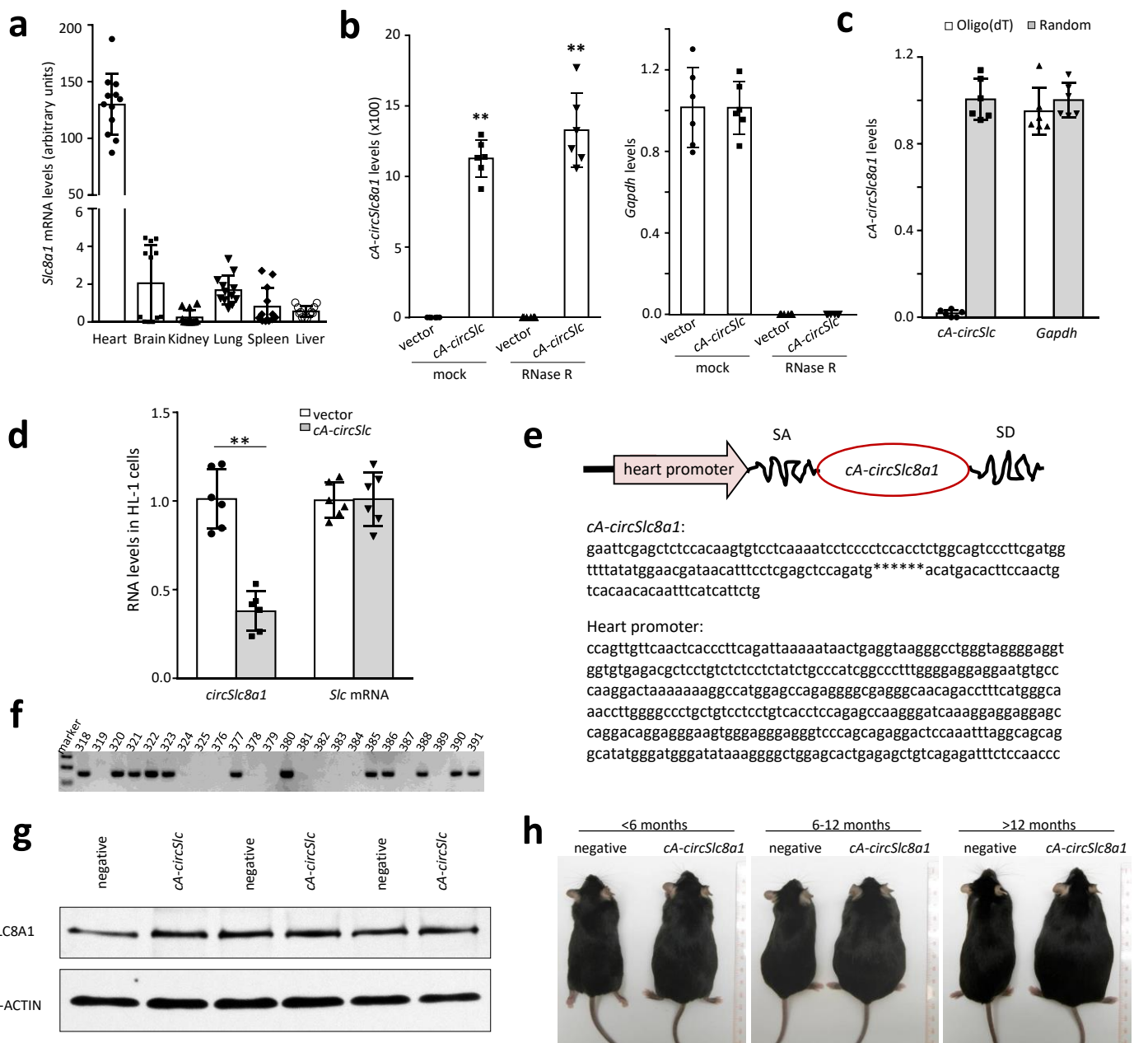


**Supplemental Information**

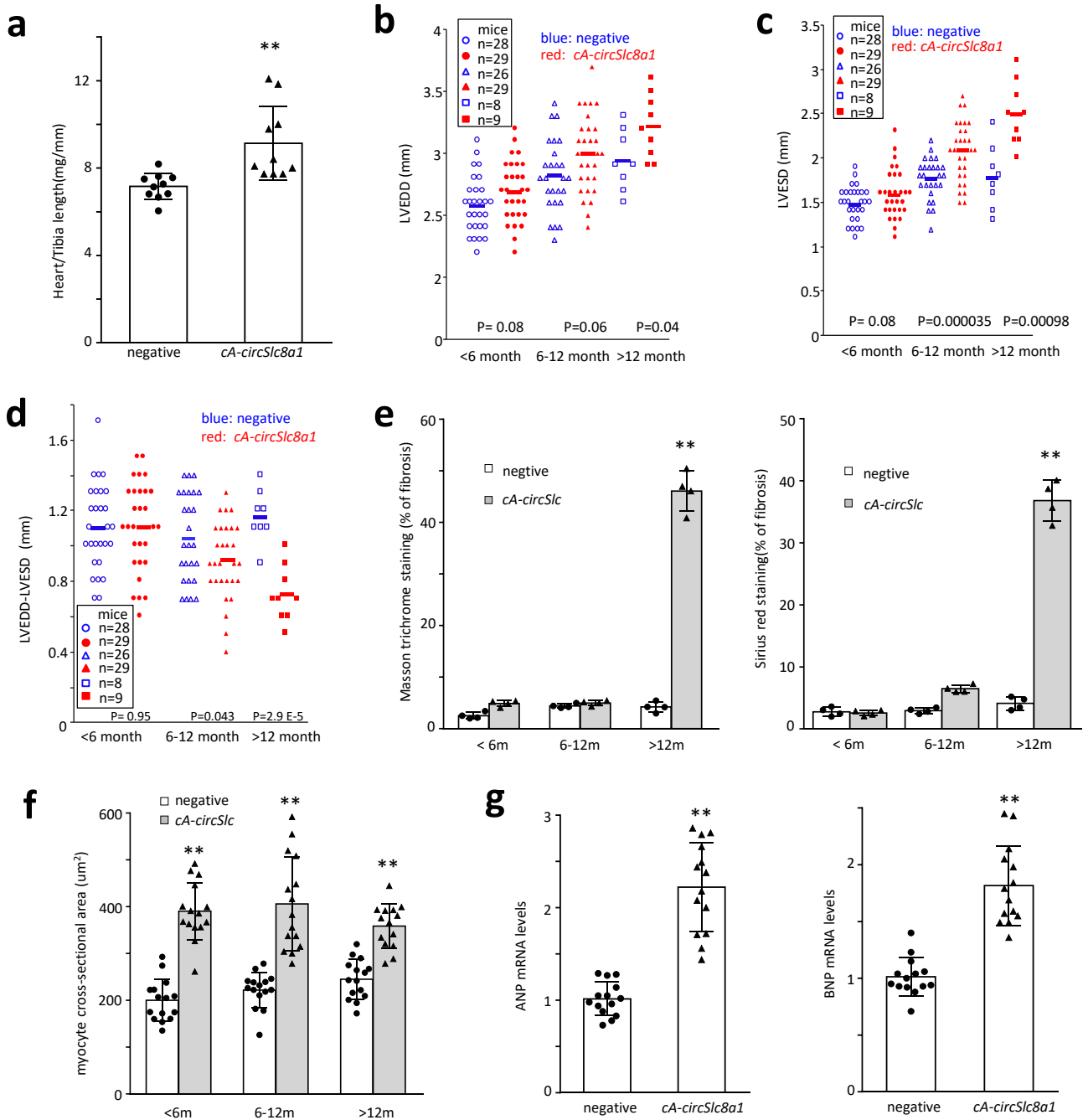
**Silencing mouse circular RNA *circSlc8a1*  
by circular antisense *cA-circSlc8a1* induces  
cardiac hepatopathy**

**Nan Wu, Feiya Li, Weining Yang, William W. Du, Faryal Mehwish Awan, Chao Zhang, Juanjuan Lyu, Sema Misir, Kaixuan Zeng, Esra Eshaghi, and Burton B. Yang**



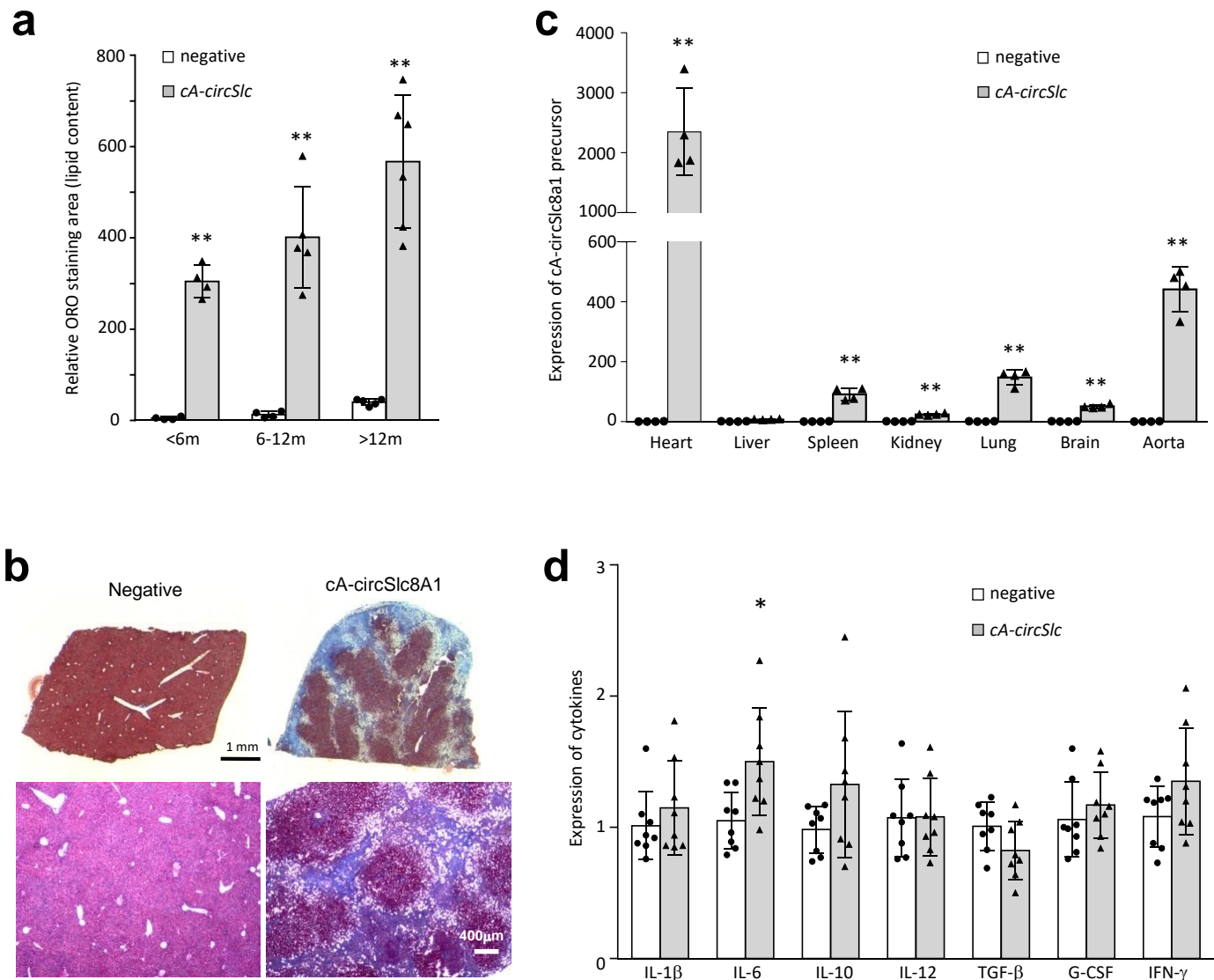
**Supplementary Fig. S1. Generation of *circSlc8a1* knockdown mice by using circular antisense-*circSlc8a1* (*cA-circSlc8a1* or *cA-circSlc*) expression construct**

- (a) The expression levels of linear *Slc8a1* mRNA in different organs. n=12
- (b) The *cA-circSlc8a1* construct was transfected into human HEK293T cells. The expression of *cA-circSlc8a1* (left) and *Slc8a1* mRNA (right) with or without RNase R treatment were determined by using mouse specific primers. n=6, \*\*<0.01 vs vector control.
- (c) The *cA-circSlc8a1* construct was transfected into human HEK293T cells. The RNAs from vector or *cA-circSlc8a1* transfected cells were reverse transcribed using random or oligo(dT) primers followed by qPCR using mouse specific primers. n=6, \*\*<0.01 vs vector control.
- (d) The levels of unbound *circSlc8a1* and *Slc8a1* mRNA in HL-1 cells transfected with *cA-circSlc8a1*. n=6, \*\*<0.01 vs vector control.
- (e) The construct were used to generate *cA-circSlc8a1* transgenic mice. The 5' and 3' sequences of *cA-circSlc8a1* and the heart promoter sequence are shown.
- (f) Genotyping that validated the establishment of *cA-circSLC8A1* (+) transgenic mice.
- (g) The levels of the SLC8A1 protein in the heart of *cA-circSlc8a1* transgenic mice.
- (h) Representative photographs of *cA-circSlc8a1* (+) transgenic mice compared to the age-matched negative mice.



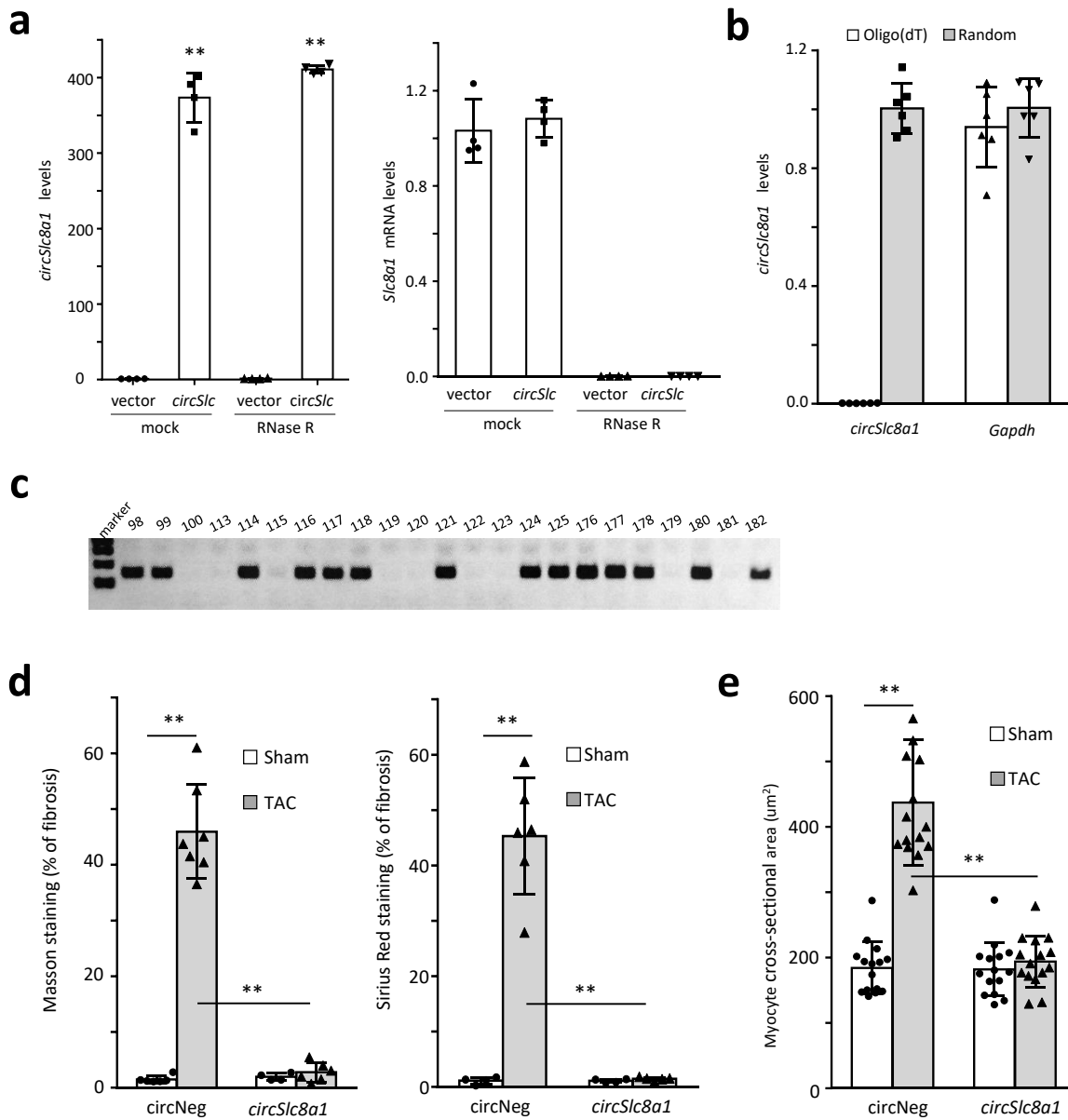
**Supplementary Fig. S2. Analysis of heart function and fibrosis in the *cA-circSlc8a1* transgenic mice.**

- (a) The heart/tibia length ratio of *cA-circSlc8a1*(+) mice was significantly higher compared to litter match negative mice. n=10, \*\* p<0.01 vs negative.
- (b) Echocardiography of *cA-circSlc8a1*(+) mice showed elevated left ventricular end-diastolic diameter (LVEDD) compared to litter match negative mice.
- (c) Echocardiography of *cA-circSlc8a1*(+) mice showed elevated left ventricular end-systolic dimension (LVESD) compared to litter match negative mice.
- (d) Echocardiography of *cA-circSlc8a1*(+) mice showed reduced LVEDD-LVESD compared to litter match negative mice.
- (e) Quantification of fibrosis area observed by Masson trichrome staining (left), Sirius red staining (right). n=4, \*\* p<0.01 vs negative.
- (f) Quantification of cross-section area of cardiomyocytes by WGA staining. n=15, \*\* p<0.01 vs negative.
- (g) RNAs isolated from heart tissues of mice aged 6-12 month old were subjected to real-time qPCR to measure levels of ANP (left) and BNP (right). n=14, \*\* p<0.01.



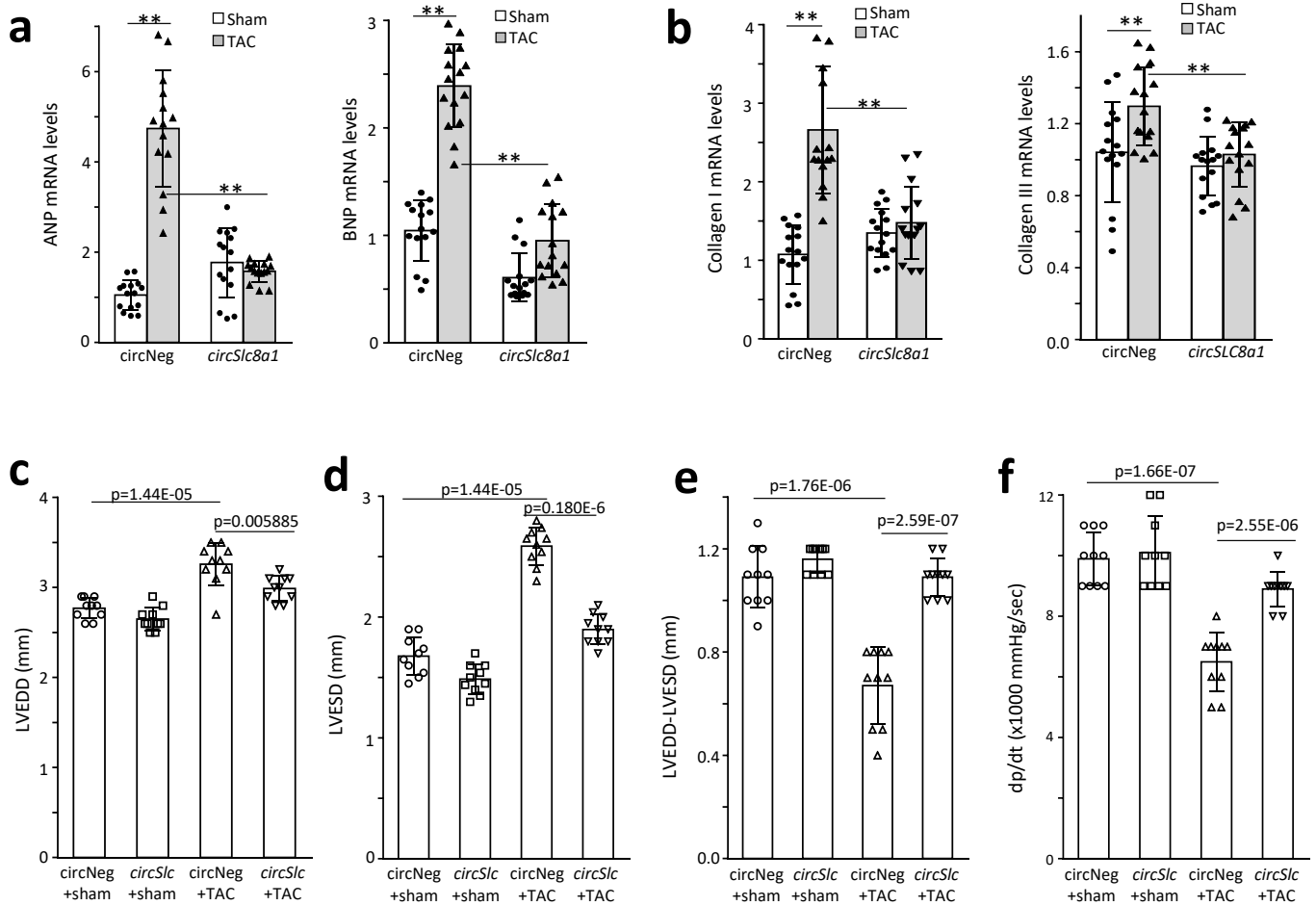
**Supplementary Fig. S3. Transgenic mice with heart-specific expression of *cA-circSlc8a1* develop hepatic steatosis.**

- (a) Quantification of lipid content observed by Oil-Red-O staining. n=6, \*\* p<0.01 vs negative.
- (b) Hepatic fibrosis/cirrhosis was developed in some of the *cA-circSlc8a1* mice (2 out of 14) at late stage, which examined by Masson trichrome staining.
- (c) The expression of *cA-circSlc8a1* precursor in different organs. n=4, \*\* p<0.01 vs negative.
- (d) The levels of cytokines measured by real-time PCR. \* p<0.05 vs negative



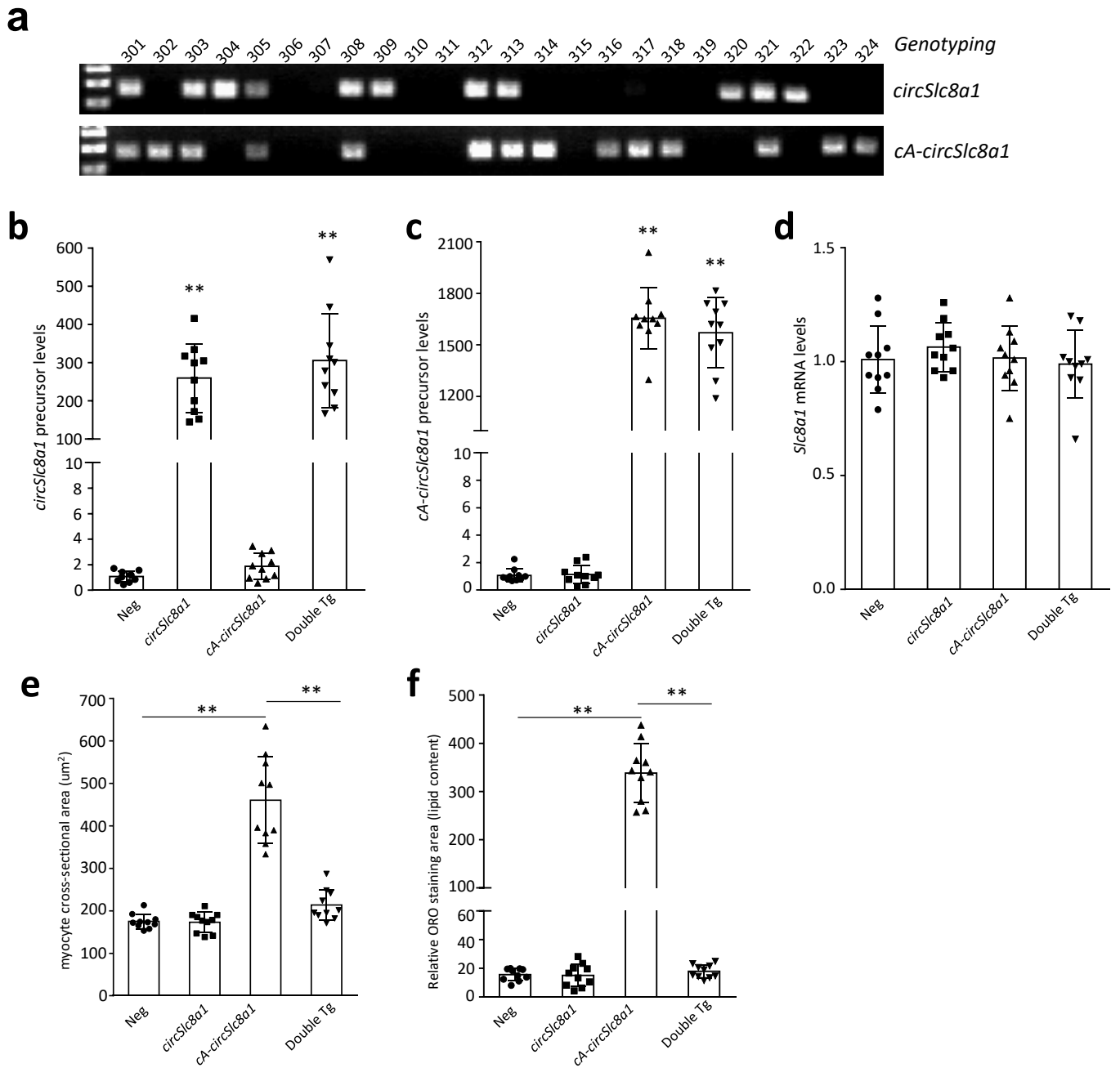
**Supplementary Fig. S4. Generation of *circSlc8a1* transgenic mice and validation of the cardiac protective effects of *circSlc8a1*.**

- (a) The *circSlc8a1* constructs were transfected into human cell line HEK293T. The levels of *circSlc8a1* (left) and *Slc8a1* mRNA (right) with or without RNase R treatment were determined by using mouse specific primers respectively. n=4, \*\*<0.01 vs vector control.
- (b) The *circSlc8a1* constructs were transfected into human cell line HEK293T. The RNA were reverse transcribed by using random or oligo(dT) primers. The levels of *circSlc8a1* were determined by using mouse specific primers. n=6, \*\*<0.01 vs vector control.
- (c) Genotyping that validated the establishment of *circSlc8a1* (+) transgenic mice.
- (d) Quantification of fibrosis area observed by Masson trichrome staining (left) and Sirius red staining (right). n=6, \*\* p<0.01
- (e) Quantification of cross-section area of cardiomyocytes by WGA staining. n=15, \*\* p<0.01



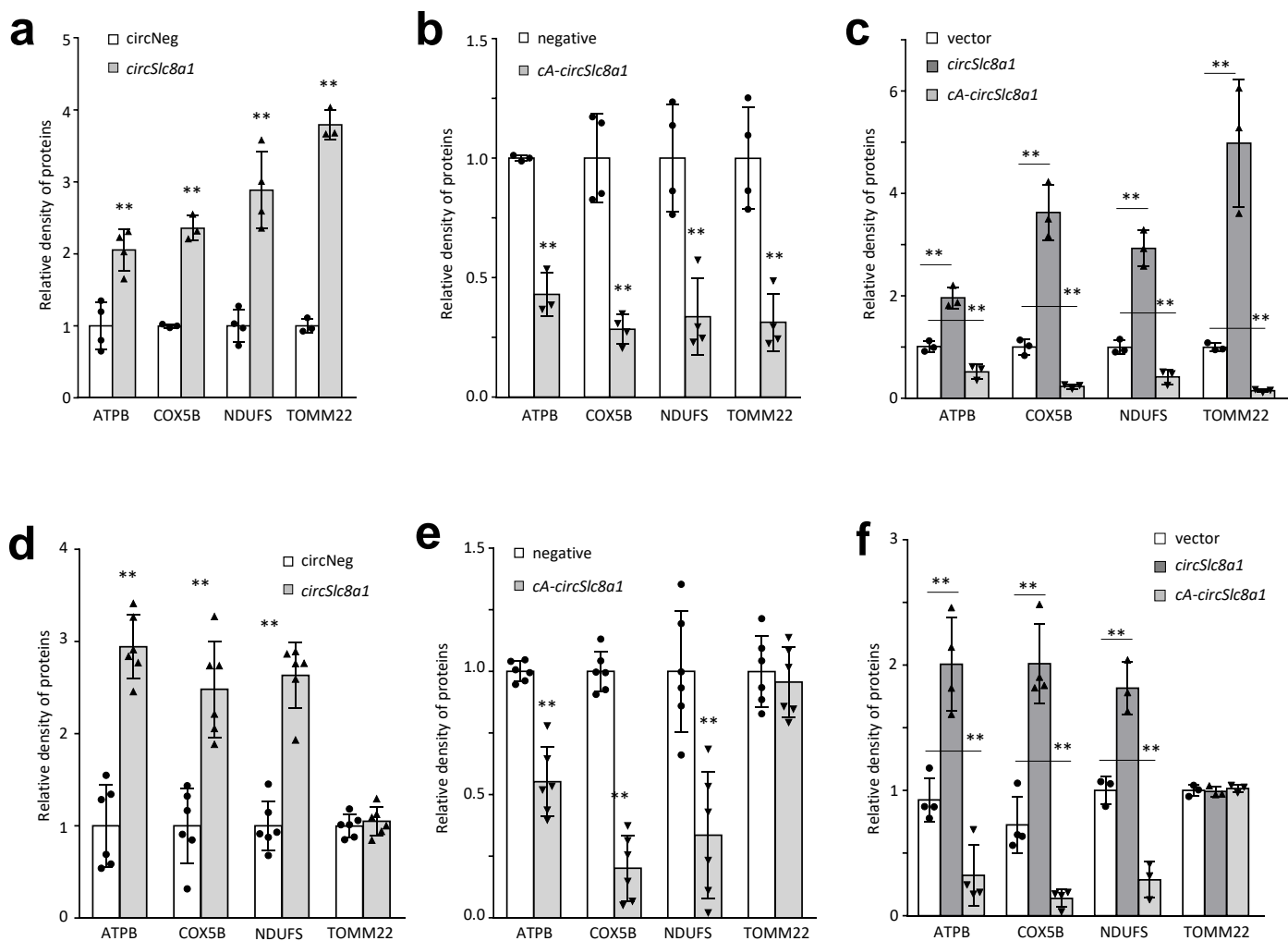
**Supplementary Fig. S5. The *circSlc8a1* protect the heart from cardiac hypertrophy, cardiac fibrosis and impaired heart function.**

- (a) The levels of heart failure markers ANP (left) and BNP (right) were remarkably increased in the heart of negative mice by TAC surgery, while were significantly lower in the *circSlc8a1* (+) mice compared to the litter match negative mice after TAC surgery. n=15, \*\* p<0.01.
- (b) The levels of cardiac fibrosis markers collagen-I (left) and collagen-III (right) were remarkably increased in the heart of negative mice by TAC surgery, while were significantly lower in the *circSlc8a1*-transgenic mice compared to the litter match negative mice after TAC surgery. n=15, \*\* p<0.01.
- (c-f) The *circSlc8a1*(+) mice subjected to TAC prevented the impair of heart function that validated by (c) LVEDD, (d) LVESD, (e) LVEDD-LVESD, and (f) left ventricular pressure (dp/dt). n=10



**Supplementary Fig. S6. Generation of double transgenic mice with ectopic expression of both *circSlc8a1* and *cA-circSlc8a1*.**

- (a) Genotyping that validated the establishment of *circSlc8a1* (+) transgenic mice.
- (b) The expression levels of *circSlc8a1* precursor in negative (Neg), *circSlc8a1* (+) transgenic mice, *cA-circSlc8a1* (+) transgenic mice, or double transgenic mice. n=10, \*\*<0.01 vs negative mice.
- (c) The expression levels of *cA-circSlc8a1* precursor in negative (Neg), *circSlc8a1* (+) transgenic mice, *cA-circSlc8a1* (+) transgenic mice, or double transgenic mice. n=10, \*\*<0.01 vs negative mice.
- (d) The expression levels of *Slc8a1* mRNA in negative (Neg), *circSlc8a1* (+) transgenic mice, *cA-circSlc8a1* (+) transgenic mice, or double transgenic mice. n=10
- (e) Quantification of cross-section area of cardiomyocytes by WGA staining. n=10, \*\* p<0.01
- (f) Quantification of lipid content observed by Oil Red O. n=10, \*\* p<0.01

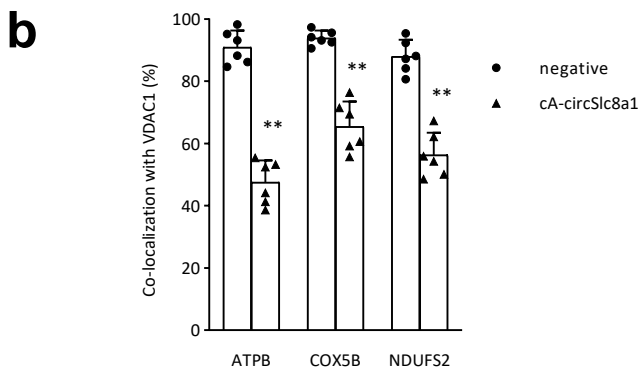
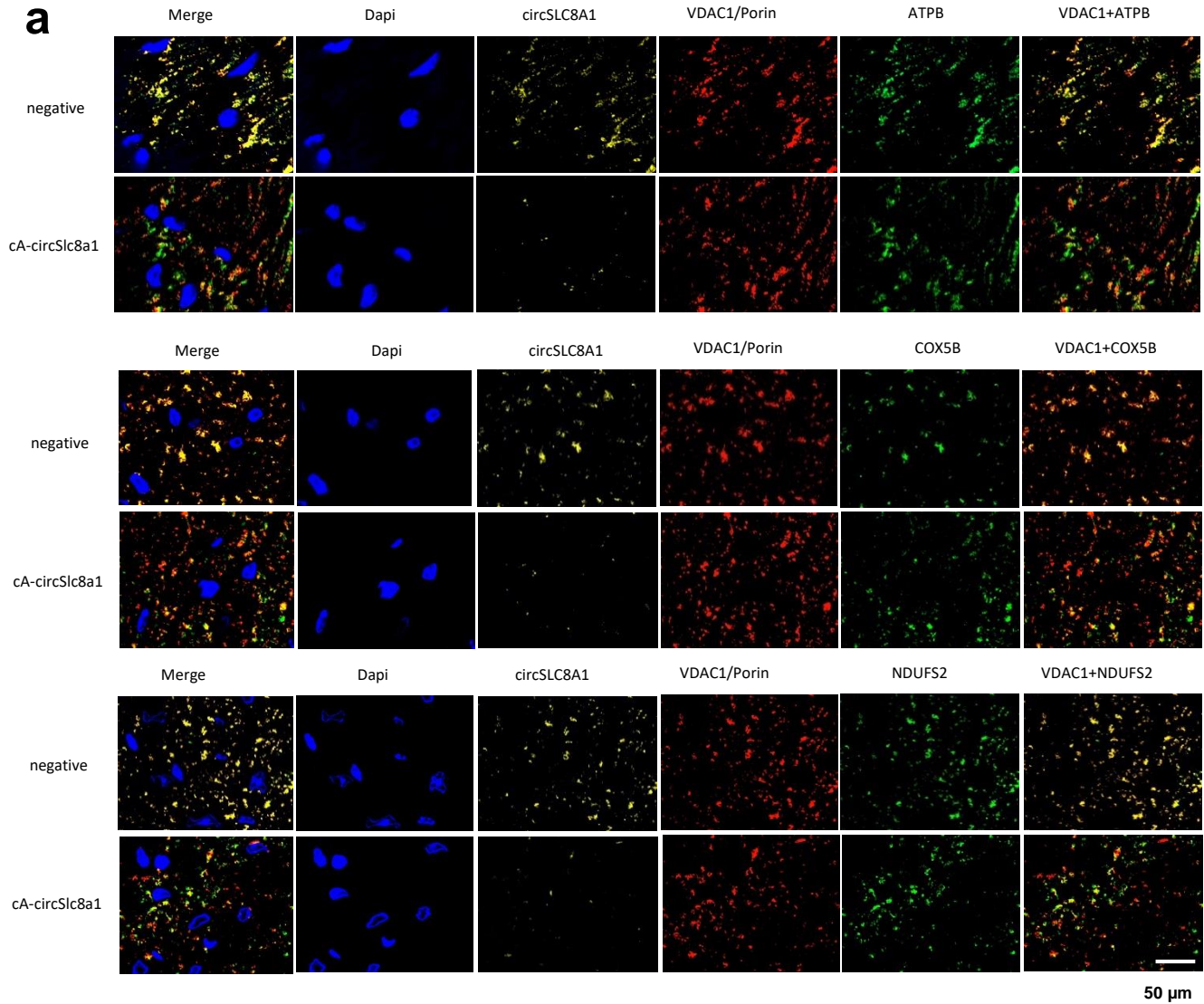


**Supplementary Fig. S7. The *circSlc8a1* protected heart function via binding with mitochondrial proteins.**

(a-c) The density of the bands in Western blot images presented in Fig.7a-c regarding the *circSlc8a1* pull down proteins was analysis. \*\*  $p < 0.01$ ,  $n = 3-4$

(d-f) The density of the bands in Western blot images presented in Fig.7d-f regarding the mitochondrial translocation of proteins was analysis. \*\*  $p < 0.01$ ,  $n = 4-6$





**Supplementary Fig. S8. Co-localization of *circSlc8a1* with ATPB, COX5B, and NDUFS2.**

Fig (a) In situ hybridization of *circSlc8a1* and immunofluorescence staining of ATPB, COX5B, and NDUFS2 in the *cA-circSlc8a1* transgenic and litter-matched negative mice. Representative photographs show co-localization of *circSlc8a1* with these mitochondrial proteins. (b) Quantitation of the staining. \*\*,  $p < 0.01$ .

**Supplementary Table 1: Protein identified by mass spectrometry analysis**

#	Identified Proteins (750)	Accession Number		Molecular Weight		circular dichroism (CD)	Fold change
		Number	ID	Weight	circNeg		
1	ATP synthase subunit beta, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Atp5f1b PE=1 SV=2	PE6480	Atp5f1b	56 kDa	662.99	1,208.20	1.82
2	ATP synthase subunit alpha, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Atp5f1a PE=1 SV=1	Q30265	Atp5f1a	60 kDa	284.4	494.04	1.74
3	Methylcrotonyl-CoA carboxylase beta chain, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Mccc2 PE=1 SV=1	Q3ULD5	Mccc2	61 kDa	204.99	284.7	1.39
4	NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Ndufs1 PE=1 SV=2	Q91VD9	Ndufs1	80 kDa	164.36	261.97	1.59
5	ATP synthase coupling factor 6, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Atp5pd PE=1 SV=3	Q9DCX2	Atp5pd	19 kDa	83.105	131.56	1.58
6	ATP synthase subunit c, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Atp5pc PE=1 SV=1	P97450	Atp5pc	12 kDa	57.25	117.23	2.05
7	NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Ndufv1 PE=1 SV=1	Q91Y70	Ndufv1	51 kDa	72.948	117.23	1.61
8	Alpha-actinin-2 OS=Mus musculus (Mouse) OX=10090 GN=Actr2 PE=1 SV=2	Q9J191	Actr2	104 kDa	87.722	114.84	1.31
9	Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Sdhb PE=1 SV=1	Q8J821	Sdhb	73 kDa	65.561	96.894	1.48
10	NADH dehydrogenase [ubiquinone] iron-sulfur protein 2, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Ndufs2 PE=1 SV=1	Q91WD5	Ndufs2	53 kDa	45.246	95.698	2.12
11	Trifunctional enzyme subunit alpha, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Hadha PE=1 SV=1	Q8BMS1	Hadha	83 kDa	30.472	92.109	3.02
12	Propionyl-CoA carboxylase alpha chain, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Pcca PE=1 SV=2	Q91ZA3	Pcca	80 kDa	55.403	88.521	1.60
13	Caveolae-associated protein 2 OS=Mus musculus (Mouse) OX=10090 GN=Cavin2 PE=1 SV=3	Q63918	Cavin2	47 kDa	63.714	86.128	1.35
14	NADH dehydrogenase [ubiquinone] iron-sulfur protein 3, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Ndufs3 PE=1 SV=2	Q9DCT2	Ndufs3	30 kDa	42.476	71.774	1.69
15	ATP synthase subunit delta, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Atp5fd PE=1 SV=1	Q9D3D9	Atp5fd	18 kDa	39.706	70.577	1.78
16	NADH dehydrogenase [ubiquinone] flavoprotein 2, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Ndufv2 PE=1 SV=2	Q9DGJ6	Ndufv2	27 kDa	48.016	69.381	1.44
17	IF rod domain-containing protein OS=Mus musculus (Mouse) OX=10090 GN=Krf83 PE=1 SV=1	ESQYI9	Krf83	53 kDa	0	52.634	1.50
18	NADH dehydrogenase [ubiquinone] iron-sulfur protein 6, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Ndufs6 PE=1 SV=2	P52503	Ndufs6	13 kDa	35.089	56.634	2.86
19	Trifunctional enzyme subunit beta, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Hadhb PE=1 SV=1	Q98JY0	Hadhb	51 kDa	17.544	50.241	2.86
20	ATP synthase subunit O, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Atp5po PE=1 SV=1	Q9DBE20	Atp5po	23 kDa	30.472	49.045	1.61
21	Alpha-crystallin B chain OS=Mus musculus (Mouse) OX=10090 GN=Cryab PE=1 SV=2	P23927	Cryab	20 kDa	30.472	47.849	1.57
22	Ceatalmer subunit epsilon OS=Mus musculus (Mouse) OX=10090 GN=Cope PE=1 SV=3	Q89079	Cope	35 kDa	22.161	46.653	2.11
23	NADH dehydrogenase [ubiquinone] iron-sulfur protein 5, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Ndufs5 PE=1 SV=1	Q8K3J1	Ndufs5	24 kDa	29.549	46.653	1.58
24	Methylcrotonyl-CoA carboxylase subunit alpha, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Mccc1 PE=1 SV=2	Q99MR8	Mccc1	79 kDa	30.472	46.653	1.53
25	Lipoamide acyltransferase component of branched-chain alpha-keto acid dehydrogenase complex, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Dbt PE=1 SV=3	P53395	Dbt	53 kDa	31.395	43.064	1.37
26	Casein kinase II subunit beta OS=Mus musculus (Mouse) OX=10090 GN=Csk2b PE=1 SV=1	P67871	Csk2b	25 kDa	24.932	39.475	1.58
27	Cytochrome c oxidase subunit 5B, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Cox5b PE=1 SV=1	P19536	Cox5b	14 kDa	17.544	38.279	2.18
28	Casein kinase II subunit alpha OS=Mus musculus (Mouse) OX=10090 GN=Csk2a1 PE=1 SV=2	Q60737	Csk2a1	45 kDa	21.238	38.279	1.80
29	Serine beta-lactamase-like protein LACTB, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Lactb PE=1 SV=1	Q8EP89	Lactb	61 kDa	19.391	28.709	1.48
30	Histone H4 OS=Mus musculus (Mouse) OX=10090 GN=H4f16 PE=1 SV=2	P62806	H4f16	11 kDa	19.391	27.513	1.42
31	ATP synthase subunit gamma, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Atp5f1c PE=1 SV=1	Q91VR2	Atp5f1c	33 kDa	17.544	25.121	1.43
32	Transcriptional activator protein Pur-alpha OS=Mus musculus (Mouse) OX=10090 GN=Pura PE=1 SV=1	P42869	Pura	35 kDa	10.157	22.728	2.24
33	RNA-binding motif protein, X chromosome OS=Mus musculus (Mouse) OX=10090 GN=RbmX PE=1 SV=1	Q9WV02	RbmX	14.774	14.774	21.532	1.46
34	2-oxoisovalerate dehydrogenase subunit alpha, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Bckdha PE=1 SV=1	P50136	Bckdha	50 kDa	16.621	21.532	1.30
35	Pentatricopeptide repeat domain-containing protein 3, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Ptcp3 PE=1 SV=2	Q14C51	Ptcp3	78 kDa	16.621	21.532	1.30
36	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 5 OS=Mus musculus (Mouse) OX=10090 GN=Ndufa5 PE=1 SV=3	Q9CYP6	Ndufa5	13 kDa	12.927	20.336	1.57
37	Adenylylate kinase isoenzyme 1 OS=Mus musculus (Mouse) OX=10090 GN=Ak1 PE=1 SV=1	Q9ROY5	Ak1	22 kDa	12.927	19.14	1.48
38	28S ribosomal protein S22, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Mps22 PE=1 SV=1	Q8CXW2	Mps22	41 kDa	14.774	19.14	1.30
39	Acy-CoA dehydrogenase family member 10 OS=Mus musculus (Mouse) OX=10090 GN=Acad10 PE=1 SV=1	ESQ0F0	Acad10	119 kDa	0	16.747	1.68
40	IF rod domain-containing protein OS=Mus musculus (Mouse) OX=10090 GN=Krt78 PE=1 SV=1	Q9JHE7	Krt78	112 kDa	9.2339	15.551	1.68
41	Protein TSSC4 OS=Mus musculus (Mouse) OX=10090 GN=Tssc4 PE=1 SV=1	Q9JHE7	Tssc4	34 kDa	9.2339	15.551	1.68
42	Hemoglobin subunit alpha OS=Mus musculus (Mouse) OX=10090 GN=Hba PE=1 SV=2	P01942	Hba	15 kDa	12.004	14.355	1.73
43	(E3-independent) E2 ubiquitin-conjugating enzyme UBE2O OS=Mus musculus (Mouse) OX=10090 GN=Ube2o PE=1 SV=3	Q6ZPL3	Ube2o	141 kDa	8.3105	14.355	1.55
44	Peroxisomal protein 22 OS=Mus musculus (Mouse) OX=10090 GN=Pdx1 PE=1 SV=1	P35700	Pdx1	22 kDa	9.2339	14.355	1.55
45	60S acidic ribosomal protein P2 OS=Mus musculus (Mouse) OX=10090 GN=Rplp2 PE=1 SV=3	P99027	Rplp2	12 kDa	10.157	14.355	1.41
46	Transcriptional activator protein Pur-beta OS=Mus musculus (Mouse) OX=10090 GN=Purb PE=1 SV=3	Q35295	Purb	34 kDa	9.2339	13.158	1.42
47	Calmodulin-1 OS=Mus musculus (Mouse) OX=10090 GN=Calm1 PE=1 SV=1	P0DP26	Calm1	17 kDa	5.5403	11.962	2.16
48	Cytochrome b-c1 complex subunit 6, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Uqcrcf PE=1 SV=2	P98028	Uqcrcf	10 kDa	5.5403	11.962	2.16
49	Histone H2B type 1-F/JL OS=Mus musculus (Mouse) OX=10090 GN=H2bc7 PE=1 SV=2	P10653	H2bc7	14 kDa	6.4637	11.962	1.85
50	cAMP-dependent protein kinase type II-alpha regulatory subunit OS=Mus musculus (Mouse) OX=10090 GN=Pkr2a PE=1 SV=2	P12367	Pkr2a	45 kDa	5.5403	10.766	1.94
51	AP-3 complex subunit sigma-2 OS=Mus musculus (Mouse) OX=10090 GN=Ap3s2 PE=1 SV=1	Q8BSZ2	Ap3s2	22 kDa	7.3871	10.766	1.46
52	Elongation factor 1-alpha 2 OS=Mus musculus (Mouse) OX=10090 GN=Eef1a2 PE=1 SV=1	P62631	Eef1a2	50 kDa	7.3871	10.766	1.46
53	Small nuclear ribonucleoprotein Sm D2 OS=Mus musculus (Mouse) OX=10090 GN=Snrdp2 PE=1 SV=1	P62317	Snrdp2	14 kDa	8.3105	10.766	1.30
54	Enhancer of rudimentary homolog OS=Mus musculus (Mouse) OX=10090 GN=Erh PE=1 SV=1	P84089	Erh	12 kDa	5.5403	9.5698	1.73
55	14-3-3 protein gamma OS=Mus musculus (Mouse) OX=10090 GN=Ywhag PE=1 SV=2	PE1982	Ywhag	28 kDa	6.4637	9.5698	1.48
56	Beta-enolase OS=Mus musculus (Mouse) OX=10090 GN=Eno3 PE=1 SV=3	P21550	Eno3	47 kDa	6.4637	9.5698	1.48
57	Junctophilin-2 OS=Mus musculus (Mouse) OX=10090 GN=Jph2 PE=1 SV=2	Q8ET78	Jph2	75 kDa	6.4637	9.5698	1.48
58	Ribosome-binding protein 1 OS=Mus musculus (Mouse) OX=10090 GN=Rtbp1 PE=1 SV=2	Q99PL5	Rtbp1	173 kDa	6.4637	9.5698	1.48
59	Serine/threonine-protein phosphatase 2A catalytic subunit alpha isoform OS=Mus musculus (Mouse) OX=10090 GN=Ppp2ca PE=1 SV=1	P63330	Ppp2ca	36 kDa	7.3871	9.5698	1.48
60	Huntingtin-interacting protein K OS=Mus musculus (Mouse) OX=10090 GN=Hypk PE=1 SV=2	Q9CR41	Hypk	15 kDa	6.4637	9.5698	1.30
61	Complement C1q and tumor necrosis factor-related protein 9 OS=Mus musculus (Mouse) OX=10090 GN=C1qtnf9 PE=1 SV=1	Q4ZJN1	C1qtnf9	35 kDa	3.6936	8.3736	2.27
62	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 11, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Ndufb11 PE=1 SV=2	Q09111	Ndufb11	17 kDa	5.5403	8.3736	1.51
63	2-oxoisovalerate dehydrogenase subunit beta, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Bckdhb PE=1 SV=2	Q6P3A8	Bckdhb	43 kDa	6.4637	8.3736	1.30



Supplementary Table 1 (continued): Protein identified by mass spectrometry analysis

#	Identified Proteins (750)	Accession Number	ID	Molecular Weight	circNeg	circSLC8A1	Fold change
64	ATP synthase subunit epsilon, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Atp5f1e PE=1 SV=2	P56382	Atp5f1e	6 kDa	6.4637	8.3736	1.30
65	Thioredoxin-dependent peroxidase reductase, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Prdx3 PE=1 SV=1	P20108	Prdx3	28 kDa	6.4637	8.3736	1.30
66	Poly(U)-binding splicing factor PUF60 OS=Mus musculus (Mouse) OX=10090 GN=Puif60 PE=1 SV=2	Q3UEB3	Puif60	60 kDa	2.7702	7.1774	2.59
67	AP-2 complex subunit sigma OS=Mus musculus (Mouse) OX=10090 GN=Ap2s1 PE=1 SV=1	P82743	Ap2s1	17 kDa	3.6936	7.1774	1.94
68	Protein NDRG2 OS=Mus musculus (Mouse) OX=10090 GN=Ndrp2 PE=1 SV=1	Q9QYG0	Ndrp2	41 kDa	3.6936	7.1774	1.94
69	Serine/arginine-rich splicing factor 7 OS=Mus musculus (Mouse) OX=10090 GN=Srsf7 PE=1 SV=1	Q8BL97	Srsf7	31 kDa	3.6936	7.1774	1.94
70	Pre-mRNA-processing factor 40 homolog A OS=Mus musculus (Mouse) OX=10090 GN=Prip40a PE=1 SV=1	Q8R1C7	Prip40a	108 kDa	4.617	7.1774	1.55
71	Sorbin and SH3 domain-containing protein 2 OS=Mus musculus (Mouse) OX=10090 GN=Sorts2 PE=1 SV=2	Q3UT12	Sorts2	132 kDa	4.617	7.1774	1.55
72	Transketolase pyruvate domain-containing protein OS=Mus musculus (Mouse) OX=10090 GN=Ogthl PE=1 SV=1	EQ7L70	Ogthl	117 kDa	4.617	7.1774	1.55
73	Glutaredoxin-related protein 5, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Girx5 PE=1 SV=2	Q8DY14	Girx5	16 kDa	5.5403	7.1774	1.30
74	Cysteine-rich protein 2 OS=Mus musculus (Mouse) OX=10090 GN=Crip2 PE=1 SV=1	Q8DXT8	Crip2	23 kDa	0	5.9811	
75	Elongation factor 1-beta OS=Mus musculus (Mouse) OX=10090 GN=Eef1b PE=1 SV=5	O70251	Eef1b	25 kDa	1.8468	5.9811	3.24
76	ADP synthase subunit I, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Atp5m1 PE=1 SV=3	P86135	Atp5m1	10 kDa	2.7702	5.9811	2.16
77	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex assembly factor 3 OS=Mus musculus (Mouse) OX=10090 GN=Ndufa3 PE=1 SV=1	Q8JKL4	Ndufa3	21 kDa	2.7702	5.9811	2.16
78	Transformin-2, protein homolog beta OS=Mus musculus (Mouse) OX=10090 GN=Tra2b PE=1 SV=1	P82996	Tra2b	34 kDa	2.7702	5.9811	2.16
79	Lipoprotein lipase OS=Mus musculus (Mouse) OX=10090 GN=Lpl PE=1 SV=3	P11152	Lpl	53 kDa	3.6936	5.9811	1.62
80	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 2 OS=Mus musculus (Mouse) OX=10090 GN=Ndufa2 PE=1 SV=3	Q8CQ75	Ndufa2	11 kDa	4.617	5.9811	1.30
81	Cytochrome c1, heme protein, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Cyc1 PE=1 SV=1	Q8D0M3	Cyc1	35 kDa	0	4.7849	
82	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 9 OS=Mus musculus (Mouse) OX=10090 GN=Ndufb9 PE=1 SV=3	Q8CQJ8	Ndufb9	22 kDa	0	4.7849	2.59
83	Mitochondrial import receptor TOM22 homolog OS=Mus musculus (Mouse) OX=10090 GN=Tom22 PE=1 SV=3	Q8CPO3	Tom22	16 kDa	1.8468	4.7849	2.59
84	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 7 OS=Mus musculus (Mouse) OX=10090 GN=Ndufa7 PE=1 SV=3	Q8Z1P6	Ndufa7	13 kDa	1.8468	4.7849	1.73
85	26S proteasome non-ATPase regulatory subunit 9 OS=Mus musculus (Mouse) OX=10090 GN=Psmd9 PE=1 SV=1	Q8CR00	Psmd9	25 kDa	2.7702	4.7849	1.73
86	HIACA ribonucleoprotein complex subunit 2 OS=Mus musculus (Mouse) OX=10090 GN=Nhp2 PE=1 SV=1	Q8CRB2	Nhp2	17 kDa	2.7702	4.7849	1.73
87	Histone H2A type 2-A OS=Mus musculus (Mouse) OX=10090 GN=H2ah2a2a1 PE=1 SV=3	Q8GSS7	H2ah2a2a1	14 kDa	2.7702	4.7849	1.73
88	Serine/arginine-rich splicing factor 1 OS=Mus musculus (Mouse) OX=10090 GN=Srsf1 PE=1 SV=3	Q8PDM2	Srsf1	28 kDa	2.7702	4.7849	1.73
89	60S acidic ribosomal protein P1 OS=Mus musculus (Mouse) OX=10090 GN=Rplp1 PE=1 SV=1	P47955	Rplp1	11 kDa	3.6936	4.7849	1.30
90	Cytochrome c oxidase subunit 7A1, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Cox7a1 PE=1 SV=1	P86392	Cox7a1	9 kDa	3.6936	4.7849	1.30
91	DNA-directed RNA polymerase I, II, and III subunit RPABC3 OS=Mus musculus (Mouse) OX=10090 GN=Polr2h PE=1 SV=3	P81174	Polr2h	17 kDa	3.6936	4.7849	1.30
92	Long-chain specific acyl-CoA dehydrogenase, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Acadl PE=1 SV=2	Q823G2	Acadl	48 kDa	3.6936	4.7849	1.30
93	Melanin-2 OS=Mus musculus (Mouse) OX=10090 GN=Mx2 PE=1 SV=1	Q88441	Mx2	30 kDa	3.6936	4.7849	1.30
94	Scaffold attachment factor B1 OS=Mus musculus (Mouse) OX=10090 GN=Saifb PE=1 SV=2	D3YX41	Saifb	105 kDa	3.6936	4.7849	1.30
95	Serine/threonine-protein phosphatase 2A, 55 kDa regulatory subunit B alpha isoform OS=Mus musculus (Mouse) OX=10090 GN=Ppp2r2a PE=1 SV=1	Q8P1F6	Ppp2r2a	52 kDa	3.6936	4.7849	1.30
96	Desmoplakin OS=Mus musculus (Mouse) OX=10090 GN=Dsp PE=1 SV=1	E9Q557	Dsp	333 kDa	0	3.5887	
97	Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-1 OS=Mus musculus (Mouse) OX=10090 GN=Gnb1 PE=1 SV=3	P82874	Gnb1	37 kDa	0	3.5887	
98	Kinesin heavy chain isoform 5C OS=Mus musculus (Mouse) OX=10090 GN=Kif5c PE=1 SV=3	P28738	Kif5c	109 kDa	0	3.5887	1.94
99	Chromobox protein homolog 3 OS=Mus musculus (Mouse) OX=10090 GN=Cbx3 PE=1 SV=2	P23198	Cbx3	21 kDa	1.8468	3.5887	1.94
100	Eukaryotic translation initiation factor 3 subunit F OS=Mus musculus (Mouse) OX=10090 GN=Elf3f PE=1 SV=2	Q8DCH4	Elf3f	38 kDa	1.8468	3.5887	1.94
101	KH domain-containing, RNA-binding, signal transduction-associated protein 1 OS=Mus musculus (Mouse) OX=10090 GN=Khdrbs1 PE=1 SV=2	Q8Q749	Khdrbs1	48 kDa	1.8468	3.5887	1.94
102	Latein OS=Mus musculus (Mouse) OX=10090 GN=Lxn PE=1 SV=2	P70202	Lxn	25 kDa	1.8468	3.5887	1.94
103	Thrombospondin type-1 domain-containing protein 7A OS=Mus musculus (Mouse) OX=10090 GN=Thsd7a PE=1 SV=2	Q89ZU6	Thsd7a	184 kDa	1.8468	3.5887	1.94
104	U1 small nuclear ribonucleoprotein A OS=Mus musculus (Mouse) OX=10090 GN=Snpa PE=1 SV=3	Q82189	Snpa	32 kDa	1.8468	3.5887	1.94
105	Vitamin D-binding protein OS=Mus musculus (Mouse) OX=10090 GN=Gc PE=1 SV=2	P21614	Gc	54 kDa	1.8468	3.5887	1.94
106	40S ribosomal protein S21 OS=Mus musculus (Mouse) OX=10090 GN=Rps21 PE=1 SV=1	Q8CQR2	Rps21	9 kDa	0	2.3925	
107	Acetyl-CoA carboxylase 2 OS=Mus musculus (Mouse) OX=10090 GN=Acacb PE=1 SV=1	E9Q4Z2	Acacb	276 kDa	0	2.3925	
108	Actin-binding LIM protein 1 OS=Mus musculus (Mouse) OX=10090 GN=Ablim1 PE=1 SV=1	Q8K4G5	Ablim1	97 kDa	0	2.3925	
109	Actin-related protein 2/3 complex subunit 2 OS=Mus musculus (Mouse) OX=10090 GN=Arpc2 PE=1 SV=3	Q8CVB6	Arpc2	34 kDa	0	2.3925	
110	Bridging integrator 2 OS=Mus musculus (Mouse) OX=10090 GN=Bin2 PE=1 SV=1	D3Z6Q9	Bin2	53 kDa	0	2.3925	
111	Cadherin-13 OS=Mus musculus (Mouse) OX=10090 GN=Cdh13 PE=1 SV=2	Q8WTR5	Cdh13	78 kDa	0	2.3925	
112	COP9 signalosome complex subunit 8 OS=Mus musculus (Mouse) OX=10090 GN=Cops8 PE=1 SV=1	Q8BV77	Cops8	23 kDa	0	2.3925	
113	E3 ubiquitin-protein ligase RIMN5A OS=Mus musculus (Mouse) OX=10090 GN=Rimn5a PE=1 SV=2	Q8VQ08	Rimn5a	44 kDa	0	2.3925	
114	Glutaryl-CoA dehydrogenase, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Gcdh PE=1 SV=2	Q80759	Gcdh	49 kDa	0	2.3925	
115	Histidine-rich calcium-binding protein OS=Mus musculus (Mouse) OX=10090 GN=Hrc PE=1 SV=1	G8E8J6	Hrc	85 kDa	0	2.3925	
116	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9, mitochondrial OS=Mus musculus (Mouse) OX=10090 GN=Ndufa9 PE=1 SV=2	Q8DC69	Ndufa9	43 kDa	0	2.3925	
117	Predicted gene 11639 OS=Mus musculus (Mouse) OX=10090 GN=Gm11639 PE=1 SV=1	AA01D5RLM8-DECOY		42 kDa	0	2.3925	
118	Protein phosphatase 1A OS=Mus musculus (Mouse) OX=10090 GN=Ppm1a PE=1 SV=1	P46443	Ppm1a	42 kDa	0	2.3925	
119	Ribose-phosphate phosphokinase OS=Mus musculus (Mouse) OX=10090 GN=Ppks111 PE=1 SV=1	Q8C3R8	Ppks111	35 kDa	0	2.3925	
120	Synaptodin-2 OS=Mus musculus (Mouse) OX=10090 GN=Synpd2 PE=1 SV=2	Q81YE8	Synpd2	117 kDa	0	2.3925	
121	Translocin-associated protein subunit alpha OS=Mus musculus (Mouse) OX=10090 GN=Sar1 PE=1 SV=1	Q8CY50	Sar1	32 kDa	0	2.3925	

Note: Red labeled proteins are mitochondrial proteins.

**Supplementary Table S2: Primer information.**

<b>Name</b>		<b>Sequence</b>
<i>circSlc8a1/cA-circSlc8a1-1</i>	Forward:	5'-ctattgaaggcacagcccagg-3'
	Reverse:	5'-gtacaataagactccaactgc-3'
<i>circSlc8a1/cA-circSlc8a1-2</i>	Forward:	5'-acagcccaggtggaggggaagac-3'
	Reverse:	5'-ggtgggagacttaatcgaagcatg-3'
<i>Slc8a1</i> mRNA	Forward:	5' gagcagccttcagagctggtcgg-3'
	Reverse:	5'-gtacaataagactccaactgc-3'
RNU6	Forward:	5'-gtgctcgcttcggcagcacata-3'
	Reverse:	5'-tggaacgcttcacgaatttgcg-3'
<i>Gapdh</i>	Forward:	5'-cccactgaagggtggagcc-3'
	Reverse:	5'-acaatcttgagtgagttgtc-3'
<i>cA-circSlc8a1</i> precursor	Forward:	5'-acagcccaggtggaggggaagac-3'
	Reverse:	5'-gagctgtcagagatttccaacc-3'
<i>cA-circSlc8a1</i> genotyping	Forward:	5'gggcccgcctcgagacacttagcctgttctt-3'
	Reverse:	5'-ggtgggagacttaatcgaagcatg-3'
<i>circSlc8a1</i> genotyping	Forward:	5'-tgtggagagctcgaattccagaa-3'
	Reverse:	5'-gcatgcatagatcttacggaaaacggcagaag-3'
<i>collagen1a1</i>	Forward:	5'-gaatggagatgatgggaagctgg-3'
	Reverse:	5'-catctccttggcaccatccaaac-3'
<i>collagen3a1</i>	Forward:	5'-gtaaagaagtctctgaagctgatg-3'
	Reverse:	5'-gcgatatctatgatggtagtctc-3'
ANP	Forward:	5'-gcggtgtccaacacagatctgatg-3'
	Reverse:	5'-ggtgggttgacctcccagtcag-3'
BNP	Forward:	5'-gagcaattcaagatgcaggtgagc-3'
	Reverse:	5'-cacacacacctgaatccccatcc-3'

