Supplementary data

CHOP-ASO ameliorates glomerular and tubular damage on top of ACE-inhibition in diabetic kidney disease

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Running *headline: CHOP-ASO in DKD*

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Supplementary Material and Methods

Reagents

The following antibodies were used in the current study: rabbit polyclonal anti-TIM-1 (T-cell transmembrane, immunoglobulin, and mucin; also known as KIM-1) and donkey anti-rabbit IgG H&L (Alexa Fluor® 594) from Abcam, Germany; mouse monoclonal anti-ATF6 and rabbit polyclonal anti-GADD153/CHOP from Novusbio, Germany; rabbit polyclonal anti-SGLT2 from Invitrogen, Germany; mouse anti-CD133 antibody from Biorbyt, United Kingdom; mouse anti-synaptopodin from Santa Cruz Biotechnology Inc., United States; rabbit polyclonal rabbit monoclonal anti-GAPDH from Sigma-Aldrich, Germany. HRP- or FITC-conjugated secondary antibodies to mouse and rabbit IgG from Cell Signaling; Donkey anti-Mouse IgG (H+L) highly cross-adsorbed secondary antibody, Alexa Fluor 488 from Thermo Fisher Scientific, Germany; TEXAS RED anti-rabbit from Jackson ImmunoResearch Laboratories, Inc, Germany. Other reagents used in the current study were as follows: HOECHST 33258, Masson's trichrome staining kit, donkey serum and sulfamethazine (broad spectrum antibiotic), Sigma-Aldrich, Germany; mouse albumin ELISA quantification kit, Bethyl Laboratories, Germany; DMEM, RPMI, Trypsin-EDTA, penicillin, streptomycin, FCS, FBS, ITS supplement and Hepes, PAA Laboratories, Germany; IFN-γ, Cell Sciences; Accu-Chek test strips, Accu-Check glucometer, and protease inhibitor cocktail, Roche Diagnostics, Germany; TrueBlack® Lipofuscin autofluorescence quencher from Biotium, United States; BCA reagent, Perbio Science; Vectashield mounting medium and DAB reagent, Vector Laboratories, United States; PVDF membrane and immobilon^{TM} western chemiluminescent HRP substrate, Millipore, United States ; periodic acid-Schiff reagent, Haemotoxylin, and powdered milk ROTH, Germany.

Antisense oligonucleotides

15-, 16- and 17-mer antisense oligonucleotides specific for human or mouse DDIT3 (Chop) were selected based on the respective RNA sequences. Main criterion for sequence selection was selectivity to avoid undesired off-target effects. LNA-modified Gapmers were ordered from Exiqon or Axolabs and dissolved in H2O (stock concentration 1 mM). Antisense oligonucleotides were added to cells without the use of a transfection reagent in vitro and without any delivery system in vivo.

Sequences of ASOs and the control oligonucleotides used in the study:

ASO ID	Sequence	Descrpition
Chop ASO 1	+T*+A*+C*G*C*T*C*A*G*T*G*C*C*T*+T*+A*+G	Used for *in vitro*
Chop ASO 2	+T*+G*+A*T*A*C*G*C*T*C*A*G*T*G*+C*+C*+T	Used for *in vitro*
ChA	+C*+T*+A*G*C*T*G*T*G*C*C*A*C*+T*+T*+T	Used for *in vivo*
Control oligo 1	+C* + G* + T*T*T*A*G*G*C*T*A*T*G*T*A* + C* + T* + T	Control oligonucleotide[1], Used for *in vivo* and *in vitro*

+ indicates LNA-modified nucleotides and * indicates PTO linkages

Histology and immuohistochemical analysis

Freshly sacrificed mice were perfused first with ice cold PBS and then with 4% buffered paraformaldehyde[2-5]. Tissues were furthered fixed with 4% buffered paraformaldehyde for 2 days, embedded in paraffin and processed for sectioning. Extracellular matrix deposition in glomeruli was assessed by Periodic acid–Schiff staining. The fractional mesangial area (FMA) was calculated following the current DCC (Diabetes Complications Consortium) protocol. Briefly, 5 µm thick sections were stained with Periodic Acid-Schiff reagent. At least 50 different superficial glomeruli per mouse were randomly chosen for analysis. For every investigated glomerulus, total glomerular area and glomerular tuft area were determined by tracing the outline of the Bowman's capsule and the tuft, respectively, using ImageJ. The FMA was calculated as the percentage of the glomerular area relative to the tuft area[5, 6]. For determination of the tubular diameter adjacent sections were compared to ensure that a sagittal tubular cross-section was analyzed. At least 30 randomly chosen tubules were analyzed per mouse using ImageJ software. Immunohistochemical detection of GADD153/CHOP, KIM-1 and ATF6α were performed using specific primary and appropriate secondary antibodies, incubated in 5 % bovine serum albumin (BSA). For immunohistochemical detection of SGLT2, 10 % donkey serum (as secondary antibody has been raised in donkey) was used as blocking solution and for the antibodies dilution. Additionally, sections were incubated with TrueBlack® Lipofuscin autofluorescence quencher (Biotium, Germany), 1X solution in 70 % ethanol for 30 sec at room temperature to reduce background. Control images, obtained following incubation with only primary or only secondary antibody, were used for background correction. Immunohistochemistry and immunofluorescence images were captured with an Olympus Bx43-Microscope (Olympus, Hamburg, Germany). The Image Pro Plus software (version 6.0) and Image J software were used for image analysis. All histological analyses were performed by two independent blinded investigators.

Transmission Electron Microscopy

Ultrastructural images of the glomerular filtration barrier were obtained by transmission electron microscopy as previously described[3, 4]. Renal tissues were fixed with a mix of 2.5 % glutaraldehyde, 2.5 % polyvidone 25, and 0.1 M sodium cacodylate (pH 7.4). After washing with 0.1 M sodium cacodylate buffer (pH 7.4), samples were postfixed in the same buffer containing 2 % osmium tetroxide and 1.5 % potassium ferrocyanide for 1 hour, washed in water, contrasted en bloc with uranyl acetate, dehydrated using an ascending series of ethanol, and embedded in glycidyl ether 100-based resin. Ultrathin sections were cut with a Reichert Ultracut S ultramicrotome (Leica Microsystems, Wetzlar, Germany), contrasted with uranyl acetate and lead citrate, and were viewed with an EM 10 CR electron microscope (Carl Zeiss NTS, Oberkochen, Germany). Thickness of the glomerular basement membrane (GBM) was analyzed using ImageJ software. For each image, the basement membrane thickness was determined at 15 adjacent and evenly distributed locations. To assess the degree of foot process effacement (FPE), the length of the GBM on each micrograph was measured and the number of foot processes per µM GBM was subsequently calculated.

Masson’s trichrome staining

Freshly sacrificed mice were perfused first with ice cold PBS and then with 4 % buffered paraformaldehyde. Tissues were furthered fixed with 4 % buffered paraformaldehyde for 2 days, embedded in paraffin and processed for sectioning. Masson’s trichrome staining (Sigma-Aldrich, Germany) was performed according to the manufacturer’s instructions[4, 7]. Tissue sections (4 µm thickness) were postfixed in preheated Bouin’s solution (Sigma-Aldrich, Germany) at 56°C for 15 min, Weigert’s iron hematoxylin solution for 5 min, Biebrich scarlet acid/fuchsin solution for 5 min, 5 % phosphotungstic/phosphomolybdic acid for 5 min, aniline blue solution for 20 min and 1 % acetic acid for 2 min. Between every staining step, the tissue sections were washed with distilled water. For histological analysis, images were captured with an Olympus Bx43 microscope (Olympus, Hamburg, Germany), and ImageJ software was used for image analysis. All histological analyses were done by an independent blinded investigator.

Analyses of blood samples

Blood samples were obtained from the inferior vena cava of 22-week-old anticoagulated mice (500 U of unfractionated heparin via intraperitoneal injection before blood sampling). Heparinized plasma was obtained by centrifugation of blood samples for 10 minutes at 2000 x g at 4°C. Plasma samples were stored at -80°C until analyses. Plasma angiotensin II was determined using a mouse Angiotensin II ELISA (Sigma Aldrich) according to the manufacturer’s instructions[4]. Plasma levels of ALT (alanine aminotransferase, U/l) and AST (aspartate aminotransferase, U/l) were measured using a enzymatic reaction on the Cobas C111 Chemistry System from Roche, Germany.

Blood pressure measurement

Blood pressure was measured using a noninvasive mouse tail-cuff blood pressure analysis system (CODA; Kent Scientific Corporation)[8].

Immunoblotting

Proteins were isolated and immunoblotting was performed as described[2-5, 7]. In brief, cell lysates were prepared in RIPA buffer (50 mM Tris at pH 7.4, 1 % Nonidet P-40, 0.25 % sodium deoxycholate, 150 mM NaCl, 1 mM EDTA, 1 mM Na_3VO_4, and 1 mM NaF supplemented with protease inhibitor cocktail). Lysates were centrifuged (10000 × g for 10 min at 4°C) and insoluble debris was discarded. The protein concentration in supernatants was quantified using BCA reagent. Equal amounts of protein were electrophoretically separated on 10 % (vol/vol) or 12.5 % (vol/vol) SDS polyacrylamide gels, transferred to PVDF membranes, and probed with the desired primary antibodies overnight at 4°C. Membranes were then washed with TBST and incubated with anti-mouse (1:2000), anti-rat IgG (1:2000) or anti-rabbit IgG (1:2000) horseradish peroxidase-conjugated antibodies, as indicated. Blots were developed with the enhanced chemiluminescence system. To compare and quantify levels of proteins, the density of each band was measured using ImageJ software. Equal loading was confirmed by immunoblotting with GAPDH antibody.

Detection of cell death by TUNEL Assay

Terminal deoxynucleotidyl transferase (TdT) dUTP Nick- End Labeling (TUNEL) assays on tissue sections were done according to the manufacturer's instructions. Briefly, sections were rehydrated, treated for eight min with PBS containing 0.1% Triton and 0.1% M sodium citrate, and incubated with terminal deoxynucleotidyl transferase in the presence of biotinylated dUTP (Biotin-dUTP) (60 min at 37°C). The tissue sections were washed 2-times with PBS for 5 min each. Sections were then incubated with horseradish peroxidase-labeled streptavidin (Streptavidin-HRP). The tissue sections were again washed 2-times with PBS for 5 min each. Dead cells were detected by HRP-DAB (3,3'-diaminobenzidine) reaction. Sections were counterstained with hematoxylin. Images were captured with an Olympus Bx43 microscope (Olympus, Hamburg, Germany), and ImageJ software was used for image analysis. The frequency of dead cells was determined by a blinded investigator by counting TUNEL positive cells and total cell number and calculating the percentage of TUNEL positive cells[2, 5].

Cell culture

Human renal proximal tubular (HKC-8) cells and embryonic kidney (HEK-293) cells were routinely grown and maintained in DMEM low glucose (5.5 mM glucose concentration) RPMI growth medium in the presence of 10 % FBS at 37°C according to manufacturer's instructions (ATCC, USA). Conditionally immortalized human podocytes were cultured as described previously[2, 3, 5]. In brief, podocytes were routinely grown on plates coated with collagen type 1 at 33°C in the presence of interferon γ (10 U/ml) to enhance expression of the thermosensitive T antigen. Under these conditions, cells proliferate and remain undifferentiated. To induce differentiation, podocytes were grown at 37°C in the absence of interferon γ for 14 days. Experiments were performed after 14 days of differentiation. HEK-293 cells and podocytes were maintained in high concentration of glucose (25 mM) for 24 h. CHOP-ASO (10 µM) or Control-ASO (10 µM) were added 24 h before exposure to the high glucose medium. Cell exposed to mannitol (20 mM) plus normal glucose concentration (5.5 mM glucose) served as controls.

RNA-seq, functional annotation and pathway analysis

RNA was extracted from renal tissue samples that were stored in RNAlater using Qiagen RNeasy mini kit plus according to the manufacturer's instructions. Preparation of RNA libraries and the subsequent RNA sequencing was carried out by Genomescan (Leiden, The Netherlands). RNA samples were processed using the NEBNext Ultra II Directional RNA Library Prep Kit for Illumina according to the manufacturer's protocol (NEB #E7760S/L). Briefly, rRNA depletion kit (NEB# E6310) was used to filter rRNA from total RNA. cDNA was synthesized after fragmentation of the rRNA-reduced-RNA, which was used for ligation with the sequencing adapters and PCR amplification of the resulting product. Fragment Analyzer was used to assess quality and yield of the sample preparation. As expected the size distribution of the resulting products in general showed a broad peak between 300-500 bp. Clustering and DNA sequencing was performed according to manufacturer's protocols on an Illumina NovaSeq6000 using a concentration of 1.1 nM of cDNA. Illumina data analysis pipeline RTA3.4.4 and Bcl2fastq (version: v2.20) was used for image analysis, base calling, and quality check.

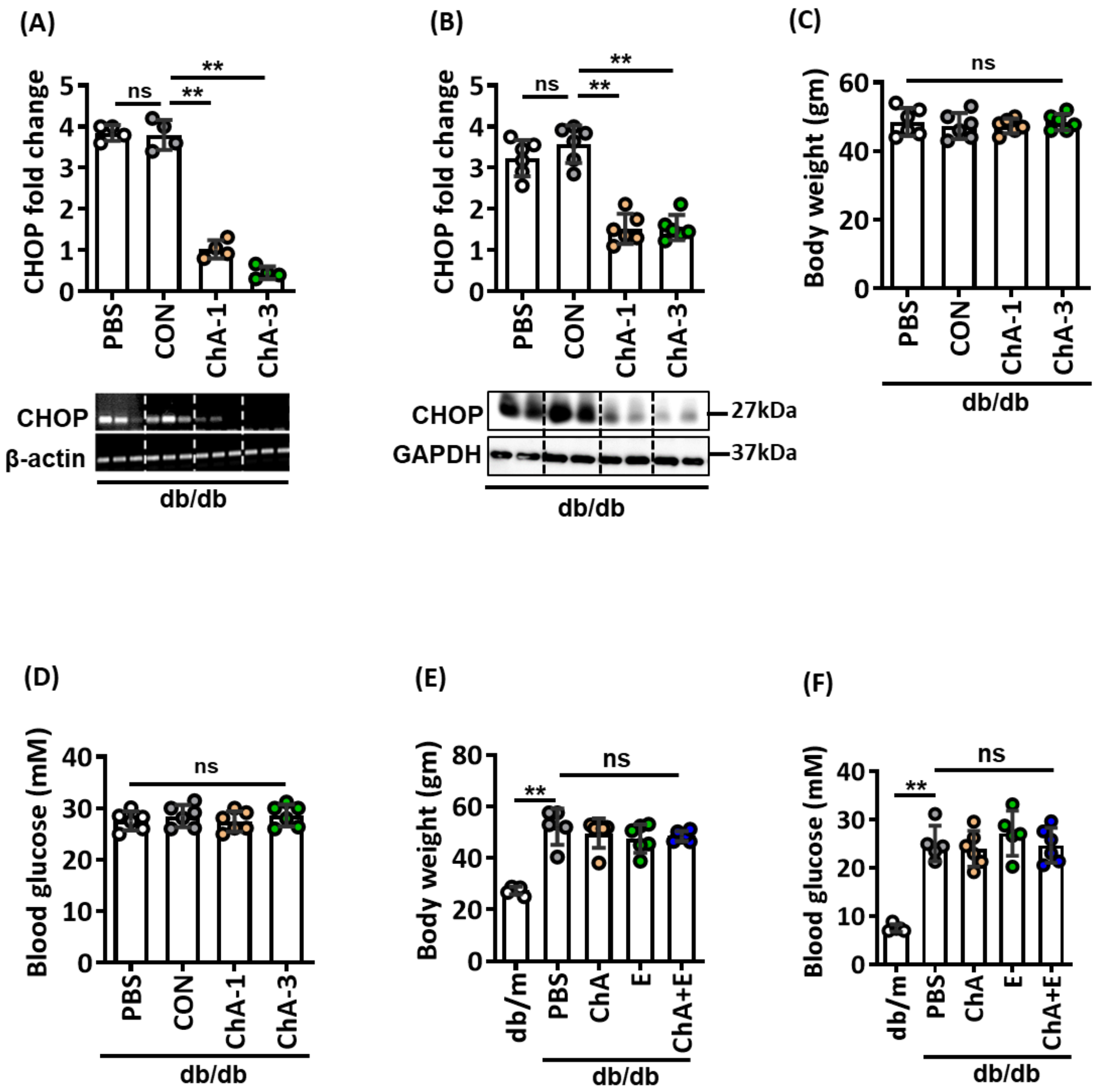
RNA sequencing data was provided from Genomescan in FASTQ format. FASTQ-files were investigated using fastQC (http://www.bioinformatics.babraham.ac.uk/projects/fastqc/) before and after trimming. Version 0.36 of trimmomatic[9] was used to filter low quality reads and to cut TruSeq adapter sequences. FASTQ Screen[10] (version: v0.14.0) was additionally applied on every FASTQ file to investigate and visualize the sequence reads. Salmon[11] was used based on gencode release m24[10] setting the flags gcBias and validate Mappings to quantify gene expression. To prepare the data for differential gene expression analysis the packages tximport[12] and GenomicFeatures[13] in R were utilized. Subsequent analysis was performed using DESeq2 package (1.24.0)[1]. To calculate and visualize the PCA (principal component analysis), the specific function plotPCA was used in combination with ggplot2 (3.3.0, https://link.springer.com/book/10.1007%2F978-3-319-24277-4). As only two samples of the ChA+E group passed QC for the RNA-seq experiments, all results based on analyses involving this group need to be treated with caution.

Pathway analysis was conducted applying the fora function of the fgsea (1.10.1) Bioconductor package [https://doi.org/10.1101/060012] using the ‘BeFree gene-disease associations’ gene sets downloaded from the DisGeNET database (http://www.disgenet.org/)[14] in Feb 2021). Only gene sets containing more than 10 genes were used for analysis. Heatmap was plotted using pheatmap (1.0.12) [Kolde R: pheatmap: Pretty Heatmaps. 2019. R package version 1.0.12. https://CRAN.R-project.org/package=pheatmap and venn diagrams were drawn using VennDiagram (1.6.20) [15].

RNAseq data access

RNA-Seq data have been deposited in the NCBI public database (BioProject accession number PRJNA721721). The data is available at https://dataview.ncbi.nlm.nih.gov/object/PRJNA721721?reviewer=oe4em1df5qhnkikmu82v64cm3i.

Supplementary Fig.1



Supplementary Figure 1 (corresponding to Figure 1).

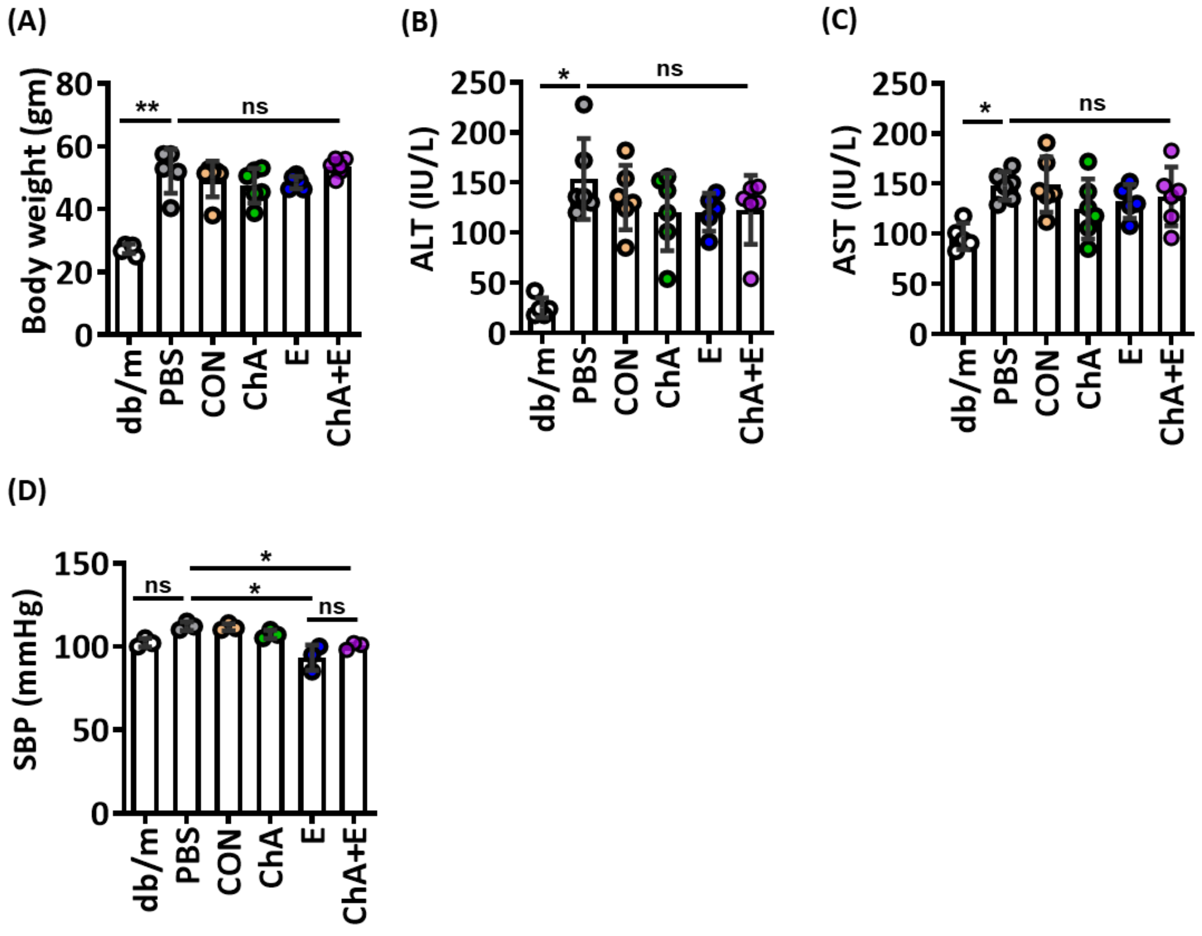
A, B: Scatter plot with bars summarizing renal mRNA (**A**, bottom: representative reverse-transcriptase-PCR gel images, β-actin was used for normalization) and protein (B, bottom: representative immunoblot images of CHOP, GAPDH was used for normalization) expression of CHOP in the dose escalation studies.

C, D: Scatter plot with bars summarizing mouse body weights (**C**) and blood glucose levels (**D**) for the CHOP-ASO dose escalation experiment.

E, F: Scatter plot with bars summarizing mouse body weights (**E**) and blood glucose levels (**F**) after treatment with CHOP-ASO (ChA), ACEi (E) or CHOP-ASO plus ACEi (ChA + E) for the disease prevention study initiated in 8-week-old db/db mice.

Nondiabetic healthy mice (db/m, 16 weeks old) and 16-week-old diabetic db/db mice treated for 8 weeks (starting at the age of 8 weeks) with PBS (PBS); nonspecific control oligonucleotide (CON); CHOP-ASO (ChA) at concentrations of 1 mg/kg (ChA-1) or 3 mg/kg (ChA-3); the ACE inhibitor enalapril (ACEi, E) or a combination of CHOP-ASO plus enalapril (ChA+E). **P*<0.05, ***P*<0.01, NS, nonsignificant (ANOVA); each dot in scatter plots represents one sample.

Supplementary Figure 2

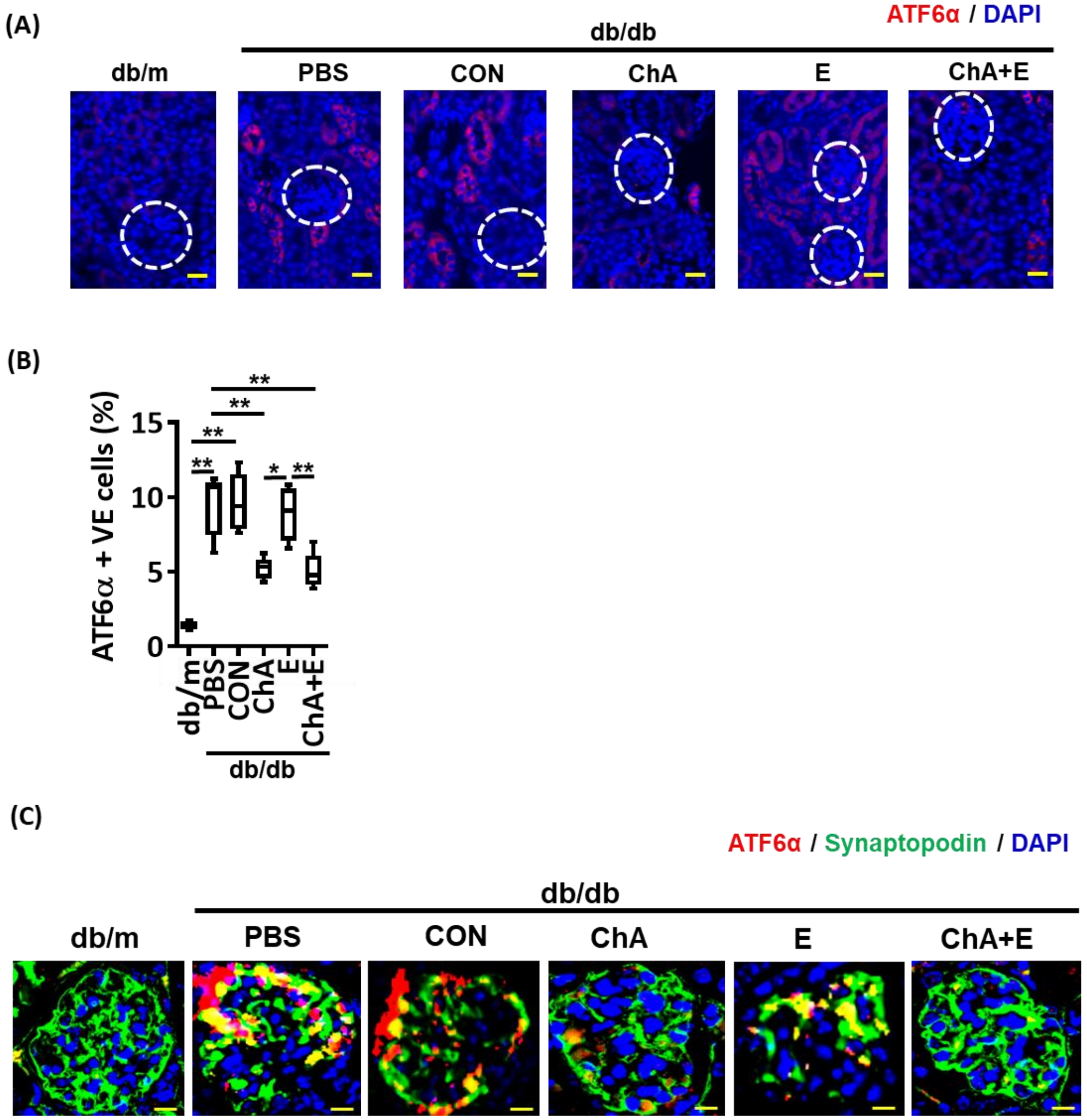


Supplementary Figure 2 (corresponding to Figure 2).

Scatter plots with bars summarizing mouse body weights (**A**), liver alanine transaminase (ALT, **B**), aspartate transaminase (AST, **C**), and systolic blood pressure (D).

In A-C, data of nondiabetic mice (db/m, 22 weeks old) and 22-week-old diabetic db/db mice treated for 6 weeks (starting at the age of 16 weeks) with PBS (PBS), nonspecific control oligonucleotide (CON), CHOP-ASO (ChA), the ACE inhibitor enalapril (ACEi, E) or a combination of CHOP-ASO plus enalapril (ChA+E) are shown. In D, same groups are shown, but mice are age 16 weeks when analyzed and interventions were initiated at age 12 weeks for further 4 weeks. ***P*<0.05, ***P*<0.01, ns, nonsignificant (A-D; ANOVA); each dot in scatter plots represents one sample.

Supplementary Figure 3



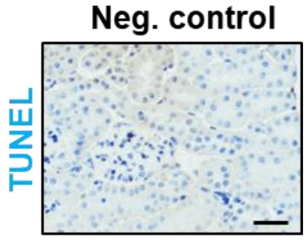
Supplementary Figure 3 (corresponding to Figure 4).

A,B: Representative immunofluorescence staining images of renal ATF6α (**A,** glomeruli indicated by the white dashed circles). ATF6α-positive cells are red, and DAPI (blue) represents nuclear counterstaining. Scale bar = 50μm. Scatter plot with bars summarizing the frequency of ATF6α (**B**)-positive renal cells using ATF6α immunofluorescence staining.

C: Representative co-immunofluorescence images showing colocalization of ATF6α (red) with synaptopodin (green) in glomeruli (**C**). Scale bar = 20μm.

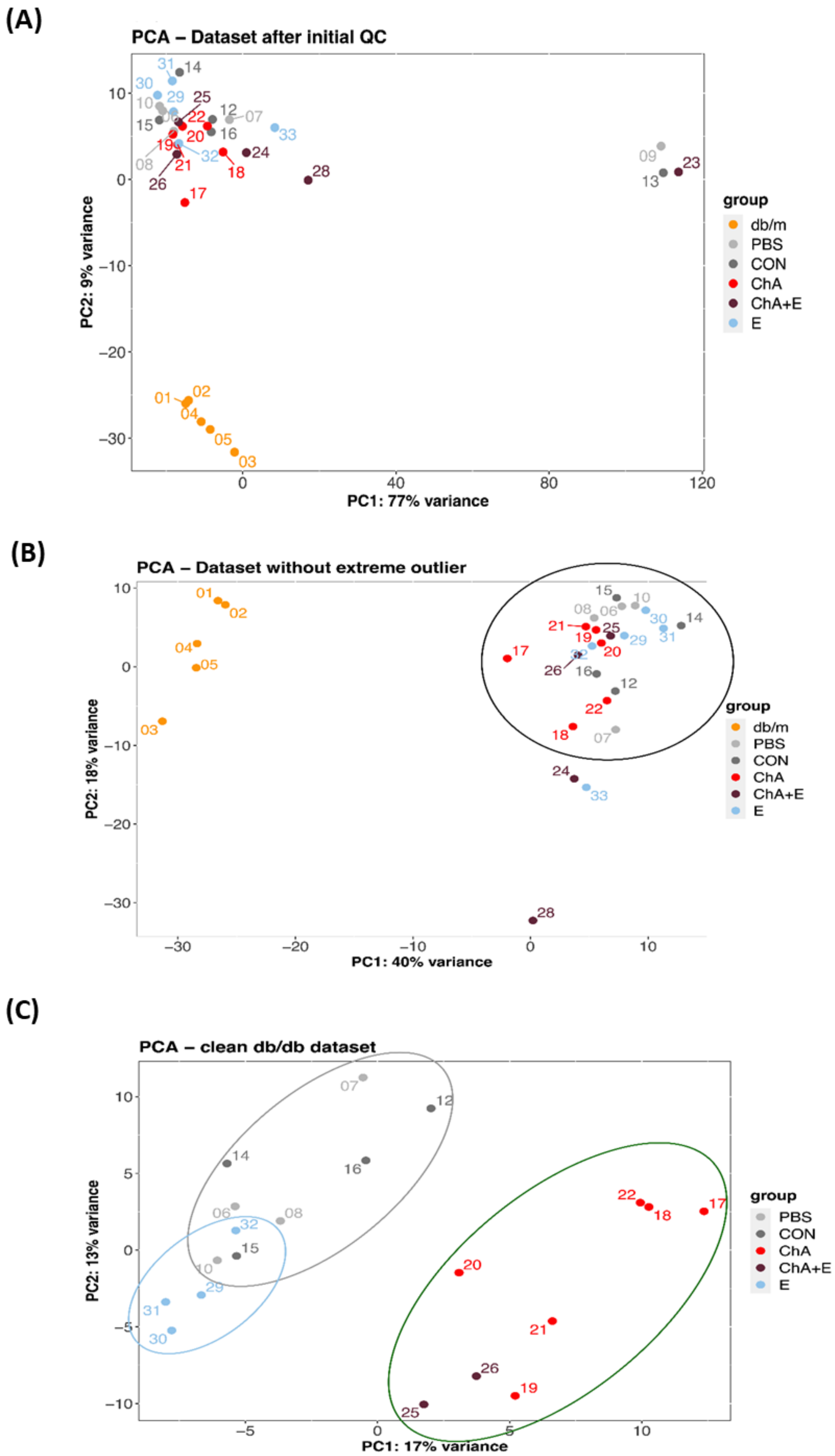
Nondiabetic healthy mice (db/m, 22 weeks old) and 22-week-old diabetic db/db mice treated for 6 weeks (starting at the age of 16 weeks) with PBS (PBS), nonspecific control oligonucleotide (CON), CHOP-ASO (ChA), the ACE inhibitor enalapril (ACEi, E) or a combination of CHOP-ASO plus enalapril (ChA+E). Scale bar, 20 μm (A); **P*<0.05, ***P*<0.01 (C, E: ANOVA); each dot in scatter plots represents one sample.

Supplementary Figure 4



Supplementary Figure 4 (corresponding to Figure 5).
Representative TUNEL staining (negative control) of renal histologic sections. Renal sections incubated only with label mix solution in the absence of terminal deoxynucleotidyl transferase (TdT) served as negative controls for TUNEL staining. TUNEL staining is indicated by brown coloring, with TUNEL-positive cells detected by the HRP-DAB reaction. Blue shows the hematoxylin counterstain. Scale bar, 50 µm.

Supplementary Figure 5

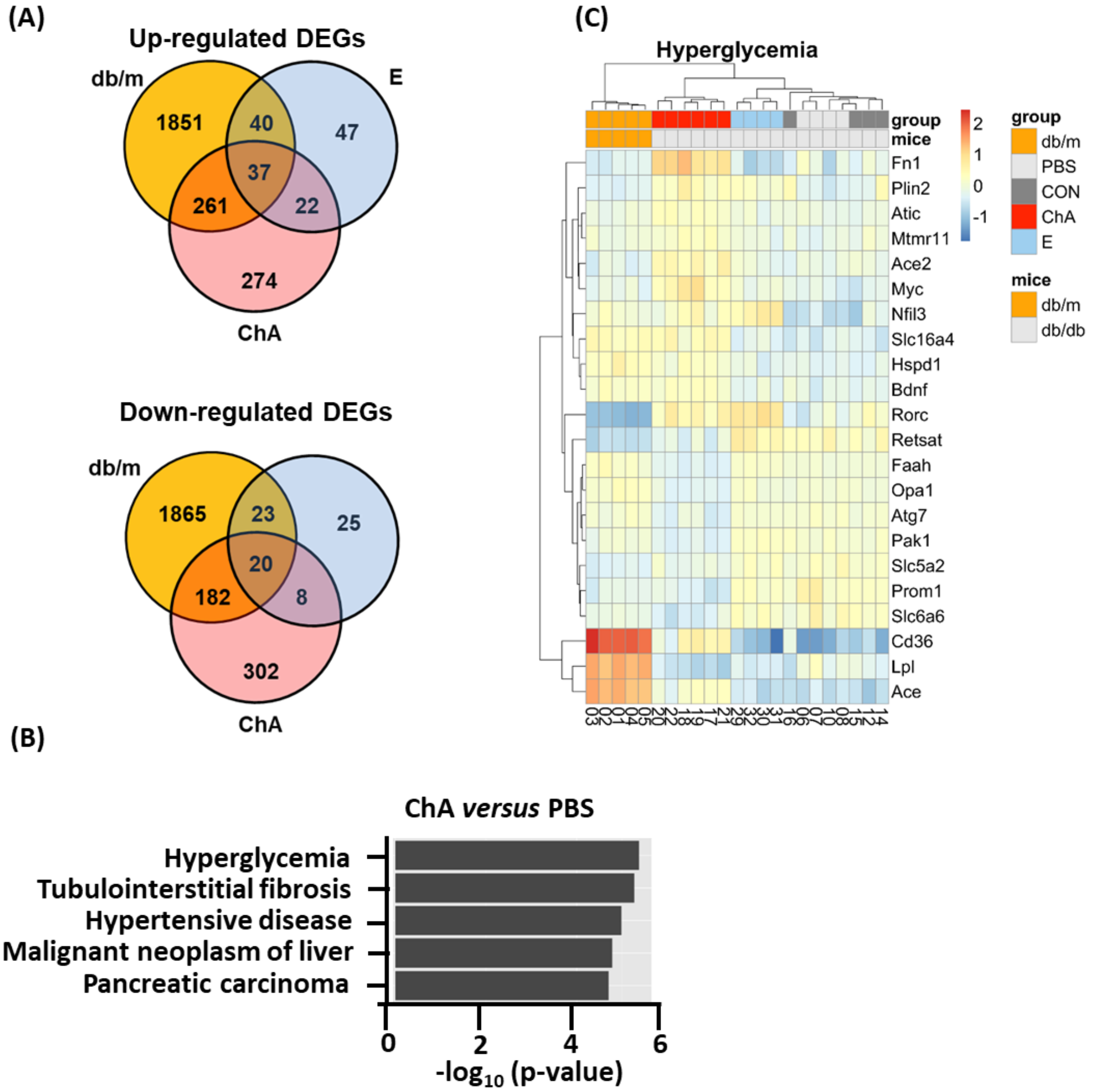


Supplementary Figure 5.

A, B, C: Principle component analyses (PCA) showing the distribution of samples across various treatment groups for the RNA-seq dataset. (**A**) Initial dataset. Three samples were excluded due to low quality of the tissue and unusually high GC content. (**B**) Dataset without the extreme outliers. Extreme outliers 09, 13 and 23 were excluded. (**C**) Clean db/db dataset. db/m control mice were excluded. Furthermore, due to high variance compared to mice with the same genetic background (db/db), samples 24, 28 and 33 were excluded. PC1; first principal component and PC2; second principal component.

Nondiabetic healthy mice (db/m, 22 weeks old) and 22-week-old diabetic db/db mice treated for 6 weeks (starting at the age of 16 weeks) with PBS (PBS), nonspecific control oligonucleotide (CON), CHOP-ASO (ChA), the ACE inhibitor enalapril (ACEi, E) or with a combination of CHOP-ASO plus enalapril (ChA+E).

Supplementary Figure 6

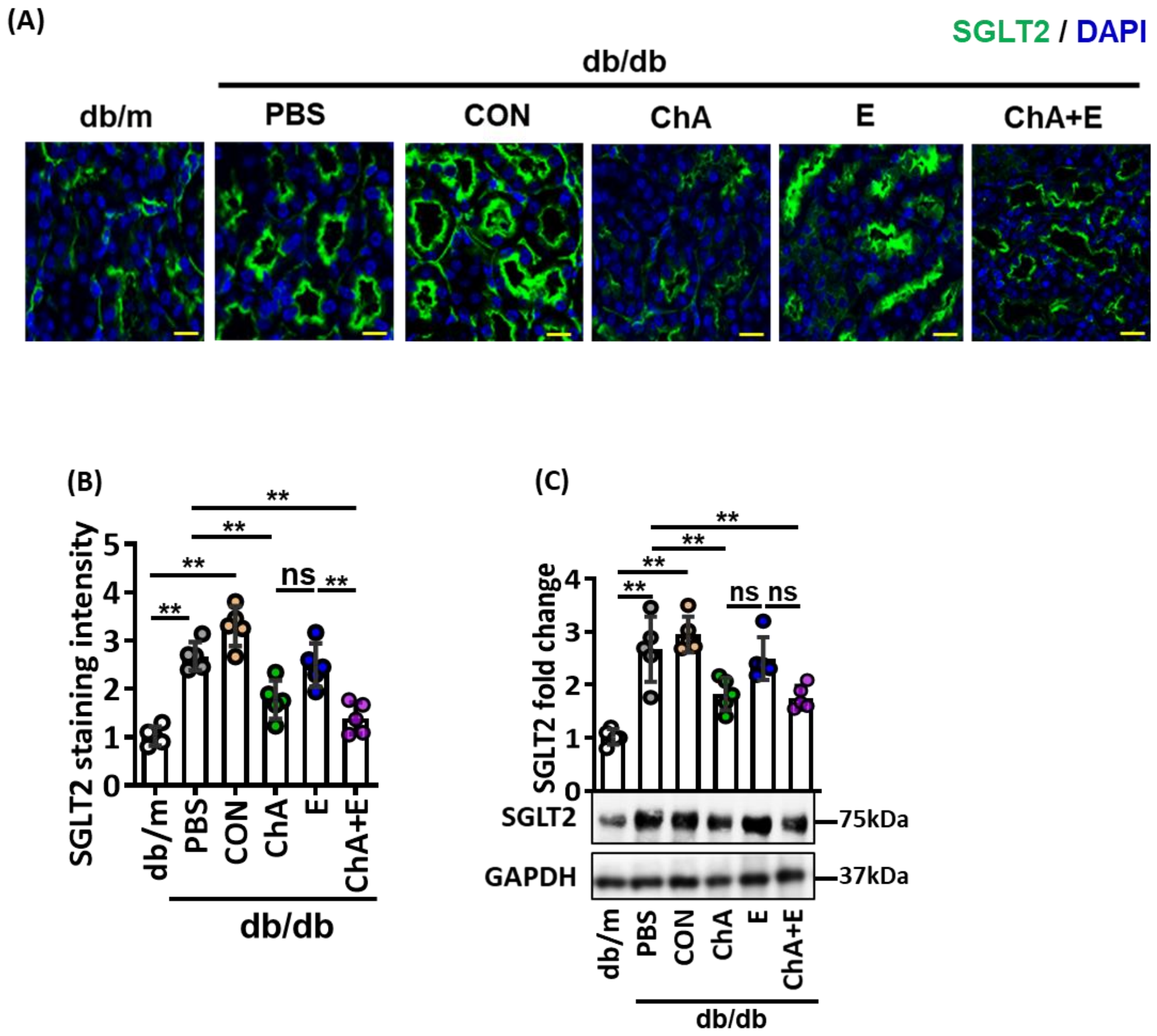


Supplementary Figure 6. Inhibition of CHOP alters renal genes expression.

Venn diagram (**A**), enriched pathways (**B**) and hyperglycemia heat map (**C,** only gene with adjusted p value < 0.0005) summarizing differential gene expression identified by RNA-seq. Venn diagram (**A**) showing overlap of genes significantly changed (induction on top, repression on bottom) in intervention groups in relation to the expression pattern in db/db mice. Due to the low number of samples matching quality criteria, the CHOP-ASO+ACEi group has been excluded. Overrepresentation analysis based on "DisGeNet: BeFree gene-disease associations" of differentially expressed genes in ChA-treated db/db mice compared to PBS-injected db/db mice. The -log10 of the p values (top 5) is shown (**B**). In the heat map, gene count values larger than the average are represented in yellow to red, while counts lower than the average are represented in blue. Transcript values close to the average value are indicated by white (**C**).

Nondiabetic healthy mice (db/m, 22 weeks old) and 22-week-old diabetic db/db mice treated for 6 weeks (starting at the age of 16 weeks) with PBS (PBS), nonspecific control oligonucleotide (CON), CHOP-ASO (ChA), or the ACE inhibitor enalapril (ACEi, E).

Supplementary Figure 7



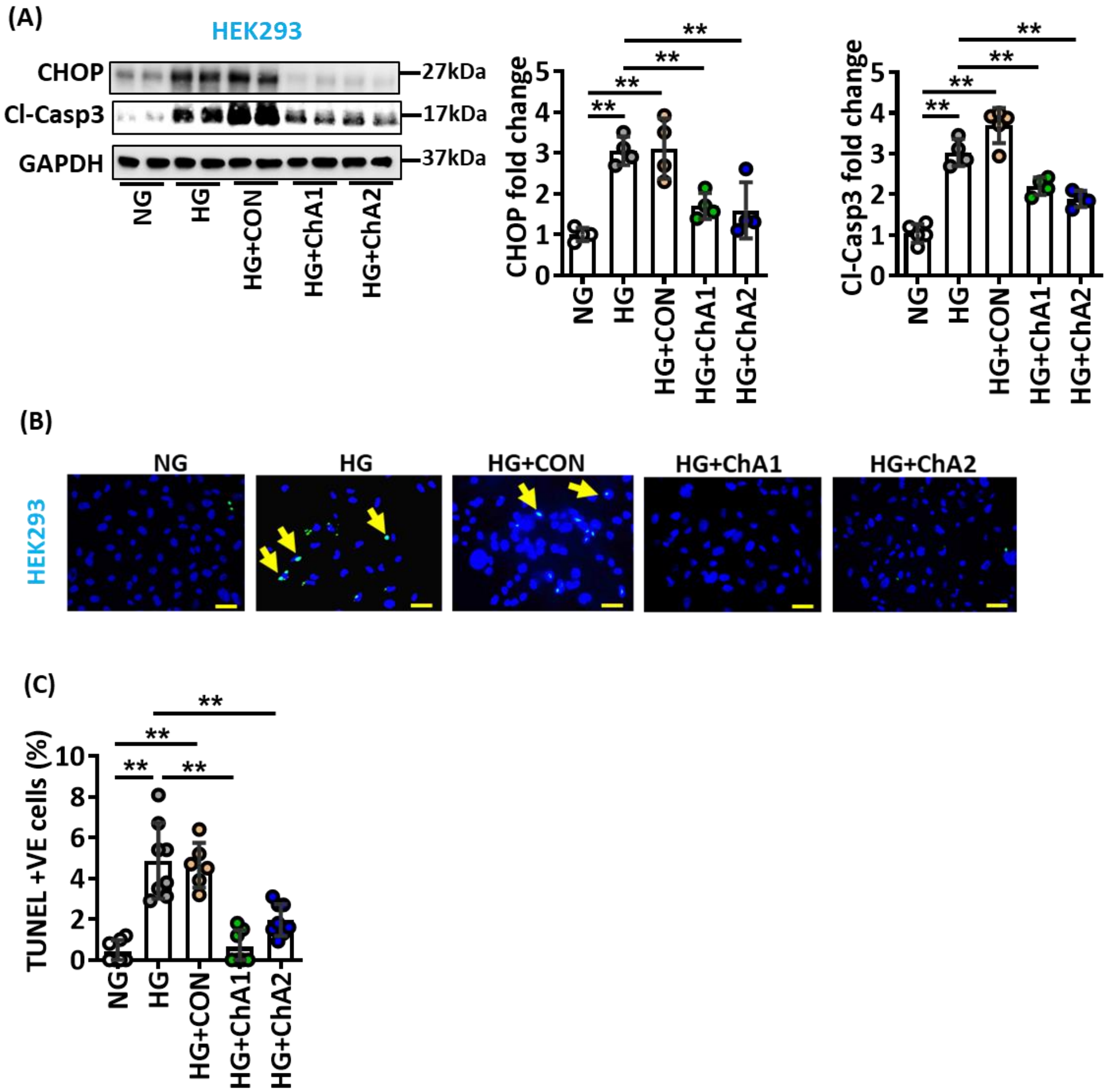
Supplementary Figure 7.

Representative immunofluorescence of renal SGLT2 expression (**A**). SGLT2-positive cells are indicated by green fluorescence; nuclei were counterstained with DAPI (blue), scale bar = 20 µm. Scatter plot with bars summarizing the relative staining intensity for SGLT2 (**B**). Representative immunoblots of renal SGLT2 expression (**C,** botto, GAPDH used as loading control) and scatter plot with bars summarizing immunoblot data (**C,** top)**.**

Nondiabetic mice (db/m, 22 weeks old) and 22-week-old diabetic db/db mice treated for 6 weeks (starting at the age of 16 weeks) with PBS (PBS), nonspecific control oligonucleotide (CON), CHOP-ASO (ChA), the ACE inhibitor enalapril (ACEi, E) or a combination of CHOP-ASO plus enalapril (ChA+E).

***P<0.01, ns, nonsignificant (ANOVA); each dot in scatter plots represents one mouse (**B, C**).

Supplementary Figure 8



Supplementary Figure 8 (corresponding to Figure 6).

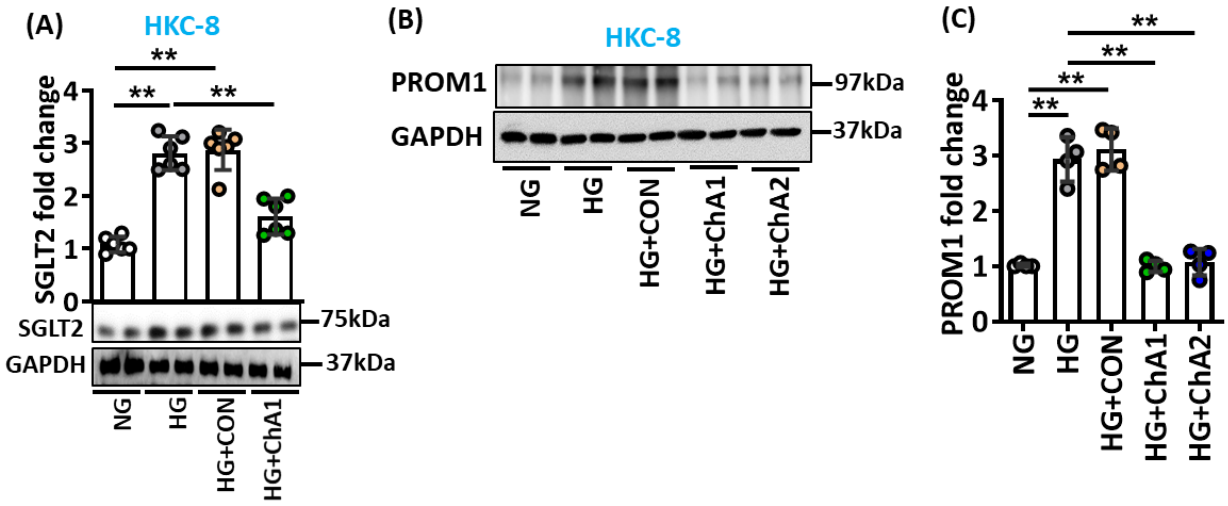
A: Representative immunoblots of CHOP and cleaved caspase-3 expression in human embryonic kidney 293 cells (**left panel**) and scatter plot with bars summarizing the CHOP (**middle panel**) and cleaved caspase-3 immunoblot data (**right panel**). Three independent repeat experiments with two technical replicates each. GAPDH was used for normalization for both cell types

B, C: Representative immunofluorescence images of TUNEL staining of human embryonic kidney cells. TUNEL-positive cells are indicated by green fluorescence, and nuclei were counterstained with DAPI (blue). Scatter plot with bars summarizing the frequency of TUNEL-positive cells (**C**). Each dot in the scatter plot with bars represents averaged data from 6 different visual fields of independent experiments (biological replicates).

Control: NG: normal glucose (5 mM glucose plus 20 mM mannitol); HG+CON: (25 mM glucose+ 10 µM nonspecific control oligonucleotide); HG: high glucose (25 mM); HG+ChA1: (25 mM glucose+ 10 µM

CHOP-ASO1; HG+ChA2: (25 mM glucose+ 10 µM CHOP-ASO2. Scale bar, 20 µm (B); $^{**}P<0.01$, (A, C: ANOVA). Each dot in scatter plots represents one sample.

Supplementary Figure 9



Supplementary Figure 9 (corresponding to Figure 6).

Representative immunoblot images of SGLT2 (**A**, bottom, GAPDH was used for normalization) and scatter plot with bars summarizing the SGLT2 immunoblot data (**A**, top). Representative immunoblot images of PROM1 (CD133) expression in HKC-8 cells (**B**, GAPDH was used for normalization) and scatter plot with bars summarizing the PROM1 immunoblot data (**C**).

Control: NG: normal glucose (5 mM glucose plus 20 mM mannitol); HG+CON: (25 mM glucose+ 10 µM nonspecific control oligonucleotide); HG: high glucose (25 mM); HG+ChA1: (25 mM glucose+ 10 µM CHOP-ASO1; HG+ChA2: (25 mM glucose+ 10 µM CHOP-ASO2. ***P*<0.01, (A, C: ANOVA); each dot in scatter plots represents one sample.

Supplementary Table 1

treatment	gene set	pval	padj	overlap	size	disease
ChA	**C0020456**	**4.19E-06**	**0.013**	**91**	**781**	**Hyperglycemia**
ChA	**C1969372**	**5.38E-06**	**0.013**	**37**	**233**	**Tubulointerstitial fibrosis**
ChA	**C0020538**	**1.03E-05**	**0.017**	**144**	**1405**	**Hypertensive disease**
ChA	**C0345904**	**1.63E-05**	**0.019**	**116**	**1091**	**Malignant neoplasm of liver**
ChA	**C0235974**	**1.97E-05**	**0.019**	**183**	**1891**	**Pancreatic carcinoma**
ChA	**C0279000**	**2.36E-05**	**0.019**	**108**	**1008**	**Liver and Intrahepatic Biliary Tract Carcinoma**
ChA	**C0596263**	**3.34E-05**	**0.023**	**374**	**4335**	**Carcinogenesis**
ChA	**C0346647**	**5.54E-05**	**0.029**	**179**	**1876**	**Malignant neoplasm of pancreas**
ChA	**C0037317**	**6.07E-05**	**0.029**	**18**	**89**	**Sleep disturbances**
ChA	**C0220630**	**6.46E-05**	**0.029**	**105**	**998**	**Adult Liver Carcinoma**
ChA	**C0011849**	**6.66E-05**	**0.029**	**178**	**1870**	**Diabetes Mellitus**
ChA	**C1833662**	**1.07E-04**	**0.043**	**9**	**28**	**Inclusion body myopathy with early-onset Paget disease**
ChA	**C0006142**	**1.16E-04**	**0.043**	**383**	**4513**	**Malignant neoplasm of breast**
ChA	**C0018799**	**1.23E-04**	**0.043**	**45**	**349**	**Heart Diseases**
ChA	**C0007103**	**1.32E-04**	**0.043**	**92**	**866**	**Malignant neoplasm of endometrium**
ChA	**C0678222**	**1.59E-04**	**0.048**	**383**	**4529**	**Breast Carcinoma**
ChA	C0278996	1.88E-04	0.052	63	548	Malignant Head and Neck Neoplasm
ChA	C0023895	1.97E-04	0.052	74	671	Liver diseases
ChA	C0004096	2.11E-04	0.052	114	1135	Asthma
ChA	C0011847	2.15E-04	0.052	156	1641	Diabetes
E	**C3714524**	**3.28E-06**	**0.016**	**6**	**29**	**Fibromyxosarcoma**
E	C0268238	4.78E-05	0.072	5	28	Triglyceride storage disease with ichthyosis
E	C0004997	5.26E-05	0.072	6	46	Benign Ovarian Neoplasm
E	C0004153	7.23E-05	0.072	39	1410	Atherosclerosis
E	C0003850	7.45E-05	0.072	39	1412	Arteriosclerosis
E	C0006142	1.13E-04	0.089	92	4513	Malignant neoplasm of breast
E	C0019196	1.64E-04	0.089	34	1209	Hepatitis C
E	C0027051	1.65E-04	0.089	32	1109	Myocardial Infarction
E	C0400966	1.77E-04	0.089	24	730	Non-alcoholic Fatty Liver Disease
E	C0740457	1.84E-04	0.089	18	468	Malignant neoplasm of kidney
E	C1969443	2.19E-04	0.096	4	21	Trifunctional Protein Deficiency With Myopathy And Neuropathy
E	C1378703	2.38E-04	0.096	18	478	Renal carcinoma
E	C0279671	2.77E-04	0.101	13	283	Cervical Squamous Cell Carcinoma
E	C0279545	3.17E-04	0.101	4	23	Adult Epithelioid Sarcoma
E	C0279989	3.17E-04	0.101	4	23	Childhood Epithelioid Sarcoma
E	C0596263	3.61E-04	0.101	87	4335	Carcinogenesis
E	C0015695	3.64E-04	0.101	20	583	Fatty Liver
E	C0678222	3.76E-04	0.101	90	4529	Breast Carcinoma
E	C4049328	4.67E-04	0.102	3	11	Renal medullary carcinoma
E	C3887523	4.67E-04	0.102	3	11	Very long chain acyl-CoA dehydrogenase deficiency

Supplementary Table 1: Results from overrepresentation analysis (ORA) were collected. The 20 gene set showing the lowest p-values were presented for each treatment indicated in the first column. Each row corresponds to a tested gene set. The columns two to six are the following: **gene set**: name of the gene set; **pval:** an enrichment p-value from hypergeometric test; **padj:** Benjamini-Hochberg (BH) adjusted p-value; **overlap:** number of significantly differentially expressed genes present in the gene set; **size:** size of the gene set; **disease:** disease corresponding to the gene set. For each treatment the gene set are sorted by their p-value. Gene sets showing an adjusted p-value <0.05 are depicted in bold.

Supplementary Table 2

GeneSymbol	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
A1cf	**2856.01**	**0.34**	**0.09**	**3.92**	**8.96E-05**	**3.62E-03**
Abca1	1928.28	-0.08	0.17	-0.50	0.616	0.861
Abca4	373.03	-0.11	0.21	-0.52	0.602	0.855
Abcc1	**931.15**	**-0.33**	**0.11**	**-3.04**	**2.40E-03**	**0.039**
Abcc4	3694.04	-0.34	0.15	-2.34	0.019	0.152
Abcg2	10803.90	0.14	0.08	1.67	0.095	0.372
Acaca	1210.76	-0.62	0.22	-2.86	4.28E-03	0.059
Acat1	18330.48	0.21	0.09	2.31	0.021	0.158
Ace	**5226.15**	**0.74**	**0.12**	**5.97**	**2.35E-09**	**7.28E-07**
Ace2	**2353.46**	**0.64**	**0.11**	**5.69**	**1.26E-08**	**3.22E-06**
Ache	171.26	0.61	0.26	2.38	0.017	0.142
Ackr3	1099.62	0.04	0.11	0.41	0.685	0.894
Acsm3	**6107.14**	**1.12**	**0.26**	**4.26**	**2.07E-05**	**1.22E-03**
Actb	41198.27	-0.08	0.08	-1.06	0.289	0.641
Acvrl1	428.45	0.11	0.16	0.68	0.494	0.794
Adcy5	161.03	-0.36	0.23	-1.58	0.114	0.409
Adipoq	39.61	-1.02	1.79	-0.57	0.568	0.837
Adipor1	4888.47	-0.06	0.08	-0.68	0.497	0.795
Adipor2	3023.62	0.01	0.07	0.19	0.846	0.952
Adk	5792.46	-0.08	0.08	-1.08	0.281	0.633
Adm	310.27	0.54	0.21	2.50	0.012	0.115
Adora2b	96.21	0.33	0.23	1.43	0.154	0.477
Adra1a	1134.47	-0.05	0.12	-0.41	0.682	0.893
Adra2b	7260.88	0.03	0.14	0.25	0.803	0.941
Ager	15.18	-0.13	0.42	-0.31	0.757	0.924
Agfg1	1795.95	0.08	0.08	0.98	0.327	0.675
Aggf1	1170.39	0.17	0.10	1.77	0.078	0.338
Agt	2320.24	-0.13	0.15	-0.92	0.358	0.701
Ahr	298.09	0.06	0.15	0.39	0.694	0.896
Ahsa1	**2675.70**	**0.34**	**0.09**	**3.69**	**2.23E-04**	**7.21E-03**
Ahsg	11.64	-0.24	1.25	-0.19	0.847	0.952
Aif1	38.21	0.06	0.56	0.10	0.922	0.978
Aimp2	453.52	0.33	0.13	2.45	0.014	0.125
Akt1	3843.87	-0.04	0.08	-0.55	0.583	0.845
Akt2	3448.84	-0.04	0.07	-0.58	0.565	0.835
Alad	3027.93	-0.14	0.08	-1.75	0.081	0.344
Alb	589.68	0.56	0.58	0.96	0.335	0.681
Aldh2	**19980.75**	**0.19**	**0.06**	**2.93**	**3.35E-03**	**0.049**
Aldob	241830.55	0.19	0.08	2.48	0.013	0.119
Alk	12.02	0.31	0.69	0.45	0.656	0.880
Alox15	732.49	0.39	0.33	1.17	0.240	0.593
Angpt1	**458.35**	**-0.47**	**0.16**	**-2.98**	**2.88E-03**	**0.044**

Angpt2	226.04	-0.50	0.22	-2.30	0.021	0.160
Angptl2	881.38	-0.04	0.15	-0.29	0.774	0.929
Angptl8	**45.78**	**1.01**	**0.34**	**2.96**	**3.10E-03**	**0.046**
Anpep	**4639.77**	**0.38**	**0.09**	**4.03**	**5.59E-05**	**2.53E-03**
Anxa5	2407.19	0.05	0.08	0.55	0.585	0.846
Aoc3	50.86	0.19	0.56	0.35	0.730	0.912
Apoa1	27.47	0.12	0.44	0.27	0.784	0.933
Apoa4	478.14	0.11	0.17	0.62	0.535	0.817
Apob	23625.19	-0.07	0.16	-0.44	0.657	0.881
Apoc3	331.33	-0.15	0.26	-0.59	0.557	0.831
Apoe	**6112.25**	**-0.69**	**0.22**	**-3.16**	**1.56E-03**	**0.030**
Apom	1283.85	0.06	0.18	0.35	0.724	0.909
App	36238.10	0.02	0.09	0.28	0.780	0.931
Appl1	865.63	-0.10	0.20	-0.53	0.598	0.852
Aprt	2143.85	0.04	0.11	0.39	0.695	0.897
Aqp3	2406.99	-0.14	0.14	-0.99	0.323	0.671
Aqp7	637.40	-0.23	0.11	-2.16	0.031	0.200
Ar	3287.10	0.03	0.12	0.26	0.791	0.935
Arf6	1766.01	-0.10	0.06	-1.67	0.094	0.372
Arg1	26.58	2.17	0.89	2.43	0.015	0.129
Arhgef7	2660.19	-0.02	0.11	-0.22	0.829	0.947
Arrb1	1756.42	0.01	0.10	0.09	0.932	0.980
Arrb2	258.56	-0.23	0.24	-0.95	0.341	0.686
Arsa	393.89	-0.39	0.14	-2.69	7.21E-03	0.082
Asah1	2101.31	-0.01	0.13	-0.11	0.912	0.975
Ascc1	1458.27	-0.07	0.12	-0.58	0.565	0.835
Aspg	862.77	-0.13	0.24	-0.55	0.582	0.845
Asrgl1	468.81	0.01	0.16	0.04	0.971	0.992
Atf3	86.65	1.39	0.64	2.17	0.030	0.197
Atg4b	1502.84	0.09	0.14	0.67	0.505	0.801
Atg5	1337.83	0.14	0.10	1.41	0.159	0.484
Atg7	**785.49**	**-0.54**	**0.11**	**-5.04**	**4.58E-07**	**5.94E-05**
Atic	**866.01**	**0.46**	**0.09**	**5.01**	**5.41E-07**	**6.62E-05**
Atm	1055.22	-0.03	0.13	-0.21	0.833	0.949
Atn1	1840.01	0.26	0.15	1.77	0.077	0.337
Atp2a3	613.45	0.18	0.16	1.08	0.280	0.633
Bax	874.20	0.02	0.12	0.19	0.846	0.952
Bche	11.00	2.15	0.94	2.29	0.022	0.162
Bcl2	522.90	-0.26	0.11	-2.28	0.022	0.164
Bdnf	**163.99**	**0.88**	**0.19**	**4.60**	**4.24E-06**	**3.63E-04**
Becn1	3508.68	-0.01	0.13	-0.05	0.957	0.988
Best1	11.60	0.29	0.64	0.46	0.646	0.876
Bhlhe22	12.82	-0.14	0.47	-0.29	0.772	0.929
Bmp4	856.35	0.31	0.14	2.18	0.029	0.194
Bmp7	1322.88	-0.18	0.09	-2.06	0.039	0.230

Bms1	904.33	0.15	0.13	1.20	0.230	0.580
Bnip3	6529.58	-0.04	0.11	-0.39	0.699	0.899
Brd2	5509.18	0.20	0.09	2.25	0.024	0.173
Brd7	1134.51	0.24	0.16	1.45	0.146	0.465
Brd9	422.17	0.01	0.12	0.11	0.911	0.974
Btc	342.28	0.04	0.18	0.19	0.846	0.952
C5ar1	26.81	0.20	0.80	0.25	0.804	0.941
Cacna1d	175.33	-0.20	0.28	-0.70	0.485	0.789
Cadm2	17.24	-0.51	0.65	-0.78	0.433	0.754
Capn1	1224.82	0.08	0.10	0.85	0.395	0.729
Casp1	29.86	-0.38	0.38	-1.01	0.315	0.665
Casp3	689.73	-0.07	0.10	-0.74	0.457	0.772
Casp8	998.21	0.32	0.13	2.42	0.016	0.133
Casr	1943.55	-0.45	0.16	-2.75	6.02E-03	0.072
Casz1	865.96	0.01	0.17	0.04	0.967	0.991
Cat	22812.41	0.09	0.09	0.99	0.324	0.671
Cav1	909.53	0.21	0.19	1.10	0.272	0.624
Ccl2	17.66	-0.02	0.53	-0.05	0.964	0.991
Ccl5	18.06	1.02	0.68	1.49	0.135	0.447
Ccn1	**1137.41**	**1.86**	**0.52**	**3.55**	**3.88E-04**	**0.011**
Ccn2	2353.01	-0.17	0.31	-0.56	0.578	0.844
Ccn3	8.88	0.37	0.75	0.49	0.626	0.865
Ccnd1	**11112.84**	**-0.73**	**0.19**	**-3.97**	**7.26E-05**	**3.08E-03**
Ccr2	133.15	0.52	0.41	1.28	0.199	0.540
Cct2	**4678.48**	**0.21**	**0.05**	**3.86**	**1.13E-04**	**4.27E-03**
Cd226	27.16	-0.39	0.73	-0.53	0.597	0.851
Cd33	44.32	-0.43	0.54	-0.79	0.427	0.751
Cd36	**4676.84**	**1.69**	**0.26**	**6.48**	**9.26E-11**	**4.52E-08**
Cd40	44.72	0.61	0.43	1.43	0.152	0.475
Cd44	89.86	0.16	0.50	0.31	0.754	0.922
Cd68	44.35	0.14	0.38	0.38	0.705	0.902
Cd86	38.95	0.35	0.55	0.64	0.524	0.812
Cdc25c	7.20	0.59	1.16	0.51	0.613	NA
Cdc42	8149.52	-0.08	0.08	-0.92	0.359	0.701
Cdh5	561.17	0.35	0.19	1.90	0.058	0.288
Cdk2	353.50	-0.03	0.13	-0.22	0.825	0.945
Cdk4	2022.41	-0.02	0.13	-0.15	0.880	0.963
Cdk5	842.23	-0.11	0.13	-0.87	0.384	0.722
Cdkn1a	698.91	0.75	0.33	2.26	0.024	0.171
Cebpa	1249.00	0.22	0.14	1.51	0.131	0.439
Cenpx	1163.23	-0.01	0.14	-0.08	0.933	0.980
Cers2	4490.20	-0.05	0.08	-0.59	0.554	0.829
Chmp2b	2017.00	0.20	0.08	2.51	0.012	0.114
Chpt1	36788.00	0.22	0.13	1.68	0.093	0.368
Chrm3	71.67	-0.29	0.31	-0.92	0.356	0.698

Clip1	2651.65	0.09	0.11	0.85	0.395	0.729
Clip2	1602.25	-0.10	0.09	-1.17	0.241	0.593
Cmklr1	98.07	0.23	0.27	0.87	0.382	0.721
Cnbp	6795.78	-0.13	0.10	-1.32	0.186	0.523
Cndp1	1353.52	0.24	0.17	1.38	0.169	0.499
Cnr1	8.69	0.35	0.98	0.36	0.718	0.907
Comp	10.39	0.20	0.66	0.29	0.769	0.928
Copa	11774.69	-0.04	0.08	-0.48	0.629	0.867
Coro7	1221.60	-0.18	0.16	-1.10	0.273	0.625
Cox4i1	18936.51	-0.07	0.10	-0.69	0.487	0.790
Cox4i2	7.00	-0.48	0.62	-0.78	0.435	NA
Cpt1a	17978.32	0.00	0.12	-0.04	0.968	0.991
Cpt2	**4867.36**	**0.46**	**0.11**	**4.04**	**5.37E-05**	**2.47E-03**
Creb1	1215.64	0.28	0.12	2.37	0.018	0.144
Crebbp	3611.45	0.09	0.17	0.53	0.594	0.850
Crem	480.79	0.05	0.19	0.26	0.798	0.938
Crk	5346.71	-0.05	0.07	-0.65	0.516	0.808
Crtc2	912.09	-0.17	0.13	-1.32	0.187	0.523
Cry1	602.24	0.60	0.22	2.78	5.43E-03	0.068
Cryz	17680.02	0.05	0.08	0.66	0.507	0.802
Csf1	211.43	0.52	0.22	2.36	0.018	0.147
Csf1r	1139.17	-0.30	0.19	-1.52	0.127	0.434
Ctdsp1	**4234.47**	**-0.15**	**0.05**	**-3.05**	**2.32E-03**	**0.039**
Ctdsp2	5433.66	-0.18	0.11	-1.64	0.100	0.383
Ctnnb1	12388.18	0.04	0.07	0.52	0.604	0.856
Ctsa	11835.42	0.01	0.09	0.13	0.896	0.970
Cux1	8858.37	0.14	0.09	1.62	0.105	0.392
Cx3cl1	1233.76	0.06	0.12	0.48	0.634	0.869
Cxcl10	212.03	0.02	0.29	0.07	0.946	0.985
Cxcl12	2613.12	0.45	0.16	2.78	5.46E-03	0.068
Cxcr3	10.27	-0.36	0.69	-0.51	0.607	0.857
Cxcr4	108.79	0.06	0.29	0.23	0.821	0.944
Cxcr6	27.70	0.16	0.70	0.23	0.819	0.944
Cyba	6798.58	-0.12	0.14	-0.82	0.410	0.739
Cybb	269.64	0.05	0.41	0.12	0.908	0.974
Cyc1	11769.14	-0.02	0.12	-0.15	0.878	0.963
Cyp1b1	**813.93**	**-0.52**	**0.17**	**-3.12**	**1.79E-03**	**0.033**
Cyp2e1	**23810.62**	**0.66**	**0.17**	**3.82**	**1.35E-04**	**4.90E-03**
Dab2	13646.05	-0.07	0.11	-0.63	0.530	0.814
Dact1	127.91	-0.30	0.21	-1.44	0.151	0.472
Dapk2	281.00	0.22	0.18	1.23	0.220	0.569
Dbp	**1376.49**	**-0.96**	**0.31**	**-3.08**	**2.10E-03**	**0.036**
Dcaf1	1414.03	0.12	0.16	0.75	0.455	0.770
Dcn	**758.66**	**0.77**	**0.18**	**4.33**	**1.47E-05**	**9.28E-04**
Ddah2	341.31	-0.14	0.15	-0.90	0.368	0.711

Ddit3	234.49	0.04	0.22	0.18	0.854	0.954
Ddit4	730.90	0.13	0.44	0.29	0.771	0.929
Ddr2	**292.13**	**0.83**	**0.24**	**3.47**	**5.30E-04**	**0.013**
Deaf1	**1077.74**	**-0.26**	**0.08**	**-3.27**	**1.09E-03**	**0.023**
Decr1	**6291.93**	**0.39**	**0.10**	**3.86**	**1.13E-04**	**4.27E-03**
Degs1	4857.33	-0.23	0.09	-2.39	0.017	0.139
Denr	691.98	-0.15	0.18	-0.81	0.417	0.743
Desi1	808.31	0.17	0.13	1.28	0.201	0.542
Dgkd	**3619.67**	**0.35**	**0.12**	**3.00**	**2.66E-03**	**0.042**
Dld	8195.70	0.04	0.07	0.59	0.552	0.828
Dlg1	2539.10	-0.08	0.07	-1.07	0.284	0.636
Dmd	444.63	0.09	0.20	0.46	0.645	0.875
Dnm1l	2528.83	0.04	0.09	0.38	0.701	0.900
Dnmt1	951.02	0.15	0.14	1.07	0.283	0.636
Doc2b	15.15	0.67	0.57	1.18	0.239	0.591
Dpp4	3359.47	0.17	0.16	1.04	0.298	0.646
Dusp1	1962.48	0.00	0.58	0.00	0.998	0.999
Dusp26	10.96	-0.88	0.66	-1.32	0.185	0.521
Dusp6	1670.92	-0.02	0.19	-0.10	0.918	0.977
Dusp9	242.79	-0.11	0.17	-0.63	0.532	0.815
Dync1h1	22915.21	0.06	0.17	0.34	0.732	0.913
E2f1	108.00	0.62	0.26	2.39	0.017	0.139
Ece1	1791.59	-0.01	0.21	-0.03	0.973	0.992
Edn1	50.49	-0.09	0.29	-0.32	0.751	0.920
Ednra	46.70	0.20	0.25	0.79	0.430	0.752
Efhd2	927.54	0.05	0.14	0.37	0.713	0.905
Egf	59962.59	-0.01	0.11	-0.12	0.901	0.971
Egfr	3535.43	0.02	0.10	0.22	0.826	0.946
Egln3	611.43	-0.18	0.12	-1.48	0.140	0.455
Egr1	558.73	2.67	0.99	2.70	NA	NA
Ehmt1	1189.87	0.02	0.11	0.21	0.832	0.949
Ehmt2	4235.80	0.06	0.08	0.76	0.446	0.764
Elavl1	2239.79	0.18	0.08	2.22	0.026	0.182
Elovl1	1991.33	0.08	0.08	0.94	0.345	0.690
Elovl5	1845.28	0.08	0.10	0.76	0.445	0.764
Emcn	967.37	0.11	0.16	0.72	0.475	0.783
Enho	55.61	0.82	0.31	2.63	8.61E-03	0.091
Eno1	**42809.20**	**0.30**	**0.07**	**4.18**	**2.92E-05**	**1.57E-03**
Eno2	42.66	-0.13	0.48	-0.26	0.794	0.936
Enpp1	1747.29	-0.20	0.12	-1.69	0.090	0.365
Entpd1	343.80	0.28	0.21	1.29	0.199	0.540
Ep300	3707.21	-0.10	0.18	-0.58	0.563	0.834
Ephb2	429.75	-0.33	0.17	-1.94	0.052	0.271
Ephx2	11244.66	0.05	0.10	0.57	0.571	0.839
Epor	114.96	-0.47	0.26	-1.85	0.065	0.305

Errfi1	17191.18	-0.45	0.16	-2.91	3.59E-03	0.051
Esr1	499.13	0.05	0.16	0.31	0.760	0.924
Esr2	6.99	-0.19	0.77	-0.25	0.802	NA
Esrrg	**2155.45**	**-0.51**	**0.16**	**-3.21**	**1.32E-03**	**0.027**
Ezh2	293.92	0.18	0.16	1.16	0.246	0.599
F2	11.13	0.22	1.08	0.21	0.836	0.949
F2rl3	10.59	0.59	0.57	1.04	0.297	0.645
F3	450.74	0.29	0.12	2.34	0.019	0.152
Faah	**2015.74**	**-0.40**	**0.07**	**-5.69**	**1.24E-08**	**3.21E-06**
Fabp4	566.35	0.21	0.18	1.19	0.234	0.586
Fam3a	762.43	0.12	0.11	1.07	0.285	0.637
Fam3c	484.61	-0.06	0.14	-0.42	0.677	0.891
Fancc	360.31	-0.10	0.21	-0.45	0.649	0.878
Fasn	3012.40	0.29	0.18	1.65	0.099	0.381
Fbrs	845.23	-0.22	0.20	-1.10	0.269	0.621
Fbxo2	66.16	-0.73	0.27	-2.76	5.82E-03	0.071
Fbxo8	2095.49	0.01	0.09	0.13	0.897	0.970
Fbxw7	421.08	-0.03	0.13	-0.24	0.809	0.942
Fgb	37.82	0.72	0.51	1.40	0.161	0.487
Fgf1	7267.08	0.05	0.12	0.44	0.663	0.884
Fgf2	46.73	0.44	0.44	0.99	0.324	0.671
Fgfbp3	41.43	-0.45	0.28	-1.63	0.102	0.387
Fgl1	34.02	-0.19	0.37	-0.51	0.607	0.857
Fgr	33.03	-0.06	0.55	-0.11	0.910	0.974
Flt1	1156.55	0.15	0.14	1.11	0.266	0.619
Flvcr1	731.70	0.13	0.14	0.90	0.370	0.712
Fmo3	20.73	0.46	0.51	0.90	0.369	0.712
Fn1	**1763.68**	**1.32**	**0.17**	**7.85**	**4.17E-15**	**8.39E-12**
Fn3k	896.07	0.10	0.10	1.00	0.315	0.665
Fos	129.84	2.05	0.95	2.14	0.032	0.205
Fosb	**19.80**	**3.55**	**1.00**	**3.53**	**4.10E-04**	**0.011**
Foxk2	1627.79	0.02	0.09	0.25	0.806	0.941
Foxm1	94.04	0.52	0.37	1.42	0.156	0.479
Foxn3	2682.82	-0.10	0.12	-0.83	0.407	0.737
Foxo1	2046.16	-0.23	0.14	-1.68	0.093	0.370
Foxo3	4953.74	-0.37	0.13	-2.76	5.78E-03	0.071
Fst	428.57	-0.52	0.18	-2.84	4.48E-03	0.060
Fto	2546.57	-0.13	0.10	-1.36	0.172	0.505
Ftsj1	663.88	-0.09	0.10	-0.89	0.373	0.714
Ftsj3	1157.99	-0.15	0.14	-1.06	0.290	0.641
Fzd4	4805.45	-0.04	0.08	-0.44	0.656	0.881
G6pc	23460.77	-0.22	0.16	-1.35	0.179	0.513
Gabpa	**1260.76**	**-0.40**	**0.10**	**-3.93**	**8.35E-05**	**3.45E-03**
Gad1	10.80	1.23	0.89	1.38	0.167	0.497
Gal3st1	745.60	-0.16	0.13	-1.23	0.220	0.570

Galnt2	2232.74	0.16	0.17	0.92	0.357	0.700
Gas6	**14650.76**	**-0.25**	**0.07**	**-3.38**	**7.24E-04**	**0.017**
Gata6	58.36	0.30	0.34	0.89	0.374	0.715
Gcgr	768.36	-0.32	0.13	-2.46	0.014	0.123
Gch1	43.84	0.45	0.25	1.80	0.072	0.324
Gclc	7436.97	0.17	0.09	1.78	0.076	0.333
Gde1	4274.97	-0.08	0.09	-0.83	0.406	0.737
Gdf15	399.70	1.33	0.56	2.37	0.018	0.146
Gfer	851.53	0.24	0.12	1.96	0.050	0.265
Gfpt1	1928.80	0.10	0.09	1.07	0.283	0.636
Gfpt2	48.88	0.24	0.32	0.75	0.451	0.768
Ggct	**503.73**	**0.92**	**0.22**	**4.14**	**3.51E-05**	**1.82E-03**
Ggt1	**24759.05**	**0.24**	**0.07**	**3.53**	**4.16E-04**	**0.011**
Ghr	20737.07	0.11	0.09	1.15	0.249	0.602
Gja1	103.17	0.31	0.27	1.13	0.258	0.609
Glis3	2962.56	-0.31	0.12	-2.56	0.010	0.102
Glo1	9816.07	0.10	0.10	0.93	0.354	0.697
Glp1r	74.96	0.51	0.33	1.57	0.117	0.415
Gls	6158.31	0.02	0.09	0.18	0.860	0.957
Glul	30138.79	0.11	0.12	0.96	0.336	0.682
Gorasp1	1385.11	-0.22	0.17	-1.26	0.206	0.551
Gper1	54.27	0.24	0.29	0.83	0.409	0.739
Gpt	**1571.97**	**0.46**	**0.14**	**3.29**	**1.01E-03**	**0.022**
Gpx1	57959.64	-0.06	0.13	-0.47	0.642	0.873
Grap2	23.98	0.71	0.75	0.95	0.342	0.687
Grk2	1877.60	0.13	0.07	1.89	0.059	0.291
Gsk3b	2516.00	-0.13	0.15	-0.84	0.402	0.734
Gstt1	3507.77	-0.31	0.11	-2.85	4.42E-03	0.060
Gusb	1235.91	0.05	0.14	0.35	0.725	0.910
Gys1	1966.81	0.04	0.10	0.45	0.653	0.880
Gys2	454.25	-0.37	0.23	-1.63	0.102	0.387
Hcls1	127.17	-0.09	0.25	-0.34	0.733	0.913
Hcn2	70.45	0.40	0.27	1.50	0.133	0.443
Hcn4	5.79	-0.97	0.78	-1.24	0.215	NA
Hdac9	16.98	0.19	0.57	0.34	0.737	0.915
Hes1	452.08	-0.10	0.18	-0.58	0.562	0.834
Hgf	99.60	-0.20	0.29	-0.69	0.489	0.791
Hhip	10.54	1.30	0.90	1.44	0.150	0.472
Hif1a	3715.50	0.19	0.08	2.36	0.018	0.147
Hipk2	3366.50	-0.08	0.17	-0.48	0.632	0.868
Hk2	27.09	0.97	0.67	1.45	0.147	0.466
Hkdc1	62.87	0.36	0.31	1.17	0.244	0.597
Hmcn1	129.34	0.51	0.26	1.98	0.047	0.256
Hmgb1	6290.43	0.15	0.10	1.61	0.108	0.396
Hmgcr	1370.75	-0.21	0.09	-2.33	0.020	0.153

Hmox1	1822.57	0.19	0.51	0.37	0.711	0.904
Hnf1a	1825.90	-0.06	0.13	-0.46	0.646	0.876
Hnf4a	42501.16	-0.09	0.08	-1.19	0.236	0.587
Hnrnpa1	1761.34	-0.04	0.12	-0.37	0.711	0.904
Hpgds	31.75	0.41	0.73	0.56	0.573	0.840
Hpse	11.88	0.39	0.64	0.61	0.544	0.823
Hsd11b1	2226.24	0.11	0.18	0.61	0.545	0.823
Hsf1	**1000.87**	**0.26**	**0.09**	**2.99**	**2.83E-03**	**0.044**
Hsp90aa1	**12234.05**	**0.54**	**0.16**	**3.35**	**8.18E-04**	**0.019**
Hspa12a	843.59	0.05	0.17	0.29	0.774	0.929
Hspa14	738.24	0.22	0.09	2.45	0.014	0.126
Hspa14	68.78	0.14	0.27	0.52	0.604	0.856
Hspa1a	1255.47	0.17	0.43	0.39	0.699	0.898
Hspa1b	2194.53	0.38	0.43	0.87	0.383	0.721
Hspa4	**5182.54**	**0.33**	**0.07**	**4.42**	**9.87E-06**	**7.04E-04**
Hspa5	15238.02	0.41	0.15	2.79	5.25E-03	0.066
Hspb8	158.50	0.16	0.18	0.90	0.370	0.712
Hspd1	**15031.77**	**0.46**	**0.09**	**4.88**	**1.04E-06**	**1.18E-04**
Hspg2	2649.48	0.16	0.10	1.62	0.106	0.393
Htr2a	9.45	1.63	0.58	2.78	5.38E-03	0.068
Icam1	578.97	-0.18	0.20	-0.89	0.372	0.714
Ide	3453.72	0.03	0.07	0.37	0.710	0.904
Ifi30	**1675.69**	**0.27**	**0.08**	**3.55**	**3.84E-04**	**0.011**
Igf1	122.34	-0.69	0.34	-2.04	0.041	0.237
Igf1r	10781.07	-0.05	0.14	-0.36	0.716	0.907
Igf2	23.56	-0.53	0.62	-0.85	0.394	0.728
Igf2bp2	323.97	0.29	0.17	1.71	0.087	0.356
Igfbp1	**168.84**	**-1.54**	**0.40**	**-3.89**	**1.01E-04**	**3.90E-03**
Igfbp2	21.15	0.88	0.73	1.20	0.229	0.580
Igfbp3	**2740.86**	**-0.73**	**0.18**	**-4.10**	**4.15E-05**	**2.04E-03**
Igfbp7	**23023.58**	**-0.39**	**0.09**	**-4.17**	**3.07E-05**	**1.63E-03**
Ikbkb	1832.02	0.03	0.10	0.27	0.784	0.933
Il18	42.29	-0.07	0.31	-0.23	0.821	0.944
Il1b	70.00	0.36	0.93	0.39	0.698	0.898
Il1r1	214.45	-0.17	0.19	-0.88	0.381	0.720
Il1rn	11.30	-0.05	0.95	-0.05	0.960	0.989
Il2rb	36.95	0.62	0.56	1.10	0.273	0.625
Il33	344.70	0.15	0.20	0.77	0.444	0.763
Il7r	9.22	0.75	0.71	1.05	0.292	0.642
Inpp5f	2196.56	-0.04	0.08	-0.48	0.631	0.868
Insr	5426.24	-0.06	0.12	-0.50	0.614	0.860
Insrr	711.46	-0.17	0.16	-1.09	0.276	0.628
Intu	708.11	0.25	0.19	1.37	0.170	0.500
Irf3	1330.97	0.08	0.10	0.85	0.396	0.729
Irf8	693.48	0.42	0.18	2.30	0.021	0.159

Irs1	1114.39	-0.13	0.15	-0.83	0.404	0.736
Irs2	1441.08	-0.20	0.32	-0.64	0.525	0.813
Itga2	31.01	0.04	0.80	0.05	0.957	0.988
Jag1	941.49	0.19	0.14	1.36	0.175	0.509
Jak2	1274.38	-0.09	0.08	-1.21	0.228	0.578
Jun	1754.33	0.94	0.41	2.32	0.020	0.154
Junb	635.76	0.39	0.52	0.75	0.453	0.769
Jund	4292.92	-0.20	0.12	-1.72	0.085	0.354
Kat2b	**3481.20**	**-0.22**	**0.07**	**-2.96**	**3.09E-03**	**0.046**
Kcnh2	36.96	0.14	0.50	0.28	0.779	0.931
Kcnj11	29.18	0.91	0.52	1.76	0.079	0.340
Kcnq1	1066.78	-0.19	0.15	-1.25	0.211	0.559
Kdm1a	1164.35	0.25	0.09	2.86	4.19E-03	0.058
Kdr	1558.34	0.15	0.15	0.95	0.340	0.686
Khsrp	2614.46	0.02	0.10	0.24	0.811	0.942
Kl	21326.57	-0.06	0.12	-0.51	0.608	0.857
Klf10	709.52	-0.31	0.26	-1.21	0.225	0.575
Klf11	350.59	-0.30	0.25	-1.20	0.229	0.579
Klf15	**3999.86**	**-0.62**	**0.15**	**-3.98**	**6.84E-05**	**2.94E-03**
Klf2	179.51	0.18	0.22	0.78	0.433	0.754
Klf4	217.75	0.07	0.20	0.33	0.743	0.917
Klf9	**6788.45**	**-0.43**	**0.12**	**-3.52**	**4.34E-04**	**0.012**
Klrk1	20.95	-0.52	0.58	-0.89	0.374	0.715
Kmt2a	1976.69	-0.10	0.30	-0.32	0.749	0.920
Kng1	45.75	0.10	0.39	0.26	0.796	0.937
Kras	1257.10	0.12	0.11	1.05	0.293	0.643
Krt20	**22.80**	**1.41**	**0.46**	**3.05**	**2.28E-03**	**0.038**
Ldha	16500.45	0.17	0.07	2.56	0.011	0.103
Ldlr	533.86	-0.22	0.19	-1.16	0.248	0.600
Lep	30.83	-0.63	2.06	-0.30	0.761	0.925
Lepr	104.62	0.09	0.26	0.33	0.743	0.917
Lgals1	605.61	0.05	0.12	0.40	0.690	0.895
Lgals3	927.65	-0.27	0.15	-1.74	0.082	0.348
Lgr6	24.70	-1.15	0.44	-2.62	8.72E-03	0.092
Lipe	673.68	0.19	0.16	1.14	0.252	0.605
Lonp1	5163.65	0.12	0.09	1.31	0.190	0.527
Lox	93.54	-0.02	0.22	-0.08	0.935	0.981
Lpar2	446.02	0.01	0.24	0.05	0.960	0.989
Lpar3	1174.75	-0.20	0.13	-1.51	0.131	0.438
Lpcat3	2372.34	0.02	0.09	0.22	0.829	0.947
Lpl	**7142.27**	**-0.67**	**0.12**	**-5.47**	**4.53E-08**	**9.49E-06**
Lrba	7167.32	-0.19	0.11	-1.82	0.069	0.315
Lrp5	2264.59	-0.25	0.12	-2.02	0.043	0.245
Ltbr	2769.81	-0.09	0.10	-0.90	0.370	0.712
Luc7l3	852.78	0.47	0.18	2.66	7.76E-03	0.086

Ly96	26.41	-0.20	0.31	-0.65	0.518	0.809
Mad2l2	**354.86**	**0.54**	**0.16**	**3.34**	**8.36E-04**	**0.019**
Malat1	99348.94	0.17	0.30	0.58	0.559	0.832
Map2	133.67	0.36	0.32	1.12	0.263	0.615
Map2k6	521.63	-0.25	0.17	-1.53	0.127	0.433
Map2k7	1024.25	0.04	0.09	0.43	0.669	0.889
Map3k5	3553.99	0.18	0.14	1.32	0.188	0.525
Map4k4	1098.04	0.29	0.16	1.84	0.066	0.308
Mapk1	4298.00	-0.11	0.10	-1.15	0.249	0.602
Mapk14	4265.11	-0.15	0.09	-1.69	0.092	0.367
Mapk3	1956.99	-0.19	0.07	-2.60	9.28E-03	0.095
Mapk7	260.56	0.10	0.13	0.81	0.417	0.743
Mapk8	537.14	0.07	0.13	0.56	0.577	0.843
Mapt	4579.08	-0.06	0.12	-0.50	0.615	0.861
Mbd2	1985.04	-0.04	0.06	-0.63	0.530	0.814
Mbl2	8.21	0.01	0.66	0.01	0.991	NA
Mcat	1114.90	-0.04	0.11	-0.39	0.700	0.899
Mcts1	339.74	0.00	0.13	0.01	0.989	0.996
Mdm2	1271.31	0.07	0.10	0.78	0.436	0.756
Mdm4	1053.89	-0.19	0.17	-1.09	0.275	0.627
Men1	1455.65	0.15	0.09	1.66	0.097	0.377
Metap2	3287.65	0.15	0.13	1.10	0.272	0.625
Mfge8	2202.71	-0.29	0.15	-1.90	0.057	0.287
Mgam	5952.88	-0.09	0.14	-0.66	0.511	0.804
Micu1	2212.82	-0.15	0.06	-2.45	0.014	0.125
Mitf	728.94	-0.06	0.12	-0.50	0.620	0.862
Mlxipl	2370.95	0.20	0.17	1.20	0.230	0.580
Mmp2	**110.02**	**1.10**	**0.31**	**3.56**	**3.76E-04**	**0.011**
Mmp7	39.31	2.19	1.95	1.12	0.261	0.613
Mmp9	**35.63**	**2.13**	**0.58**	**3.66**	**2.52E-04**	**8.00E-03**
Mmrn1	39.89	-0.16	0.37	-0.44	0.661	0.883
Mok	204.78	-0.57	0.22	-2.63	8.58E-03	0.091
Mpg	437.68	-0.25	0.17	-1.51	0.131	0.439
Mrap2	5.80	0.01	0.86	0.01	0.994	NA
Msi2	3412.31	-0.27	0.10	-2.81	4.96E-03	0.064
Mta2	2261.56	0.00	0.07	0.03	0.974	0.992
Mthfr	1126.70	0.10	0.16	0.63	0.527	0.813
Mtmr11	**2182.79**	**0.50**	**0.10**	**5.12**	**3.07E-07**	**4.19E-05**
Mtor	**9833.42**	**0.28**	**0.09**	**3.24**	**1.20E-03**	**0.025**
Myc	**310.75**	**1.29**	**0.20**	**6.47**	**9.79E-11**	**4.64E-08**
Myd88	571.70	0.22	0.11	2.05	0.041	0.235
Mylk	2848.22	-0.11	0.13	-0.82	0.412	0.740
Nampt	6942.25	0.17	0.10	1.64	0.100	0.383
Ncf1	72.34	-0.05	0.36	-0.13	0.895	0.970
Nck1	670.01	0.14	0.13	1.08	0.282	0.634

Ncoa1	2289.71	-0.14	0.12	-1.18	0.239	0.591
Ncoa2	3235.81	0.10	0.11	0.88	0.377	0.717
Nedd4l	3193.79	0.01	0.14	0.10	0.922	0.978
Nes	507.60	-0.08	0.20	-0.41	0.681	0.893
Neu1	13759.25	-0.26	0.11	-2.46	0.014	0.124
Nexn	32.69	0.27	0.39	0.68	0.498	0.796
Nfat5	2076.83	-0.10	0.19	-0.52	0.604	0.856
Nfe2	8.06	-0.74	0.78	-0.95	0.343	NA
Nfe2l2	3118.94	0.20	0.08	2.38	0.018	0.143
Nfil3	**653.62**	**1.08**	**0.20**	**5.27**	**1.35E-07**	**2.32E-05**
Nfkb1	1226.33	0.10	0.09	1.17	0.243	0.596
Nfkbia	953.09	-0.03	0.33	-0.08	0.934	0.981
Ngdn	811.04	0.18	0.10	1.78	0.074	0.329
Ngf	41.04	0.37	0.36	1.03	0.302	0.652
Nlrc4	67.63	0.12	0.28	0.45	0.653	0.880
Nlrp3	21.58	0.56	0.57	0.98	0.326	0.674
Nod2	63.95	-0.38	0.31	-1.22	0.221	0.570
Nos1	101.05	-0.55	0.38	-1.46	0.145	0.464
Nos2	23.06	-0.65	0.68	-0.95	0.340	0.686
Nos3	121.67	-0.08	0.18	-0.46	0.642	0.873
Notch1	1013.77	-0.19	0.14	-1.32	0.186	0.522
Nox4	18536.08	-0.13	0.13	-0.97	0.332	0.679
Npy	22.22	-0.26	0.43	-0.60	0.546	0.824
Nqo1	**2519.13**	**-0.36**	**0.10**	**-3.44**	**5.82E-04**	**0.015**
Nr1h2	2436.69	-0.10	0.08	-1.26	0.206	0.551
Nr3c1	4523.55	-0.01	0.09	-0.11	0.913	0.975
Nr3c2	892.30	-0.02	0.15	-0.10	0.917	0.976
Nr4a1	273.83	1.02	0.80	1.28	0.202	0.543
Nr4a2	13.90	0.25	0.49	0.50	0.618	0.861
Nrg4	34.86	0.68	0.41	1.63	0.102	0.387
Nrtn	225.79	-0.56	0.20	-2.82	4.86E-03	0.063
Nsa2	2617.86	0.12	0.11	1.02	0.309	0.659
Nt5c2	2374.63	0.25	0.09	2.84	4.52E-03	0.061
Nucb2	466.85	-0.11	0.14	-0.78	0.437	0.757
Ogg1	321.63	-0.07	0.14	-0.47	0.639	0.871
Opa1	**4962.63**	**-0.39**	**0.07**	**-5.25**	**1.51E-07**	**2.46E-05**
Orai1	433.30	-0.16	0.12	-1.31	0.191	0.528
P2rx1	**145.41**	**0.65**	**0.21**	**3.04**	**2.34E-03**	**0.039**
P2rx3	19.08	1.16	0.86	1.35	0.176	0.511
P2rx4	1849.96	-0.16	0.12	-1.35	0.178	0.512
P2rx5	109.27	0.22	0.23	0.96	0.336	0.681
P2rx7	58.33	0.47	0.41	1.14	0.255	0.607
P2ry1	234.77	-0.10	0.14	-0.70	0.484	0.789
P2ry12	10.11	0.03	0.76	0.03	0.973	0.992
P2ry2	**288.82**	**-0.60**	**0.19**	**-3.21**	**1.32E-03**	**0.027**

Pak1	**1608.12**	**-0.50**	**0.08**	**-6.22**	**4.93E-10**	**1.85E-07**
Parp1	1917.85	0.15	0.09	1.66	0.098	0.379
Pawr	960.39	0.36	0.13	2.77	5.67E-03	0.070
Pck1	**161998.72**	**0.54**	**0.18**	**3.03**	**2.48E-03**	**0.040**
Pck2	771.94	0.31	0.15	2.09	0.037	0.222
Pcna	1093.70	0.12	0.12	0.99	0.321	0.669
Pcsk9	143.11	0.07	0.25	0.30	0.766	0.926
Pde5a	315.62	-0.15	0.18	-0.85	0.397	0.730
Pdhx	1582.27	0.16	0.11	1.44	0.150	0.471
Pdk1	2637.68	0.19	0.12	1.63	0.103	0.387
Pdk4	989.14	-0.06	0.47	-0.13	0.894	0.969
Pdpn	264.92	-0.44	0.17	-2.66	7.86E-03	0.086
Pecam1	1035.51	0.27	0.15	1.80	0.073	0.324
Pes1	1930.82	0.14	0.07	1.96	0.050	0.267
Pfkm	2318.32	0.00	0.08	-0.04	0.972	0.992
Phlpp1	1186.23	-0.07	0.13	-0.54	0.590	0.848
Pick1	743.93	0.07	0.11	0.64	0.525	0.813
Pid1	106.49	0.23	0.36	0.65	0.514	0.807
Pik3ca	3310.51	0.11	0.16	0.68	0.498	0.796
Pik3cb	1369.19	0.02	0.08	0.27	0.784	0.933
Pik3cd	109.50	-0.12	0.40	-0.30	0.762	0.925
Pik3cg	56.26	0.08	0.33	0.23	0.820	0.944
Pik3r1	2514.69	0.20	0.11	1.88	0.060	0.293
Pim1	229.08	-0.35	0.24	-1.44	0.149	0.469
Pin1	1104.11	-0.22	0.12	-1.88	0.060	0.293
Pin4	133.24	0.22	0.32	0.67	0.506	0.801
Pkm	11688.31	-0.22	0.08	-2.76	5.73E-03	0.070
Pla2g6	936.69	0.03	0.15	0.19	0.848	0.952
Plagl1	294.67	-0.40	0.26	-1.55	0.122	0.422
Plat	934.09	-0.03	0.17	-0.15	0.879	0.963
Plaur	113.14	-0.23	0.27	-0.83	0.407	0.737
Plg	43.55	0.71	0.43	1.65	0.100	0.382
Plin2	**3938.68**	**0.76**	**0.14**	**5.48**	**4.34E-08**	**9.31E-06**
Pltp	142.29	0.05	0.26	0.18	0.860	0.957
Plxna1	1705.98	-0.27	0.15	-1.87	0.061	0.295
Pml	926.61	-0.08	0.13	-0.59	0.553	0.829
Pnpla3	8.81	-1.21	0.87	-1.39	0.165	0.493
Pnpo	3283.52	-0.03	0.07	-0.38	0.705	0.902
Pold4	358.73	0.04	0.15	0.28	0.776	0.930
Poldip2	4466.44	0.00	0.08	-0.03	0.979	0.993
Pole4	559.46	-0.10	0.15	-0.68	0.497	0.796
Pomc	17.66	0.21	0.48	0.44	0.663	0.884
Pon2	400.17	0.06	0.15	0.42	0.672	0.890
Ppara	3319.92	-0.23	0.17	-1.36	0.174	0.507
Ppard	754.04	0.32	0.20	1.54	0.123	0.425

Pparg	62.97	-1.07	0.54	-1.99	0.046	0.254
Ppargc1a	3310.36	-0.24	0.10	-2.48	0.013	0.120
Ppia	12920.67	0.06	0.11	0.50	0.617	0.861
Ppid	585.92	0.20	0.12	1.65	0.098	0.379
Ppif	**2088.26**	**0.27**	**0.07**	**3.63**	**2.79E-04**	**8.59E-03**
Ppp1r11	847.23	-0.17	0.15	-1.13	0.260	0.612
Ppp2ca	6380.83	0.08	0.06	1.40	0.160	0.485
Prdx6	5757.67	0.06	0.08	0.67	0.505	0.801
Prkaa1	1064.98	-0.02	0.07	-0.29	0.773	0.929
Prkaa2	9279.20	0.00	0.08	0.00	1.000	1.000
Prkab1	1298.73	-0.04	0.09	-0.46	0.645	0.875
Prkca	**640.62**	**-0.69**	**0.21**	**-3.30**	**9.72E-04**	**0.021**
Prkcb	44.11	0.29	0.38	0.75	0.453	0.769
Prkcd	2461.21	-0.08	0.07	-1.20	0.230	0.581
Prkci	**1461.19**	**0.20**	**0.06**	**3.08**	**2.05E-03**	**0.036**
Prkcz	4165.16	-0.12	0.07	-1.72	0.086	0.355
Prkd1	310.23	-0.16	0.12	-1.40	0.163	0.489
Prmt1	1449.49	-0.01	0.10	-0.05	0.957	0.988
Prom1	**3443.84**	**-0.85**	**0.11**	**-7.56**	**4.03E-14**	**5.90E-11**
Prox1	450.58	-0.09	0.22	-0.40	0.693	0.896
Psip1	580.75	0.11	0.13	0.84	0.399	0.732
Ptbp2	**443.44**	**-0.61**	**0.17**	**-3.56**	**3.70E-04**	**0.011**
Ptch1	1242.65	0.01	0.16	0.05	0.963	0.990
Pten	6162.51	0.10	0.07	1.41	0.159	0.483
Ptgds	127.90	-0.80	0.31	-2.55	0.011	0.103
Ptgs1	692.81	-0.10	0.12	-0.80	0.422	0.747
Ptgs2	40.68	-0.15	0.39	-0.39	0.696	0.898
Ptk2b	3285.82	-0.08	0.10	-0.78	0.437	0.756
Ptpa	3839.26	-0.08	0.09	-0.95	0.342	0.687
Ptpn1	**1924.64**	**-0.40**	**0.11**	**-3.77**	**1.64E-04**	**5.73E-03**
Ptpn2	495.50	0.29	0.11	2.60	9.27E-03	0.095
Ptpn4	1979.49	0.02	0.18	0.09	0.929	0.980
Ptpn9	1288.48	-0.17	0.07	-2.52	0.012	0.112
Ptpru	505.39	-0.06	0.18	-0.34	0.733	0.913
Ptrh1	118.75	-0.05	0.22	-0.23	0.817	0.943
Rab10	3068.27	0.00	0.08	0.04	0.965	0.991
Rab8a	2617.99	0.10	0.17	0.61	0.545	0.823
Rac1	5185.66	0.06	0.07	0.90	0.370	0.712
Rack1	15572.10	0.04	0.11	0.32	0.751	0.920
Rapgef5	549.11	0.12	0.15	0.84	0.400	0.732
Rara	758.65	-0.28	0.12	-2.34	0.019	0.151
Rasgrp1	254.01	0.05	0.19	0.29	0.775	0.930
Rbm45	867.31	0.13	0.11	1.12	0.262	0.614
Rbp4	20.26	0.34	0.65	0.53	0.595	0.850
Rcan1	3358.89	0.55	0.31	1.78	0.075	0.330

Rcbtb1	1529.19	-0.25	0.13	-2.02	0.043	0.243
Rela	1063.67	0.33	0.12	2.74	6.12E-03	0.073
Renbp	1921.10	-0.06	0.12	-0.49	0.624	0.864
Retn	15.60	-1.01	1.85	-0.55	0.585	0.846
Retsat	**9820.20**	**-0.55**	**0.12**	**-4.73**	**2.29E-06**	**2.23E-04**
Rfc1	1260.83	0.01	0.11	0.14	0.890	0.967
Rheb	2242.11	0.21	0.07	2.82	4.75E-03	0.063
Rhot1	2475.02	0.10	0.06	1.55	0.121	0.422
Ripk1	1303.65	-0.20	0.08	-2.63	8.48E-03	0.090
Ripk2	152.75	-0.25	0.17	-1.43	0.152	0.475
Rnf10	9952.51	0.03	0.06	0.52	0.605	0.856
Rnf19a	1617.17	-0.01	0.07	-0.15	0.882	0.964
Robo4	290.27	0.24	0.16	1.54	0.123	0.426
Rock1	2164.67	0.20	0.12	1.66	0.096	0.376
Rorc	**3973.33**	**0.74**	**0.14**	**5.23**	**1.67E-07**	**2.66E-05**
Ros1	9.70	-1.25	0.62	-2.01	0.044	0.246
Rpain	555.16	-0.44	0.16	-2.77	5.52E-03	0.069
Rpl10	1044.53	-0.18	0.18	-1.04	0.298	0.646
Rpl29	10473.55	0.02	0.11	0.19	0.847	0.952
Rpl36a	1122.03	0.07	0.19	0.37	0.715	0.906
Rps19	8509.70	0.04	0.11	0.34	0.737	0.915
Rps6kb1	865.41	0.10	0.13	0.76	0.445	0.764
Rptor	**1699.39**	**-0.26**	**0.09**	**-3.02**	**2.49E-03**	**0.040**
Runx2	34.41	1.54	0.56	2.73	6.24E-03	0.074
S100a1	6939.04	-0.11	0.11	-0.97	0.332	0.679
S100a8	43.36	-0.02	1.16	-0.02	0.986	0.995
S1pr1	231.45	0.00	0.27	0.00	0.996	0.999
S1pr2	114.58	0.22	0.31	0.71	0.481	0.787
S1pr3	303.07	-0.14	0.20	-0.70	0.482	0.788
Sat1	6646.79	-0.03	0.13	-0.24	0.812	0.942
Scp2	23453.55	-0.09	0.07	-1.28	0.199	0.540
Scpep1	3398.30	0.13	0.08	1.73	0.083	0.349
Scube1	52.13	0.24	0.50	0.49	0.627	0.866
Sdc2	**3148.48**	**0.37**	**0.08**	**4.47**	**7.85E-06**	**6.01E-04**
Sdc4	11784.04	-0.05	0.07	-0.76	0.449	0.766
Sele	14.04	-0.25	0.60	-0.41	0.681	0.893
Selenop	61704.86	-0.30	0.17	-1.75	0.080	0.343
Selp	11.91	0.47	0.82	0.58	0.565	0.835
Sema3c	**2307.42**	**0.57**	**0.15**	**3.91**	**9.31E-05**	**3.68E-03**
Sema6a	532.09	0.48	0.17	2.80	5.06E-03	0.065
Serp1	5619.43	0.03	0.10	0.25	0.804	0.941
Serpine1	48.80	1.09	0.48	2.27	0.023	0.167
Serpinf1	25.95	0.96	0.56	1.70	0.088	0.360
Setd2	2832.91	0.40	0.15	2.66	7.91E-03	0.087
Setd7	873.68	0.24	0.22	1.08	0.279	0.631

Sgk1	6191.97	-0.16	0.41	-0.39	0.700	0.899
Sgpl1	2633.33	-0.02	0.09	-0.19	0.849	0.952
Sgsm3	671.56	0.11	0.18	0.62	0.535	0.817
Sh2b1	1465.56	-0.02	0.09	-0.19	0.848	0.952
Shbg	7.25	-0.53	0.65	-0.81	0.416	NA
Sik1	2884.43	0.07	0.14	0.51	0.611	0.859
Sim1	814.20	-0.22	0.16	-1.41	0.160	0.484
Sirpa	**3141.99**	**-0.36**	**0.11**	**-3.11**	**1.89E-03**	**0.034**
Sirt1	745.11	0.03	0.13	0.25	0.801	0.940
Sirt2	2224.99	0.04	0.07	0.54	0.589	0.848
Sirt3	2775.25	-0.03	0.10	-0.30	0.764	0.926
Sirt5	**413.49**	**0.32**	**0.11**	**3.04**	**2.40E-03**	**0.039**
Sirt6	266.75	0.11	0.13	0.88	0.381	0.720
Slc11a2	2064.69	0.01	0.15	0.06	0.950	0.986
Slc12a9	533.04	-0.10	0.16	-0.66	0.507	0.802
Slc16a1	2675.63	0.34	0.20	1.73	0.084	0.351
Slc16a3	37.14	0.42	0.77	0.54	0.588	0.847
Slc16a4	**1447.19**	**0.81**	**0.11**	**7.24**	**4.58E-13**	**4.61E-10**
Slc17a5	2008.03	0.20	0.07	2.66	7.85E-03	0.086
Slc19a1	3891.37	0.05	0.09	0.57	0.567	0.837
Slc1a3	83.98	-0.16	0.23	-0.70	0.484	0.789
Slc20a1	**799.20**	**0.54**	**0.17**	**3.14**	**1.68E-03**	**0.031**
Slc22a8	11758.00	-0.36	0.14	-2.61	9.16E-03	0.095
Slc24a3	32.28	0.57	0.48	1.18	0.238	0.590
Slc25a19	1810.79	0.17	0.10	1.74	0.082	0.346
Slc25a3	26631.53	-0.02	0.07	-0.21	0.831	0.948
Slc29a2	125.26	0.21	0.20	1.05	0.293	0.643
Slc2a1	**1570.17**	**-0.42**	**0.10**	**-4.11**	**3.91E-05**	**1.95E-03**
Slc2a2	8283.48	0.01	0.10	0.05	0.957	0.988
Slc2a3	27.05	-1.75	0.64	-2.75	5.97E-03	0.072
Slc2a4	**965.03**	**-0.47**	**0.12**	**-3.78**	**1.54E-04**	**5.44E-03**
Slc30a7	800.89	-0.21	0.14	-1.47	0.142	0.458
Slc35a1	1113.59	0.00	0.07	-0.02	0.988	0.996
Slc35g1	818.62	-0.17	0.14	-1.23	0.217	0.566
Slc38a4	197.95	0.06	0.21	0.29	0.770	0.928
Slc39a7	2800.93	-0.02	0.09	-0.20	0.842	0.951
Slc5a1	2540.93	0.17	0.11	1.53	0.126	0.431
Slc5a2	**20742.46**	**-0.38**	**0.08**	**-4.52**	**6.19E-06**	**4.88E-04**
Slc5a3	9514.18	-0.06	0.14	-0.40	0.686	0.894
Slc6a6	**12122.60**	**-0.77**	**0.12**	**-6.45**	**1.10E-10**	**5.05E-08**
Slc9a1	1001.32	-0.02	0.17	-0.12	0.905	0.973
Slpi	82.94	1.06	0.87	1.21	0.225	0.575
Smad2	**1428.16**	**0.37**	**0.11**	**3.34**	**8.44E-04**	**0.019**
Smad3	1449.12	0.09	0.14	0.64	0.520	0.809
Smim1	**2087.13**	**-0.31**	**0.08**	**-3.81**	**1.37E-04**	**4.97E-03**

Smn1	302.55	0.34	0.12	2.88	4.00E-03	0.056
Smug1	758.23	0.18	0.20	0.89	0.376	0.717
Snai2	36.38	0.94	0.34	2.79	5.23E-03	0.066
Snap23	2539.00	-0.04	0.10	-0.39	0.698	0.898
Snap47	2086.46	0.00	0.07	-0.03	0.977	0.993
Snca	108.43	-0.76	0.29	-2.60	9.34E-03	0.096
Sned1	280.61	-0.08	0.33	-0.23	0.820	0.944
Soat1	899.16	0.04	0.16	0.23	0.820	0.944
Socs3	110.73	-0.02	0.46	-0.04	0.971	0.992
Sod1	7916.71	-0.01	0.09	-0.13	0.899	0.970
Sod2	10325.59	0.27	0.19	1.41	0.157	0.482
Sord	82573.51	-0.01	0.08	-0.16	0.871	0.961
Sort1	**1810.76**	**-0.36**	**0.10**	**-3.66**	**2.54E-04**	**8.05E-03**
Sp1	2476.26	-0.06	0.11	-0.54	0.592	0.849
Sparc	2565.33	0.42	0.17	2.48	0.013	0.120
Sphk1	234.35	-0.35	0.21	-1.64	0.100	0.383
Spp1	39107.25	-0.30	0.13	-2.29	0.022	0.162
Src	1203.12	-0.09	0.10	-0.88	0.380	0.720
Srebf1	1364.15	-0.11	0.14	-0.82	0.409	0.739
Srebf2	2739.17	-0.17	0.10	-1.66	0.097	0.377
Srsf10	1367.99	0.35	0.13	2.77	5.69E-03	0.070
Srxn1	3054.85	0.21	0.11	1.94	0.053	0.274
St13	8961.11	0.31	0.11	2.84	4.53E-03	0.061
St3gal4	307.71	-0.26	0.19	-1.34	0.181	0.515
Stam	1237.00	0.20	0.11	1.87	0.061	0.295
Stap2	133.29	-0.17	0.20	-0.88	0.378	0.718
Stat3	3401.43	0.11	0.22	0.50	0.617	0.861
Stat5a	637.32	-0.11	0.15	-0.75	0.454	0.770
Stk11	2101.95	-0.09	0.11	-0.86	0.392	0.727
Stk24	1741.94	-0.19	0.10	-1.93	0.054	0.277
Suv39h1	408.52	-0.12	0.13	-0.94	0.348	0.692
Tat	7.55	1.94	1.24	1.56	0.119	NA
Tbc1d1	5907.38	-0.09	0.06	-1.41	0.159	0.483
Tbxa2r	72.68	-0.39	0.30	-1.29	0.197	0.537
Tcf21	**469.80**	**0.71**	**0.20**	**3.54**	**4.04E-04**	**0.011**
Tcf3	834.45	-0.06	0.12	-0.50	0.615	0.861
Tcf7l2	411.60	-0.09	0.17	-0.50	0.616	0.861
Tek	**923.47**	**0.48**	**0.15**	**3.12**	**1.81E-03**	**0.033**
Tfam	1727.96	0.05	0.14	0.38	0.701	0.900
Tfe3	789.95	0.15	0.10	1.45	0.147	0.466
Tfrc	2112.71	-0.02	0.14	-0.15	0.882	0.964
Tg	6.98	0.33	0.73	0.45	0.652	NA
Tgfb1	286.65	0.50	0.19	2.69	7.19E-03	0.082
Tgfb3	45.61	0.68	0.32	2.10	0.036	0.219
Tgm2	10127.54	-0.04	0.10	-0.42	0.676	0.891

Thbs1	2965.59	0.33	0.12	2.67	7.48E-03	0.084
Thbs2	**151.32**	**0.83**	**0.22**	**3.68**	**2.34E-04**	**7.53E-03**
Thrap3	2967.12	0.15	0.11	1.43	0.154	0.477
Ticam1	938.70	0.04	0.10	0.44	0.663	0.884
Timp1	8.27	0.69	0.90	0.77	0.440	NA
Timp2	823.84	0.09	0.16	0.54	0.590	0.848
Timp3	51567.36	0.09	0.10	0.95	0.342	0.687
Tkt	8644.15	0.09	0.08	1.13	0.259	0.611
Tlr1	27.35	-0.68	0.48	-1.43	0.154	0.477
Tlr2	106.34	-0.18	0.29	-0.62	0.538	0.819
Tlr4	126.49	0.02	0.22	0.10	0.917	0.976
Tm7sf2	333.03	0.02	0.18	0.09	0.932	0.980
Tmprss2	5715.34	-0.10	0.07	-1.35	0.177	0.512
Tnf	6.96	0.41	1.08	0.38	0.702	NA
Tnfrsf11b	15.90	1.06	0.89	1.20	0.231	0.582
Tnfrsf14	23.38	-0.01	0.52	-0.01	0.988	0.996
Tnfrsf1a	1759.99	0.01	0.10	0.15	0.877	0.963
Tnfrsf1b	164.65	0.20	0.32	0.63	0.526	0.813
Tnfsf10	1277.50	0.11	0.17	0.66	0.510	0.804
Tnfsf14	6.33	0.66	0.84	0.79	0.431	NA
Tpt1	30595.42	0.00	0.09	-0.05	0.961	0.990
Trib3	**28.39**	**1.63**	**0.53**	**3.09**	**1.97E-03**	**0.035**
Trpc3	35.68	0.45	0.34	1.32	0.186	0.522
Trpc6	14.76	-0.45	0.52	-0.87	0.382	0.721
Trpm7	5961.18	-0.15	0.07	-2.06	0.039	0.231
Trpv4	3264.67	0.14	0.09	1.61	0.107	0.395
Tsc2	3522.15	-0.12	0.13	-0.95	0.341	0.686
Tsc22d4	1474.03	0.18	0.14	1.28	0.200	0.541
Tspo	2552.94	-0.10	0.12	-0.84	0.401	0.733
Ttr	61.21	-0.28	0.43	-0.66	0.511	0.804
Tvp23b	1296.06	-0.01	0.08	-0.14	0.889	0.967
Txn2	5476.58	-0.06	0.10	-0.60	0.550	0.826
Txnip	9887.67	-0.19	0.16	-1.20	0.232	0.583
Ube2v1	3455.15	-0.08	0.05	-1.53	0.126	0.430
Ucp2	2068.15	0.04	0.15	0.25	0.801	0.940
Ugcg	424.03	-0.06	0.13	-0.42	0.672	0.890
Ulk1	2345.64	-0.09	0.14	-0.66	0.508	0.802
Unc13a	36.95	1.08	0.49	2.22	0.026	0.182
Unc13b	652.28	0.01	0.13	0.04	0.967	0.991
Usp14	1266.38	0.18	0.09	1.99	0.047	0.255
Utrn	2491.85	-0.09	0.15	-0.60	0.547	0.825
Vasp	931.87	0.06	0.11	0.52	0.600	0.853
Vat1	1946.31	0.11	0.08	1.41	0.158	0.483
Vcam1	269.64	0.08	0.28	0.29	0.773	0.929
Vcan	39.85	0.41	0.48	0.85	0.395	0.729

Vdac1	22212.76	0.07	0.07	0.99	0.324	0.672
Vdac2	8374.89	-0.05	0.06	-0.79	0.432	0.753
Vdr	9048.15	0.10	0.13	0.76	0.448	0.765
Vegfa	3801.07	-0.12	0.12	-0.99	0.324	0.671
Vegfb	1203.62	0.02	0.08	0.25	0.801	0.940
Vegfc	78.12	0.45	0.30	1.51	0.132	0.439
Vim	964.87	0.15	0.17	0.90	0.368	0.710
Vps51	1033.84	0.02	0.11	0.21	0.833	0.949
Vwf	130.57	-1.31	0.56	-2.35	0.019	0.150
Wfs1	634.09	0.16	0.13	1.28	0.199	0.540
Wnk1	17910.68	-0.02	0.11	-0.21	0.836	0.949
Xiap	2439.64	-0.04	0.08	-0.45	0.649	0.878
Xpr1	3671.23	-0.12	0.10	-1.13	0.259	0.610
Ywhaz	15938.34	0.18	0.07	2.59	9.61E-03	0.097
Yy1	2619.15	0.17	0.14	1.24	0.214	0.561
Zbtb7c	109.78	-0.51	0.21	-2.43	0.015	0.130
Zdhhc7	1131.51	0.02	0.09	0.18	0.855	0.955
Zeb1	338.89	-0.12	0.45	-0.27	0.788	0.934
Zfp69	149.09	-0.21	0.17	-1.23	0.217	0.566

Supplementary Table 2: List of differentially expressed genes in CHOP-ASO (ChA) versus PBS treated (PBS) db/db mice in the hyperglycemia gene set.

GeneSymbol: HGNC gene symbol; **baseMean:** mean of normalized counts for all samples **log2FoldChange:** log2 fold change; **lfcSE:** standard error; **stat**: Wald statistic; **pvalue:** Wald test p-value; **padj:** BH adjusted p-values; Genes showing an adjusted p-value <0.05 are depicted in bold.

List of reagents (used in current study)

Antibodies

Target antigen	Vendor or Source	Catalog #	Working concentration	Persistent ID / URL
anti-TIM-1	Abcam	ab47635	1:500	https://www.abcam.com/tim-1-antibody-ab47635.html
anti-ATF6	Santa Cruz Biotechnology	sc-166659	1:500	https://www.scbt.com/de/p/atf-6alpha-antibody-f-7
anti-GADD153/CHOP	Novus Biologicals	NB600-1335	1:1000	https://www.novusbio.com/primary-antibodies/gadd153-chop
anti-SGLT2	Invitrogen	PA5-75567	1:500	https://www.thermofisher.com/antibody/product/SGLT2-Antibody-Polyclonal/PA5-75567
Cleaved-caspase 3	Cell Signaling Technology	9661	1:1000	https://www.cellsignal.com/products/primary-antibodies/cleaved-caspase-3-asp175-antibody/9661
Mouse anti-CD133 (PROM1)	Biorbyt	orb372326	1:1000	https://www.biorbyt.com/cd133-antibody-orb372326.html
Mouse anti- Synaptopodin	Santa Cruz Biotechnology	sc-515842	1:50	https://www.scbt.com/p/synaptopodin-antibody-d-9
Rabbit anti-GAPDH	Sigma Aldrich	G9545	1:10000	https://www.sigmaaldrich.com/catalog/product/sigma/g9545?lang=en&region=CA
Anti-mouse IgG, HRP-linked Antibody	Cell Signaling Technology	7076	1:4000	https://www.cellsignal.com/products/secondary-antibodies/anti-mouse-igg-hrp-linked-antibody/7076?site-search-type=Products
Anti-rabbit IgG, HRP-linked Antibody	Cell Signaling Technology	7074	1:4000	https://www.cellsignal.com/products/secondary-antibodies/anti-rabbit-igg-hrp-linked-antibody/7074?site-search-type=Products
Donkey Anti-Rabbit IgG H&L (Alexa Fluor® 594)	abcam	ab150076	1:400	https://www.abcam.com/donkey-rabbit-igg-hl-alexa-fluor-594-ab150076.html
Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor 488	Thermo Fisher Scientific	A-21202	1:400	https://www.thermofisher.com/antibody/product/Donkey-anti-Mouse-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21202

Reagents and Kits

Reagents	Vendor or Source	Catalog #	Persistent ID / URL
Hematoxylin solution acc. to Gill II	CARL ROTH	T864.2	https://www.carlroth.com/com/en/cytological-routine-staining/hematoxylin-solution-acc-to-gill-ii/p/t864.2
Agarose Standard	CARL ROTH	3810.3	https://www.carlroth.com/com/en/agarose-gelling-reagents/agarose-standard/p/3810.3

Aqueous Mounting Medium	ZYTOMED	ZY-AMT030	https://www.zytomed-systems.com/storage/uploads/datasheets/en/ZY-AMT_EN.pdf
Takyon™ Rox SYBR Core Kit blue dTTP	Takyon	UF-RSCT-B0201	https://www.eurogentec.com/en/catalog/takyon-rox-sybr-core-kit-blue-dttp~b177cfdf-bb9a-4893-8b7f-f49288f8bab4
Trichrome Stain (Masson) Kit	Sigma Aldrich	HT15	https://www.sigmaaldrich.com/catalog/product/sigma/ht15?lang=en&region=CA
RNeasy Mini Kit	QIAGEN	74106	https://www.qiagen.com/de/shop//sample-technologies/rna/rneasy-mini-kit/
cDNA synthesis Kit	Invitrogen	18080051	https://www.thermofisher.com/order/catalog/product/18080051?SID=srch-hj-18080051#/18080051?SID=srch-hj-18080051
Pierce™ BCA protein assay kit	Perbio Science	23227	https://www.thermofisher.com/order/catalog/product/23227#/23227
Vector shield mounting medium with DAPI	Vector Laboratories	H-1200-10	https://vectorlabs.com/vectashieldr-plus-antifade-mounting-medium-with-dapi.html
PVDF membrane	Merck Millipore	IPVH00010	https://www.merckmillipore.com/DE/de/search/IPVH00010?search=&TrackingSearchType=SB+-+homepage-search-box+-+OLD&SearchContextPageletUUID=&SearchTerm=IPVH00010
Immobilion™ chemiluminescent HRP substrate	Merck Millipore	WBKLS0500	https://www.merckmillipore.com/DE/de/search/WBKLS0500?search=&TrackingSearchType=SB+-+Search+Result+Search+Box&SearchContextPageletUUID=&SearchTerm=WBKLS0500
Powdered milk	CARL ROTH	T145.2	https://www.carlroth.com/de/de/blockierungsreagenzien/milchpulver/p/t145.2
Albumin fraction	CARL ROTH	8076.2	https://www.carlroth.com/de/de/blockierungsreagenzien/albumin-fraktion-v/p/8076.2
Rotiphorese® Gel	CARL ROTH	3029.1	https://www.carlroth.com/de/de/page-fertigloesungen/rotiphoresegel-30-%28375%3A1%29/p/3029.1
Donkey serum	Sigma Aldrich	D9663	https://www.sigmaaldrich.com/catalog/product/sigma/d9663?lang=en&region=CA
TrueBlack® Lipofuscin autofluorescence quencher	Biotium	23007	https://biotium.com/product/trueblack-lipofuscin-autofluorescence-quencher/
Trizol Reagent	Life Technologies	15596018	https://www.thermofisher.com/order/catalog/product/15596018?SID=srch-hj-

			15596018#/15596018?SID=srch-hj-15596018
Phosphate Buffer Saline (PBS)	Thermo Fisher Scientific	10-010-031	https://www.thermofisher.com/order/catalog/product/10010031?SID=srch-hj-10010031#/10010031?SID=srch-hj-10010031
Rompun 2%	Bayer		https://covetrus.de/a/rompun-2prozent-flasche-25-ml/02.2049.25256.770081
Ketamine	Beta-pharm		https://www.betapharm.de/Ketamin
Tween-20	CARL ROTH	9127.1	https://www.carlroth.com/de/de/reagenzien-zur-dna-rna-analyse/tween-20/p/9127.1
2-Propanol	CARL ROTH	CP41.1	https://www.carlroth.com/de/de/von-a-bis-z/2-propanol/p/cp41.1
HBSS	Thermo Fisher Scientific	14025-050	https://www.thermofisher.com/order/catalog/product/14025100#/14025100
Protease Inhibitor Cocktail	Roche Diagnostics	11 836 153 001	https://www.sigmaaldrich.com/catalog/product/roche/11836153001?lang=en&region=CA
ACCU-CHEK glucometer	Roche Diagnostics	447470	https://www.medicalexpo.de/prod/roche/product-71020-447470.html
ACCU-CHEK blood glucose strips	Roche Diagnostics	05942861	https://www.vitalisto.de/accu-chek-inform-ii-teststreifen-quantitative-blutzuckerbestimmung

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