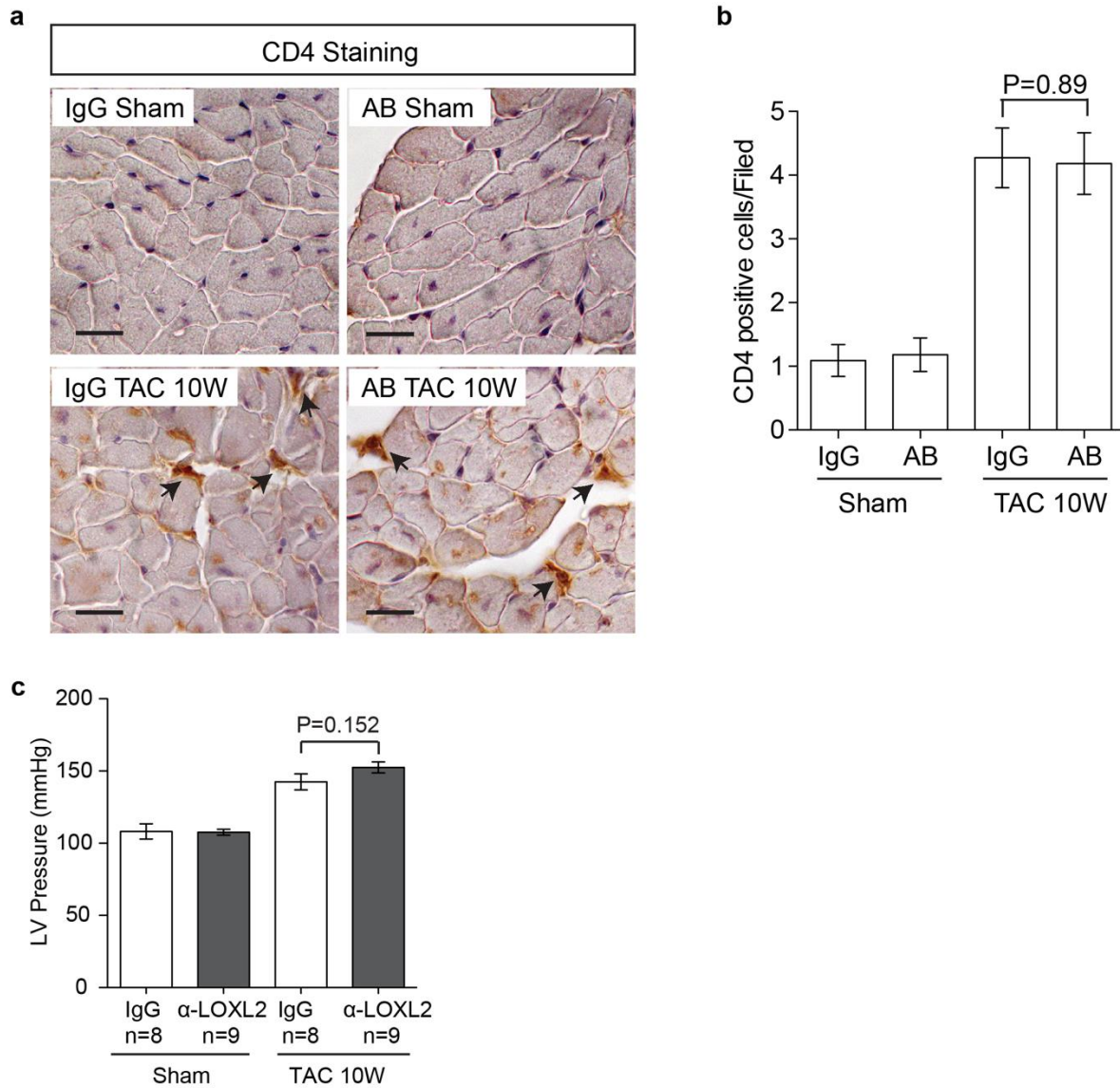
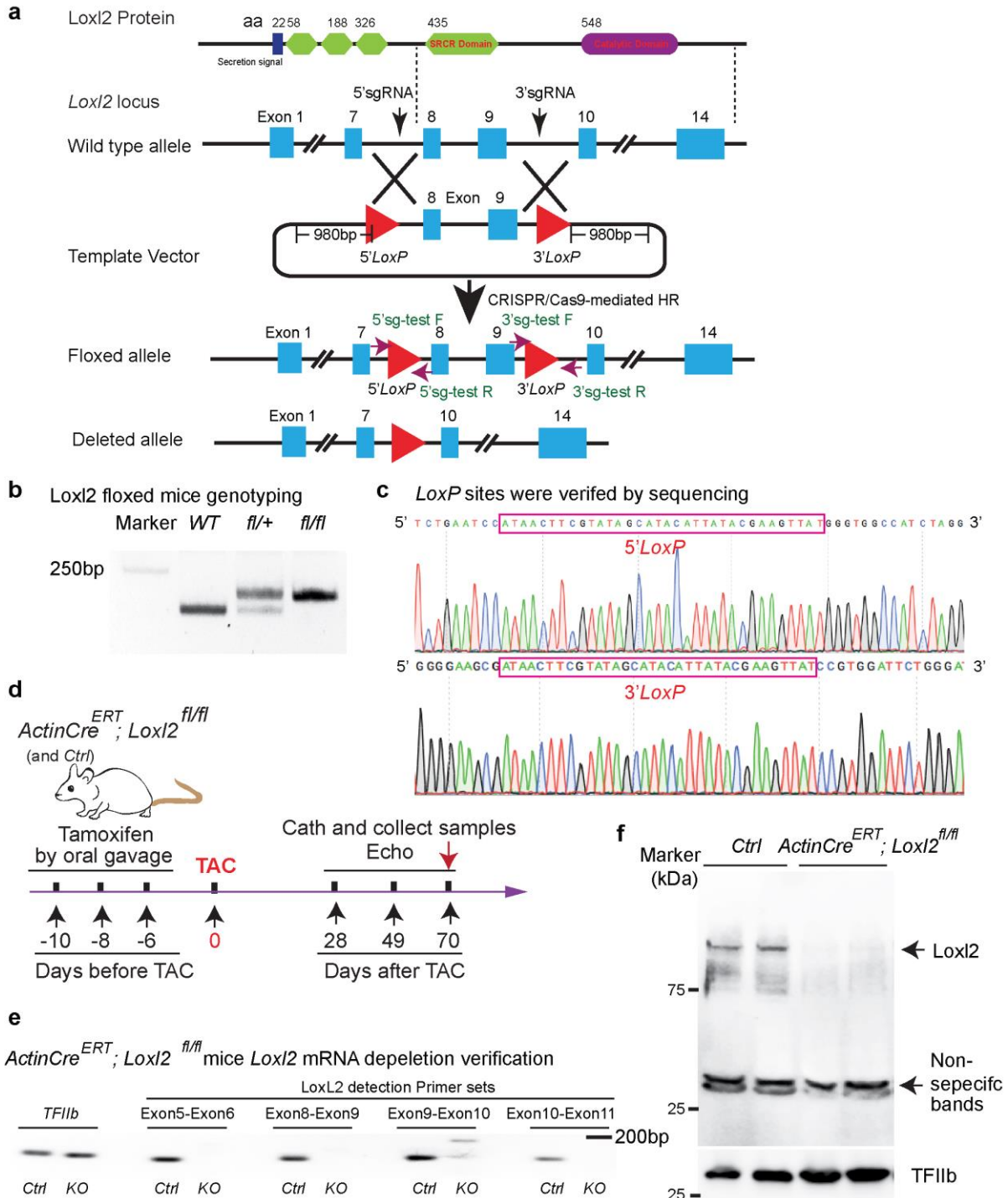


Supplementary Figure 1. *Lox*, *Lox1*–*4* mRNA detection in mouse heart tissues after TAC. (a–e) Quantitation of *Lox2* (a), *Lox* (b), *Lox1* (c), *Lox3* (d), and *Lox4* (e) mRNA in mouse heart ventricles 1–10 weeks after sham/TAC operation, normalized to *TFIIb*. *n*=4–5 mice per group. *P*-value: Student's t-test. Error bar: SEM.

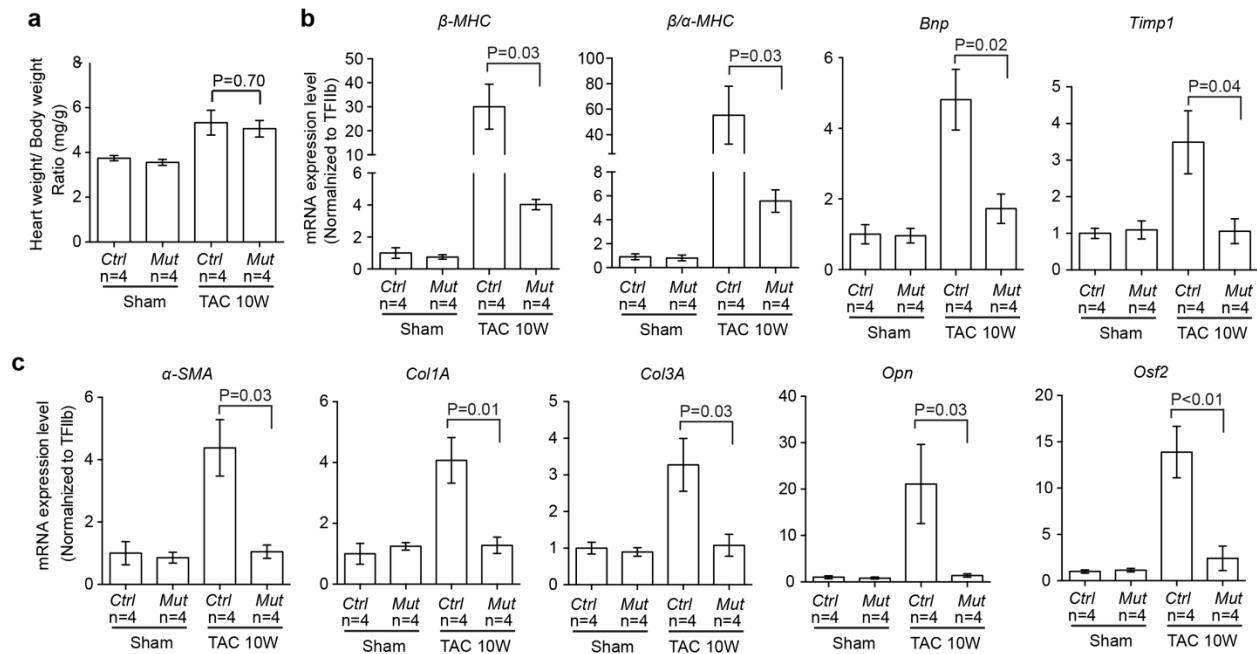


Supplementary Figure 2. LOXL2 antibody treatment has no effects on immune cell infiltration or hypertrophy. (a) Immunostaining of CD4 in the heart 10 weeks after sham/TAC operation of IgG or LoxL2 antibody treated mice. Scale bars, 10 μ m. Blue: Hematoxylin. Brown: CD4. (b) Quantitation of CD4 positive cells/field. $n=4$ mice per group. P -value: Student's t-test. Error bar: SEM. (c) Quantitation of left ventricular pressure of IgG1- or α -LOXL2-treated mice 10 weeks after sham or TAC operation. $n=8-9$ per group. P -value: Student's t-test. Error bar: SEM.

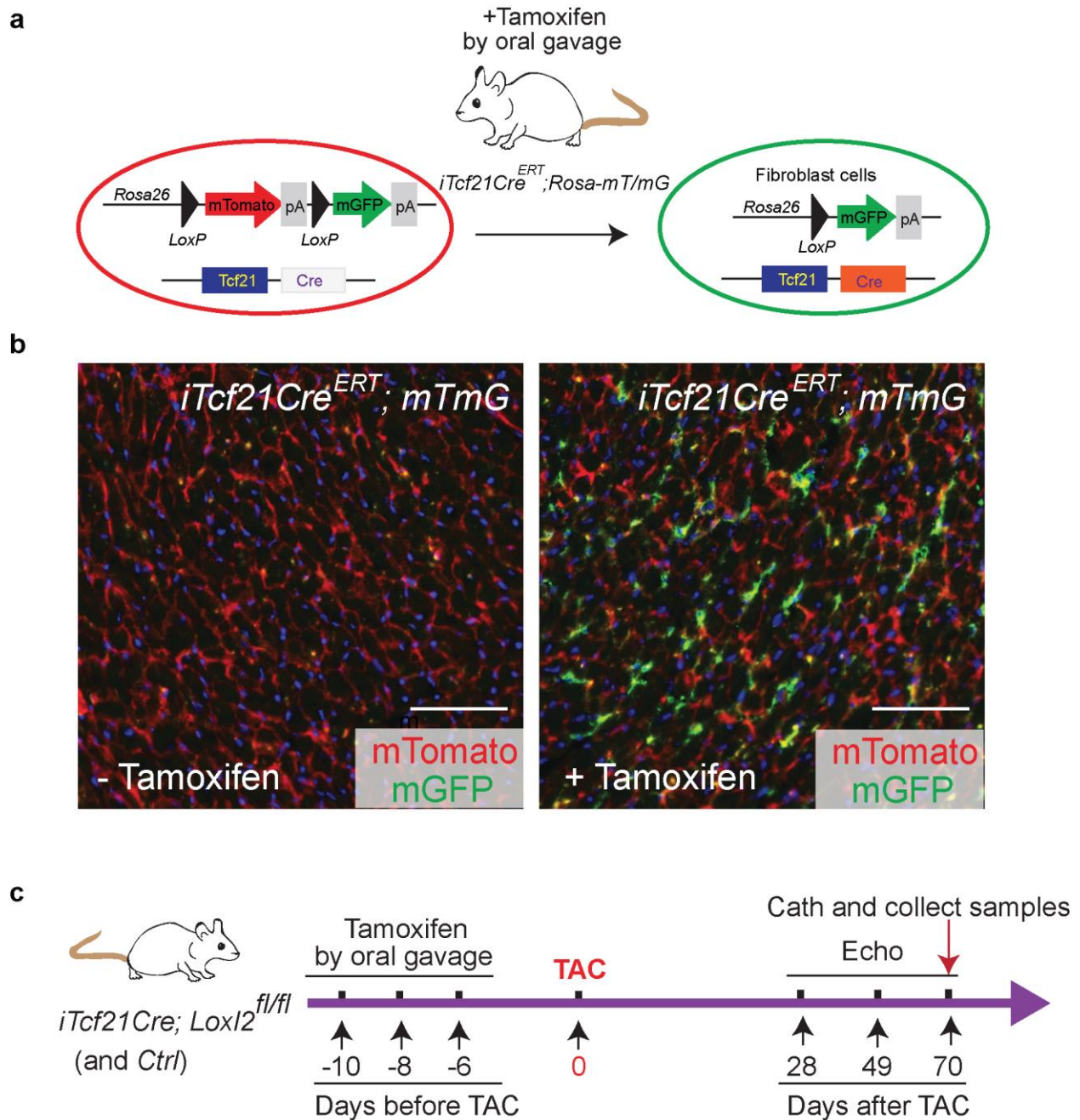


Supplementary Figure 3. Generation of *Lox12* floxed alleles by CRISPR/Cas9 editing. (a) Exon 8 and 9 are flanked by 5' and 3'LoxP sequences in one homologous recombination (HR) reaction to generate LoxP-flanked (floxed) *Lox12* allele. Once

recombined by the Cre recombinase, the *LoxP* sequences loop out and cause the deletion of exon 8 and 9 from the genome (deleted allele), resulting in disruption of gene regions encoding the SRCR and the downstream catalytic domains. **(b, c)** Identification of mouse genotypes by PCR **(b)** with the indicated primers (F1, R1) and sequencing verification of 5' and 3' *LoxP* sites **(c)**. WT, wild-type mice; fl/+, *Lox12*^{fl/+} mice; fl/fl, *Lox12*^{fl/fl} mice. **(d)** Experimental scheme for *Lox12* deletion by Tamoxifen administration. **(e, f)** qPCR and western blotting of heart tissues of *ActinCre*^{ERT};*Lox12*^{fl/fl} KO mice, using PCR primers that target non-deleted regions of *Lox12* **(e)** and polyclonal antibody against *Lox12* **(f)**.

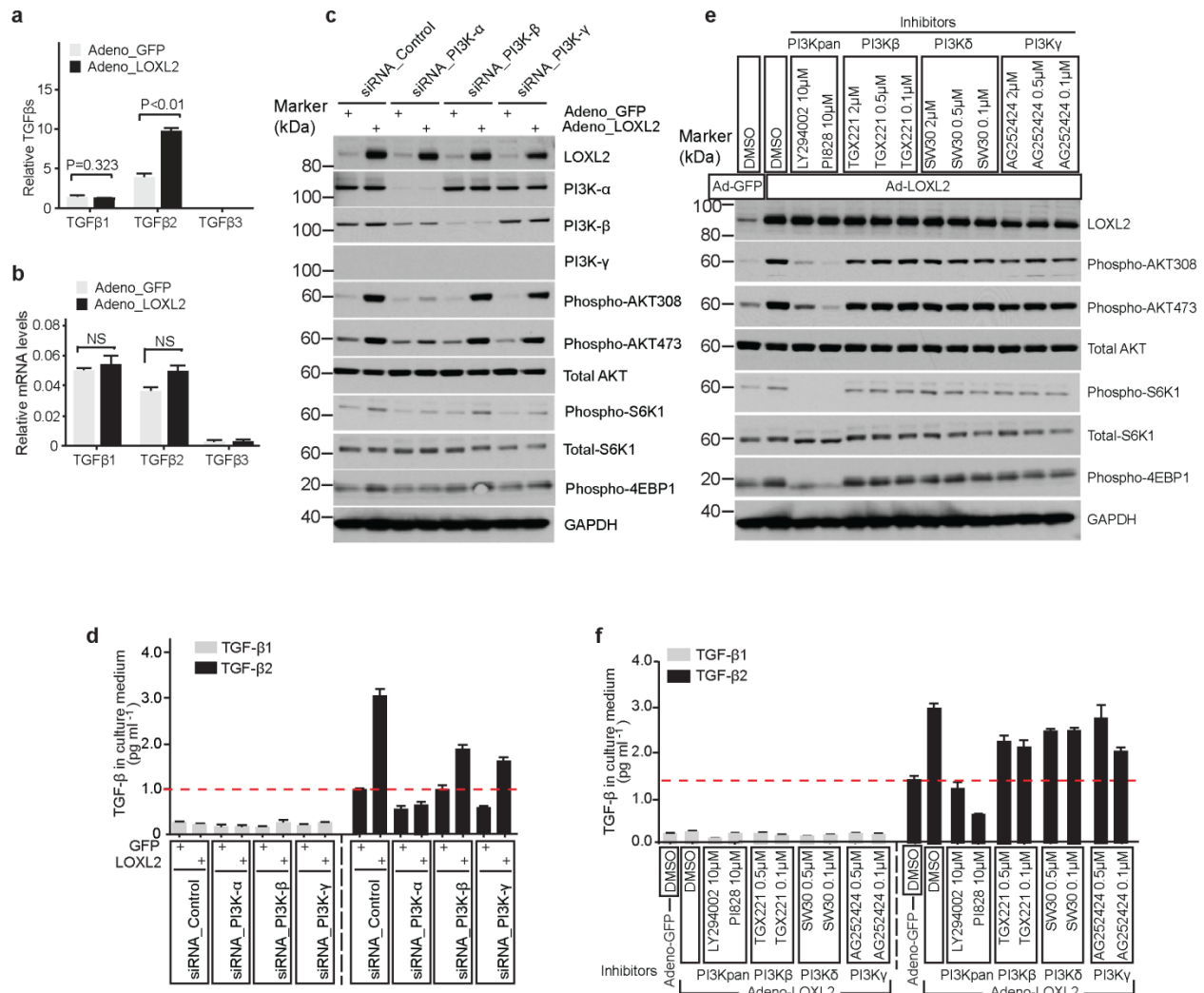


Supplementary Figure 4. *Loxl2* global knockout prevents TAC-induced cardiac interstitial fibrosis and heart dysfunction. (a) Ventricle–body weight ratio of hearts harvested 10 weeks after sham or TAC operation. *Ctrl*: *ActinCre*^{ERT}; *Loxl2*^{fl/+}, *Loxl2*^{fl/fl} or *Loxl2*^{fl/+}. *Mut*: *ActinCre*^{ERT}; *Loxl2*^{fl/fl}. *n*=4 per group. *P*-value: Student’s t-test. Error bar: SEM. (b) Quantitation of cardiac stress marker genes- β -MHC, β/α -MHC, *Bnp* and *Timp1* in the control and mutant mice hearts 10 weeks after sham or TAC operation. *Ctrl*: *ActinCre*^{ERT}; *Loxl2*^{fl/+}, *Loxl2*^{fl/fl} or *Loxl2*^{fl/+}. *Mut*: *ActinCre*^{ERT}; *Loxl2*^{fl/fl}. *n*=4 per group *P*-value: Student’s t-test. Error bar: SEM. (c) Quantitation of cardiac fibrosis marker genes- α -SMA, *Col1A*, *Col3A*, *OPN*, and *OSF2* in the control and mutant mice hearts 10 weeks after sham or TAC operation. *Ctrl*: *ActinCre*^{ERT}; *Loxl2*^{fl/+}, *Loxl2*^{fl/fl} or *Loxl2*^{fl/+}. *Mut*: *ActinCre*^{ERT}; *Loxl2*^{fl/fl}. *n*=4 per group. *P*-value: Student’s t-test. Error bar: SEM.

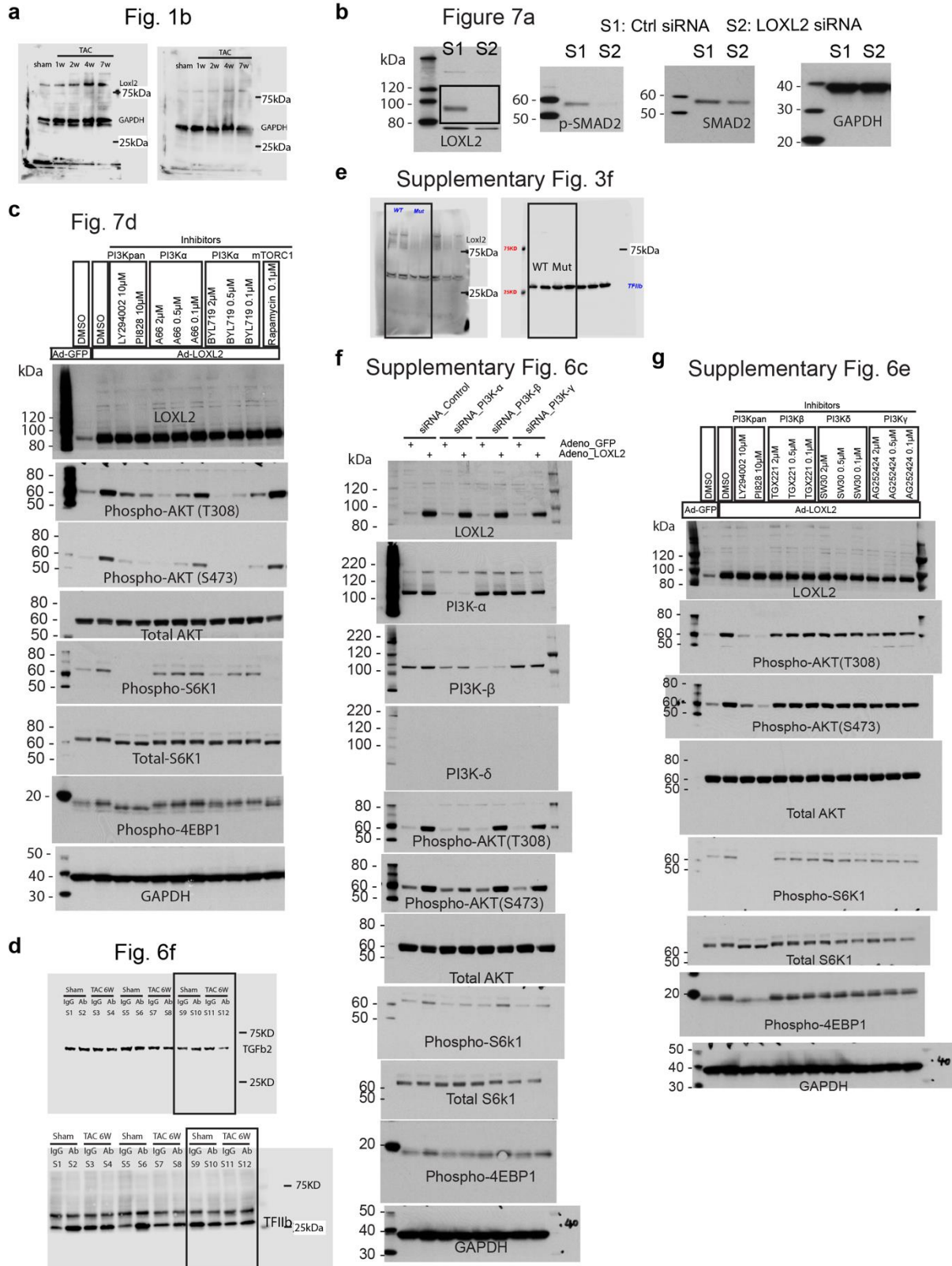


Supplementary Figure 5. Tissue-specific knockout of Loxl2 in cardiac fibroblasts.

(a) Genetic scheme for tissue-specific knockout of Loxl2 in cardiac fibroblasts. (b) Fluorescent images of $iTcf21Cre^{ERT}; mTmG$ mice with or without tamoxifen treatment. Green: GFP indicating Cre activity in fibroblasts in cardiac interstitium. Scale bars, 20 μ m. Red: Tomato indicating cellular sites that do not have Cre activity. (c) Experimental scheme of Cre induction in cardiac fibroblast by Tamoxifen.



Supplementary Figure 6. LOXL2 promotes TGF-β2 production through PI3Kα/AKT/mTORC1. (a, b) TGF-β production (a) and quantitation of *TGF-β* mRNAs (b) in human cardiac fibroblasts infected with adenovirus carrying LOXL2 or GFP. $n=4$, P -value: Student's t-test. Error bar: SEM. (c) Western blot of LOXL2, PI3Kα, PI3Kβ, PI3Kδ, p-AKT, AKT, p-S6K1, S6K1, and p-4E-BP1 with or without PI3Kα, PI3Kβ, and PI3Kδ siRNA in human cardiac fibroblasts infected with GFP/LOXL2. (d) TGF-β production in human cardiac fibroblasts with or without PI3Kα, β, and δ siRNA. $n=4$, P -value: Student's t-test. Error bar: SEM. (e) Western blot of LOXL2, p-AKT, AKT, p-S6K1, S6K1, and p-4E-BP1 with or without PI3K, PI3Kβ and δ inhibitors in cells infected with GFP/LOXL2. (f) TGF-β production in human cardiac fibroblasts with or without PI3K, PI3Kβ, and δ inhibitors. $n=4$, P -value: Student's t-test. Error bar: SEM.



Supplementary Figure 7. The uncropped images of Western Blot Analyses. (a-c) The

original western blot images of Fig. 1b (a), Fig. 7a (b), Fig. 7d (c) and Fig. 7f (d). (e-g) The original western blot images of supplementary Fig. 3f (e), supplementary Fig. 6c (f), and supplementary Fig. 6e (g).

Supplementary Table 1. Demographics of control subjects and patients with HFrEF and HFpEF for biomarker studies.

Control Subjects

Age	Gender	Ethnicity	CAD*
66	M	White	Yes
60	M	White	Yes
59	M	White	Yes
62	F	White	No
58	M	White	No
40	F	White	No
53	F	White	No
42	F	White	No
68	F	White	No
53	M	White	No
53	F	White	No
57	F	White	Yes
38	F	White	No
57	F	White	No
71	M	White	No
56	M	White	No
48	F	White	No
70	M	White	Yes
88	F	White	No
65	M	White	No
79	M	White	No
49	M	Black	No
64	M	White	No
77	F	White	No
62	F	White	No
64	M	White	No
70	M	White	No
53	F	White	No
74	F	White	No
69	M	White	No
71	F	White	No
81	F	White	No
60	F	White	No
82	F	White	No

*CAD: Coronary Artery Disease

Patients with HF_rEF

Age	Gender	Ethnicity	CAD
56	F	Black	No
71	M	White	Yes
69	M	White	Yes
76	F	White	Yes
59	M	Black	No
56	F	Black	Yes
68	F	White	Yes
58	M	Black	No
58	F	White	Yes
65	F	White	Yes
54	M	White	Yes
76	M	White	Yes
59	M	White	Yes
44	F	White	Yes
73	M	White	Yes
89	F	White	No
67	M	White	No
80	M	White	No
45	M	Black	No
59	M	White	Yes
79	F	White	Yes

Patients with LVAD**
(EF≤35%) HF_rEF

Age	Gender	Ethnicity	CAD
53	M	White	Yes
35	M	White	No
40	M	White	Yes
55	M	White	Yes
60	M	White	Yes
73	M	White	No
68	F	White	No
57	M	White	No
30	M	White	Yes
34	M	White	No

**LVAD: Left Ventricular Assistant Device

Patients with LVAD
(EF≥40%)

Age	Gender	Ethnicity	CAD
35	F	White	No
53	F	White	Yes
26	F	White	No
52	F	White	No
43	M	White	No

Patients with HF_pEF

Age	Gender	Ethnicity	CAD
73	F	White	Yes
38	M	White	
41	M	White	
68	F	White	Yes
72	F	White	Yes
82	M	White	Yes
78	M	White	Yes
79	F	Black	Yes
61	M	White	Yes
93	F	White	No
60	M	Black	No
69	M	White	Yes
24	M	White	No
35	M	White	No
82	F	Black	No
62	F	White	No
62	M	White	Yes
73	M	White	Yes
56	F	White	Yes
72	F	White	Yes
70	M	White	Yes
76	F	White	Yes
90	F	White	Yes
57	F	White	Yes
85	F	White	No