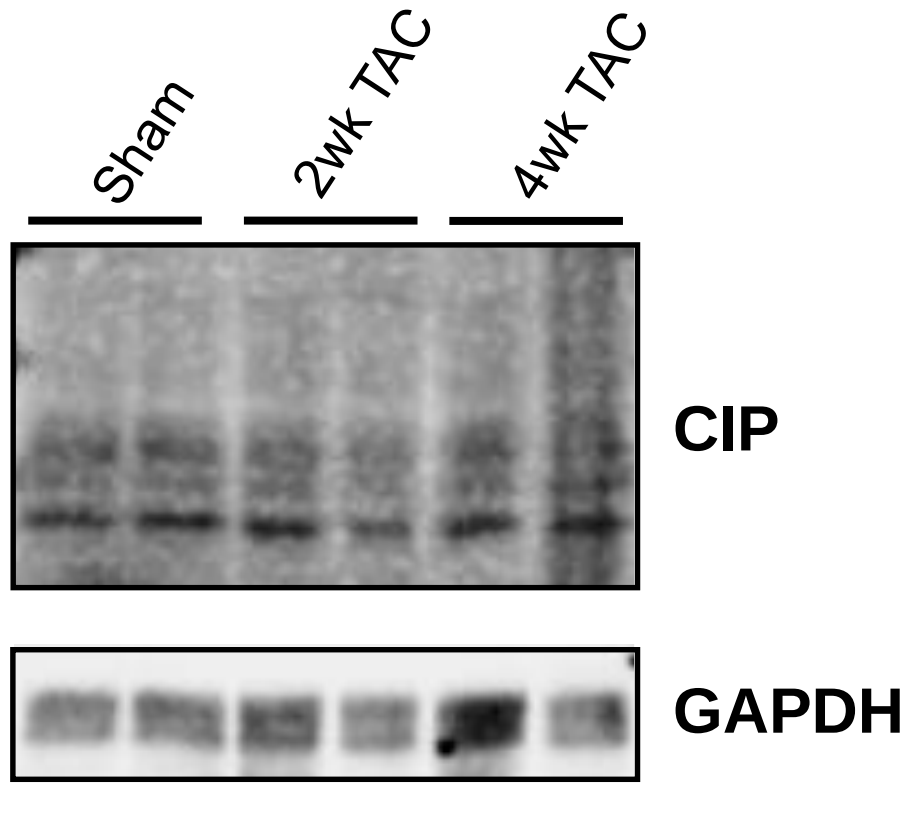
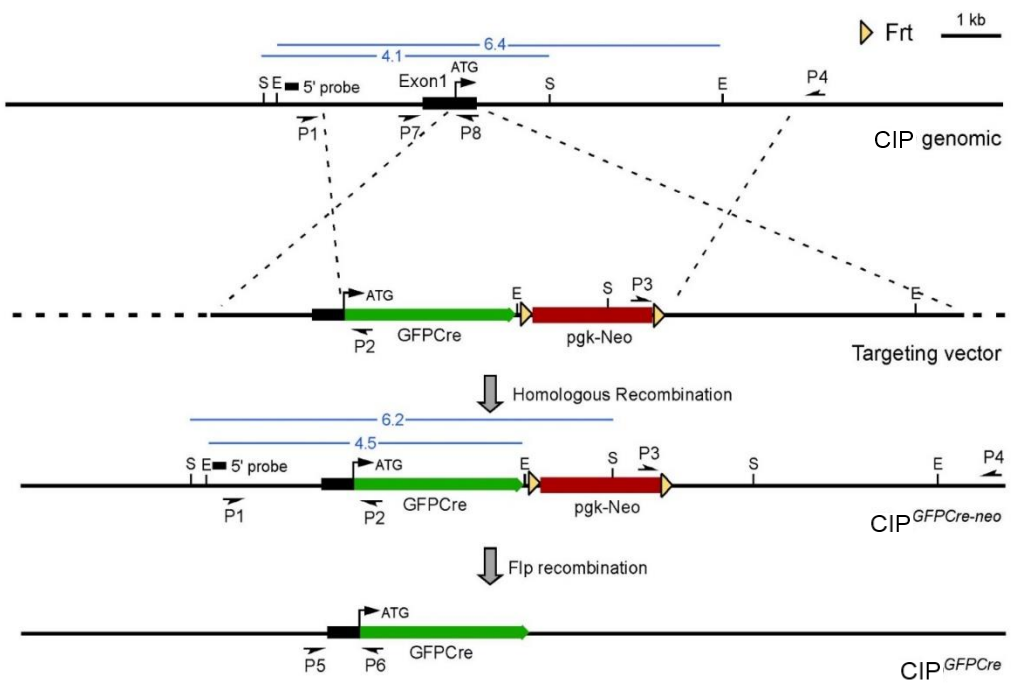


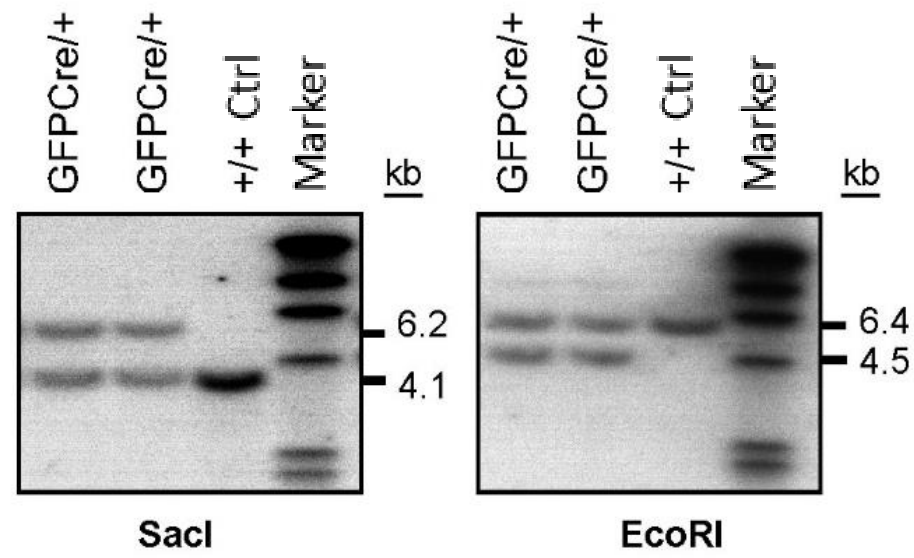
Supplemental figure 1. The expression of CIP in cardiac hypertrophy.

Detection of the expression of CIP in the stressed heart and sham controls by western blot. No significant difference of CIP expression were observed in hypertrophic hearts induced by transverse aortic constriction (TAC).

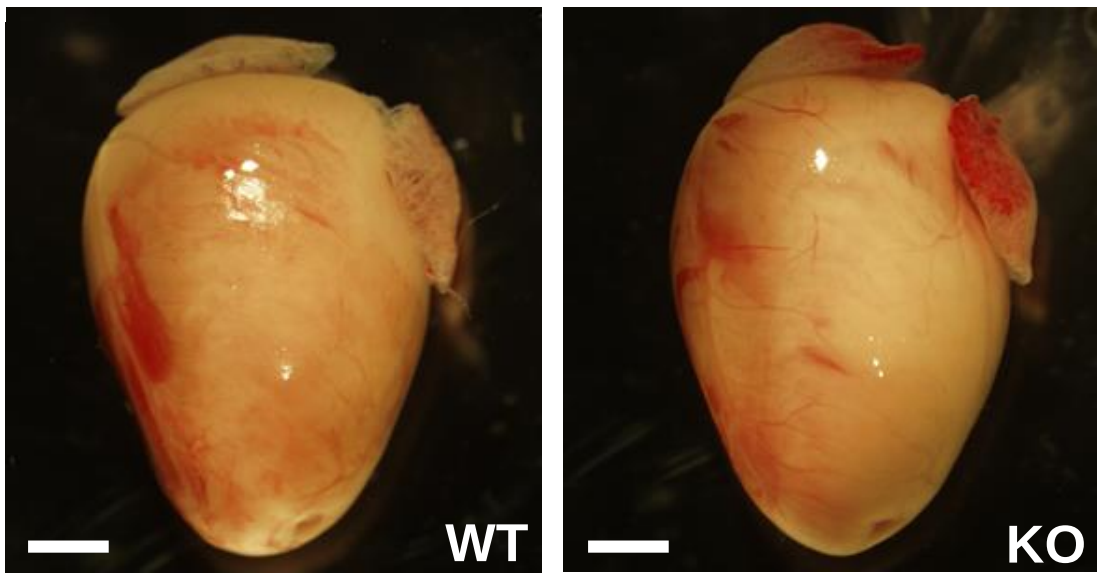
A



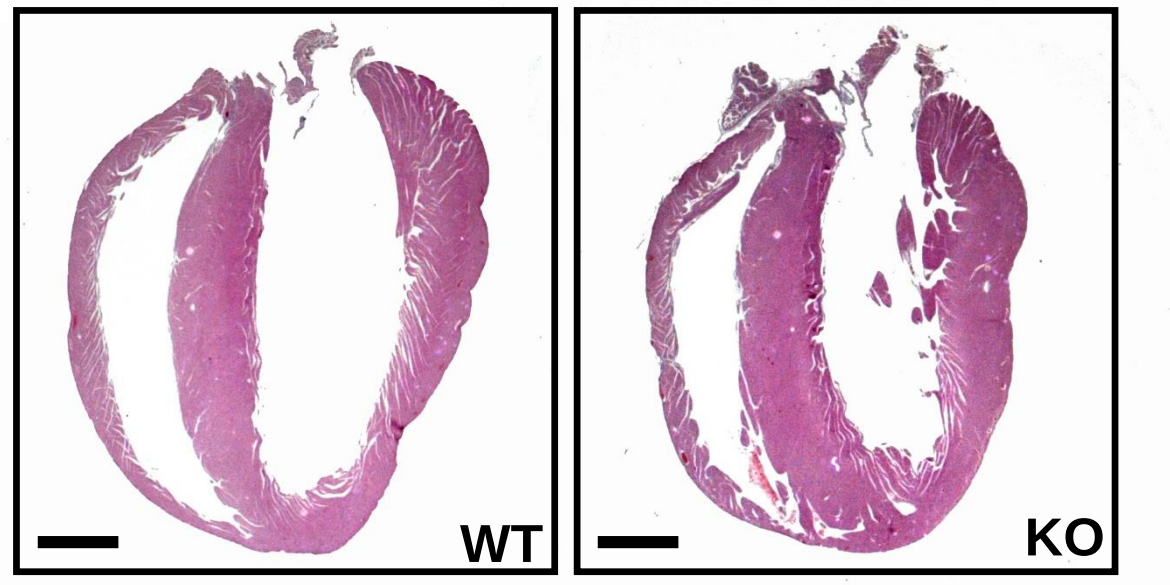
B



C



D

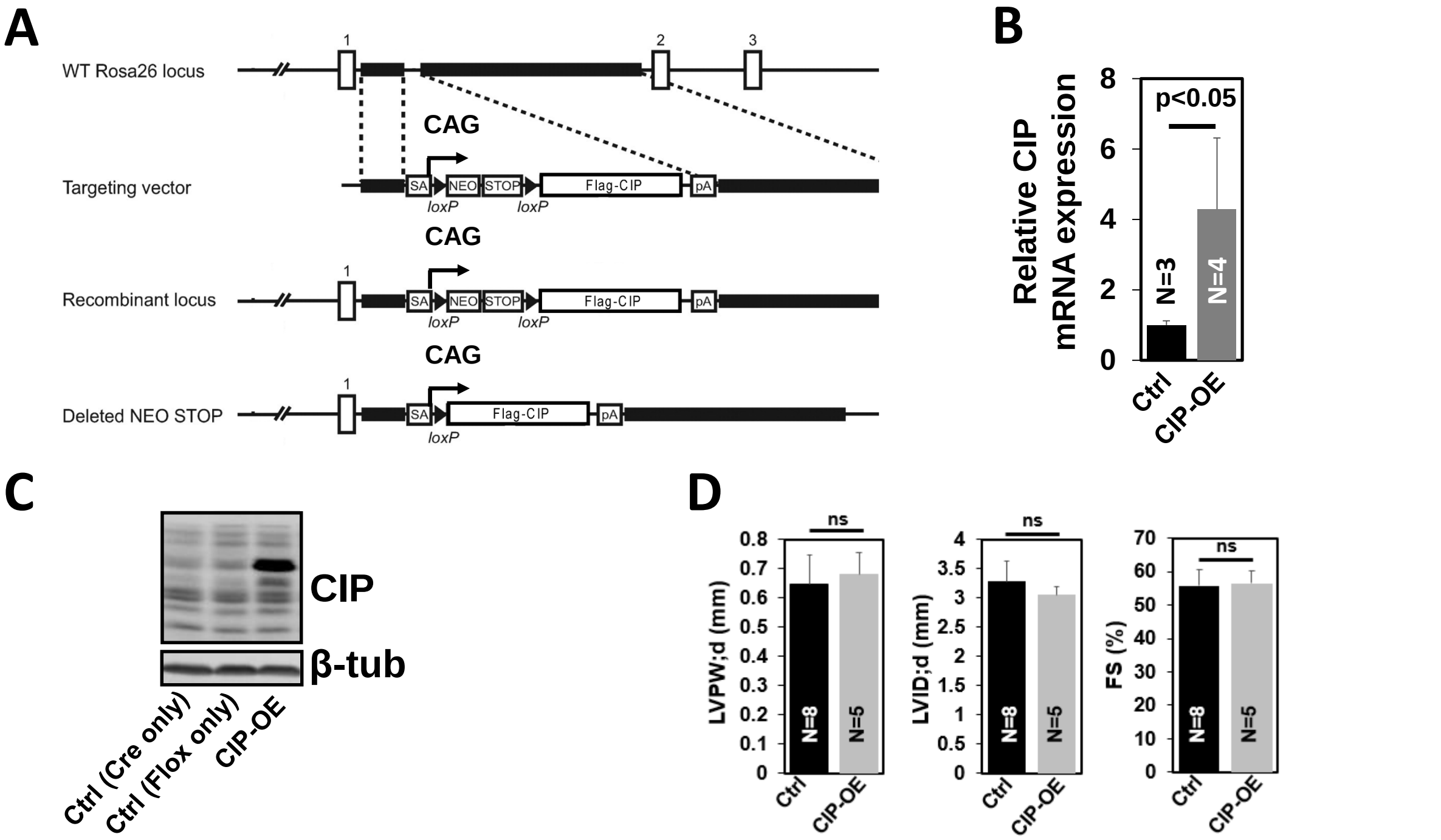


E

Distribution of genotypes

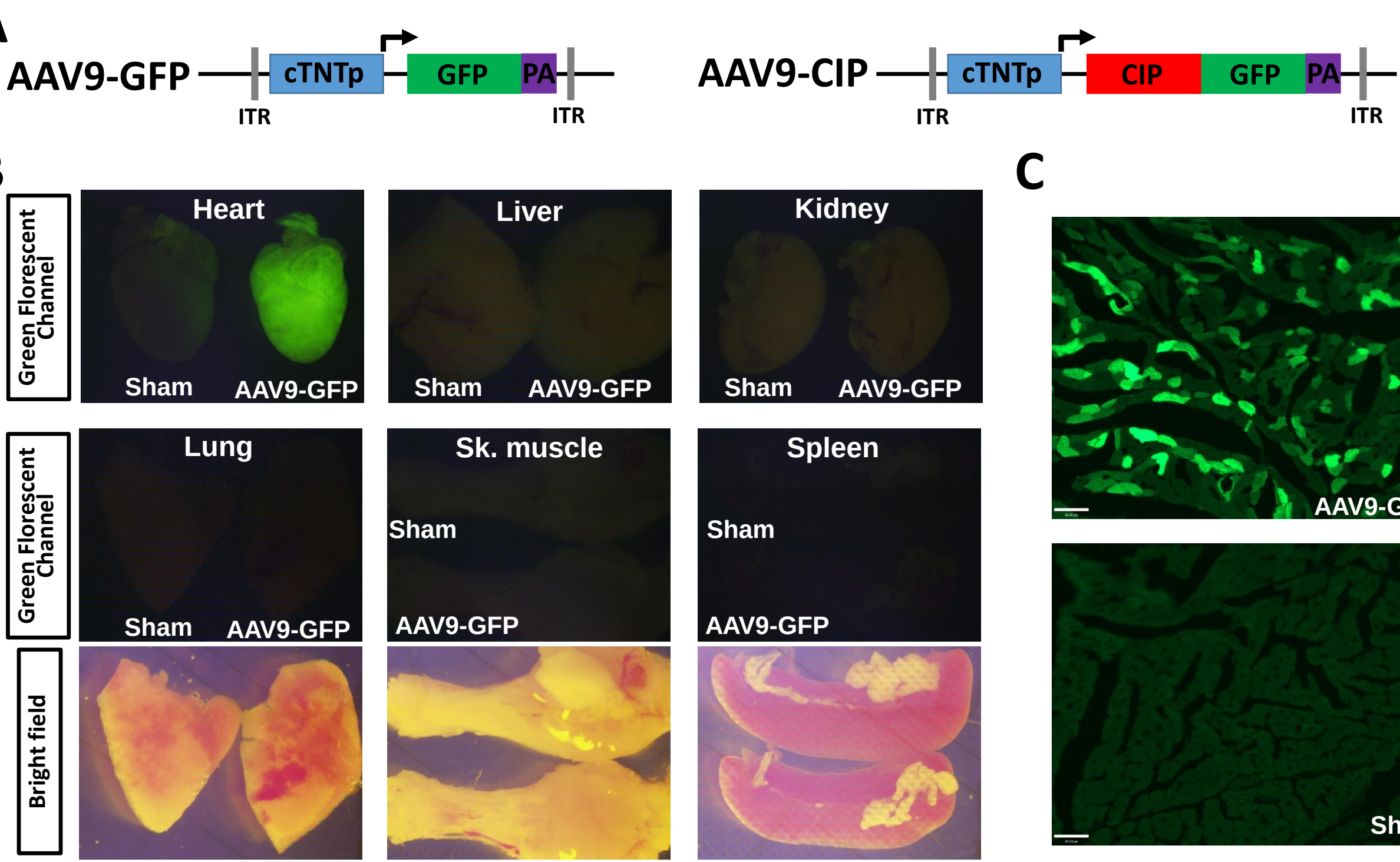
WT	Het	KO
65 (23.9%)	132 (48.5%)	75 (27.6%)

Supplemental figure 2. Generation of CIP-KO mice.
(A) Strategy of generating CIP-KO mice. **(B)** Detection of the DNA recombination in targeted ES cells by southern blot. **(C)** Representative images of gross heart morphology of 3-month-old CIP-KO and control heart. **(D)** Representative images of heart section of 3-month-old CIP-KO and control heart. **(E)** The distribution of genotypes of progeny come from the intercrossing of CIP-Het. Bar=1 mm.



Supplemental figure 3. Generation of CIP-OE mice.

(A) Strategy of generating CIP-OE mice. **(B)** Detection of the overexpression of CIP in CIP-OE and control hearts by qRT-PCR. **(C)** Detection of the overexpression of CIP in CIP-OE and control hearts by western blot. **(D)** Left ventricle posterior wall (LVPW;d) thickness, left ventricle internal dimension (LVID;d) and fraction shortening (FS) of 10-week-old CIP-OE and control mice. N number for each group is indicated.



Supplemental figure 4. Generation of AAV9 for cardiac overexpression of transgene *in vivo* **(A)** Schematic of AAV9-GFP and AAV9-CIP vectors. **(B)** Detection of GFP signals in multiple organs collected from AAV9-GFP-injected or sham-operated mice. AAV9-GFP (10^{11} virus genomes/pup) and PBS (sham) were injected into P2 pups. Different organs were collected at the age of two weeks for GFP signal detection. **(C)** Immunofluorescence detecting GFP in heart sections from AAV9-GFP-injected or sham-operated mice. Bar=38μm.

Sample	Age	Gender	Type of heart failure
Patient-1	39	Male	Dilated cardiomyopathy
Patient-2	50	Male	Dilated cardiomyopathy
Patient-3	34	Male	Dilated cardiomyopathy
Patient-4	55	Male	Dilated cardiomyopathy
Patient-5	53	Female	Dilated cardiomyopathy
Patient-6	53	Male	Dilated cardiomyopathy
Patient-7	51	Male	Dilated cardiomyopathy
Patient-8	60	Male	Dilated cardiomyopathy
Patient-9	62	Male	Dilated cardiomyopathy
Patient-10	55	Male	Dilated cardiomyopathy

Supplemental table 1. Information of heart samples from patients used in this study. Age, gender and etiology of heart failure are included.

	Baseline		Epinephrine treatment		Propranolol treatment	
	CIP-WT (N=5)	CIP-KO (N=5)	CIP-WT (N=5)	CIP-KO (N=5)	CIP-WT (N=5)	CIP-KO (N=5)
Heart Rate (BPM)	654.3 ± 16.7	685.0 ± 37.8	686.6 ± 70.4	681.7 ± 77.9	618.2 ± 15.0	611.8 ± 14.2
PR Interval (ms)	33.3 ± 1.5	32.8 ± 2.8	34.4 ± 2.8	34.1 ± 4.0	33.6 ± 1.6	34.2 ± 2.6
QRS Interval (ms)	9.1 ± 0.4	9.5 ± 0.8	9.2 ± 0.6	9.5 ± 0.8	8.7 ± 0.4	9.4 ± 1.0

Supplemental table 2. Ambulatory ECG data of 3-month-old CIP-KO mice and their control littermates. The ECG was recorded without any treatment (baseline), or with epinephrine or propranolol treatment.

	WT Sham (N=8)	KO Sham (N=7)	WT TAC (N=14)	KO TAC (N=12)
IVS;d (mm)	0.773±0.093	0.780±0.102	1.177±0.226**	0.895±0.117##
IVS;s (mm)	1.474±0.106	1.440±0.116	1.690±0.158**	1.156±0.208##
LVID;d (mm)	3.633±0.299	3.642±0.354	3.908±0.444	4.634±0.478##
LVID;s (mm)	1.864±0.266	1.900±0.343	2.549±0.596**	3.805±0.717##
LVPW;d (mm)	0.865±0.077	0.818±0.108	1.229±0.112**	1.009±0.089##
LVPW;s (mm)	1.499±0.141	1.395±0.140	1.745±0.214**	1.290±0.163##
EF (%)	80.56±3.79	80.06±4.97	64.53±12.47**	37.68±13.94##
FS (%)	48.85±3.90	48.16±5.04	35.53±9.20**	18.50±7.59##
LV Mass (mg)	103.46±8.36	101.01±16.29	204.91±50.13**	189.85±31.60
LV Mass (Corrected, mg)	82.76±6.69	80.81±13.03	163.93±40.10**	151.88±25.28
LV Vol;d (uL)	56.15±11.65	56.68±13.29	67.43±17.51	100.42±24.10##
LV Vol;s (uL)	10.99±4.11	11.75±5.02	25.46±13.52**	65.25±29.02##
Heart Rate (BPM)	675±41	632±44	604±78	611±46

Supplemental table 3. Echocardiography examination of CIP-KO mice and their littermates after 4 weeks transverse aortic constriction (TAC) or sham operation (Sham). **: $P_{WT\ (sham)\ vs.\ WT\ (TAC)}<0.01$; ##: $P_{WT\ (TAC)\ vs.\ KO\ (TAC)}<0.01$.

	CIP-WT;CnA (N=7)	CIP-KO;CnA (N=6)
IVS;d (mm)	0.835±0.235	0.713±0.081
IVS;s (mm)	1.163±0.238	0.852±0.163*
LVID;d (mm)	4.553±0.464	5.211±0.443*
LVID;s (mm)	3.229±0.364	4.614±0.516**
LVPW;d (mm)	1.089±0.198	0.840±0.137*
LVPW;s (mm)	1.340±0.242	0.971±0.128**
EF (%)	55.93±3.58	24.80±6.87**
FS (%)	29.10±2.39	11.58±3.38**
LV Mass (mg)	190.27±59.62	176.18±21.24
LV Mass (Corrected, mg)	152.22±47.70	140.94±16.99
LV Vol;d (uL)	96.24±22.96	131.25±26.45*
LV Vol;s (uL)	42.60±11.71	99.55±27.14**
Heart Rate (BPM)	402±69	362±114

Supplemental table 4. Echocardiography examination of 10-week-old CIP-KO; calcineurin-tg (CnA) compound mice and their control littermates (CIP-WT;CnA). *: $P_{\text{CIP-WT;CnA vs. CIP-KO;CnA}}<0.05$; **: $P_{\text{CIP-WT;CnA vs. CIP-KO;CnA}}<0.01$.

	6 months		12 months	
	Ctrl; LMNA-Het (N=5)	**CIP-KO; LMNA-Het (N=5)**	**Ctrl; LMNA-Het (N=7)**	**CIP-KO; LMNA-Het (N=6)**
IVS;d (mm)	0.464±0.075	0.477±0.018	0.731±0.078	0.679±0.142
IVS;s (mm)	0.574±0.113	0.615±0.073	1.010±0.146	0.851±0.119
LVID;d (mm)	3.944±0.213	3.989±0.138	4.095±0.219	4.771±0.241**
LVID;s (mm)	1.968±0.183	2.339±0.213*	2.530±0.272	3.405±0.380**
LVPW;d (mm)	0.615±0.073	0.640±0.071	0.765±0.077	0.705±0.086
LVPW;s (mm)	1.100±0.061	1.043±0.223	1.068±0.100	0.897±0.096**
EF (%)	81.88±2.99	72.17±7.93*	68.89±5.23	54.88±8.88**
FS (%)	50.13±3.15	41.23±6.69*	38.34±4.07	28.72±5.60**
LV Mass (mg)	69.05±9.73	73.38±7.65	112.02±13.91	131.96±25.11
LV Mass (Corrected, mg)	55.24±7.78	58.71±6.12	89.62±11.13	105.27±20.08
LV Vol;d (uL)	67.92±8.70	69.63±5.59	74.26±9.46	106.32±12.56**
LV Vol;s (uL)	12.37±3.10	19.11±4.42*	23.38±6.09	48.39±13.96**
Heart Rate (BPM)	593±46	578±16	648±22	647±22

Supplemental table 5. Echocardiography examination of 6-month-old and 12-month-old CIP-KO;LMNA-Het compound mice and their control littermates. *: $P_{Ctrl;LMNA\text{-}Het\ vs.\ CIP\text{-}KO;LMNA\text{-}Het}<0.05$; **: $P_{Ctrl;LMNA\text{-}Het\ vs.\ CIP\text{-}KO;LMNA\text{-}Het}<0.01$.

	Ctrl Sham (N=8)	CIP-OE Sham (N=8)	Ctrl TAC (N=11)	CIP-OE TAC (N=6)
IVS;d (mm)	0.853±0.055	0.828±0.061	1.039±0.168**	1.220±0.119#
IVS;s (mm)	1.382±0.112	1.411±0.035	1.435±0.285	1.811±0.159##
LVID;d (mm)	3.785±0.130	3.540±0.302	4.714±0.481**	3.002±0.267##
LVID;s (mm)	1.915±0.147	1.784±0.267	3.642±0.728**	1.510±0.178##
LVPW;d (mm)	0.784±0.023	0.788±0.063	0.912±0.166*	1.341±0.136##
LVPW;s (mm)	1.428±0.056	1.440±0.059	1.277±0.290	1.811±0.233##
EF (%)	81.39±2.53	81.82±3.83	45.85±14.05**	82.30±3.17##
FS (%)	49.45±2.65	49.79±3.88	23.30±8.13**	49.73±3.60##
LV Mass (mg)	110.97±9.28	97.79±12.20	202.26±39.39**	153.27±22.67#
LV Mass (Corrected, mg)	88.78±7.42	78.23±9.76	161.81±31.51**	122.61±18.14#
LV Vol;d (uL)	61.45±4.98	52.81±10.32	104.48±25.30**	35.45±7.72##
LV Vol;s (uL)	11.50±2.22	9.86±3.77	59.14±29.54**	6.30±1.89##
Heart Rate (BPM)	635±68	599±64	588±42	598±69

Supplemental table 6. Echocardiography examination of CIP-OE mice and their control littermates after 10 weeks transverse aortic constriction (TAC) or sham operation (Sham).*: $P_{Ctrl\ (sham)\ vs.\ Ctrl\ (TAC)}<0.05$; **: $P_{Ctrl\ (sham)\ vs.\ Ctrl\ (TAC)}<0.01$; #: $P_{Ctrl\ (TAC)\ vs.\ CIP\text{-}OE\ (TAC)}<0.05$; ##: $P_{Ctrl\ (TAC)\ vs.\ CIP\text{-}OE\ (TAC)}<0.01$.