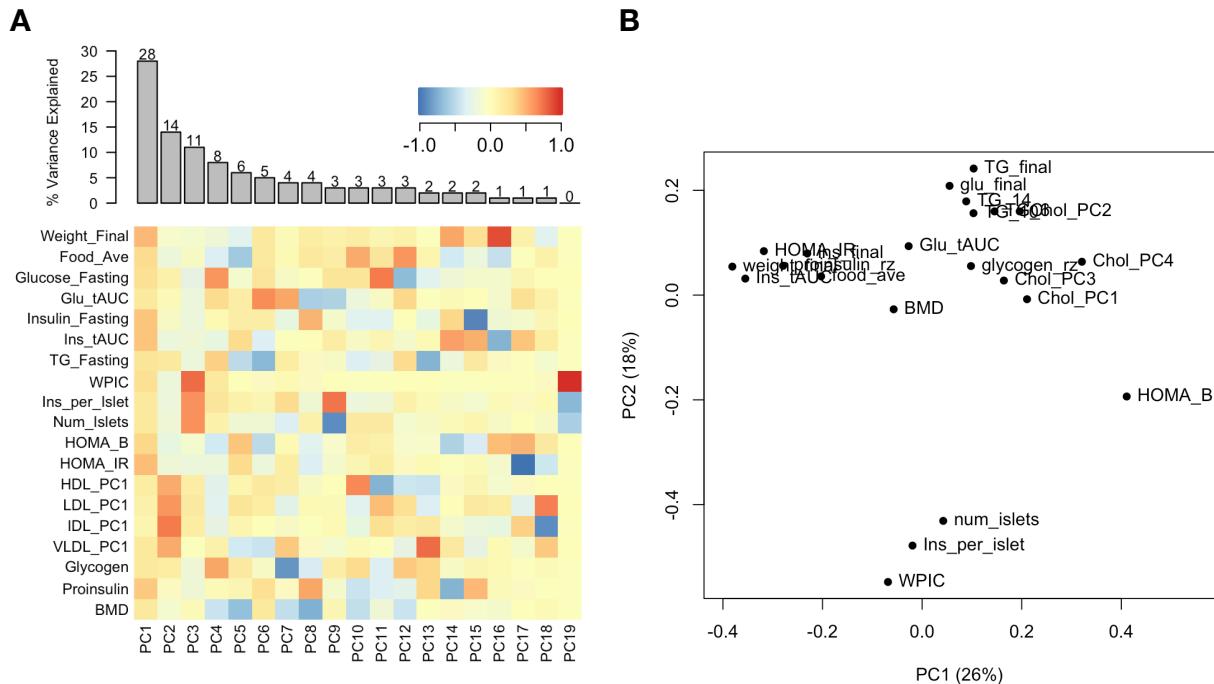


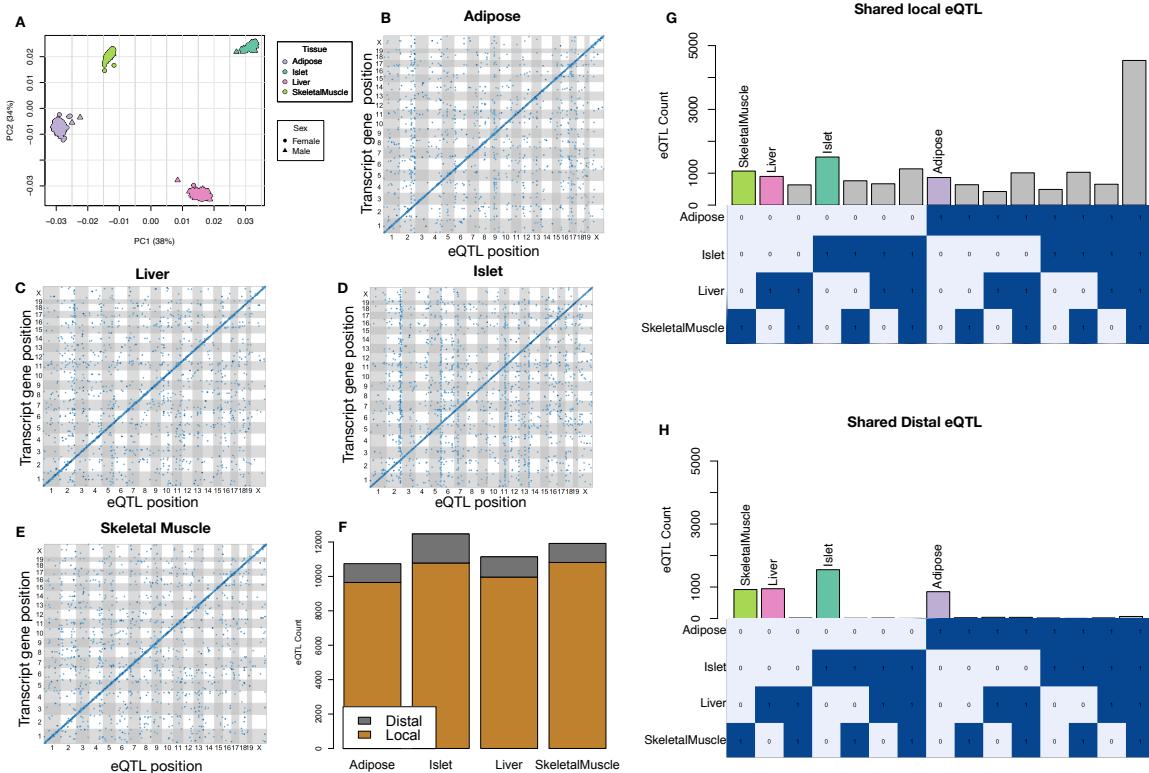
1 Supplementary Figures for: Transcripts with high distal heritability
 2 mediate genetic effects on complex metabolic traits

3

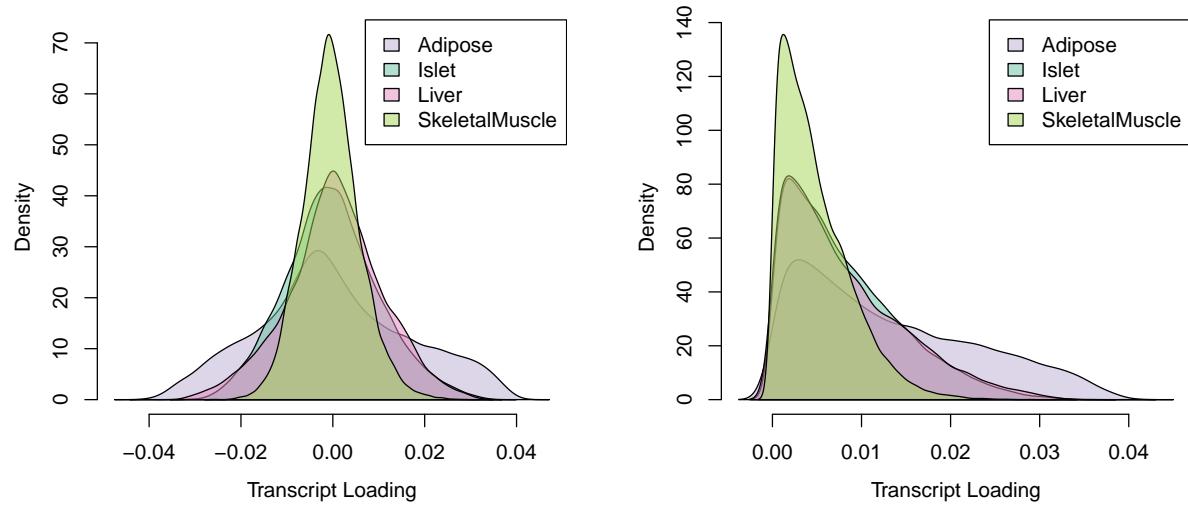


Supplementary Figure 1: Trait matrix decomposition. **A** The heat map shows the loadings of each trait onto each principal component of the trait matrix derived from 471 DO mice (231 females and 240 males). The bars at the top show the percent variance explained for each principal component. **B** Traits plotted by the first and second principal components of the trait matrix. This view shows clustering of traits into insulin- and weight-related traits, lipid-related traits, and ex-vivo pancreatic measurements. Source data are provided as a Source Data file.

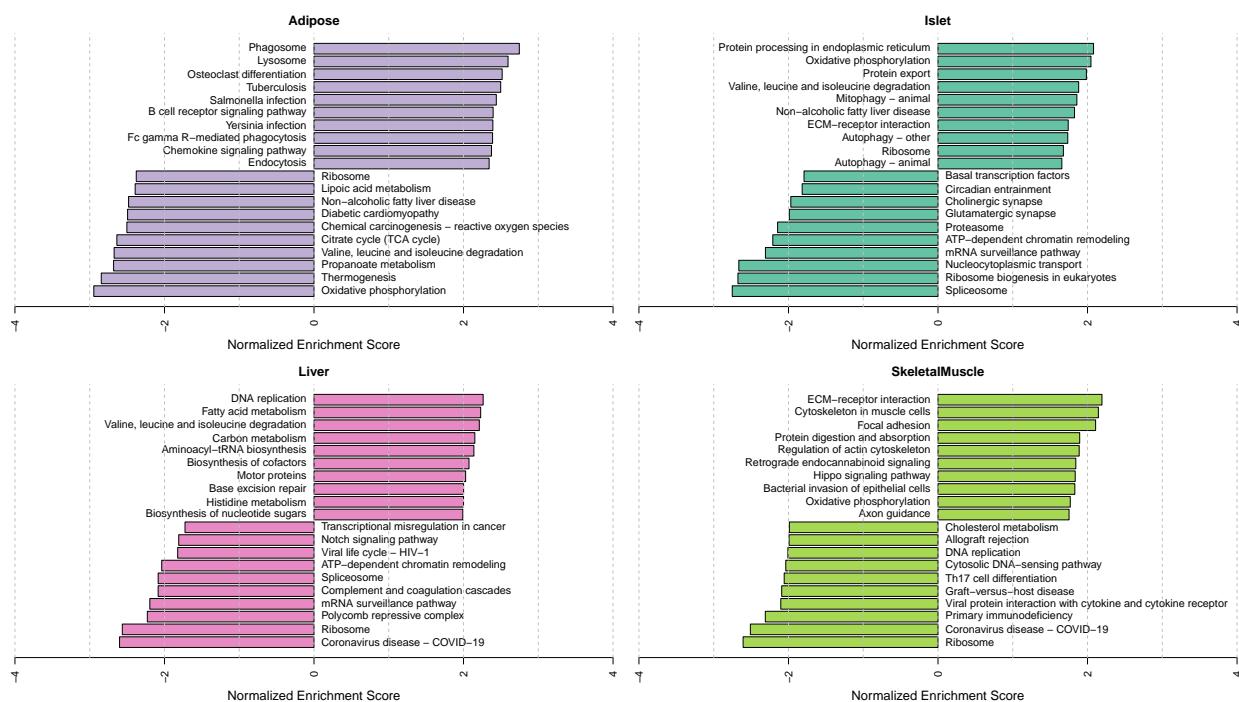
Supplemental Figure



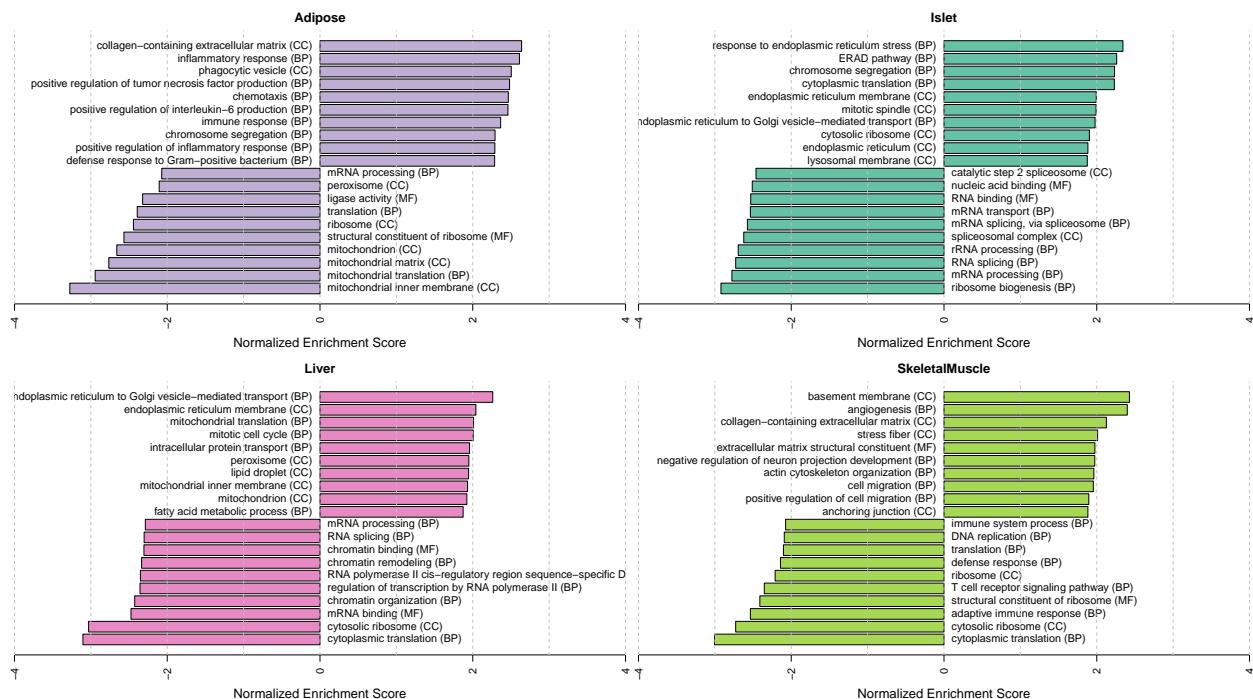
Supplementary Figure 2: Overview of eQTL analysis in DO mice. **A.** RNA seq samples from the four different tissues clustered by tissue. **B.-E.** eQTL maps are shown for each tissue. The *x*-axis shows the position of the mapped eQTL, and the *y*-axis shows the physical position of the gene encoding each mapped transcript. Each dot represents an eQTL with a minimum LOD score of 8, which represents a genome-wide permutation-based threshold of $p < 0.01$. The dots on the diagonal are locally regulated eQTL for which the mapped eQTL is at the within 4Mb of the encoding gene. Dots off the diagonal are distally regulated eQTL for which the mapped eQTL is distant from the gene encoding the transcript. **F.** Comparison of the total number of local and distal eQTL with a minimum LOD score of 8 in each tissue. All tissues have comparable numbers of eQTL. Local eQTLs are much more numerous than distal eQTL. **G.** Counts of transcripts with local eQTL shared across multiple tissues. The majority of local eQTLs were shared across all four tissues. **H.** Counts of transcripts with distal eQTL shared across multiple tissues. The majority of distal eQTL were tissue-specific and not shared across multiple tissues. For both G and H, eQTL for a given transcript were considered shared in two tissues if they were within 4Mb of each other. Colored bars indicate the counts for individual tissues for easy of visualization. Source data are provided as a Source Data file.



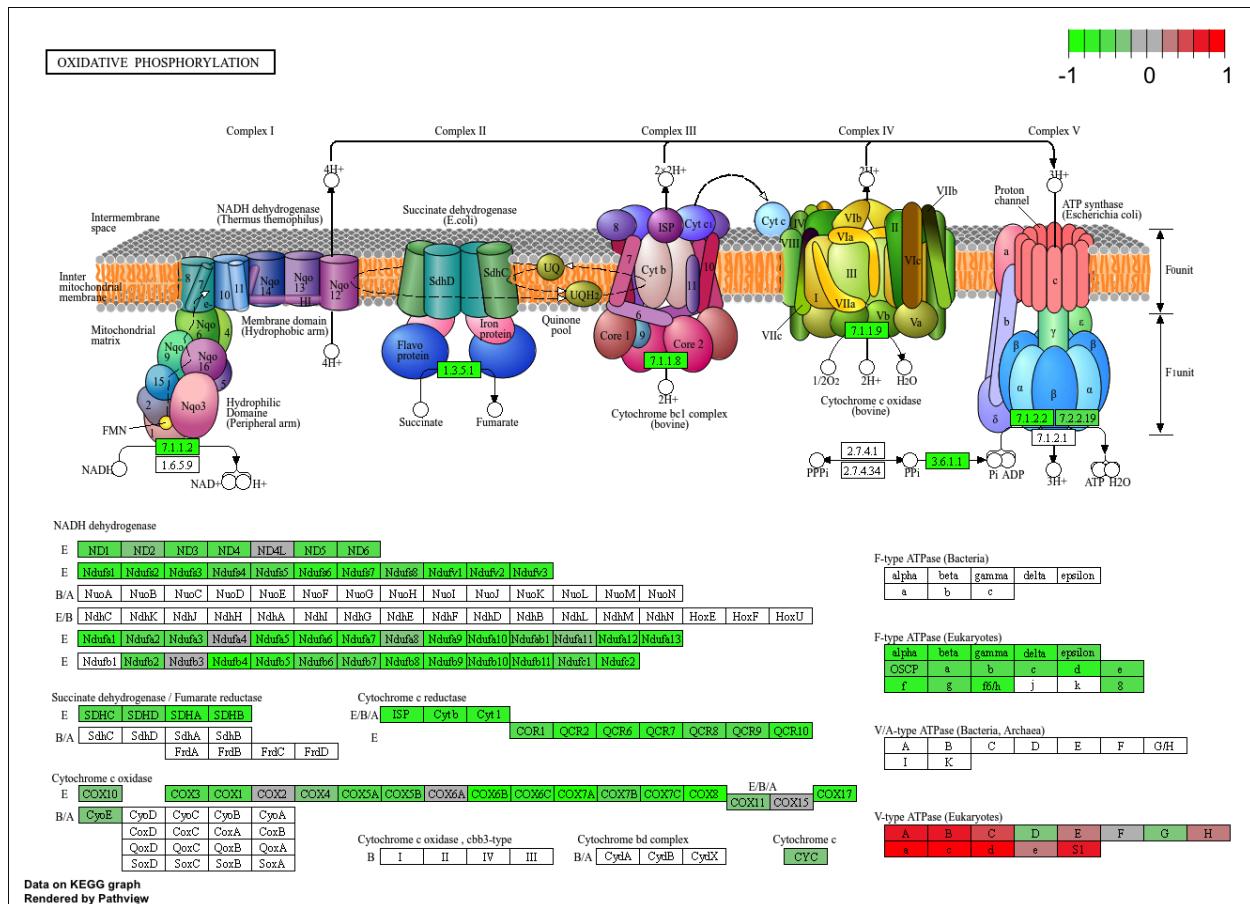
Supplementary Figure 3: Direct comparisons of transcript loadings across tissues also shown in main Figure 4D. **A.** Distributions of transcript loadings are shown as density curves and are differentially colored to indicate tissue. Transcripts in adipose tissue had both the largest positive and negative loadings. **B.** Direct comparison of absolute values of transcript loadings across tissues. Transcripts in adipose tissue had the largest loadings overall, while those in skeletal muscle had the smallest. Source data are provided as a Source Data file. The data shown in this figure are the same as in Fig 4D in the main text and the data are stored in Fig4D_observed.txt.



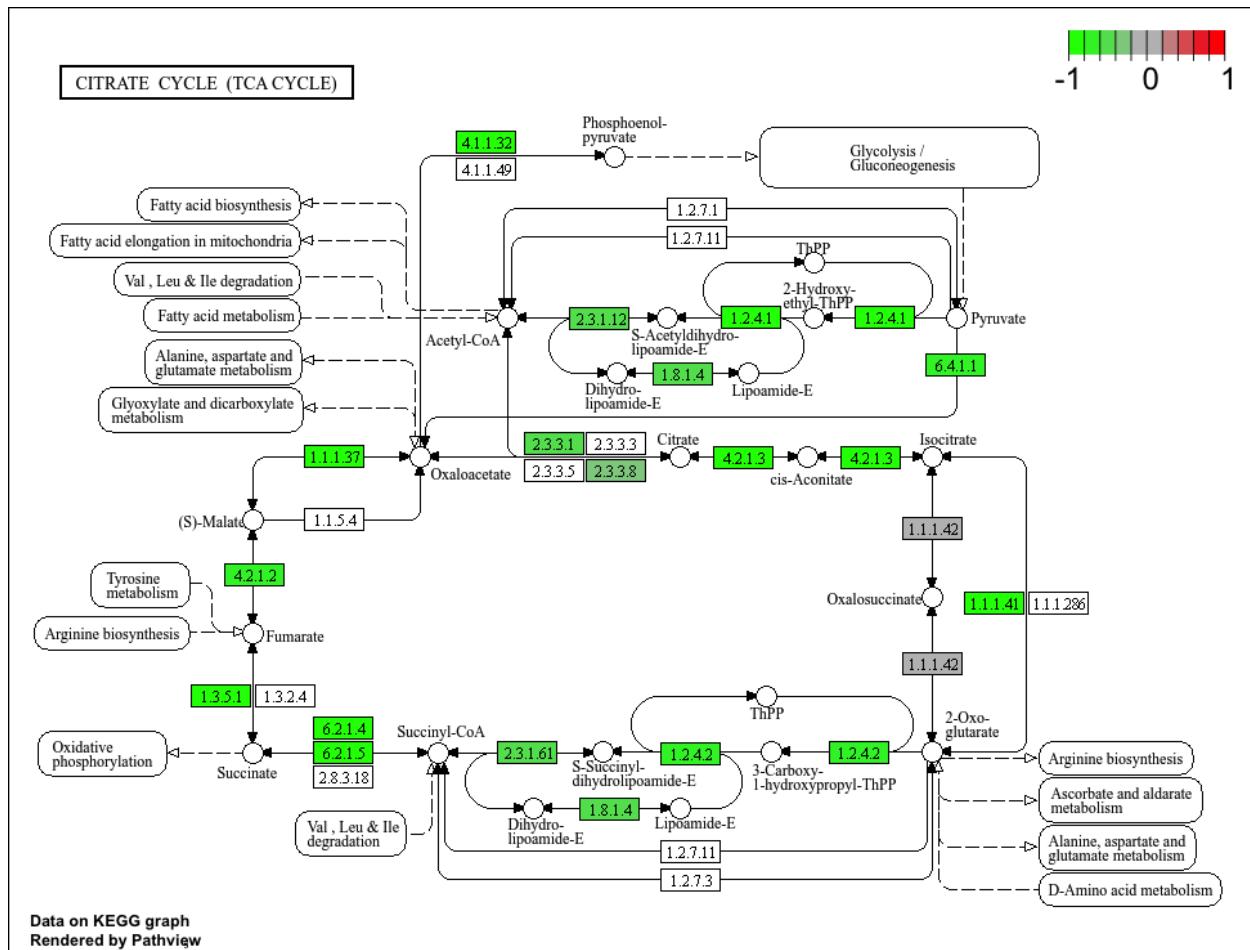
Supplementary Figure 4: Bar plots showing normalized enrichment scores (NES) for KEGG pathways as determined by fast gene score enrichment analysis (fgsea). Only the top 10 positive and top 10 negative scores are shown. Colors indicate tissue. The name beside each bar shows the name of each enriched KEGG pathway. Source data are provided as a Source Data file.



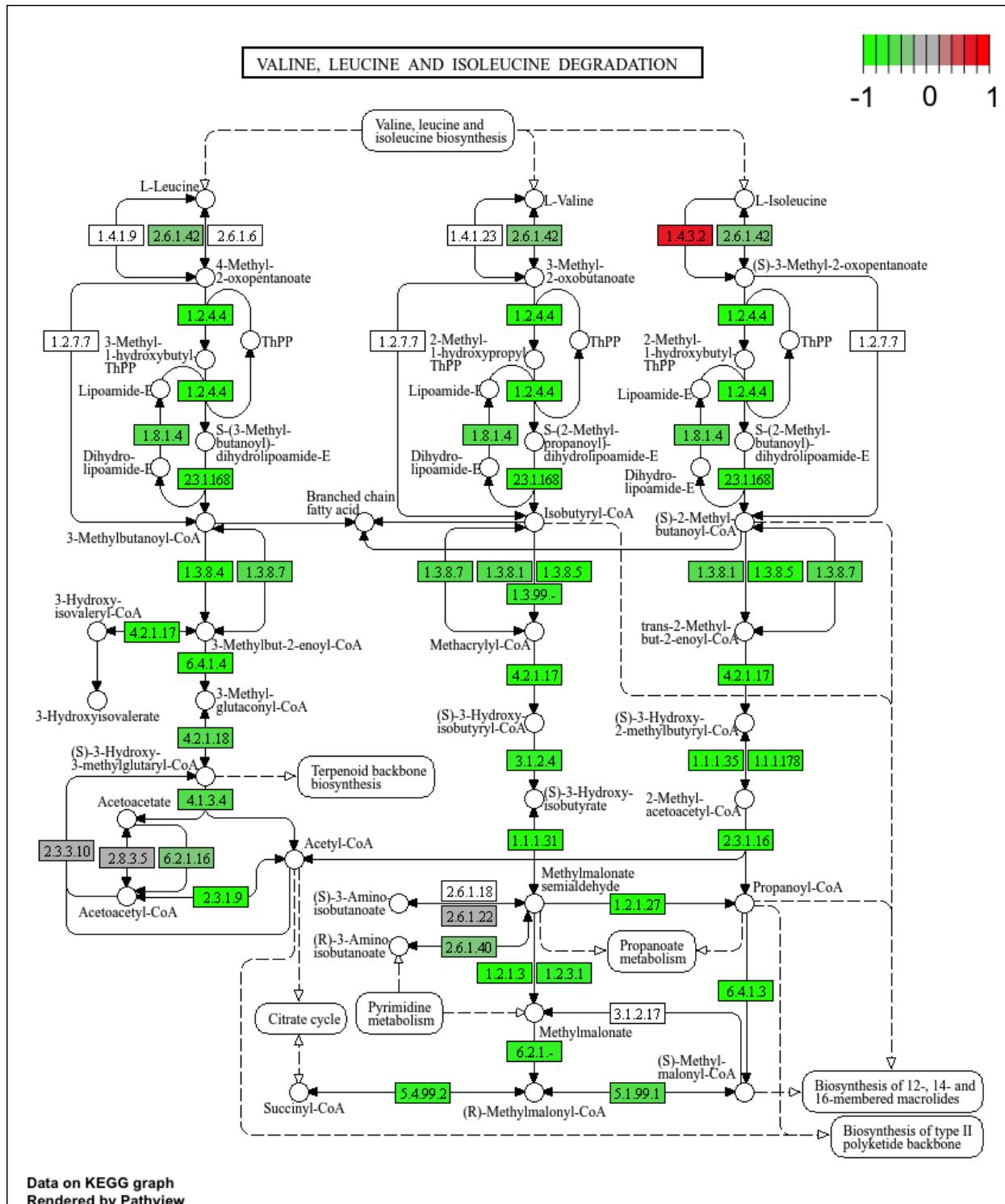
Supplementary Figure 5: Bar plots showing normalized enrichment scores (NES) for GO terms as determined by fast gene score enrichment analysis (fgsea). Only the top 10 positive and top 10 negative scores are shown. Colors indicate tissue. The name beside each bar shows the name of each enriched GO term. The letters in parentheses indicate whether the term is from the biological process ontology (BP), the molecular function ontology (MF), or the cellular compartment ontology (CC). Source data are provided as a Source Data file.



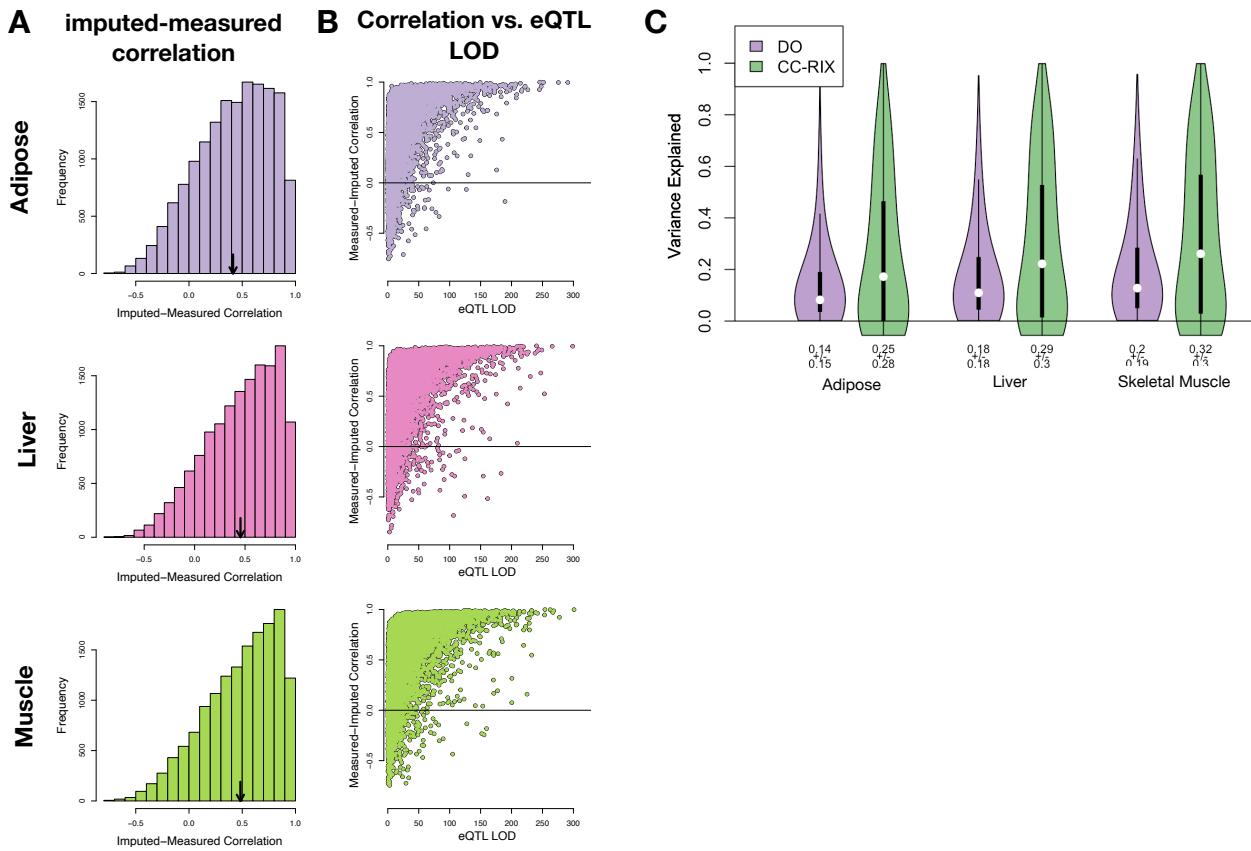
Supplementary Figure 6: The KEGG pathway for oxidative phosphorylation in mice. Each element is colored based on its HDMA loading from adipose tissue scaled to run from -1 to 1. Genes highlighted in green had negative loadings, and those highlighted in red had positive loadings. Almost the entire pathway was strongly negatively loaded indicating that increased expression of genes involved in oxidative phosphorylation was associated with reduced MDI. Source data are provided as a Source Data file.



Supplementary Figure 7: The KEGG pathway for the TCA (citric acid) cycle in mice. Each element is colored based on its HDMA loading from adipose tissue scaled to run from -1 to 1. Genes highlighted in green had negative loadings, and those highlighted in red had positive loadings. Many genes in the cycle were strongly negatively loaded indicating that increased expression of genes involved in the TCA cycle was associated with reduced MDI. Source data are provided as a Source Data file.



Supplementary Figure 8: The KEGG pathway for branched-chain amino acid degradation in mice. Each element is colored based on its HDMA loading from adipose tissue scaled to run from -1 to 1. Genes highlighted in green had negative loadings, and those highlighted in red had positive loadings. Almost the entire pathway was strongly negatively loaded indicating that increased expression of genes involved in branched-chain amino acid degradation was associated with reduced MDI. Source data are provided as a Source Data file.



Supplementary Figure 9: Validation of transcript imputation in the CC-RIX. **A.** Distributions of correlations between imputed and measured transcripts in the CC-RIX across tissues distinguished by color. The arrows indicate the mean of each distribution. All distributions were skewed toward positive correlations and had positive means near a Pearson correlation (r) of 0.5. **B.** The relationship between the correlation between measured and imputed expression in the CC-RIX (x -axis) and eQTL LOD score. As expected, imputations are more accurate for transcripts with strong local eQTL. **C.** Variance explained by local genotype in the DO (purple) and CC-RIX (green). Source data are provided as a Source Data file.

id	norm_cs	cell_iname	pert_type	raw_cs▲	fdr_q_nlog10	set_type	src_set_id
		HA1E	TRT_CP	-0.97	15.65	PCL	CP_PROTEIN_SYNTHESIS_INHIBITOR
		PC3	TRT_SH.CGS	-0.90	15.65	PATHWAY_SET	BIOCARTA_EIF4_PATHWAY
		A375	TRT_CP	-0.87	15.65	MOA_CLASS	RAF_INHIBITOR
		HCC515	TRT_CP	-0.84	15.65	PCL	CP_TOPOISOMERASE_INHIBITOR
		HEPG2	TRT_SH.CGS	-0.82	15.65	PATHWAY_SET	BIOCARTA_BCR_PATHWAY
		PC3	TRT_CP	-0.77	15.65	MOA_CLASS	MTOR_INHIBITOR
		HCC515	TRT_CP	-0.76	15.65	PCL	CP_GLUCOCORTICOID_RECEPTORAGONIST
		HCC515	TRT_CP	-0.76	15.65	MOA_CLASS	GLUCOCORTICOID_RECEPTORAGONIST
		A375	TRT_CP	-0.72	15.65	MOA_CLASS	MTOR_INHIBITOR
		-666	TRT_CP	-0.70	15.65	PCL	CP_PROTEIN_SYNTHESIS_INHIBITOR
		-666	TRT_CP	-0.68	15.65	PCL	CP_JAK_INHIBITOR
		A549	TRT_CP	-0.67	15.65	PCL	CP_GLUCOCORTICOID_RECEPTORAGONIST
		A549	TRT_CP	-0.67	15.65	MOA_CLASS	GLUCOCORTICOID_RECEPTORAGONIST
		-666	TRT_CP	-0.57	15.65	PCL	CP_MTOR_INHIBITOR
		-666	TRT_CP	-0.55	15.65	MOA_CLASS	MTOR_INHIBITOR
		-666	TRT_CP	-0.55	15.65	PCL	CP_PI3K_INHIBITOR
		-666	TRT_CP	0.85	15.65	MOA_CLASS	PKC_ACTIVATOR

Supplementary Figure 10: CMAP results using the adipose tissue composite transcript as an input. Table includes results from all cell types sorted with a $-\log_{10}(q) > 15$. The results are sorted by the correlation of the query to the input with the most negative results at the top. Source data are provided as a Source Data file.

<small>norm_CS</small>	<small>id</small>	<small>cell_name</small>	<small>pert_type</small>	<small>raw_CS▲</small>	<small>fdr_q_nlog10</small>	<small>set_type</small>	<small>src_set_id</small>
		VCAP	TRT_SH.CGS	-0.99	15.65	PATHWAY_SET REACTOME_DOWNSTREAM_TCR_SIGNALING	
		VCAP	TRT_SH.CGS	-0.99	15.65	PATHWAY_SET REACTOME_NOD1_2_SIGNALING_PATHWAY	
		A549	TRT_SH.CGS	-0.92	15.65	PATHWAY_SET BIOCARTA_TNFR1_PATHWAY	
		VCAP	TRT_SH.CGS	-0.92	15.65	PATHWAY_SET HALLMARK_WNT_BETA_CATENIN_SIGNALING	
		HT29	TRT_CP	-0.92	15.65	PCL CP_TUBULIN_INHIBITOR	
	-666		TRT_OE	-0.88	15.65	PCL OE_CELL_CYCLE_INHIBITION	
		VCAP	TRT_SH.CGS	-0.87	15.65	PATHWAY_SET REACTOME_P75_NTR_RECECTOR_MEDiated_SIGNALLING	
		HT29	TRT_CP	-0.86	15.65	MOA_CLASS TUBULIN_INHIBITOR	
		MCF7	TRT_CP	-0.85	15.65	PCL CP_TUBULIN_INHIBITOR	
	-666		TRT_CP	-0.81	15.65	PCL CP_PROTEASOME_INHIBITOR	
	-666		TRT_SH.CGS	-0.80	15.65	PATHWAY_SET REACTOME_DOWNREGULATION_OF_ERBB2_ERBB3_SIGNALING	
	HCC515		TRT_CP	-0.80	15.65	PCL CP_GLUCOCORTICOID_RECECTORAGONIST	
	HCC515		TRT_CP	-0.80	15.65	MOA_CLASS GLUCOCORTICOID_RECECTORAGONIST	
	A549		TRT_OE	-0.78	15.65	PATHWAY_SET REACTOME_RAF_MAP_KINASE CASCADE	
	A549		TRT_OE	-0.78	15.65	PATHWAY_SET PID_RAS_PATHWAY	
	-666		TRT_SH.CGS	-0.78	15.65	PCL KD_RIBOSOMAL_40S_SUBUNIT	
	A549		TRT_OE	-0.76	15.65	PATHWAY_SET REACTOME_SIGNALLING_TO_P38_VIA_RIT_AND_RIN	
	A549		TRT_OE	-0.76	15.65	PATHWAY_SET REACTOME_PROLONGED_ERK_ACTIVATION_EVENTS	
	A549		TRT_OE	-0.73	15.65	PATHWAY_SET PID_TCR_RAS_PATHWAY	
	HA1E		TRT_OE	-0.73	15.65	PATHWAY_SET REACTOME_SHC RELATED_EVENTS	
	HA1E		TRT_OE	-0.71	15.65	PATHWAY_SET PID_EPHB_FWD_PATHWAY	
	-666		TRT_CP	-0.70	15.65	MOA_CLASS GLYCOGEN_SYNTHASE_KINASE_INHIBITOR	
	HA1E		TRT_OE	-0.70	15.65	PATHWAY_SET PID_GMCSF_PATHWAY	
	A549		TRT_OE	-0.69	15.65	PATHWAY_SET REACTOME_SIGNALLING_TO_ERKS	
	-666		TRT_LIG	-0.69	15.65	PATHWAY_SET PID_ERBB_NETWORK_PATHWAY	
	-666		TRT_CP	-0.67	15.65	MOA_CLASS PROTEASOME_INHIBITOR	
	-666		TRT_CP	-0.66	15.65	PCL CP_GLYCOGEN_SYNTHASE_KINASE_INHIBITOR	
	-666		TRT_CP	0.73	15.65	MOA_CLASS MTOR_INHIBITOR	

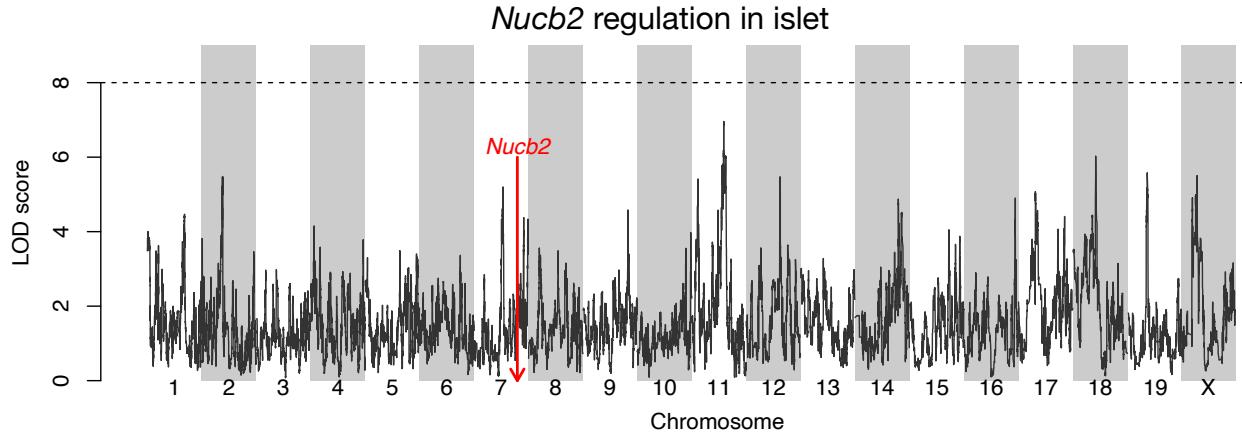
Supplementary Figure 11: CMAP results using the pancreatic islet tissue composite transcript as an input. Table includes results from all cell types sorted with a $-\log_{10}(q) > 15$. The results are sorted by the correlation of the query to the input with the most negative results at the top. Source data are provided as a Source Data file.

norm_CS	id	cell_iname	pert_type	raw_CS ▲	fdr_q_nlog10	set_type	src_set_id
		ASC	TRT_CP	-0.94	0.79	PCL	CP_PARP_INHIBITOR
		ASC	TRT_CP	-0.94	0.79	MOA_CLASS	PROTEIN_TYROSINE_KINASE_INHIBITOR
		ASC	TRT_CP	-0.84	0.45	MOA_CLASS	BTK_INHIBITOR
		ASC	TRT_CP	-0.81	0.39	MOA_CLASS	LEUCINE_RICH_REPEAT_KINASE_INHIBITOR
		ASC	TRT_CP	-0.81	0.79	PCL	CP_HSP_INHIBITOR
		ASC	TRT_CP	-0.80	0.93	PCL	CP_EGFR_INHIBITOR
		ASC	TRT_CP	-0.79	0.32	MOA_CLASS	T-TYPE_CALCIUM_CHANNEL_BLOCKER
		ASC	TRT_CP	-0.79	1.09	PCL	CP_MTOR_INHIBITOR
		ASC	TRT_CP	-0.76	0.97	PCL	CP_PI3K_INHIBITOR
		ASC	TRT_CP	-0.75	0.20	MOA_CLASS	HISTONE_DEMETHYLASE_INHIBITOR
		ASC	TRT_CP	-0.74	0.42	PCL	CP_IKK_INHIBITOR
		ASC	TRT_CP	-0.74	0.83	PCL	CP_AURORA_KINASE_INHIBITOR
		ASC	TRT_CP	-0.74	0.17	PCL	CP_LEUCINE_RICH_REPEAT_KINASE_INHIBITOR
		ASC	TRT_CP	-0.72	0.36	PCL	CP_BRROMODOMAIN_INHIBITOR
		ASC	TRT_CP	-0.71	1.09	MOA_CLASS	TYROSINE_KINASE_INHIBITOR
		ASC	TRT_CP	-0.70	0.82	PCL	CP_PROTEIN_SYNTHESIS_INHIBITOR
		ASC	TRT_CP	-0.67	0.69	PCL	CP_SRC_INHIBITOR
		ASC	TRT_CP	-0.67	0.81	MOA_CLASS	AURORA_KINASE_INHIBITOR
		ASC	TRT_CP	-0.65	0.89	MOA_CLASS	FLT3_INHIBITOR
		ASC	TRT_CP	-0.62	0.40	MOA_CLASS	FGFR_INHIBITOR
		ASC	TRT_CP	-0.59	0.66	MOA_CLASS	MEK_INHIBITOR
		ASC	TRT_CP	-0.59	0.13	MOA_CLASS	SYK_INHIBITOR
		ASC	TRT_CP	-0.58	0.01	PCL	CP_PKC_INHIBITOR
		ASC	TRT_CP	-0.58	0.65	PCL	CP_HDAC_INHIBITOR
		ASC	TRT_CP	-0.58	0.65	PCL	CP_ATPASE_INHIBITOR
		ASC	TRT_CP	-0.53	0.09	PCL	CP_FLT3_INHIBITOR
		ASC	TRT_CP	-0.53	0.42	PCL	CP_P38_MAPK_INHIBITOR
		ASC	TRT_CP	-0.53	0.22	MOA_CLASS	IKK_INHIBITOR
		ASC	TRT_CP	-0.52	0.58	PCL	CP_VEGFR_INHIBITOR
		ASC	TRT_CP	-0.51	-0.00	PCL	CP_T_TYPE_CALCIUM_CHANNEL_BLOCKER

Supplementary Figure 12: CMAP results using the adipose tissue composite transcript as an input. Table includes the top 30 results derived only from normal adipocytes (ASC) regardless of significance. The results are sorted by the correlation of the query to the input with the most negative results at the top. Source data are provided as a Source Data file.

id	norm_CS	cell_iname	pert_type	raw_CS	fdr_q_nlog10	set_type	src_set_id
		YAPC	TRT_CP	-1.00	0.67	MOA_CLASS	ABL_KINASE_INHIBITOR
		YAPC	TRT_CP	-0.99	0.66	PCL	CP_CDK_INHIBITOR
		YAPC	TRT_CP	-0.97	1.41	PCL	CP_TOPOISOMERASE_INHIBITOR
		YAPC	TRT_CP	-0.95	0.70	MOA_CLASS	THYMIDYLATE_SYNTHASE_INHIBITOR
		YAPC	TRT_CP	-0.95	0.62	MOA_CLASS	ADRENERGIC_INHIBITOR
		YAPC	TRT_CP	-0.94	0.50	MOA_CLASS	BENZODIAZEPINE_RECECTOR_ANTAGONIST
		YAPC	TRT_CP	-0.89	0.63	PCL	CP_RIBONUCLEOTIDE_REDUCTASE_INHIBITOR
		YAPC	TRT_CP	-0.88	0.52	MOA_CLASS	VASOPRESSIN_RECECTOR_ANTAGONIST
		YAPC	TRT_CP	-0.85	0.63	MOA_CLASS	ANGIOTENSIN_RECECTOR_ANTAGONIST
		YAPC	TRT_CP	-0.85	0.33	PCL	CP_CANNABINOID_RECECTORAGONIST
		YAPC	TRT_CP	-0.84	0.30	PCL	CP_RETINOID_RECECTORAGONIST
		YAPC	TRT_CP	-0.83	1.19	MOA_CLASS	NFKB_PATHWAY_INHIBITOR
		YAPC	TRT_CP	-0.83	0.54	MOA_CLASS	DNA_ALKYLATING_DRUG
		YAPC	TRT_CP	-0.80	0.50	MOA_CLASS	CHOLESTEROL_INHIBITOR
		YAPC	TRT_CP	-0.79	0.15	MOA_CLASS	SULFONYLUREA
		YAPC	TRT_CP	-0.78	0.52	MOA_CLASS	HIV_INTEGRASE_INHIBITOR
		YAPC	TRT_CP	-0.78	0.13	MOA_CLASS	LEUKOTRIENE_INHIBITOR
		YAPC	TRT_CP	-0.78	0.45	PCL	CP_PPAR_RECECTORAGONIST
		YAPC	TRT_CP	-0.78	0.54	MOA_CLASS	INSULIN_SENSITIZER
		YAPC	TRT_CP	-0.77	0.51	MOA_CLASS	ESTROGEN_RECECTORANTAGONIST
		YAPC	TRT_CP	-0.77	0.76	MOA_CLASS	DNA_SYNTHESIS_INHIBITOR
		YAPC	TRT_XPR	-0.77	0.67	PATHWAY_SET	BIOCARTA_PARKIN_PATHWAY
		YAPC	TRT_CP	-0.77	0.51	PCL	CP_VEGFR_INHIBITOR
		YAPC	TRT_CP	-0.75	0.39	MOA_CLASS	RNA_SYNTHESIS_INHIBITOR
		YAPC	TRT_CP	-0.72	0.60	MOA_CLASS	BCR-ABL_KINASE_INHIBITOR
		YAPC	TRT_XPR	-0.71	0.66	PATHWAY_SET	BIOCARTA_EIF_PATHWAY
		YAPC	TRT_XPR	-0.69	0.54	PATHWAY_SET	PID_CIRCADIAN_PATHWAY
		YAPC	TRT_CP	-0.68	0.77	MOA_CLASS	TOPOISOMERASE_INHIBITOR
		YAPC	TRT_XPR	-0.64	0.49	PATHWAY_SET	BIOCARTA_CBL_PATHWAY
		YAPC	TRT_CP	-0.64	0.53	MOA_CLASS	TUBULIN_INHIBITOR

Supplementary Figure 13: CMAP results using the pancreatic islet composite transcript as an input. Table includes the top 30 results derived only from YAPC cells, which are derived from pancreatic carcinoma cells. Results are shown regardless of significance and are sorted by the correlation of the query to the input with the most negative results at the top. Source data are provided as a Source Data file.



Supplementary Figure 14: Regulation of *Nucb2* expression in islet. *Nucb2* is encoded on mouse chromosome 7 at 116.5 Mb (red arrow). In islets the heritability of *Nucb2* expression levels is 69% heritable. This LOD score trace shows that there is no local eQTL at the position of the gene, nor any strong distal eQTLs anywhere else in the genome. The horizontal dashed line shows the genome-wide FDR threshold of 0.01. Source data are provided as a Source Data file.