SUPPLEMENTAL MATERIAL

Detailed Methods

All chemicals and reagents were obtained from Sigma-Aldrich (St. Louis, MO, USA), unless otherwise stated. All experiments were performed at room temperature (20–24°C).

Study design

The study was designed to investigate whether the mild HDAC class I/IIa inhibitor VPA attenuates atrial remodeling in mice with cardiomyocyte specific expression of the human CREM isoform CREM-IbΔC-X. These mice show extensive atrial remodeling and develop AF spontaneously starting with first atrial ectopies at an age of 5 weeks[1,2]. At this age, we started VPA administration for short-term (7 weeks) or long-term (25 weeks) treatment (**Figure 1A**). Mice were housed under a 12h light / 12h night cycle at an ambient temperature of 22±2°C and fed standard chow. Periodic ECG recordings documented development of AF. After the respective treatment periods, mice were sacrificed and hearts were removed for subsequent experimental procedures. Adult male TG and wildtype (WT) mice were randomly assigned to vehicle (VEH) or VPA treatment groups (WT_{VEH}, WT_{VPA}, TG_{VEH}, TG_{VPA}). Male mice were chosen to reduce scattering and consequently the number of animals needed for experiments since the phenotype in male TG mice was more pronounced and developed more rapidly. The applied VPA concentration was chosen to achieve serum levels reported for HDAC inhibition[3]. The number of mice was chosen based on the experience from previous experiments performed on TG mice. Investigators were not blinded and no data excluded from analysis. During long-term treatment, one TG_{VEH} mouse and four TG_{VPA} mice died (n.s.) and were censored within the analysis for the Kaplan-Meier-analysis in **Figure 5**. The analysis of TG x HDAC2KO mice and the respective controls was performed in a blinded fashion. All experiments on animals conform to the Directive 2010/63/EU of the European Parliament and were approved by the local animal welfare authorities (LANUV; North Rhine-Westphalia, Germany; AZ 84-02.04.2011.A155; 84-02.04.2015.A418).

Generation of HDAC2KO mice

Cardiomyocyte-specific HDAC2KO mice were generated by cross-breeding HDAC2$^{loxP/loxP}$ (JaxB6.Cg-Hdac2tm1.1Rdp/J mice; JAX *022625, the Jackson Laboratory) with mice carrying a transgene for the Cre-recombinase under the control of cardiomyocyte-specific α-myosin heavy chain promotor (αMHC$^{Cre+/-}$ mice[4]). Electron microscopy analysis was performed on male/female mice on atria from control mice (CTR: FVB/N$^{Cre+/-}$), TG (CREM-IbΔC-X$^{Cre+/-}$), HDAC2KO and TG x HDAC2KO.

Serum preparation

After short- and long-term VPA treatment, blood was collected via punctuation of the heart with a syringe. To separate the serum samples, the blood samples were centrifuged at 14,000 x *g* for 5 min. Serum of each mouse was stored at -80°C before analyzing its VPA concentration. VPA serum concentration was measured in the Center for Laboratory Medicine, University Hospital Münster.

Electrocardiography recordings

ECG recording was performed in mice during long-term treatment (week 5-30) every two weeks starting from week 10 of age as described[5]. Mice were anaesthetized with inhalation of 1.5 to 2 % vaporized isoflurane (Forane®, Abbott) in combination with oxygen-nitrous oxide mixture. Anesthetized mice were positioned supine on a 37°C heating plate and 5 subcutaneous limb electrodes were placed after loss of the toe pinch reflex. Electrodes were connected to an external biological amplifier (Dual Bio Amp, ADInstruments, Dunedin, New Zealand) and a data acquisition unit (PowerLab 2/20, ADInstruments). Development of AF was determined using LabChart 7 Pro software (ADInstruments). AF was defined by absence of P-waves in combination with an irregular ventricular rate. ECG parameters for VPA safety observations were determined in WT_{VEH} and WT_{VPA} mice at 30 weeks of age - the end of the long-term treatment period (25 weeks of VPA therapy).

Isolation of atrial cardiomyocytes

After short-term treatment (week 5-12) atrial cardiomyocytes from respective animals were isolated according to a published protocol[6] which was modified for CREM-IbΔC-X mice. Mice were euthanized with carbon dioxide inhalation. The heart was excised and perfused retrogradely with Tyrode's solution (in mM: 136 NaCl, 5.4 KCl, 1 $MgCl_2$ x 6 H_2O 5 HEPES, 0.33 NaH_2PO_4 x H_2O, 11.1 Glucose, 1 $CaCl_2$; pH 7.4 adjusted with NaOH) in a modified Langendorff-apparatus for 3 min at 37 °C. After 5 min of calcium-free Tyrode solution, atria were enzymatically digested with collagenase Type II (Worthington, 230U/mg) in low calcium-Tyrode solution (Tyrode solution containing 12.5 µM $CaCl_2$, 2.5 mM taurine and 1 mg/ml bovine serum albumin) for 25 min (WT) or up to 45 min (TG). Enzymatic activity was stopped by perfusion with low calcium-Tyrode solution with 6 % newborn calf serum for 5 min. Soft atria were cut into small pieces. For retrieving atrial cardiomyocytes pieces were triturated two times in 800 µl of modified Kraftbrühe (KB)-buffer containing (in mM) 12.5 KCl, 5 KH_2PO4, 5 DL-aspartic acid potassium salt, 50 L-glutamic potassium salt, 2 $MgSO_4$ x 7 H_2O, 20 taurine, 0.5 EGTA, 5 creatine, 5 HEPES, 20 glucose (pH 7.2 adjusted with KOH) plus 12.5 µM $CaCl_2$ and 1mg/mL bovine serum albumin. Until use, the cells were kept in KB-buffer on ice.

Patch-clamp experiments

Atrial cardiomyocytes were slowly adapted from KB-buffer to 1 mM Ca^{2+} with the above mentioned Tyrode's solution (10 ml/h). Spindle-shaped, clear striated myocytes were selected randomly for electrophysiological studies. Action potentials were recorded using the perforated patch technique with amphotericin B (300µg/ml) as previously described[5,7]. Patch pipettes were pulled (P97; Sutter Instruments Inc., Novato, CA) from borosilicate glass capillaries (Science Products, Hofheim, Germany). Pipettes with 3–5 MΩ resistance were filled with a pipette solution containing in mM: 5 NaCl, 120 KCl, 2.5 MgATP, 1 EGTA, and 5 HEPES pH 7.4. Data were acquired and filtered at 10 kHz using an EPC-800 amplifier, sampled with an 18-bit A/D converter InstruTech ITC-18 under the control of the PatchMaster software

(HEKA Elektronik, Lambrecht, Germany). Action potentials (APs) were triggered at 1 Hz frequency with a suprathreshold current stimulus of 2-4 ms duration. Three to five consecutive AP traces were averaged and action potential duration was measured from the peak to 50, 70 and 90 % repolarization. The acute effect of 1 mM VPA was tested on Ca^{2+}-tolerant atrial myocytes. Action potentials were recorded before and 10 minutes after VPA application at room temperature. We measured the following action potentials parameters: amplitude, slope of depolarization and duration at 50, 70 and 90% repolarization.

Sodium currents were recorded in voltage-clamp mode (500 ms test pulse duration; -80 to +70 mV, Δ10 mV, -80 mV holding potential) under basal conditions and after acute application of 1 mM VPA. To estimate the Na^+-current amplitudes, from the peak of the inward current we subtracted the mean current measured at the end of the test pulse, as described above. To estimate the acute effect of VPA in each tested cell, the Na^+-currents recorded in the absence and presence of VPA at all potentials were normalized to the maximum Na^+-current recorded in the absence of VPA (measured at -50 mV). Normalized values were averaged and plotted against the test potentials. Since we focused on possible acute changes mediated by VPA vs basal conditions, other currents were left unblocked and recordings performed at physiological sodium concentrations.

Histological and electron microscopic analysis

Histology

For histological examination of the atria, longitudinal sections of hearts were prepared and immediately fixed in 4% buffered formalin, dehydrated, and embedded in paraffin. Sections of 5-µm thickness were deparaffinized, rehydrated, and stained using Masson`s trichrome protocol[8]. Image-Pro Plus software (Media Cybernetics Incorporation, Rockville, MD, USA) was used to quantify the collagen in the atria.

Ultrastructural analysis

For electron microscopy[9], small pieces of atrial tissue were fixed over night by immersion with 2.5 % glutaraldehyde in 0.1 M phosphate buffer. After fixation, the specimens were further fixed in phosphate

buffered 1% osmium tetraoxide for 2 h, dehydrated in graded ethanol series, and embedded in glycidyl ether. After 2 days ultrathin sections were cut, placed on a cupper mesh and stained with uranyl acetate and lead citrate. The sections were investigated under a Philips EM 208S transmission electron microscope. An area of 100 µm² of each picture was analyzed regarding amount of sarcomeric structure, mitochondria, and collagen formation by hand with ImageJ software. The analysis of TG x HDAC2KO mice and the respective controls was performed in a blinded fashion.

Western Blot analysis

Frozen atria were homogenized by sonication 3 times for 10s on ice in a medium containing 20% SDS and 10 mM $NaHCO_3$ (Ultrasonic-Homogenizer HTU Soni130, Heinemann). Homogenates were centrifuged at 14,000 x *g* for 20 min, and supernatants were subjected to SDS-gel electrophoresis. Protein content was determined according to LOWRY, using BSA as a standard. For immunoblot analysis of all proteins, 40 µg of individual samples were electrophoretically separated on 10% SDS-polyacrylamide gels and transferred to nitrocellulose. Membranes were blocked with 5% milk powder in TBST for 2 h at room temperature. After 2 times washing in TBS and TBST, blots were incubated over night at 4°C with different primary antibodies (dilution 1:1000) raised against the following proteins:

AcH4: Rabbit polyclonal anti-Histone H4 (acetyl K8) antibody (ab15823, abcam)

H4: Rabbit polyclonal anti-Histone H4 antibody (ab10158, abcam)

The secondary antibody (1:5,000; ECL Rabbit IgG, HRP-linked whole antibody; GE Healthcare) was incubated for 2 h at room temperature. After washing in TBS and TBST, signals were visualized using the ECL Western Blotting Substrate (Promega) and the ChemiDoc™ XRS (BioRad) with Image Lab™ Software (BioRad).

Chromatin immunoprecipitation and quantitative real-time PCR

ChIP was performed as described[7] modified for atrial tissue. Genomic DNA from TG or WT mouse atria was cross-linked with 1% formaldehyde in PBS (Thermo Scientific, *28906, methanol-free) for 7 min at

room temperature (RT). After quenching the formaldehyde and washing with phosphate-buffered saline (PBS) the tissue pellet was resuspended in cell lysis buffer (1% NP40, 10 mM NaCl, 10 mM Tris-HCl pH 8, supplemented with protease inhibitor cocktail tablets; Thermo Scientific). Cells were homogenized with a 2 ml dounce tissue grinder (WheatonTM, 10 ups and downs with loose and tight douncer) on ice. Pellet was resuspended in 250 µl sonification buffer and sonificated for 10 s with 60% amplitude (Ultrasonic-Homogenizer HTU Soni130, Heinemann) on ice. After over-night incubation at -80°C the sample was diluted with 200 µl ChIP dilution buffer. Chromatin was sonicated with 5 x 10 s pulses (10 s on / 59 s off intervals, 60% amplitude) at 4°C (next steps were done at 4°C). Pellet was precleared with 40 µl of blocked protein A/G (50/50%)-agarose beads for 1 h. Chromatin was incubated with rabbit polyclonal HA tag antibody (2.5 µg, ab9110, abcam) over-night and captured with 40 µl blocked protein A/G beads for 3h. The beads were washed as described by Schulte et al.[7] and were eluated 2 times with 75 µl elution buffer at 37°C. Crosslinks were reversed by over-night incubation with 200 mM NaCl at 67°C. Eluate was resuspended in 0.08 mg/ml proteinase K and 0.1 mg/ml RNAse A for 1.5 h at 55°C. DNA was purified with Mini PCR Purification Kit (Qiagen) and amplified with the GenomePlex® Complete Whole Genome Amplification (WGA4) Kit (Sigma-Aldrich®) following manufacturer's instructions. PCR product was purified with PCR Purification Kit (Qiagen) according to manufacturer's instructions (ChIP DNA). Quantitative real-time PCR (qPCR) was performed to identify the enrichment of genomic DNA fragments (ChIP DNA of TG vs. WT). The mix of 10 ng of ChIP DNA, 2 µl of each primer (10 pM, each), 10 µl Quanti-Fast SYBR Green PCR Master Mix (Roche) and 4 µl H2O were used for SYBR qPCR. Reactions were incubated at 95°C for 5 min, followed by 45 cycles at 95°C for 10 sec, 60°C for 15 sec, and 72°C for 20 sec. Primers (forward: for; reverse: rev) used for qPCR of mouse genomic DNA were:

Atp5l: for: GATCGCCACATTAGCTTGCG, rev: ATGTGGCCCCTTAAAGCTCC

Ces1d: for: GGCCAGAAACCCATCCAACA, rev: AGGCTGTGAAATGTGTCCGT

Gapdh (reference): for: TGCACCACCAACTGCTTA, rev: GGATGCAAGGATGATGTTC

Myl7: for: GTGTGGCTGGTCTCTTGTTC, rev: GGAGCCTGGTCACAAGAGAT

Ndufa8: for: TCCTTCAAGTCCCCTTTGGC, rev: CTCCCGGTGTACTGCATGTT

Ndufa12: for: ATCTACCAGCATACCGACGC, rev: GTACCCAGAAAGCGACCCTG

Ndufs7: for: GGGTTTCCGCTGGTGTCTAT, rev: CCCAGGACTACGCCACTCTC

Pdha1: for: CCCTGGTTGACTTGGGTGAG, rev: CCTCGCTAAGTAGTCCAAGCT

Tnni3: for: AGAGGCAGAGAACAGGATCG, rev: GCGCTAGAGTCAAAGGAGGA

Uqcr10: for: GCTTACCCATCTTCCCCAGT, rev: ATTCACTCCCCATGCCAGAA

Statistical analysis of qPCR data in Table S3 was executed with the REST software (Relative Expression Software Tool V2.0.13[10,11]).

Proteome analysis of atrial tissue

Proteome analysis was performed as published[12]. Atrial tissue samples (n=5-8 each group) were homogenized using a Mikro Dismembrator (B Braun, Melsungen, Germany) at 2,600 rpm for 2 min in urea buffer (8 M urea/2 M thiourea). Nucleic acid fragmentation was achieved by sonication on ice three times for 5 s at 80 % energy using a Sonoplus (Bandelin, Berlin, Germany). The homogenates were centrifuged at 16,000 x *g* for 1 h at 4 °C. Protein concentration was determined by Bradford using BSA as standard. To generate a defined set of peptides 4 µg protein were reduced, alkylated, and digested with Lys-C (1:100) for 3 h followed by proteolysis with trypsin over night at 37 °C. The peptides obtained were purified on C18 material (µZipTip, Millipore Merck, Darmstadt, Germany) and subsequently separated by C18 Reverse phase liquid chromatography (nanoAcquity UPLC system, 10 cm, Waters, Manchester, UK) in a linear gradient of 0.1 % acetic acid in acetonitrile from 5 % up to 25 % within 65 min (flow rate: 400 nl/min). MS analysis was performed on a LTQ-Orbitrap Velos hybrid mass spectrometer (Thermo Electron, Bremen, Germany). The mass-to-charge ratio (m/z) and fragmentation spectra of all peptides were recorded. MS data were analyzed to identify and quantify the detected peptides, and assemble it to proteins. Peptides and proteins were identified by searching MS data against a forward-reverse UniProt database with a restriction on *Mus musculus* using the Sorcerer™ software platform with SEQUEST algorithm. The annotation of peptides was carried out at a false-positive rate of <1 % that is equivalent to a peptide probability >0.88. Shared peptides were excluded. Only proteins with a probability ≥0.9 and more than 1 peptide were used

for quantification and functional analyses. Peptide intensities from fragmentation spectra were summed up before protein ratios were calculated. A statistical evaluation of the results was performed with Gene Data Analyst. In this process intensities of changed proteins of all groups were normalized to proteins of VEH-treated WT atria (WT_{VEH}=1).

Ingenuity® Pathway Software (Qiagen) and the Kyoto Encyclopedia of Genes and Genomes [KEGG] database were used to assign proteins displaying altered levels in atrial tissues to biological pathways.

Supplemental References

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Supplemental Figures and Tables

Figure S1

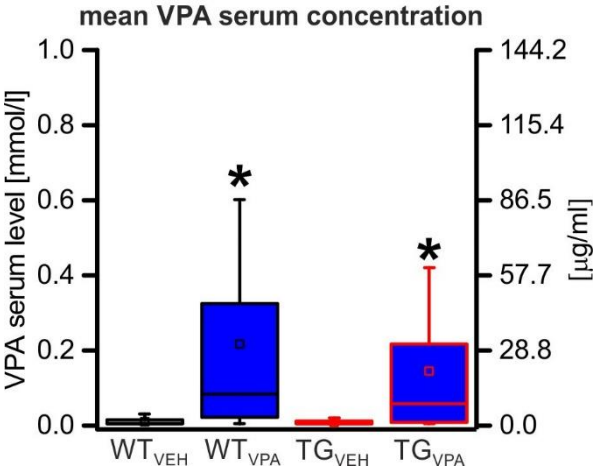


Figure S1 – figure supplement 1: VPA serum concentration in mice

Detected average VPA serum concentration in VEH- and VPA- treated WT and TG mice (short-term and long-term treated mice; n=10-30 animals/group; *P<0.05 vs. VEH; Box: 25th-75th percentile, whiskers: 10th-90th percentile, square: mean, horizontal line: median). Note that blood samples were collected randomly during daytime, and thus values will range between actual trough and peak VPA levels in mice.

Figure S2

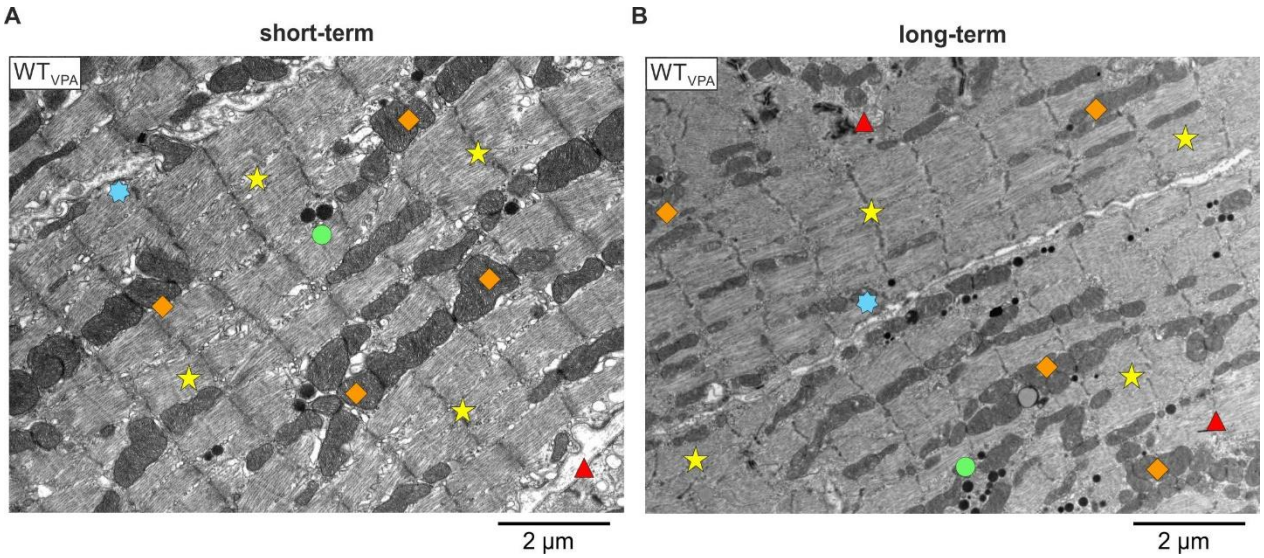
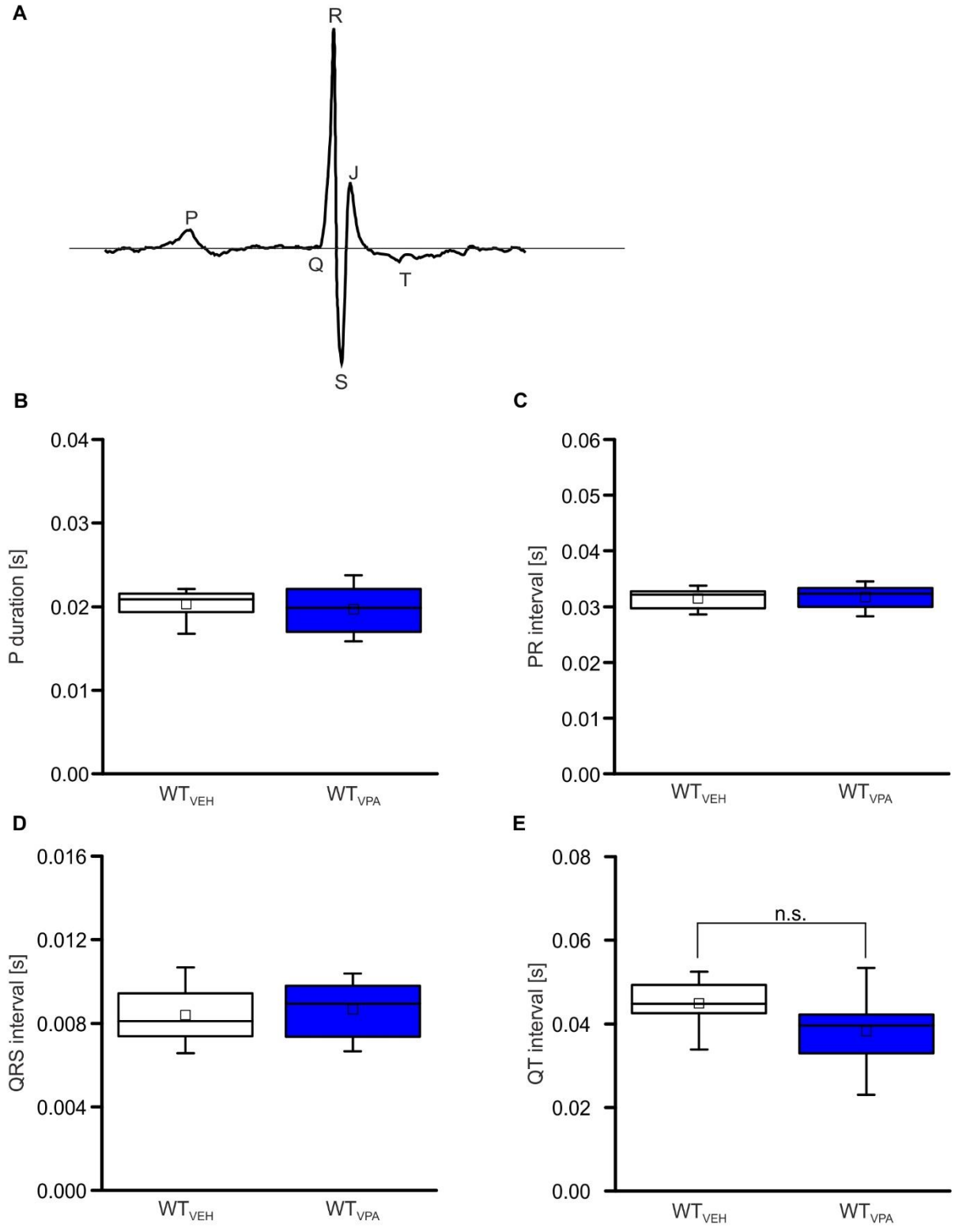


Figure S2 – figure supplement 1: VPA effect on atrial ultrastructure in WT mice.

Representative EM pictures of atrial tissue from **A** short-term and **B** long-term VPA-treated WT mice used for statistical analysis of ultrastructural parameters displayed in **Figure 2** (sarcomeres, mitochondria, collagen fibers, lipofuscin granules, glycogen). (n=3-4 animals/group; average of 16-18 pictures/animal)

Figure S3


A
R
J
P
Q
T
S
B
P duration [s]
0.04
0.03
0.02
0.01
0.00
WT VEH
WT VPA
C
PR interval [s]
0.06
0.05
0.04
0.03
0.02
0.01
0.00
WT VEH
WT VPA
D
QRS interval [s]
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0.012
0.008
0.004
0.000
WT VEH
WT VPA
E
QT interval [s]
0.08
0.06
0.04
0.02
0.00
n.s.
WT VEH
WT VPA

Figure S3: No arrhythmogenic alterations in ECG parameters after long-term VPA treatment in WT. **A** representative ECG recording from WT mice. **B-D** P duration, PR interval and QRS interval were not different between WT_{VPA} and WT_{VEH} at an age of 30 weeks (25 weeks of VPA therapy). **E** the QT interval was non-significantly decreased after VPA treatment (n=8 animals/group).

Figure S4

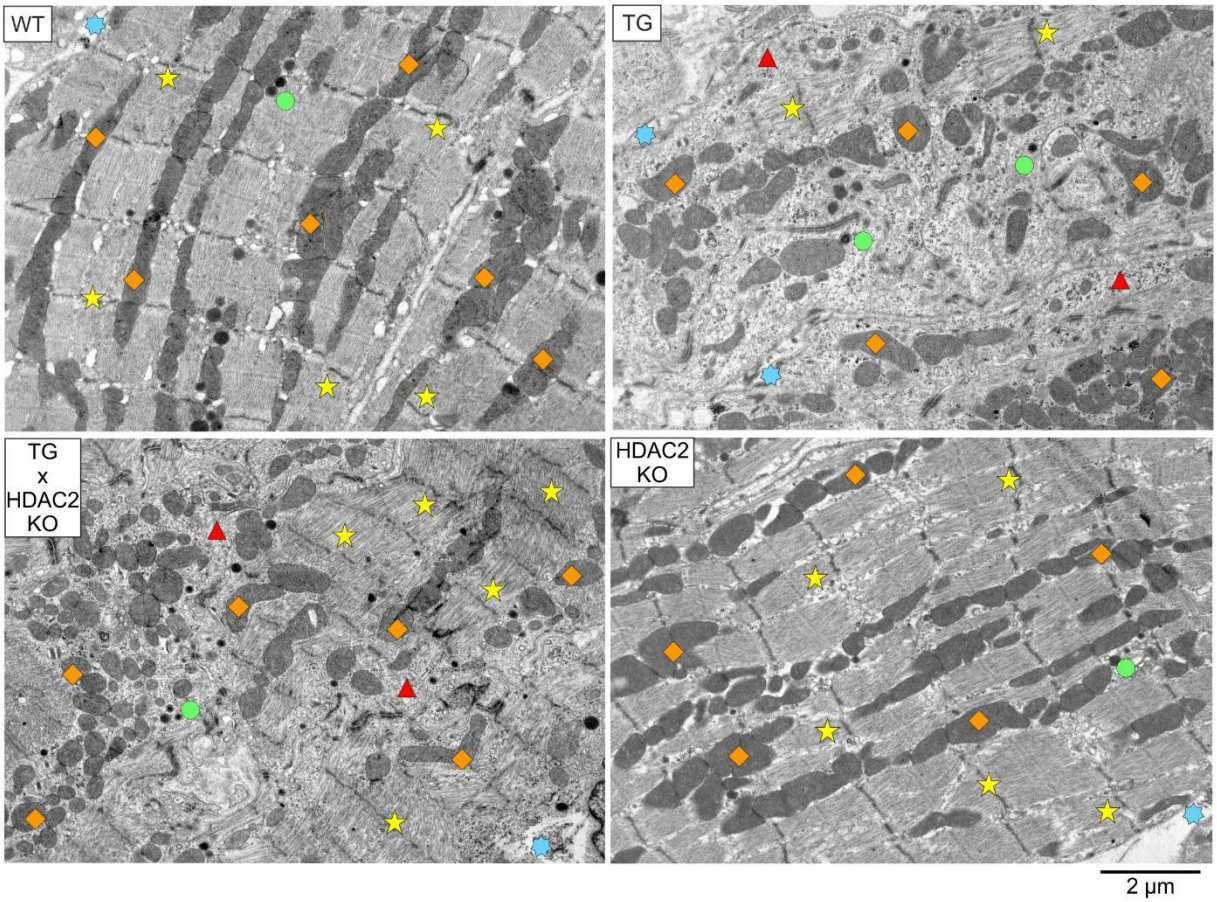


Figure S4: Genetic inactivation of HDAC2 attenuated ultrastructural remodeling in TG atria. Representative electron microscopic images of atrial tissue from all four groups used for statistical analysis of ultrastructural parameters displayed in Figure 6. Sarcomeres (sarcomeres, mitochondria, collagen fibers, lipofuscin granules, glycogen). All four groups were αMHC$^{Cre+/-}$.

Figure S5

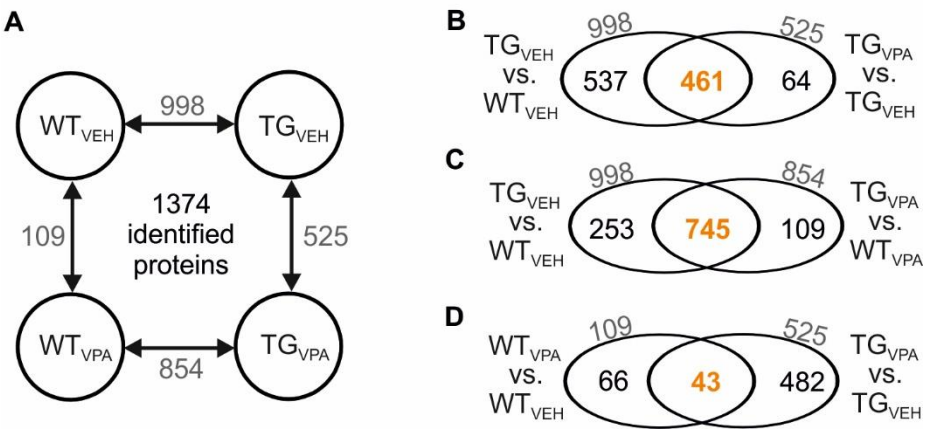


Figure S5: Analysis of proteomic changes induced by the VPA treatment. A Number of proteins that were differentially regulated in atria of indicated treatment groups. (n=5-8 animals/group) after short-term treatment (12 weeks of age). Venn diagrams **(B-D)**, displaying the intersection of in each case two sets of regulated proteins derived from the comparison displayed in A. **B** 461 proteins differentially regulated in TG_{VEH} vs. WT_{VEH} atria were concurrently altered by the VPA treatment. **C** 745 proteins were altered due to the TG genotype independently of VPA. **D** Only 43 proteins were regulated by VPA independently of the genotype.

Figure S6

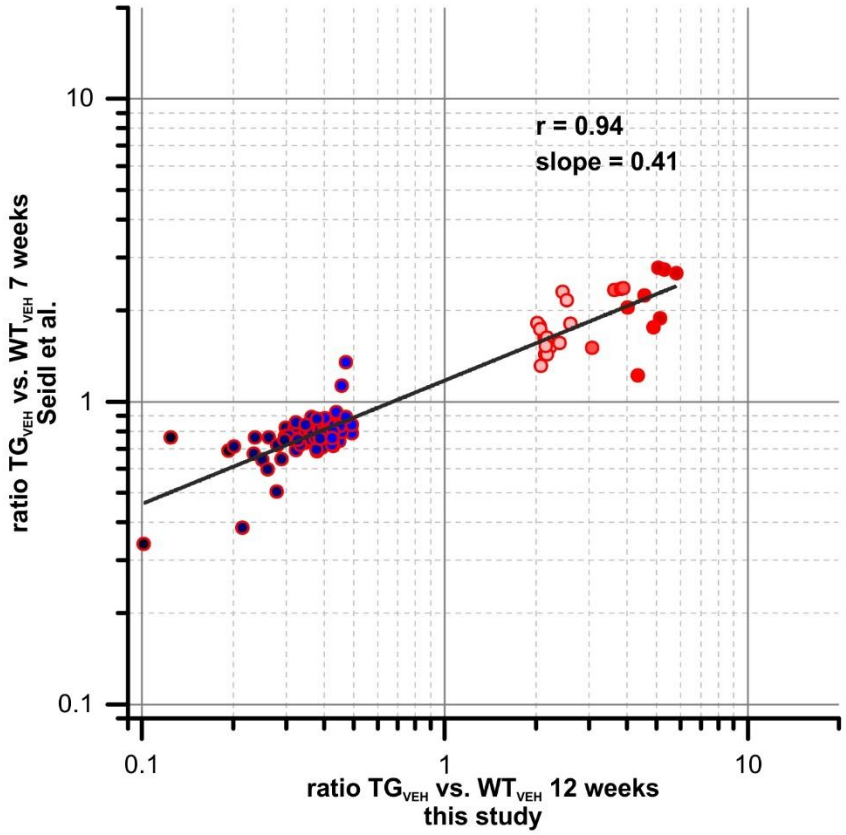
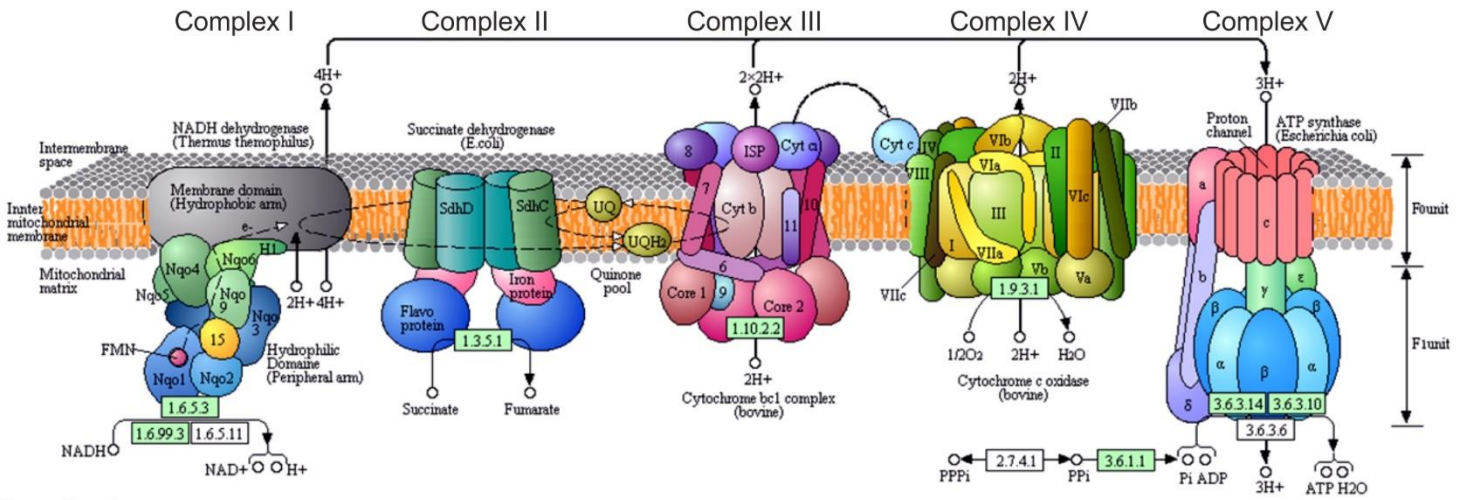


Figure S6: Corresponding protein expression ratios for TG_{VEH} vs. WT_{VEH} at 7 and 12 weeks of age.

Corresponding expression ratios (TG_{VEH} vs. WT_{VEH}) are displayed for those of the 295 strongest regulated proteins in TG_{VEH} at 12 weeks of age that have also been identified in an independent dataset derived at 7 weeks of age published recently by Seidl et al.[13] (red: upregulation, blue: downregulation, black line: linear regression curve) in TG_{VEH} vs. WT_{VEH}, . Note that almost all proteins (102/104) regulated at 12 weeks of age were already regulated at 7 weeks of age, before the onset of AF, in the same direction.

Figure S7

Oxidative phosphorylation



Complex I

ND1, ND2, ND3, ND4, ND5, ND6,
NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS5, NDUFS6,☆NDUFS7, NDUFS8, NDUFV1, NDUFV2, NDUFV3,
NDUFA1, NDUFA2, NDUFA3, NDUFA4, NDUFA5, NDUFA6, NDUFA7,☆NDUFA8, NDUFA9, NDUFA10, NDUFA11,☆NDUFA12, NDUFA13,
NDUFB2, NDUFB3, NDUFB4, NDUFB5, NDUFB6, NDUFB7, NDUFB8, NDUFB9, NDUFB10, NDUFB11, NDUFC1, NDUFAB1, NDUFC2, NDUFAF3

Complex II

SDHA, SDHB, SDHC, SDHD

Complex III

UQCRFS1, CYCB, CYC1, UQCRC1, UQCRC2, UQCRH, UQCRB, UQCRQ,☆UQCR10, UQCR11

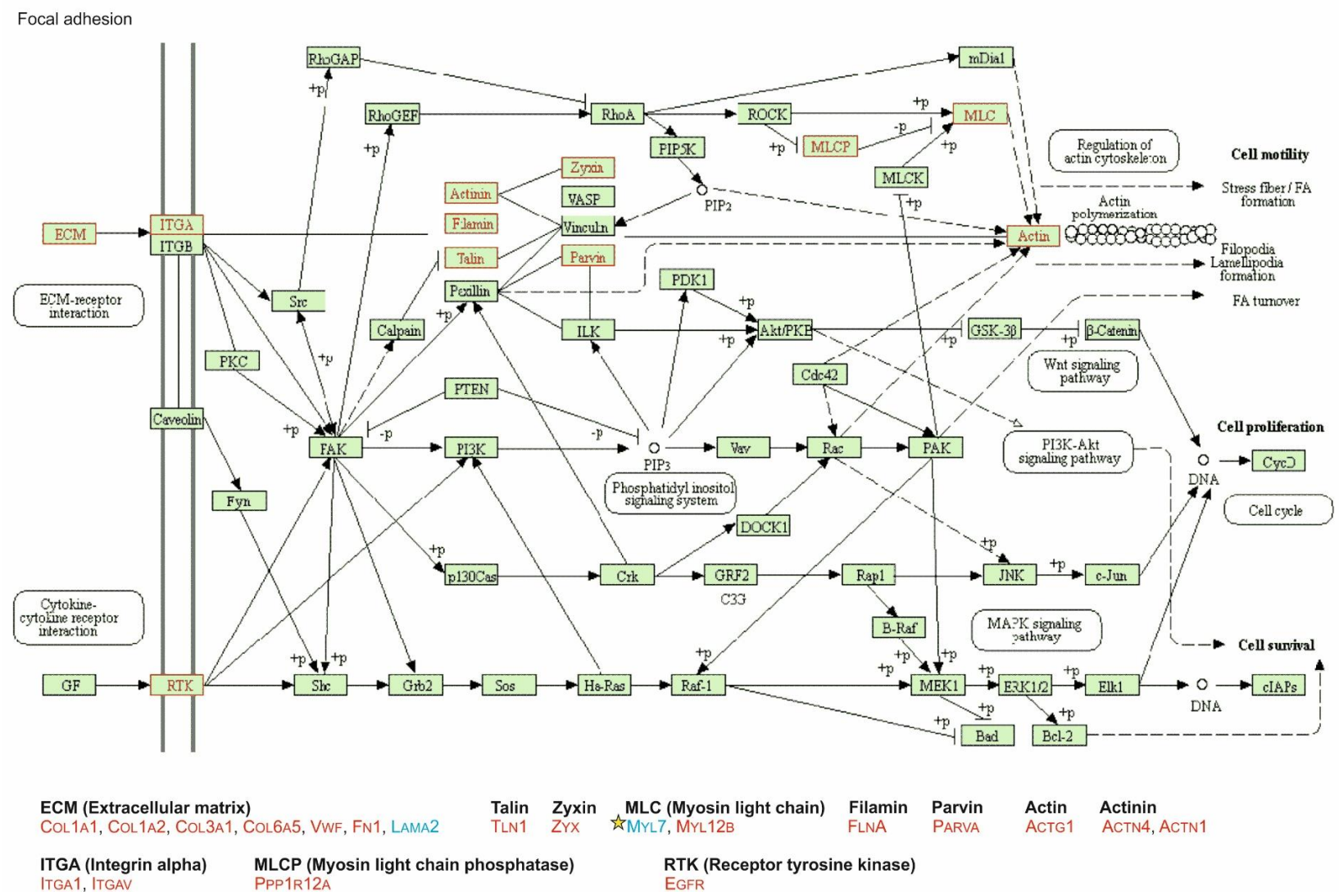
Complex IV

COX10, COX3, COX2, COX1, COX4I1, COX4I2, COX5A, COX5B, COX6A-C, COX7A1, COX7B, COX7C, COX8, COX11, COX17, COX15

Complex V

ATP5A1, ATP5B, ATP5C1, ATP5D,☆ATP5L, ATP5O, ATP6, ATP5F1, ATP5G1-3, ATP5H, ATP5K, ATP5J2, ATP5E, ATP5J, ATP5I, ATP8,
ATP6V1A-H, ATP6V0A-E, ATP6AP1

Figure S8


Focal adhesion
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RhoGEF
RhoA
mDia1
ROCK
MLC
MLCP
MLCK
PIP5K
PIP2
Regulation of actin cytoskeleton
Cell motility
Stress fiber / FA formation
Actin polymerization
Filopodia
Lamellipodia formation
FA turnover
Actinin
Zyxin
VASP
Filamin
Vinculin
Talin
Parvin
Actin
ECM
ITGA
ITGB
ECM-receptor interaction
Src
Calpain
Paxillin
PDK1
ILK
Akt/PKB
GSK-3β
β-Catenin
Wnt signaling pathway
PKC
Cdc42
PTEN
Caveolin
FAK
PI3K
PIP3
Vav
Rac
PAK
PI3K-Akt signaling pathway
Cell proliferation
CycD
DNA
Phosphatidyl inositol signaling system
Fyn
DOCK1
Cell cycle
p130Cas
Crk
GRF2
C3G
Rap1
JNK
c-Jun
Cytokine-cytokine receptor interaction
B-Raf
MAPK signaling pathway
Cell survival
GF
RTK
Shc
Grb2
Sos
Ha-Ras
Raf-1
MEK1
ERK1/2
Elk1
DNA
cIAPs
Bad
Bcl-2
ECM (Extracellular matrix)
COL1A1, COL1A2, COL3A1, COL6A5, VWF, FN1, LAMA2
Talin
TLN1
Zyxin
ZYX
MLC (Myosin light chain)
MYL7, MYL12B
Filamin
FLNA
Parvin
PARVA
Actin
ACTG1
Actinin
ACTN4, ACTN1
ITGA (Integrin alpha)
ITGA1, ITGAV
MLCP (Myosin light chain phosphatase)
PPP1R12A
RTK (Receptor tyrosine kinase)
EGFR

Figure S9

Hypertrophic cardiomyopathy (DCM) and Arrhythmogenic rigth ventricular cardiomyopathy (ARVC)

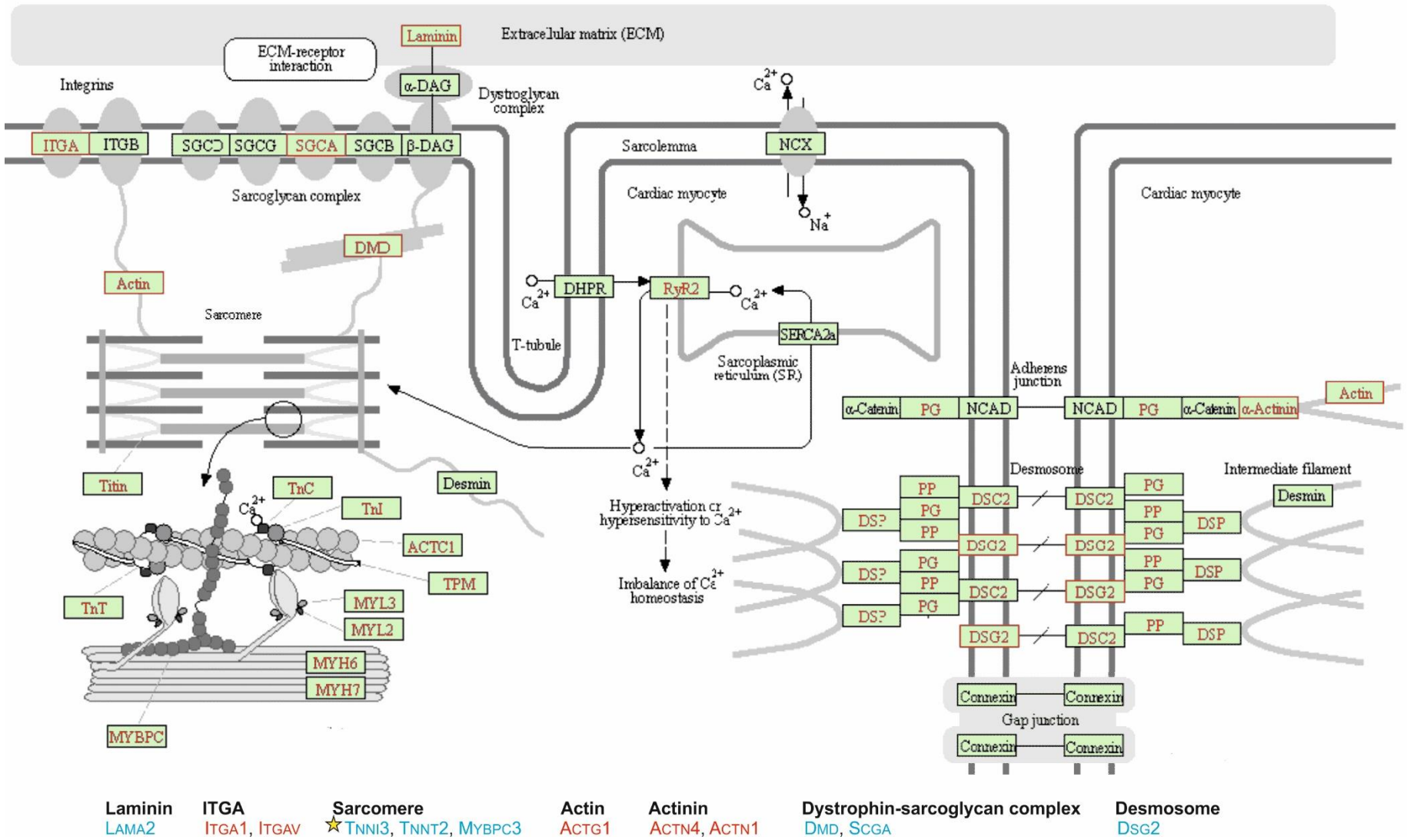

Figure S10

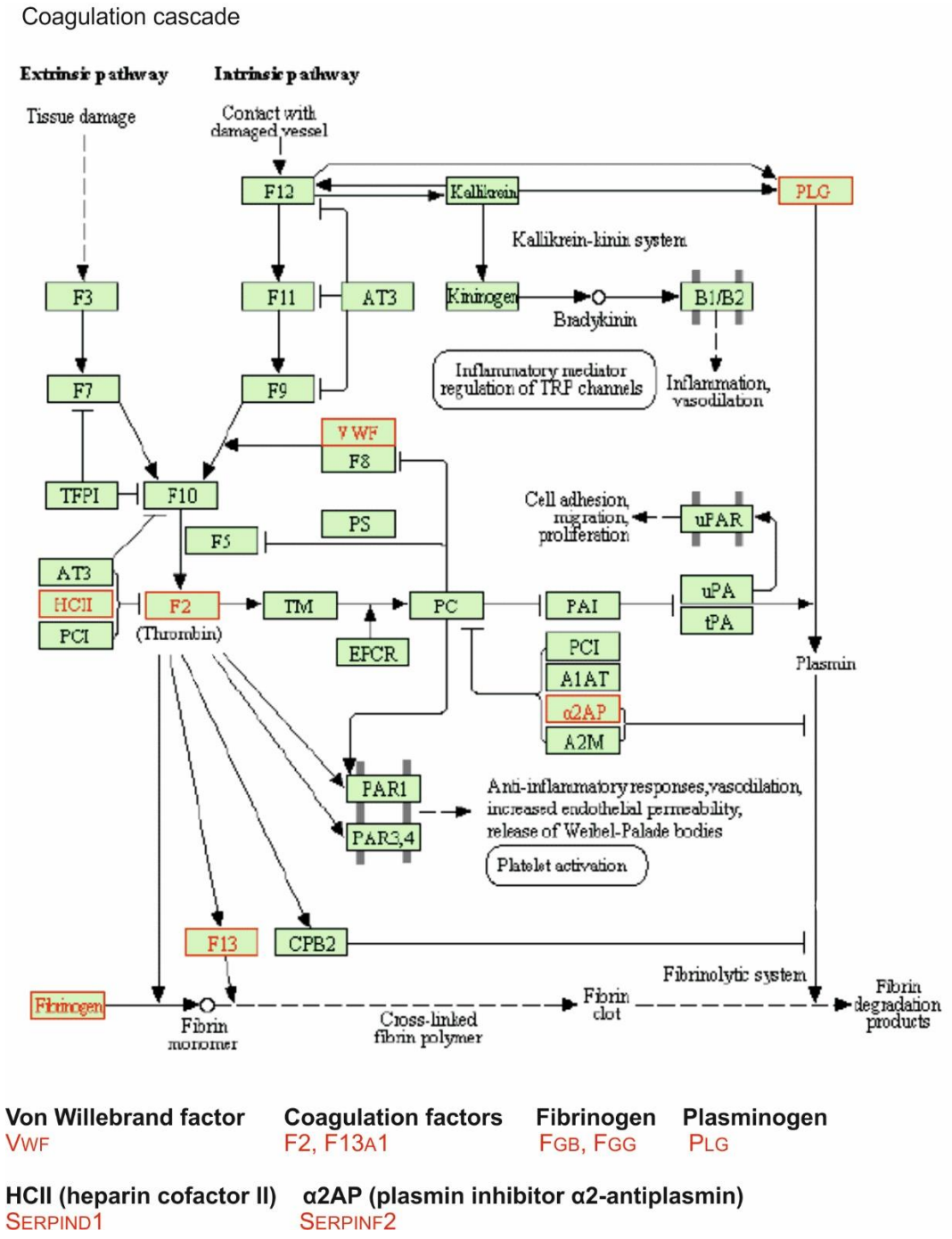

Figure S7-10: Examples of KEGG pathways including proteins altered in TG_{VEH} vs. WT_{VEH} mice which were counter-regulated by VPA. S7: Oxidative phosphorylation, **S8:** Focal adhesion **S9:** Hypertrophic cardiomyopathy (DCM) and Arrhythmogenic right ventricular cardiomyopathy (ARVC) (combined) **S10:** Coagulation. Pathway maps were taken from KEGG PATHWAY Database

(http://www.genome.jp/kegg/pathway.html). Regulated proteins are listed below each pathway (blue=downregulated; red=upregulated) ☆ encoding gene was validated as CREM-target by ChIP.

Table S1: Proteins regulated more than 2-fold (↑↓) in TG_{VEH} in comparison to WT_{VEH} and significantly by VPA (n=295).

Symbol	Protein name	TG_{VEH} vs. WT_{VEH}	WT_{VPA} vs. WT_{VEH}	TG_{VPA} vs. WT_{VEH}	TG_{VPA} vs. TG_{VEH}
ALDH1B1*	Aldehyde dehydrogenase X, mitochondrial	**0.10**	1.11	0.21	**2.04**
CES1D*†	Carboxylesterase 1D	**0.13**	1.15	0.27	**2.19**
FAM210A	Protein FAM210A	**0.17**	1.07	0.62	**3.56**
MYL7*†	Myosin regulatory light chain 2, atrial isoform	**0.19**	1.06	0.41	**2.14**
GSTK1	Glutathione S-transferase kappa 1	**0.20**	0.97	0.33	**1.66**
MYBPHL*	Myosin-binding protein H-like	**0.20**	0.99	0.32	**1.56**
GPC1*	Glypican-1	**0.21**	1.05	0.35	**1.65**
CCBL2	Kynurenine--oxoglutarate transaminase 3	**0.22**	1.12	0.44	**1.99**
MYL4*	Myosin light chain 4	**0.24**	1.02	0.46	**1.98**
NDUFA4*	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 4	**0.24**	0.94	0.61	**2.56**
MCEE	Methylmalonyl-CoA epimerase, mitochondrial	**0.25**	0.96	0.38	**1.55**
COX7A1*	Cytochrome c oxidase subunit 7A1, mitochondrial	**0.25**	0.96	0.49	**1.96**
TNNI3†	Troponin I, cardiac muscle	**0.25**	0.93	0.52	**2.07**
ADCK3	Chaperone activity of bc1 complex-like, mitochondrial	**0.25**	0.98	0.48	**1.87**
ACSL1*	Long-chain-fatty-acid--CoA ligase 1	**0.26**	1.10	0.41	**1.58**
ATP5L*†	ATP synthase subunit g, mitochondrial	**0.26**	1.02	0.69	**2.61**
TXLNB	Beta-taxilin	**0.27**	0.93	0.41	**1.52**
MACROD1*	O-acetyl-ADP-ribose deacetylase MACROD1	**0.28**	0.91	0.45	**1.62**
PDK4	[Pyruvate dehydrogenase (acetyl-transferring)] kinase isozyme 4, mitochondrial	**0.28**	1.12	0.51	**1.83**
MYH6*	Myosin-6	**0.28**	0.98	0.47	**1.69**
CLYBL	Citrate lyase subunit beta-like protein, mitochondrial	**0.29**	0.95	0.42	**1.46**
ACOT13	Acyl-coenzyme A thioesterase 13	**0.29**	0.92	0.49	**1.70**
DSG2	Desmoglein-2	**0.29**	1.09	0.50	**1.72**
TPPP3*	Tubulin polymerization-promoting protein family member 3	**0.29**	0.97	0.37	**1.27**
TNNT2	Troponin T, cardiac muscle	**0.29**	1.03	0.52	**1.80**
ECHS1*	Enoyl-CoA hydratase, mitochondrial	**0.30**	0.99	0.47	**1.58**
GOT1*	Aspartate aminotransferase, cytoplasmic	**0.30**	0.96	0.51	**1.72**
TPM1*	Tropomyosin alpha-1 chain	**0.30**	1.05	0.56	**1.86**
ECI1	Enoyl-CoA delta isomerase 1, mitochondrial	**0.30**	1.05	0.46	**1.53**
MYOM1*	Myosin-binding protein H-like	**0,31**	0,94	0,48	**1,58**
COQ9*	Ubiquinone biosynthesis protein COQ9, mitochondrial	**0.31**	0.94	0.57	**1.83**
PDK2*	[Pyruvate dehydrogenase (acetyl-transferring)] kinase isozyme 2, mitochondrial	**0.32**	0.98	0.54	**1.69**

DNAJA4	DnaJ homolog subfamily A member 4	**0.32**	1.07	0.52	**1.61**
PRDX3*	Thioredoxin-dependent peroxide reductase, mitochondrial	**0.32**	0.99	0.51	**1.58**
PFKM*	6-phosphofructokinase, muscle type	**0.32**	1.08	0.50	**1.55**
MURC	Muscle-related coiled-coil protein	**0.32**	1.01	0.58	**1.79**
NDUFAF3	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex assembly factor 3	**0.33**	0.92	0.57	**1.73**
CSRP3	Cysteine and glycine-rich protein 3	**0.33**	1.05	0.65	**1.99**
SELENBP1*	Selenium-binding protein 1	**0.33**	0.86	0.48	**1.48**
ATP5I*	ATP synthase subunit e, mitochondrial	**0.33**	0.92	0.57	**1.72**
CRAT*	Carnitine O-acetyltransferase	**0.33**	0.99	0.49	**1.48**
NDUFB5	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 5, mitochondrial	**0.33**	0.96	0.70	**2.11**
ACSS1	Acetyl-coenzyme A synthetase 2-like, mitochondrial	**0.33**	0.97	0.58	**1.72**
UQCR10†	Cytochrome b-c1 complex subunit 9	**0.34**	1.07	0.68	**2.03**
ALDH4A1	Delta-1-pyrroline-5-carboxylate dehydrogenase, mitochondrial	**0.34**	0.99	0.52	**1.52**
FAHD1	Acylpyruvase FAHD1, mitochondrial	**0.34**	0.93	0.53	**1.55**
DBT	Lipoamide acyltransferase component of branched-chain alpha-keto acid dehydrogenase complex, mitochondrial	**0.34**	0.92	0.52	**1.52**
SOD2*	Superoxide dismutase [Mn], mitochondrial	**0.35**	1.06	0.61	**1.76**
NDUFS3*	NADH dehydrogenase [ubiquinone] iron-sulfur protein 3, mitochondrial	**0.35**	0.93	0.58	**1.67**
IVD*	Isovaleryl-CoA dehydrogenase, mitochondrial	**0.35**	1.01	0.50	**1.44**
NDUFB3	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 3	**0.36**	1.07	0.67	**1.88**
NDUFA8†	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 8	**0.36**	1.07	0.65	**1.82**
ETFB*	Electron transfer flavoprotein subunit beta	**0.36**	0.97	0.59	**1.64**
HSD17B8	Estradiol 17-beta-dehydrogenase 8	**0.36**	0.97	0.46	**1.28**
ACAA2*	3-ketoacyl-CoA thiolase, mitochondrial	**0.36**	1.09	0.60	**1.65**
ETFA*	Electron transfer flavoprotein subunit alpha, mitochondrial	**0.36**	0.98	0.57	**1.55**
NDUFA6*	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 6	**0.37**	1.02	0.65	**1.78**
NDUFA13*	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 13	**0.37**	1.01	0.58	**1.59**
MDH1	Malate dehydrogenase, cytoplasmic	**0.37**	0.95	0.62	**1.68**
SUOX	Sulfite oxidase, mitochondrial	**0.37**	1.16	0.66	**1.78**
NDUFS4*	NADH dehydrogenase [ubiquinone] iron-sulfur protein 4, mitochondrial	**0.37**	1.01	0.63	**1.68**
ATP5C1*	ATP synthase subunit gamma, mitochondrial	**0.37**	0.94	0.60	**1.61**
NDUFV2*	NADH dehydrogenase [ubiquinone] flavoprotein 2, mitochondrial	**0.38**	0.97	0.60	**1.59**
ATP5O*	ATP synthase subunit O, mitochondrial	**0.38**	0.93	0.61	**1.62**
TIMM9	Mitochondrial import inner membrane translocase subunit Tim9	**0.38**	1.03	0.69	**1.83**

SUCLG2*	Succinyl-CoA ligase [GDP-forming] subunit beta, mitochondrial	**0.38**	1.02	0.55	**1.46**
ACADM*	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial	**0.38**	0.99	0.57	**1.50**
AIFM1*	Apoptosis-inducing factor 1, mitochondrial	**0.38**	0.99	0.55	**1.44**
GCDH	Glutaryl-CoA dehydrogenase, mitochondrial	**0.38**	1.03	0.62	**1.61**
UQCRFS1	Cytochrome b-c1 complex subunit Rieske, mitochondrial	**0.38**	1.02	0.61	**1.59**
ACAD10	Acyl-CoA dehydrogenase family member 10	**0.38**	0.96	0.75	**1.95**
NDUFS8*	NADH dehydrogenase [ubiquinone] iron-sulfur protein 8, mitochondrial	**0.38**	1.10	0.60	**1.57**
LDHB	L-lactate dehydrogenase B chain	**0.39**	1.03	0.69	**1.78**
TACO1	Translational activator of cytochrome c oxidase 1	**0.39**	0.94	0.64	**1.66**
UQCRB*	Cytochrome b-c1 complex subunit 7	**0.39**	0.99	0.61	**1.57**
S100A1*	Protein S100-A1	**0.39**	1.09	0.49	**1.28**
MUT	Methylmalonyl-CoA mutase, mitochondrial	**0.39**	0.95	0.55	**1.41**
NDUFA10*	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 10, mitochondrial	**0.39**	1.01	0.61	**1.57**
NDUFS7*†	NADH dehydrogenase [ubiquinone] iron-sulfur protein 7, mitochondrial	**0.39**	1.02	0.62	**1.60**
NNT*	NAD(P) transhydrogenase, mitochondrial	**0.39**	1.10	0.58	**1.48**
MYBPC3	Myosin-binding protein C, cardiac-type	**0.39**	0.93	0.64	**1.62**
PSMB3	Proteasome subunit beta type-3	**0.40**	0.98	0.74	**1.88**
UQCRC2*	Cytochrome b-c1 complex subunit 2, mitochondrial	**0.40**	1.02	0.67	**1.70**
PDHB*	Pyruvate dehydrogenase E1 component subunit beta, mitochondrial	**0.40**	0.96	0.62	**1.57**
SUCLG1	Succinyl-CoA ligase [ADP/GDP-forming] subunit alpha, mitochondrial	**0.40**	1.09	0.64	**1.61**
COX5B*	Cytochrome c oxidase subunit 5B, mitochondrial	**0.40**	1.06	0.62	**1.56**
CYC1	Cytochrome c1, heme protein, mitochondrial	**0.40**	1.04	0.65	**1.62**
ATP5B*	ATP synthase subunit beta, mitochondrial	**0.40**	0.97	0.60	**1.51**
NDUFA12*†	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 12	**0.40**	1.02	0.62	**1.56**
CD36*	Platelet glycoprotein 4	**0.40**	1.16	0.60	**1.48**
NDUFAB1	Acyl carrier protein, mitochondrial	**0.40**	1.08	0.72	**1.80**
COX4I1*	Cytochrome c oxidase subunit 4 isoform 1, mitochondrial	**0.40**	1.00	0.60	**1.48**
VDAC3*	Voltage-dependent anion-selective channel protein 3	**0.40**	1.03	0.58	**1.43**
NDUFB6	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 6	**0.41**	0.98	0.78	**1.92**
ASRGL1	Isoaspartyl peptidase/L-asparaginase	**0.41**	1.14	0.68	**1.66**

PDHA1*†	Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial	**0.41**	0.99	0.65	**1.58**
COX5A*	Cytochrome c oxidase subunit 5A, mitochondrial	**0.41**	1.12	0.61	**1.49**
ACP6	Lysophosphatidic acid phosphatase type 6	**0.41**	1.14	0.85	**2.06**
SDHB	Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial	**0.41**	1.03	0.71	**1.71**
DLD	Dihydrolipoyl dehydrogenase, mitochondrial	**0.41**	1.01	0.66	**1.61**
NDUFS2*	NADH dehydrogenase [ubiquinone] iron-sulfur protein 2, mitochondrial	**0.41**	1.06	0.64	**1.54**
APOOL	Apolipoprotein O-like	**0.41**	1.00	0.66	**1.60**
CHCHD3	Coiled-coil-helix-coiled-coil-helix domain-containing protein 3, mitochondrial	**0.42**	1.00	0.70	**1.65**
ALDH6A1	Methylmalonate-semialdehyde dehydrogenase [acylating], mitochondrial	**0.42**	0.97	0.58	**1.37**
COQ3	Hexaprenyldihydroxybenzoate methyltransferase, mitochondrial	**0.42**	1.06	0.71	**1.67**
MYOZ2*	Myozenin-2	**0.42**	1.03	0.68	**1.60**
GLRX*	Glutaredoxin-1	**0.42**	0.91	0.54	**1.28**
SPR	Sepiapterin reductase	**0.43**	0.92	0.53	**1.25**
CPT2*	Carnitine O-palmitoyltransferase 2, mitochondrial	**0.43**	1.11	0.57	**1.34**
ACADS*	Short-chain specific acyl-CoA dehydrogenase, mitochondrial	**0.43**	1.00	0.57	**1.35**
IDH3G*	Isocitrate dehydrogenase [NAD] subunit gamma 1, mitochondrial	**0.43**	1.02	0.64	**1.49**
HSPE1*	10 kDa heat shock protein, mitochondrial	**0.43**	0.92	0.55	**1.28**
SUCLA2	Succinyl-CoA ligase [ADP-forming] subunit beta, mitochondrial	**0.43**	0.99	0.61	**1.43**
NDUFA7	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 7	**0.43**	1.06	0.58	**1.35**
MRPS36	28S ribosomal protein S36, mitochondrial	**0.43**	1.16	0.68	**1.56**
HADHB*	Trifunctional enzyme subunit beta, mitochondrial	**0.44**	1.09	0.73	**1.67**
VDAC1*	Voltage-dependent anion-selective channel protein 1	**0.44**	1.01	0.65	**1.48**
APOO	Apolipoprotein O	**0.44**	1.03	0.79	**1.81**
NDUFB8*	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 8, mitochondrial	**0.44**	1.06	0.66	**1.50**
ACADL*	Long-chain specific acyl-CoA dehydrogenase, mitochondrial	**0.44**	0.98	0.68	**1.54**
FH*	Fumarate hydratase, mitochondrial	**0.45**	0.95	0.66	**1.49**
CISD1*	CDGSH iron-sulfur domain-containing protein 1	**0.45**	1.11	0.75	**1.69**
UQCRQ*	Cytochrome b-c1 complex subunit 8	**0.45**	1.17	0.95	**2.11**
ACADSB	Short/branched chain specific acyl-CoA dehydrogenase, mitochondrial	**0.45**	1.01	0.60	**1.34**
DLAT	Dihydrolipoyllysine-residue acetyltransferase component of pyruvate dehydrogenase complex, mitochondrial	**0.45**	1.00	0.68	**1.50**

NDUFV1*	NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial	**0.45**	1.05	0.64	**1.42**
DLST	Dihydrolipoyllysine-residue succinyltransferase component of 2-oxoglutarate dehydrogenase complex, mitochondrial	**0.45**	0.96	0.72	**1.59**
APOBEC2	Probable C->U-editing enzyme APOBEC-2	**0.45**	0.92	0.72	**1.59**
D10JHU81E	ES1 protein homolog, mitochondrial	**0.46**	1.02	0.67	**1.47**
PPIF	Peptidyl-prolyl cis-trans isomerase F, mitochondrial	**0.46**	1.02	0.60	**1.31**
NDUFS5	NADH dehydrogenase [ubiquinone] iron-sulfur protein 5	**0.46**	1.06	0.73	**1.59**
TMOD1	Tropomodulin-1	**0.46**	0.99	0.72	**1.58**
PDHX*	Pyruvate dehydrogenase protein X component, mitochondrial	**0.46**	0.99	0.66	**1.44**
NDUFB7	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 7	**0.46**	0.97	0.74	**1.61**
MDH2	Malate dehydrogenase, mitochondrial	**0.46**	0.91	0.71	**1.55**
DDT	D-dopachrome decarboxylase	**0.46**	0.96	0.66	**1.43**
AUH	Methylglutaconyl-CoA hydratase, mitochondrial	**0.46**	1.03	0.71	**1.54**
NDUFA2	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 2	**0.46**	1.03	0.66	**1.42**
LAMA2	Laminin subunit alpha-2	**0.46**	1.05	0.71	**1.54**
SDHA	Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial	**0.46**	1.06	0.72	**1.56**
ACYP1	Acylphosphatase-1	**0.47**	1.03	0.64	**1.39**
TCAP	Telethonin	**0.47**	1.04	0.66	**1.41**
ECI2	Enoyl-CoA delta isomerase 2, mitochondrial	**0.47**	0.95	0.68	**1.45**
COQ5	2-methoxy-6-polyprenyl-1,4-benzoquinol methylase, mitochondrial	**0.47**	0.96	0.68	**1.46**
TIMM13	Mitochondrial import inner membrane translocase subunit Tim13	**0.47**	0.92	0.66	**1.42**
DNAJA3	DnaJ homolog subfamily A member 3, mitochondrial	**0.47**	1.12	0.67	**1.44**
ART3	Ecto-ADP-ribosyltransferase 3	**0.47**	1.17	0.94	**1.99**
PGM1*	Phosphoglucomutase-1	**0.47**	0.94	0.64	**1.36**
CPOX	Coproporphyrinogen-III oxidase, mitochondrial	**0.48**	1.17	0.75	**1.59**
RMDN1	Regulator of microtubule dynamics protein 1	**0.48**	0.92	0.69	**1.45**
NDUFC2	NADH dehydrogenase [ubiquinone] 1 subunit C2	**0.48**	1.17	0.67	**1.40**
DTNA	Dystrobrevin alpha	**0.48**	1.05	0.72	**1.50**
DMD	Dystrophin	**0.48**	1.03	0.68	**1.42**
MRPL12	39S ribosomal protein L12, mitochondrial	**0.48**	1.00	0.75	**1.55**
PRDX2	Peroxiredoxin-2	**0.48**	0.97	0.71	**1.48**
PHB2	Prohibitin-2	**0.48**	1.01	0.79	**1.64**
HSPD1	60 kDa heat shock protein, mitochondrial	**0.49**	0.95	0.63	**1.28**

COQ7	Ubiquinone biosynthesis protein COQ7 homolog	**0.49**	1.24	0.93	**1.89**
SGCA	Alpha-sarcoglycan	**0.49**	1.03	0.73	**1.48**
SDPR*	Serum deprivation-response protein	**0.49**	1.08	0.75	**1.51**
HINT1	Histidine triad nucleotide-binding protein 1	**0.49**	1.09	0.69	**1.39**
NDUFA9*	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9, mito.	**0.49**	1.15	0.75	**1.52**
DNM2	Dynamin-2	**2.02**	1.15	1.71	**0.85**
GNAI2*	Guanine nucleotide-binding protein G(i) subunit alpha-2	**2.03**	1.10	1.51	**0.75**
PDIA4	Protein disulfide-isomerase A4	**2.03**	0.97	1.42	**0.70**
SH3BGRL	SH3 domain-binding glutamic acid-rich-like protein	**2.03**	0.98	1.38	**0.68**
PRKCSH	Glucosidase 2 subunit beta	**2.03**	1.06	1.43	**0.70**
CALR*	Calreticulin	**2.06**	1.03	1.61	**0.78**
HSP90B1*	Endoplasmin	**2.07**	0.99	1.53	**0.74**
ANXA2*	Annexin A2	**2.08**	1.09	1.39	**0.67**
RPN1	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 1	**2.08**	1.12	1.56	**0.75**
ARPC3	Actin-related protein 2/3 complex subunit 3	**2.10**	1.00	1.39	**0.66**
ORM1	Alpha-1-acid glycoprotein 1	**2.10**	0.67	0.98	**0.47**
PARVA	Alpha-parvin	**2.10**	1.09	1.48	**0.71**
ITIH1	Inter-alpha-trypsin inhibitor heavy chain H1	**2.10**	0.91	1.15	**0.55**
LRP1	Prolow-density lipoprotein receptor-related protein 1	**2.13**	0.89	1.42	**0.67**
YWHAQ*	14-3-3 protein theta	**2.13**	1.05	1.58	**0.74**
AP2A2	AP-2 complex subunit alpha-2	**2.14**	0.99	1.55	**0.72**
HYOU1	Hypoxia up-regulated protein 1	**2.15**	1.00	1.56	**0.73**
CKAP4*	Cytoskeleton-associated protein 4	**2.15**	1.13	1.51	**0.70**
CFL1*	Cofilin-1	**2.16**	0.99	1.33	**0.62**
VIM*	Vimentin	**2.17**	1.08	1.37	**0.63**
CFB	Complement factor B	**2.18**	0.99	1.30	**0.60**
PDIA3*	Protein disulfide-isomerase A3	**2.18**	1.03	1.47	**0.68**
PPP1R12A	Protein phosphatase 1 regulatory subunit 12A	**2.20**	1.09	1.50	**0.68**
MYADM	Myeloid-associated differentiation marker	**2.20**	1.10	1.56	**0.71**
COPA	Coatomer subunit alpha	**2.22**	1.14	1.52	**0.69**
CLTC*	Clathrin heavy chain 1	**2.23**	1.03	1.58	**0.71**
SNX2	Sorting nexin-2	**2.24**	1.10	1.67	**0.75**
PEA15	Astrocytic phosphoprotein PEA-15	**2.24**	0.95	1.48	**0.66**
C9	Complement component C9	**2.25**	0.42	0.62	**0.27**
ARF4	ADP-ribosylation factor 4	**2.26**	1.02	1.53	**0.67**
CAPZA1	F-actin-capping protein subunit alpha-1	**2.27**	1.11	1.59	**0.70**
ITIH2	Inter-alpha-trypsin inhibitor heavy chain H2	**2.27**	0.88	1.27	**0.56**
ACTR3	Actin-related protein 3	**2.27**	0.94	1.33	**0.59**
CD200	OX-2 membrane glycoprotein	**2.28**	1.18	1.27	**0.56**
ESYT1	Extended synaptotagmin-1	**2.30**	0.87	1.42	**0.62**
COPG1	Coatomer subunit gamma-1	**2.31**	0.98	1.53	**0.66**
SERPINF2	Alpha-2-antiplasmin	**2.38**	0.98	1.48	**0.62**

SERPINA3K*	Serine protease inhibitor A3K	**2.39**	0.83	1.13	**0.47**
SERPINA3N	Serine protease inhibitor A3N	**2.41**	1.03	1.82	**0.76**
DAB2	Disabled homolog 2	**2.43**	0.92	1.38	**0.57**
LGALS1*	Galectin-1	**2.45**	1.06	1.73	**0.70**
C8B	Complement component C8 beta chain	**2.45**	0.54	0.86	**0.35**
CLIC1	Chloride intracellular channel protein 1	**2.49**	1.02	1.85	**0.74**
PLG	Plasminogen	**2.51**	0.91	1.39	**0.55**
F2	Prothrombin	**2.53**	1.03	1.65	**0.65**
SEPT2	Septin-2	**2.53**	1.13	1.80	**0.71**
TAGLN2*	Transgelin-2	**2.53**	0.97	1.45	**0.57**
RRBP1	Ribosome-binding protein 1	**2.55**	1.02	1.78	**0.70**
SERPING1	Plasma protease C1 inhibitor	**2.56**	1.04	1.86	**0.73**
SERPINH1*	Serpin H1	**2.60**	1.07	1.71	**0.66**
AMBP	Protein AMBP	**2.63**	0.84	1.47	**0.56**
LPP	Lipoma-preferred partner homolog	**2.63**	1.07	1.55	**0.59**
TPM3	Tropomyosin alpha-3 chain	**2.69**	0.94	1.22	**0.45**
CTSC	Dipeptidyl peptidase 1	**2.70**	1.11	1.43	**0.53**
TINAGL1	Tubulointerstitial nephritis antigen-like	**2.77**	1.10	1.86	**0.67**
MYOF	Myoferlin	**2.78**	0.85	1.33	**0.48**
FBLN2	Fibulin-2	**2.78**	1.46	1.27	**0.46**
FTL1	Ferritin light chain 1	**2.79**	0.81	1.62	**0.58**
SF1	Splicing factor 1	**2.79**	1.19	1.48	**0.53**
COL6A5	Collagen alpha-5(VI) chain	**2.82**	1.00	0.91	**0.32**
IQGAP1	Ras GTPase-activating-like protein IQGAP1	**2.84**	0.98	1.41	**0.50**
P4HA1	Prolyl 4-hydroxylase subunit alpha-1	**2.87**	1.11	1.77	**0.62**
AP2B1	AP-2 complex subunit beta	**2.87**	1.07	1.89	**0.66**
CAP1	Adenylyl cyclase-associated protein 1	**2.88**	0.86	1.52	**0.53**
MYL12B	Myosin regulatory light chain 12B	**2.91**	0.98	1.38	**0.47**
CORO1C	Coronin-1C	**2.92**	0.80	1.43	**0.49**
ATL3	Atlastin-3	**2.96**	1.15	1.71	**0.58**
EGFR	Epidermal growth factor receptor	**2.96**	0.52	0.73	**0.25**
MYH11	Myosin-11	**2.99**	0.86	1.03	**0.34**
COL1A1	Collagen alpha-1(I) chain	**3.00**	1.29	1.40	**0.47**
F13A1	Coagulation factor XIII A chain	**3.03**	0.83	1.58	**0.52**
HEXB	Beta-hexosaminidase subunit beta	**3.03**	0.81	1.62	**0.54**
TLN1*	Talin-1	**3.06**	0.99	1.69	**0.55**
SFXN3	Sideroflexin-3	**3.07**	1.09	1.90	**0.62**
ARHGDIB	Rho GDP-dissociation inhibitor 2	**3.07**	0.94	1.48	**0.48**
THY1	Thy-1 membrane glycoprotein	**3.07**	1.10	1.53	**0.50**
SEPT7	Septin-7	**3.28**	1.14	2.06	**0.63**
HSD11B1	Corticosteroid 11-beta-dehydrogenase isozyme 1	**3.28**	0.39	1.74	**0.53**
HIP1	Huntingtin-interacting protein 1	**3.29**	1.02	2.29	**0.70**
ITGA1	Integrin alpha-1	**3.31**	0.78	1.33	**0.40**
CTSZ	Cathepsin Z	**3.33**	1.01	1.80	**0.54**
TWF1	Twinfilin-1	**3.33**	1.08	1.94	**0.58**
SERPIND1	Heparin cofactor 2	**3.39**	1.11	2.26	**0.67**
PDLIM7	PDZ and LIM domain protein 7	**3.40**	0.58	1.48	**0.43**
FKBP10	Peptidyl-prolyl cis-trans isomerase FKBP10	**3.41**	0.80	1.77	**0.52**

C8A	Complement component C8 alpha chain	**3.49**	0.67	1.00	**0.29**
VWF	von Willebrand factor	**3.52**	0.71	1.69	**0.48**
ZYX	Zyxin	**3.56**	1.00	2.23	**0.63**
FBLN1	Fibulin-1	**3.56**	1.01	1.63	**0.46**
SEPT8	Septin-8	**3.58**	0.96	2.19	**0.61**
FAM129A	Protein Niban	**3.61**	0.73	1.86	**0.52**
TPM4*	Tropomyosin alpha-4 chain	**3.63**	0.87	1.62	**0.45**
FAM129B	Niban-like protein 1	**3.68**	0.96	1.80	**0.49**
BASP1	Brain acid soluble protein 1	**3.70**	1.03	1.32	**0.36**
CYFIP1	Cytoplasmic FMR1-interacting protein 1	**3.72**	1.36	1.94	**0.52**
FGG*	Fibrinogen gamma chain	**3.82**	0.94	1.18	**0.31**
FGB*	Fibrinogen beta chain	**3.90**	0.85	1.10	**0.28**
MRC1	Macrophage mannose receptor 1	**3.92**	1.03	1.75	**0.45**
COL1A2	Collagen alpha-2(I) chain	**3.93**	1.26	1.23	**0.31**
ACTG1*	Actin, cytoplasmic 2	**4.01**	1.10	1.96	**0.49**
EMILIN1	EMILIN-1	**4.23**	0.86	2.29	**0.54**
HTRA1	Serine protease HTRA1	**4.31**	1.13	2.00	**0.46**
ACTN4*	Alpha-actinin-4	**4.34**	0.95	2.66	**0.61**
CSRP2	Cysteine and glycine-rich protein 2	**4.48**	1.30	1.66	**0.37**
COTL1	Coactosin-like protein	**4.53**	0.83	1.86	**0.41**
ARPC1B	Actin-related protein 2/3 complex subunit 1B	**4.54**	1.19	2.35	**0.52**
FBN1	Fibrillin-1	**4.56**	1.23	2.37	**0.52**
ACTN1	Alpha-actinin-1	**4.63**	1.02	1.85	**0.40**
MYH9*	Myosin-9	**4.88**	1.00	1.87	**0.38**
LMCD1	LIM and cysteine-rich domains protein 1	**4.91**	1.05	1.94	**0.40**
RCN3	Reticulocalbin-3	**4.97**	1.25	2.50	**0.50**
LCP1	Plastin-2	**5.00**	0.78	1.8	**0.36**
CYGB	Cytoglobin	**5.01**	0.98	3.16	**0.63**
S100A6	Protein S100-A6	**5.01**	1.04	1.7	**0.34**
FN1*	Fibronectin	**5.07**	0.98	1.33	**0.26**
MYL6*	Myosin light polypeptide 6	**5.13**	1.09	2.11	**0.41**
PLS3	Plastin-3	**5.14**	0.93	2.26	**0.44**
FMO2	Dimethylaniline monooxygenase [N-oxide-forming] 2	**5.15**	1.07	3.01	**0.59**
MRC2	C-type mannose receptor 2	**5.28**	0.89	2.76	**0.52**
PRELP*	Prolargin	**5.32**	1.13	2.98	**0.56**
PPIC	Peptidyl-prolyl cis-trans isomerase C	**5.44**	0.91	3.05	**0.56**
ITGAV	Integrin alpha-V	**5.47**	1.94	2.94	**0.54**
COL14A1	Collagen alpha-1(XIV) chain	**5.76**	0.93	2.77	**0.48**
COL3A1	Collagen alpha-1(III) chain	**5.77**	1.34	2.16	**0.37**
FLNA*	Filamin-A	**5.82**	1.02	1.88	**0.32**
ANXA1	Annexin A1	**6.36**	0.98	2.62	**0.41**
TAGLN	Transgelin	**6.44**	0.89	2.15	**0.33**
EFEMP1	EGF-containing fibulin-like extracellular matrix protein 1	**6.46**	0.87	3.68	**0.57**
BGN	Biglycan	**6.62**	1.05	2.53	**0.38**
ELN	Elastin	**7.16**	0.55	2.15	**0.3**
LOXL1	Lysyl oxidase homolog 1	**8.24**	0.90	2.57	**0.31**
IGFBP7	Insulin-like growth factor-binding protein 7	**11.07**	1.17	4.32	**0.39**

Proteins were selected according to a protein expression ratio TG_{VEH} vs. WT_{VEH} atria <0.5 or >2. Intensities of detected proteins were normalized to the respective VEH group set to 1. Ratios for TG_{VEH} vs. WT_{VEH} and TG_{VPA} vs. TG_{VEH} are printed in bold. †CREM-target validated by ChIP. * denotes proteins already regulated at 7 weeks in TG_{VEH} vs. WT_{VEH}[13].

Table S2: Assignment of the selected 295 regulated proteins to Ingenuity Canonical Pathways.

Canonical pathway	Symbol	Protein name	Fold Change	
			TG_{VEH} vs. WT_{VEH}	TG_{VPA} vs. TG_{VEH}
Integrin Signaling	ACTG1*	Actin, gamma 1	4.01	-2.05
	ACTN1	Actinin, alpha 1	4.63	-2.50
	ACTN4*	Actinin, alpha 4	4.34	-1.63
	ACTR3	ARP3 actin-related protein 3 homolog	2.27	-1.71
	ARF4	ADP-ribosylation factor 4	2.26	-1.48
	ARPC3	Actin related protein 2/3 complex, subunit 3	2.10	-1.52
	ARPC1B	Actin related protein 2/3 complex, subunit 1B	4.54	-1.93
	ITGA1	Integrin, alpha 1	3.31	-2.50
	ITGAV	Integrin, alpha V	5.47	-1.86
	MYL7†	Myosin, light chain 7, regulatory	-5.17	2.14
	MYL12B	Myosin regulatory light chain 12B	2.91	-2.11
	PARVA	Parvin, alpha	2.10	-1.42
	PPP1R12A	Protein phosphatase 1, regulatory, subunit 12a	2.20	-1.46
	TLN1*	Talin 1	3.06	-1.82
	ZYX	Zyxin	3.56	-1.60
Rac Signaling	ACTR3	ARP3 actin-related protein 3 homolog	2.27	-1.71
	ARPC3	Actin related protein 2/3 complex, subunit 3	2.10	-1.52
	ARPC1B	Actin related protein 2/3 complex, subunit 1B	4.54	-1.93
	CFL1*	Cofilin 1 (non-muscle)	2.16	-1.62
	CYFIP1	Cytoplasmic FMR1 interacting protein 1	3.72	-1.92
	IQGAP1	IQ motif containing GTPase activating	2.84	-2.02
Leukocyte Extravasation Signaling	ACTG1*	Actin, gamma 1	4.01	-2.05
	ACTN1	Actinin, alpha 1	4.63	-2.50
	ACTN4*	Actinin, alpha 4	4.34	-1.63
	GNAI2*	Guanine nucleotide-binding protein G(i) subunit alpha-2	2.03	-1.34
	ITGA1	Integrin, alpha 1	3.31	-2.50
	MYL6*	Myosin, light chain 6, alkali, smooth muscle and non-muscle	5.13	-2.43
	THY1	Thy-1 membrane glycoprotein	3.07	-2.01
Oxidative Phosphorylation	ATP5B*	ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide	-2.51	1.51
	ATP5C1*	ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1	-2.67	1.61
	ATP5J*	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit F6	-2.74	1.58

ATP5L*†	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit G	-3.80	2.61
ATP5O*	ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit	-2.66	1.62
COX4I1*	cytochrome c oxidase subunit IV isoform 1	-2.48	1.48
COX5A*	cytochrome c oxidase subunit Va	-2.44	1.49
COX7A1*	cytochrome c oxidase subunit VIIa polypeptide 1 (muscle)	-4.01	1.96
CYC1	cytochrome c-1	-2.51	1.62
NDUFA2	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex	-2.17	1.42
NDUFA4*	NDUFA4, mitochondrial complex associated	-4.24	2.56
NDUFA6*	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6	-2.73	1.78
NDUFA7	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7	-2.31	1.35
NDUFA8†	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8, 19kDa	-2.79	1.82
NDUFA9*	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 9	-2.03	1.52
NDUFA10*	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 10, 42kDa	-2.57	1.57
NDUFA12*†	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 12	-2.50	1.56
NDUFA13*	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 13	-2.73	1.59
NDUFAB1	NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1	-2.49	1.80
NDUFB3	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3	-2.81	1.88
NDUFB5	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5	-3.00	2.11
NDUFB6	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6	-2.46	1.92
NDUFB7	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 7	-2.18	1.61
NDUFB8*	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 8	-2.27	1.50
NDUFS2*	NADH dehydrogenase (ubiquinone) Fe-S protein 2, (NADH-coenzyme Q reductase)	-2.42	1.54
NDUFS3*	NADH dehydrogenase (ubiquinone) Fe-S protein 3, (NADH-coenzyme Q reductase)	-2.88	1.67
NDUFS4*	NADH dehydrogenase (ubiquinone) Fe-S protein 4, (NADH-coenzyme Q reductase)	-2.68	1.68
NDUFS7*†	NADH dehydrogenase (ubiquinone) Fe-S protein 7, (NADH-coenzyme Q reductase)	-2.56	1.60

	NDUFS8*	NADH dehydrogenase (ubiquinone) Fe-S protein 8, (NADH-coenzyme Q reductase)	-2.60	1.57
	NDUFV1*	NADH dehydrogenase (ubiquinone) flavoprotein 1	-2.22	1.42
	NDUFV2*	NADH dehydrogenase (ubiquinone) flavoprotein 2	-2.66	1.59
	SDHA	succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	-2.15	1.56
	SDHB	succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	-2.43	1.71
	UQCR10†	ubiquinol-cytochrome c reductase, complex III subunit X	-2.98	2.03
	UQCRB*	ubiquinol-cytochrome c reductase binding protein	-2.59	1.57
	UQCRC2*	ubiquinol-cytochrome c reductase core protein II	-2.53	1.70
	UQCRFS1	ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1	-2.61	1.59
	UQCRQ*	ubiquinol-cytochrome c reductase, complex III subunit VII	-2.23	2.11
Signaling by Rho Family GTPases	ACTG1*	Actin, gamma 1	4.01	-2.05
	ACTR3	ARP3 actin-related protein 3 homolog	2.27	-1.71
	ARPC1B	Actin related protein 2/3 complex, subunit 1B	4.54	-1.93
	ACTR3	ARP3 actin-related protein 3 homolog	2.27	-1.71
	CFL1*	Cofilin 1 (non-muscle)	2.16	-1.62
	CYFIP1	Cytoplasmic FMR1 interacting protein 1	3.72	-1.92
	GNAI2*	Guanine nucleotide-binding protein G(i) subunit alpha-2	2.03	-1.34
	IQGAP1	IQ motif containing GTPase activating	2.84	-2.02
	MYL4*	Myosin, light chain 4, alkali, atrial	-4.26	1.98
	MYL6*	Myosin, light chain 6, alkali, smooth muscle and non-muscle	5.13	-2.43
	MYL7†	Myosin, light chain 7, regulatory	-5.17	2.14
	MYL12B	Myosin regulatory light chain 12B	2.91	-2.11
	PPP1R12A	Protein phosphatase 1, regulatory, subunit 12a	2.20	-1.46
	SEPT2	Septin 2	2.53	-1.41
	SEPT7	Septin 7	3.28	-1.59
	SEPT8	Septin 8	3.58	-1.64
	VIM*	Vimentin	2.17	-1.59
Remodeling of Epithelial Adherens Junctions	ACTG1*	Actin, gamma 1	4.01	-2.05
	ACTN1	Actini, alpha 1	4.63	-2.50
	ACTN4*	Actinin, alpha 4	4.34	-1.63
	ACTR3	ARP3 actin-related protein 3 homolog	2.27	-1.71
	ARPC1B	Actin related protein 2/3 complex, subunit 1B	4.54	-1.93
	ARPC3	Actin related protein 2/3 complex, subunit 3	2.10	-1.52

	DNM2	Dynamin 2	2.02	-1.18
	IQGAP1	IQ motif containing GTPase activating	2.84	-2.02
	ZYX	Zyxin	3.56	-1.60
Thrombin Signaling	EGFR	Epidermal growth factor receptor	2.96	-4.06
	F2	Coagulation factor II (thrombin)	2.53	-1.53
	GNAI2*	Guanine nucleotide-binding protein G(i) subunit alpha-2	2.03	-1.34
	MYL4*	Myosin, light chain 4, alkali, atrial	-4.26	1.98
	MYL6*	Myosin, light chain 6, alkali, smooth muscle and non-muscle	5.13	-2.43
	MYL7†	Myosin, light chain 7, regulatory	-5.17	2.14
	MYL12B	Myosin regulatory light chain 12B	2.91	-2.11
	PDIA3*	Protein disulfide isomerase family A	2.18	-1.48
	PPP1R12A	Protein phosphatase 1, regulatory, subunit 12a	2.20	-1.46
Coagulation System	F13A1	Coagulation factor XIII A chain	3.03	-1.92
	F2	Coagulation factor II (thrombin)	2.53	-1.53
	FGB*	Fibrinogen, beta chain	3.90	-3.53
	FGG*	Fibrinogen, gamma chain	3.82	-2.25
	PLG	Plasminogen	2.51	-1.81
	SERPIND1	Heparin cofactor 2	3.39	-1.50
	SERPINF2	Alpha-2-antiplasmin	2.38	-1.61
	VWF	Von Willebrand factor	3.52	-2.08
Acute Phase Response Signaling	AMBP	Alpha-1-microglobulin/bikunin precursor	2.63	-1.79
	C9	Complement component 9	2.25	-3.65
	CFB	Complement factor B	2.18	-1.68
	F2	Coagulation factor II (thrombin)	2.53	-1.53
	FGB*	Fibrinogen, beta chain	3.90	-3.53
	FGG*	Fibrinogen, gamma chain	3.82	-2.25
	FN1*	Fibronectin 1	5.07	-3.82
	FTL	Ferritin, light polypeptide	2.79	-1.72
	ITIH2	Inter-alpha-trypsin inhibitor heavy chain H2	2.27	-1.79
	PLG	Plasminogen	2.51	-1.81
	SERPINA3N	Serine protease inhibitor A3N	2.41	-2.12
	SERPIND1	Heparin cofactor 2	3.39	-1.50
	SERPINF2	Alpha-2-antiplasmin	2.38	-1.61
	SERPING1	Plasma protease C1 inhibitor	2.56	-1.38
	SOD2*	Superoxide dismutase, mitochondrial	-2.89	1.76
	VWF	Von Willebrand factor	3.52	-2.08
Regulation of Actin-based Motility by Rho	ACTR3	ARP3 actin-related protein 3 homolog	2.27	-1.71
	ARPC3	Actin related protein 2/3 complex, subunit 3	2.10	-1.52

	ARPC1B	Actin related protein 2/3 complex, subunit 1B	4.54	-1.93
	CFL1*	Cofilin 1 (non-muscle)	2.16	-1.62
	MYL4*	Myosin, light chain 4, alkali, atrial	-4.26	1.98
	MYL6*	Myosin, light chain 6, alkali, smooth muscle and non-muscle	5.13	-2.43
	MYL7†	Myosin, light chain 7, regulatory	-5.17	2.14
	MYL12B	Myosin regulatory light chain 12B	2.91	-2.11
	PPP1R12A	Protein phosphatase 1, regulatory, subunit 12a	2.20	-1.46
	NDUFA4*	NDUFA4, mitochondrial complex associated	-4.24	2.56
	AIFM1*	Apoptosis-inducing factor 1, mitochondrial	-2.64	1.44
	ATP5B*	ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide	-2.51	1.51
Mitochondrial Dysfunction	ATP5C1*	ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1	-2.67	1.61
	ATP5J*	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit F6	-2.74	1.58
	ATP5L*†	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit G	-3.80	2.61
	ATP5O*	ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit	-2.66	1.62
	COX4I1*	cytochrome c oxidase subunit IV isoform 1	-2.48	1.48
	COX5A*	cytochrome c oxidase subunit Va	-2.44	1.49
	COX7A1*	cytochrome c oxidase subunit VIIa polypeptide 1 (muscle)	-4.01	1.96
	CYC1	cytochrome c-1	-2.51	1.62
	NDUFA10*	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 10, 42kDa	-2.57	1.57
	NDUFA12*†	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 12	-2.50	1.56
	NDUFA13*	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 13	-2.73	1.59
	NDUFA2	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex	-2.17	1.42
	NDUFA6*	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6	-2.73	1.78
	NDUFA7	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7	-2.31	1.35
	NDUFA8†	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8, 19kDa	-2.79	1.82
	NDUFA9*	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 9	-2.03	1.52
	NDUFAB1	NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1	-2.49	1.80

NDUFB3	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3	-2.81	1.88
NDUFB5	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5	-3.00	2.11
NDUFB6	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6	-2.46	1.92
NDUFB7	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 7	-2.18	1.61
NDUFB8*	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 8	-2.27	1.50
NDUFS2*	NADH dehydrogenase (ubiquinone) Fe-S protein 2, (NADH-coenzyme Q reductase)	-2.42	1.54
NDUFS3*	NADH dehydrogenase (ubiquinone) Fe-S protein 3, (NADH-coenzyme Q reductase)	-2.88	1.67
NDUFS4*	NADH dehydrogenase (ubiquinone) Fe-S protein 4, (NADH-coenzyme Q reductase)	-2.68	1.68
NDUFS7*†	NADH dehydrogenase (ubiquinone) Fe-S protein 7, (NADH-coenzyme Q reductase)	-2.56	1.60
NDUFS8*	NADH dehydrogenase (ubiquinone) Fe-S protein 8, (NADH-coenzyme Q reductase)	-2.60	1.57
NDUFV1*	NADH dehydrogenase (ubiquinone) flavoprotein 1	-2.22	1.42
NDUFV2*	NADH dehydrogenase (ubiquinone) flavoprotein 2	-2.66	1.59
PDHA1*†	Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial	-2.45	1.58
PRDX3*	Thioredoxin-dependent peroxide reductase, mitochondrial	-3.11	1.58
SDHA	succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	-2.15	1.56
SDHB	succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	-2.43	1.71
SOD2*	Superoxide dismutase, mitochondrial	-2.89	1.76
UQCR10†	ubiquinol-cytochrome c reductase, complex III subunit X	-2.98	2.03
UQCRB*	ubiquinol-cytochrome c reductase binding protein	-2.59	1.57
UQCRC2*	ubiquinol-cytochrome c reductase core protein II	-2.53	1.70
UQCRQ*	ubiquinol-cytochrome c reductase, complex III subunit VII	-2.23	2.11
UQCRSF1	ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1	-2.61	1.59
VDAC1*	Voltage-dependent anion-selective channel protein 1	-2.28	1.48

	VDAC3*	Voltage-dependent anion-selective channel protein 3	-2.47	1.43
RhoA Signaling	ACTG1*	Actin, gamma 1	4.01	-2.05
	ACTR3	ARP3 actin-related protein 3 homolog	2.27	-1.71
	ARPC1B	Actin related protein 2/3 complex, subunit 1B	4.54	-1.93
	ARPC3	Actin related protein 2/3 complex, subunit 3	2.10	-1.52
	CFL1*	Cofilin 1 (non-muscle)	2.16	-1.62
	MYL12B	Myosin regulatory light chain 12B	2.91	-2.11
	MYL4*	Myosin, light chain 4, alkali, atrial	-4.26	1.98
	MYL6*	Myosin, light chain 6, alkali, smooth muscle and non-muscle	5.13	-2.43
	MYL7*†	Myosin, light chain 7, regulatory	-5.17	2.14
	PPP1R12A	Protein phosphatase 1, regulatory, subunit 12a	2.20	-1.46
	SEPT2	Septin 2	2.53	-1.41
	SEPT7	Septin 7	3.28	-1.59
	SEPT8	Septin 8	3.58	-1.64
ILK Signaling	ACTG1*	Actin, gamma 1	4.01	-2.05
	ACTN1	Actini, alpha 1	4.63	-2.50
	ACTN4*	Actinin, alpha 4	4.34	-1.63
	CFL1*	Cofilin 1 (non-muscle)	2.16	-1.62
	FLNA*	Filamin-A	5.82	-3.09
	MYH11	Myosin-11	2.99	-2.91
	MYH6*	Myosin-6	-3.56	1.69
	MYH9*	Myosin-9	4.88	-2.61
	MYL4*	Myosin, light chain 4, alkali, atrial	-4.26	1.98
	MYL6*	Myosin, light chain 6, alkali, smooth muscle and non-muscle	5.13	-2.43
	MYL7*†	Myosin, light chain 7, regulatory	-5.17	2.14
	PARVA	Parvin, alpha	2.10	-1.42
	PPP1R12A	Protein phosphatase 1, regulatory, subunit 12a	2.20	-1.46
	VIM*	Vimentin	2.17	-1.59
Actin Cytoskeleton Signaling	ACTG1*	Actin, gamma 1	4.01	-2.05
	ACTN1	Actini, alpha 1	4.63	-2.50
	ACTN4*	Actinin, alpha 4	4.34	-1.63
	ACTR3	ARP3 actin-related protein 3 homolog	2.27	-1.71
	ARPC1B	Actin related protein 2/3 complex, subunit 1B	4.54	-1.93
	ARPC3	Actin related protein 2/3 complex, subunit 3	2.10	-1.52
	CFL1*	Cofilin 1 (non-muscle)	2.16	-1.62
	CYFIP1	Cytoplasmic FMR1-interacting protein 1	3.71	-1.92
	F2	Coagulation factor II (thrombin)	2.53	-1.53
	FLNA*	Filamin-A	5.82	-3.09
	FN1*	Fibronectin 1	5.07	-3.82
	IQGAP1	IQ motif containing GTPase activating	2.84	-2.02

	MYH11	Myosin-11	2.99	-2.91
	MYH6*	Myosin-6	-3.56	1.69
	MYH9*	Myosin-9	4.88	-2.61
	MYL12B	Myosin regulatory light chain 12B	2.91	-2.11
	MYL4*	Myosin, light chain 4, alkali, atrial	-4.26	1.98
	MYL6*	Myosin, light chain 6, alkali, smooth muscle and non-muscle	5.13	-2.43
	MYL7*†	Myosin, light chain 7, regulatory	-5.17	2.14
	PPP1R12A	Protein phosphatase 1, regulatory, subunit 12a	2.20	-1.46
	TLN1*	Talin 1	3.06	-1.82
Paxillin Signaling	ACTG1*	Actin, gamma 1	4.01	-2.05
	ACTN1	Actini, alpha 1	4.63	-2.50
	ACTN4*	Actinin, alpha 4	4.34	-1.63
	ITGA1	Integrin, alpha 1	3.31	-2.50
	ITGAV	Integrin, alpha V	5.47	-1.86
	PARVA	Parvin, alpha	2.10	-1.42
	TLN1*	Talin 1	3.06	-1.82

Displayed are fold-change values for TG_{VEH} vs. WT_{VEH} and TG_{VPA} vs TG_{VEH}, reflecting regulation in TG and the respective counter-regulation by VPA, respectively. (blue=downregulation; red=upregulation). †CREM-target validated by ChIP. *denotes proteins already changed at 7 weeks in TG_{VEH} vs. WT_{VEH}[13].

Table S3: ChIP analysis of putative CREM target genes.

Gene symbol	Protein name	Std. Error	Enrichment TG vs. WT
Atp5l*	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit G	1.4-3.0	2.2↑
Ces1d*	Carboxylesterase 1D	1.2-5.8	2.2↑
Gapdh	Glycerinaldehyd-3-phosphat-Dehydrogenase		1.0
Myl7*	Myosin, light chain 7, regulatory	0.9-2.8	1.6↑
Ndufa8	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 8	3.0–20.3	7.7↑
Ndufa12*	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 12	1.7–3.7	2.9↑
Ndufs7*	NADH dehydrogenase [ubiquinone] iron-sulfur protein 7, mitochondrial	2.0–8.6	4.1↑
Pdha1*	Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial	1.5–4.7	2.8↑
Tnni3	Troponin I, cardiac muscle	1.3-4.1	2.6↑
Uqcr10	Ubiquinol-cytochrome c reductase, complex III subunit X	3.4-23.8	8.1↑

Quantitative RT-PCR was performed on precipitated DNA fragments, and Ct values were analyzed with REST software (ΔΔCt-method; normalized to *Gapdh*; n=6-8). *denotes proteins already regulated at 7 weeks in TG_{VEH} vs. WT_{VEH}[13].