**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 HDAC2loxP/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<sup>Cre</sup>+/− mice<sup>4</sup>). Electron microscopy analysis was performed on male/female mice on atria from control mice (CTR: FVB/N<sup>Cre</sup>+/−, TG (CREM<sup>IbΔC</sup>-X<sup>Cre</sup>+/−), 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<sup>5</sup>. Mice were anaesthetized with inhalation of 1.5 to 2 % vaporized isoflurane (Forane<sup>®</sup>, 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<sub>VEH</sub> and WT<sub>VPA</sub> 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 protocol⁶ 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 MgCl₂ x 6 H₂O, 5 HEPES, 0.33 NaH₂PO₄ x H₂O, 11.1 Glucose, 1 CaCl₂; 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 CaCl₂, 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 tritrated two times in 800 µl of modified Kraftbrühe (KB)-buffer containing (in mM) 12.5 KCl, 5 KH₂PO₄, 5 DL-aspartic acid potassium salt, 50 L-glutamic potassium salt, 2 MgSO₄ x 7 H₂O, 20 taurine, 0.5 EGTA, 5 creatine, 5 HEPES, 20 glucose (pH 7.2 adjusted with KOH) plus 12.5 µM CaCl₂ 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 Ca²⁺ 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 described⁵. 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.
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\textsuperscript{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\textsuperscript{+}-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\textsuperscript{+}-currents recorded in the absence and presence of VPA at all potentials were normalized to the maximum Na\textsuperscript{+}-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. Image-Pro Plus software (Media Cybernetics Incorporation, Rockville, MD, USA) was used to quantify the collagen in the atria.

**Ultrastructural analysis**

For electron microscopy, 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 \( \mu m^2 \) 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 \( \mu g \) 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 (Ultrasound-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: ATGTGGCCCTTAAAGCTCC

Ces1d: for: GGCACGAAACCATCACAACA, rev: AGGCTGTGAAATGTGTCCGT

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

Myl7: for: GTGTGGCTGGTCTCTGTTC, rev: GAGCCCTGGTCACAAGAGAT

Ndufa8: for: TCCTTCAAGTCCCCTTTGCC, rev: CTCGCCGTGTACTGCATGTT
Ndufa12: for: ATCTACCAGCATAACGACGC, rev: GTACCCAGAAAGCGACCCCTG
Ndufs7: for: GGTTTGCCGCTGGTGTCTAT, rev: CCCAGACTACCCACTCTC
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<sub>VEH</sub>=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.
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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

B

P duration [s]

WT<sub>VEH</sub>  WT<sub>VPA</sub>

0.00  0.01  0.02  0.03  0.04

C

PR interval [s]

WT<sub>VEH</sub>  WT<sub>VPA</sub>

0.00  0.01  0.02  0.03  0.04  0.05  0.06

D

QRS interval [s]

WT<sub>VEH</sub>  WT<sub>VPA</sub>

0.000  0.004  0.008  0.012  0.016

E

QT interval [s]

WT<sub>VEH</sub>  WT<sub>VPA</sub>

0.00  0.02  0.04  0.06  0.08

n.s.
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\textsubscript{VPA} and WT\textsubscript{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<sup>Cre<sup>+</sup></sup>-.
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 TGVEH vs. WTVEH 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: Corresponding protein expression ratios for TG\textsubscript{VEH} vs. WT\textsubscript{VEH} at 7 and 12 weeks of age.

Corresponding expression ratios (TG\textsubscript{VEH} vs. WT\textsubscript{VEH}) are displayed for those of the 295 strongest regulated proteins in TG\textsubscript{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.\textsuperscript{13} (red: upregulation, blue: downregulation, black line: linear regression curve) in TG\textsubscript{VEH} vs. WT\textsubscript{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
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, Ndufs3, Ndufs4, Ndufs5, Ndufs6, Ndufs7, Ndufs8, Ndufs9, Ndufs10, Ndufs11, Ndufs12, Ndufs13

Complex II
Sdha, Sdhb, Sdhc, Sdhd

Complex III
Uqcrfs1, Cycb, Cyc1, Uqcr1, Uqcr2, Uqcrh, Uqcrb, Uqcro, Uqcr10, Uqcr11

Complex IV
Cox10, Cox3, Cox2, Cox1, Cox4i, Cox4i2, Cox5a, Cox5b, Cox6a-c, Cox7a, 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

ECM (Extracellular matrix)
COL1A1, COL1A2, COL3A1, COL6A5, VWF, FN1, LAMA2

Talin
TNN1

Zyxin
ZYY

MLC (Myosin light chain)
FLNA
PARVA

Actinin
ACTG1

Actinin
ACTN4, ACTN1

ITGA (Integrin alpha)
ITGA1, ITGA4

MLCP (Myosin light chain phosphatase)
Ppp1R12A

RTK (Receptor tyrosine kinase)
EGFR

ECM-receptor interaction

Cell motility
Stress fiber/FA formation

Filopodia/Lamellipodia formation
FA turnover

Cell proliferation

Cell survival

Cytokine-cytokine receptor interaction

Pik3C

PI3K

PIK3

Phosphorylated monolol signaling system

B-Raf

ERK1/2

MAPK signaling pathway

DNA

Cell cycle

DNA

cIAP2
Figure S9
Hypertrophic cardiomyopathy (DCM) and Arrhythmogenic right ventricular cardiomyopathy (ARVC)
Figure S7-10: Examples of KEGG pathways including proteins altered in TG<sub>VEH</sub> vs. WT<sub>VEH</sub> 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<sub>VEH</sub> in comparison to WT<sub>VEH</sub> and significantly by VPA (n=295).

| Symbol      | Protein name                                    | TG<sub>VEH</sub> vs. WT<sub>VEH</sub> | WT<sub>VEH</sub> vs. WT<sub>VEH</sub> | WT<sub>VEH</sub> vs. TG<sub>VEH</sub> | TG<sub>VEH</sub> vs. TG<sub>VEH</sub> |
|-------------|------------------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| 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–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                                |
| ECHEL1*     | 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                                |
| ECII        | 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 |
| Gene       | Description                                                                 | Log2 Fold Change |
|------------|-------------------------------------------------------------------------------|------------------|
| DNAJA4     | DnaJ homolog subfamily A member 4                                             | 0.32             |
| PRDX3*     | Thioredoxin-dependent peroxide reductase, mitochondrial                      | 0.32             |
| PFKM*      | 6-phosphofructokinase, muscle type                                            | 0.32             |
| MURC       | Muscle-related coiled-coil protein                                            | 0.32             |
| NDUFAF3    | NADH dehydrogenase [ubiquinone] 1 alpha subcomplex assembly factor 3         | 0.33             |
| CSRP3      | Cysteine and glycine-rich protein 3                                           | 0.33             |
| SELENBP1*  | Selenium-binding protein 1                                                    | 0.33             |
| ATP5I*     | ATP synthase subunit e, mitochondrial                                         | 0.33             |
| NDUFB5     | NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 5, mitochondrial   | 0.33             |
| ACSS1      | Acetyl-coenzyme A synthetase 2-like, mitochondrial                            | 0.33             |
| UQCR10†    | Cytochrome b-c1 complex subunit 9                                             | 0.34             |
| ALDH4A1    | Delta-1-pyrroline-5-carboxylate dehydrogenase, mitochondrial                 | 0.34             |
| FAHD1      | Acylpyruvase FAHD1, mitochondrial                                             | 0.34             |
| DBT        | Lipoamide acyltransferase component of branched-chain alpha-keto acid dehydrogenase complex, mitochondrial | 0.34             |
| SOD2*      | Superoxide dismutase [Mn], mitochondrial                                      | 0.35             |
| NDUFS3*    | NADH dehydrogenase [ubiquinone] iron-sulfur protein 3, mitochondrial         | 0.35             |
| IVD*       | Isovaleryl-CoA dehydrogenase, mitochondrial                                   | 0.35             |
| NDUFB3     | NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 3                 | 0.36             |
| NDUFA8†    | NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 8                | 0.36             |
| ETFB*      | Electron transfer flavoprotein subunit beta                                  | 0.36             |
| HSD17B8    | Estradiol 17-beta-dehydrogenase 8                                             | 0.36             |
| ACAA2*     | 3-ketoacyl-CoA thiolase, mitochondrial                                       | 0.36             |
| ETFA*      | Electron transfer flavoprotein subunit alpha, mitochondrial                  | 0.36             |
| NDUFA6*    | NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 6                | 0.37             |
| NDUFA13*   | NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 13               | 0.37             |
| MDH1       | Malate dehydrogenase, cytoplasmic                                            | 0.37             |
| SUOX       | Sulfite oxidase, mitochondrial                                                | 0.37             |
| NDUFS4*    | NADH dehydrogenase [ubiquinone] iron-sulfur protein 4, mitochondrial         | 0.37             |
| ATP5C1*    | ATP synthase subunit gamma, mitochondrial                                    | 0.37             |
| NDUFV2*    | NADH dehydrogenase [ubiquinone] flavoprotein 2, mitochondrial               | 0.38             |
| ATP5O*     | ATP synthase subunit O, mitochondrial                                         | 0.38             |
| TIMM9      | Mitochondrial import inner membrane translocase subunit Tim9                 | 0.38             |
| Gene   | Description                                                                 | Fold Change | Expression | **p**-value | **q**-value |
|--------|----------------------------------------------------------------------------|-------------|------------|-------------|-------------|
| 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        |
| UQCRCC2*| 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        |
| NDUFA1B| 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        |
| Gene   | Description                                                                 | Ratio 1 | Ratio 2 | Ratio 3 | Ratio 4 |
|--------|------------------------------------------------------------------------------|---------|---------|---------|---------|
| 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   | Hexaprenylidihydroxybenzoate 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    |
| Gene      | Description                                                                 | Value1 | Value2 | Value3 | Value4 |
|-----------|------------------------------------------------------------------------------|--------|--------|--------|--------|
| NDUVF1    | 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   |
| Gene   | Description                                                                 | FDR  | Control | NaN    | Log2 Fold Change |
|--------|-----------------------------------------------------------------------------|------|---------|--------|-----------------|
| 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            |
| SH3BGR | 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-diphosphoglucosyltransferase 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            |
| Gene Symbol | Description | Value 1 | Value 2 | Value 3 | Value 4 |
|-------------|-------------|---------|---------|---------|---------|
| 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    |
| C5B         | Complement component C5 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    |
| RRPB1       | 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        | Dipeptidyldipeptidase 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 | 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        | Adenyl 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    |
| HEB1        | Beta-hexosaminidase subunit beta | 3.03    | 0.81    | 1.62    | 0.54    |
| TAN1*       | Talin-1 | 3.06    | 0.99    | 1.69    | 0.55    |
| SFXN3       | Sideroflexin-3 | 3.07    | 1.09    | 1.90    | 0.62    |
| ARHGDB1     | 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    |
| FKB10       | Peptidyl-prolyl cis-trans isomerase | 3.41    | 0.80    | 1.77    | 0.52    |
| Gene | Description                             | Fold Change (Log2) | p-value |
|------|-----------------------------------------|--------------------|---------|
| C8A  | Complement component C8 alpha chain     | 3.49               | 0.29    |
| VWF  | von Willebrand factor                   | 3.52               | 0.48    |
| ZYX  | Zyxin                                  | 3.56               | 0.63    |
| FBLN1| Fibulin-1                               | 3.56               | 0.46    |
| SEPT8| Septin-8                                | 3.58               | 0.61    |
| FAM129A| Protein Niban                         | 3.61               | 0.52    |
| TPM4*| Tropomysin alpha-4 chain               | 3.63               | 0.45    |
| FAM129B| Niban-like protein 1                   | 3.68               | 0.49    |
| BASP1| Brain acid soluble protein 1            | 3.70               | 0.36    |
| VWF  | von Willebrand factor                   | 3.52               | 0.71    |
| ZYX  | Zyxin                                  | 3.56               | 1.00    |
| FBLN1| Fibulin-1                               | 3.56               | 0.67    |
| SEPT8| Septin-8                                | 3.58               | 2.19    |
| FAM129A| Protein Niban                         | 3.61               | 1.00    |
| TPM4*| Tropomysin alpha-4 chain               | 3.63               | 1.86    |
| FAM129B| Niban-like protein 1                   | 3.68               | 1.80    |
| BASP1| Brain acid soluble protein 1            | 3.70               | 1.63    |
| CYFIP1| Cytoplasmic FMR1-interacting protein 1 | 3.72               | 1.94    |
| FGG* | Fibrinogen gamma chain                 | 3.82               | 1.18    |
| FGB* | Fibrinogen beta chain                  | 3.90               | 1.10    |
| MRC1 | Macrophage mannose receptor 1          | 3.92               | 1.75    |
| COL1A2| Collagen alpha-2(I) chain              | 3.93               | 1.23    |
| ACTG1*| Actin, cytoplasmic 2                   | 4.01               | 1.96    |
| EMILIN1| EMILIN-1                               | 4.23               | 2.29    |
| HTRA1| Serine protease HTRA1                  | 4.31               | 2.00    |
| ACTN4*| Alpha-actinin-4                        | 4.34               | 2.66    |
| CSRPR2| Cysteine and glycine-rich protein 2    | 4.48               | 1.66    |
| COTL1 | Coactosin-like protein                 | 4.53               | 1.86    |
| ARPC1B| Actin-related protein 2/3 complex subunit 1B | 4.54               | 2.35    |
| FBN1 | Fibrilllin-1                           | 4.56               | 2.37    |
| ACTN1| Alpha-actinin-1                        | 4.63               | 1.85    |
| MYH9* | Myosin-9                               | 4.88               | 1.87    |
| LMCD1| LIM and cysteine-rich domains protein 1| 4.91               | 1.94    |
| RCN3 | Reticulocalbin-3                      | 4.97               | 2.50    |
| LCP1 | Plastin-2                              | 5.00               | 1.8     |
| CYGB | Cytoglobin                             | 5.01               | 3.16    |
| S100A6| Protein S100-A6                       | 5.01               | 1.7     |
| FN1* | Fibronectin                            | 5.07               | 1.33    |
| MYL6*| Myosin light polypeptide 6             | 5.13               | 2.11    |
| PLS3 | Plastin-3                              | 5.14               | 2.26    |
| FMO2 | Dimethylalanine monoxygenase [N-oxide-forming] | 5.15               | 3.01    |
| MRC2 | C-type mannose receptor 2              | 5.28               | 2.76    |
| PRELP*| Prolargin                              | 5.32               | 2.98    |
| PPIC | Peptidyl-prolyl cis-trans isomerase C  | 5.44               | 3.05    |
| ITGAV| Integnin alpha-V                      | 5.47               | 2.94    |
| COL1A1| Collagen alpha-1(XIV) chain            | 5.76               | 2.77    |
| COL3A1| Collagen alpha-1(III) chain            | 5.77               | 2.16    |
| FLNA*| Filamin-A                              | 5.82               | 1.88    |
| ANXA1| Annexin A1                             | 6.36               | 2.62    |
| TAGLN| Transgelin                             | 6.44               | 2.15    |
| EFEMP1| EGF-containing fibulin-like extracellular matrix protein 1 | 6.46               | 3.68    |
| BGN | Biglycan                               | 6.62               | 2.53    |
| ELN | Elastin                                | 7.16               | 2.15    |
| LOXL1| Lysyl oxidase homolog 1                | 8.24               | 2.57    |
| IGFBP7| Insulin-like growth factor-binding protein 7 | 11.07              | 4.32    |
Proteins were selected according to a protein expression ratio $\text{TG}_{\text{VEH}} \text{ vs. } \text{WT}_{\text{VEH}}$ atria $<$0.5 or $>$2. Intensities of detected proteins were normalized to the respective VEH group set to 1. Ratios for $\text{TG}_{\text{VEH}} \text{ vs. } \text{WT}_{\text{VEH}}$ and $\text{TG}_{\text{VPA}} \text{ vs. } \text{TG}_{\text{VEH}}$ are printed in bold. †CREM-target validated by ChIP. * denotes proteins already regulated at 7 weeks in $\text{TG}_{\text{VEH}} \text{ vs. } \text{WT}_{\text{VEH}}$.
Table S2: Assignment of the selected 295 regulated proteins to Ingenuity Canonical Pathways.

| Canonical pathway                  | Symbol   | Protein name                                                                 | Fold Change |
|-----------------------------------|----------|------------------------------------------------------------------------------|-------------|
|                                   |          |                                                                              | TG<sub>VEH</sub> vs. WT<sub>VEH</sub> | TG<sub>VPA</sub> vs. TG<sub>VEH</sub> |
| **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                    |
|                                   | GNA2*    | 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 F0 complex, subunit F6         | -2.74       | 1.58                     |
| Gene Symbol | Description                                                                 | Fold Change (Exp) | Fold Change (Ctrl) |
|-------------|------------------------------------------------------------------------------|-------------------|-------------------|
| 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 isomol 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*     | NADH dehydrogenase (ubiquinone) 1 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              |
| Gene Symbol | Description                                                                 | Fold Change | P-value |
|-------------|------------------------------------------------------------------------------|-------------|---------|
| 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    |
| UQCRF2*     | 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    |
| 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   |

**Signaling by Rho Family GTPases**

| Gene Symbol | Description                                                                 | Fold Change | P-value |
|-------------|------------------------------------------------------------------------------|-------------|---------|
| 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   |
| 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   |

**Remodeling of Epithelial Adherens Junctions**

| Gene Symbol | Description                                                                 | Fold Change | P-value |
|-------------|------------------------------------------------------------------------------|-------------|---------|
| 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   |
| 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   |
| Gene          | Description                                                   | Fold Change | p-value   |
|--------------|---------------------------------------------------------------|-------------|-----------|
| DNM2         | Dynamin 2                                                    | 2.02        | -1.18     |
| IQGAP1       | IQ motif containing GTPase activating                        | 2.84        | -2.02     |
| ZYX          | Zyxin                                                        | 3.56        | -1.60     |
| 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     |
| 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     |
| 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     |
| ACTR3        | ARP3 actin-related protein 3 homolog                         | 2.27        | -1.71     |
| ARPC3        | Actin related protein 2/3 complex, subunit 3                 | 2.10        | -1.52     |
| Protein   | Description                                                                 | Control | Experiment |
|-----------|-----------------------------------------------------------------------------|---------|------------|
| 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       |
| 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       |
| Gene Symbol | Protein Name | Description | Fold Change | p-Value |
|-------------|--------------|-------------|-------------|---------|
| 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 |
| UQCR2       | 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 |
|--------|---------------------------------------------------|-------|-------|
| 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 |
| ACTG1* | Actin, gamma 1 | 4.01 | -2.05 |
| ACTN1  | Actinin, 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 |
| 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 |
| 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 |
| Gene Symbol | Description                                                                 | Fold Change 1 | Fold Change 2 |
|-------------|------------------------------------------------------------------------------|---------------|---------------|
| 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**

| Gene Symbol | Description            | Fold Change 1 | Fold Change 2 |
|-------------|------------------------|---------------|---------------|
| ACTG1*      | Actin, gamma 1         | 4.01          | -2.05         |
| ACTN1       | Actinin, 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<sub>VEH</sub> vs. WT<sub>VEH</sub> and TG<sub>VPA</sub> vs TG<sub>VEH</sub>, 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<sub>VEH</sub> vs. WT<sub>VEH</sub><sup>13</sup>. 
### 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       | Glycerinaldehyde-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<sub>VEH</sub> vs. WT<sub>VEH</sub><sup>13</sup>.