

Genotypes	<i>Trbp</i> <sup>fl/+</sup>	<i>Trbp</i> <sup>fl/fl</sup>	<i>cTNT-Cre</i> <sup>TG</sup> ; <i>Trbp</i> <sup>fl/+</sup>	<i>cTNT-Cre</i> <sup>TG</sup> ; <i>Trbp</i> <sup>fl/fl</sup>	Total
Number	36	33	30	27	126
Percentage (%)	28.5	26.2	23.8	21.3	100

( $\chi^2=1.429$ ,  $p=0.69885131$ )

**Supplementary Table 1.** Genotyping results of postnatal 0.5 (p0.5) pups from *cTNT-Cre*<sup>TG</sup>; *Trbp*<sup>fl/+</sup> and *Trbp*<sup>fl/fl</sup> intercrossing.

	p2.5		2w		3w		1m		2m	
	Ctrl (n=4)	<i>Trbp</i> <sup>CKO</sup> (n=5)	Ctrl (n=5)	<i>Trbp</i> <sup>CKO</sup> (n=5)	Ctrl (n=5)	<i>Trbp</i> <sup>CKO</sup> (n=3)	Ctrl (n=6)	<i>Trbp</i> <sup>CKO</sup> (n=5)	Ctrl (n=6)	<i>Trbp</i> <sup>CKO</sup> (n=4)
Heart Rate(BPM)	372±37	371±53	634±33	572 ±44*	631±74	562±22	615±32	556±42*	623±45	595±74
IVS;d (mm)	0.241±0.031	0.274±0.052	0.301±0.063	0.285±0.0519	0.370±0.055	0.371±0.050	0.393±0.040	0.445±0.024*	0.546±0.156	0.510±0.085
IVS;s (mm)	0.282±0.056	0.290±0.058	0.379±0.023	0.383±0.067	0.467±0.137	0.492±0.056	0.501±0.055	0.478±0.106	0.581±0.127	0.597±0.101
LVID;d (mm)	1.314±0.161	1.331±0.086	2.542±0.232	2.440±0.223	2.549±0.345	2.763±0.284	3.273±0.376	3.606±0.278	3.193±0.357	4.118±0.517**
LVID;s (mm)	0.389±0.034	0.408±0.069	0.933±0.161	1.165±0.128*	1.079±0.165	1.780±0.179**	1.431±0.323	2.796±0.261**	1.409±0.344	3.246±0.609**
LVPW;d (mm)	0.322±0.022	0.333±0.052	0.375±0.065	0.391±0.077	0.483±0.102	0.447±0.031	0.514±0.073	0.504±0.125	0.617±0.048	0.543±0.104
LVPW;s (mm)	0.322±0.038	0.349±0.038	0.725±0.16	0.583±0.067	0.622±0.198	0.528±0.015	0.814±0.065	0.590±0.095**	0.800±0.172	0.617±0.130
EF (%)	96.51±0.38	95.97±1.75	92.55±2.23	84.90±3.62**	88.31±5.23	66.94±2.37**	87.25±5.19	45.76±8.07**	87.00±7.65	43.69±6.45**
FS (%)	70.30±1.39	69.33±4.90	63.40±4.27	52.20±4.13**	57.19±7.71	35.57±1.85**	56.61±7.45	22.42±4.87**	56.25±7.65	21.54±6.45**
LV Mass (mg)	4.67±1.28	5.19±0.94	18.30±5.88	17.09±5.82	25.18±10.81	26.10±3.13	40.27±7.95	50.29±8.79	54.84±21.35	72.25±15.94
LV Mass (Corrected mg)	3.73±1.02	4.15±0.75	14.64±4.70	13.67±4.65	20.15±8.65	20.88±2.50	32.22±6.36	40.23±7.03	43.87±17.08	57.80±12.75
LV Vol;d (uL)	4.38±1.37	4.45±0.71	23.54±5.37	21.26±4.63	24.01±7.62	28.95±7.50	44.03±11.76	55.05±10.24	41.42±11.08	76.34±21.99**
LV Vol;s (uL)	0.15±0.04	0.18±0.09	1.80±0.84	3.17±0.86*	2.63±1.05	9.56±2.54	5.80±2.65	29.78±7.26**	5.65±3.29	44.21±19.42**

**Supplementary Table 2.** Echocardiography analyses of cardiac function of *Trbp*<sup>CKO</sup> mice and their control littermates (Ctrl) at different timepoints. P2.5: postnatal day 2.5; 2w: 2 weeks after birth; 3w: 3 weeks after birth; 1m: 1 month after birth; 2m: 2 months after birth; \*: P(Ctrl VS. *Trbp*<sup>CKO</sup>) <0.05, \*\*: P(Ctrl VS. *Trbp*<sup>CKO</sup>) <0.01.

	Ctrl/AAV-Luc (n=14)	<i>Trbp</i> <sup>CKO</sup> /AAV-Luc (n=6)	Ctrl/AAV-Trbp (n=5)	<i>Trbp</i> <sup>CKO</sup> /AAV-Trbp (n=8)	Ctrl/AAV-Hopx (n=14)	<i>Trbp</i> <sup>CKO</sup> /AAV-Hopx (n=17)
Heart Rate (BPM)	657±43	511±57**	597±38	556±34	664±36	503±92
IVS;d (mm)	0.588±0.83	0.505±0.114	0.479±0.120	0.470±0.096	0.611±0.111	0.562±0.130
IVS;s (mm)	0.832±0.144	0.581±0.095**	0.672±0.041	0.684±0.124	0.876±0.198	0.630±0.174
LVID;d (mm)	3.160±0.252	3.524±0.313*	2.790±0.597	2.663±0.405 <sup>##</sup>	3.331±0.307	3.415±0.272
LVID;s (mm)	1.311±0.214	2.737±0.306**	1.248±0.415	1.221±0.203 <sup>##</sup>	1.493±0.270	2.448±0.303
LVPW;d (mm)	0.627±0.065	0.554±0.117	0.520±0.041	0.503±0.112	0.627±0.097	0.554±0.078
LVPW;s (mm)	0.935±0.097	0.657±0.117**	0.754±0.166	0.734±0.082	0.964±0.106	0.701±0.102
EF (%)	89.06±3.81	44.95±13.41**	86.93±5.78	86.32±3.24 <sup>##</sup>	86.65±4.00	55.25±10.37
FS (%)	58.61±5.05	22.16±7.60**	55.76±8.19	54.13±4.12 <sup>##</sup>	55.45±4.80	28.34±6.59
LV Mass (mg)	55.10±8.28	56.26±17.68	36.62±18.64	32.12±14.01 <sup>#</sup>	61.71±11.53	56.37±12.56
LV Mass (Corrected mg)	44.08±6.62	45.01±14.14	29.30±14.91	25.69±11.22 <sup>#</sup>	49.37±9.22	45.10±10.5
LV Vol;d (uL)	40.11±7.83	52.23±10.83*	31.09±14.30	27.00±10.48 <sup>##</sup>	45.70±9.81	48.40±9.33
LV Vol;s (uL)	4.47±2.05	28.42±8.15**	4.43±3.66	3.70±1.53 <sup>##</sup>	6.35±2.99	21.71±6.71

**Supplementary Table 3.** Echocardiography analyses of cardiac function of 1-month old *Trbp*<sup>CKO</sup> mice and their control littermates (Ctrl) injected with AAV-Luciferase(AAV-Luc), AAV-Trbp, or AAV-Hopx. \*: P (Ctrl/AAV-Luc VS. *Trbp*<sup>CKO</sup>/AAV-Luc) <0.05; \*\*: P (Ctrl/AAV-Luc VS. *Trbp*<sup>CKO</sup>/AAV-Luc) <0.01; #: P(*Trbp*<sup>CKO</sup>/AAV-Luc VS. *Trbp*<sup>CKO</sup>/AAV-Trbp) <0.05; ##: P(*Trbp*<sup>CKO</sup>/AAV-Luc VS. *Trbp*<sup>CKO</sup>/AAV-Trbp) <0.01; &.:P(*Trbp*<sup>CKO</sup>/AAV-Luc VS. *Trbp*<sup>CKO</sup>/AAV-Hopx) <0.05; &&.: P(*Trbp*<sup>CKO</sup>/AAV-Luc VS. *Trbp*<sup>CKO</sup>/AAV-Hopx) <0.01.

	Ctrl/AAV-Scramble (n=8)	<i>Trbp</i> <sup>ckO</sup> /AAV-Scramble (n=9)	Ctrl/AAV-Sox6 shRNA (n=6)	<i>Trbp</i> <sup>ckO</sup> /AAV-Sox6 shRNA (n=12)
Heart Rate (BPM)	633±58	574±27*	648±41	607±34 <sup>#</sup>
IVS;d (mm)	0.449±0.055	0.391±0.069	0.456±0.056	0.413±0.065
IVS;s (mm)	0.563±0.061	0.477±0.105	0.617±0.045	0.546±0.065
LVID;d (mm)	2.854±0.309	3.670±0.403**	3.148±0.184	2.882±0.250 <sup>##</sup>
LVID;s (mm)	1.248±0.237	2.760±0.578**	1.377±0.234	1.419±0.275 <sup>##</sup>
LVPW;d (mm)	0.490±0.049	0.462±0.063	0.514±0.234	0.478±0.046
LVPW;s (mm)	0.708±0.102	0.486±0.054**	0.702±0.052	0.664±0.094 <sup>##</sup>
EF (%)	87.82±3.69	49.65±16.10**	87.30±4.57	82.86±6.91 <sup>##</sup>
FS (%)	56.47±4.91	25.34±9.70**	56.33±6.50	50.89±7.68 <sup>##</sup>
LV Mass (mg)	33.24±7.19	45.88±11.17*	40.59±3.17*	31.63±5.81 <sup>##</sup>
LV Mass (Corrected mg)	26.59±5.75	36.70±8.94*	32.47±2.53*	25.30±4.65 <sup>##</sup>
LV Vol;d (uL)	31.50±8.85	57.94±16.01**	39.54±5.61	32.08±6.59 <sup>##</sup>
LV Vol;s (uL)	3.98±2.15	30.40±14.85**	5.08±2.01	5.61±2.72 <sup>##</sup>

**Supplementary Table 4.** Echocardiography analyses of cardiac function of 1-month old *Trbp*<sup>ckO</sup> mice and their control littermates (Ctrl) injected with AAV-Scramble or AAV-Sox6 shRNA. \*: P (Ctrl/AAV-Scramble VS. *Trbp*<sup>ckO</sup>/AAV-Scramble) <0.05; \*\*: P (Ctrl/AAV-Scramble VS. *Trbp*<sup>ckO</sup>/AAV-Scramble)<0.01; #: P(*Trbp*<sup>ckO</sup>/AAV-Scramble VS. *Trbp*<sup>ckO</sup>/AAV-Sox6 shRNA) <0.05; ##: P(*Trbp*<sup>ckO</sup>/AAV-Scramble VS. *Trbp*<sup>ckO</sup>/AAV-Sox6 shRNA) <0.01.

	AAV-Luc (n=6)	AAV-Sox6 (n=7)
Heart Rate (BPM)	672±46	570±47**
IVS;d (mm)	0.474±0.047	0.452±0.061
IVS;s (mm)	0.567±0.104	0.433±0.065*
LVID;d (mm)	3.054±0.328	4.124±0.164**
LVID;s (mm)	1.386±0.177	3.457±0.322**
LVPW;d (mm)	0.537±0.088	0.437±0.055*
LVPW;s (mm)	0.684±0.063	0.502±0.048**
EF (%)	86.45±2.41	34.10±11.23**
FS (%)	54.63±3.08	16.25±5.97**
LV Mass (mg)	41.48±11.76	58.89±6.30**
LV Mass (Corrected mg)	33.18±9.41	47.11±5.04**
LV Vol;d (uL)	37.14±9.55	75.41±7.15**
LV Vol;s (uL)	5.06±1.56	49.96±10.80**

**Supplementary Table 5.** Echocardiography analyses of cardiac function of 1-month old wild type mice injected with AAV-Luciferase (AAV-Luc) or AAV-Sox6. \*: P (AAV-Luc VS. AAV- Sox6) <0.05; \*\*: P (AAV-Luc VS. AAV- Sox6)<0.01.

	Ctrl (n=7)	<i>Trbp</i> <sup>CKO</sup> (n=8)	<i>miR-208a</i> <sup>TG</sup> (n=9)	<i>Trbp</i> <sup>CKO</sup> ; <i>miR-208a</i> <sup>TG</sup> (n=7)
Heart Rate (BMP)	597±40	560±58	619±45	551±41
IVS;d (mm)	0.494±0.051	0.486±0.121	0.525±0.124	0.471±0.058
IVS;s (mm)	0.698±0.126	0.563±0.072*	0.754±0.091	0.652±0.144
LVID;d (mm)	3.223±0.330	3.287±0.264	3.392±0.243	3.200±0.346
LVID;s (mm)	1.568±0.485	2.401±0.374**	1.747±0.229	1.564±0.303###
LVPW;d (mm)	0.567±0.100	0.516±0.083	0.584±0.057	0.521±0.074
LVPW;s (mm)	0.755±0.125	0.617±0.095*	0.766±0.050	0.751±0.088#
EF (%)	83.05±9.44	53.57±11.71**	80.78±4.44	83.01±6.21###
FS (%)	52.12±10.39	27.19±7.04**	48.61±4.47	51.18±6.93###
LV Mass (mg)	47.81±8.81	45.90±7.49	55.31±11.73	43.26±7.02
LV Mass (Corrected mg)	38.25±7.05	36.72±6.00	44.25±9.38	34.61±5.61
LV Vol;d (uL)	42.29±10.51	44.10±8.47	47.52±8.05	41.63±10.22
LV Vol;s (uL)	7.91±5.99	20.94±8.31**	9.26±3.04	7.19±3.82###

**Supplementary Table 6.** Echocardiography analyses of cardiac function of 1-month old *Trbp*<sup>CKO</sup> mice, *miR-208a* transgenic(*miR-208a*<sup>TG</sup>) mice, *Trbp*<sup>CKO</sup>; *miR-208a*<sup>TG</sup> and their control littermates (Ctrl). \*: P (Ctrl VS. *Trbp*<sup>CKO</sup>) <0.05; \*\*: P (Ctrl VS. *Trbp*<sup>CKO</sup>)<0.01; #: P(*Trbp*<sup>CKO</sup> VS. *Trbp*<sup>CKO</sup>; *miR-208a*<sup>TG</sup>) <0.05; ###: P(*Trbp*<sup>CKO</sup> VS. *Trbp*<sup>CKO</sup>; *miR-208a*<sup>TG</sup>) <0.01.

<b>Oligos</b>	<b>Sequences (5'→3')</b>
Trbp-qF	aggaggggaatgagtgaagagg
Trbp-qR	gaaggctgatcgggtct
Anf-qF	cacagatctgatggattcaaga
Anf-qR	cctcatctctaccggcatc
Hopx-qF	agacaggcaccagcatcc
Hopx-qR	ccaggatctccacctggtc
Sox6-qF	ttacaaccacagacagattgagc
Sox6-qR	tgctgtggagtgtatgg
Cdca8-qF	ccgacagacagaccctcct
Cdca8-qR	agggcctgctgtttcct
Ckap2l-qF	agaaactgtcgccgtagagc
Ckap2l-qR	ttggggctcttagctttcc
Cenp-f-qF	ttgaggtagcacgacttcagtt
Cenp-f-qR	ttttggcaccgaacaacac
Cenp-p-qF	gcagaatgtgcaaaacg
Cenp-p-qR	caaagattcccactcctcaga
Myh6-qF	gtgctcagagctcaagaagga
Myh6-qR	ttgatgcttttcttttcc
Myh7-qF	ctcagagctcaagcgggata
Myh7-qR	ccagccatctcctctgtca
Myh7b-qF	gcacggagctcaagaaagac
Myh7b-qR	gccatctctctgtcaggttct
Tnni2-qF	gagatgaggagaagcgcaac
Tnni2-qR	cgctatctggagcatcacac
Tpm2-qF	cgagggtggctgagagtaaag
Tpm2-qR	tccagggattcaagttgtg
Myl1-qF	caatggctgcatcaactatga
Myl1-qR	gccatagggtgtcttgaactgg
Myl7-qF	ccggaggaagagctggac
Myl7-qR	aggcactcaggatggcttc
Myl9-qF	gataaggaggacctgcacga
Myl9-qR	gccctccagatactcgctctg
Tnnc1-qF	cgacagcaaaggggaagtctg
Tnnc1-qR	tgtagccatcagcgtttttg
Myl3-qF	aagaaggatgatgccaaagc
Myl3-qR	gctcaggctctggtgcag
pre-miR-208a-qF	gagctttggccgggttatac
pre-miR-208a-qR	acaagcttttctctgctcta
18sr-qF	gcaattattcccatgaacg
18sr-qR	gggacttaataacgcaagc
Scramble shRNA	cctaaggtaagtcgccctcgctcgagcgagggcgacttaaccttagg
Sox6 shRNA-1	cctatattcctccgaaatacctcgaggtatttcggaaggaatatagg
Sox6 shRNA-2	tgatcccaaatacagactatagctcgagctatagctgatttgggatca
miR-208a-3p antisense	acaagcttttctctgctctat
miR-208a-5p antisense	gtataaccggggccaaaagctc
miR-378a-3p antisense	ccttctgactccaagtccagt
miR-378a-5p antisense	acacaggacctggagtcaggag
miR-1a-3p antisense	atacatactctttacattcca
U6 antisense	aaaatatggaacgcttcacgaatttgcg

**Supplementary Table 7. Sequences of oligos used in the study**