SUPPLEMENTAL MATERIAL

DETAILED METHODS

Measurement of arterial blood pressure

A non-invasive computerized tail-cuff system was used to measure arterial blood pressure (BP-2000; Visitech Systems, Inc.) in conscious mice (n=5-10). Mice were acclimated to handling and placement in the apparatus before data acquisition. Briefly, for 5 consecutive days, a cuff was placed around the tail in all mice and repeated arterial pressure measurements were obtained 5 times. On the fifth day, the last systolic and diastolic pressures were recorded.

Electrocardiograms (ECGs)

Mice were lightly anesthetized with 0.5–2% isoflurane in oxygen, administered via nose cone and adjusting the isoflurane delivery to maintain the heart rate around 500±50 bpm. Surface ECGs were obtained by using bipolar limb leads (leads I, II, and III) and unipolar limb leads (leads aVR, aVL, and aVF) for 5 minutes in basal conditions (MP36R, BIOPAC Systems, Inc.). Later, isoproterenol (I6504, Sigma-Aldrich) was injected i.p. (1.5 mg/kg), and ECGs were measured over 15 minutes. ECGs were analyzed by a blinded expert using Acqknowledge 4.1.1 for MP36R (BIOPAC Systems, Inc.). Mean values were calculated from 10 consecutive standard ECG time intervals and waves.

RNA extraction and qRT-PCR

Total RNA was extracted from the LV wall or cells using TRIzol (15596026, Thermo Fisher Scientific). First-strand cDNA was synthesized using 100 ng of total RNA and a High Capacity cDNA Reverse Transcription Kit (4368814, Thermo Fisher Scientific). Quantitative PCR (qRT-PCR) was carried out in an Applied Biosystems real-time PCR thermocycler using SYBR Green (4367659, Thermo Fisher Scientific) for 40 cycles (95º for 15 sec, 60º for 60 sec.) Primers used for qRT-PCR are listed in Online Table I. Results were analyzed with the LinReg method and software, which calculates the PCR efficiency of each sample independently.[57] The average efficiency of each mRNA was then used to calculate the relative expression of each gene, which was normalized to that of Gapdh.

iCLIP library preparation

Neonatal cardiomyocytes were isolated from wild type mice (C57BL/6) at P0 as described.[59] Around 8 million cells were plated on 10 cm^2 dishes. The day after cardiomyocytes isolation, cells were transfected with 15 µg SRSF4-GFP modRNA using 21 µL Lipofectamine 2000.Forty-eight hours post transfection, cells were irradiated (150 mJ/cm^2 UV light (254 nm) on ice) and iCLIP was performed as previously described,[60] with specific modifications. Cells were lysed for 10 minutes on ice and sonicated with 3 pulses each 10 seconds at 20% amplitude with 20 seconds pause. Crosslinked RNA samples were digested using RNaseI (Ambion) at a 1:200 dilution, at 37°C for exactly 3 min at 1100 rpm. The RNA size after digestion was around 80-200 nucleotides. Samples were treated with 2 µl of RNase Inhibitor (Promega), after the RNaseI treatment to reduce the RNA degradation. Digested RNA-protein complexes were immunopurified using Protein G Dynabeads® (ThermoFisher Scientific) coupled with a goat anti-GFP antibody (D. Drechsel, MPI-CBG, Dresden), rotating during 1.5 hours at 4ºC. T4 PNK (NEB) was used in order to dephosphorylate the 3' RNAs at 37°C for 20 minutes in a thermomixer at 1100 rpm. RNA fragments were ligated to pre-adenylated DNA 3' adapters (IDT), using T4 RNA ligase (NEB) overnight at 16°C, 1100 rpm. RNAs 5' ends were radio-labeled by P32-γ-ATP (PerkinElmer). Samples were run in a NuPAGE gel (Bio-Rad) at 180 V for 50 min, and transferred into a nitrocellulose membrane at 40 V for 2 hours. RNAs were isolated from the membrane. In order to remove crosslinked proteins, samples were treated with proteinase K. Isolated and purified RNA fragments were reverse-transcribed using barcoded RT-primers and SuperscriptIV (ThermoFisher Scientific). cDNA fragments were purified and size-selected by gel electrophoresis. cDNAs were circularized using CircLigase™ (Epicentre) and re-linearized with BamHI (NEB). The final cDNA libraries containing 5' and 3' adapters due to the circularization and linearization steps were amplified using AccuPrime (ThermoFisher Scientific). Finally, cDNA libraries were sequenced on an Illumina HiSeq2000 sequencing system (single-end 75 nucleotide reads, 20 million reads per replicate).

Functional analysis

Gene Ontology categories and KEGG pathways were downloaded from the Enrichr website,[58,59] and upregulated or downregulated genes enriched in each category were identified. For alternative splicing analysis, a gene was classified as included if at least one exon showed an increased inclusion rate (PSI) and as skipped if any of the exons showed a reduced inclusion rate; therefore, a gene could be assigned to both categories. The background gene set included those genes with at least one alternative splicing event detected and tested for differential splicing. Functional categories with at least 5 genes in the whole dataset were assessed for overrepresentation by logistic regression analysis in

statsmodels.[60] Benjamini-Hochberg multiple test correction was applied to obtain p-values adjusted for false discovery rate (FDR).

DNA constructs

The SRSF4-GFP chimera was generated by inserting SRSF4 cDNA (Origene) into pEGFP-N1. For *GAS5* overexpression experiments, *GAS5* cDNA was obtained from abm (ORF020064). Modified RNAs (modRNA) for *SRSF4-GFP* and *GAS5* were cloned and produced as previously described.[57]

Cardiomyocyte isolation, transfection, and treatments.

Neonatal cardiomyocytes were isolated from control and SRSF4 KO mice at P0.[34] Starting 24 h after isolation, cells were treated with 100 μM dexamethasone (D4902, Sigma-Aldrich) or DMSO (D2650, Sigma-Aldrich) for 72 h. For the *GAS5* overexpression experiments, cells where transfected one day before dexamethasone treatment with 15 μg of *GAS5* modRNA or control modRNA, using Lipofectamine 2000 (11668027, Thermo Fisher Scientific). For the *GAS5* stability experiments, cells were treated with 10 μg/mL actinomycin D (ActD) (A9415, Sigma) starting 24 h after isolation, and cells were collected 4, 8, and 14 h later. For NMD inhibition experiments, cells were treated with 50 μM NMD inhibitor (530838, Sigma) or DMSO for 7 h, starting 24 h after isolation.

Western Blotting

Left ventricular myocardium was lysed in RIPA buffer in the presence of protease inhibitor (04693159001, Roche Diagnostics). Lysates were separated by SDS-PAGE gels (10%) and transferred to PVDF membranes. Membranes were blocked with 5% skimmed milk in 1X TBS, 0.1% Tween® 20 at 4°C with gentle shaking, overnight. The following primary antibodies were used: anti-GR (3660, Cell Signalling) at 1:1000 dilution, anti-SRSF4 (NBP2-04144, Novus) at 1:200 dilution, anti-α-tubulin (T6199, Sigma) at 1:3000 dilution, and anti-GAPDH (ab8245, Abcam) at 1:1000 dilution. Secondary antibodies included anti-mouse P0447 and anti-rabbit P0448, both from Dako, were used at 1:3000 dilution. Membranes were developed using ECL reagent (RPN2106, GE Healthcare Life Sciences).

Immunofluorescence

Hearts were fixed in 4% paraformaldehyde (PFA) in PBS and included in paraffin. For immunofluorescence, 5 µm sections were unmasked with citrate solution, incubated with wheat-germ agglutinin tetramethylrhodamine conjugate (W849, Thermo Fisher Scientific) at 1:100 dilution, permeabilized with 0.3% Triton X-100/PBS, and blocked with blocking solution (10% FCS, 0.3% BSA in PBS/0.1% Tween-20). Sections were incubated with anti-cardiac troponin I (ab58544, Abcam) diluted 1:200. The secondary antibody was Alexa 488-labeled goat anti-rabbit (A-11034, Thermo Fisher Scientific) diluted 1:200. Isolated cardiomyocytes were cultured on coverslips coated with fibronectin (F2006, Sigma-Aldrich) and were fixed in 4% PFA and blocked with blocking solution. Fixed cardiomyocytes were incubated with the same antibodies and concentrations as the heart sections. Nuclei were stained with DAPI (D1306, Thermo Fisher Scientific). Heart sections and isolated cardiomyocytes samples were mounted in Vectashield mounting medium (H-1000, Vector Laboratories). As a negative control, secondary antibody alone was used.

DEX treatment in vivo

SRSF4 KO and control mice at 6 weeks old were treated with DEX (15 mg/100 g BW, orally, once daily) for 14 days. On the last day of treatment, LV walls of SRSF4 KO and control mice were analyzed by echocardiography, and animals were sacrificed in order to obtain LV heart samples.

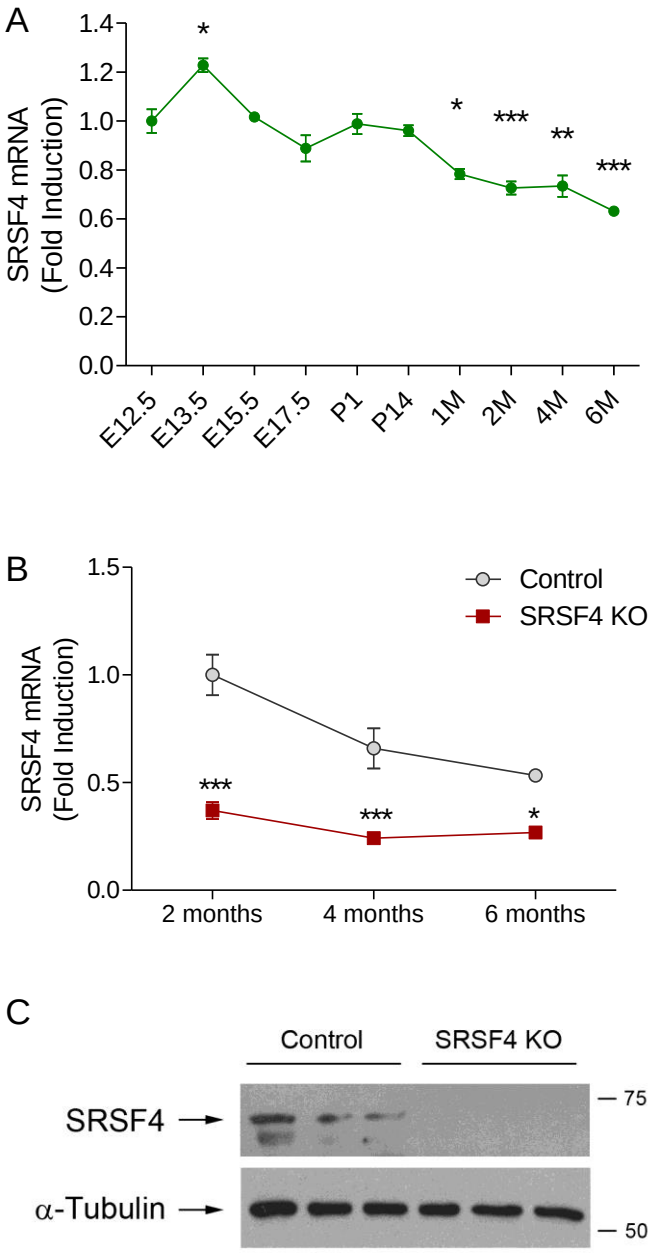
Adeno-associated virus production and injection

Adeno-associated viruses were produced by the CNIC Viral Vectors Unit in HEK293 cells using serotype 9 capsid proteins. For viral administration, mice were anesthetized with 3-3.5% sevoflurane in 100% oxygen. A total of 50 µL of saline (0.9% NaCl), containing 5×10^{10} VP/mL, were injected per mouse through the femoral vein in a single injection.

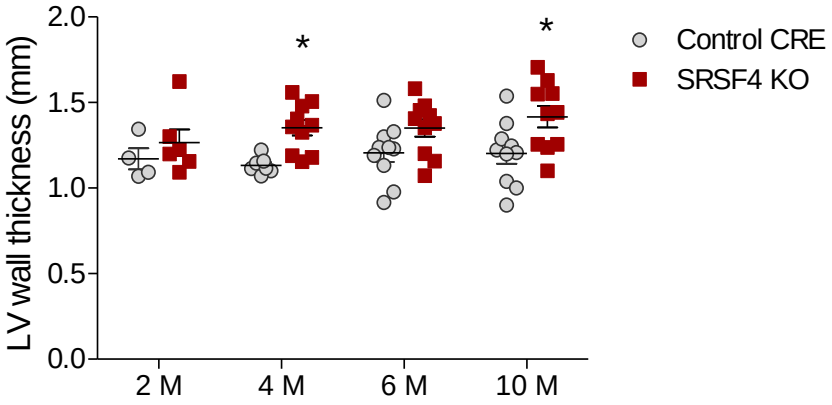
Cushing´s syndrome patients

We downloaded the processed gene count data from adipose tissue of Cushing's syndrome patients and controls from GEO (accession GSE66446). Analysis was performed using DESeq2 R library.[61] No additional QC analysis was performed to the one from the original publication. Differential expression analysis was performed using apeglm for shrinkage of log (Fold changes) across all genes and then extracted the results for GAS5 and SRSF4 genes.[62]

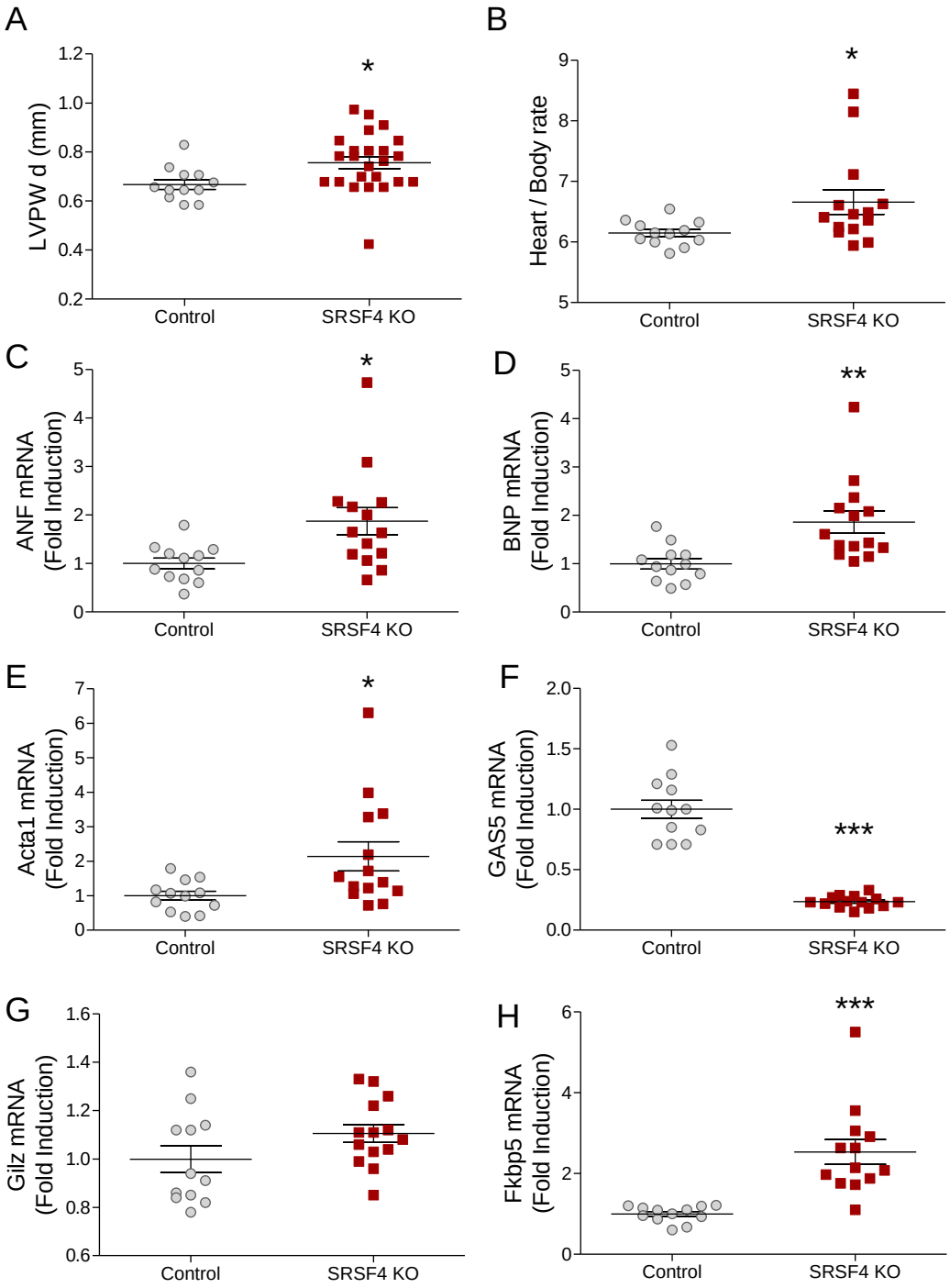
ONLINE FIGURES AND FIGURE LEGENDS



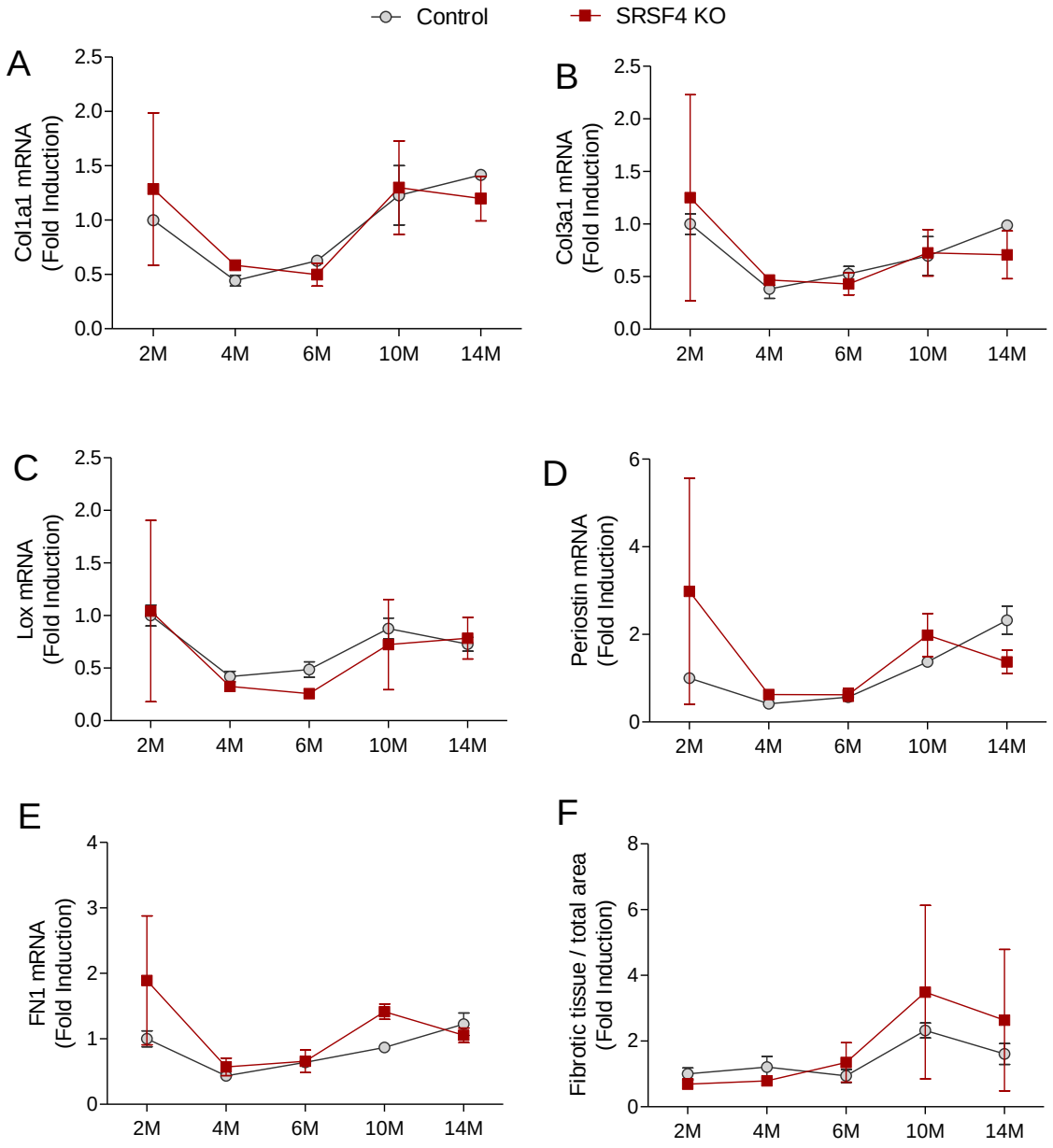
Online Figure I. SRSF4 expression in wild type, control and SRSF4 KO mice. A, qRT-PCR analysis of SRSF4 mRNA expression in the heart of wild type mice (C57BL/6), ranging from embryonic development to adult age. Data are shown as mean ±SEM; n=3 mice per group, except for the E17.5 group (n=4). *p<0.05, **p<0.01, ***p<0.001 vs E12.5; Kruskal-Wallis test followed by Dunn's Multiple comparison test. **B**, qRT-PCR analysis of SRSF4 mRNA expression in KO and control hearts at different ages. Data are shown as mean ±SEM, n=4 mice per group, except for control mice at 2 months (n=5). *p<0.05, **p<0.01, ***p<0.001 SRSF4 KO vs Control; 2-way ANOVA followed by Bonferroni's post-test. **C**, Western blot showing SRSF4 expression in control and SRSF4 KO mice.



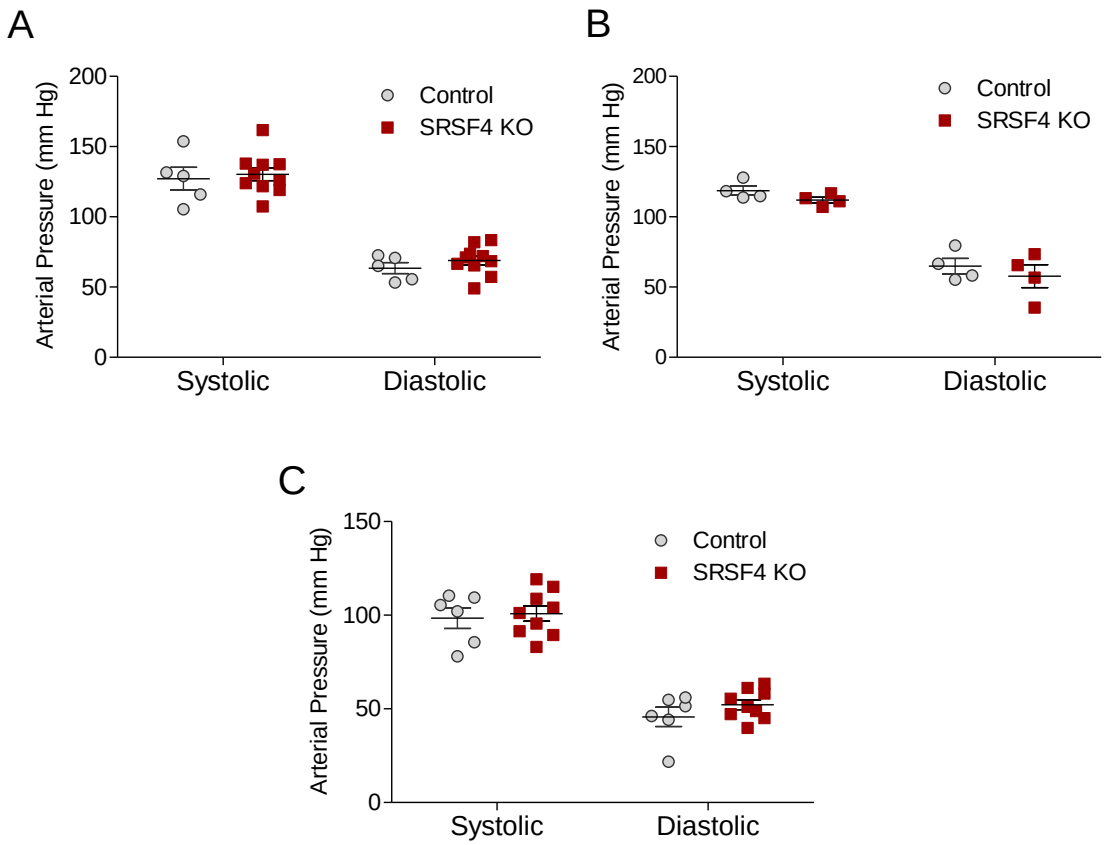
Online Figure II. LV wall thickness is significantly increased in SRSF4 KO mice compared to Nkx 2.5-Cre mice. Echocardiography analysis of left ventricular wall thickness in SRSF4 KO mice and Nkx 2.5-Cre mice (Control CRE) at different ages from 2 to 10 months. Symbols represent individual animals. Data are shown as mean ±SEM. *p<0.05, SRSF4 KO vs control CRE; 2-way ANOVA followed by Bonferroni's correction.



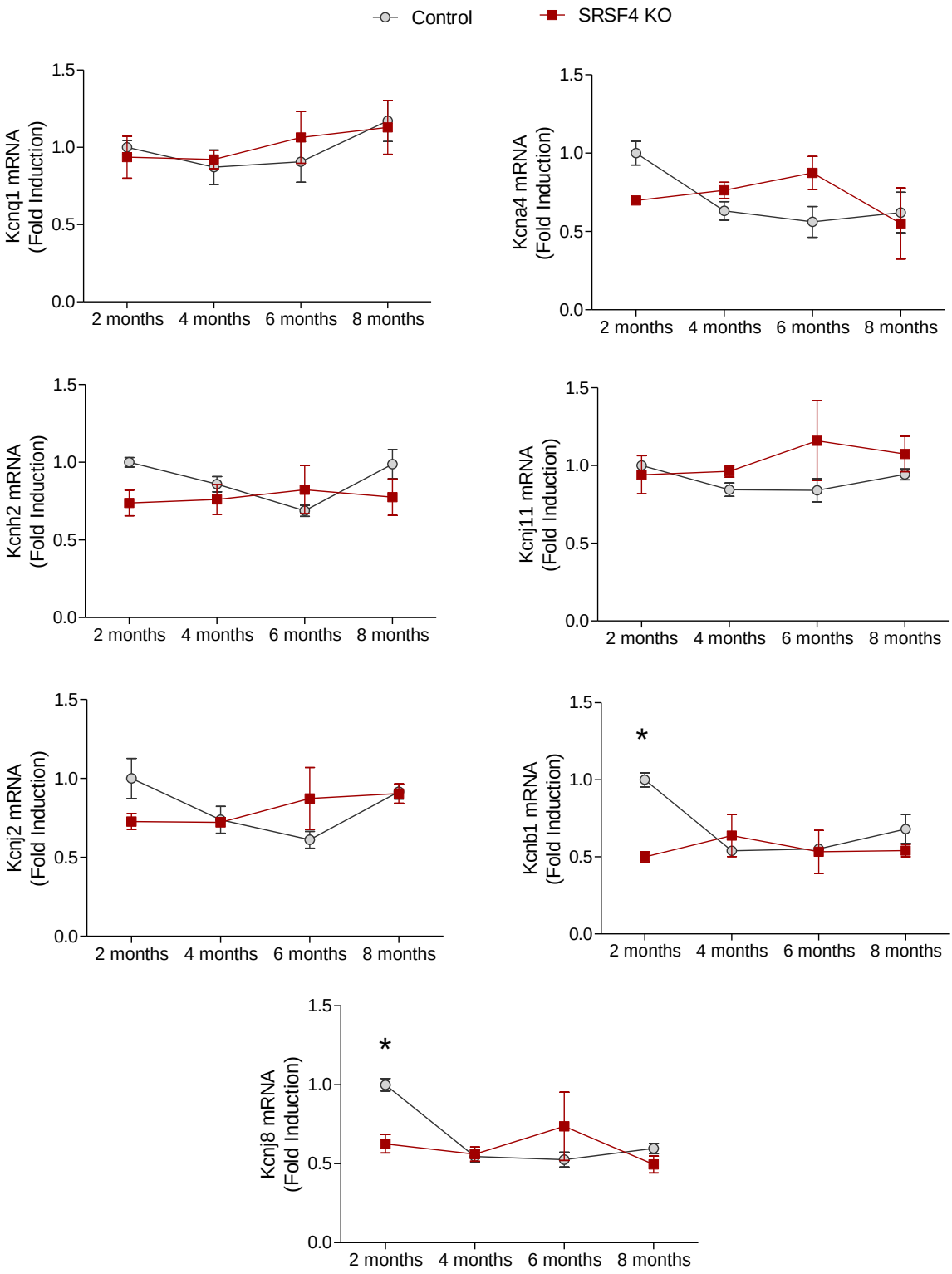
Online Figure III. Loss of SRSF4 induces cardiac hypertrophy in female mice. A, Echocardiography analysis of left ventricular posterior wall in diastole (LVPWd). **B**, Heart weight/body weight rate. **C-H**, mRNA expression of hypertrophy markers (C-E), GAS5 (F), and the GR targets Gilz and Fkbp5 (G-H) in control and SRSF4 KO hearts. Data are shown as mean ±SEM. Symbols represent individual animals. *p<0.05, ***p<0.001 for SRSF4 KO (red) vs control (grey); Student-t test in panels A, F and G. *p<0.05, **p<0.01, ***p<0.001 for SRSF4 KO (red) vs control (grey), Mann-Whitney test in panels B, C, D, E and H.



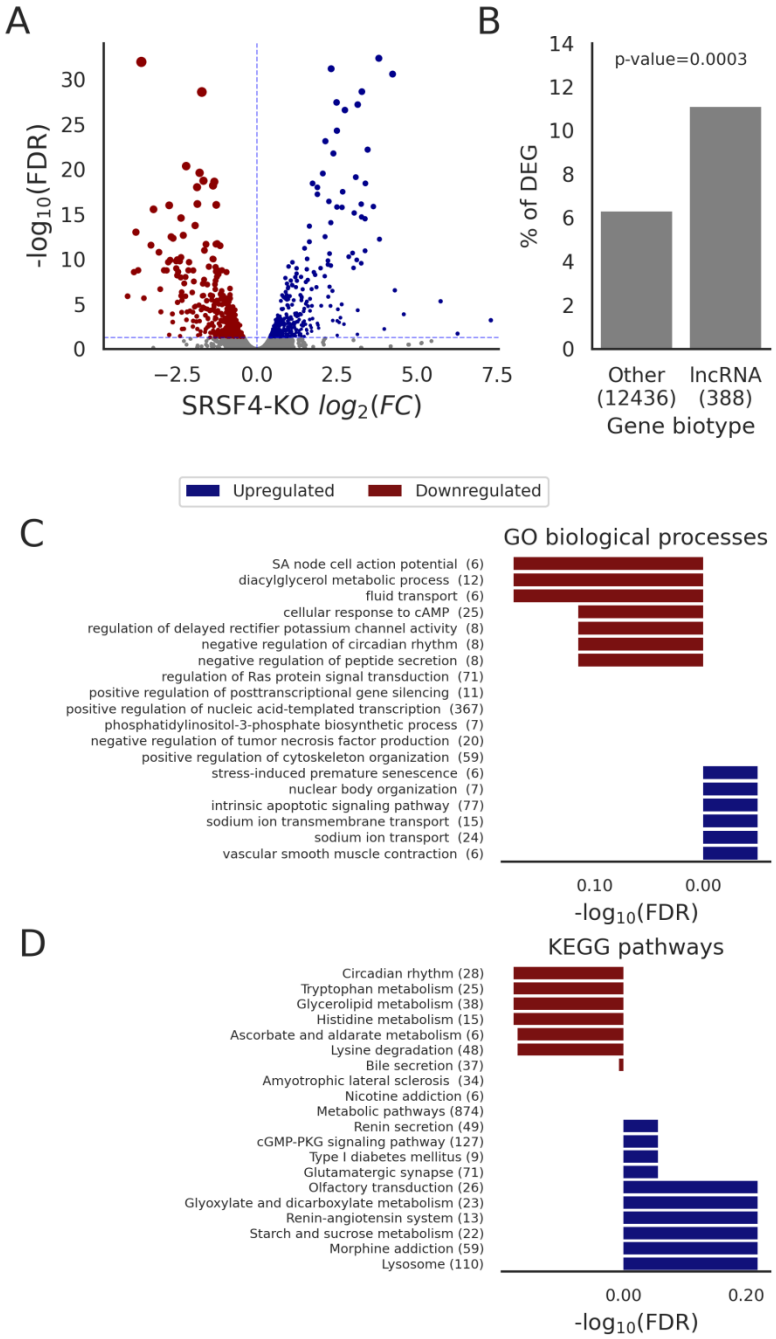
Online Figure IV. SRSF4 KO mice do not show changes in fibrosis markers. A-C, qRT-PCR analysis of Col1a1 (A), Col1a3 (b), Lox (C), periostin (D) and fibronectin (E) mRNA expression in the heart of control and SRSF4 KO mice, ranging from 2 to 14 months of age. **F**, Quantification of the fibrotic tissue in histological heart sections of control and SRSF4 KO mice, ranging from 2 to 14 months of age. Data are shown as mean ±SEM; n=3 mice per group, except for 4M and 6M (n=4 per group). No significant differences ($p<0.05$) were found; 2-way ANOVA followed by Bonferroni's correction.



Online Figure V. **SRSF4 KO and control mice show similar blood pressure**. Systolic and diastolic blood pressure were measured in 2-month-old (A), 4-month-old (B) and 10-month-old (C) control and SRSF4 KO mice. Data are shown as mean ±SEM. Symbols represent individual animals. No significant differences ($p<0.05$) were found.

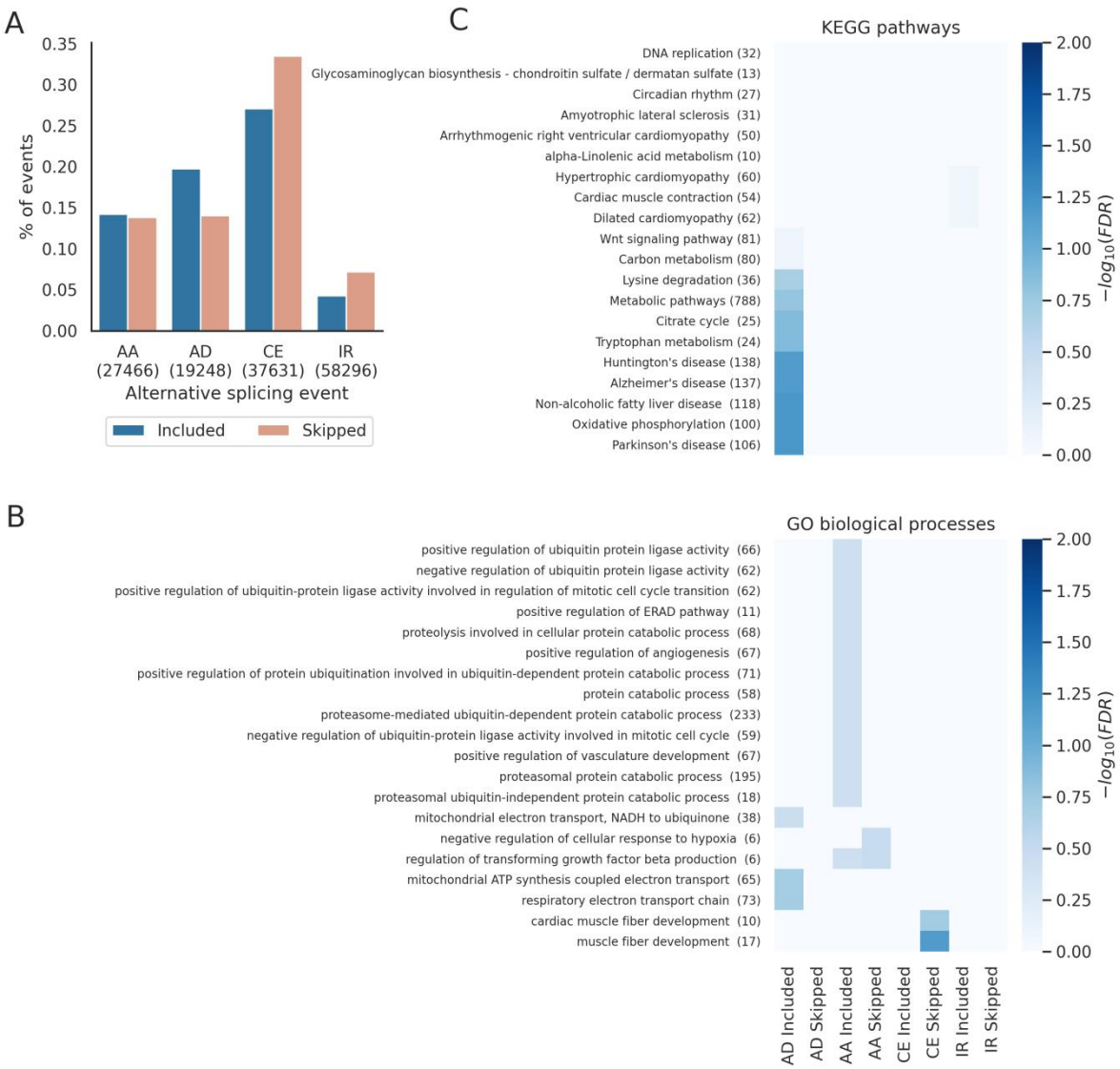


Online Figure VI. mRNA expression of different potassium ion channels in the heart of control and SRSF4KO mice. Data are shown as mean ±SEM, n=3 mice per group. *p<0.05, SRSF4 KO vs Control, 2-way ANOVA followed by Bonferroni's post-test.

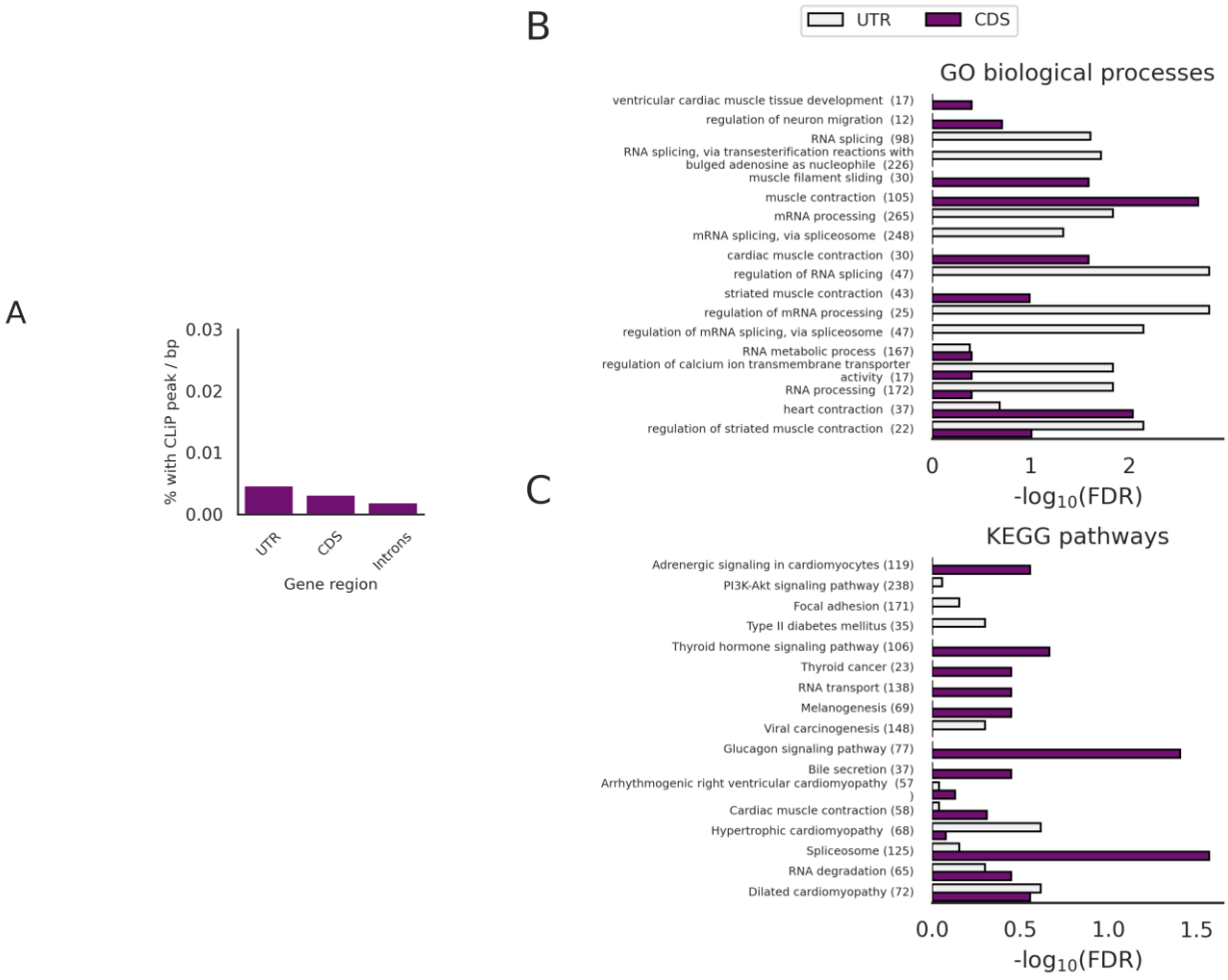


Online Figure VII. Enrichment analysis of differentially expressed genes in SRSF4 KO hearts. A, Volcano plot representing the $\log_2$ transformation of the fold change (FC) on the x-axis against the -log10 of the adjusted p-value (FDR) on the y-axis. Each dot represents a gene. Genes were considered to be differentially expressed (DEG) whenever the adjusted p-value was below 0.05. **B**, Proportion of DEGs among genes annotated as lncRNA and those with any other annotation. Over-representation analysis was performed with a one-sided Fisher test. **C, D**, Representation of the top 10 Gene Ontology (GO) categories (C) and

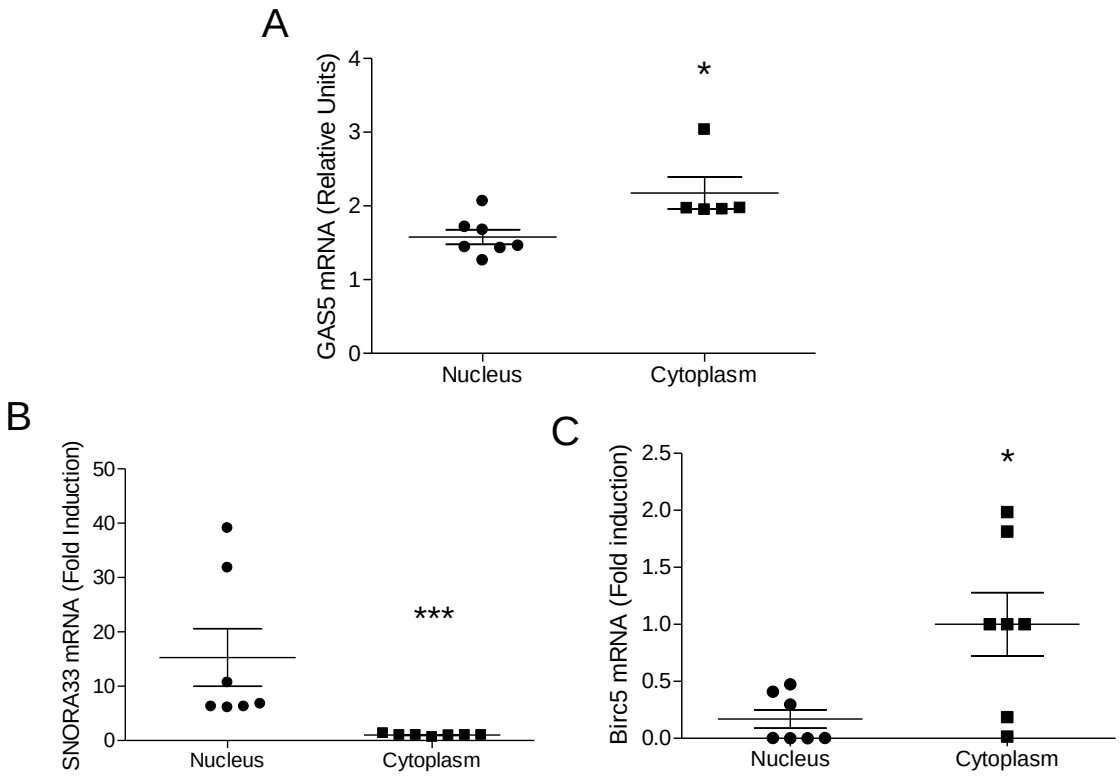
KEGG pathways (D) associated with up and downregulated genes by their $-\log_{10}$ transformation of the FDR adjusted p-value.



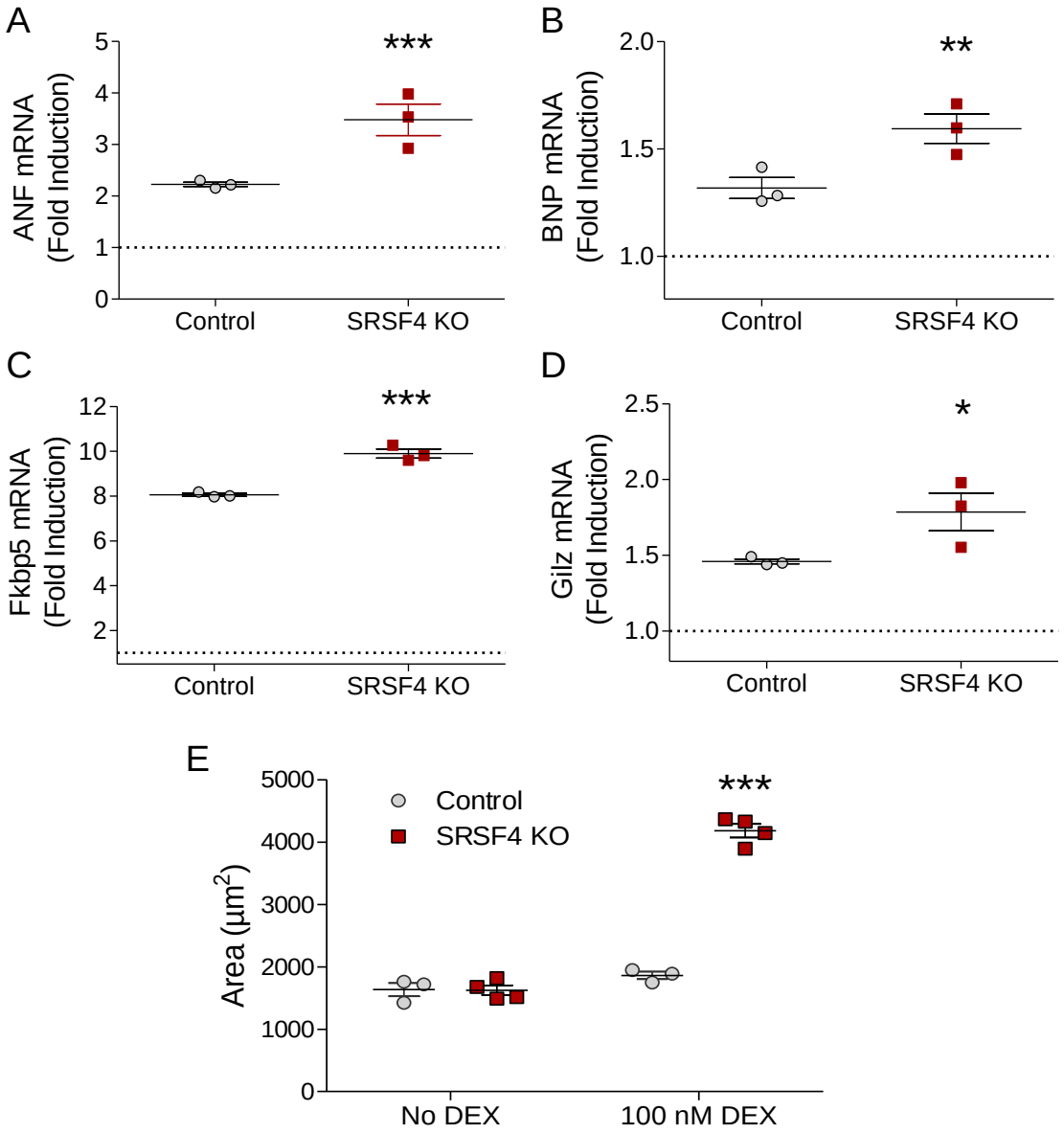
Online Figure VIII. Alternative splicing changes in cardiac-specific SRSF4 KO mice. A, Percentage of AS events showing either increased (Included) or decreased (Skipped) inclusion rates (PSI) in the KO compared with control mice. Events were considered to be significantly changed when there was 95% a posterior probability of having an absolute difference in PSI higher than 0. **B, C**, Representation of the top Gene Ontology (GO) categories (B) and KEGG pathways (C) associated with up and downregulated genes by their -$\log_{10}$ transformation of the FDR adjusted p-value for each type of alternative splicing event.



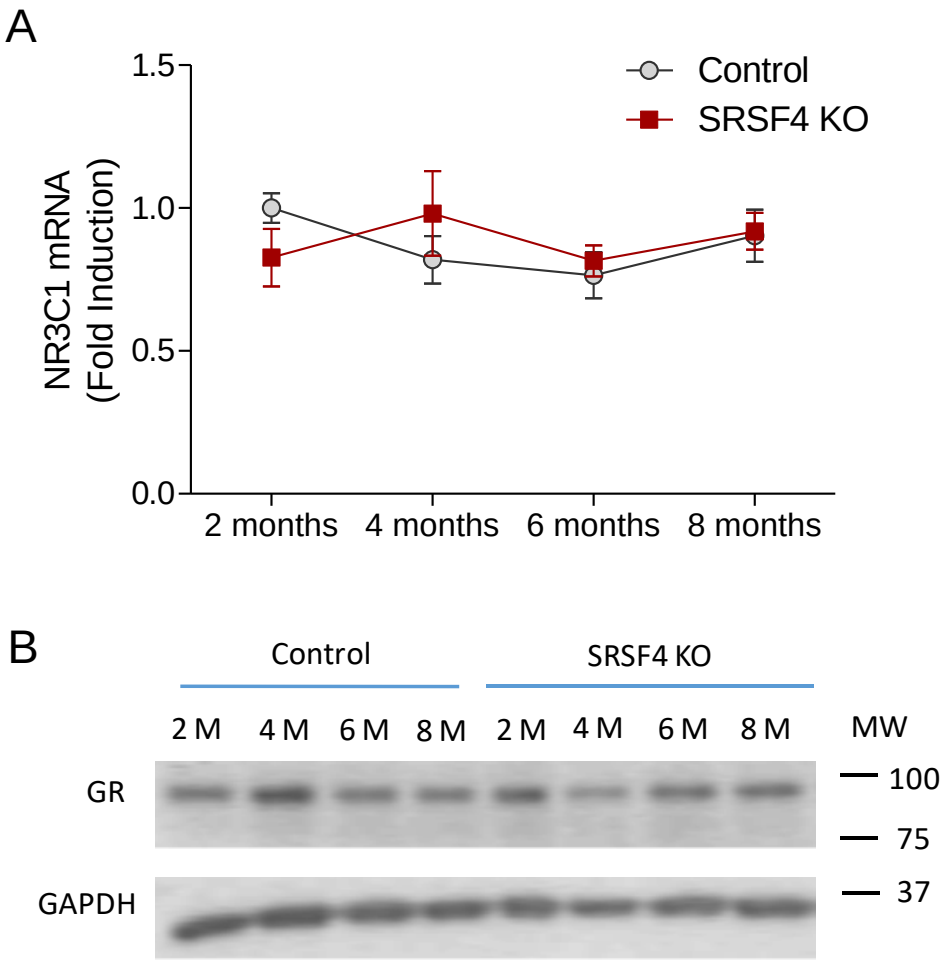
Online Figure IX. Individual-nucleotide resolution UV crosslinking and immunoprecipitation (iCLIP) analysis of SRSF4-RNA binding in neonatal cardiomyocytes. A, Percentage of base pairs bound by SRSF4 in iCLIP experiments depending on the gene region. UTR, untranslated region or non-conding exonic regions; CDS, coding regions; Introns, intronic regions. **B, C**. Representation of the top Gene Ontology (GO) categories (B) and KEGG pathways (C) associated with genes bound by SRSF4 either in the UTRs or the CDS by their -log10 transformation of the FDR adjusted p-value. **D**, Binding motifs derived from iCLIP binding regions for all peaks and only those located on the UTRs.



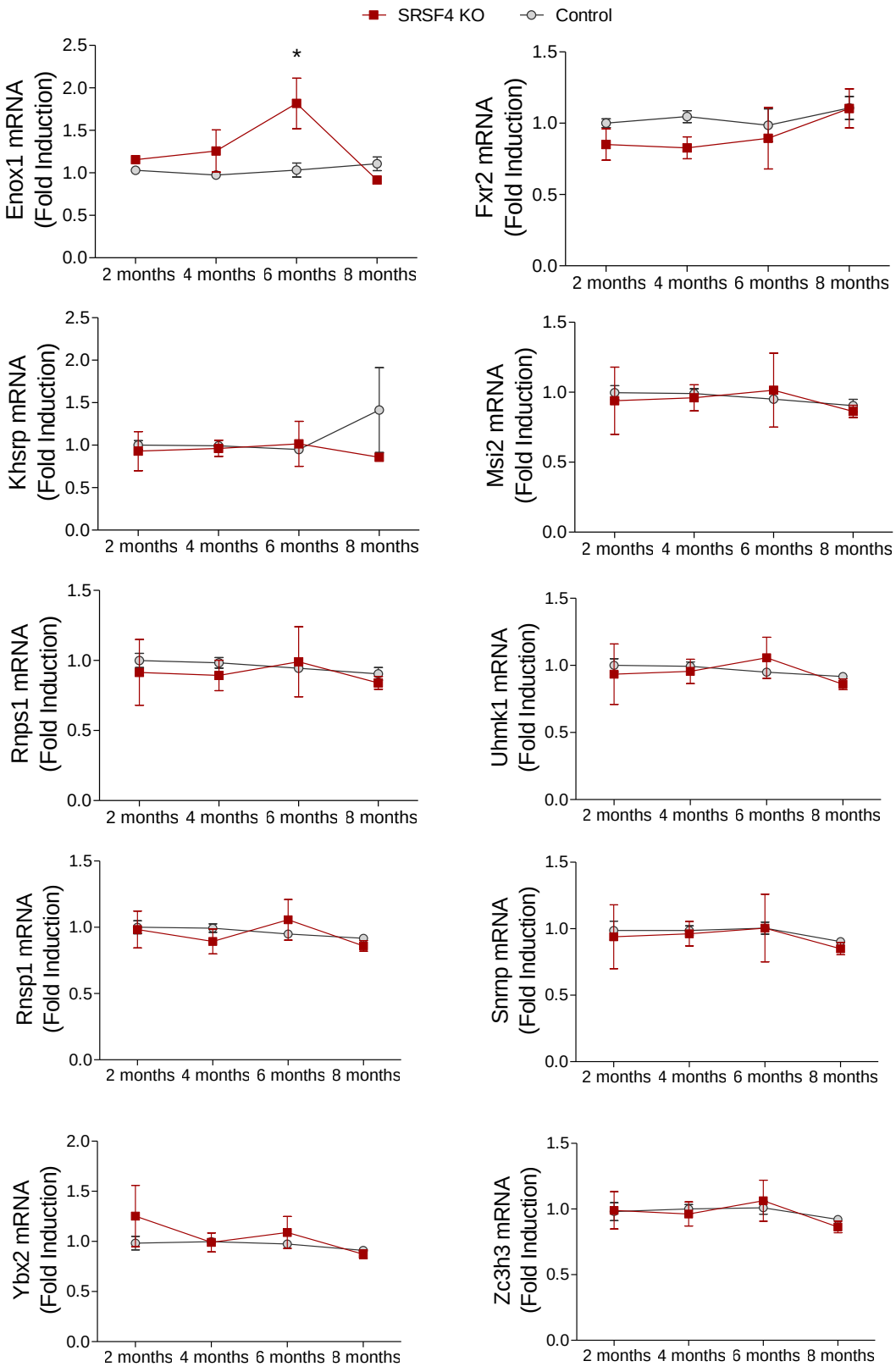
Online Figure X. GAS5 is localized both in the nucleus and in the cytoplasm. **A-C**, qRT-PCR analysis of GAS5 mRNA expression (A), SNORA33 (B), and Birc5 (C) in isolated cardiomyocytes from control mice hearts. Data are shown as mean ±SEM. Every symbol represents a sample from an independent neonatal cardiomyocyte isolation (biological replicate). *p<0.05, ***p<0.001 for Nucleus vs Cytoplasm, Mann Whitney test.



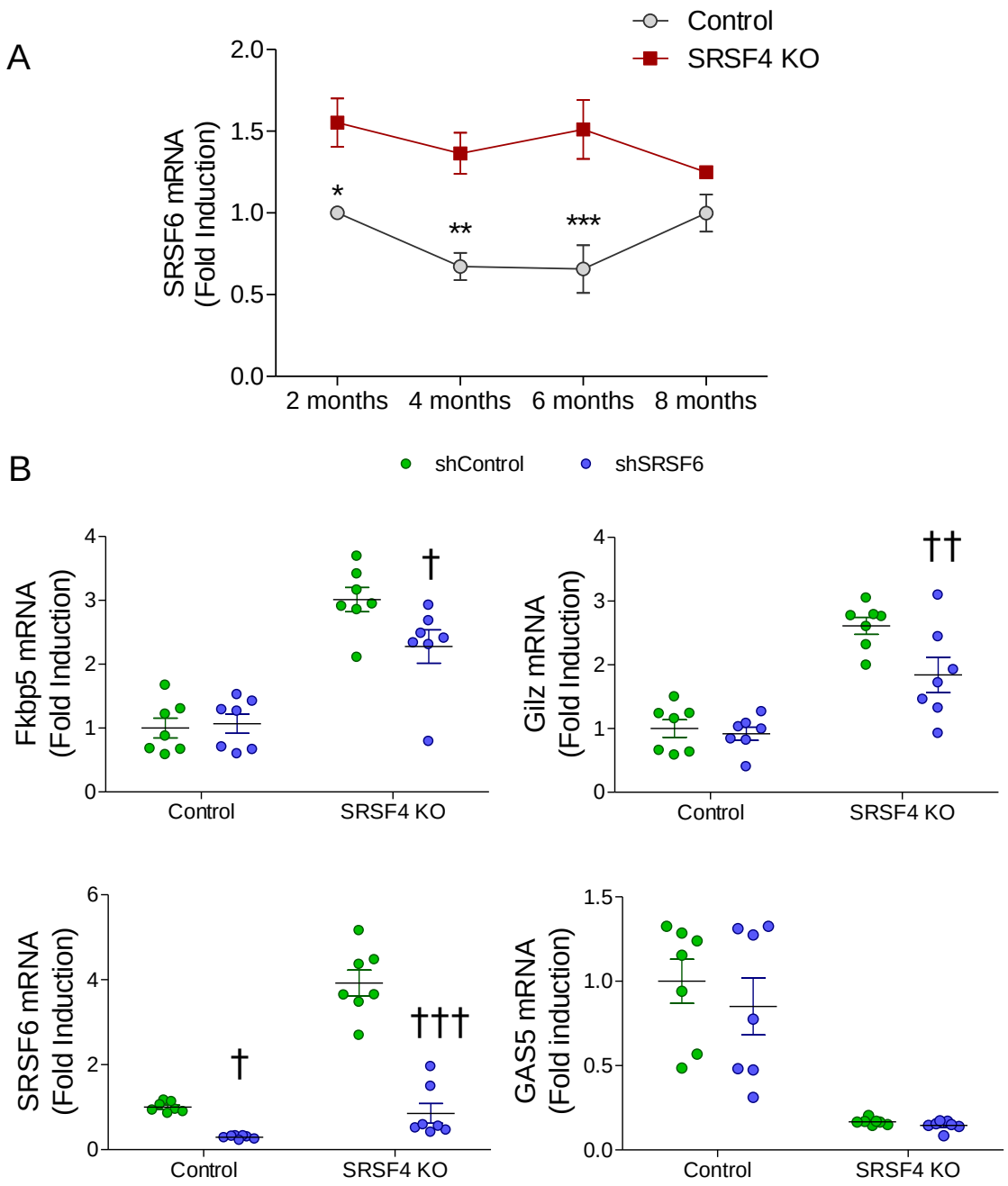
Online Figure XI. Glucocorticoid-induced cardiomyocyte hypertrophy is increased in the absence of SRSF4. **A-D**, qRT-PCR analysis of hypertrophy markers (A, B) and known GR targets (C, D) in control and SRSF4 KO neonatal cardiomyocytes treated with 100 nM DEX. Values for each group were normalized to the mean value for control cells treated with DMSO (dotted line). Data are shown as mean ±SEM, and symbols represent individual samples from 3 independent experiments (biological replicates); *p<0.05, **p<0.01, ***p<0.001; Student t-test. **E**, Surface area of control and SRSF4 KO neonatal cardiomyocytes treated with 100nm DEX or DMSO (No DEX). Data are shown as mean ±SEM, and symbols represent the average of individual cardiomyocytes in each biological replicate. ***p<0.001 SRSF4 KO vs Control with 100 nM DEX; 2-way ANOVA followed by the Bonferroni post-test.



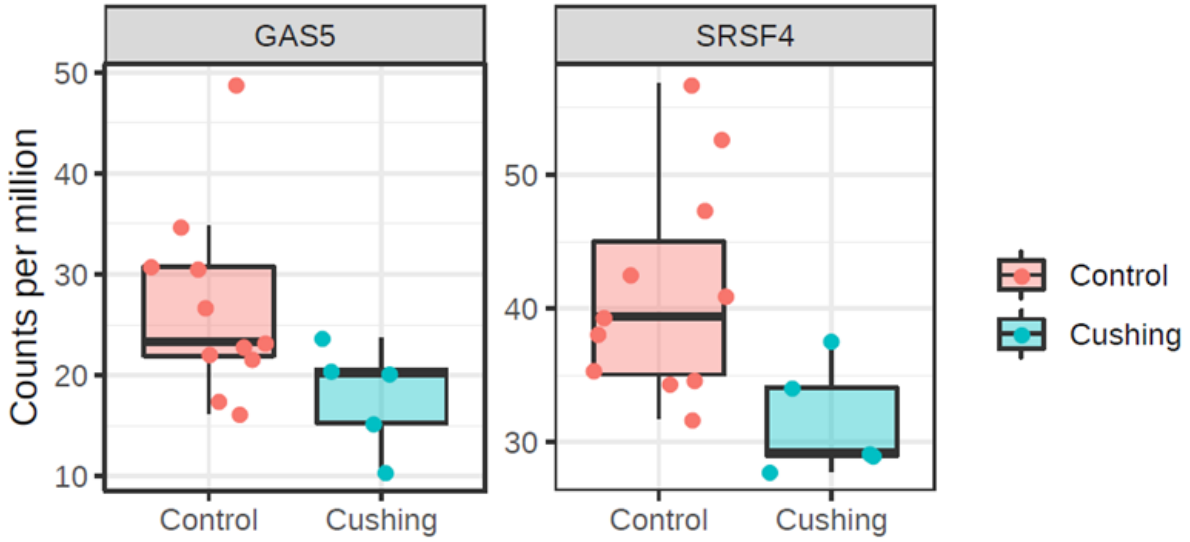
Online Figure XII. SRSF4 KO and control mice show similar GR expression. A, B, qRT-PCR analysis of NR3C1 mRNA expression (A) and western blot analysis of NR3C1 (GR) protein expression (B) in SRSF4 KO and control hearts at different ages ranging from 2 to 8 months. Data are shown as mean ±SEM. n=3 mice per time point in panel A. M, months. n=1 for each age and group in panel B.



Online Figure XIII. qRT-PCR analysis of several RBPs in the myocardium of SRSF4 KO and control mice. Data are shown as mean ±SEM, n=3 mice per group. *p<0.05, SRSF4 KO vs Control, 2-way ANOVA followed by Bonferroni´s post-test.



Online Figure XIV. SRSF6 is necessary for the activation of the GR in SRSF4 KO cardiomyocytes. A, qRT-PCR analysis of SRSF6 mRNA expression in KO and control hearts at different ages. Data are shown as mean ±SEM, n=4 mice per group, except for SRSF4 KO mice at 4M (n=5). *p<0.05, **p<0.01, ***p<0.001 SRSF4 KO vs Control, 2-way ANOVA followed by Bonferroni's post-test. **B**, qRT-PCR analysis of Fkbp5, Gilz, SRSF6 y GAS5 in control and SRSF4KO neonatal cardiomyocytes infected with lentivirus expressing shControl or shSRSF6. Data are shown as mean ±SEM. Symbols represent biological replicates. †p<0.05, ††p<0.01, †††p<0.001 shSRSF6 vs shControl, 2-way ANOVA followed by Bonferroni's post-test.



Online Figure XV. GAS5 and SRSF4 expression is reduced in Cushing´s syndrome patients. GAS5 and SRSF4 mRNA expression is shown as counts per million (CPM) derived from RNA-seq data obtained from adipose tissue of patients with Cushing´s syndrome and controls (accession GSE66446).

ONLINE TABLES

Online Table I. SYBR Green primer sequences used for qRT-PCR (5'-3').

Gen	Forward	Reverse
SRSF4	GATCCTGGAGGTGGATCTGA	ACAGGTCTTTGCCGTTCAGT
GAPDH	CTGCACCACCAACTGCTTAG	AGATCCACGACGGACACATT
BNP	GCCAGTCTCCAGAGCAATTC	TCTTTTGTGAGGCCTTGGTC
MYH7	CAACTGGAGGAGGAGGTCAA	CCTCTGTATGGCATCCGTCT
GAS5	TCTCACAGCCAGTTCTGTGG	TCTGGTCTTCTATTCTAGCACATTG
ANF	GATGGATTTCAAGAACCTGCT	CCTGCTTCCTCAGTCTGCTC
Fkbp5	CGAAGGAGCAACGGTAAAAG	ATCGGAATGTCGTGGTCTTC
Gilz	AGGCCATGGACCTCGTGA	TCAGGTGCTGGCTCTTCAG
NR3C1	AGGCCGCTCAGTGTTTTCTA	GAGCACACCAGGCAGAGTTT
ENOX1	TAAGTGAGCTGGCTCCCAAG	AGCCTGTGGAGAAGAAGACG
FXR2	AAAGCACTGGGAGCCAACT	CTTCATTGCGGGACATGAG
KHSRP	ATCGGAGGTGATGCTGCTAC	GGAAGCCAGTTTCTTGCTGT
MSI2	GTTTCGTCACCTTCGCAGAC	CGACGAGGAAATGCAACTTT
PNO1	CCGATTGTAGAACATTTGGGACT	CTCCACCTGAAAGCCAAGAA
RNPS1	TTTGAGAATCCCGATGAAGC	ACATGGGAGGTGGTGGAAG
SNRNP35	CGGTGGAAACGGTTTTTCT	CTCCACACAGCTCGGTCAT
UHMK1	ATGGTTTCCGCAAAGAGAGG	GCAATTCCGAAACACTGACA
YBX2	AGTCCTGGGCACAGTCAAAT	AATAGCTGTCTGGTGAACAAAGA
ZC3H3	CCTTCCCCTCATCTCTACCC	CCTTGTACAGAACCCCTCCA
SRSF6	GATGGCTACAGCTACGGAAG	CTTTAAGTCTTGCCAACTGCAAC
Col1a1	GTGCCACTCTGACTGGAAGA	CTGACCTGTCTCCATGTTGC
Col3a1	CACCCTTCTTCATCCCACTC	ATGTCATCGCAAAGGACAGA
LOX	GCTGCGGAAGAAAACTGC	CCTTGGTTCTTCACTCTTTGC
Birc5	TTTTTCTGCTTTAAGGAATTGGA	CTCTGTCTGTCCAGTTTCAAGA
SNORA33	GCCAGCCAATTAATCTGCTTAT	TAGCCACTTTCAGGGACCTT
KCNQ1	ACGGGTTGGAAGTGTTTCGT	AGAGCGGCATACTGCTCAAT
KCNA4	TGGAAAAGGGGAAACAAATC	GTTCCAGCAGAGGCAAACTC
KCNH2	GAGATCCTGCGGGGTGAT	CACATCCCCATTGGACTTTC
KCNJ11	CCTGAGGAATATGTGCTGACC	AGTGTGTGGCCATTTGAGGT
KCNJ2	TGTAATCCCCACTTCCACTCC	TATTTATTAATGAGGAGAGATGGATGC
KCNB1	CTGGAGAAGCCCAACTCATC	GGCTCTGTAGCTCAGGCAGT
KCNJ8	AGGCACCATGGAGAAGAGTG	AAAACCGTGATGGCCAGA
Periostin	AACGTCTGTGCCCTCCAG	AGCCTTTCATCCCTTCCATT
Fibronectin1	AATCGTGCAGCCTCAATCC	GGCTTGCTCTCGCAGTTAAA

Online Table II. Loss of SRSF4 leads to Left Ventricular hypertrophy. Echocardiography analysis of control and SRSF4 KO mice at different ages. Data are presented as mean values ±SEM. LVWT, left ventricular wall thickness; LVEF, left ventricular ejection fraction; LVVOLd, left ventricular end diastolic volume; IVRT, isovolumetric relaxation time. *p<0.05, **p<0.01, ***p<0.001 for SRSF4 KO vs Control; 2-way ANOVA followed by the Bonferroni post-test.

	6 months		10 months		14 months	
	Control	**SRSF4 KO**	**Control**	**SRSF4 KO**	**Control**	**SRSF4 KO**
n	6	10	8	10	5	9
LVWT (mm)	1.15±0.04	1.35±0.05	1.13±0.05	1.41±0.06**	1.07±0.07	1.38±0.05**
LV Mass	83.44±4.2	110.01±8.97	84.85±7.31	125.6±10.98*	81.14±9.17	123.1±6.53**
Normalized Cardiac Mass	2.55±0.09	3.39±0.20	2.94±0.16	3.88±0.28**	2.85±0.22	4.46±0.28***
LVEF (%)	54.97±2.01	53.44±2.83	55.26±2.22	50.86±5.12	54.46±2.23	57.21±1.94
LVVOLd (µl)	67.20±2.97	67.14±2.91	55.72±3.32	61.36±3.01	61.73±2.87	67.64±3.37
Body Weight (BW) g	32.48±0.43	30.67±3.70	27.30±1.67	33.02±5.46	30.66±2.32	28.87±1.87
Heart Weight (HW) mg	162±5.83	176.67±12.02	136.47±8.82	207.50±24.96**	148.33±3.07	179.56±5.88*
HW/BW ratio	4.98±0.12	5.82±0.28	5.01±0.34	6.45±0.51*	4.94±0.29	6.33±0.26**
n	6	6	6	6	6	6
IVRT (ms)	10.83±0.80	11.52±1.38	13.13±0.46	14.67±0.34	13.65±0.65	17.53±1.01*

Online Table III (see online dataset). Differential gene expression analysis using RSEM indexed by gene id with the corresponding associated gene symbol. "AvrExp" is the estimated average expression in the whole experiment. “Ave_SRSF4_KO” is the average expression of the SRSF4 KO mice and “Ave_Control” of the control mice. “foldChange” represents the expression fold change in the KO compared with control and “logFC” its log_2 transformation. “P.Value” and “adj.P.Val” represent the p-value and multiple test adjusted p-value for the differences between the two conditions.

Online Table IV (see online dataset). Results of differential splicing analysis using vast-tools. "EVENT": Vast-tools event id. "SRSF4-KO_PSI": estimated percent spliced in (PSI) in the SRSF4 cardiac-specific KO mice. “COORD” represents coordinates of the AS event as annotated by vast-tools in mm9 reference genome. “GENE” Gene symbol of the gene in which the event is located. "Control_PSI", PSI in the control mice. "dPSI", estimated difference in PSI between Control and SRSF4 KO mice. "P(|dPSI| > x)>0.95", difference in inclusion rate for which there is a 95% probability that the real absolute differences between genotypes is higher than that value. Values higher than 0 represent significantly changed events.

Online Table V (see online dataset). mRNAs with iCLIP binding sites. iCLIP peaks in exons, coding sequence (CDS) and introns were identified for those genes that showed differential expression. “1” represents SRSF4 binding to that region in the gene, whereas “0” means there were no SRSF4 peaks identified in that region.

Online Table VI. Genes that are differentially expressed in SRSF4 KO cardiomyocytes and are also direct targets of SRSF4.

ID Ensembl	Gene
ENSMUSG00000001870	Ltbp1
ENSMUSG00000003228	Grk5
ENSMUSG00000011256	Adam19
ENSMUSG00000016921	Srsf6
ENSMUSG00000017692	Rhbdl3
ENSMUSG00000019848	Popdc3
ENSMUSG00000020646	Mboat2
ENSMUSG00000021219	Rgs6
ENSMUSG00000022111	Uchl3
ENSMUSG00000022587	Ly6e
ENSMUSG00000023067	Cdkn1a
ENSMUSG00000024072	Yipf4
ENSMUSG00000024780	Cdc37l1
ENSMUSG00000025579	Gaa
ENSMUSG00000026131	Dst
ENSMUSG00000026483	Fam129a
ENSMUSG00000026520	Pycr2
ENSMUSG00000026610	Esrrg
ENSMUSG00000026944	Abca2
ENSMUSG00000027381	Bcl2l11
ENSMUSG00000028911	Srsf4
ENSMUSG00000031636	Pdlim3
ENSMUSG00000037270	4932438A13Rik
ENSMUSG00000037940	Inpp4b
ENSMUSG00000038335	Tsr1
ENSMUSG00000039958	Mettl20
ENSMUSG00000042719	Naa25
ENSMUSG00000043445	Pgp
ENSMUSG00000050565	Tor1aip2
ENSMUSG00000051451	Crebzf
ENSMUSG00000053332	**GAS5**
ENSMUSG00000053886	Sh2d4a
ENSMUSG00000054752	Fsd1l
ENSMUSG00000059895	Ptp4a3
ENSMUSG00000060913	Trim55
ENSMUSG00000061589	Dot1l
ENSMUSG00000062210	Tnfaip8
ENSMUSG00000064302	Clasp1
ENSMUSG00000066232	Ipo7
ENSMUSG00000070509	Rgma
ENSMUSG00000073409	H2-Q6
ENSMUSG00000074221	Zfp568