Table of Contents

Supplementary Table S1. T2D *cis*-NEMG functions. The 50 *cis*-NEMGs are sorted into functional groups. A brief summary of protein function is provided, with the relevant KEGG[1] pathways, KEGG ontology terms and/or Genecards summaries (www.genecards.org)[2] presented. Colour-coded circles correspond to Figure 2 (main text). The fourth column includes citations and brief explanations for any genes which have been previously linked with diabetes in the literature. This list aims to identify all relevant publications but may not be exhaustive.

- Amino acid metabolism
- Butanoate metabolism
- Propanoate metabolism
- Mitochondrial transport
- Lipid metabolism
- TCA cycle / glycolysis
- Autophagy & calcium homeostasis
- Oxidative phosphorylation
- Mitochondrial translation
- Mitochondrial transcription
- Protein / ion transport
- Mitochondrial organization
- Apoptosis
- DNA damage response

Gene	Summary of protein function (KO=KEGG ontology)	Group	Evidence linking *cis*-gene to diabetes in the literature
ABAT	**4-Aminobutyrate aminotransferase**. Encodes Gamma-aminobutyric acid transaminase (GABA-T). **KEGG pathways:** alanine, aspartate and glutamate metabolism; valine, leucine and isoleucine (BCAA) degradation; beta-Alanine metabolism; propanoate metabolism; butanoate metabolism		Hepatic ABAT expression is positively associated with plasma insulin and negatively with insulin sensitivity (IS) in humans[3]. GABA-T function is reduced in Diabetic rat retinas[4]. GABA-T knockdown improves IS in obese mice, causing weight loss and decreased food intake[3]. GABA stimulates β-cell replication, enhances insulin secretion, protects against apoptosis and suppresses glucagon secretion[5-11]. GABA-treated high-fat diet (HFD)-mice show ↑glucose tolerance, ↑IS, ↓inflammation and ↑T_{reg}[6].
ABCA13	**ATP Binding Casette Subfamily A Member 13.** KEGG pathways: ABC transporters		-
ABCB9	KEGG pathways: ABC transporters; Lysosome		Locus associated with T2D[12; 13]. *ABCB9* implicated by eQTL analysis[14].
ACAD11	**Acyl-CoA Dehydrogenase Family Member 11**. KO: lipid metabolism. Genecards: "Acyl-CoA dehydrogenase, that exhibits maximal activity towards saturated C22-CoA"		Polymorphisms in the *ACAD11* paralog, *ACAD10*, have been associated with T2D[15].
ACADS	**Acyl-CoA dehydrogenase short chain**. KEGG pathways: Fatty acid degradation; BCAA degradation; beta-alanine, propanoate, butanoate, carbon and fatty metabolism.		ACADS-deficient mice were resistant to HFD-induced obesity and insulin resistance (IR)[16; 17]. Polymorphism associated with reduced glucose-stimulated insulin release[18].
ACSS1	**Acyl-CoA synthetase short chain family member 1.** KEGG pathways: Glycolysis / gluconeogenesis; pyruvate metabolism; glyoxylate and dicarboxylate metabolism; propanoate metabolism. KEGG Orthology: lipid metabolism.		-
ALDH2	**Aldehyde dehydrogenase.** KEGG pathways: fatty acid degradation; arginine and proline metabolism; BCAA degradation; histidine metabolism; tryptophan metabolism; beta-alanine metabolism; glycerolipid metabolism; pyruvate metabolism		May play a role in preventing high-glucose induced cellular dysfunction[19]. Coding mutation associated with T2D and fasting blood glucose[20-22]. May protect against Diabetic cardiomyopathy[23].

ALKBH3	**Alpha-ketoglutarate dependent dioxygenase.** KO: DNA repair and recombination proteins.	-
CCDC58	**Coiled-coil domain containing 58.**	-
CISD2	**CDGSH iron sulfur domain 2.** Genecards: "Regulatory of autophagy… required for BCL2-mediated depression of endoplasmic reticulum [calcium] stores during autophagy."	Mutations cause Wolfran syndrome, which manifests with early-onset diabetes[24-27].
CLIC4	**Chloride intracellular channel protein 4**. KO: ion channels.	Sensitises pancreatic β-cells to apoptosis[28].
COA6	**Cytochrome c oxidase assembly factor 6.** KEGG pathways: thermogenesis. KO: mitochondrial respiratory chain complex assembly factors / complex-IV assembly factors	-
COX7A2	**Cytochrome c oxidase subunit 7a.** KEGG pathways: oxidative phosphorylation; thermogenesis	-
COXPD7	**Chr12 open reading frame 65.** KO: mitochondrial biogenesis / mitochondrial transcription and translation factors.	-
COQ10B	**Coenzyme Q-binding protein.** KO: COQ10.	CoQ10 treatment in Diabetic rat models improve metabolic measures[29; 30] and protects against Diabetic nephropathy[31; 32]. CoQ10 supplementation improves HbA1C levels in individuals with diabetes[33].
CPS1	**Carbamoyl-phosphate synthase 1.** KEGG pathways: arginine biosynthesis; alanine, aspartate and glutamate metabolism; biosynthesis of amino acids.	Genetic variance associated with lower risk of T2D and altered glycine metabolite levels[34]. SNP associated with BMI and directionally consistent with T2D association[35-37].
CYB5R2	**Cytochrome-b5 reductase.** KEGG pathways: amino sugar and nucleotide sugar metabolism.	-
DIABLO	**DIABLO**. KEGG pathways: Apoptosis.	-
FEN1	**Flap endonuclease 1**. KEGG pathways: DNA replication; base excision repair; non-homologous end-joining.	-
FLJ38973	**Chr2 open reading frame 69.**	-
GATC	**Aspartyl-tRNA(Asn)/glutamyl-tRNA(Gln) aminotransferase subunit C.** KEGG pathways: aminoacyl-tRNA biosynthesis. KO: mitochondrial transcription and translation factors.	SNPs associated with diabetic kidney disease in Type 1 diabetes patients[38].
GLS2	**Glutaminase 2**. KEGG pathways: arginine biosynthesis; alanine, aspartate and glutamate metabolism; D-glutamine and D-glutamate metabolism.	*GLS2* missense mutations cause increased glucose production, while mouse knockouts cause lower blood glucose levels in insulin resistant conditions[39]. Genetic variants associated with higher fasting plasma glucose[40; 41].
GPAM	**Glycerol-3-phosphate acyltransferase, mitochondrial.** KEGG pathways: glycerolipid metabolism; glycerophospholipid metabolism.	Knockout mice show hyperinsulinemia and reduced glucose tolerance[42]. Overexpression causes IR[43-45] and knock-down improves IS[46].

HEBP1	**Nuclear factor, erythroid 2 like 2.** Genecards: "Promotes calcium mobilization and chemotaxis in monocytes and dendritic cells".		-
HINT3	**Histidine triad nucleotide binding protein 3.**		-
HSPD1	**Heat shock protein family D (Hsp60) member 1.** KEGG pathways: RNA degradation; Type 1 diabetes mellitus. Genecards: "This protein is essential for the folding of newly imported proteins in the mitochondria."		Tissue-specific alterations in Hsp60 levels in T2D[47; 48], which can be altered by hyperglyemic conditions[49]. Implicated in hyperglycemia-induced renal tubular dysfunction[50]. Dysregulated in T2D hypothalamus[51]. An important modulator of inflammation in autoimmune diabetes[52-55]. Immunity to the Hsp60 peptide p277 can cause diabetes in mice[56]. Hsp60 modulates adiponectin signalling[57].
IDH3A	**Isocitrate dehydrogenase 3 (NAD+) alpha.** KEGG pathways: citrate cycle (TCA cycle); biosynthesis of amino acids		Decreased expression in T2D skeletal muscle[58]. Knock-down in combination with IDH2 may perturb glucose-stimulated insulin secretion[59].
LACTB	**Serine beta-lactamase-like protein LACTB, mitochondrial.** KEGG pathways: none. KO: serine peptidases. Genecards: "Acts as a regulator of mitochondrial lipid metabolism... by decreasing protein levels of PISD…" [2]: forms stable filaments in the mitochondrial intermembrane space, promoting mitochondrial organization and micro-compartmentalization.		-
MARCH5	**MARCH5.** KEGG pathways: none. KO: RING-type E3 ubiquitin transferase. Genecards: "…plays a crucial role in the control of mitochondrial morphology by acting as a positive regulator of mitochondrial fission. May play a role in the prevention of cell senescence acting as a regulatory of mitochondrial quality control."		-
MAIP1	**Matrix AAA peptidase interacting protein 1.** KEGG pathways: none. Genecards: "Promotes sorting of SMDT1 - a core regulatory component of a calcium channel in the mitochondrial inner membrane - in mitochondria by ensuring its maturation."		-
MARS2	**Methionyl-tRNA synthetase.** KEGG pathways: aminoacyl-tRNA biosynthesis.		-
MCCC1	**Methylcrotonoyl-coA carboxylase subunit alpha, mitochondrial.** KEGG pathways: valine, leucine and isoleucine degradation.		Part of a gene network regulated proportionally with IS[60]. Down-regulated in IR adipose tissue[61; 62]. SIRT4 regulates IS in the pancreas via activation of MCCC1[63].
MFF	**Mitochondrial fission factor.** KEGG pathways: none. KO: mitochondrial dynamics / fission and fusion factors.		Excess MFF acts with NR4A1 to initiate mitochondrial fission and apoptosis in diabetic nephropathy[64]. MFF interacts with Mfi, which increases GSIS when knocked-down in mice[65].
MRPL11	**Mitochondrial ribosomal protein L11.**		-
MRPS33	**Mitochondrial ribosomal protein S33.**		*MRPS33* expression is altered and skeletal muscle IS is improved by *PLIN2* overexpression[66]. Differential methylation observed with gestational diabetes mellitus[67].

MTERF2	**Transcription termination factor, mitochondrial**. KO: mitochondrial transcription and translation factors.		-
MTFR1L	**Mitochondrial fission regulator 1 like.** Genecards: "An important paralog of this gene is MTFR2"		-
NAXD	**ATP-dependent NAD(P)H-hydrate dehydratase.** KEGG pathways: none. KO: hydro-lyases. Genecards: "Allows the repair of both epimers of NAD(P)HX, a damaged form of NAD(P)H"		-
NDUFB4	**NADH dehydrogenase (ubiquinone) 1 beta subcomplex subunit 4**. KEGG pathways: oxidative phosphorylation; thermogenesis		Expression is decreased in T2D muscle and adipose[68; 69]. Differentially expressed in mice with diabetic nephropathy[70]. Expression of the related *NDUFB6* correlates with IS[71].
NDUFV3	**NADH dehydrogenase (ubiquinone) flavoprotein 3.** KEGG pathways: oxidative phosphorylation; thermogenesis.		Altered expression in response to insulin[72]. Minor allele in *NDUFV3* associated with lower plasma glucose after oral glucose tolerance test[73].
NIF3L1	**NGG1 interacting factor 3 like 1.** Genecards: "May function as a transcriptional corepressor through its interaction with COP2."		Interacts and forms a complex with WBSCR14, which is linked with Williams-Beuren syndrome (WBS) which manifests with impaired glucose tolerance and silent diabetes[74].
PCCA	**Propionyl-coA carboxylase alpha chain.** KEGG pathways: BCAA, propanoate, glyoxylate and dicarboxylate metabolism		Decreased expression in IR adipose[62].
PDHA2	**Pyruvate dehydrogenase E1 component alpha subunit.** KEGG pathways: glycolysis / gluconeogenesis; citrate cycle (TCA cycle); pyruvate metabolism		Knock-out of the paralogue PDHA1 in mouse islets impairs insulin secretion[75].
PGAM5	**PGAM family member 5, mitochondrial serine/threonine protein phosphatase.** KEGG pathways: mitophagy; necroptosis; TNF signaling		PGAM5 aggrevates development of diabetic renal tubular injury[76]. PGAM5-deficient mice are resistant to high-fat-diet-induced obesity and lipid accumulation[77].
PISD	**Phosphatidylserine decarboxylase.** KEGG pathways: glycerophospholipid metabolism.		-
SFXN2	**Sideroflexin 2.** KO: regulator of mitochondrial biogenesis; transporters; solute carrier family; protein involved in Fe-S cluster biogenesis.		Expression is associated with waist-hip ratio[78]. Gene expression increased in β-cell differentiation and in islets of diabetic rat models[79].
SLC25A26	**Solute carrier family 25.** KO: mitochondrial carrier. Genecards: "transports S-adenosylmethionine (SAM) into the mitochondria."		-
SUOX	**Sulfite oxidase.** KEGG pathway: sulfur metabolism. Genecards: "This enzyme catalyses sulphite oxidation, the final reaction in the oxidative degradation of the sulfur amino acids cysteine and methionine."		Dysreglated in the kidney of T1D mouse model[80]. Locus is associated with T1D and gene expression is associated with T1D risk variants[81-83].
TOMM20	**Mitochondrial import receptor subunit TOM20.** Genecards: "Central component of the receptor complex responsible for the recognition and translocation of cytosolically synthesized mitochondrial proteins."		-
TRMT11	**tRNA (guanine19-N2)-methyltransferase.** KO: tRNA modifications.		-

Supplementary Methods

GEO gene expression datasets quality control and analyses.

Gene expression datasets

Datasets of T2D or insulin resistant (IR) case vs. control gene expression data for the tissues subcutaneous adipose, skeletal muscle, liver and pancreas were identified from the GEO database, using the search string:

(((((T2D OR Type 2 Diab* OR IGT OR insulin resistan* OR IFG OR pre*diab* OR impaired fasting glucose OR impaired glucose tolerance)) AND (homo sapiens[Organism] OR human[Organism])) AND cel[Supplementary Files]) AND expression profiling by array[DataSet Type]) AND (muscle OR skeletal muscle OR adipose OR adipo* OR omental OR subcutaneous OR skeletal muscle OR vastus lateralis OR rectus abdominus OR liver OR hepat* OR pancreas OR islet OR beta cell* OR myotub*)

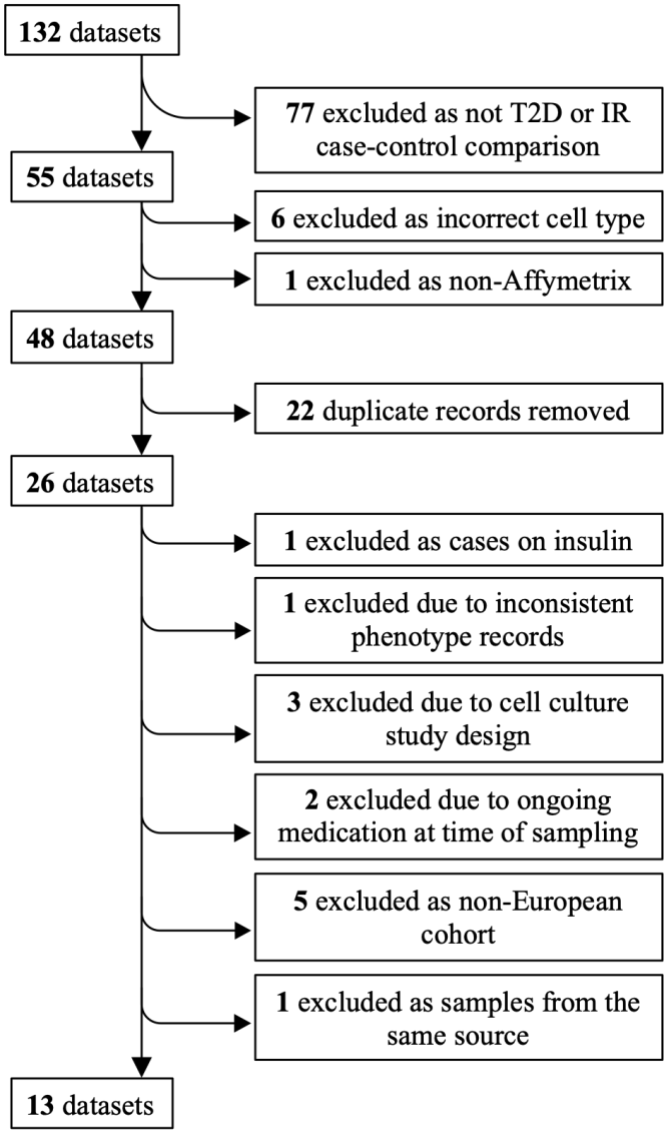
Dataset suitability and quality control (QC)

In order to detect heritable changes in gene expression, strict inclusion and exclusion criteria, shown in Table S2, were applied to maximise homogeneity between datasets and reduce potential confounding of environmental effects or study design. In order to maintain consistency with our subcutaneous adipose eQTL design, datasets in which cases were treated with insulin were excluded in order to enrich for insulin resistant cases rather than insulin deficiency.

Supplementary Table S2. GEO gene expression datasets inclusion and exclusion criteria. *Pancreas datasets were exempt since samples were taken post-mortem and this information was not always available.

Inclusion criteria	Exclusion criteria
T2D or insulin resistant case-control study	Ongoing medications at the time of sampling*
Baseline gene expression measures	Non-European cohort
Raw data available as CEL files	Measurements from cultured cells
Data generated on an Affymetrix array	
Skeletal muscle, adipose, liver or pancreas	

Following preliminary filtering using the GEO search string above, dataset summaries were manually compared to the inclusion and exclusion criteria. Figure S1 shows the exclusion of datasets during this review stage. 26 datasets were subject to full text review, of which 13 were included in the final analysis; these are listed in Table S3. Detailed summary information regarding the study design and subjects for all datasets are presented in Table S4.



Supplementary Figure S1. GEO gene expression dataset selection. Gene expression datasets were excluded based on the inclusion and exclusion criteria listed in Table S2.

Supplementary Table S3. GEO gene expression datasets. Summary information for the final gene expression datasets obtained from GEO using the inclusion and exclusion criteria listed in Table S2. T2D = Type 2 diabetes, IR = insulin resistant. [a]Dataset GSE13070 provided data for both skeletal muscle and adipose. [b]Dataset GSE25462 also included information for unaffected, normoglycemic but IR offspring with one or two parents with T2D.

GEO datasets included in meta-analysis				
GEO ID	**Case/Control**	**Phenotype**	**Array**	**Tissue**
GSE13070[a]	51/18	IR	HG-U133_ Plus2	Skeletal muscle
GSE22435	10/7	T2D+IR	HG-U133_ Plus2	Skeletal muscle
GSE25462[b]	11/15	T2D	HG-U133_ Plus2	Skeletal muscle
GSE27949	10/11	IR	HG-U133_ Plus2	Subcutaneous adipose

GSE20950	9/10	IR	HG-U133_ Plus2	Subcutaneous adipose
GSE26637	5/5	IR	HG-U133_ Plus2	Subcutaneous adipose
GSE13070[a]	28/6	T2D	HG-U133_ Plus2	Subcutaneous adipose
GSE94753	18/21	IR	HuGene-1_1-st	Subcutaneous adipose
GSE15653	13/5	T2D	HG-U133A	Liver
GSE64998	7/8	T2D	HuGene-1_1-st	Liver
GSE76894	19/83	T2D	HG-U133_ Plus2	Pancreas
GSE25724	6/7	T2D	HG-U133A	Pancreas
GSE41762	20/57	T2D	HuGene-1_0-st	Pancreas

Microarray statistical analysis

All analyses were carried out using R version 3.6. For all datasets, raw CEL files were downloaded from GEO and corresponding R annotation packages were downloaded: Human Genome U133 Plus 2.0 Array, *hgu133plus2.db* v3.2.3 (21276 genes)[84]; Affymetrix Human Full Length HuGeneFL Array, *pd.hu6800* v3.2.3 (6021 genes)[85]; Affymetrix Human Gene 1.0 ST Array, *hugene10stprobeset.db* (20212 genes)[86]; Affymetrix Human Genome U95 Version 2 Array, *pd.hg.u95av2* (9667 genes)[87]. Raw data was normalized using Robust Multi-array Averaging (RMA) from the Bioconductor package, *oligo* v.1.48.0[88] and used to calculate gene-centric Z scores measuring differential expression between cases and controls, using a linear mixed-effects model to include multiple probes per gene as a random effect (in R, *lmer* from the *lme4* package for >1 probe or *lm* for 1 probe). Where available, age and BMI were included as covariates (see Table S4).

$$y = expression \sim caco + age + bmi + (1|probe)$$

Meta-analysis of gene sets was carried out according to Choi et al.[89] using the R package *GeneMeta* v.1.56.0.

For the purposes of meta-analysis, study design and dataset similarities were scrutinized according to the inclusion and exclusion criteria, resulting in the meta-analysis of datasets with the most consistent designs and lowest potential for confounding. Datasets in which cases were insulin treated were excluded in order to (1) enrich for insulin resistant individuals over insulin deficient, to be consistent with the study design of eQTL mapping in subcutaneous adipose (a tissue implicated in peripheral insulin resistance) and (2) reduce confounding of gene expression results due to insulin exposure. Inter-dataset correlations of gene level summary Z statistics (Z scores), representing case vs control expression on a global scale are presented in Figure S2. Global correlations were calculated using Z scores for genes with an absolute Z score >1 in both datasets in order to reduce non-significant noise.

Supplementary Table S4. Summary information for all GEO gene expression datasets analysed.

Skeletal Muscle

GEO ID, tissue & date submitted	Ca/Co (M/F)[a]	Array[b]	Ethnicity	Medication	Disease duration	Inclusion and Exclusion	Co-variates	BMI[c]	Age[c]	Fasting state	Family history
GSE13070[90] *Vastus lateralis* Oct 2008	NGT 18 T2D 51 **Mostly male*	HG-U133_ Plus2	-	Discontinued two weeks prior.	-	Exclusion: Active cardiac, liver, or renal disease or long-term complications from diabetes.	-	NGT 24.6±0.8* T2D 35.5±0.8*	NGT 25±0.8* T2D 36±0.8*	-	-
GSE22435[91] *Rectus abdominus* Aug 2011	NGT 0/7 T2D 0/10	HG-U133_ Plus2	Finnish	None	Diagnosed during the study (IGT=4 and T2D=3). No known glucose intolerance before.	Inclusion: receiving chole-cystectomy & post-menopausal. Normal liver, kidney and thyroid function, no history of excessive alcohol intake, and no major chronic illness.	Age & BMI	NGT 27.4±5.4 T2D 31.70±6.5	NGT 60±5.0 T2D 60±4.8	-	-
GSE25462[92] *Vastus lateralis* Mar 2011	FH- 7/8 FH+ 11/14 T2D 6/5	HG-U133_ Plus2	-	None (educational interventions)	T2D subjects >1 year. FH+ individuals have NGT.	-	Age & BMI	NGT 25.1±3.3 1 parent 27.7±5.6 2 parents 28.4±6.9 T2D 32.80±8.1	NGT 38±12.0 1 parent 36±10.0 2 parents 40±12.0 T2D 50±14.0	Yes	Number of parents with T2D for controls.

Subcutaneous adipose

GEO ID, tissue & date submitted	Ca/Co (M/F)[a]	Array[b]	Ethnicity	Medication	Disease duration	Inclusion and Exclusion	Co-variates	BMI[c]	Age[c]	Fasting state	Family history
GSE27949[93] Mar 2011	NGT 11 IGT 10 T2D 12	HG-U133_ Plus2	'Likely Scandin-avian'	Discontinued 24h or one week (hypo-glycemic) prior.	-	Exclusion: treatment with insulin, recent or ongoing infection, history of malignant disease or treatment with anti-inflammatory drugs.	Age & BMI	NGT 30.55±6.1 IGT 31.86±8.1 T2D 31.68±8.1	NGT 44±13.0 IGT 57±11.0 T2D 56±6.8	Yes	-
GSE20950[94] Mar 2010	NGT 2/8 IGT 4/5	HG-U133_ Plus2	-	-	Patients diagnosed during the study.	Exclusion: T2D	-	NGT 48±3* IGT 49±7* *Matched*	NGT 39±6* IGT 43±9*	-	-
GSE26637[95] Jan 2011	NGT 0/5 IGT 0/5	HG-U133_ Plus2	'Caucasian'	None	N/A	Inclusion: 18-60yrs; no known acute/chronic disease; BMI<40; not pregnant and not taking glucose tolerance-altering treatment.	-	NGT 22.0±0.7* IGT 32.5±1.7*	NGT 33±6* IGT 39±5*	-	-
GSE13070[90] Oct 2008	NGT 6 T2D 28	HG-U133_ Plus2	-	Discontinued two weeks prior.	-	Exclusion: active cardiac, liver, or renal disease or long-term complications from diabetes.	-	NGT 24.6±0.8* T2D 35.5±0.8*	NGT 25±0.8* T2D 36±0.8*	-	-
GSE94753[96] Feb 2017	NGT 0/21	Hu	Residents of	2 contraceptive pills, 4 SSRI, 1	-	-	-	NGT 41±5* IGT 40±6*	NGT 36±7.8 IGT 40±8.1	Yes	

	IR 0/18	Gene-1_1-st	Stockholm, Sweden.	Duloxetine, 2 thiazide and amiloride. One IGT subject on multiple medications.							

Liver

GEO ID, tissue & date submitted	Ca/Co (M/F)[a]	Array[b]	Ethnicity	Medication	Disease duration	Inclusion and Exclusion	Co-variates	BMI[c]	Age[c]	Fasting state	Family history
GSE15653[97] Apr 2009	13/5	HG-U133A	-	None known	Diagnosed during the study	Inclusion: normal hepatic and thyroid function, no history of excessive alcohol intake, and no other chronic illness (undergoing gastric bypass surgery).	Age & BMI	NGT 51.5±4.4 T2D 52.4±6.6	NGT 39±10.9 T2D 46±12.4	Yes	-
GSE64998[98] Jan 2015	NGT 7/0 T2D 8/0	HuGene-1_1-st	'Caucasian'	-	-	Inclusion: obese men undergoing Roux-en Y gastric bypass surgery.	-	NGT 38.6±2.0* T2D 40.3±3.1*	NGT 46±7.6* T2D 41±11*	-	-

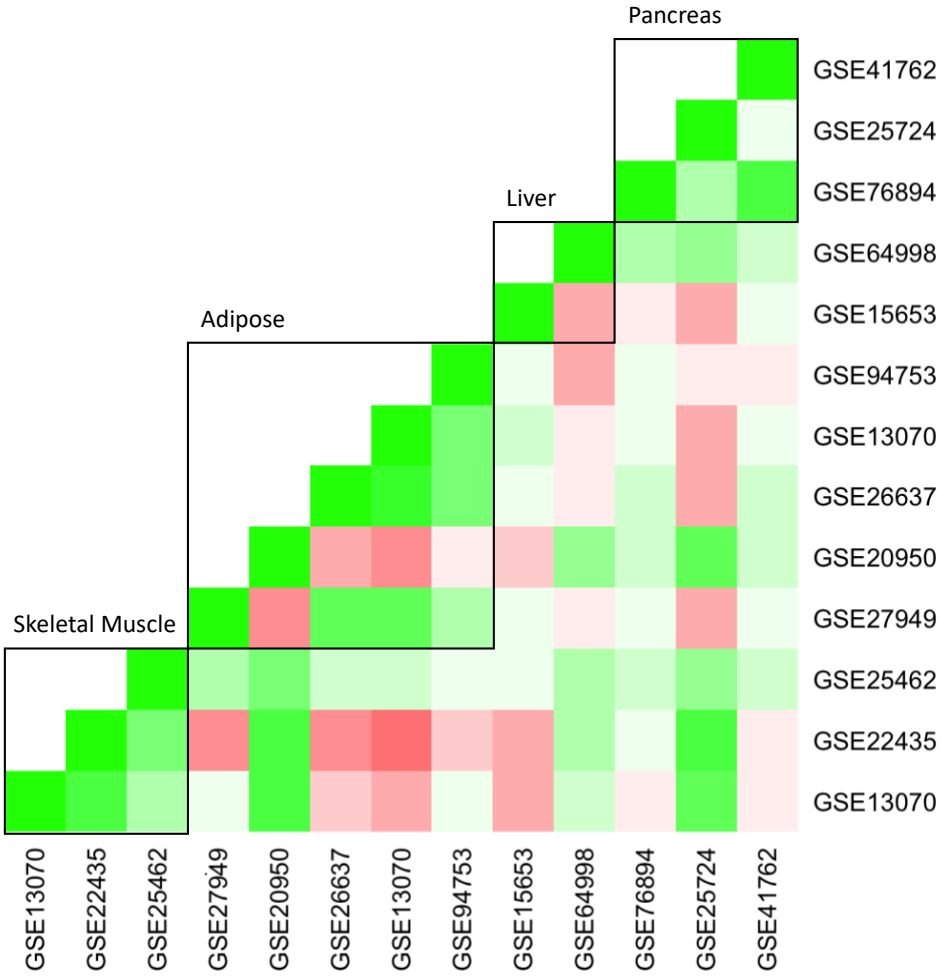
Pancreas

GEO ID, tissue & date submitted	Ca/Co (M/F)[a]	Array[b]	Ethnicity	Medication	Disease duration	Cause of death	Co-variates	BMI[c]	Age[c]	Fasting state	Family history
GSE25724[99] Pancreatic islets Nov 2010	NGT 4/3 T2D 3/3	HG-U133A	-	-	-	-	Age & BMI	NGT 24.8±2.5 T2D 26±2.2	NGT 58±17.3 T2D 71±9.2	-	-
GSE76894[100; 101] Pancreatic islets Dec 2017	NGT 83 T2D 19	HG-U133_Plus2	Donors obtained in Pisa.	-	-	-	Age & BMI	NGT 26.5±3.6 T2D 25.8±4.2	NGT 60±16.2 T2D 72±7.5	-	-
GSE41762[102] Pancreatic islets Oct 2012	NGT 33/24 T2D 11/9	Hu Gene-1_0-st	Nordic Islet Trans-plantation Programme	-	-	-	Age & BMI	NGT 25.4±3.1 T2D 28.5±4.6	NGT 56±10.6 T2D 59±9.3	-	-

[a]NGT: normal glucose tolerance, IR: insulin resistant, T2D: Type 2 diabetes, FH: family history (of T2D). M=Male, F=Female.

[b]Array. HG-U133_Plus2= Affymetrix Human Genome U133 Plus 2.0 Array (n=21276 genes); HG-U133A Affymetrix Human Genome U133 Array (n=13931 genes); Hu6800=Affymetrix Human Full Length HuGeneFL Array (n=6021 genes); HG_U95A=Affymetrix Human Genome U95A Array (n=9666 genes); HuGene-1_0-st=Affymetrix Human Gene 1.0 ST Array (n=20212 genes); HG_U95Av2=Affymetrix Human Genome U95 Version 2 Array (n=9667 genes); U133_X3P, Affymetrix Human X3P Array (n=21157 genes); HuGene-1_1-st=Affymetrix Human Gene 1.1 ST Array (n=20212 genes). [c]Age and BMI, mean ± standard deviation. *individual sample level statistics not available.

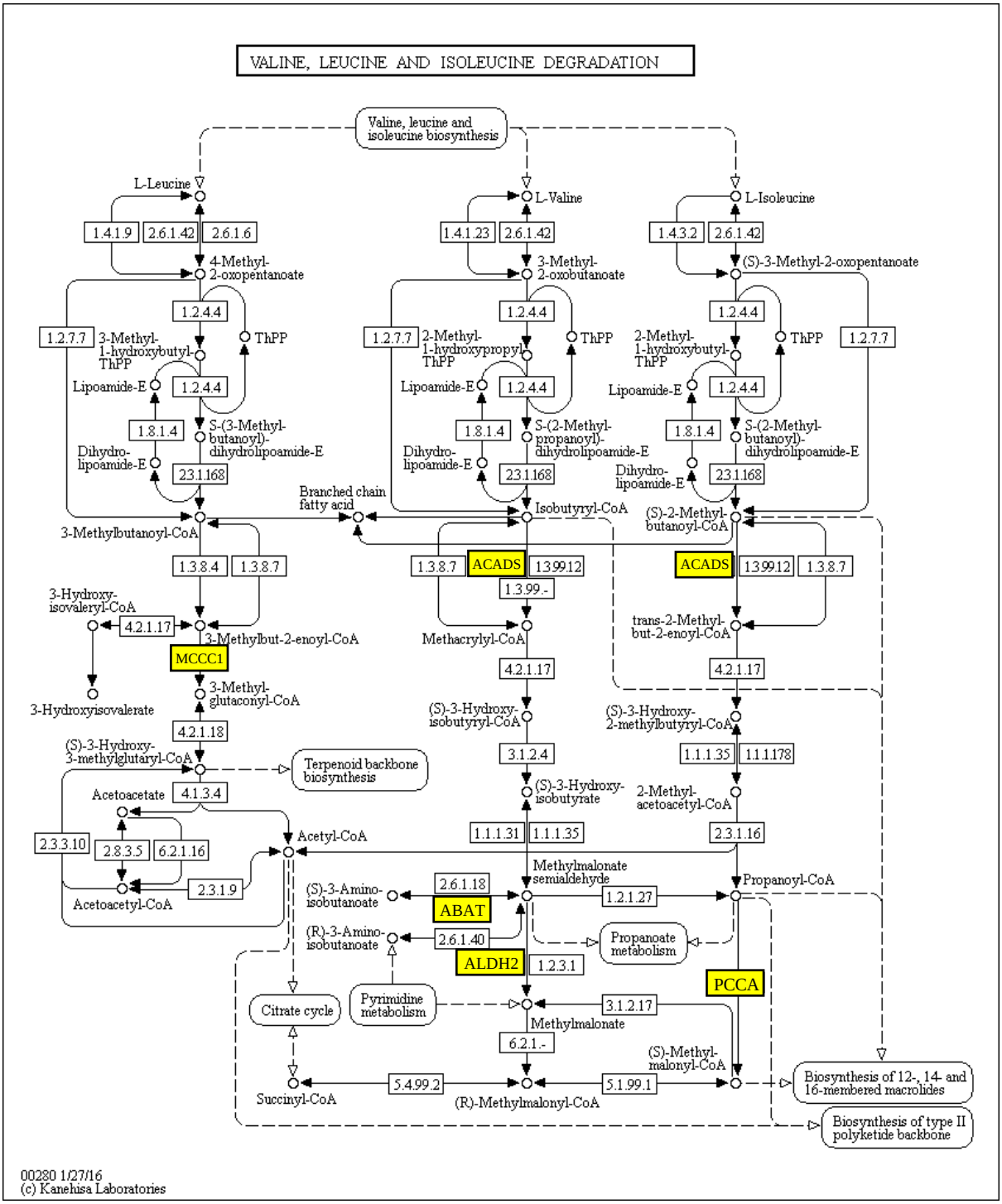
Supplementary Figure S2. GEO dataset correlations. Gene expression datasets showing the global correlation of gene Z scores (absolute Z>1) for all datasets. Correlation ranges from -1 (red), 0 (white) to +1 (green).



Gene set enrichment analysis

Gene set enrichment analysis was carried out using the Bioconductor R package *piano*[103]. Gene sets were loaded as ensembl gene IDs and analysis was carried out using the Wilcoxon rank-sum method with 10,000 permutations. Gene sets included the total T2D *cis*-genes (n = 763), T2D *cis*-NEMGs (n = 50) and three negative controls sets of 50 'non-T2D' NEMGs (NEMGs *not* identified as T2D *cis*-genes in this study). Gene sets representing mitochondrial pathways were downloaded from the Broad Institutes' Molecular Signatures Database (MSigDB)[104; 105], C2 Curated Gene Sets, and HGNC gene identifiers were converted to ensembl in R using *biomaRt* v.2.40.3[106].

Supplementary Figure S3. Five T2D *cis*-NEMGs on the branched chain amino acid catabolism (BCAA) pathway. The figure below is the KEGG pathway for BCAA catabolism[1]. The highlighted enzymes in yellow are encoded by five *cis*-NEMGs: *PCCA*, *MCCC1*, *ABAT*, *ACADS* and *ALDH2*.



Supplementary Table S5. Gene set enrichment analysis for all GEO datasets. Gene set enrichment analysis (GSEA) results, testing differential expression of three gene sets: (1) the total T2D *cis*-genes (n = 763) and (2) the T2D *cis*-NEMGs (n = 50) against the genomic background and (3) the T2D *cis*-NEMGs against a background of all NEMGs (n = 1,204). For the first two GSEA, false discovery rate (FDR) *q*-values are presented, while uncorrected *p*-values are presented for the third analysis (this is due to the limited power to detect an enrichment of *cis*-NEMG differential expression against the background of highly correlated NEMGs). GSEA were calculated with a Wilcoxon statistic and gene sampling using 10,000 permutations. *n.s.* = not significant. ↓ indicates a significant test (*q*-value <0.05 or *p*-value <0.05) for decreased expression relative to the background, ↑ indicates significant increased expression and no arrow indicates a significant result for a test of non-directional enrichment (both increased and decreased).

ADIPOSE (SUBCUTANEOUS)

		GSE27949	GSE20950	GSE26637	GSE13070	GSE101492
Vs. genomic background	Total *cis*-genes (*q*-value)	↑ 0.017	↓ 2.5*e*-04	↑ 0.027	↑ 0.003	↓ 0.025
	Cis-NEMGs (*q*-value)	*n.s.*	↓<1.7*e*-04	*n.s.*	↓ 0.047	↓ 0.049
Vs. all NEMGs	T2D *cis*-NEMGs (*p*-value)	↑0.023	*n.s.*	*n.s.*	*n.s.*	*n.s.*

SKELETAL MUSCLE

		GSE25462	GSE13070	GSE22435
Vs. genomic background	Total *cis*-genes (*q*-value)	*n.s.*	↓ 0.054	↓ 0.002
	T2D *cis*-NEMGs (*q*-value)	↓<4.0*e*-04	↓<1.0*e*-04	↓<2.0*e*-04
Vs. all NEMGs	T2D *cis*-NEMGs (*p*-value)	↓ 0.040	*n.s.*	↓0.086

LIVER

		GSE15653	GSE64998
Vs. genomic background	Total *cis*-genes (*q*-value)	*n.s.*	↓ 0.010
	Cis-NEMGs (*q*-value)	*n.s*	↓ 0.008
Vs. all NEMGs	T2D *cis*-NEMGs (*p*-value)	*n.s.*	*n.s.*

PANCREAS

		GSE76894	GSE25724	GSE41762
Vs. genomic background	Total *cis*-genes (*q*-value)	0.035	*n.s.*	0.018
	Cis-NEMGs (*q*-value)	*n.s.*	↓<1.3*e*-04	*n.s.*
Vs. all NEMGs	T2D *cis*-NEMGs (*p*-value)	*n.s.*	↓ 0.016	↓ 0.008

Supplementary Table S6. All mitochondrial pathways tested for enrichment. A total of 41 gene sets, containing >25% of genes within the combined MitoCarta2.0[107] and MitoCarta+[108] databases, were downloaded from the Molecular Signatures Database (MSigSB) curated gene sets (C2)[105; 109]. These gene sets were subsequently tested for evidence of enrichment by count in the total 763 T2D *cis*-genes, compared to the genomic background.

MSigDB C2 Gene Set (Source)		
(KEGG)	Tryptophan metabolism	Mitochondrial tRNA aminoacylation
Valine leucine and isoleucine degradation	**(Reactome)**	Mitochondrial calcium ion transport
Butanoate metabolism	Release of apoptotic factors from the mitochondria	Pyruvate metabolism and citric acid TCA cycle
Propanoate metabolism	Purine catabolism	Mitochondrial protein import
PPAR signaling pathway	Activated AMPK stimulates FAO in muscle	Metabolism of amino acids and derivatives
Lysine degradation	Gluconeogenesis	Pyrimidine metabolism
Glycolysis and gluconeogenesis	Mitochondrial fatty acid β-oxidation	Fatty acid triacylglycerol and ketone body metabolism
Oxidative phosphorylation	Pyrimidine catabolism	Mitochondrial biogenesis
Fatty acid metabolism	Synthesis of very long chain fatty acyl CoAs	**(Others)**
Glycine, serine and threonine metabolism	Fatty-acyl CoA biosynthesis	(Mootha) mitochondria
Alanine aspartate and glutamate metabolism	TCA cycle and respiratory electron transport	(Biocarta) mitochondria pathway
Glyoxylate and dicarboxylate metabolism	Branched chain amino acid catabolism	(Wong) mitochondria gene module
Citrate / TCA cycle	Tyrosine metabolism	Biotin carboxylases (manually defined)
Beta alanine metabolism	Respiratory electron transport	
Pyruvate metabolism	Synthesis and interconversion of nucleotide di- and	
Arginine and proline metabolism	triphosphates	

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