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**Title:** ATF6 regulates cardiac hypertrophy by transcriptional induction of the mTORC1 activator, Rheb

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4 ATF6 regulates cardiac hypertrophy by transcriptional induction of the mTORC1  
5 activator, Rheb  
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29 **Short Title:** ATF6 regulates cardiac growth

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1   **ABSTRACT:**

2   **Rationale:** ER stress dysregulates ER proteostasis, which activates the transcription  
3   factor, ATF6, an inducer of genes that enhance protein folding and restore proteostasis.  
4   Due to increased protein synthesis, it is possible that protein folding and, thus, ER  
5   proteostasis are challenged during cardiac myocyte growth. However, it is not known  
6   whether ATF6 is activated, and if so, what its function is during hypertrophic growth of  
7   cardiac myocytes.

8   **Objective:** To examine the activity and function of ATF6 during cardiac hypertrophy.

9   **Methods and Results:** We found that ATF6 was activated and ATF6-target genes were  
10   induced in mice subjected to an acute model of trans-aortic constriction (TAC), or to  
11   free-wheel exercise, which promote adaptive cardiac myocyte hypertrophy with  
12   preserved cardiac function. Cardiac myocyte-specific deletion of *Atf6* (ATF6 cKO)  
13   blunted TAC- and exercise-induced cardiac myocyte hypertrophy and impaired cardiac  
14   function, demonstrating a role for ATF6 in compensatory myocyte growth. Transcript  
15   profiling and chromatin immunoprecipitation identified *RHEB* as an ATF6-target gene in  
16   the heart. *RHEB* is an activator of mTORC1, a major inducer of protein synthesis and  
17   subsequent cell growth. Both TAC and exercise upregulated *RHEB*, activated mTORC1,  
18   and induced cardiac hypertrophy in WT mouse hearts, but not in ATF6 cKO hearts.  
19   Mechanistically, knockdown of ATF6 in neonatal rat ventricular myocytes blocked  
20   phenylephrine (PE)-, and insulin-like growth factor 1 (IGF1)-mediated *Rheb* induction,  
21   mTORC1 activation, and myocyte growth, all of which were restored by ectopic RHEB  
22   expression. Moreover, AAV9-RHEB restored cardiac growth to ATF6 cKO mice  
23   subjected to TAC. Finally, ATF6 induced *RHEB* in response to growth factors, but not in  
24   response to other activators of ATF6 that do not induce growth, indicating that ATF6  
25   target gene induction is stress-specific.

26   **Conclusions:** Compensatory cardiac hypertrophy activates ATF6, which induces *Rheb*  
27   and activates mTORC1. Thus, ATF6 is a previously unrecognized link between growth  
28   stimuli and mTORC1-mediated cardiac growth.

29

30   **Key Words:**

31   Myocytes, cardiac protein folding, proteostasis, cardiac hypertrophy, ATF6, *Rheb*,  
32   mTORC1

33

1   **Non-standard Abbreviations and Acronyms**

2	AAV	adeno-associated virus
3	AdV	adenovirus
4	ANOVA	analysis of variance
5	ATF6	activating transcription factor 6 alpha
6	ATF6 cKO	ATF6 alpha conditional knockout
7	Cat	Catalase
8	ER	endoplasmic reticulum
9	Grp78	78 kilodalton glucose-regulated protein, Hapa5
10	HR	heart rate
11	HW	heart weight
12	ICF	immunocytofluorescence
13	LV	left ventricle
14	LVEDV	left ventricular end diastolic volume
15	LVESV	left ventricular end systolic volume
16	LVIDD	left ventricular inner diameter in diastole
17	LVIDS	left ventricular inner diameter in systole
18	PWTD	left ventricular posterior wall thickness in diastole
19	PWTS	left ventricular posterior wall thickness in systole
20	Rheb	Ras homologue enriched in brain
21	SR	sarcoplasmic reticulum
22	TAC	transverse aortic constriction
23	TL	tibia length
24	TM	tunicamycin
25	UPR	unfolded protein response
26		
27		
28		

1      **INTRODUCTION:**

2  
3      Protein homeostasis, or proteostasis involves the coordination of protein synthesis  
4 and folding to ensure proteome integrity and vital cell function<sup>1</sup>. In cardiac myocytes the  
5 endoplasmic reticulum (ER) is a major site of synthesis of proteins that are critical for  
6 proper function of the heart, including many calcium-handling proteins, receptors, and  
7 secreted proteins, such as hormones, stem cell homing factors, and growth factors<sup>2,3</sup>.  
8 Therefore, ER proteostasis maintains the integrity of the cardiac myocyte proteome and,  
9 thus, cardiac contractility. Increased protein synthesis in growing cardiac myocytes must  
10 be balanced by increased protein-folding to avoid the accumulation of toxic misfolded  
11 proteins; thus growth poses a potential challenge to cardiac myocyte proteostasis<sup>4</sup>.  
12 However, the molecular mechanisms underlying the maintenance of ER proteostasis  
13 during cardiac myocyte growth are not well understood.

14     ER proteostasis is controlled in all mammalian cells by several ER-transmembrane  
15 sensors of protein misfolding, including the adaptive transcription factor, ATF6<sup>5</sup>. When  
16 protein synthesis surpasses the capacity of the protein-folding machinery, increases in  
17 misfolded proteins cause the translocation of the ER-transmembrane, 670-amino acid,  
18 90 kD form of ATF6, to the Golgi, where it is clipped, liberating an N-terminal fragment  
19 that serves as a transcription factor. This 50 kD active form of ATF6 regulates a gene  
20 program that is responsible for the expression of numerous proteins that enhance ER  
21 protein folding, which adaptively restores the balance between protein synthesis and  
22 folding<sup>6,7</sup>. Thus, nodal proteostasis regulators, such as ATF6, that sense and maintain  
23 this balance could play important roles in optimizing cardiac myocyte growth; however,  
24 neither the activation nor the function of ATF6 in the setting of hypertrophic cardiac  
25 growth has been examined. Accordingly, here we studied the effects of *Atf6* deletion in  
26 mouse hearts and in cultured cardiac myocytes during physiologically-relevant  
27 maneuvers known to promote compensatory cardiac hypertrophy in either a concentric  
28 (pressure overload)<sup>8</sup> or eccentric (exercise)<sup>9</sup> manner, positing that the absence of ATF6  
29 would imbalance proteostasis, which would be maladaptive.

30     Both growth maneuvers activated ATF6, and *Atf6* deletion was maladaptive, as  
31 evidenced by impaired cardiac function. However, surprisingly, cardiac myocyte growth  
32 was also impaired upon *Atf6* deletion. This was unexpected, since *Atf6* is not known to  
33 be required for cardiac myocyte growth. Further mechanistic studies showed that ATF6  
34 is activated as a result of the increased demands placed on the ER protein folding  
35 machinery during growth-related increases in protein synthesis. Moreover we found that  
36 *Atf6* serves a previously unrecognized role as a molecular link between growth stimuli  
37 and activation of mammalian/mechanistic target of rapamycin complex 1 (mTORC1), a  
38 major promoter of protein synthesis and consequent growth of cardiac myocytes<sup>10-15</sup>.  
39 Two conditions need to be met for mTORC1 to be activated; 1) in response to a growth  
40 stimulus, mTORC1 needs to translocate to organelles, such as lysosomes<sup>16</sup>, where it  
41 encounters the small GTPase activator of mTORC1, Rheb<sup>17</sup>, and 2) Rheb must be  
42 active and present in sufficient quantities<sup>18</sup>. In terms of Rheb activation, it is known that  
43 growth stimuli lead to the phosphorylation and, thus, inhibition of the Rheb GTPase-  
44 activating protein (GAP), TSC1/TSC2<sup>19</sup>, which increases the GTP-loading state and,  
45 thus, the activity of Rheb. However, the molecular mechanisms underlying the *Rheb*  
46 gene expression are less well understood. Here, we showed, for the first time, that ATF6  
47 is an inducer of *Rheb*, and in this way, ATF6 coordinates protein synthesis and protein  
48 folding, ensuring the adaptive maintenance of proteostasis in growing cardiac myocytes.  
49 Thus, ATF6 is a newly identified and essential member of mTORC1 growth signaling in  
50 cardiac myocytes in the heart.

1   **Methods:**

2   Further details on the Methods can be found in the Online Supplement.

3   *Laboratory Animals*: The research reported in this paper has been reviewed and  
4   approved by the SDSU Institutional Animal Care and Use Committee and it conforms to  
5   the Guide for the Care and Use of Laboratory Animals published by the National  
6   Research Council.

7   *ATF6 Floxed Mice*: *Atf6 $\alpha^{fl/fl}$*  mice used in this study were generated by Dr. Gokhan S.  
8   Hotamisligil<sup>20</sup>. All of the mice used in this study were 10 week-old males.

9   *Statistics*: Unless otherwise stated, values shown are mean  $\pm$  SEM and statistical  
10   treatments are either a t-test or a one-way ANOVA followed by Newman-Keuls *post hoc*  
11   analysis.

12

1    **RESULTS:**

- 2    • ATF6 is required for cardiac myocyte hypertrophy in response to pressure overload

3       To examine the role of *Atf6* in cardiac myocytes on heart growth, we generated an  
4       *Atf6* conditional knockout mouse (ATF6 cKO) by injecting *Atf6*<sup>f/f</sup> mice with a recombinant  
5       AAV9 that encodes *Cre* under the control of the *cardiac troponin T* promoter (**Fig. 1A**).  
6       Compared to *Atf6*<sup>f/f</sup> injected with AAV9-Con, injection with AAV9-CRE effectively  
7       reduced *Atf6* mRNA from cardiac myocytes isolated from *Atf6*<sup>f/f</sup> mice, but not non-  
8       cardiac myocytes, or liver (**Fig. 1B**). *Atf6*<sup>f/f</sup> mice injected with AAV9-Con (Con) or AAV9-  
9       CRE (ATF6 cKO), were subjected to TAC and examined 7d later, when hypertrophic  
10      growth is maximal<sup>21</sup> and structural remodeling is compensatory<sup>22,23</sup>. TAC activated ATF6  
11      in Con mouse hearts, as evidenced by increased levels of the active, 50 kD form of  
12      ATF6 (**Fig. 1C**). This was unexpected, since ATF6 is not known to be activated in  
13      cardiac myocytes by any growth stimulus. Coordinate with ATF6 activation, TAC  
14      increased expression of numerous canonical ATF6 target genes (**Fig. 1C-D; Online Fig.**  
15      **IA**). As expected, ATF6 was undetectable in ATF6 cKO mouse hearts (**Fig. 1C-D**). TAC  
16      increased Con mouse heart weights, but, surprisingly, this growth effect was significantly  
17      blunted in ATF6 cKO mouse hearts (**Fig. 1E**). TAC increased *Nppa* and *Nppb*  
18      expression to similar extents in both Con and ATF6 cKO mice, while the induction of  
19      *Myh7* and *Col1a1* was slightly greater in the ATF6 cKO mice (**Fig. 1F**). This, coupled  
20      with the decrease in *Atp2a2* i.e. SERCA2a in ATF6 cKO mice, suggests a blunted  
21      compensatory response in the absence of ATF6. In Con mouse hearts, cardiac function,  
22      including fractional shortening was preserved, while chamber dimensions were  
23      unchanged after TAC (**Fig. 1G; Online Table I**) and cardiac myocyte size was increased  
24      (**Fig. 1H**), consistent with the compensatory nature of cardiac hypertrophy in mice at this  
25      time after pressure overload<sup>24</sup>. However, in contrast to Con, in ATF6 cKO mice  
26      subjected to TAC myocyte size was decreased compared to Con (**Fig. 1H**) and fractional  
27      shortening was impaired (**Fig. 1G**) with increased chamber dimensions, such as LVEDV  
28      and LVESV, despite high frequency Doppler measurements between right and left  
29      carotid arteries demonstrating consistent and identical pressure overload in TAC-  
30      operated Con and ATF6 cKO mice (**Online Table I**). Along with increased plasma levels  
31      of cTnI (**Online Fig. IB**), these results are consistent with the initial stages of chamber  
32      dilation, as well as myocardial damage and decompensation in the ATF6 cKO mice.  
33      Thus, ATF6 is activated by pressure overload and is required for hypertrophy.  
34

- 35    • ATF6 is required for cardiac myocyte hypertrophy in response to exercise

36       To assess the breadth of the impact of ATF6 on heart growth, we examined the  
37       effects of cardiac myocyte-specific ATF6 deletion in mice subjected to free-wheel  
38       exercise<sup>25, 26</sup> (**Fig. 2A**). Similar to TAC, exercise surprisingly activated ATF6 and  
39       induced ATF6 target genes in Con, but not in ATF6 cKO mice (**Fig. 2B-C**). As expected,  
40       compared to Con sedentary mice, Con mice subjected to exercise exhibited increased  
41       heart weights and LV wall thickness, as well as myocyte size (**Fig. 2D, 2F; Online Table**  
42       **II**). While *Nppa* and *Nppb* were mildly increased, *Atp2a2* was robustly increased by  
43       exercise in Con mouse hearts, and there was no change in *Myh7* or *Col1a1* (**Fig. 2E**);  
44       this gene profile is typical of adaptive cardiac hypertrophy in exercising mice<sup>24, 27</sup>. In  
45       contrast to Con, in ATF6 cKO mice subjected to exercise there was no change in heart  
46       weights or LV wall thickness (**Fig. 2D; Online Table II**), reduced increases in myocyte  
47       size (**Fig. 2F**), and reduced induction of ATF6 target genes (**Fig. 2C**). Compared to  
48       exercised Con mice, exercised ATF6 cKO mice showed no increase in *Nppa*, and

1 neither Con nor ATF6 cKO mice showed significant changes in *Nppb* or *Myh7*.  
2 Importantly, while Con mice exhibited decreased *Col1a1* and increased *Atp2a2* after  
3 exercise, which are beneficial genetic changes typical of this regime, the ATF6 cKO  
4 mice failed to adapt and had increased *Col1a1* and no change in *Atp2a2* (**Fig. 2E**).  
5 Thus, ATF6 is activated by exercise and is required for compensatory hypertrophy in this  
6 exercise model.  
7

8 • Rheb is an ATF6-inducible gene in the heart

9 Since there are no known *Atf6*-inducible genes that are required for cardiac myocyte  
10 growth, we turned to transcript profiling for clues to the identities of such genes. RNA  
11 sequencing of the hearts of our previously published transgenic mice that express  
12 activated ATF6<sup>28</sup> (**Online Table III**) revealed that ATF6 induced 51 genes in the gene  
13 ontology category, small GTPase mediated signal transduction; this category includes  
14 the ras-related small GTPase, Ras homologue enriched in brain (*RHEB*) (**Fig. 3A**;  
15 **Online Fig. IIA**). Rheb is required for activation of mTORC1, however, only in the  
16 presence of a growth stimulus. Accordingly, we focused on *Rheb* as a candidate gene  
17 through which ATF6 might contribute to cardiac hypertrophy, pursuing the hypothesis  
18 that increased *Rheb* gene expression and subsequent mTORC1 activation under growth  
19 conditions are *Atf6*-dependent. The upregulation of *RHEB* by ATF6 in mouse hearts  
20 observed by RNA sequencing was confirmed by qRT-PCR (**Online Fig. IIB**). Consistent  
21 with ATF6 as a possible transcriptional inducer of *Rheb* was our finding that the *Rheb*  
22 promoter has two potential ATF6 binding sites, which we call ER stress response  
23 elements (ERSEs)-1 and -2 (**Fig. 3B**). Chromatin immunoprecipitation (ChIP) showed  
24 that ATF6 binds to both sites in the *RHEB* gene in neonatal rat ventricular myocytes  
25 (NRVM) (**Fig. 3C**). The progressive decline in *RHEB* promoter activity in plasmids that  
26 encode 5'-truncation deletions of the rat *RHEB* promoter driving luciferase demonstrated  
27 the importance of these putative ERSEs in ATF6-mediated *RHEB* promoter activation  
28 (**Online Fig. IIC**). To mechanistically investigate the functional involvement of these  
29 ERSEs further, we mutated either or both ERSE (**Fig. 3D**). Mutating either ERSE  
30 decreased ATF6 *RHEB* promoter activation by ATF6, however, the promoter-proximal  
31 site, i.e. ERSE-1 appeared to have the largest effect (**Fig. 3E**). To determine whether  
32 ATF6 is sufficient to induce *Rheb* in the heart, *in vivo*, mice were injected with a  
33 recombinant AAV9 that encodes activated ATF6, i.e. ATF6(1-373). qRT-PCR and  
34 immunoblotting demonstrated that activated ATF6 increased *RHEB* mRNA and protein  
35 in the heart (**Online Fig. IID-F**). These results are the first demonstration in any cell type  
36 that ATF6 induces *RHEB*, implicating ATF6 as a critical link between growth stimuli and  
37 mTORC1 activation.  
38

39 • RHEB induction during pressure-overload and exercise requires ATF6

40 We found that *RHEB* was strongly induced in Con mice after either TAC or exercise,  
41 but not in ATF6 cKO mouse hearts (**Fig. 3F-K**). Thus, ATF6 is necessary for the  
42 upregulation of RHEB in these models of cardiac hypertrophy, *in vivo*. Since RHEB is  
43 required for mTORC1 activation in response to a growth stimulus, we assessed  
44 mTORC1 pathway activation. As expected, pressure-overload and exercise both  
45 activated mTORC1, as shown by increased phosphorylation of mTORC1 (Ser2448), p70  
46 ribosomal S6 kinase (S6K; Thr389), and eukaryotic translation initiation factor 4E-  
47 binding protein 1 (4E-BP1; Thr37/46); however, mTORC1 activation was blunted in  
48 ATF6 cKO mouse hearts (**Fig. 3G, J**), consistent with the key role for ATF6 in mTORC1  
49 activation by growth stimuli. To examine whether ATF6 might affect other signaling

pathways leading to mTORC1 activation, we assessed the phosphorylation of Akt on Ser308 and the phosphorylation of TSC2, both of which lie upstream of Rheb in the mTORC1 signaling pathway. We found that pressure overload increased phosphorylation of Akt (Thr308) and TSC2 (Thr1462), as expected; however, in contrast to Rheb expression, neither of these phosphorylation events were affected by *ATF6* deletion (**Online Fig. IIIA**). Thus, the deficit in mTORC1 activation in *ATF6* cKO mice must reside downstream of Akt and TSC2, i.e. Rheb. We also examined whether *ATF6* deletion affected other well known canonical hypertrophy signaling pathways, but found that neither phosphorylation of Akt on Ser473, Erk phosphorylation (**Online Fig. IIIA**) or calcineurin activation (**Online Fig. IIIB**) were affected by *ATF6* deletion. These results pinpoint the growth deficit in the *ATF6* cKO mouse hearts to the inability to upregulate Rheb.

13

- 14 • RHEB is required for PE- and IGF1-induced cardiac myocyte growth

15 To explore the mechanistic relationship between *ATF6* and *RHEB* we used *RHEB*  
16 and *ATF6* loss-of-function approaches in NRVM treated with the  $\alpha_1$ -adrenergic  
17 receptor agonist, phenylephrine (PE) or insulin-like growth factor 1 (IGF1), which  
18 recapitulate much of the intracellular signaling during pressure-overload or exercise-  
19 induced hypertrophy, respectively<sup>29</sup>. Knocking down either *ATF6* or *RHEB* abrogated the  
20 effects of PE or IGF1 on cardiac myocyte hypertrophy, fetal gene induction, *ATF6* target  
21 gene induction and mTORC1 signaling (**Fig. 4A-E; Online Fig. IVA, IVC; Fig. 5A-E;**  
22 **Online Fig. IVB**), but had no effect on mTORC2 signaling, as assessed by  
23 phosphorylation of Akt on Ser-473 (**Online Fig. IVD-E**). To further substantiate the  
24 results with *Rheb* siRNA, we used a different *Rheb* loss-of-function approach involving  
25 the *Rheb* inhibitor, Lonafarnib<sup>30</sup>. Lonafarnib mimicked the effects of *Rheb* siRNA on PE-  
26 and IGF1-mediated *ATF6* activation, mTORC1 signaling, *ATF6* gene induction and  
27 growth in NRVM (**Online Fig. V**).

28 To complement *ATF6* loss-of-function approach, we used a gain-of-function  
29 approach, examining the effects of ectopic expression of *ATF6* and *RHEB*. In the  
30 absence of a growth stimulus, ectopic expression of *ATF6* did not increase myocyte  
31 growth, as expected, due to the absence of mTORC1 activation under these conditions  
32 (**Online Fig. VIA Con**). Either PE or IGF1 increased myocyte growth, which was  
33 completely blocked by the mTORC1 inhibitor, rapamycin, as expected (**Online Fig. VIA,**  
34 **PE and IGF1, red vs blue**). Ectopic *ATF6* augmented the growth-promoting effects of  
35 PE and IGF1, which were also completely blocked by rapamycin (**Online Fig. VIA, PE**  
36 **and IGF1, black and green**). Moreover, ectopic *ATF6* slightly augmented PE- and  
37 IGF1-stimulated NRVM growth, however, it was not able to restore growth in cells  
38 treated with either *RHEB* siRNA or Lonafarnib (**Online Fig. VIB-C**). As expected, ectopic  
39 expression of *RHEB* had no effect in the absence of a growth stimulus; however, upon a  
40 growth stimulus, the loss of growth and mTORC1 activation seen with *ATF6* siRNA were  
41 completely restored by ectopically expressed *RHEB* (**Fig. 4F-H; Fig. 5F-H**).

42

- Mechanistic Relationship between Growth Signaling and the UPR

43 The unfolded protein response (UPR), which in addition to *ATF6*, is mediated by  
44 PERK and IRE1<sup>5</sup>, is activated by the misfolding of proteins induced by a variety of  
45 chemical and pathophysiological treatments, most of these do not promote growth. In  
46 fact, the UPR is not widely considered to be growth-promoting. Accordingly, since we  
47 found here that *ATF6* can be activated during growth, we assessed how growth affected  
48 the other arms of the UPR. We found that PE and IGF1 activated all three arms of the

1 UPR in a rapamycin-sensitive manner (**Online Fig. VIIA**), indicating that mTORC1  
2 activation is required for UPR activation during growth. We then individually knocked  
3 down *ATF6*, *PERK* and *IRE1*, and found that only *ATF6* knockdown blunted growth  
4 (**Online Fig. VIIB-C**). To ensure that the effects of *ATF6* on growth are dependent on  
5 the transcriptional effects of *ATF6*, we showed that NRVM infected with AdV-*ATF6*(1-  
6 373) [active] exhibited increased growth in response to PE, especially when endogenous  
7 *ATF6* was knocked down, however AdV-*ATF6*(94-373) [transcriptionally inactive] did not  
8 (**Online Fig. VIID**).

9 Next, we examined the effect on mTORC1 signaling of other UPR stimulators that do  
10 not affect growth, such as tunicamycin (TM), which increases ER protein misfolding by  
11 inhibiting protein glycosylation in the ER. In contrast to PE, activation of *ATF6* by TM  
12 was not dependent on *RHEB* (**Fig. 6A-B**). Additionally, while *RHEB* knockdown blocked  
13 PE- and IGF1-mediated induction of *ATF6* target genes, (**Fig. 4E, 5E**), it had no effect  
14 on TM-mediated induction of *ATF6* target genes (**Fig. 6C**). Thus, there are  
15 RHEB/growth-dependent and RHEB/growth-independent pathways that lead to *ATF6*  
16 activation and induction of *ATF6* target genes.

17 • Stimulus-dependent Differential Induction of *ATF6* Target Genes

18 We dived deeper into the mechanism of RHEB/growth-dependent and RHEB/growth-  
19 independent pathways of *ATF6* activation. We previously showed that *ATF6* induces  
20 some proteins targeted to the ER, where they enhance protein folding (e.g.  
21 *HSPA5/GRP78*), and others located outside the ER, where they serve other functions.  
22 One example of the latter is our finding that I/R activates *ATF6*-dependent induction of  
23 *catalase (CAT)*, which resides in peroxisomes and neutralizes damaging ROS. Here, we  
24 provide an additional example of an *ATF6*-inducible gene, *RHEB*, that encodes a protein  
25 that resides outside the ER. Because of the differences in the locations and functions of  
26 *Hspa5*, *Cat*, and *Rheb*, we posited that they might be differentially induced by treatments  
27 that cause ER protein misfolding (TM), or oxidative stress (I/R) but do not induce growth,  
28 or to a treatment that induces growth (PE). While, for the most part, the mRNA levels for  
29 all three genes were increased by all the treatments, the quantitative nature of induction  
30 differed depending on the treatments, such that TM, sl/R, and PE had the greatest  
31 effects on induction of *Hspa5*, *Cat*, and *Rheb*, respectively (**Fig. 6D**). Notably, *CAT*  
32 induction was highly selective, showing an approximate 6-fold induction by sl/R, and  
33 much less induction by either TM or PE (**Fig. 6D, Cat**). Remarkably, *RHEB* induction  
34 was also highly selective, showing the least induction by TM or sl/R, while being induced  
35 by over 5-fold by PE (**Fig. 6D, Rheb**). Importantly, all of these effects depended on  
36 *ATF6* (**Fig. 6E**).  
37

38 To dissect this stimulus-dependent differential gene induction further, we showed  
39 that promoter/luciferase reporter constructs for *Hspa5*, *Cat*, and *Rheb* (**Fig. 6F**) were  
40 also differentially induced by TM, sl/R and PE, mimicking mRNA induction (**Fig. 6G**).  
41 Importantly, as with the mRNA, all of these effects depended upon *ATF6* (**Fig. 6H**).  
42

43 These stimulus-specific effects of *ATF6* on *Hspa5*, *Cat*, and *Rheb* could be due to  
44 the stimulus-dependent binding of *ATF6* to the ERSEs in these genes. To test this, we  
45 developed a new method for measuring *ATF6* binding to the *HSPA5*, *CAT*, and *RHEB*  
46 promoters in cells treated with TM, sl/R or PE. To this end we generated a recombinant  
47 AdV FLAG full-length p90 *ATF6*, i.e. *ATF6*(1-670), which remains in the ER in the  
48 absence of ER stress, and, therefore, can not bind to ERSEs. NRVM expressing FLAG-  
49 *ATF6*(1-670) were treated with TM, sl/R or PE, each of which induce the formation of the

1 FLAG-tagged N-terminal, active p50 form of ATF6, so it can bind to ERSEs. ChIP  
2 demonstrated that the binding of ATF6 to these genes differed, depending on the  
3 stimulus, mimicking the mRNA induction and promoter activation (**Fig. 6I**). These effects  
4 were not seen with AdV encoding only FLAG, verifying ATF6-specificity (**Fig. 6J**). This  
5 shows, for the first time in any cell type, that ATF6 can be activated by a broad spectrum  
6 of conditions that affect proteostasis in a variety of ways, yet the relative induction of  
7 ATF6 targets differs in a condition-dependent manner.

8

- 9     • Ectopic Expression of RHEB Restores Cardiac Growth to ATF6 cKO Mouse Hearts

10 Next, we assessed the effects of ectopic expression of *RHEB* in the heart, *in vivo*  
11 using a new recombinant AAV9-RHEB (**Fig. 7A**). In ATF6 cKO mice, AAV9-RHEB  
12 effectively restored the loss of mTORC1 signaling, hypertrophic growth and cardiac  
13 function, as well as the hypertrophic and ATF6 gene programs in response to TAC (**Fig.**  
14 **7B-F; Online Table IV**). Thus, it is by increasing RHEB that ATF6 influences mTORC1  
15 signaling and subsequent cardiac myocyte growth, fetal gene expression and ATF6-  
16 target gene expression.

17

- 18     • ATF6 Activation in Response to Growth Requires mTORC1 Activation, Protein  
19         Synthesis and Protein Misfolding

20 To this point, mTORC1 and ATF6 activation were shown to be dependent on each  
21 other under the growth conditions examined. To account for this interdependence, we  
22 posited a temporal sequence of events, wherein the initial event is mTORC1 activation,  
23 which depends on basal levels of Rheb (**Fig. 8A, Step 1**). This initial mTORC1 activation  
24 precedes, but drives initial increases in protein synthesis that place demands on the  
25 protein-folding machinery (**Fig. 8A, Step 2**), which activates ATF6. Then, ATF6 serves  
26 canonical- and non-canonical roles (**Fig. 8A, Steps 3, 4**), the latter of which includes  
27 *RHEB* induction (**Fig. 8A, Step 5**), which is necessary to sustain mTORC1 activation  
28 (**Fig. 8A, Step 6**) and the continued increases in protein synthesis that required for  
29 growth and cardiac myocyte hypertrophy (**Fig. 8A, Step 7**). To examine this hypothesis,  
30 a TAC time course was carried out. At 3h of TAC, a time when mTORC1 is activated,  
31 but protein synthesis has not yet increased, mTORC1 signaling was activated, but ATF6  
32 was not activated and *RHEB* was not induced (**Fig. 8B, 3h**). However, at both 2 and 7d  
33 of TAC, when protein synthesis is increased, mTORC1 signaling and ATF6 were  
34 activated, and *RHEB* was induced (**Fig. 8B, 2d and 7d**). As expected, heart weights  
35 increased as a function of TAC time from 3h to 7d (**Fig. 8C; Online Table V**). Thus,  
36 mTORC1 activation occurred soon after TAC and preceded ATF6 activation. Further  
37 supporting our hypothesis that initially, mTORC1 activation precedes ATF6 activation  
38 were results of a 3h TAC experiment in ATF6 cKO mice, where, in contrast to longer  
39 times of TAC (i.e. 7d - **Fig. 3G**), the deletion of ATF6 did not affect mTORC1 activation  
40 (**Fig. 8D**). As expected, heart weights did not change under these conditions (**Fig. 8E;**  
41 **Online Table VI**).

42 Consistent with these results, when examining the effect of PE and IGF1 at the  
43 earliest time points, just prior to when protein synthesis is greatest in NRVM, knocking  
44 down ATF6 did not affect mTORC1 activation (**Online Fig. VIIIA**), but again, ATF6  
45 activation was rapamycin-dependent (**Online Fig. VIIIB**). Moreover, inhibiting protein  
46 synthesis with cycloheximide had no effect on mTORC1 activation at these short times  
47 of PE or IGF1 treatment, but impaired ATF6 activation and *RHEB* induction, indicating  
48 that protein synthesis is required for ATF6 activation and subsequent *RHEB* induction

1 (Online Fig. VIIIC). Finally, in NRVM treated with the chemical chaperone, 4PBA, PE  
2 and IGF1 activated mTORC1 however, ATF6 was not activated and *RHEB* was not  
3 induced (Online Fig. VIIID), indicating the increase in protein folding demand driven by  
4 increases in protein synthesis are responsible for activating ATF6.  
5  
6

1    **DISCUSSION:**

2    • ATF6 is Required for Growth of the Heart

3    While previous studies reported increased expression of a few ER stress genes in  
4    mouse models of pressure overload, implicating ER protein misfolding<sup>31-34</sup>, prior to our  
5    study here, neither the activation nor the roles for ATF6 in cardiac myocytes during  
6    cardiac growth had been examined. Here, we showed, for the first time that ATF6, a  
7    major mediator of the UPR, is activated by diverse growth stimuli and that ATF6 is  
8    required for growth of the heart in response to these stimuli. We determined that the  
9    mechanism of this effect involves ATF6-mediated induction of *RHEB* (Fig. 8A). It was  
10   surprising to find that ATF6 is required for heart growth, considering the UPR is not  
11   widely known to be involved in growth processes. However, this non-canonical role for  
12   ATF6 complements its canonical role as a sensor of misfolded proteins in the ER and,  
13   as such, a sensor of increases in protein folding demand, which occur during growth.  
14   Thus, ATF6 maintains proteostasis and proteome integrity when the heart is stimulated  
15   to grow in a compensatory manner.

16   We also found that, depending on the stimulus, ATF6 target genes are differentially  
17   expressed due to the unique effects that the stresses have on ATF6 binding to, and  
18   thus, transcriptional activation of ATF6 target genes. Such differential ATF6 target gene  
19   induction by treatments that all activate ATF6 suggests that there are yet-to-be-  
20   described regulatory layers that fine-tune the ATF6 gene program to best adapt to the  
21   conditions. Some possible mechanisms that could contribute to this differential  
22   expression are beginning to emerge, as it has been shown that ATF6 can interact with  
23   other transcription factors, such as Nrf1, PGC1 $\alpha$  and  $\beta$ , and ERR $\gamma$ <sup>35-37</sup> which changes  
24   the transcriptional programming in ways that fine-tune ATF6 target gene induction.

26   • Rheb in the Heart

27   Rheb was originally documented as an mTORC1 activator in the brain<sup>38</sup>, this role has  
28   been demonstrated in numerous other tissues and organs<sup>17, 39, 40</sup>. Global deletion of  
29   *Rheb* is embryonic lethal, in part due to cardiac defects<sup>41</sup>, demonstrating the importance  
30   of Rheb-mediated mTORC1 activation in heart growth and development. The growth-  
31   promoting effect of *Rheb* gain-of-function was demonstrated in adult rat ventricular  
32   myocytes transfected with adenovirus encoding *Rheb*<sup>42</sup>. However, overexpression of  
33   *Rheb* in transgenic mice increased infarct size, in part because Rheb inappropriately  
34   decreased autophagy, which is adaptive in this disease setting<sup>43</sup>. Pharmacological  
35   inhibition of Rheb in mice subjected to TAC for three weeks was cardioprotective<sup>14</sup>.  
36   These findings differ from our study, perhaps because different times after TAC were  
37   studied, or different approaches to decreasing Rheb. It is also possible that Rheb  
38   induction and mTORC1 activation have different roles in a severe afterload-induced  
39   hypertrophy model, such that acute activation works in a compensatory manner, but  
40   chronic activation drives decompensation. The  $\alpha$ MHC-CRE-dependent conditional  
41   deletion of *Rheb* from mouse cardiac myocytes resulted in atrophic hearts, heart failure,  
42   and death within 1-2 weeks after birth, a timeframe that aligns with the time of  $\alpha$ MHC  
43   expression after birth<sup>12, 44</sup>. Although there have been no studies prior to ours  
44   mechanistically connecting *Atf6* with *Rheb* induction, one study in tumor cells<sup>45</sup>, and  
45   another in the setting of Huntington's disease<sup>46</sup>, have implicated such a connection and,  
46   therefore, support the findings reported here.

1     • Feedback Regulation of ATF6-mediated Growth

2       Our study describes a mechanism whereby ATF6 matches protein synthesis with  
3       folding in times of increased growth; since this constitutes a positive feedback  
4       mechanism, we reason that there must also be mechanisms that interrupt this feedback,  
5       thereby limiting the rate of growth driven by the ATF6-Rheb-mTORC1 axis. One such  
6       mechanism might involve Rheb itself, which has been shown to activate PERK<sup>47</sup>.  
7       Mechanisms such as this underscore the complexities of proteostasis, raising questions  
8       about how Rheb switches from protein synthesis activator to inhibitor.

9     • Conclusions

10      The results of our study firmly place ATF6 in a critical position as a determinant of  
11      cardiac growth (**Fig. 8A**). Moreover, since ATF6 is ubiquitously expressed, our findings  
12      underscore the widespread importance of the ATF6-Rheb-mTORC1-growth signaling  
13      axis described here in non-cardiac cells and tissues in addition to the heart.

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15   **DISCLOSURES**

16   NONE

17

18

19

20

1      **Figure Legends:**

2

3      **Figure 1. Effect of cardiac myocyte-specific ATF6 gene deletion in hearts of**  
4      **mice subjected to TAC.**

5

6      **A**, Protocol for AAV9 administration to ATF6<sup>f/f</sup> mice and TAC. **B**, ATF6 mRNA  
7      levels determined by qRT-PCR on isolated cardiac myocytes (CM), non-cardiac  
8      myocytes (NCM), and liver extracts from ATF6<sup>f/f</sup> mice injected with AAV9-Con  
9      (Con) or AAV9-CRE (i.e. ATF6 cKO). **C**, Immunoblot of LV extracts from Con or  
10     ATF6 cKO mice. **D**, mRNA for ATF6 target genes determined by qRT-PCR. **E**,  
11     Heart weight/tibia lengths (HW/TL). **F**, mRNA levels for fetal genes determined  
12     by qRT-PCR. *Nppa*, natriuretic peptide A; *Nppb*, natriuretic peptide B; *Myh7*, β-  
13     myosin heavy chain; *Col1a1*, Collagen 1A1; *Atp2a2*, Serca2a. **G**, Fractional  
14     shortening (%), determined by echocardiography, see Online Table I. **H**,  
15     Confocal immunofluorescence microscopy (ICF) analysis of mouse heart  
16     sections for laminin (green). Data are mean ± SEM. \*P≤0.05, \*\*P≤0.01, #P≤0.001  
17     different from Con Sham, or from the value shown by the bar.

18

19      **Figure 2. Effect of cardiac myocyte-specific ATF6 gene deletion in hearts of**  
20      **mice subjected to free wheel exercise.**

21

22      **A**, Protocol for AAV9 administration to ATF6<sup>f/f</sup> mice and free wheel exercise. **B**,  
23      Immunoblot of LV extracts from Con or ATF6 cKO mice. **C**, mRNA levels for  
24      ATF6 target genes determined by qRT-PCR. **D**, Heart weights/tibia lengths  
25      (HW/TL). **E**, mRNA levels for fetal genes determined by qRT-PCR. **F**, ICF  
26      analysis of mouse heart sections for laminin (green). Data are mean ± SEM.  
27      \*P≤0.05, \*\*P≤0.01, #P≤0.001. Echocardiography details are in Online Table II.

28

29      **Figure 3. Regulation of Rheb Expression by ATF6.**

30

31      **A**, Heat map of transcript profiling showing z-score-transformed RPKM values  
32      (Reads Per Kilobase per Million mapped reads) with hierarchical clustering of  
33      transcripts of control and ATF6 transgenic mouse hearts. Differentially expressed  
34      genes with p values and FDR ≤0.05 and a subset of genes annotated with term  
35      GO:0007264 are shown. All the genes increased or decreased by ATF6 are in  
36      Online Table III. **B**, Locations of consensus ATF6-binding motifs, i.e. ER stress  
37      response elements 1 and 2 (ERSE-1 and 2) and their sequences in the *RHEB*  
38      gene 5'-flanking region. Nucleotide differences from canonical ERSE elements  
39      are bold. **C**, Neonatal rat ventricular myocytes (NRVM) were infected with AdV  
40      encoding control or FLAG-ATF6(1-373) [active form], and then ATF6 binding to  
41      endogenous ERSE-1 or ERSE-2, as well as to the endogenous *PDIA6* ERSE,  
42      used here as a positive control, and the negative control targets heme  
43      oxygenase 1 (*ho-1*) and *gapdh* were examined by chromatin immunoprecipitation  
44      (ChIP). **D**, Locations of ERSE-1 and 2 in the *RHEB* 5'-flanking region, their  
45      sequences (lower case), and the mutations that were made (bold and upper  
46      case). **E**, NRVM were transfected with rat-*rheb*(-1067/+123)-Luc WT, M2, M1 or

1 M1/M2 then infected with AdV FLAG-ATF6(1-373)., Then, 48h later, luciferase  
2 activity was measured in extracts. **F-H**, mRNA for *RHEB* determined by qRT-  
3 PCR (**F**) and Rheb protein and mTOR pathway components measured by  
4 immunoblots (**G**) and quantified by densitometry (**H**) from Con or ATF6 cKO  
5 mouse heart extracts after 7 days of Sham or TAC. **I-K**, mRNA for *RHEB*  
6 determined by qRT-PCR (**I**) and Rheb protein and mTOR pathway components  
7 immunoblots (**J**) and quantified by densitometry (**K**) from Con or ATF6 cKO  
8 mouse heart extracts after 4 weeks of sedentary or free wheel exercise (Run).  
9 Data are mean ± SEM. \* $P\leq 0.05$ , \*\* $P\leq 0.01$ , # $P\leq 0.001$ .

10  
11 **Figure 4. Effects of ATF6- and RHEB knockdown and ectopic Rheb**  
12 **expression on phenylephrine-induced hypertrophy in cultured cardiac**  
13 **myocytes.**

14  
15 **A-E**, NRVM were transfected with a nontargeted siRNA (siCon) or with siRNAs  
16 targeted to either rat *ATF6* (siAtf6) or *RHEB* (siRheb), and then treated ±  
17 phenylephrine (PE; 50μM) for 48 hours. **A**, Cell surface area was determined by  
18 photomicroscopy and morphometry. **B**, ICF of NRVM for α-actinin (blue) and  
19 TOPRO-3 (red). Bar = 50μm. **C**, qRT-PCR examination of *Nppa* and *Nppb*.  
20 Values are expressed as fold-of-control cardiac myocytes in the absence of PE.  
21 **D**, Immunoblot of NRVM. **E**, mRNA for ATF6 target genes determined by qRT-  
22 PCR. Values are expressed as fold-of-control myocytes in the absence of PE. **F-**  
23 **H**, NRVM were transfected with a control plasmid or a plasmid encoding Flag-  
24 Rheb and either siCon or siAtf6, followed by treatment ± PE for 48 hours. Cell  
25 surface area (**F**) was determined by morphometry after ICF (**G**). NRVM were  
26 stained for FLAG (green; isolated channel displayed in inset), α-actinin (blue),  
27 and TOPRO-3 (red). Bar = 50μm. Only FLAG-positive cells were used for cell  
28 surface area analysis. **H**, Immunoblot of NRVM. Data are mean ± SEM. \* $P\leq 0.05$ ,  
29 \*\* $P\leq 0.01$ , # $P\leq 0.001$ .

30  
31 **Figure 5. Effects of ATF6- and RHEB knockdown and ectopic Rheb**  
32 **expression on insulin like growth factor 1-induced hypertrophy in cultured**  
33 **cardiac myocytes.**

34  
35 **A-E**, NRVM were transfected with siCon, siAtf6 or siRheb, then treated ± IGF1  
36 (100ng/ml) for 48 hours. **A**, Cell surface area was determined by was determined  
37 by morphometry after ICF . **B**, ICF of NRVM for α-actinin (blue) and TOPRO-3  
38 (red). Bar = 50μm. **C**, qRT-PCR for *Nppa* and *Nppb*. Values are fold-of-control  
39 myocytes in the absence of IGF1. **D**, Immunoblot of NRVM. **E**, mRNA levels of  
40 ATF6 target genes determined by qRT-PCR. Values are fold-of-control myocytes  
41 in the absence of IGF1. **F-H**, NRVM were transfected with a control plasmid or a  
42 plasmid encoding Flag-Rheb and then either siCon or siAtf6, followed by  
43 treatment ± IGF1 for 48 hours. Cell surface area (**F**) was determined by  
44 morphometry after ICF (**G**). NRVM were stained for FLAG (green; isolated  
45 channel displayed in inset), α-actinin (blue) and TOPRO-3 (red). Bar = 50μm.

1 Only FLAG-positive cells were used for cell surface area analysis. **H**, Immunoblot  
2 of NRVM. Data are mean  $\pm$  SEM. \* $P\leq 0.05$ , \*\* $P\leq 0.01$ , # $P\leq 0.001$ .

3

4 **Figure 6. Examination of Rheb Requirement for Growth-dependent but not**  
5 **Growth-independent Activation of the ATF6.**

6

7 **A-B**, NRVM were transfected with siCon, siAtf6 or siRheb then treated  $\pm$   
8 tunicamycin (TM; 10 $\mu$ g/mL) (**A**) or PE (50 $\mu$ M) (**B**) for 24 hours, then analyzed for  
9 ATF6 activation by immunoblotting. **C**, mRNA levels for ATF6 target genes  
10 determined by qRT-PCR. Values are fold-of-control, i.e. not treated with TM. **D**,  
11 NRVM were transfected with siCon (**D**) or siAtf6 (**E**), then treated  $\pm$  TM  
12 (10 $\mu$ g/mL), or PE (50 $\mu$ M) for 24 hours, or subjected to simulated  
13 ischemia/reperfusion (sl/R; 8 hours of sl, followed by 24 hours of reperfusion)  
14 and mRNA for ATF6 target genes determined by qRT-PCR. **F**, Diagram of  
15 constructs that encode luciferase driven by the *grp78*, *catalase*, and *rheb* 5'-  
16 flanking region. **G, H**, NRVM were transfected with human-*grp78*(-284/+221)-Luc  
17 WT, rat-*catalase*(-1161/+131)-Luc WT, or rat-*rheb*(-1067/+123)-Luc WT and then  
18 transfected with siCon (**G**) or siAtf6 (**H**), then treated  $\pm$  TM (10 $\mu$ g/mL), or PE  
19 (50 $\mu$ M) for 24 hours, or subjected to sl/R and luciferase activity measured in  
20 extracts. **I, J**, NRVM infected with AdV FLAG-ATF6(1-670) (**I**) or control (**J**), and  
21 then ATF6 binding to the endogenous *grp78*, *catalase*, or *rheb* genes, as well as  
22 to the negative control gene, *gapdh*, examined by ChIP under the same  
23 experimental conditions described above. Data are mean  $\pm$  SEM. \* $P\leq 0.05$ ,  
24 \*\* $P\leq 0.01$ , # $P\leq 0.001$ .

25

26 **Figure 7. Effect of cardiac myocyte-specific ectopic Rheb expression in**  
27 **ATF6 gene deleted mouse hearts subjected to TAC.**

28

29 **A**, Experimental protocol for AAV9 administration to ATF6<sup>fl/fl</sup> mice and TAC. **B**,  
30 Heart weights/tibia lengths (HW/TL). **C**, Fractional shortening (%), as determined  
31 by echocardiography, see Online Table IV. **D**, mRNA for fetal genes determined  
32 by qRT-PCR. **E**, mRNA for ATF6 target genes determined by qRT-PCR. **F**,  
33 Immunoblots of LV extracts. Data are mean  $\pm$  SEM. \* $P\leq 0.05$ , \*\* $P\leq 0.01$ ,  
34 # $P\leq 0.001$ .

35

36

37 **Figure 8. Mechanism whereby ATF6 acts as a nodal regulator of both**  
38 **protein synthesis and protein folding during cardiac hypertrophy.**

39

40 **A**, Shown are the temporal sequence of steps involved in mediating the initial  
41 (Steps 1-4) and sustained (Steps 5-7) aspects of growth and the interdependent  
42 roles of mTORC1 and ATF6. **B, C**, Immunoblot of LV extracts (**B**) and heart  
43 weights/tibia lengths (HW/TL) (**C**) from WT mice subjected to TAC for 3 hours, 2  
44 days, or 7 days. Echocardiography details in Online Table V. **D, E**, Immunoblot of  
45 LV extracts (**D**) and heart weights/tibia lengths (HW/TL) (**E**) from Con or ATF6

1 cKO mice subjected to 3 hours of TAC. Echocardiography details in Online Table  
2 VI. Data are mean  $\pm$  SEM. \* $P\leq 0.05$ , # $P\leq 0.001$ .

3

4

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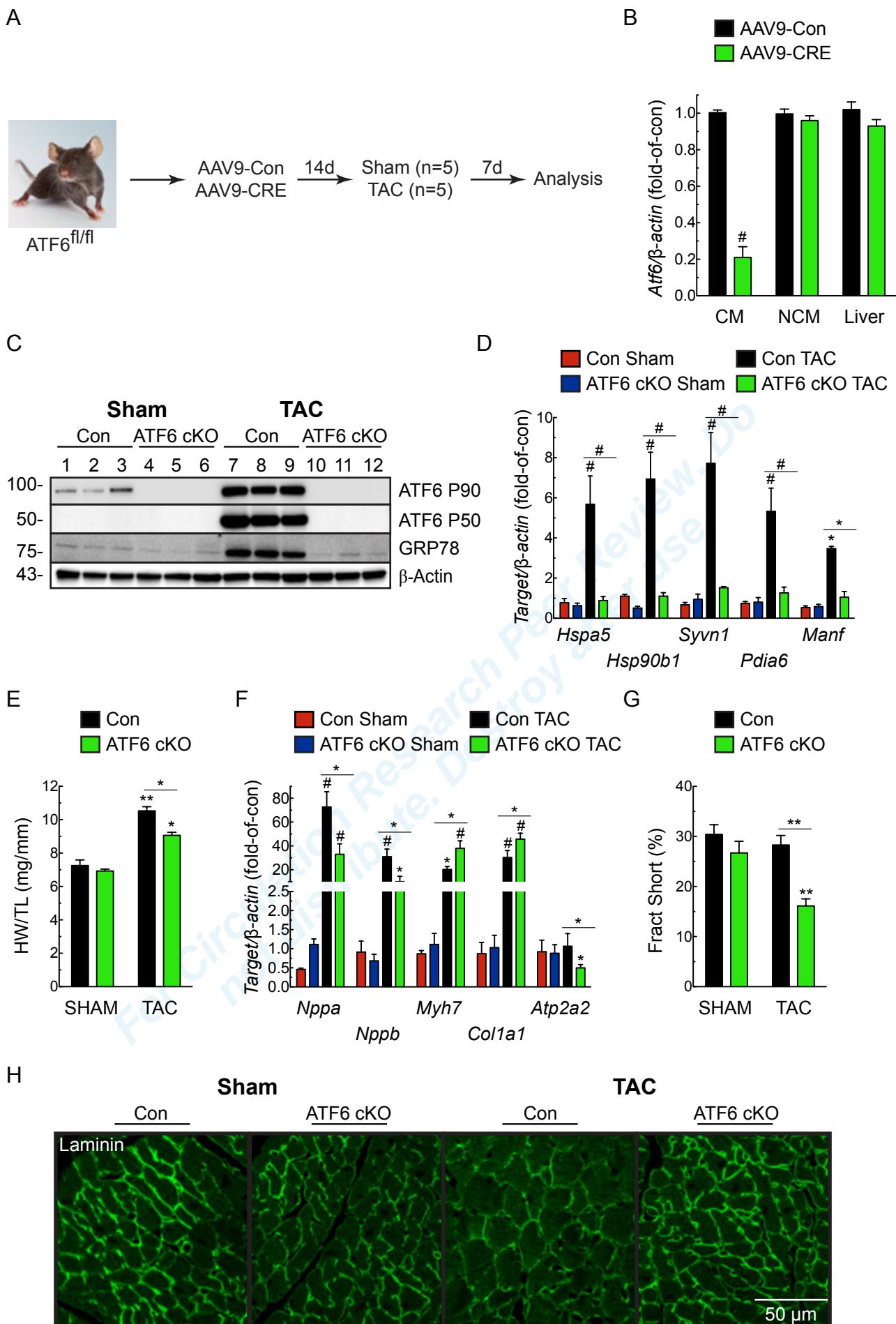
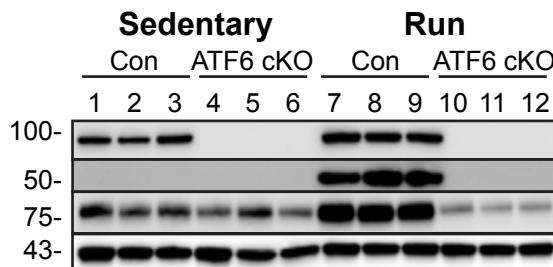


Figure 1

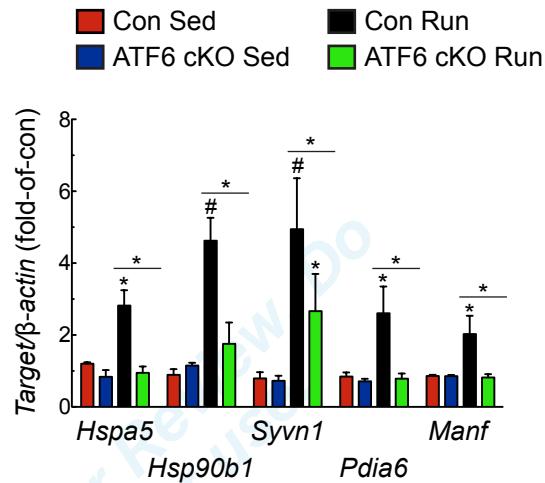
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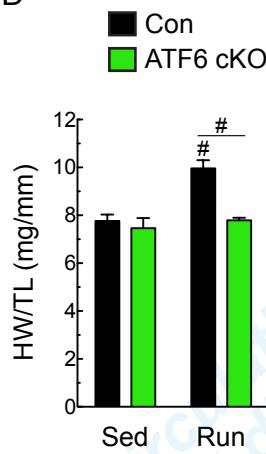
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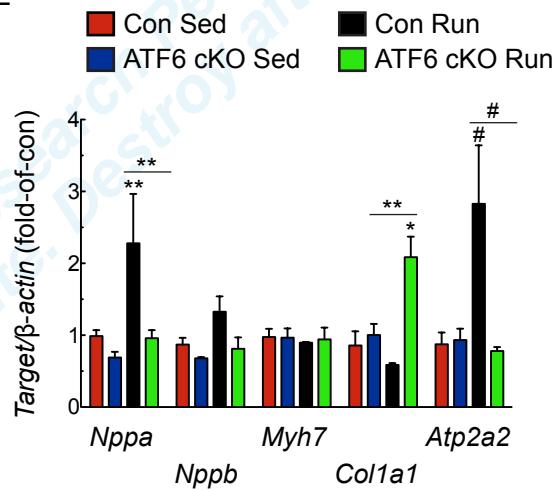
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E



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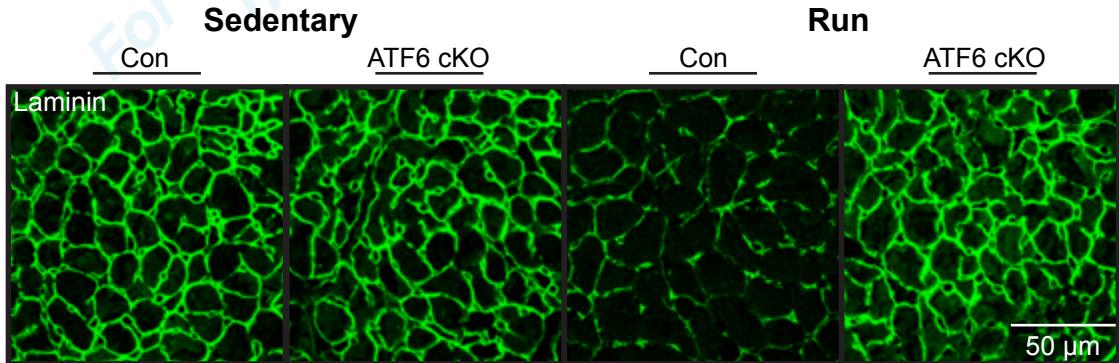


Figure 2

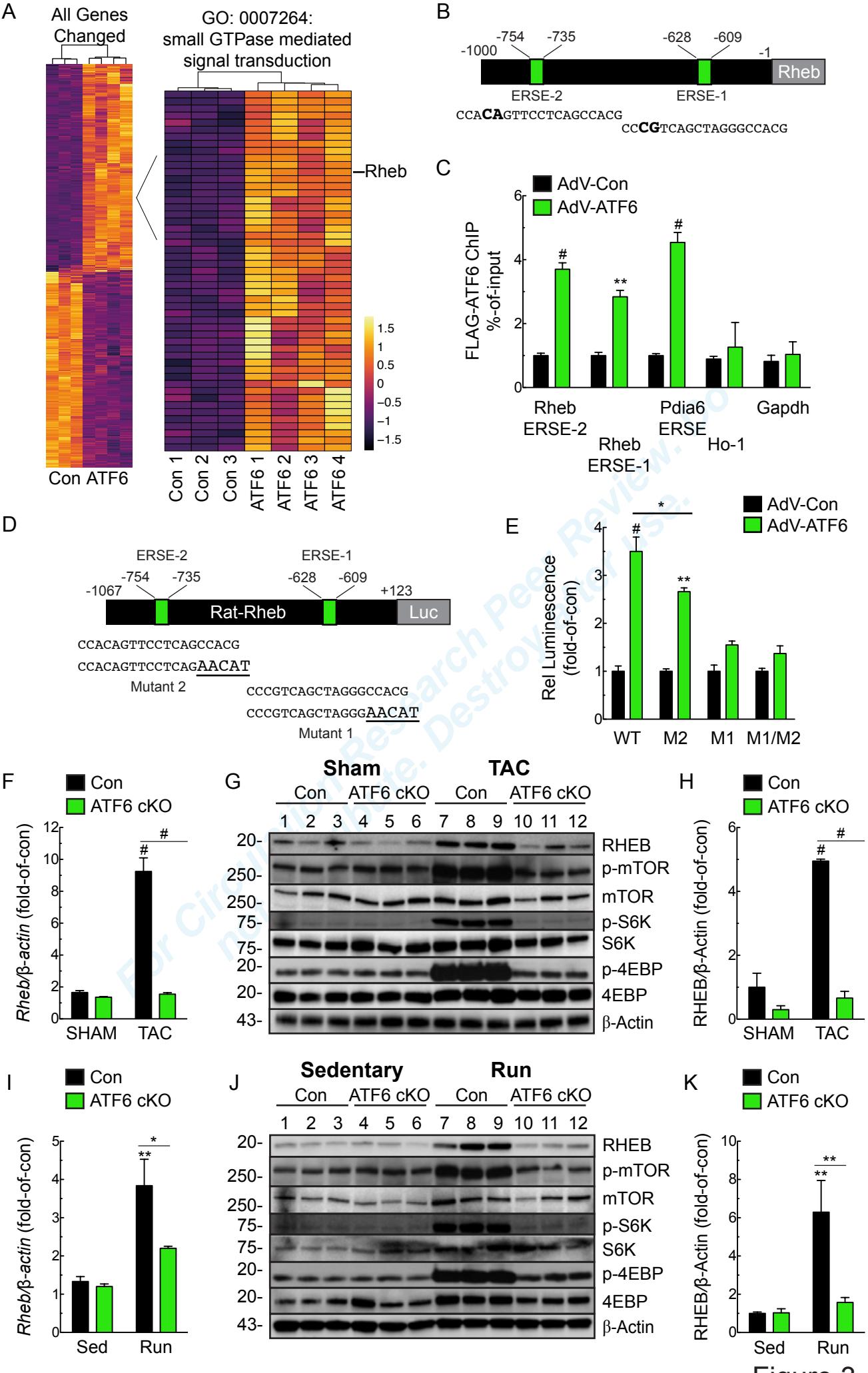
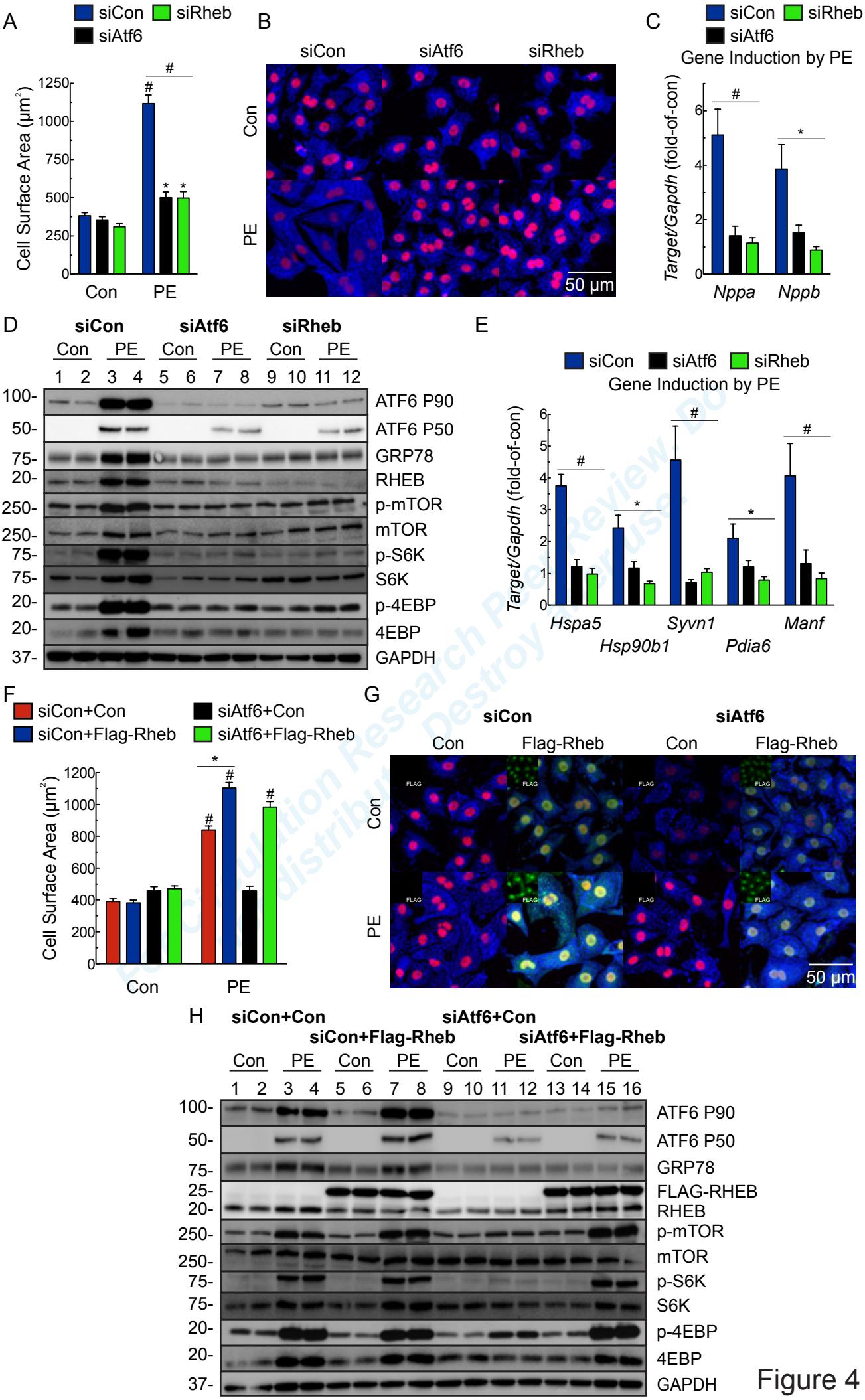
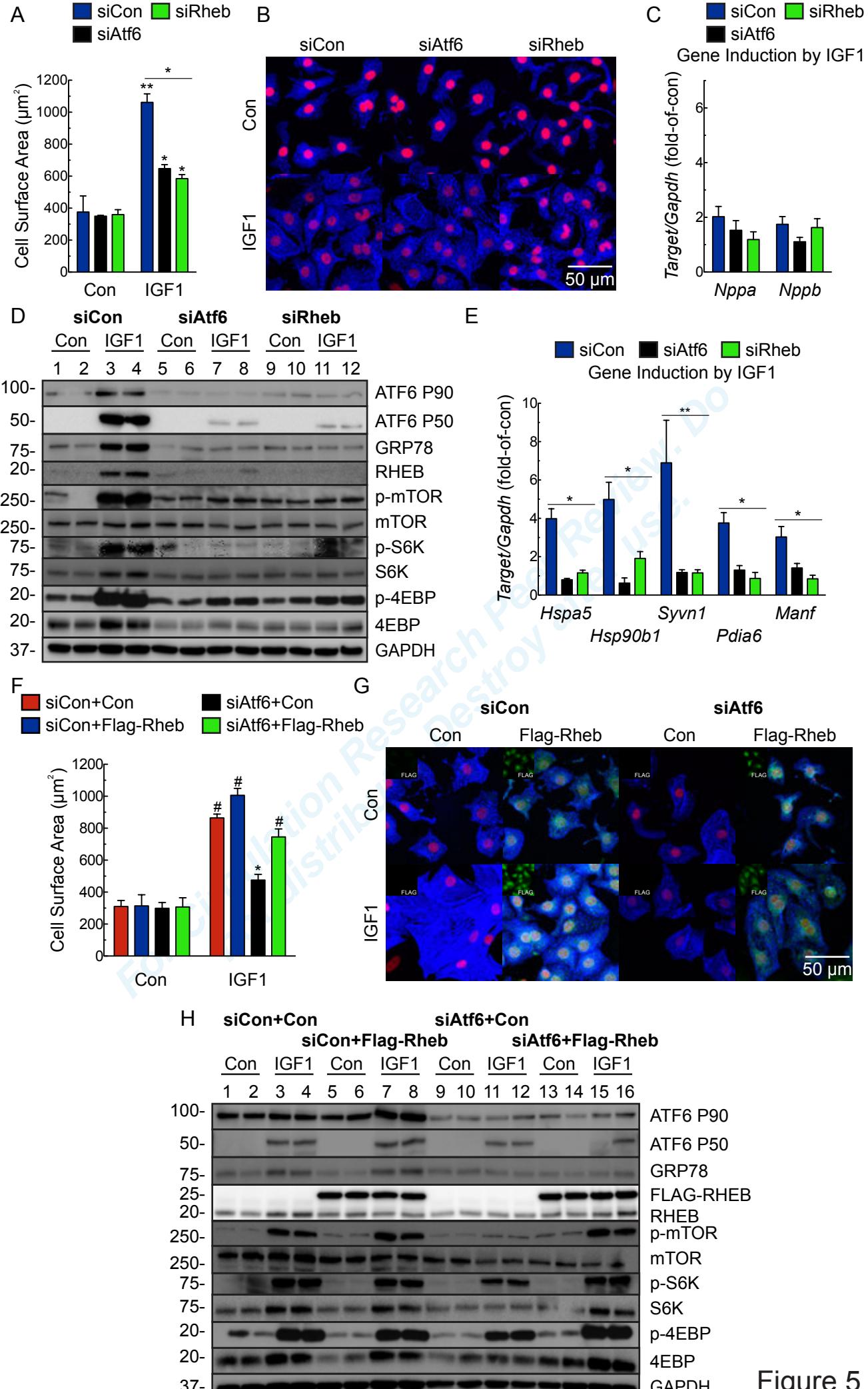


Figure 3





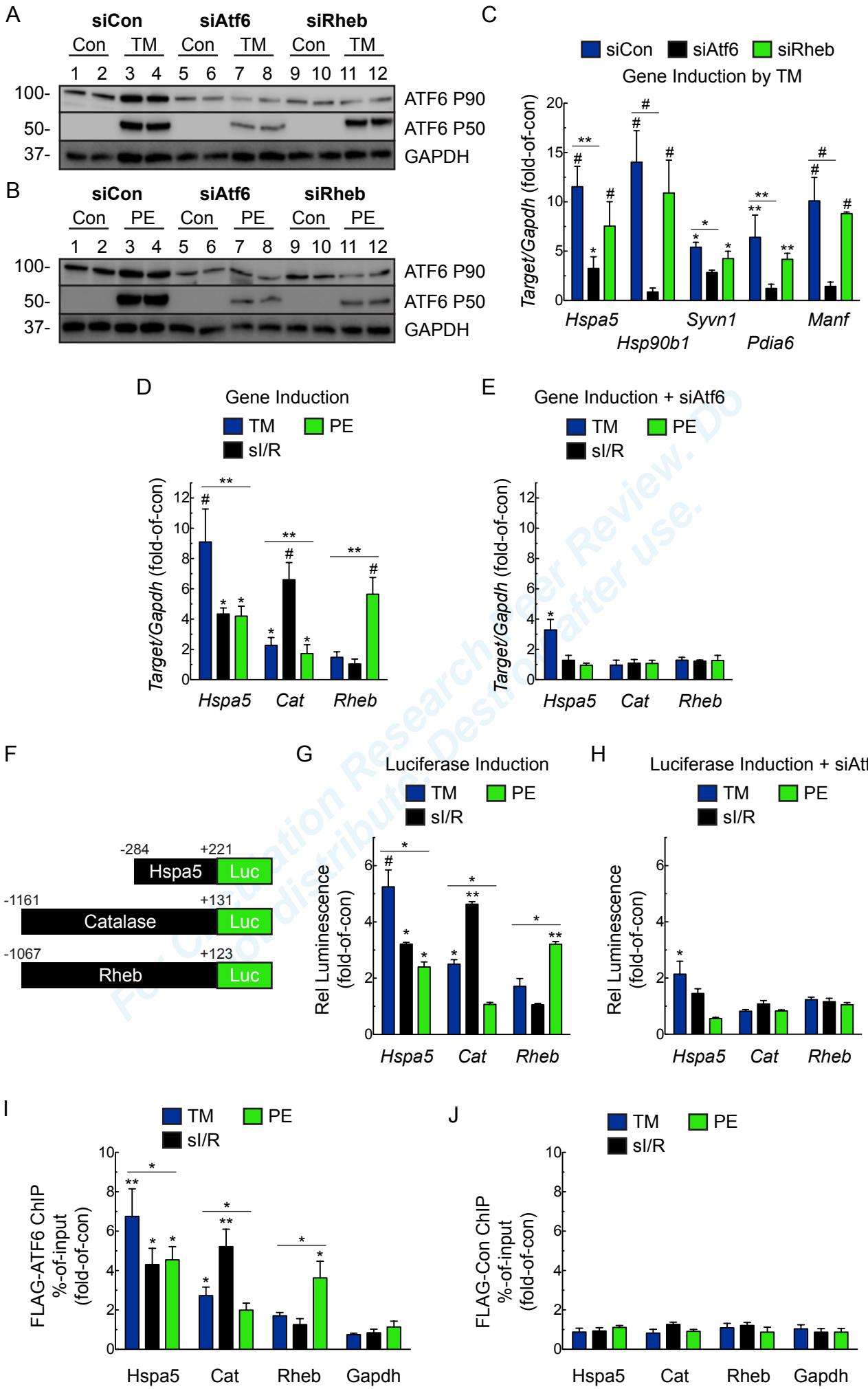
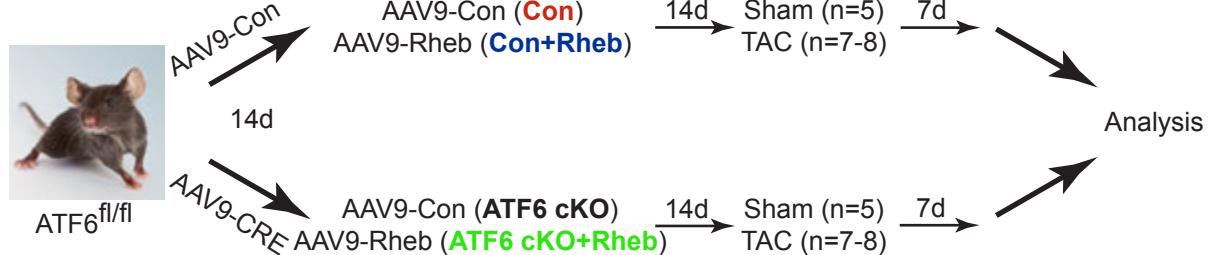
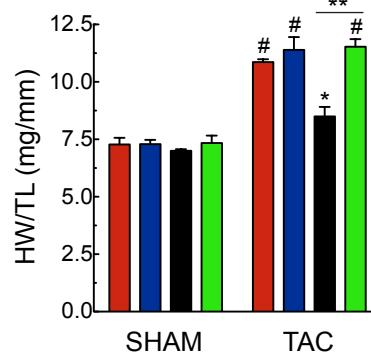


Figure 6

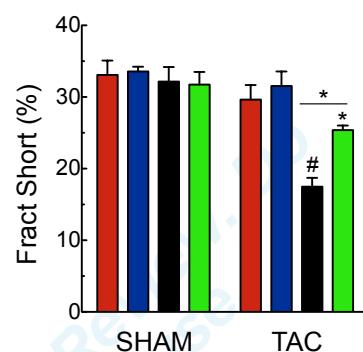
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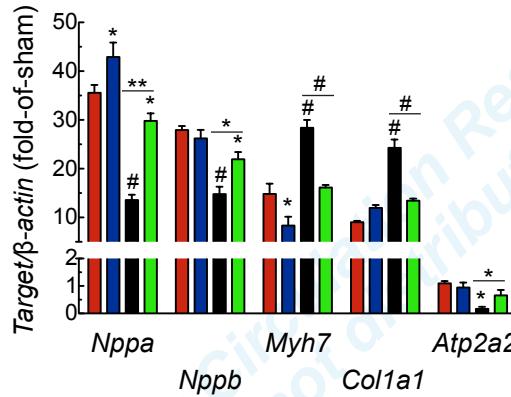
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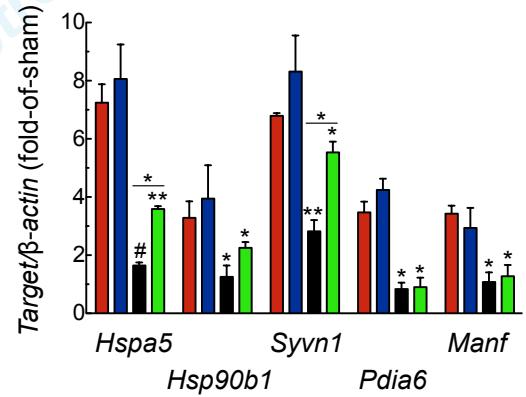
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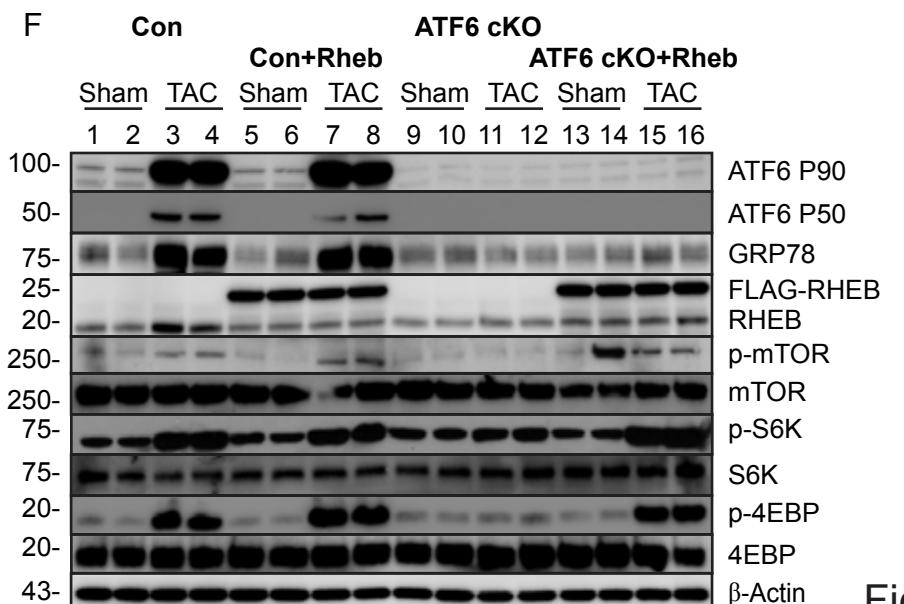
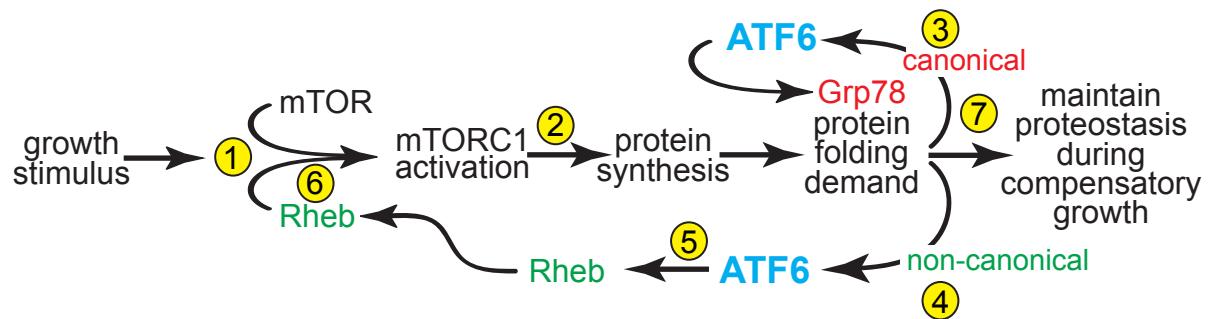
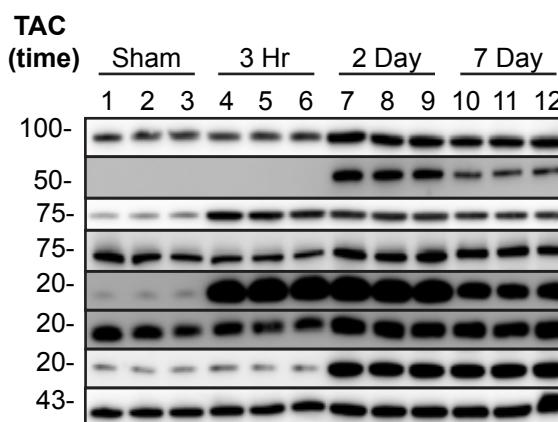
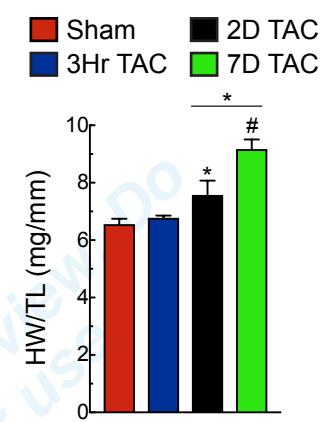
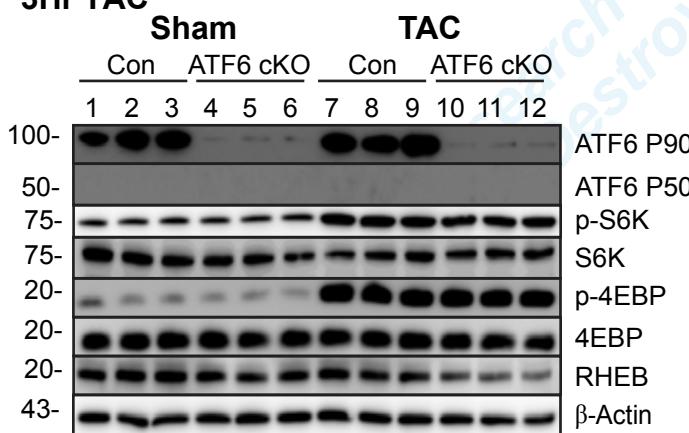


Figure 7

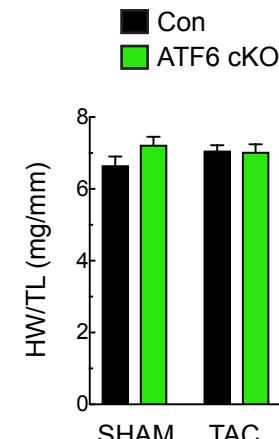
A

**B WT TAC Timecourse**

C

**D 3Hr TAC**

E



## Supplemental Material

### Detailed Methods

#### Laboratory animals

The research reported in this article has been reviewed and approved by the San Diego State University Institutional Animal Care and Use Committee (IACUC), and conforms to the Guide for the Care and Use of Laboratory Animals published by the National Research Council. ATF6-floxed (ATF6<sup>f/f</sup>) mice were a generous gift from Dr. Gokhan S. Hotamisligil. Briefly, ATF6-floxed mice were generated with a targeting construct flanking exons 8 and 9 of ATF6 with LoxP sequences on a C57B/6J background, as previously described<sup>1</sup>.

#### Animal numbers

A total of 184 mice were used for this study. ATF6<sup>f/f</sup> C57BL/6J mice injected with AAV9-Con (Con) (n=81) and their ATF6<sup>f/f</sup> littermates injected with AAV9-Cre (ATF6 cKO) (n=80); for certain experimental paradigms Con and ATF6 cKO mice were subsequently injected with either AAV9-Con (n=37), AAV9-Rheb (n=13) or AAV9-ATF6 (n=24); ATF6 TG C57BL/6J mice (n=4) and their non-transgenic littermates (n=3). Male wild-type C57BL/6J mice were purchased from Jackson Laboratories for the TAC time course experiment (n=16). All animals were fed *ad libitum* for all experimental purposes and kept on a traditional 12-hour light/dark cycle. All animal sacrifice and tissue harvest was consistently performed between the hours of 12pm-3pm when we have observed animals to be in a fasted and sedentary state.

#### Cultured cardiac myocytes (NRVM) and experimental design

Neonatal rat ventricular myocytes (NRVMs) were isolated via enzymatic digestion, purified by Percoll density gradient centrifugation, and maintained in Dulbecco's modified Eagle's medium (DMEM)/F12 supplemented with 10% fetal bovine serum (FBS) and antibiotics (100 units/ml penicillin and 100 µg/ml streptomycin) on plastic culture plates that had been pre-treated with 5 µg/ml fibronectin, as previously described<sup>2</sup>. For all NRVM experiments, plating density was maintained at  $2.5 \times 10^5$  cells/well on 12-well plates. Sixteen hours after plating, NRVM were subjected to respective treatments. For stimulated *in vitro* hypertrophy in NRVM, an initial period of serum starvation was implemented by replacing all culture media with 0.5 ml of glucose-free DMEM for 48 hours. NRVM culture media was then replaced with DMEM/F12 supplemented with BSA (1 mg/ml) containing either control, phenylephrine (50 µM) or IGF1 (100ng/ml) for an additional 48 hours. Experiments in which Lonafarnib (2 µM; Cayman Chemical, Cat#193275-84-2), rapamycin (20nM; Sigma-Aldrich), cyclohexamide

(100 µg/ml; Sigma-Aldrich, Cat#C1988) or 4-phenylbutyrate (100 µM; Sigma-Aldrich, Cat#SML0309) were administered was performed as previously described<sup>3-6</sup>, treatment was performed after serum starvation in conjunction with respective phenylephrine or IGF1 administration. Images were obtained with an IX70 fluorescence microscope (Olympus, Melville, NY). For *in vitro* chemical UPR activation, sixteen hours after plating NRVM and AMVM were treated with tunicamycin (10 µg/ml) for 24 hours in DMEM/F12 supplemented with bovine serum albumin (BSA) (1 mg/ml) for NRVM. For *in vitro* ischemia/reperfusion (I/R), ischemia was simulated by replacing all culture media with 0.5 ml of glucose-free DMEM containing 2% dialyzed FBS, then incubated at 0.1% O<sub>2</sub> in a hypoxia chamber with an oxygen controller (ProOx P110 oxygen controller, Biospherix, Parish, NY) for 8 hours or 3 hours for NRVM or AMVM, respectively, as previously described<sup>2</sup>. Reperfusion was simulated by replacing culture media with DMEM/F12 supplemented with BSA (1 mg/ml) for NRVM or maintaining media for AMVM and incubating at 21% O<sub>2</sub> for an additional 24 hours.

## Immunoblotting

NRVM were lysed and subjected to immunoblot analysis, as previously described<sup>2</sup>. In brief, cultures were lysed with VC lysis buffer made from 20 mM Tris-HCl (pH 7.5), 150 mM NaCl, 0.1% SDS, 1% Triton X-100, protease inhibitor cocktail (Roche Diagnostics, Indianapolis, IN) and phosphatase inhibitor cocktail (Roche Diagnostics). Mouse heart tissues were homogenized in modified RIPA buffer with 2% SDS. Lysates were clarified by centrifugation at 15,000xg for 15 min at 4°C, and the protein concentration was determined using DC protein assay (Bio-Rad, Hercules, CA). Samples comprising 15 µg of protein were mixed with Laemmli sample buffer, boiled, then subjected to SDS-PAGE followed by transfer onto PVDF membranes for immunoblotting. Full-length Atf6 (p90) was detected with an antibody from SAB Signalway Antibody (1:1000, cat# 32008, College Park, MD), while active Atf6 (p50) was detected with an antibody from Proteintech (1:1000, cat# 24169-1-AP, Rosemont, IL). Other antibodies used include: anti-KDEL antibody (1:8,000, cat# ADI-SPA-827, Enzo Life Sciences, Farmingdale, NY), which was used to detect GRP78, anti-IRE1 (1:500, cat# sc-390960, Santa Cruz), anti-XBP1s (1:1000, cat# 619502, BioLegend, San Diego, CA), anti-phospho-PERK (1:1000, cat# 3179, Cell Signaling), anti-PERK (1:1000, cat# 3192, Cell Signaling), anti-Gapdh (1:25000, cat# G109a, Fitzgerald Industries International Inc.), anti-β-actin (1:1000, cat# sc-47778, Santa Cruz), and anti-FLAG (1:3,000, cat#F1804, Sigma-Aldrich, St. Louis, MO). The following antibodies were purchased from Cell Signaling (Danvers, MA): anti-RHEB (1:1,000, cat#13879s), anti-Phospho-mTOR (Ser2448, 1:1,000, cat#2971s), anti-mTOR (1:1,1000, cat#2972s), anti-Phospho-AKT (Ser473, 1:1,000, cat#9271s), anti-Phospho-ATK (Thr308, 1:1000, cat#13038s), anti-AKT (1:1,000, cat#9272s), anti-Phospho-S6K (1:1,000, cat#9205s), anti-S6K (1:1,000, cat#9202s), anti-Phospho-4EBP (1:1,000, cat#2855s), anti-4EBP (1:1,000, cat#9452s), anti-Phospho-TSC2 (Thr1462, 1:1000, 3617s), anti-TSC2 (1:1000, 3990s), anti-

Phospho-ERK1/2 (Thr202/Tyr204, 1:1000, 9101s), and anti-ERK1/2 (1:1000, 9102s).

## Adenovirus

Recombinant adenoviruses (AdV) encoding 3XFLAG-tagged constitutively active ATF6, ATF6 $\alpha$ (1-373), 3XFLAG-tagged transcriptionally dead ATF6, ATF6 $\alpha$ (94-373), and 3XFLAG-tagged full-length inactive ATF6, ATF6 $\alpha$ (1-670) were generated using AdEasy system essentially as previously described<sup>7</sup>. Transduction of NRVM was performed by incubating cultures for 5 hours with the appropriate AdV at a multiplicity of infection of one.

## Plasmid transfection

Transfection of plasmids into NRVM was achieved using electroporation as previously described<sup>8</sup>. Briefly, 1 million NRVM were suspended in 300  $\mu$ l DMEM/F12 supplemented with BSA (1 mg/ml) and mixed with 10  $\mu$ g of CMV-Flag-Rheb (AddGene plasmid #19996), or a Rheb promoter-luciferase construct of choice (see below), or an empty vector control plasmid. Subsequently, each mixture was then electroporated in a Bio-Rad gene pulser at 500 V, 25 microfarads, 100  $\Omega$  in a 0.2 cm gap cuvette. Transfected NRVM viability is approximately 50% and were then plated into four-chamber Lab Tek chamber slides at  $0.75 \times 10^5$  NRVM per 2  $\text{cm}^2$  chamber.

## Rheb promoter-luciferase constructs

The promoter region of the rat RHEB gene spanning nucleotides -1067 to +123 was amplified by PCR using ggatcgacgcgtcagtacccctgttcagaaa as the forward primer, which introduced an *M*luI site (underlined) just 5' of rat RHEB -1067, and ggatcgctcgagcttggtagcCTgGTCAGC as the reverse primer, which introduced an *Xba*I site (underlined) just 3' of rat RHEB +123. Upper case nucleotides match those in the rat RHEB gene. The amplified product was then cloned into pGL2p to generate rat-RHEB(-1067/+123)-Luc. Truncated versions of rat-RHEB luciferase were cloned into pGL2p using a similar strategy and the same reverse primer coupled with the following forward primers:  
ggaacgacgcgtTCACCACCCACACTAAGC (-723), and  
ggaacgacgcgtGAACAGTGTCTCCTGGC (-390) to generate rat-RHEB(-723/+123)-Luc and rat-RHEB(-390/+123)-Luc, respectively. Upper case nucleotides of these primers correspond to rat RHEB gene sequences. Informatics analyses identified putative ER stress response elements in the rat RHEB gene at nucleotide positions -754 to -736 and -628 to -610 in the rat RHEB gene, which we called ERSE-2 and ERSE-1, respectively. These elements in rat-RHEB(-1067/+123)-Luc were mutated by site-directed mutagenesis in ways

predicted to ablate ATF6 binding using RHEB-ERSE-2 mut sense primer, CCCACAGTTCCTCAGaacatATAAAGCTTAGTCAC and RHEB-ERSE-2 mut antisense primer, GTGACTAACGCTTATTatgttCTGAGGAACTGTGGG RHEB-ERSE-1 mut sense primer, GCCCGTCAGCTAGGGaacatCGCCTCACGCC, and RHEB-ERSE-1 mut antisense primer, GGC GTGAGGCGatgttCCCTAGCTGACGGGC. PCR-based mutagenesis was performed using the QuikChange XL Site-Directed Mutagenesis Kit (Agilent Technologies, Santa Clara, CA). Lower case letters represent mutated nucleotides; upper case letters represent nucleotides that are identical to those in the rat RHEB gene. Plasmids were transfected into NRVM and luciferase activity was determined as previously described<sup>2</sup>.

### **Luciferase reporter assay**

Luciferase reporter assays were performed as previously described<sup>2</sup>. Briefly, suspended NRVMs were co-transfected by electroporation with Rheb promoter-luciferase constructs described above, human-Hspa5(-284/+221), or rat-Catalase(-1161/+131) promoter-luciferase constructs previously described<sup>2, 9</sup> along with pCH110 plasmids encoding SV40-beta-galactosidase and pGL2B, as described previously<sup>10</sup>. NRVMs were plated overnight and then infected with different forms of Adv-ATF6 or subjected to respective experimental paradigms. NRVMs were lysed after 48 h, and the activities of luciferase and beta-galactosidase were measured using an Optocompt II luminometer (MGM Instruments, Hamden, CT).

### **Small interfering RNA (siRNA) transfection**

Transfection of siRNA into NRVM was achieved using HiPerfect Transfection Reagent (Qiagen, Valencia, CA) following the vendor's protocol as previously described<sup>2</sup>. Briefly, NRVM culture medium was replaced with DMEM/F12 supplemented with 0.5% FBS without antibiotics, 120 nM siRNA, and 1.25 µl HiPerfect / 1 µl siRNA, then incubated for 16 hours, after which the culture medium was replaced with DMEM/F12 supplemented with BSA (1 mg/ml) for an additional 48 hours. The following targeting siRNAs were used: rat ATF6 (assay ID# RSS315363, Stealth siRNA, Thermo Fisher), rat RHEB (assay ID# RSS352522, Stealth siRNA, Thermo Fisher), rat PERK (assay ID# s132055, Silencer Select siRNA, Thermo Fisher), and rat IRE1 (assay ID# RSS363210, Stealth siRNA, Thermo Fisher). A non-targeting sequence (cat# 12935300, Thermo Fisher) was used as a control siRNA.

### **Immunocytofluorescence (ICF) and immunohistochemistry**

NRVM were plated on fibronectin and laminin-coated glass chamber slides, respectively as previously described<sup>2</sup>. Briefly, cells were fixed with 4% paraformaldehyde, followed by permeabilization with 0.5% Triton-X. Adult mouse hearts were paraffin-embedded after fixation in neutral buffered 10% formalin via abdominal aorta retroperfusion as previously described<sup>3</sup>. Primary antibodies used were anti- $\alpha$ -actinin (1:200, cat# A7811, Sigma-Aldrich), anti-tropomyosin (1:200, cat# T9283, Sigma-Aldrich), anti-RHEB (1:50, cat#13879s, Cell Signaling), and anti-laminin (1:30, cat# L9393, Sigma-Aldrich). Slides were incubated with appropriate fluorophore-conjugated secondary antibodies (1:100, Jackson ImmunoResearch Laboratories, West Grove, PA) followed by nuclei counter stain Topro-3 (1:1000, Thermo Fisher). Images were obtained using laser scanning confocal microscopy on an LSM 710 confocal laser scanning microscope (Carl Zeiss, Oberkochen, Germany).

### Quantitative real-time PCR (qRT-PCR)

Total RNA was isolated from NRVM or mouse hearts as previously described<sup>3</sup> using Quick-RNA MiniPrep kit (Zymo Research, Irvine, CA) or RNeasy Mini kit (Qiagen), respectively. cDNA synthesis was performed using SuperScript III First-Strand Synthesis System (Thermo Fisher). qRT-PCR was performed using Maxima SYBR Green/ROX qPCR Master Mix in a StepOnePlus RT-PCR System (Thermo Fisher). All qPCR probes were obtained from Integrated DNA Technologies, as previously described<sup>2, 6</sup>. Rheb-specific qPCR primers are listed below:

Gene (rat)	Forward Primer	Reverse Primer
Rheb - 1	CAGCAGGGCAGGATGAATA	GCTTGCCGTGGATAACTTTAAT
Rheb - 2	AAGATGCCTCAGTCCAAGTC	GATCAGCTTGGTGAATGTGTTT
Gene (mouse)		
Rheb - 1	CCATGGCAAGTTGTTGGATATG	TCTTCATAGCTGATCACCCCTTC
Rheb - 2	ACGTCTGACTCTGTCCAAATG	TGCCAACAGGAGGCAATAA

### Adeno-Associated virus serotype 9 (AAV9)

The plasmid encoding the human cardiac troponin T promoter driving Cre-recombinase was provided as a gift from Dr. Oliver Muller<sup>9</sup>. AAV9 preparation was carried out as previously described<sup>2</sup>. Non-anesthetized 8-week old ATF6<sup>f/f</sup> mice were injected with 100  $\mu$ L of AAV9-control or AAV9-cTnT-Cre containing 1x10<sup>11</sup> viral particles via the lateral tail vein using a 27-gauge syringe and housed for 2 weeks before either sacrifice or experimental initiation. To generate AAV9-FLAG-Rheb, a plasmid encoding FLAG-Rheb was obtained from Addgene (Addgene 19996). The region of this construct containing FLAG-Rheb was excised with EcoR1 and Xho1, then, after addition of an EcoR1/Nhe1 linker, it

was ligated into the Nhe1 and Xho1 sites of the AAV shuttle vector, pTRUF-CMVenhMLC800. AAV9 were then prepared and administered as previously described in accordance with the respective experimental paradigms<sup>2</sup>.

### Chromatin immunoprecipitation (ChIP)

ChIP assays were performed essentially as previously described<sup>2, 11</sup>. Briefly, AdV-Con, AdV-FLAG-ATF6(1-373), or AdV-FLAG-ATF6(1-670) infected NRVM were treated with fixing buffer (50 mM HEPES-KOH, pH 7.5, 100 mM NaCl, 1 mM EDTA, 0.5 mM EGTA, and 1% formaldehyde) for 10 min, quenched with 125 mM glycine, and scraped into ice-cold PBS. Cells were centrifuged, resuspended in lysis buffer (50 mM HEPES, pH 7.9, 140 mM NaCl, 1 mM EDTA, 10% glycerol, 0.5% NP-40, 0.25% Triton X-100, and protease inhibitor cocktail), and incubated on ice for 10 min. After centrifugation at 1,800 x g for 10 min, the pellets were washed with buffer containing 10 mM Tris, pH 8.1, 200 mM NaCl, 1 mM EDTA, and 0.5 mM EGTA, resuspended in shearing buffer (0.1% SDS, 1 mM EDTA, and 10 mM Tris, pH 8.1), and then transferred to microTUBEs (Covaris, Woburn, MA). Chromatin was sheared by sonication for 15 min using an M220 focused ultrasonicator (Covaris). Triton X-100 and NaCl were added to the final concentration of 1% Triton and 150 mM NaCl followed by centrifugation at 16,000 x g for 10 min. Immunoprecipitation was performed by incubated 140 µl of sheared chromatin with 5 µg of anti-FLAG antibody (cat# F1804, Sigma-Aldrich) and 260 µl of immunoprecipitation buffer (0.1% SDS, 1 mM EDTA, 10 mM Tris, pH 8.1, 1% Triton X-100, and 150 mM NaCl) at 4°C overnight. Protein A/G magnetic beads (5 µl, BcMag, Bioclone, San Diego, CA) were added to the mixtures and incubated at 4°C for 1.5 h. Magnetic beads were sequentially washed with low salt wash buffer (0.1% SDS, 1% Triton X-100, 2 mM EDTA, 20 mM HEPES-KOH, pH7.9, and 150 mM NaCl), high salt wash buffer with 500 mM NaCl, LiCl wash buffer (100 mM Tris-HCl, pH 7.5, 0.5 M LiCl, 1% NP-40, and 1% deoxycholate acid), and TE buffer (10 mM Tris-HCl, pH 8.0 and 0.1 mM EDTA). Immune complexes were eluted by incubating beads with proteinase K digestion buffer (20 mM HEPES, pH 7.9, 1 mM EDTA, 0.5% SDS, and 0.4 mg/ml proteinase K) at 50°C for 15 min. Formaldehyde crosslinking was reversed by incubating with 0.3 M NaCl and 0.3 mg/ml RNase A at 65°C overnight. Samples were further incubated with 550 µg/ml proteinase K at 50°C for 1h. DNA was purified using NucleoSpin Gel and PCR Clean-up Kit (Macherey-Nagel, Bethlehem, PA) and eluted by 30 µl of water. Two µl of DNA was used for qRT-PCR analysis with primers targeting rat Rheb ERSE-1 (5'-CTGCACAGATTCCATTCTCCC-3' and 5'-TGTCTATACTTTAAATT-3'), rat Rheb ERSE-2 (5'-TGACAGCCAACCTACAGCC-3' and 5'-GAAGCGCGGTCAATTGGT-3'), rat Hspa5 (5'-GGTGGCATGAACCAACCAG-3' and 5'-GCTTATATATCCTCCCCGC-3'), rat Cat (5'-CTACCCACCAATTAGTACCAAATAA-3' and 5'-AGAAGGGACAGGATTGGAAG-3'), rat Pdia6 ERSE (5'-CACATGAGCGAAATCCACAGA-3' and 5'-ACTAGTCGAGCCATGCTGAT-3'),

rat HO-1 (5'-GGGCTACTCCGTCTCCTG-3' and 5'-CCTTCCAGAACCTCTACTCTACTC-3'), or rat Gapdh (5'-ATGCGGTTCTAGGTTCACG-3' and 5'-ATGTTTCTGGGGTGCAAAG-3'). Pdia6 served as a positive control for a known ATF6 target gene in cardiac myocytes while HO-1 and Gapdh served as negative controls. ChIP signals obtained from the qRT-PCR were normalized to the input DNA.

### **<sup>3</sup>H-Leucine incorporation and trichloroacetic acid precipitation of protein**

NRVM <sup>3</sup>H-Leucine incorporation was performed as previously described<sup>6</sup>. Briefly, NRVM were plated at a density of  $2.5 \times 10^5$  cells/well on 12-well plastic culture plates. After 48 hours of serum starvation in DMEM/F-12, NRVM culture media was replaced with DMEM/F12 supplemented with BSA (1 mg/ml) containing either control, phenylephrine (50  $\mu$ M), IGF1 (100ng/ml), or Lonafarnib (2  $\mu$ M) for an additional 48 hours. To this media was added 1  $\mu$ Ci of <sup>3</sup>H-Leucine (PerkinElmer NET460A001MC L-[3,4,5-<sup>3</sup>H(N)]-Leucine, 100 to 150 Ci/mmol). After 48 hours, the media was removed, cultures were washed 3 times with 1 ml DMEM/F-12 and cells were subsequently scraped from culture dishes with 0.5 ml of 25% trichloroacetic acid and transferred to 1.5 ml microcentrifuge tubes. Protein precipitation was induced using 50  $\mu$ l of a 10mg/ml solution of BSA and samples were allowed to freeze overnight. Upon thawing, precipitates were collected by centrifugation at 4°C at ~20,000xg for 20 minutes. Supernatants were removed by manual aspiration and precipitated protein dissolved in 200  $\mu$ l of base buffer (1% Triton X-100, 1M NaOH) at 37°C for two hours. Radioactivity in solubilized material was quantified by scintillation counting in glass scintillation vials using 180  $\mu$ l of solubilized protein into 10 ml of Ecoscint scintillation fluid. Each vial was counted for a minimum of 2 minutes with at least six separate myocyte cultures per treatment.

### **Cultured cardiac myocyte area**

NRVM (minimum of n=3 cultures per treatment) were visualized by phase-contrast microscopy and images were obtained with an IX70 fluorescence microscope (Olympus, Melville, NY) as previously described<sup>6</sup>. Cell surface area was determined using NIH Image J software from a minimum of 100 cells per image using three separate fields from each cell culture.

### **Transverse aortic constriction**

Transverse aortic constriction (TAC) was performed as previously described<sup>6</sup>. Briefly, adult male mice were anesthetized using a 2% isofluorane/O<sub>2</sub> mixture and intubated. Mice were treated with buprenorphine (0.1 mg/kg IP) and a partial trans-sternal thoracotomy performed using aseptic technique. An approximately

1.5 cm vertical left parasternal skin incision was made, underlying pectoralis muscle retracted, and the chest cavity entered through the fourth intercostal space. Using hooked retractors, adjacent ribs were retracted to expose the heart and aortic arch. The aorta was isolated from annexed tissue, and the artery partially ligated between the innominate and left common carotid arteries with 6-0 silk. The calibrated constriction of the aorta was performed by placing a dull 27-gauge needle to the side of the artery, the ligature tied firmly to both the needle and the artery, and, subsequently, the needle was removed leaving a calibrated stenosis of the aorta. Sham operated mice were exposed to the same procedure, except that the aorta was not constricted. The thoracic cavity was closed and the animals were allowed to recover. Animals were injected once with buprenorphine (0.1 mg/kg IP) about 12 h after recovery in order to reduce any post-operative discomfort. In case any animals displayed signs of pain or distress after this period, additional doses of buprenorphine were administered as needed. Immediately prior to sacrifice, animals were anesthetized and constriction levels were quantified by measuring alterations in Doppler velocities of the innominate and left carotid arteries 7 days post-TAC, as previously described<sup>12</sup>. Mean carotid peak blood flow velocities were determined using a 20 MHz Doppler probe (Indus Instruments, Houston, TX) and ratios of innominate (RC) to left carotid (LC) were determined to evaluate consistency across animals in both SHAM and TAC groups. Just prior to sacrifice, post-TAC, animals were anesthetized and 0.5 mL of arterial blood were obtained via inferior vena cava puncture. Blood was placed in heparin- and EDTA-coated vacutainer (BD Vacutainer) and centrifuged at 3000 rpm for 10 minutes and plasma samples were analyzed for cardiac troponin I with a Mouse cTnI High-Sensitivity ELISA kit (Life Diagnostics, Inc.). A calcineurin phosphatase activity assay was performed using a calcineurin tissue extract assay kit (cat#BML-AK816-0001, Enzo Life Sciences) according to the manufacturer's protocol. Briefly, free phosphate was removed from LV tissue extracts by passing through a desalting column and calcineurin phosphatase activity was measured spectrophotometrically by detecting free phosphate released from the synthetic RII phosphopeptide.

### **Free-wheel exercise protocol**

Free-wheel exercise protocol was performed as previously described<sup>13</sup>. Briefly, adult male mice were housed individually in cages containing rodent exercise wheels of a 5.356 in diameter (Model InnoWheel, BioServe) and provided with food and water *ad libitum*. The wheels were equipped with a digital magnetic counter to record revolutions of the wheel during bouts of exercise. Sedentary mice were maximally housed and provided with food and water *ad libitum* in cages not equipped with exercise wheels.

## **Transthoracic echocardiography**

Transthoracic echocardiography was performed using an ultrasound imaging system (Vevo 2100 System, Fujifilm VisualSonics, Toronto, Ontario, Canada) as described<sup>2</sup>.

## **Transcript profiling and bioinformatics**

ATF6 TG and non-transgenic littermates were treated with tamoxifen (10 mg/kg IP) daily for 5 days as previously described<sup>14</sup>. Total RNA was isolated from mouse left ventricular extracts and RNA sequencing was carried out on Illumina Nextseq at CellNetworks Deep Sequencing Core Facility at Heidelberg University. Sequencing adapter residues and low quality bases were removed from raw sequencing reads prior to all other analysis steps using Flexbar version 3.0.3<sup>15</sup>. Subsequently, reads mapping to known ribosomal RNA species were excluded from further analyses using Bowtie2 version 2.3.0 with a custom rRNA-index and only keeping non-aligning reads<sup>16</sup>. Principal read mapping against the mouse reference genome (mm10, ENSEMBL build 85) was performed with the STAR aligner, version 2.5.3a<sup>17</sup>. The read-to-transcript assignment was carried out using the R package Rsubread version 1.24.2<sup>18</sup> and the ENSEMBL gene annotation mm10/build85. The resulting count table was further processed with the edgeR R package<sup>19</sup> to construct the list of differentially expressed genes. The final heatmap was generated using the pheatmap R package version 1.0.10<sup>20</sup>.

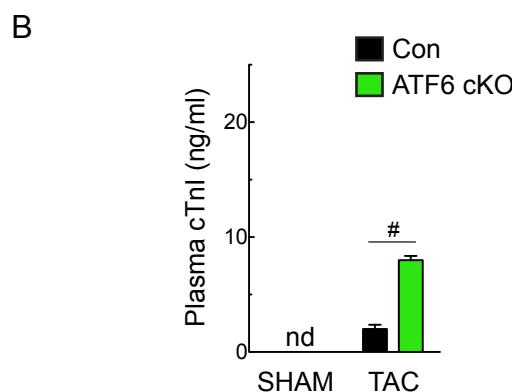
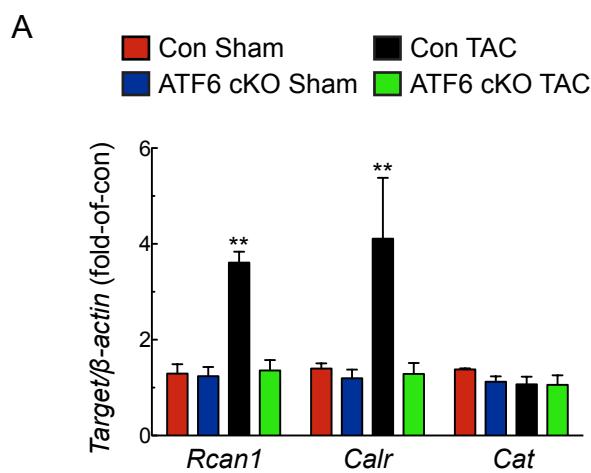
## **Statistics**

For studies involving induction of myocardial hypertrophy, either through surgical TAC or isoproterenol infusion, cohort sizes were based on a predictive power analysis to achieve 5% error and 80% power. Cell culture experiments were performed with at least three cultures for each treatment. Two-group comparisons were performed using Student's two-tailed t-test, and all multiple group comparisons were performed using a one-way ANOVA with a Newman-Keuls post-hoc analysis. Data are represented as mean with all error bars indicating  $\pm$  SEM. \* $P<0.05$ , \*\* $P<0.01$ , # $P<0.001$ .

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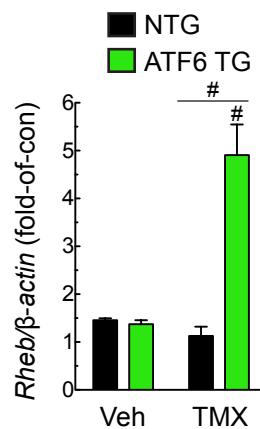


**Online Figure I. Effect of cardiac myocyte-specific ATF6 gene deletion in mice subjected to TAC:** A, mRNA for ATF6 target genes was determined by qRT-PCR. B, Troponin I (cTnI) levels were measured in plasma samples collected from Con or ATF6 cKO mice. Data are represented as mean  $\pm$  s.e.m. \*\* $P \leq 0.01$ , # $P \leq 0.001$ .

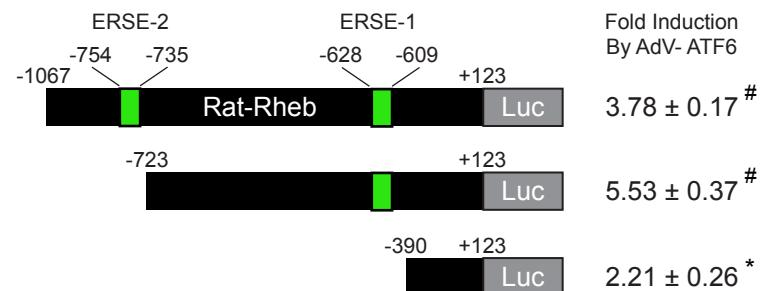
### A GO:0007264: small GTPase mediated signal transduction

Rhoq	Arf2	Rheb	Tiam2	Rap1a	Pak4	Rap2b
Arhgap44	Rala	Mapkap1	Nckap1	Rhod	Farp1	Pak3
Ctnnal1	Arhgap12	Rhoa	Arhgap35	Arhgdia	Jun	Rnd1
Ralgps1	Map2k1	Arhgef10l	Spata13	Hras	Rap2a	Gpr35
Kras	Kpnb1	Rnd3	Shoc2	Git1	Kank1	Pdpn
Erbb2	Rhoc	Stmn1	Aif1	Sdcbp	Rras2	Dok2
Ralb	Hmox1	Net1	Cdc42	Itga3	Col3a1	Ect2
Arhgap1	Bcl6					

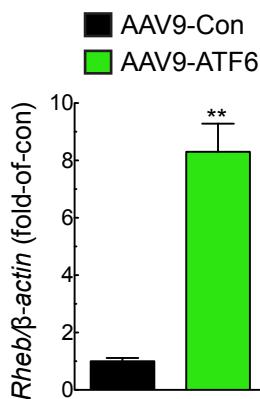
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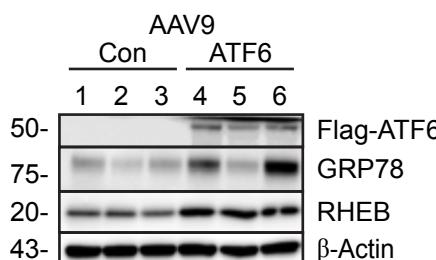
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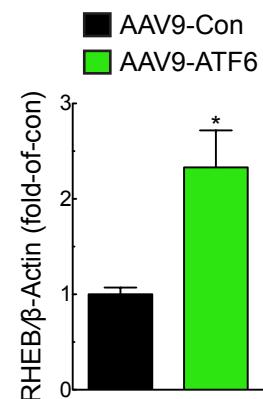
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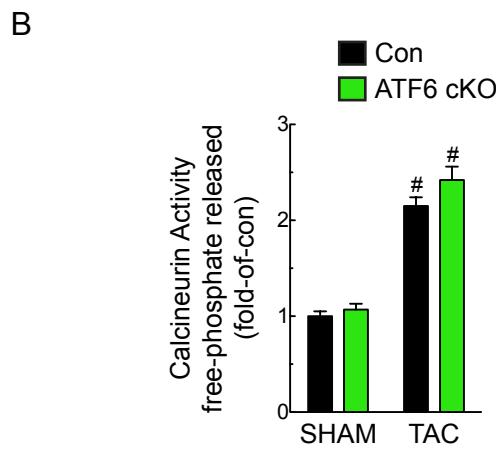
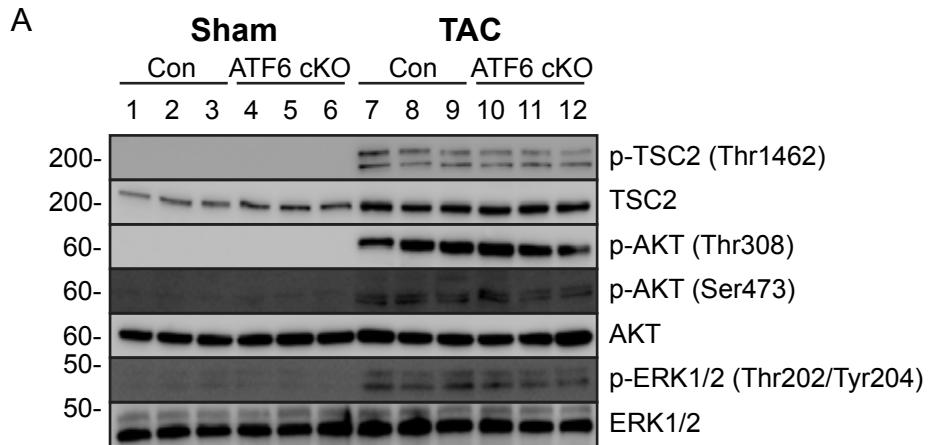
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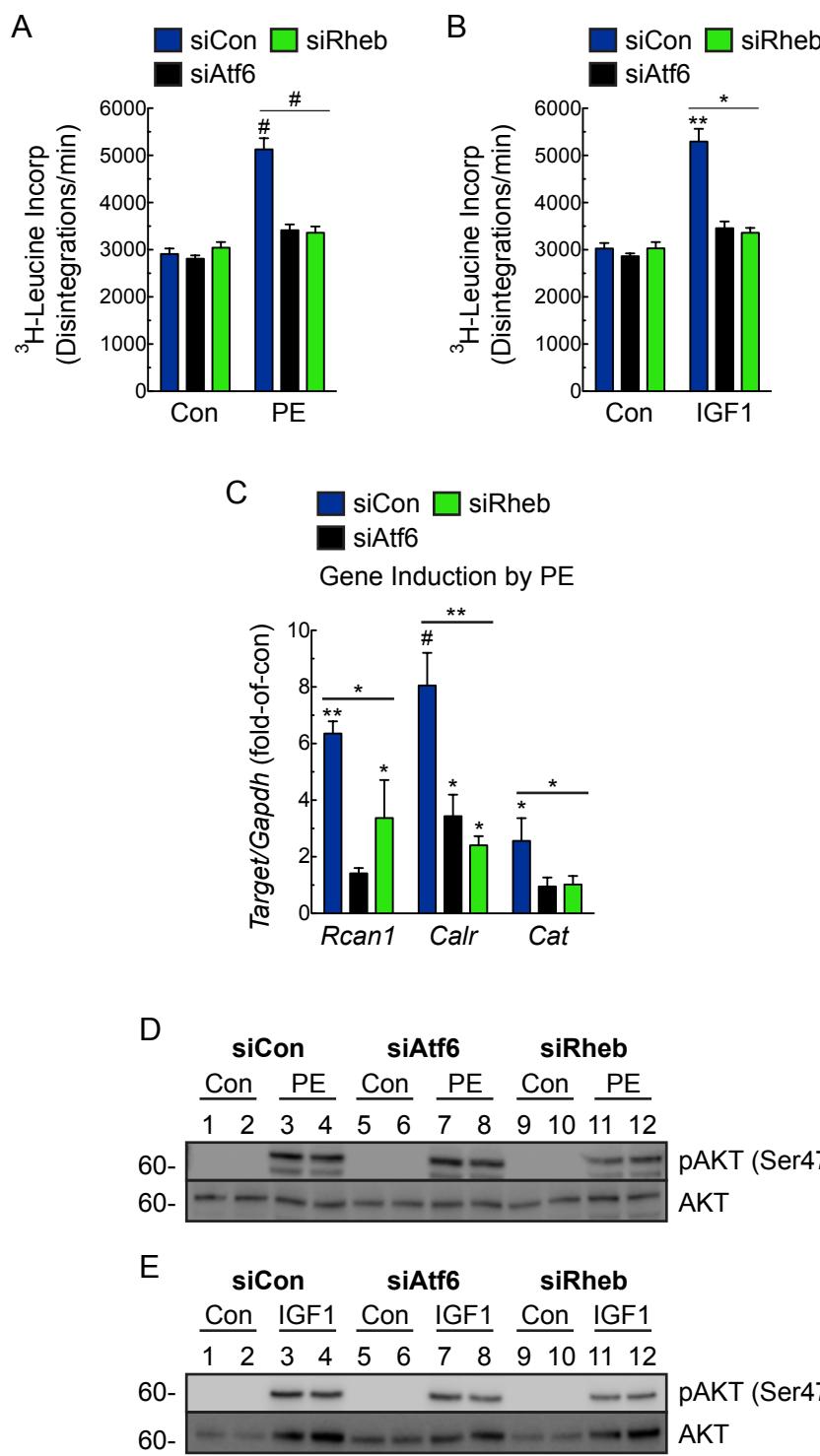
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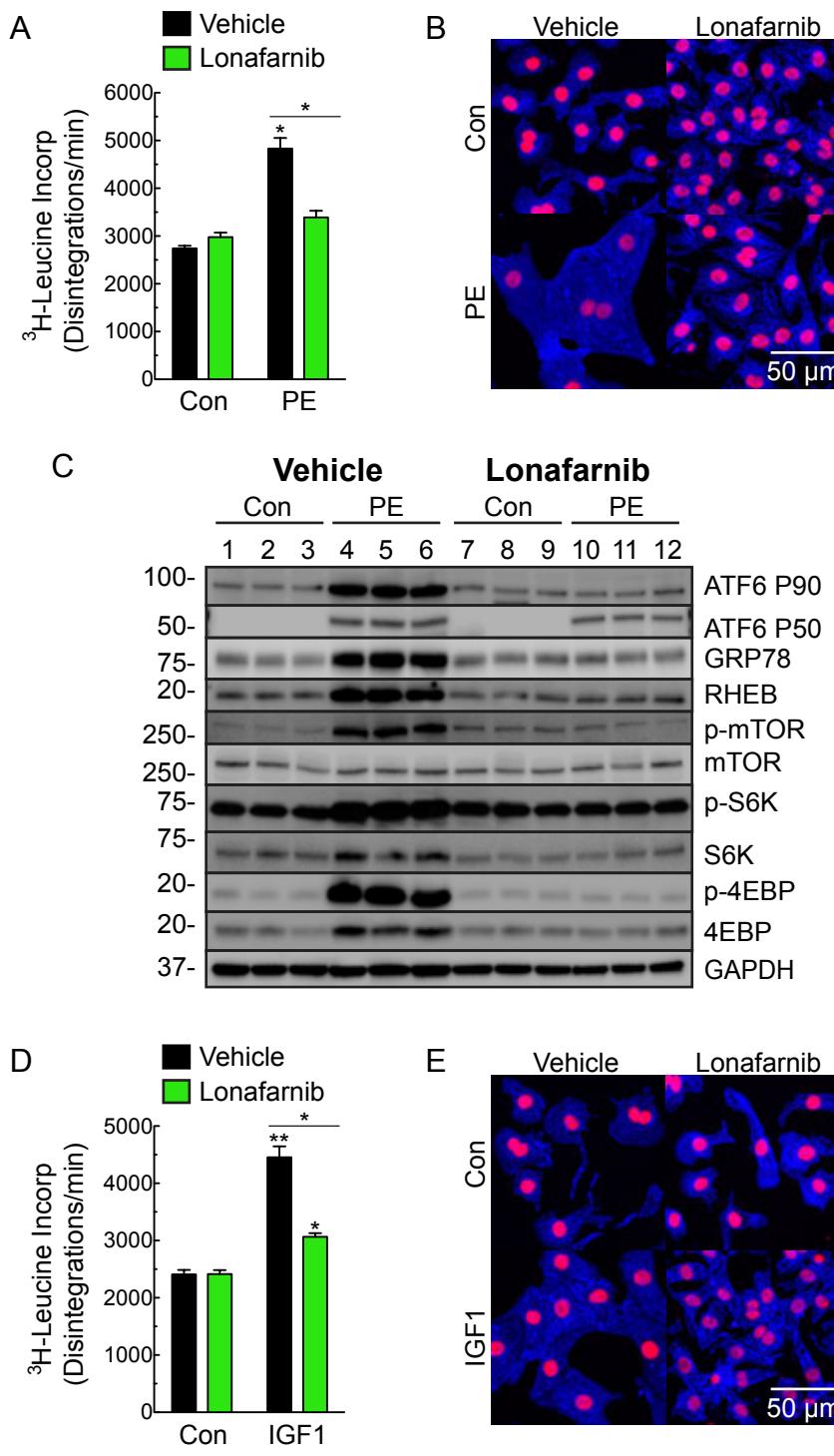
**Online Figure II. ATF6-dependent induction of Rheb in mouse hearts:** A, Table of a subset of induced genes represented by respective gene symbols in ATF6 TG mice with p values and FDR <0.05 annotated with ensemble biological process term GO:0007264. B, mRNA for Rheb was determined by qRT-PCR using LV extracts from ATF6-transgenic (ATF6 TG) and non-transgenic littermates after 5 days of tamoxifen administration (10mg/kg), which activates ATF6 in this mouse line. C, Diagram of constructs encoding different truncated forms of the rat rheb 5'-flanking sequence driving luciferase, as shown (left), i.e. rat-rheb(-1067/+123)-Luc, rat-rheb(-723/+123)-Luc, and rat-rheb(-390/+123)-Luc were transfected into NRVM which were then infected with AdV encoding ATF6(1-373) [active form], or with a control AdV. Luciferase enzyme activity in AdV-ATF6-infected cells was normalized to luciferase enzyme activity in AdV-Con-infected cells to determine the fold-induction by ATF6 (right). D, mRNA for Rheb was determined by qRT-PCR from LV extracts from mice treated 4 weeks with AAV9-Con or AAV9-ATF6. E, F, Immunoblot (E) and densitometry quantification (F) of RHEB protein expression AAV9-Con or AAV9-ATF6 mouse heart extracts. Data are represented as mean±s.e.m. \*P≤0.05, \*\*P≤0.01, #P≤0.001.



**Online Figure III. Effects of ATF6 deletion on regulators of the mTORC1 pathway in hearts of mice subjected to TAC:** **A**, Immunoblot of TSC2, AKT, and ERK1/2 protein phosphorylation and expression in LV extracts from Con or ATF6 cKO mice after 7 days of Sham or TAC. **B**, Calcineurin activity as measured by free-phosphate release in LV extracts from Con or ATF6 cKO mice after 7 days of Sham or TAC. Data are represented as mean  $\pm$  s.e.m. #P  $\leq$  0.001.



**Online Figure IV. Effect of ATF6 and RHEB knockdown on the mTORC1 pathway at cardiac myocyte hypertrophy: A-E.** NRVM were transfected with a nontargeted siRNA (siCon) or siRNAs targeted to rat ATF6 (siAtf6) or RHEB (siRheb), and then treated with or without phenylephrine (PE; 50 $\mu$ M) or IGF1 (100ng/ml) for 48 hours. **A, B,** Incorporation of  $^3$ H-leucine into TCA-precipitable protein in NRVM extracts was measured by scintillation counting. **E,** mRNA for ATF6 target genes was determined by qRT-PCR in coordination with target genes presented in Figure 4E.**D, E,** Immunoblot of NRVM. Phosphorylation of AKT on Ser473 is indicative of mTORC2 activity. Data are represented as mean  $\pm$  s.e.m. \*P $\leq$ 0.05, \*\*P $\leq$ 0.01, #P $\leq$ 0.001.



**Online Figure V. Rheb-inhibitor, Lonafarnib, inhibition of cardiac myocyte hypertrophy:** A-C, NRVM were treated with or without PE (50μM) for 48 hours in the presence or absence of the Rheb inhibitor, Lonafarnib (2μM). A, Incorporation of  $^3\text{H}$ -leucine into TCA-precipitable protein in NRVM extracts was measured by scintillation counting. B, ICF of NRVM stained for  $\alpha$ -actinin (blue) and TOPRO-3 (red). Bar = 50μm. C, Immunoblot of NRVM. D-E, NRVM were treated with or without IGF1 (100ng/ml) for 48 hours in the presence or absence of the Rheb inhibitor, Lonafarnib (2μM). D, Incorporation of  $^3\text{H}$ -leucine into TCA-precipitable protein in NRVM extracts was measured by scintillation counting. E, ICF of NRVM stained for  $\alpha$ -actinin (blue) and TOPRO-3 (red). Bar = 50μm. Data are represented as mean $\pm$ s.e.m. \*P $\leq$ 0.05, \*\*P $\leq$ 0.01.

A

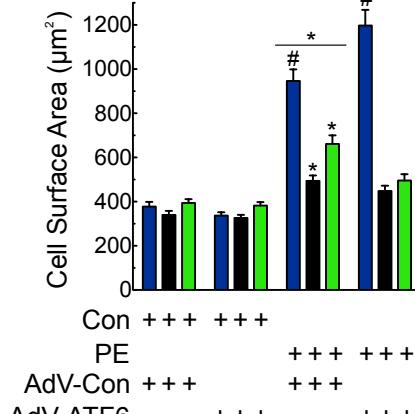
	AdV-Con + Con	AdV-ATF6 + Con
Con	~350	~350
PE	~950	~1250*
IGF1	~900	~1150*

	AdV-Con + Rap	AdV-ATF6 + Rap
Con	~250	~350
PE	~350	~450
IGF1	~400	~400

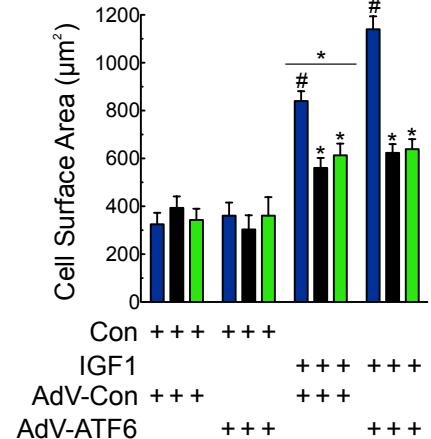
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siCon    Lonafarnib  
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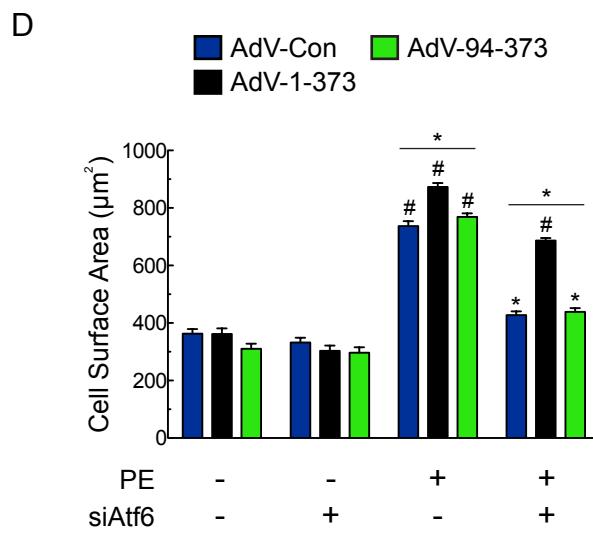
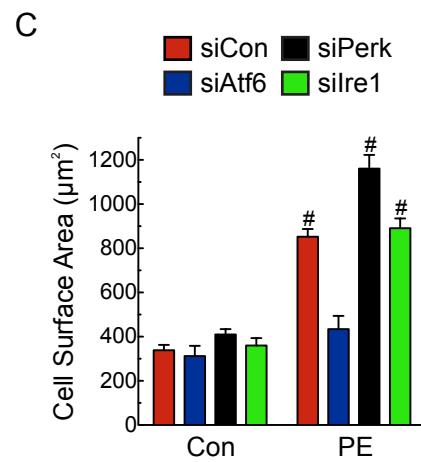
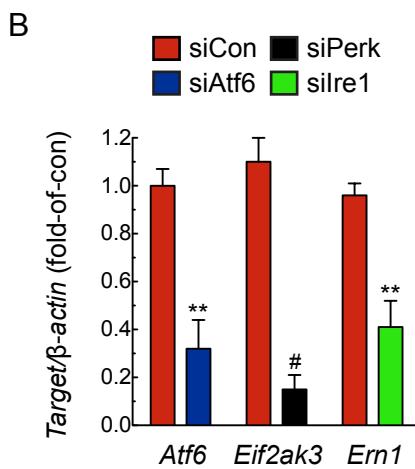
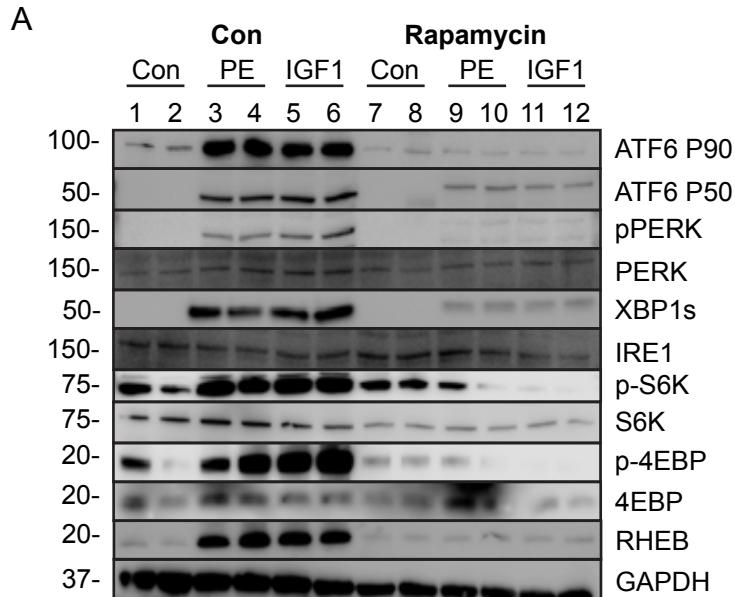
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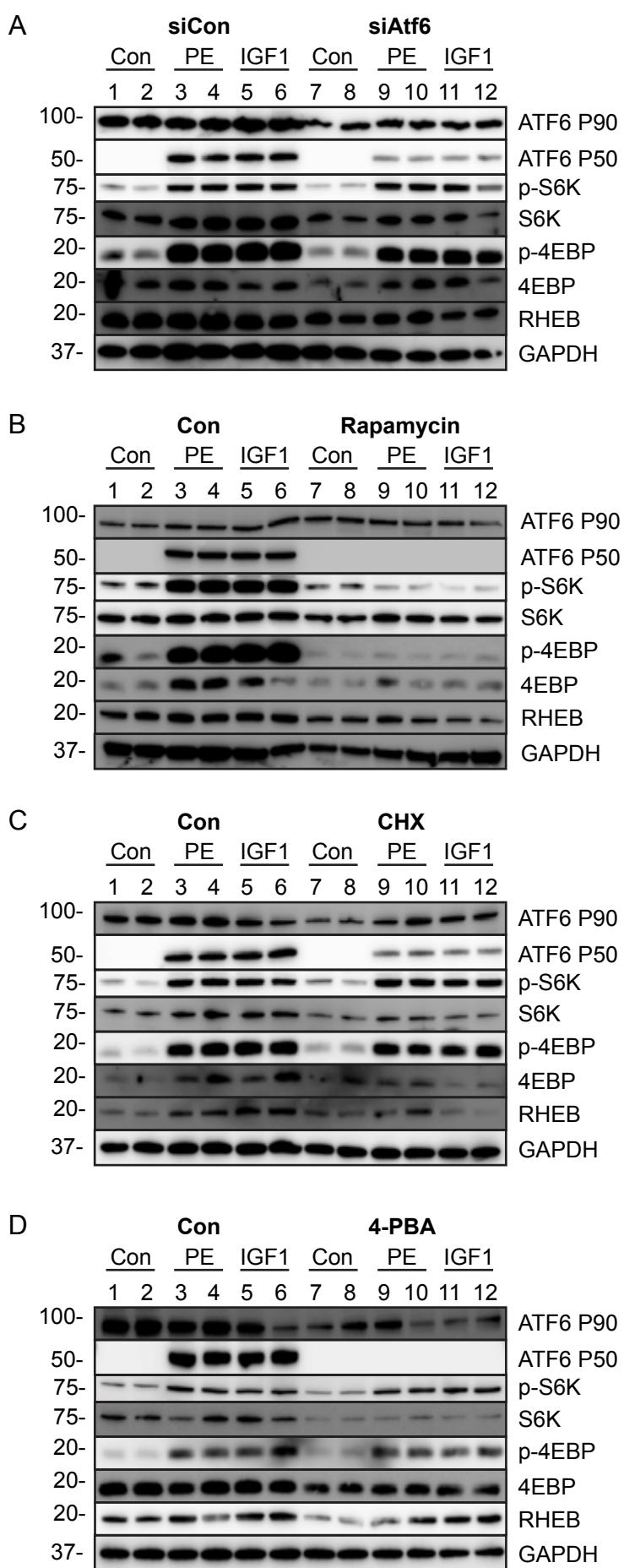


**Online Figure VI. Effect of ATF6 overexpression on cardiac myocyte hypertrophy:**  
**A**, NRVM were infected with AdV encoding control or FLAG-ATF6(1-373) [active form] and then treated with or without phenylephrine (PE; 50µM) or IGF1 (100ng/ml), with or without rapamycin (20nM) for 48 hours, as shown. Cell surface area was determined by photomicroscopy and morphometry, then expressed as mean $\pm$ s.e.m after analyzing at least 100 cells per treatment per experiment. **B-C**, NRVM were transfected with a non-targeted siRNA (siCon) or siRNA targeted to rat RHEB (siRheb), and then infected with AdV encoding control or FLAG-ATF6(1-373) [active form]. NRVM were then treated with or without phenylephrine (PE; 50µM) (**B**) or IGF1 (100ng/ml) (**C**) with or without Lonafarnib (2µM) for 48 hours, as shown. Data are represented as mean $\pm$ s.e.m. \*P $\leq$ 0.05, \*\*P $\leq$ 0.01, #P $\leq$ 0.001.

Online Figure VI



**Online Figure VII. mTORC1-dependent activation of the UPR during cardiac myocyte hypertrophy:** **A**, Immunoblot of NRVM after treatment with or without phenylephrine (PE; 50 $\mu$ M) or IGF1 (100ng/ml), with or without rapamycin (20nM) for 48 hours, as shown. **B, C**, NRVM were transfected with siCon or siRNAs targeted to rat ATF6 (siAtf6), PERK (siPerk), or IRE1 (silre1) and then treated with or without phenylephrine (PE; 50 $\mu$ M) for 48 hours. Atf6, Perk (Eif2ak3) and Ire1 (Ern1) mRNA levels were determined by qRT-PCR (**B**), and cell surface area was determined by photomicroscopy and morphometry (**C**). **D**, NRVM were transfected with a nontargeted siRNA (siCon) or siRNA targeted to rat ATF6 (siAtf6) and were then infected with AdV encoding control, FLAG-ATF6(1-373) [active] or FLAG-ATF6(94-373) [inactive due to deletion of transcriptional activation domain], then treated with or without phenylephrine (PE; 50 $\mu$ M) for 48 hours. Cell surface area was determined by photomicroscopy and morphometry, then expressed as mean $\pm$ s.e.m after analyzing at least 100 cells per treatment per experiment. Data are represented as mean $\pm$ s.e.m. \*P $\leq$ 0.05, \*\*P $\leq$ 0.05, #P $\leq$ 0.001.



**Online Figure VIII. Protein synthesis-dependent activation of the UPR during cardiac myocyte hypertrophy:** **A**, Immunoblot of NRVM transfected with a nontargeted siRNA (siCon) or with siRNA targeted to rat ATF6 (siAtf6) and then treated with or without phenylephrine (PE; 50 $\mu$ M) or IGF1 (100ng/ml) for 6 hours. **B**, Immunoblot of NRVM after treatment with or without phenylephrine (PE; 50 $\mu$ M) or IGF1 (100ng/ml), with or without rapamycin (20nM) for 6 hours, as shown. **C**, Immunoblot of NRVM after co-treatment with or without cyclohexamide (CHX; 100 $\mu$ g/ml) and either phenylephrine (PE; 50 $\mu$ M) or IGF1 (100ng/ml) for 6 hours. **D**, Immunoblot of NRVM after pretreatment with 4-phenylbutyrate (4-PBA; 100 $\mu$ M) for 24 hours and subsequent co-treatment with or without 4-PBA (100 $\mu$ M) and either phenylephrine (PE; 50 $\mu$ M) or IGF1 (100ng/ml) for an additional 6 hours.

**Table I:** 7-day TAC echocardiographic parameters for Con and ATF6 cKO mice

	Con Sham (n = 5)	ATF6 cKO Sham (n = 5)	Con TAC (n = 5)	ATF6 cKO TAC (n = 6)
FS (%)	30.40±1.91	26.71±2.31	28.28±1.89	16.12±1.41 <sup>1,2</sup>
EF (%)	58.60±2.72	52.64±3.72	55.46±2.86	34.30±2.74 <sup>1,2</sup>
LVEDV ( $\mu$ l)	53.75±5.29	62.55±4.99	51.26±2.23	68.32±5.21 <sup>2</sup>
LVESV ( $\mu$ l)	22.47±3.07	30.08±3.98	22.83±1.80	45.35±4.73 <sup>2</sup>
LVIDD (mm)	3.56±0.15	3.80±0.13	3.51±0.06	3.95±0.13 <sup>2</sup>
LVIDS (mm)	2.48±0.14	2.80±0.16	2.52±0.08	3.32±0.15 <sup>1,2</sup>
PWTD (mm)	0.86±0.13	0.89±0.15	1.51±0.11 <sup>1</sup>	1.01±0.10 <sup>2</sup>
PWTS (mm)	1.17±0.10	1.04±0.12	1.76±0.10 <sup>1</sup>	1.07±0.11 <sup>2</sup>
AWTD (mm)	0.88±0.07	0.76±0.05	1.40±0.08 <sup>1</sup>	0.97±0.07 <sup>1,2</sup>
AWTS (mm)	1.08±0.04	1.02±0.08	1.72±0.03 <sup>1</sup>	1.10±0.07 <sup>2</sup>
HR (bpm)	519±13.27	540±2.63	524±3.71	523±13.47
DPLR (RC/LC)	0.91±0.05	1.11±0.08	4.56±0.25 <sup>1</sup>	4.85±0.34 <sup>1</sup>
HW (mg)	118.98±5.41	120.62±3.35	183.36±6.14 <sup>1</sup>	154.08±3.09 <sup>1,2</sup>
BW (g)	21.57±0.78	23.85±0.80	25.78±0.64 <sup>1</sup>	24.43±0.59
TL (mm)	16.40±0.24	17.40±0.24	17.40±0.24	17.00±0.00
HW/BW (mg/g)	5.53±0.27	5.06±0.08	7.12±0.20 <sup>1</sup>	6.32±0.16 <sup>1,2</sup>
HW/TL (mg/mm)	7.26±0.33	6.93±0.11	10.53±0.25 <sup>1</sup>	9.06±0.18 <sup>1,2</sup>

FS = fractional shortening

EF = ejection fraction

LVEDV = left ventricular end diastolic volume

LVESV = left ventricular end systolic volume

LVIDD = left ventricular inner diameter in diastole

LVIDS = left ventricular inner diameter in systole

PWTD = left ventricular posterior wall thickness in diastole

PWTS = left ventricular posterior wall thickness in systole

AWTD = left ventricular anterior wall thickness in diastole

AWTS = left ventricular anterior wall thickness in systole

HR = heart rate in beats per minute

DPLR = Doppler ratio of right carotid blood flow velocity to left carotid blood flow velocity

HW = heart weight

BW = body weight

TL = tibia length

HW/BW = heart weight/body weight

HW/TL = heart weight/tibia length

Statistical analyses used a one-way ANOVA with a Newman-Keuls post-hoc analysis.

<sup>1</sup> = p ≤ 0.05 different from respective Sham<sup>2</sup> = p ≤ 0.05 different from Con TAC

**Table II: 4-week Free Wheel echocardiographic parameters for Con and ATF6 cKO mice**

	Con Sedentary (n = 5)	ATF6 cKO Sedentary (n = 5)	Con Run (n = 5)	ATF6 cKO Run (n = 5)
FS (%)	29.19±1.46	24.22±1.64	29.24±1.74	23.03±1.75 <sup>2</sup>
EF (%)	56.42±2.33	48.55±2.70	57.06±2.74	46.53±3.00 <sup>2</sup>
LVEDV ( $\mu$ l)	79.56±16.48	72.38±6.33	50.38±7.60	71.78±5.85 <sup>2</sup>
LVESV ( $\mu$ l)	35.29±7.76	37.64±4.35	22.29±3.93	38.54±4.11 <sup>2</sup>
LVIDD (mm)	4.13±0.40	4.04±0.15	3.44±0.24	4.03±0.14 <sup>2</sup>
LVIDS (mm)	2.93±0.30	3.07±0.16	2.45±0.21	3.10±0.14 <sup>2</sup>
PWTD (mm)	0.75±0.14	0.89±0.14	1.77±0.11 <sup>1</sup>	0.79±0.03 <sup>2</sup>
PWTS (mm)	1.08±0.08	1.21±0.15	2.06±0.08 <sup>1</sup>	1.08±0.04 <sup>2</sup>
AWTD (mm)	0.81±0.06	0.84±0.07	1.22±0.08 <sup>1</sup>	0.96±0.09 <sup>2</sup>
AWTS (mm)	1.11±0.03	1.14±0.05	1.48±0.07 <sup>1</sup>	1.09±0.07 <sup>2</sup>
HR (bpm)	491±9.28	500±9.36	506±9.11	556±8.70 <sup>1,2</sup>
DIST (km/wk)	n/a	n/a	8.11±1.79	8.65±0.87
HW (mg)	132.02±4.51	128.32±7.28	171.16±5.24 <sup>1</sup>	137.02±1.40 <sup>2</sup>
BW (g)	27.23±0.51	25.14±0.90	24.80±0.66 <sup>1</sup>	24.43±0.43
TL (mm)	17.00±0.00	17.20±0.20	17.20±0.20	17.60±0.24
HW/BW (mg/g)	4.85±0.14	5.09±0.16	6.90±0.13 <sup>1</sup>	5.61±0.09 <sup>1,2</sup>
HW/TL (mg/mm)	7.77±0.27	7.46±0.42	9.96±0.35 <sup>1</sup>	7.79±0.11 <sup>2</sup>

FS = fractional shortening

EF = ejection fraction

LVEDV = left ventricular end diastolic volume

LVESV = left ventricular end systolic volume

LVIDD = left ventricular inner diameter in diastole

LVIDS = left ventricular inner diameter in systole

PWTD = left ventricular posterior wall thickness in diastole

PWTS = left ventricular posterior wall thickness in systole

AWTD = left ventricular anterior wall thickness in diastole

AWTS = left ventricular anterior wall thickness in systole

HR = heart rate in beats per minute

DIST = average distance ran per week

HW = heart weight

BW = body weight

TL = tibia length

HW/BW = heart weight/body weight

HW/TL = heart weight/tibia length

Statistical analyses used a one-way ANOVA with a Newman-Keuls post-hoc analysis.

<sup>1</sup> = p ≤ 0.05 different from respective Sedentary

<sup>2</sup> = p ≤ 0.05 different from Con Run

**Online Table III - Genes Changed by ATF6 in the Heart**

		$p \leq 0.05$		
Gene No.	Gene Symbol	ENSEMBL ID	$\log_2 FC$	
1	Derl3	ENSMUSG0000009092	11.81357136	
2	Bmp10	ENSMUSG00000030046	10.08553123	
3	Serpib1c	ENSMUSG00000079049	9.474748328	
4	Esr1	ENSMUSG00000019768	9.008620439	
5	Saa3	ENSMUSG00000040026	8.404639259	
6	Rec8	ENSMUSG0000002324	7.080680613	
7	Gm8424	ENSMUSG00000081194	6.43393998	
8	Sdf2l1	ENSMUSG00000022769	6.422401383	
9	Vmn2r3	ENSMUSG00000091572	6.388726375	
10	Gm1627	ENSMUSG00000100987	6.167009426	
11	Slc7a11	ENSMUSG00000027737	6.022939919	
12	Epyc	ENSMUSG00000019936	5.970480515	
13	Far1	ENSMUSG00000030759	5.898776763	
14	Myl7	ENSMUSG00000020469	5.765310795	
15	Ube2c	ENSMUSG0000001403	5.703447206	
16	Arntl	ENSMUSG00000055116	5.68993575	
17	Pdia4	ENSMUSG00000025823	5.653529589	
18	Mthfd2	ENSMUSG0000005667	5.640699455	
19	Slc6a2	ENSMUSG00000055368	5.588147698	
20	Slc7a3	ENSMUSG00000031297	5.585746991	
21	Pak3	ENSMUSG00000031284	5.576617158	
22	Chil3	ENSMUSG00000040809	5.544097671	
23	Mybphl	ENSMUSG00000068745	5.418282086	
24	Pycr1	ENSMUSG00000025140	5.415421318	
25	Mefv	ENSMUSG00000022534	5.273792403	
26	Psat1	ENSMUSG00000024640	5.200998995	
27	Serpina3f	ENSMUSG00000066363	5.179387737	
28	Baalc	ENSMUSG00000022296	5.165927848	
29	Myl4	ENSMUSG00000061086	5.142184528	
30	Sln	ENSMUSG00000042045	5.062686483	
31	Ptx3	ENSMUSG00000027832	5.060941359	
32	Prkcz	ENSMUSG00000029053	5.04750561	
33	Gm33474	ENSMUSG00000106554	4.984196961	
34	Acox2	ENSMUSG00000021751	4.824390864	
35	Phgdh	ENSMUSG00000053398	4.816582392	
36	Ptprt	ENSMUSG00000053141	4.730415496	
37	Manf	ENSMUSG00000032575	4.726713953	
38	Asns	ENSMUSG00000029752	4.620079425	
39	Gm11382	ENSMUSG00000074973	4.614035415	
40	Polr3k	ENSMUSG00000038628	4.549235916	
41	Tnni1	ENSMUSG00000026418	4.526836544	
42	Cxcl5	ENSMUSG00000029371	4.443899107	
43	Tubb3	ENSMUSG00000062380	4.421978788	

44	Tk1	ENSMUSG00000025574	4.417099686	
45	Mlana	ENSMUSG00000024806	4.402834241	
46	Ccl2	ENSMUSG00000035385	4.389626965	
47	Selp	ENSMUSG00000026580	4.375541912	
48	P4hb	ENSMUSG00000025130	4.375151476	
49	Gabrg3	ENSMUSG00000055026	4.295137994	
50	Mcoln2	ENSMUSG00000011008	4.238921524	
51	Timp1	ENSMUSG00000001131	4.214956842	
52	7530428D23Rik	ENSMUSG00000103441	4.200585247	
53	Mmp12	ENSMUSG00000049723	4.177679228	
54	Sphkap	ENSMUSG00000026163	4.144898204	
55	Bmp3	ENSMUSG00000029335	4.139366775	
56	Il1rn	ENSMUSG00000026981	4.091671943	
57	Hsp90b1	ENSMUSG00000020048	4.073873276	
58	Clec4e	ENSMUSG00000030142	4.040821306	
59	Prkc2	ENSMUSG00000108314	4.038600449	
60	Dok5	ENSMUSG00000027560	3.978150578	
61	E2f1	ENSMUSG00000027490	3.975272909	
62	Hp	ENSMUSG00000031722	3.959608332	
63	Hyou1	ENSMUSG00000032115	3.944982062	
64	Fgf12	ENSMUSG00000022523	3.939196334	
65	Sycp2	ENSMUSG00000060445	3.935533061	
66	Gdf15	ENSMUSG00000038508	3.934450583	
67	Rbm15b	ENSMUSG00000074102	3.931228987	
68	Spp1	ENSMUSG00000029304	3.740713979	
69	Ccl7	ENSMUSG00000035373	3.738093438	
70	Tmem163	ENSMUSG00000026347	3.731074518	
71	Gm7967	ENSMUSG00000100009	3.730896653	
72	Adamts4	ENSMUSG0000006403	3.718658173	
73	Xrcc3	ENSMUSG00000021287	3.706565382	
74	Cxcr6	ENSMUSG00000048521	3.700892285	
75	Plac8	ENSMUSG00000029322	3.680345573	
76	Creld2	ENSMUSG00000023272	3.666193145	
77	Tnc	ENSMUSG00000028364	3.591714397	
78	Rxfp1	ENSMUSG00000034009	3.535189978	
79	Tnfsf18	ENSMUSG00000066755	3.524499913	
80	Ereg	ENSMUSG00000029377	3.416991129	
81	Gm7901	ENSMUSG00000101431	3.414907051	
82	Cxcl10	ENSMUSG00000034855	3.389971448	
83	Card14	ENSMUSG00000013483	3.357137465	
84	Aldh18a1	ENSMUSG00000025007	3.34458723	
85	Dnajb11	ENSMUSG0000004460	3.343407519	
86	Gm15344	ENSMUSG00000084899	3.294729535	
87	Slc2a6	ENSMUSG00000036067	3.284007038	
88	Ccr2	ENSMUSG00000049103	3.277942748	
89	Cyp2e1	ENSMUSG00000025479	3.272304905	
90	Lrp8	ENSMUSG00000028613	3.2721959	

91	Socs3	ENSMUSG00000053113	3.254763524	
92	Hspa5	ENSMUSG00000026864	3.226595312	
93	Tspyl2	ENSMUSG00000041096	3.182915422	
94	Nxpe5	ENSMUSG00000047592	3.170840319	
95	Slc27a3	ENSMUSG00000027932	3.160858267	
96	Ch25h	ENSMUSG00000050370	3.156766066	
97	Lman1l	ENSMUSG00000056271	3.086917291	
98	Hn1l	ENSMUSG00000024165	3.058111074	
99	D030028A08Rik	ENSMUSG00000078700	3.024411342	
100	Trib3	ENSMUSG00000032715	3.01669847	
101	Oip5	ENSMUSG00000072980	3.007680092	
102	Calr	ENSMUSG00000003814	3.002423682	
103	Ptrh1	ENSMUSG00000053746	2.996601041	
104	Sel1l	ENSMUSG00000020964	2.984189709	
105	Pgp	ENSMUSG00000043445	2.977330198	
106	Fhl1	ENSMUSG00000023092	2.962677997	
107	Hspa1a	ENSMUSG00000091971	2.946993662	
108	Akr1b3	ENSMUSG00000001642	2.926261072	
109	Aldh1a2	ENSMUSG00000013584	2.923052074	
110	Gm37006	ENSMUSG00000103885	2.917999382	
111	Slfn4	ENSMUSG00000000204	2.911860183	
112	Gm10097	ENSMUSG00000096553	2.910195446	
113	F10	ENSMUSG00000031444	2.898660594	
114	Gm12138	ENSMUSG00000082087	2.871691575	
115	Cdkn2b	ENSMUSG00000073802	2.859130135	
116	4732465J04Rik	ENSMUSG00000101517	2.838500759	
117	Mt2	ENSMUSG00000031762	2.836149018	
118	Serpina3n	ENSMUSG00000021091	2.821965398	
119	Cilp2	ENSMUSG00000044006	2.806837587	
120	Elk1	ENSMUSG0000009406	2.803602336	
121	Ints3	ENSMUSG00000027933	2.794929571	
122	Gm6644	ENSMUSG00000100309	2.788194109	
123	2610028H24Rik	ENSMUSG0000009114	2.776943846	
124	Lmtd1	ENSMUSG00000054966	2.766244614	
125	B230217C12Rik	ENSMUSG00000050538	2.760138761	
126	Sele	ENSMUSG00000026582	2.753570014	
127	Ebp	ENSMUSG00000031168	2.744096448	
128	Alkbh2	ENSMUSG00000044339	2.704625956	
129	Gm6736	ENSMUSG00000071414	2.697352753	
130	Fgr	ENSMUSG00000028874	2.688598098	
131	Eda2r	ENSMUSG00000034457	2.682140385	
132	Serpina3g	ENSMUSG00000041481	2.656149339	
133	Itgax	ENSMUSG00000030789	2.646619905	
134	Hspa1b	ENSMUSG00000090877	2.614593952	
135	Stbd1	ENSMUSG00000047963	2.612770661	
136	Slc7a5	ENSMUSG00000040010	2.611412306	
137	Fanca	ENSMUSG00000032815	2.600943825	

138	Gpr141	ENSMUSG00000053101	2.599376007	
139	Myc	ENSMUSG00000022346	2.593094825	
140	Gm9768	ENSMUSG00000108391	2.589201067	
141	Serpina9	ENSMUSG00000058260	2.569835526	
142	H2-Ke6	ENSMUSG00000073422	2.539940112	
143	B430219N15Rik	ENSMUSG00000085211	2.535694452	
144	Lgals3	ENSMUSG00000050335	2.519191675	
145	Pilra	ENSMUSG00000046245	2.516259782	
146	Dolpp1	ENSMUSG00000026856	2.514853363	
147	Gm43660	ENSMUSG00000107352	2.505444971	
148	Gm3571	ENSMUSG00000090610	2.49879397	
149	Pdia6	ENSMUSG00000020571	2.490430091	
150	Ppp1r3d	ENSMUSG00000049999	2.480900989	
151	Shisa6	ENSMUSG00000053930	2.47963875	
152	Tnfrsf12a	ENSMUSG00000023905	2.479420744	
153	Fos	ENSMUSG00000021250	2.471681076	
154	C920009B18Rik	ENSMUSG00000097352	2.461909181	
155	Cpne5	ENSMUSG00000024008	2.456456201	
156	Gm4841	ENSMUSG00000068606	2.452944216	
157	Tfec	ENSMUSG00000029553	2.45290359	
158	Cenpw	ENSMUSG00000075266	2.449517084	
159	Tlr1	ENSMUSG00000044827	2.449281283	
160	Gm24305	ENSMUSG00000095590	2.445442278	
161	Gtse1	ENSMUSG00000022385	2.431922128	
162	Gm29040	ENSMUSG00000099576	2.428158893	
163	Rab26os	ENSMUSG00000093565	2.423793102	
164	Arf2	ENSMUSG00000062421	2.42044934	
165	Dnajc3	ENSMUSG00000022136	2.41721018	
166	Cdk2ap2	ENSMUSG00000024856	2.41009384	
167	1200007C13Rik	ENSMUSG00000087684	2.390563475	
168	Clec4d	ENSMUSG00000030144	2.384137488	
169	Cdkn1a	ENSMUSG00000023067	2.375206669	
170	Hmox1	ENSMUSG0000005413	2.374030372	
171	Ddias	ENSMUSG00000030641	2.3659262	
172	Csf2rb2	ENSMUSG00000071714	2.362173452	
173	2210407C18Rik	ENSMUSG00000037145	2.360698164	
174	Dkk3	ENSMUSG00000030772	2.36049145	
175	Gm26606	ENSMUSG00000097337	2.358506742	
176	Lrrc71	ENSMUSG00000023084	2.338508612	
177	Xbp1	ENSMUSG00000020484	2.336362417	
178	Ncam1	ENSMUSG00000039542	2.332206947	
179	Cxcl1	ENSMUSG00000029380	2.332199941	
180	Gprin3	ENSMUSG00000045441	2.317360823	
181	Sept5	ENSMUSG00000072214	2.313294592	
182	Syvn1	ENSMUSG00000024807	2.306530263	
183	Egr2	ENSMUSG00000037868	2.304716168	
184	Thbs1	ENSMUSG00000040152	2.295796614	

185	Kcnc3	ENSMUSG00000062785	2.290653415	
186	Kifc1	ENSMUSG00000079553	2.287334021	
187	Gale	ENSMUSG00000028671	2.284048043	
188	Nans	ENSMUSG00000028334	2.275578636	
189	Nusap1	ENSMUSG00000027306	2.255037554	
190	Rcan1	ENSMUSG00000022951	2.212202653	
191	Slfn1	ENSMUSG00000078763	2.212112935	
192	Gm17709	ENSMUSG00000091952	2.209253708	
193	Avil	ENSMUSG00000025432	2.201618781	
194	Mvd	ENSMUSG0000006517	2.199845318	
195	Unc5c	ENSMUSG00000059921	2.196062762	
196	Sesn2	ENSMUSG00000028893	2.195520396	
197	Cdca3	ENSMUSG00000023505	2.191457262	
198	Napsa	ENSMUSG00000002204	2.188994743	
199	Chka	ENSMUSG00000024843	2.186135159	
200	Zfp850	ENSMUSG00000096916	2.184406999	
201	2200002D01Rik	ENSMUSG00000030587	2.182975708	
202	Tbcb	ENSMUSG0000006095	2.182783885	
203	Cenpk	ENSMUSG00000021714	2.180064742	
204	Ormdl2	ENSMUSG00000025353	2.177591587	
205	Clec4n	ENSMUSG00000023349	2.172999515	
206	2810474O19Rik	ENSMUSG00000032712	2.169593649	
207	Ms4a4c	ENSMUSG00000024675	2.169515604	
208	Nde1	ENSMUSG00000022678	2.146751019	
209	Serpina3i	ENSMUSG00000079014	2.138122645	
210	Asf1b	ENSMUSG00000005470	2.137415133	
211	Ears2	ENSMUSG00000030871	2.137228298	
212	Gpr35	ENSMUSG00000026271	2.134014304	
213	Junb	ENSMUSG00000052837	2.133716588	
214	Spc25	ENSMUSG00000005233	2.129056067	
215	Dmxl1	ENSMUSG00000037416	2.127947217	
216	Msr1	ENSMUSG00000025044	2.126320408	
217	Wfs1	ENSMUSG00000039474	2.121447861	
218	Uck2	ENSMUSG00000026558	2.113344049	
219	Zfp324	ENSMUSG00000004500	2.097824653	
220	Adam8	ENSMUSG00000025473	2.09172395	
221	Ccl12	ENSMUSG00000035352	2.08771107	
222	Kctd8	ENSMUSG00000037653	2.078933632	
223	Ntng2	ENSMUSG00000035513	2.064808181	
224	Sfrp5	ENSMUSG00000018822	2.061985858	
225	Pdia3	ENSMUSG00000027248	2.058758685	
226	Sh2d5	ENSMUSG00000045349	2.053762515	
227	Adamts15	ENSMUSG00000033453	2.051962365	
228	Slamf8	ENSMUSG00000053318	2.041095586	
229	Lad1	ENSMUSG00000041782	2.039938823	
230	Nlrp3	ENSMUSG00000032691	2.034710962	
231	Gm10130	ENSMUSG00000095315	2.026437197	

232	Eif1a	ENSMUSG00000057561	2.022963037	
233	Samsn1	ENSMUSG00000022876	2.017177449	
234	Ankrd42	ENSMUSG00000041343	2.015608579	
235	Morf4l2	ENSMUSG00000031422	2.003946107	
236	Slc6a9	ENSMUSG00000028542	2.002328136	
237	Xlr3b	ENSMUSG00000073125	2.002130317	
238	Piga	ENSMUSG00000031381	2.001658825	
239	Nfil3	ENSMUSG00000056749	1.997276455	
240	1500015O10Rik	ENSMUSG00000026051	1.981376136	
241	Aldh1l2	ENSMUSG00000020256	1.980183895	
242	Tpx2	ENSMUSG00000027469	1.979014627	
243	Slc20a1	ENSMUSG00000027397	1.978291357	
244	Blvrb	ENSMUSG00000040466	1.971647348	
245	Hist1h2ab	ENSMUSG00000061615	1.970698593	
246	Bex1	ENSMUSG00000050071	1.963875025	
247	Tnf	ENSMUSG00000024401	1.963341889	
248	Lrrc10b	ENSMUSG00000090291	1.960004863	
249	D16Ert472e	ENSMUSG00000022864	1.942668191	
250	2900092N22Rik	ENSMUSG00000104034	1.935048799	
251	Pnpo	ENSMUSG00000018659	1.933798517	
252	Adam12	ENSMUSG00000054555	1.920686384	
253	Btg2	ENSMUSG00000020423	1.919087802	
254	Chad	ENSMUSG00000039084	1.916603137	
255	Idi1	ENSMUSG00000058258	1.911564895	
256	M6pr-ps	ENSMUSG00000080832	1.907252581	
257	Rtn4	ENSMUSG00000020458	1.890110721	
258	Stx11	ENSMUSG00000039232	1.877917576	
259	Vcp-rs	ENSMUSG00000083327	1.866506145	
260	2700038G22Rik	ENSMUSG00000097180	1.857497369	
261	Rnd1	ENSMUSG00000054855	1.856688099	
262	Serpinh1	ENSMUSG00000070436	1.856610681	
263	Vcp	ENSMUSG00000028452	1.854155205	
264	Tubb4b-ps2	ENSMUSG00000099997	1.853558273	
265	AW011738	ENSMUSG00000078349	1.840325275	
266	Pin1	ENSMUSG00000032171	1.829870336	
267	Pcdh11x	ENSMUSG00000034755	1.829636281	
268	Mettl27	ENSMUSG00000040557	1.827642833	
269		ENSMUSG00000064168	1.824874552	
270	Adamts8	ENSMUSG00000031994	1.822492136	
271	Nfkbid	ENSMUSG00000036931	1.821751403	
272	Nhp2	ENSMUSG00000001056	1.821565655	
273	Icam4	ENSMUSG00000001014	1.816106568	
274	Ginm1	ENSMUSG00000040006	1.811234451	
275	Cd44	ENSMUSG00000005087	1.806952418	
276	Tenm4	ENSMUSG00000048078	1.806469533	
277	Ccnf	ENSMUSG00000072082	1.79495856	
278	Gm28187	ENSMUSG00000099375	1.790163645	

279	Al506816	ENSMUSG00000105987	1.786008502	
280	Tnfaip2	ENSMUSG0000021281	1.780321378	
281	Gas2l3	ENSMUSG0000074802	1.776794858	
282	Hsf2bp	ENSMUSG0000002076	1.776085215	
283	Fasn	ENSMUSG0000025153	1.772576521	
284	Rhoq	ENSMUSG0000024143	1.77164729	
285	Zfp469	ENSMUSG0000043903	1.764803209	
286	Rrp12	ENSMUSG0000035049	1.764797566	
287	B3gnt5	ENSMUSG0000022686	1.763194956	
288	Sqle	ENSMUSG0000022351	1.74614843	
289	Gm44193	ENSMUSG00000107559	1.744119957	
290	2700078F05Rik	ENSMUSG00000103722	1.74092107	
291	Atf3	ENSMUSG0000026628	1.736691794	
292	Dusp5	ENSMUSG0000034765	1.735880351	
293	Armc7	ENSMUSG0000057219	1.7290977	
294	Myrfl	ENSMUSG0000034057	1.72736617	
295	BC022687	ENSMUSG0000037594	1.724962995	
296	Uchl1	ENSMUSG0000029223	1.723117731	
297	Mybl1	ENSMUSG0000025912	1.712405563	
298	Snhg15	ENSMUSG0000085156	1.708595817	
299	Trmt61a	ENSMUSG0000060950	1.700813943	
300	Engase	ENSMUSG0000033857	1.700119749	
301	Gm14857	ENSMUSG0000081289	1.695715714	
302	Slc2a8	ENSMUSG0000026791	1.69467734	
303	Hagh	ENSMUSG0000024158	1.694606394	
304	Txnr1	ENSMUSG0000020250	1.692519589	
305	Cfp	ENSMUSG0000001128	1.688643231	
306	Vwc2	ENSMUSG0000050830	1.68668911	
307	Fam167a	ENSMUSG0000035095	1.686618007	
308	Itgam	ENSMUSG0000030786	1.682160168	
309	Ddit3	ENSMUSG0000025408	1.681542641	
310	Map3k3	ENSMUSG0000020700	1.675749333	
311	Pvt1	ENSMUSG0000097039	1.675264628	
312	Bcl3	ENSMUSG0000053175	1.673181926	
313	Cenpi	ENSMUSG0000031262	1.673171107	
314	Slc1a4	ENSMUSG0000020142	1.672319322	
315	Loxl4	ENSMUSG0000025185	1.66021152	
316	Birc5	ENSMUSG0000017716	1.655877869	
317	Emb	ENSMUSG0000021728	1.650733426	
318	Sbno2	ENSMUSG0000035673	1.650593127	
319	Ubald2	ENSMUSG0000050628	1.650501705	
320	Chac1	ENSMUSG0000027313	1.646133269	
321	Fst	ENSMUSG0000021765	1.646130913	
322	Klra2	ENSMUSG0000030187	1.645709693	
323	Uggt1	ENSMUSG0000037470	1.644961843	
324	Mmp3	ENSMUSG0000043613	1.642238674	
325	Gm9260	ENSMUSG00000106239	1.638809044	

326	Csf2rb	ENSMUSG00000071713	1.638798976	
327	Arid4a	ENSMUSG00000048118	1.637927577	
328	Mpv17l2	ENSMUSG00000035559	1.637687304	
329	Egr1	ENSMUSG00000038418	1.633002072	
330	Pgk1	ENSMUSG00000062070	1.629109112	
331	Trp63	ENSMUSG00000022510	1.62107416	
332	Tnni2	ENSMUSG00000031097	1.618747065	
333	Cyb5r1	ENSMUSG00000026456	1.609318021	
334	Slc17a7	ENSMUSG00000070570	1.604700213	
335	Gm42725	ENSMUSG00000105601	1.603763447	
336	Igf2bp2	ENSMUSG00000033581	1.600812966	
337	Thop1	ENSMUSG0000004929	1.600765487	
338	Suco	ENSMUSG00000040297	1.598969712	
339	Sertad3	ENSMUSG00000055200	1.598348345	
340	Ect2	ENSMUSG00000027699	1.595965295	
341	Cd200r1	ENSMUSG00000022667	1.595525098	
342	Cdca2	ENSMUSG00000048922	1.595195402	
343	Shroom3	ENSMUSG00000029381	1.581363529	
344	Cat	ENSMUSG00000027187	1.581206905	
345	Isyna1	ENSMUSG00000019139	1.580324046	
346	Gclm	ENSMUSG00000028124	1.578931649	
347	Tuba1c	ENSMUSG00000043091	1.578448169	
348	Ccr1	ENSMUSG00000025804	1.577197402	
349	Ckap2	ENSMUSG00000037725	1.570621326	
350	E2f8	ENSMUSG00000046179	1.566293037	
351	Top2a	ENSMUSG00000020914	1.564537824	
352	Gars	ENSMUSG00000029777	1.563576397	
353	Pgbd5	ENSMUSG00000050751	1.560744026	
354	Gm37018	ENSMUSG00000102950	1.559964399	
355	Mxd1	ENSMUSG0000001156	1.559822684	
356	2310030G06Rik	ENSMUSG00000032062	1.558835095	
357	Gm12092	ENSMUSG00000084850	1.557193143	
358	Os9	ENSMUSG00000040462	1.556819869	
359	Calu	ENSMUSG00000029767	1.552245573	
360	Sptlc2	ENSMUSG00000021036	1.547928702	
361	Hmgcs1	ENSMUSG00000093930	1.541408389	
362	Plek	ENSMUSG00000020120	1.53988097	
363	Pemt	ENSMUSG0000000301	1.539235376	
364	Spdl1	ENSMUSG00000069910	1.535588415	
365	Appl1	ENSMUSG00000040760	1.534526106	
366	Ankrd1	ENSMUSG00000024803	1.532520407	
367	Agtrap	ENSMUSG00000029007	1.530067499	
368	Odc1	ENSMUSG00000011179	1.529290011	
369	Ccl11	ENSMUSG00000020676	1.5290234	
370	Gm5526	ENSMUSG00000084817	1.528484975	
371	Zfp593	ENSMUSG00000028840	1.525871795	
372	Ppib	ENSMUSG00000032383	1.525753398	

373	Gm37258	ENSMUSG00000102760	1.522556443	
374	Neto2	ENSMUSG00000036902	1.516386822	
375	Kpnrb1	ENSMUSG0000001440	1.516098943	
376	Hist1h3g	ENSMUSG00000099517	1.515072055	
377	Cks2	ENSMUSG00000062248	1.50652198	
378	Gm37795	ENSMUSG00000102813	1.506341996	
379	Pclaf	ENSMUSG00000040204	1.505488381	
380	Cdk1	ENSMUSG00000019942	1.502538423	
381	B230217O12Rik	ENSMUSG00000097785	1.502532816	
382	Cep55	ENSMUSG00000024989	1.502132531	
383	Gm13481	ENSMUSG00000086353	1.498347419	
384	Clec3a	ENSMUSG00000008874	1.49783155	
385	Itga7	ENSMUSG00000025348	1.49235615	
386	Cdc6	ENSMUSG00000017499	1.487626593	
387	Pirt	ENSMUSG00000048070	1.487265198	
388	Vcan	ENSMUSG00000021614	1.484980991	
389	Fln	ENSMUSG00000068699	1.48355526	
390	Angptl6	ENSMUSG00000038742	1.483255396	
391	Tbccd1	ENSMUSG00000004462	1.480213903	
392	Lilrb4a	ENSMUSG00000062593	1.478050587	
393	Gm14636	ENSMUSG00000073274	1.477286849	
394	Hist2h2ab	ENSMUSG00000063689	1.474500867	
395	Gm43499	ENSMUSG00000106739	1.473440243	
396	Slc9a7	ENSMUSG00000037341	1.47208978	
397	Pmm1	ENSMUSG00000022474	1.469739665	
398	Lcp1	ENSMUSG00000021998	1.465687722	
399	Togaram2	ENSMUSG00000045761	1.462654704	
400	Kcnma1	ENSMUSG00000063142	1.453088907	
401	Tubb4b	ENSMUSG00000036752	1.451557295	
402	Gm10698	ENSMUSG00000079884	1.45061928	
403	Al839979	ENSMUSG00000107355	1.449119566	
404	Ccne1	ENSMUSG00000002068	1.447445984	
405	Add3	ENSMUSG00000025026	1.447244999	
406	Piwil2	ENSMUSG00000033644	1.44722344	
407	Hist1h1a	ENSMUSG00000049539	1.446221052	
408	Ptpn7	ENSMUSG00000031506	1.445728984	
409	Gm42514	ENSMUSG00000105553	1.442490661	
410	Ctps	ENSMUSG00000028633	1.438371947	
411	Coro1a	ENSMUSG00000030707	1.437823862	
412	Rasef	ENSMUSG00000043003	1.437469131	
413	Mgl2	ENSMUSG00000040950	1.436187652	
414	Mettl1	ENSMUSG0000006732	1.436107039	
415	Icam1	ENSMUSG00000037405	1.435857964	
416	Tnfaip6	ENSMUSG00000053475	1.435627103	
417	Acta2	ENSMUSG00000035783	1.435284206	
418	Atf4	ENSMUSG00000042406	1.433688739	
419	Copz1	ENSMUSG00000060992	1.430038805	

420	Gm5621	ENSMUSG00000057626	1.429304345	
421	Cd52	ENSMUSG00000000682	1.428954184	
422	1110038B12Rik	ENSMUSG00000092203	1.428291662	
423	Spry3	ENSMUSG00000036966	1.427522411	
424	Slc1a2	ENSMUSG00000005089	1.426300546	
425	Tubb2a	ENSMUSG00000058672	1.421754195	
426	Pold4	ENSMUSG00000024854	1.420881931	
427	Wisp1	ENSMUSG00000005124	1.417477785	
428	Dpep2	ENSMUSG00000053687	1.41535261	
429	Ms4a6d	ENSMUSG00000024679	1.411589263	
430	Dtl	ENSMUSG00000037474	1.409796483	
431	Siah2	ENSMUSG00000036432	1.408822208	
432	Stox2	ENSMUSG00000038143	1.407948117	
433	Gadd45g	ENSMUSG00000021453	1.407408956	
434	Gm12989	ENSMUSG00000083678	1.404923716	
435	Mcm10	ENSMUSG00000026669	1.403036914	
436	Shank1	ENSMUSG00000038738	1.401781001	
437	Casq1	ENSMUSG0000007122	1.400434602	
438	Ddx39	ENSMUSG0000005481	1.39988641	
439	Kif4	ENSMUSG00000034311	1.399067027	
440	Ssr3	ENSMUSG00000027828	1.398708309	
441	Hist1h3b	ENSMUSG00000069267	1.394372841	
442	Tfcp2l1	ENSMUSG00000026380	1.393161629	
443	Taf13	ENSMUSG00000048100	1.392998942	
444	Gm7993	ENSMUSG00000107092	1.388597857	
445	Gm45531	ENSMUSG00000110353	1.387891961	
446	Gm1966	ENSMUSG00000073902	1.387819539	
447	Chek1	ENSMUSG00000032113	1.38723691	
448	Sptbn4	ENSMUSG00000011751	1.386241892	
449	Rp2	ENSMUSG00000060090	1.385912245	
450	Atf5	ENSMUSG00000038539	1.385340179	
451	Dcaf11	ENSMUSG00000022214	1.381885962	
452	Fam46b	ENSMUSG00000046694	1.378167116	
453	Ckap4	ENSMUSG00000046841	1.377983134	
454	Ccnb2	ENSMUSG00000032218	1.375884366	
455	Slc39a14	ENSMUSG00000022094	1.373201831	
456	Gcat	ENSMUSG0000006378	1.372933003	
457	Parvg	ENSMUSG00000022439	1.372192156	
458	Dlg2	ENSMUSG00000052572	1.371734306	
459	Fzd5	ENSMUSG00000045005	1.371696261	
460	Fam26e	ENSMUSG00000049872	1.367206577	
461	Il33	ENSMUSG00000024810	1.363591102	
462	Col8a2	ENSMUSG00000056174	1.363224893	
463	Kn1	ENSMUSG00000027326	1.362172771	
464	Tubb4b-ps1	ENSMUSG00000095159	1.361518755	
465	Gmppb	ENSMUSG00000070284	1.360384561	
466	Edem1	ENSMUSG00000030104	1.359504073	

467	Xpo1	ENSMUSG00000020290	1.358919462	
468	Mmp9	ENSMUSG00000017737	1.354393221	
469	B4galT5	ENSMUSG00000017929	1.346974419	
470	Prg4	ENSMUSG0000006014	1.342563561	
471	Snhg5	ENSMUSG00000097195	1.338052351	
472	Gm12250	ENSMUSG00000082292	1.336648238	
473	Nr6a1	ENSMUSG00000063972	1.335957529	
474	Brca1	ENSMUSG00000017146	1.335918773	
475	Rufy4	ENSMUSG00000061815	1.335781939	
476	Wdr46	ENSMUSG00000024312	1.335465454	
477	Pask	ENSMUSG00000026274	1.335125088	
478	Pgk1-rs7	ENSMUSG00000066632	1.333537124	
479	Ccl9	ENSMUSG00000019122	1.331399831	
480	Gm6158	ENSMUSG00000090381	1.330544091	
481	Uhrf1	ENSMUSG0000001228	1.324781216	
482	Ush1c	ENSMUSG00000030838	1.319572423	
483	Aldh1a3	ENSMUSG00000015134	1.318057841	
484	Cdca8	ENSMUSG00000028873	1.317159825	
485	Ncf4	ENSMUSG00000071715	1.313516064	
486	Fbxo36	ENSMUSG00000073633	1.312734301	
487	Col12a1	ENSMUSG00000032332	1.311033634	
488	Shisa3	ENSMUSG00000050010	1.311018626	
489	Tbrg1	ENSMUSG00000011114	1.311000765	
490	Ccr5	ENSMUSG00000079227	1.310358961	
491	Gm15328	ENSMUSG00000086095	1.308210775	
492	Derl2	ENSMUSG00000018442	1.307259566	
493	Pde4b	ENSMUSG00000028525	1.306643448	
494	Nr2c2ap	ENSMUSG00000071078	1.304422618	
495	Kif9	ENSMUSG00000032489	1.302670479	
496	Herpud1	ENSMUSG00000031770	1.302564699	
497	Slc41a3	ENSMUSG00000030089	1.30110197	
498	Kcnq1ot1	ENSMUSG000000101609	1.300853761	
499	Ppa1	ENSMUSG00000020089	1.299245627	
500	Pdk3	ENSMUSG00000035232	1.298552717	
501	Arid5a	ENSMUSG00000037447	1.297558156	
502	F730043M19Rik	ENSMUSG00000052125	1.29514611	
503	Atp8b4	ENSMUSG00000060131	1.294764027	
504	Eef1e1	ENSMUSG00000001707	1.293534944	
505	Dcbld2	ENSMUSG00000035107	1.290393328	
506	Spn	ENSMUSG00000051457	1.290033875	
507	B4galnt1	ENSMUSG00000006731	1.28891425	
508	MsrB1	ENSMUSG00000075705	1.281903924	
509	Zfp697	ENSMUSG00000050064	1.279477024	
510	Lrrc49	ENSMUSG00000047766	1.276088543	
511	Rfx7	ENSMUSG00000037674	1.274375178	
512	Rras2	ENSMUSG00000055723	1.273857494	
513	B930095G15Rik	ENSMUSG00000085133	1.273024667	

514	6430548M08Rik	ENSMUSG00000031824	1.2728817	
515	Hs3st3b1	ENSMUSG00000070407	1.272752395	
516	Pak4	ENSMUSG00000030602	1.271858364	
517	Rpl3-ps1	ENSMUSG00000084349	1.269581012	
518	Dcun1d4	ENSMUSG00000051674	1.269561257	
519	Tmem189	ENSMUSG00000090213	1.268538681	
520	Hcn1	ENSMUSG00000021730	1.268156092	
521	Tmem50b	ENSMUSG00000022964	1.267450664	
522	Lpin3	ENSMUSG00000027412	1.267349798	
523	Wbp1	ENSMUSG00000030035	1.266661045	
524	Pim1	ENSMUSG00000024014	1.265560591	
525	Ncapg	ENSMUSG00000015880	1.2654372	
526	Hectd2os	ENSMUSG00000087579	1.264197733	
527	Nipsnap3b	ENSMUSG00000015247	1.263768222	
528	G530011O06Rik	ENSMUSG00000072844	1.263713637	
529	Esd	ENSMUSG00000021996	1.261243754	
530	Otub2	ENSMUSG00000021203	1.259221277	
531	Tctn2	ENSMUSG00000029386	1.258207556	
532	Mum1l1	ENSMUSG00000042515	1.257306282	
533	Npl	ENSMUSG00000042684	1.251704294	
534	Slc10a3	ENSMUSG00000032806	1.251594014	
535	Nme1	ENSMUSG00000037601	1.248493132	
536	Cass4	ENSMUSG00000074570	1.247895241	
537	Mfsd12	ENSMUSG00000034854	1.247329755	
538	Nppb	ENSMUSG00000029019	1.247247828	
539	Mesd	ENSMUSG00000038503	1.245358334	
540	Eif2ak3	ENSMUSG00000031668	1.244652688	
541	Gm7367	ENSMUSG00000047370	1.237312066	
542	Kcnj5	ENSMUSG00000032034	1.236827526	
543	Tfg	ENSMUSG00000022757	1.23233869	
544	6430710C18Rik	ENSMUSG00000085427	1.231385968	
545	Phlda3	ENSMUSG00000041801	1.231236934	
546	Rgs7bp	ENSMUSG00000021719	1.228422741	
547	Ostc	ENSMUSG00000041084	1.226963586	
548	Adat3	ENSMUSG00000035370	1.224450689	
549	Mafk	ENSMUSG00000018143	1.224360772	
550	Ccna2	ENSMUSG00000027715	1.22429789	
551	Stat3	ENSMUSG00000004040	1.220096548	
552	Fam122b	ENSMUSG00000036022	1.214434032	
553	Usp18	ENSMUSG00000030107	1.213368784	
554	Esyt1	ENSMUSG00000025366	1.210954025	
555	Alcam	ENSMUSG00000022636	1.210629983	
556	Mki67	ENSMUSG00000031004	1.206938756	
557	Psma5	ENSMUSG00000068749	1.206060018	
558	Cars	ENSMUSG00000010755	1.205057184	
559	Spag5	ENSMUSG0000002055	1.205018018	
560	Ptgs2	ENSMUSG00000032487	1.203540576	

561	Akip1	ENSMUSG00000031023	1.202559927	
562	Myh7	ENSMUSG00000053093	1.20046659	
563	Trim16	ENSMUSG00000047821	1.200163728	
564	Hsp90aa1	ENSMUSG00000021270	1.198763826	
565	Zbp1	ENSMUSG00000027514	1.198082831	
566	Tfrc	ENSMUSG00000022797	1.197497585	
567	Tmem173	ENSMUSG00000024349	1.196917013	
568	Rrp9	ENSMUSG00000041506	1.196173589	
569	Ccl8	ENSMUSG00000009185	1.195247161	
570	Aspm	ENSMUSG00000033952	1.194041169	
571	Gm38359	ENSMUSG00000103317	1.193897614	
572	Dok2	ENSMUSG00000022102	1.193717167	
573	Tyk2	ENSMUSG00000032175	1.190501275	
574	Esco2	ENSMUSG00000022034	1.185134026	
575	Rpl3	ENSMUSG00000060036	1.183677711	
576	Rpl10	ENSMUSG0000008682	1.183173662	
577	Cenpn	ENSMUSG00000031756	1.182370776	
578	Casp4	ENSMUSG00000033538	1.181148662	
579	Gm7332	ENSMUSG00000080875	1.175857669	
580	Zbtb3	ENSMUSG00000071661	1.175706805	
581	D10Wsu102e	ENSMUSG00000020255	1.175461387	
582	Fam72a	ENSMUSG00000055184	1.174842741	
583	Gipc1	ENSMUSG00000019433	1.173894119	
584	Hspa1l	ENSMUSG00000007033	1.172493484	
585	Stt3b	ENSMUSG00000032437	1.170914991	
586	Itgb2	ENSMUSG00000000290	1.169997355	
587	Arrdc3	ENSMUSG00000074794	1.169678464	
588	Nudcd1	ENSMUSG00000038736	1.168817163	
589	Pik3r3	ENSMUSG00000028698	1.167333543	
590	Ppan	ENSMUSG0000004100	1.166826929	
591	Clec11a	ENSMUSG0000004473	1.164850642	
592	Nr4a2	ENSMUSG00000026826	1.163633754	
593	Trmt10a	ENSMUSG0000004127	1.162878389	
594	Plxnb2	ENSMUSG00000036606	1.161690849	
595	Gja5	ENSMUSG00000057123	1.160544506	
596	Hist1h2af	ENSMUSG00000061991	1.159729615	
597	Slc16a6	ENSMUSG00000041920	1.157421983	
598	Mdn1	ENSMUSG00000058006	1.157364083	
599	Capg	ENSMUSG00000056737	1.156060338	
600	Anln	ENSMUSG00000036777	1.156054529	
601	Sash3	ENSMUSG00000031101	1.153727702	
602	Dbf4	ENSMUSG0000002297	1.15302495	
603	Ttf2	ENSMUSG00000033222	1.152826279	
604	Gm8394	ENSMUSG00000050490	1.152190004	
605	Hck	ENSMUSG0000003283	1.149489868	
606	Cage1	ENSMUSG00000044566	1.146471431	
607	Knstrn	ENSMUSG00000027331	1.146277923	

608	Fzd2	ENSMUSG00000050288	1.145634205	
609	Mx1	ENSMUSG00000000386	1.14494589	
610	Dstn	ENSMUSG00000015932	1.142341577	
611	Tlr2	ENSMUSG00000027995	1.141801924	
612	Usp1	ENSMUSG00000028560	1.140379401	
613	Prkcsh	ENSMUSG0000003402	1.140233021	
614	Ptpre	ENSMUSG00000041836	1.138809485	
615	Dph5	ENSMUSG00000033554	1.13657609	
616	SrpX	ENSMUSG00000090084	1.134293016	
617	Olfm1	ENSMUSG00000026833	1.133848828	
618	HeatR1	ENSMUSG00000050244	1.133491875	
619	Azin1	ENSMUSG00000037458	1.132883442	
620	Rpsa-ps9	ENSMUSG00000082895	1.132775108	
621	Ppp1r15a	ENSMUSG00000040435	1.131558837	
622	Snhg1	ENSMUSG00000108414	1.130862556	
623	Grk3	ENSMUSG00000042249	1.130640537	
624	Aurka	ENSMUSG00000027496	1.129311021	
625	Ift43	ENSMUSG0000007867	1.127582151	
626	Ing1	ENSMUSG0000045969	1.125978778	
627	Zfp566	ENSMUSG0000078768	1.125891655	
628	Fgl2	ENSMUSG0000039899	1.123987257	
629	Pdpn	ENSMUSG0000028583	1.122759466	
630	Asb16	ENSMUSG0000034768	1.122276057	
631	Aqp4	ENSMUSG0000024411	1.122151756	
632	Aars	ENSMUSG0000031960	1.120957875	
633	Dusp23	ENSMUSG0000026544	1.11810292	
634	Paip2b	ENSMUSG0000045896	1.115897527	
635	Gstcd	ENSMUSG0000028018	1.115730709	
636	Coq8b	ENSMUSG0000003762	1.115288686	
637	Rap2b	ENSMUSG0000036894	1.114326427	
638	Cntn2	ENSMUSG0000053024	1.112534684	
639	Zmynd19	ENSMUSG0000026974	1.111641171	
640	Tmbim1	ENSMUSG0000006301	1.111517063	
641	Grk5	ENSMUSG0000003228	1.110747505	
642	Tmed2	ENSMUSG00000029390	1.109476899	
643	Smyd5	ENSMUSG0000033706	1.102683445	
644	Iltk	ENSMUSG0000035941	1.101475027	
645	C330027C09Rik	ENSMUSG0000033031	1.099547502	
646	Abca12	ENSMUSG0000050296	1.095786221	
647	Vars	ENSMUSG0000007029	1.093832221	
648	Sars	ENSMUSG0000068739	1.093735011	
649	Map2k3os	ENSMUSG0000042549	1.091347636	
650	Gm6210	ENSMUSG0000107951	1.089886298	
651	Lmbrd2	ENSMUSG0000039704	1.087412152	
652	Stip1	ENSMUSG0000024966	1.086537039	
653	Ubfd1	ENSMUSG0000030870	1.085322293	
654	Tubb6	ENSMUSG0000001473	1.085001017	

655	Ung	ENSMUSG00000029591	1.08455813	
656	Socs1	ENSMUSG00000038037	1.083140057	
657	Shq1	ENSMUSG00000035378	1.082574401	
658	Tiam2	ENSMUSG00000023800	1.082496268	
659	Hist1h2ac	ENSMUSG00000069270	1.082203199	
660	Nol12	ENSMUSG00000033099	1.082003866	
661	Dpy19l1	ENSMUSG00000043067	1.079606873	
662	Arrdc4	ENSMUSG00000042659	1.079340688	
663	Plk4	ENSMUSG00000025758	1.078923652	
664	Avpi1	ENSMUSG00000018821	1.078296992	
665	Wdr44	ENSMUSG00000036769	1.077086586	
666	Runx1	ENSMUSG00000022952	1.076810666	
667	Tmem45a	ENSMUSG00000022754	1.076558315	
668	Opn3	ENSMUSG00000026525	1.073604491	
669	Ppox	ENSMUSG00000062729	1.073267217	
670	Bbc3	ENSMUSG0000002083	1.072287344	
671	Iars	ENSMUSG00000037851	1.071964574	
672	Gsk3b	ENSMUSG00000022812	1.070813224	
673	Clcf1	ENSMUSG00000040663	1.064614037	
674	Tesk2	ENSMUSG00000033985	1.063742128	
675	Cenpt	ENSMUSG00000036672	1.06146737	
676	Ttc41	ENSMUSG00000044937	1.061089629	
677	Cdc7	ENSMUSG00000029283	1.059243045	
678	Gpatch4	ENSMUSG00000028069	1.05907009	
679	Gm12346	ENSMUSG00000083899	1.058665929	
680	Has2	ENSMUSG00000022367	1.057616501	
681	Pold2	ENSMUSG00000020471	1.056373421	
682	Pim2	ENSMUSG00000031155	1.054490917	
683	Slc26a2	ENSMUSG00000034320	1.05224895	
684	Phkg2	ENSMUSG00000030815	1.052031009	
685	Vbp1	ENSMUSG00000031197	1.051255794	
686	Bcat1	ENSMUSG00000030268	1.050279226	
687	Tmem184c	ENSMUSG00000031617	1.049938119	
688	Gm5812	ENSMUSG00000051639	1.048363636	
689	Cers6	ENSMUSG00000027035	1.047851043	
690	Il17ra	ENSMUSG0000002897	1.047462251	
691	Derl1	ENSMUSG00000022365	1.047444175	
692	Wif1	ENSMUSG00000020218	1.047119083	
693	Cks1b	ENSMUSG00000028044	1.046554899	
694	Ccdc134	ENSMUSG00000068114	1.045129946	
695	Farp1	ENSMUSG00000025555	1.04389361	
696	Tars	ENSMUSG00000022241	1.043266521	
697	Rpn2	ENSMUSG00000027642	1.039931574	
698	Nop16	ENSMUSG00000025869	1.03963659	
699	Msmo1	ENSMUSG00000031604	1.038855593	
700	Cdv3-ps	ENSMUSG00000090389	1.037316451	
701	Yif1a	ENSMUSG00000024875	1.037258808	

702	Zfp568	ENSMUSG00000074221	1.036068891	
703	Col7a1	ENSMUSG00000025650	1.034000942	
704	Oasl1	ENSMUSG00000041827	1.033131634	
705	Mcfd2	ENSMUSG00000024150	1.025906718	
706	Slc7a7	ENSMUSG00000000958	1.025602479	
707	Rab6a	ENSMUSG00000030704	1.024779016	
708	Erp29	ENSMUSG00000029616	1.02083526	
709	1810055G02Rik	ENSMUSG00000035372	1.01858213	
710	Lrrc59	ENSMUSG00000020869	1.018185595	
711	Heatr5a	ENSMUSG00000035181	1.018091303	
712	Marcks1	ENSMUSG00000047945	1.017402547	
713	Mvp	ENSMUSG00000030681	1.017384365	
714	Per1	ENSMUSG00000020893	1.017223008	
715	Aif1	ENSMUSG00000024397	1.016551272	
716	Gnl3	ENSMUSG00000042354	1.01648494	
717	Hells	ENSMUSG00000025001	1.016223913	
718	Mcm5	ENSMUSG00000005410	1.0143332	
719	N4bp2os	ENSMUSG00000106978	1.013382364	
720	Krt80	ENSMUSG00000037185	1.012635222	
721	Hist1h2bb	ENSMUSG00000075031	1.01137536	
722	Psmd11	ENSMUSG00000017428	1.011018617	
723	Nsdhl	ENSMUSG00000031349	1.010787814	
724	Fam174b	ENSMUSG00000078670	1.010025926	
725	Gm7895	ENSMUSG00000100347	1.009476227	
726	Gm25360	ENSMUSG00000094655	1.009366206	
727	St6galnac4	ENSMUSG00000079442	1.009190701	
728	Steap2	ENSMUSG00000015653	1.008242338	
729	M6pr	ENSMUSG0000007458	1.007816687	
730	Spi1	ENSMUSG00000002111	1.005558321	
731	Srm	ENSMUSG0000006442	1.005149292	
732	Gm6563	ENSMUSG00000051255	1.004539333	
733	Cmtr2	ENSMUSG00000046441	1.004455668	
734	Isoc2a	ENSMUSG00000086784	1.002035749	
735	Mob3c	ENSMUSG00000028709	1.001988325	
736	Atad5	ENSMUSG00000017550	1.000331972	
737	Kcnn3	ENSMUSG0000000794	0.99982441	
738	Dnajb9	ENSMUSG00000014905	0.999482146	
739	B230216N24Rik	ENSMUSG00000089706	0.999150399	
740	Olfml2b	ENSMUSG00000038463	0.998856338	
741	Col11a2	ENSMUSG00000024330	0.99846639	
742	Bambi	ENSMUSG00000024232	0.998400037	
743	Cotl1	ENSMUSG00000031827	0.997762408	
744	Snap23	ENSMUSG00000027287	0.99717774	
745	Mak16	ENSMUSG00000031578	0.996282623	
746	Rnf5	ENSMUSG00000015478	0.995026243	
747	Snhg4	ENSMUSG00000097769	0.994877612	
748	Dusp8	ENSMUSG00000037887	0.992982688	

749	Shisa4	ENSMUSG00000041889	0.991855458	
750	Gsg1l	ENSMUSG00000046182	0.991643791	
751	Canx	ENSMUSG00000020368	0.99103089	
752	Gm8203	ENSMUSG00000101878	0.989511615	
753	Armc6	ENSMUSG0000002343	0.989498202	
754	Slx4ip	ENSMUSG00000027281	0.98930013	
755	Gm13456	ENSMUSG00000082536	0.988812863	
756	Ints2	ENSMUSG00000018068	0.987187817	
757	Golt1b	ENSMUSG00000030245	0.985137192	
758	Hspb1	ENSMUSG0000004951	0.984501964	
759	Rpf2	ENSMUSG00000038510	0.984054313	
760	Scml4	ENSMUSG00000044770	0.983279986	
761	Ppp1r14b	ENSMUSG00000056612	0.982912048	
762	Nme6	ENSMUSG00000032478	0.982882597	
763	Ccl6	ENSMUSG00000018927	0.982589258	
764	Lhfpl2	ENSMUSG00000045312	0.980846806	
765	Rnf181	ENSMUSG00000055850	0.980432741	
766	Mb21d1	ENSMUSG00000032344	0.980115292	
767	Cad	ENSMUSG00000013629	0.979420976	
768	Got1	ENSMUSG00000025190	0.979355287	
769	Lmcd1	ENSMUSG00000057604	0.978649847	
770	Lamc2	ENSMUSG00000026479	0.97554956	
771	Cyld	ENSMUSG00000036712	0.974943338	
772	Nktr	ENSMUSG00000032525	0.971355026	
773	Gm4540	ENSMUSG00000092072	0.971285941	
774	Cnpy3	ENSMUSG00000023973	0.971164845	
775	Glipr2	ENSMUSG00000028480	0.970473478	
776	Fam98c	ENSMUSG00000030590	0.97018368	
777	Bcl6	ENSMUSG00000022508	0.969489625	
778	Stat2	ENSMUSG00000040033	0.96069757	
779	Gm14048	ENSMUSG00000080989	0.959293156	
780	Zdhhc24	ENSMUSG0000006463	0.958629392	
781	Ifi211	ENSMUSG00000026536	0.957641599	
782	Gm12655	ENSMUSG00000087128	0.95733895	
783	Map1b	ENSMUSG00000052727	0.95634716	
784	Il6st	ENSMUSG00000021756	0.95314068	
785	Pck2	ENSMUSG00000040618	0.953104793	
786	Ubtd1	ENSMUSG00000025171	0.952484985	
787	Gm13127	ENSMUSG00000070610	0.952072131	
788	Il4ra	ENSMUSG00000030748	0.950384327	
789	Suv39h2	ENSMUSG00000026646	0.950314164	
790	Hgf	ENSMUSG00000028864	0.949086932	
791	Hmgcr	ENSMUSG00000021670	0.948321994	
792	Stk19	ENSMUSG00000061207	0.94671894	
793	Enah	ENSMUSG00000022995	0.945605411	
794	Cenpl	ENSMUSG00000026708	0.945413278	
795	Mllt3	ENSMUSG00000028496	0.944147681	

796	Gm38253	ENSMUSG00000102780	0.943228673	
797	Dram1	ENSMUSG00000020057	0.942235891	
798	Fkbp2	ENSMUSG00000056629	0.939827021	
799	Gm28229	ENSMUSG00000101335	0.939355326	
800	Lair1	ENSMUSG00000055541	0.938493164	
801	Mapkapk2	ENSMUSG0000016528	0.936458386	
802	Pcgf6	ENSMUSG00000025050	0.935665477	
803	Zfp367	ENSMUSG00000044934	0.934484588	
804	Tm2d2	ENSMUSG00000031556	0.933364167	
805	Sec11a	ENSMUSG00000025724	0.930747552	
806	Kif5b	ENSMUSG0000006740	0.930384309	
807	Clvs1	ENSMUSG00000041216	0.929682573	
808	5430416N02Rik	ENSMUSG00000097772	0.927749382	
809	Gpx4	ENSMUSG00000075706	0.926359853	
810	Mroh1	ENSMUSG00000022558	0.926118233	
811	Klf6	ENSMUSG00000000078	0.92183922	
812	Cenpc1	ENSMUSG00000029253	0.921501563	
813	Nfkb2	ENSMUSG00000025225	0.920852777	
814	Rnf19b	ENSMUSG00000028793	0.920537936	
815	Osmr	ENSMUSG00000022146	0.918933908	
816	Pus7	ENSMUSG00000057541	0.917310055	
817	Sarnp	ENSMUSG00000078427	0.916958299	
818	Mt1	ENSMUSG00000031765	0.916867703	
819	Enho	ENSMUSG00000028445	0.91608576	
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821	Rasl11b	ENSMUSG00000049907	0.913181622	
822	Fkbp11	ENSMUSG00000003355	0.913036698	
823	Plau	ENSMUSG00000021822	0.912940093	
824	Lipa	ENSMUSG00000024781	0.910771572	
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827	Sac3d1	ENSMUSG00000024790	0.909267499	
828	Jpt1	ENSMUSG00000020737	0.909190468	
829	Apex1	ENSMUSG00000035960	0.908491689	
830	Trmt6	ENSMUSG00000037376	0.907990576	
831	Rheb	ENSMUSG00000028945	0.907606311	
832	Fam198b	ENSMUSG00000027955	0.907554858	
833	Bax	ENSMUSG00000003873	0.907449126	
834	Rpn1	ENSMUSG00000030062	0.906935746	
835	Gm11478	ENSMUSG00000083992	0.905994986	
836	Zdhhc9	ENSMUSG00000036985	0.905808959	
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839	Rcl1	ENSMUSG00000024785	0.901908816	
840	Tpp2	ENSMUSG00000041763	0.901477192	
841	Snhg6	ENSMUSG00000098234	0.899789841	
842	Lgi2	ENSMUSG00000039252	0.897646502	

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844	Lrif1	ENSMUSG00000056260	0.895298737	
845	Kif11	ENSMUSG00000012443	0.892626767	
846	Thsd4	ENSMUSG00000032289	0.892486283	
847	Rragd	ENSMUSG00000028278	0.889950586	
848	Ccdc86	ENSMUSG00000024732	0.889519185	
849	Usp53	ENSMUSG00000039701	0.889057897	
850	Mob3a	ENSMUSG00000003348	0.888369885	
851	Zfas1	ENSMUSG00000074578	0.887650048	
852	Nop58	ENSMUSG00000026020	0.887388208	
853	Gm6223	ENSMUSG00000096647	0.887365225	
854	Gfod1	ENSMUSG00000051335	0.887152785	
855	Tmem97	ENSMUSG00000037278	0.886737284	
856	Jun	ENSMUSG00000052684	0.886098371	
857	Ncs1	ENSMUSG00000062661	0.885836675	
858	Csf2ra	ENSMUSG00000059326	0.884172744	
859	Ltv1	ENSMUSG00000019814	0.884018053	
860	Sh3pxd2b	ENSMUSG00000040711	0.880479476	
861	Tob1	ENSMUSG00000037573	0.880452628	
862	Man1a	ENSMUSG0000003746	0.880287851	
863	Dusp10	ENSMUSG00000039384	0.879694355	
864	Gm45457	ENSMUSG00000110411	0.878622714	
865	Tprn	ENSMUSG00000048707	0.876324704	
866	March3	ENSMUSG00000032656	0.876120534	
867	Hist1h1c	ENSMUSG00000036181	0.872327463	
868	Rpl36a-ps3	ENSMUSG00000071141	0.871135433	
869	Trabd	ENSMUSG00000015363	0.870610656	
870	Gm12295	ENSMUSG00000085162	0.870583756	
871	Cstf3	ENSMUSG00000027176	0.870545915	
872	Prkaca	ENSMUSG0000005469	0.870147833	
873	BC031181	ENSMUSG00000036299	0.870006603	
874	Yrdc	ENSMUSG00000028889	0.869735199	
875	Mtmmr4	ENSMUSG00000018401	0.866029558	
876	Hsd17b12	ENSMUSG00000027195	0.86408055	
877	Snrnp25	ENSMUSG00000040767	0.86236488	
878	Slc35b1	ENSMUSG00000020873	0.862043131	
879	Uxs1	ENSMUSG00000057363	0.861861965	
880	Rhoc	ENSMUSG0000002233	0.861369588	
881	Atp8b2	ENSMUSG00000060671	0.859678124	
882	Relb	ENSMUSG0000002983	0.859378177	
883	Arhgap19	ENSMUSG00000025154	0.859244571	
884	Klhl21	ENSMUSG00000073700	0.858928128	
885	Ier5	ENSMUSG00000056708	0.858885901	
886	Slc35e4	ENSMUSG00000048807	0.858665598	
887	Ifi205	ENSMUSG00000054203	0.856980021	
888	Igtp	ENSMUSG00000078853	0.855072616	
889	Fam96b	ENSMUSG00000031879	0.854406453	

890	Arpc3	ENSMUSG00000029465	0.854351924	
891	Clock	ENSMUSG00000029238	0.853340465	
892	Grwd1	ENSMUSG00000053801	0.852420254	
893	Tuba1a	ENSMUSG00000072235	0.851395906	
894	Mtbp	ENSMUSG00000022369	0.847799005	
895	Baz1a	ENSMUSG00000035021	0.847175088	
896	Tlr4	ENSMUSG00000039005	0.846219844	
897	Hsp25-ps1	ENSMUSG00000078915	0.845951106	
898	Gm45220	ENSMUSG00000109279	0.844793295	
899	Abca4	ENSMUSG00000028125	0.84421429	
900	Lrrc3b	ENSMUSG00000045201	0.844018318	
901	Hnrnpa3	ENSMUSG00000059005	0.842870906	
902	Tsr1	ENSMUSG00000038335	0.842141274	
903	Rhod	ENSMUSG00000041845	0.840435869	
904	Creld1	ENSMUSG00000030284	0.840289076	
905	Dda1	ENSMUSG00000074247	0.839225255	
906	Vwa5a	ENSMUSG00000023186	0.838955985	
907	Abi3bp	ENSMUSG00000035258	0.838946299	
908	Prmt3	ENSMUSG00000030505	0.838927104	
909	Zfp322a	ENSMUSG00000046351	0.836133767	
910	Fam46a	ENSMUSG00000032265	0.836070746	
911	Stmn1	ENSMUSG00000028832	0.835738151	
912	Mis12	ENSMUSG00000040599	0.835615698	
913	Oat	ENSMUSG00000030934	0.834136647	
914	Med19	ENSMUSG00000027080	0.833175877	
915	Pla2g4a	ENSMUSG00000056220	0.83298215	
916	Dzip3	ENSMUSG00000064061	0.83208629	
917	Gda	ENSMUSG00000058624	0.831307598	
918	Tcea1-ps1	ENSMUSG00000067869	0.830474395	
919	Rbmx2	ENSMUSG00000031107	0.830185857	
920	Gas5	ENSMUSG00000053332	0.830002317	
921	Tlnrd1	ENSMUSG00000070462	0.829861228	
922	Ipo5	ENSMUSG00000030662	0.8274388	
923	Golim4	ENSMUSG00000034109	0.826919132	
924	Zbtb40	ENSMUSG00000060862	0.825764322	
925	Gcsh	ENSMUSG00000034424	0.825080405	
926	Nubp1	ENSMUSG00000022503	0.823716909	
927	Adgrd1	ENSMUSG00000044017	0.823705721	
928	Eif4a-ps4	ENSMUSG00000101188	0.822285582	
929	Tgfbr1	ENSMUSG00000007613	0.819006418	
930	Sec23a	ENSMUSG00000020986	0.818675812	
931	Katnb1	ENSMUSG00000031787	0.815531235	
932	Ascc3	ENSMUSG00000038774	0.815042677	
933	Creb3l2	ENSMUSG00000038648	0.81439726	
934	Amer1	ENSMUSG00000050332	0.812900011	
935	Gtf2f2	ENSMUSG00000067995	0.812866099	
936	Psmid14	ENSMUSG00000026914	0.811361474	

937	Tcea1	ENSMUSG00000033813	0.810968429	
938	Fads3	ENSMUSG00000024664	0.809540069	
939	Spata13	ENSMUSG00000021990	0.808825986	
940	Fcgr2b	ENSMUSG00000026656	0.808137326	
941	Gm12258	ENSMUSG00000072915	0.80795738	
942	Fxyd5	ENSMUSG0000009687	0.807277415	
943	Tyrobp	ENSMUSG00000030579	0.807110129	
944	Selenoi	ENSMUSG00000075703	0.805764874	
945	Tnfrsf11a	ENSMUSG00000026321	0.805378296	
946	Surf4	ENSMUSG00000014867	0.805330078	
947	Ahnak2	ENSMUSG00000072812	0.80520946	
948	Xpot	ENSMUSG00000034667	0.805192336	
949	Rpl13a	ENSMUSG00000074129	0.804787789	
950	Ankrd49	ENSMUSG00000031931	0.804318284	
951	Lmnb2	ENSMUSG00000062075	0.804229027	
952	Tmem183a	ENSMUSG00000042305	0.80371481	
953	Ifi204	ENSMUSG00000073489	0.803687915	
954	Mydgf	ENSMUSG00000019579	0.803441204	
955	Pja2	ENSMUSG00000024083	0.802786062	
956	Erbb2	ENSMUSG00000062312	0.802684133	
957	Nckap1l	ENSMUSG00000022488	0.801160539	
958	Eef1a1	ENSMUSG00000037742	0.79904953	
959	Popdc3	ENSMUSG00000019848	0.797193966	
960	Rps19bp1	ENSMUSG00000051518	0.796956637	
961	Galns	ENSMUSG00000015027	0.79645697	
962	Actr3	ENSMUSG00000026341	0.795827554	
963	Gpx3	ENSMUSG00000018339	0.795421727	
964	Pinx1	ENSMUSG00000021958	0.794583212	
965	Emd	ENSMUSG00000001964	0.794213198	
966	Dap	ENSMUSG00000039168	0.793663404	
967	Fryl	ENSMUSG00000070733	0.793585949	
968	Gm12844	ENSMUSG00000084260	0.792949051	
969	Cenpx	ENSMUSG00000025144	0.792844995	
970	Alg8	ENSMUSG00000035704	0.792373737	
971	Nars	ENSMUSG00000024587	0.79112078	
972	Klf7	ENSMUSG00000025959	0.790947492	
973	Ddx31	ENSMUSG00000026806	0.790395442	
974	Mogs	ENSMUSG00000030036	0.788864385	
975	Med10	ENSMUSG00000021598	0.788246323	
976	Ifrd1	ENSMUSG00000001627	0.7880196	
977	Rrp15	ENSMUSG00000001305	0.786998678	
978	Extl1	ENSMUSG00000028838	0.786757054	
979	Prr13	ENSMUSG00000023048	0.786660343	
980	Gpn2	ENSMUSG00000028848	0.786223513	
981	Mvk	ENSMUSG00000041939	0.785041015	
982	Casp3	ENSMUSG00000031628	0.783183801	
983	Ddx50	ENSMUSG00000020076	0.783123916	

984	Usp39	ENSMUSG00000056305	0.782950199	
985	Wdr4	ENSMUSG00000024037	0.782833194	
986	Gpn1	ENSMUSG00000064037	0.782525316	
987	Ppm1b	ENSMUSG00000061130	0.781952441	
988	Snd1	ENSMUSG0000001424	0.781466948	
989	Ikbkg	ENSMUSG0000004221	0.781330934	
990	Dynll1	ENSMUSG0000009013	0.780116711	
991	Arpc4	ENSMUSG00000079426	0.779585176	
992	Ccdc115	ENSMUSG00000042111	0.779252872	
993	Eif4a1	ENSMUSG00000059796	0.778100092	
994	Ftsj3	ENSMUSG00000020706	0.777306748	
995	Fbxw9	ENSMUSG00000008167	0.777211512	
996	Leo1	ENSMUSG00000042487	0.776732527	
997	Rhoa	ENSMUSG0000007815	0.776493294	
998	Gm12112	ENSMUSG00000081254	0.77566347	
999	Bahcc1	ENSMUSG00000039741	0.775052378	
1000	Pum3	ENSMUSG00000041360	0.774948414	
1001	Gm45221	ENSMUSG00000109005	0.774602671	
1002	Lyz2	ENSMUSG00000069516	0.774524955	
1003	1600002K03Rik	ENSMUSG00000035595	0.774418722	
1004	Fkbp7	ENSMUSG0000002732	0.773717985	
1005	Fn1	ENSMUSG00000026193	0.773362062	
1006	Sap30l	ENSMUSG00000020519	0.773262893	
1007	Tes	ENSMUSG00000029552	0.772626119	
1008	Slc39a6	ENSMUSG00000024270	0.771398846	
1009	Zc2hc1a	ENSMUSG00000043542	0.771017675	
1010	Thyn1	ENSMUSG00000035443	0.770797183	
1011	Ddah1	ENSMUSG00000028194	0.769961103	
1012	Ccng1	ENSMUSG00000020326	0.769197013	
1013	Sgms2	ENSMUSG00000050931	0.768717188	
1014	Taf7	ENSMUSG00000051316	0.768132124	
1015	Adprhl1	ENSMUSG00000031448	0.767639577	
1016	Wdpcp	ENSMUSG00000020319	0.766627398	
1017	Utp18	ENSMUSG00000054079	0.765916084	
1018	Aen	ENSMUSG00000030609	0.765640168	
1019	Fosl2	ENSMUSG00000029135	0.76503642	
1020	Eprs	ENSMUSG00000026615	0.76403217	
1021	Spcs3	ENSMUSG00000054408	0.763733035	
1022	Zfp202	ENSMUSG00000025602	0.763239857	
1023	Ddx21	ENSMUSG00000020075	0.761090656	
1024	Ifit3b	ENSMUSG00000062488	0.760911452	
1025	Itga3	ENSMUSG0000001507	0.760586711	
1026	Sec61b	ENSMUSG00000053317	0.760554414	
1027	Acot9	ENSMUSG00000025287	0.760485931	
1028	Rap2a	ENSMUSG00000051615	0.760193646	
1029	Plxna1	ENSMUSG00000030084	0.760040367	
1030	Col3a1	ENSMUSG00000026043	0.759873146	

1031	Litaf	ENSMUSG00000022500	0.757875884	
1032	Ugdh	ENSMUSG00000029201	0.75650923	
1033	Slc25a5	ENSMUSG00000016319	0.755661677	
1034	Taf4b	ENSMUSG00000054321	0.755349399	
1035	Atp6v1h	ENSMUSG00000033793	0.755164921	
1036	Pprc1	ENSMUSG00000055491	0.754992697	
1037	Ero1lb	ENSMUSG00000057069	0.754878836	
1038	Atp13a3	ENSMUSG00000022533	0.754297559	
1039	Scara3	ENSMUSG00000034463	0.753649119	
1040	Rab20	ENSMUSG00000031504	0.753365513	
1041	Pfkp	ENSMUSG00000021196	0.750610364	
1042	Fam185a	ENSMUSG00000047221	0.750106396	
1043	Snhg12	ENSMUSG00000086290	0.749717222	
1044	Cib1	ENSMUSG00000030538	0.74771931	
1045	Bola2	ENSMUSG00000047721	0.746320287	
1046	Selenos	ENSMUSG00000075701	0.745582972	
1047	Cbx6	ENSMUSG00000089715	0.745101247	
1048	Wars	ENSMUSG00000021266	0.743841568	
1049	Cacna1h	ENSMUSG00000024112	0.742510804	
1050	Arhgef10l	ENSMUSG00000040964	0.741971201	
1051	Zwint	ENSMUSG00000019923	0.740927247	
1052	Ywhaz	ENSMUSG00000022285	0.739821073	
1053	Hspf1	ENSMUSG00000029657	0.739234336	
1054	Lars	ENSMUSG00000024493	0.738810973	
1055	Amn1	ENSMUSG00000068250	0.73819553	
1056	Dapk3	ENSMUSG00000034974	0.735756947	
1057	Rars	ENSMUSG00000018848	0.735425061	
1058	Sap130	ENSMUSG00000024260	0.735274982	
1059	Clptm1l	ENSMUSG00000021610	0.735101427	
1060	Fbl	ENSMUSG00000046865	0.732474301	
1061	Itpk1	ENSMUSG00000057963	0.732267051	
1062	Sema3a	ENSMUSG00000028883	0.732207001	
1063	Mon1b	ENSMUSG00000078908	0.732016876	
1064	Shoc2	ENSMUSG00000024976	0.731088633	
1065	Hist1h3e	ENSMUSG00000069273	0.731064742	
1066	Fem1b	ENSMUSG00000032244	0.731036087	
1067	Urb2	ENSMUSG00000031976	0.730985248	
1068	Actn1	ENSMUSG00000015143	0.729523694	
1069	Tmem167	ENSMUSG00000012422	0.728202541	
1070	Utp20	ENSMUSG00000004356	0.727887583	
1071	Acsl3	ENSMUSG00000032883	0.726157803	
1072	Hipk2	ENSMUSG00000061436	0.726075305	
1073	Hfe	ENSMUSG00000006611	0.725174423	
1074	Wdr75	ENSMUSG00000025995	0.725124244	
1075	2310022B05Rik	ENSMUSG00000031983	0.724824673	
1076	Smg1	ENSMUSG00000030655	0.724789024	
1077	Rps26	ENSMUSG00000025362	0.723623341	

1078	Pfn1	ENSMUSG00000018293	0.723399628	
1079	Nup88	ENSMUSG00000040667	0.721541853	
1080	Spata24	ENSMUSG00000024352	0.72114141	
1081	P2ry2	ENSMUSG00000032860	0.720427675	
1082	Cav3	ENSMUSG00000062694	0.719875911	
1083	Cfl1	ENSMUSG00000056201	0.719785535	
1084	Herc4	ENSMUSG00000020064	0.719381863	
1085	Selenof	ENSMUSG00000037072	0.719245944	
1086	Cxcl16	ENSMUSG00000018920	0.717932582	
1087	Gm10110	ENSMUSG00000062093	0.716952245	
1088	Cyb5r3	ENSMUSG00000018042	0.716716913	
1089	Slc3a2	ENSMUSG00000010095	0.716602287	
1090	Noc3l	ENSMUSG00000024999	0.716426765	
1091	Ddx54	ENSMUSG00000029599	0.715670612	
1092	Mcrs1	ENSMUSG00000037570	0.714953137	
1093	Igf1r	ENSMUSG00000005533	0.714498197	
1094	Prkcd	ENSMUSG00000021948	0.7128372	
1095	Fam49b	ENSMUSG00000022378	0.712197402	
1096	Nop2	ENSMUSG00000038279	0.710666914	
1097	Ttc9c	ENSMUSG00000071660	0.707842691	
1098	Zfp954	ENSMUSG00000062116	0.707420379	
1099	Zfpm1	ENSMUSG00000049577	0.706576066	
1100	Pgs1	ENSMUSG00000017715	0.706202908	
1101	Tspyl5	ENSMUSG00000038984	0.705293119	
1102	Mpp7	ENSMUSG00000057440	0.704277435	
1103	Tnfrsf1a	ENSMUSG00000030341	0.704189614	
1104	Otulin	ENSMUSG00000046034	0.704115093	
1105	Kank1	ENSMUSG00000032702	0.702975445	
1106	Rpsa	ENSMUSG00000032518	0.702748438	
1107	Rcc2	ENSMUSG00000040945	0.702261881	
1108	Srxn1	ENSMUSG00000032802	0.701460756	
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1112	Asna1	ENSMUSG00000052456	0.698282921	
1113	Ckb	ENSMUSG0000001270	0.698075616	
1114	Nifk	ENSMUSG00000026377	0.697968583	
1115	Lmo4	ENSMUSG00000028266	0.697798413	
1116	Rrp7a	ENSMUSG00000018040	0.69721061	
1117	Rps15a	ENSMUSG00000008683	0.695995515	
1118	Nsd2	ENSMUSG00000057406	0.695643756	
1119	Nup43	ENSMUSG00000040034	0.695320906	
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1121	Ifi27	ENSMUSG00000064215	0.694884649	
1122	Gas7	ENSMUSG00000033066	0.694061823	
1123	Sertad1	ENSMUSG00000008384	0.692249697	
1124	Vcam1	ENSMUSG00000027962	0.691728936	

1125	Ralb	ENSMUSG0000004451	0.69153584	
1126	Igsf10	ENSMUSG0000036334	0.691271506	
1127	Gm10073	ENSMUSG0000060019	0.68938212	
1128	Stam	ENSMUSG0000026718	0.689018094	
1129	Maged1	ENSMUSG0000025151	0.68891575	
1130	Plpp1	ENSMUSG0000021759	0.688901161	
1131	Gan	ENSMUSG0000052557	0.686545609	
1132	Synpo2l	ENSMUSG0000039376	0.686398231	
1133	Htt	ENSMUSG0000029104	0.686383182	
1134	Gem	ENSMUSG0000028214	0.686188335	
1135	Pvr	ENSMUSG0000040511	0.685411045	
1136	Lins1	ENSMUSG0000053091	0.683541269	
1137	Cyb561	ENSMUSG0000019590	0.683530223	
1138	Heatr5b	ENSMUSG0000039414	0.683422176	
1139	Pabpc4	ENSMUSG0000011257	0.682692924	
1140	Fam111a	ENSMUSG0000024691	0.682321473	
1141	Nudt4	ENSMUSG0000020029	0.681346251	
1142	Erc8	ENSMUSG0000021694	0.681173255	
1143	Tspan31	ENSMUSG000006736	0.680937093	
1144	Sema3c	ENSMUSG0000028780	0.680773986	
1145	Slc25a28	ENSMUSG0000040414	0.680093591	
1146	Zbtb7b	ENSMUSG0000028042	0.679923023	
1147	9130011E15Rik	ENSMUSG0000039901	0.678730954	
1148	Anxa6	ENSMUSG0000018340	0.677924858	
1149	Csnk1g1	ENSMUSG0000032384	0.67790772	
1150	Aste1	ENSMUSG0000032567	0.677790507	
1151	Mx2	ENSMUSG0000023341	0.677562512	
1152	Ago2	ENSMUSG0000036698	0.677518908	
1153	Gm8355	ENSMUSG0000093798	0.676679781	
1154	Polr2h	ENSMUSG0000021018	0.67613414	
1155	B4galt1	ENSMUSG0000028413	0.676056464	
1156	Col27a1	ENSMUSG0000045672	0.67596004	
1157	Dysf	ENSMUSG0000033788	0.675477748	
1158	Ebna1bp2	ENSMUSG0000028729	0.675301472	
1159	Snrpa	ENSMUSG0000061479	0.675264485	
1160	Sacm1l	ENSMUSG0000025240	0.674974673	
1161	Sept11	ENSMUSG0000058013	0.674586578	
1162	Nip7	ENSMUSG0000031917	0.67427054	
1163	Zfp35	ENSMUSG0000063281	0.673101415	
1164	Rpsa-ps10	ENSMUSG0000047676	0.67298466	
1165	Rbm19	ENSMUSG0000029594	0.671834375	
1166	Papss1	ENSMUSG0000028032	0.670756067	
1167	Gm15710	ENSMUSG0000084111	0.669958309	
1168	Atp10a	ENSMUSG0000025324	0.66964081	
1169	Eif2s2	ENSMUSG0000074656	0.669289656	
1170	Rhobtb3	ENSMUSG0000021589	0.669280554	
1171	Ifit1	ENSMUSG0000034459	0.669162863	

1172	Rps27l	ENSMUSG00000036781	0.668752047	
1173	Mex3c	ENSMUSG00000037253	0.668191088	
1174	Rangap1	ENSMUSG00000022391	0.667900592	
1175	Tmtc3	ENSMUSG00000036676	0.667784074	
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1179	Slc35b4	ENSMUSG00000018999	0.663657564	
1180	Nt5e	ENSMUSG00000032420	0.662443118	
1181	Alg14	ENSMUSG00000039887	0.662411485	
1182	Bak1	ENSMUSG00000057789	0.66107869	
1183	Sulf2	ENSMUSG00000006800	0.660960059	
1184	Plekho2	ENSMUSG00000050721	0.660295218	
1185	Clic4	ENSMUSG00000037242	0.660096493	
1186	Gmds	ENSMUSG00000038372	0.659058531	
1187	Dennd4a	ENSMUSG00000053641	0.658649715	
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1191	Gys1	ENSMUSG0000003865	0.655983247	
1192	Dnaaf5	ENSMUSG00000025857	0.654063659	
1193	Rps19-ps6	ENSMUSG00000096942	0.654044111	
1194	Aimp2	ENSMUSG00000029610	0.652181821	
1195	Ranbp1	ENSMUSG00000005732	0.651469332	
1196	Akirin1	ENSMUSG00000023075	0.651233528	
1197	Magt1	ENSMUSG00000031232	0.651042114	
1198	Tmem8b	ENSMUSG00000078716	0.650505945	
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1202	Cttn	ENSMUSG00000031078	0.647377419	
1203	Csrp1	ENSMUSG00000026421	0.646229032	
1204		ENSMUSG00000109908	0.646091023	
1205	Calm1	ENSMUSG0000001175	0.645126522	
1206	Btg1	ENSMUSG00000036478	0.645011658	
1207	Thumpd3	ENSMUSG00000030264	0.643791002	
1208	Eif6	ENSMUSG00000027613	0.643730306	
1209	Alg12	ENSMUSG00000035845	0.64288158	
1210	Prelid1	ENSMUSG00000021486	0.642585588	
1211	Sft2d1	ENSMUSG00000073468	0.642332084	
1212	Gtf2f1	ENSMUSG0000002658	0.641609494	
1213	Arhgdia	ENSMUSG00000025132	0.641402122	
1214	Lpp	ENSMUSG00000033306	0.641290026	
1215	Herc2	ENSMUSG00000030451	0.641123786	
1216	Ssr4	ENSMUSG0000002014	0.64044671	
1217	Sec11c	ENSMUSG00000024516	0.639828566	
1218	Osbpl9	ENSMUSG00000028559	0.639498317	

1219	Net1	ENSMUSG00000021215	0.637143851	
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1222	Cyp51	ENSMUSG0000001467	0.63435002	
1223	Col6a3	ENSMUSG00000048126	0.633595473	
1224	Pign	ENSMUSG00000056536	0.63355999	
1225	Tuba1b	ENSMUSG00000023004	0.63198989	
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1228	Ppp2r1b	ENSMUSG00000032058	0.630364598	
1229	Tmem43	ENSMUSG00000030095	0.630081801	
1230	Nup98	ENSMUSG00000063550	0.629392191	
1231	Lrrc28	ENSMUSG00000030556	0.629353958	
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1233	Map2k1	ENSMUSG00000004936	0.628573741	
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1235	Cbwd1	ENSMUSG00000024878	0.6280778	
1236	Sdad1	ENSMUSG00000029415	0.627165797	
1237	Col1a1	ENSMUSG00000001506	0.626620549	
1238	Exosc2	ENSMUSG00000039356	0.625799426	
1239	Alkbh6	ENSMUSG00000042831	0.624868934	
1240	Mtm1	ENSMUSG00000031337	0.624794263	
1241	Tma16	ENSMUSG00000025591	0.624759039	
1242	Git1	ENSMUSG00000011877	0.623695541	
1243	Chchd6	ENSMUSG00000030086	0.62330958	
1244	Ptpn2	ENSMUSG00000024539	0.621793951	
1245	Noc4l	ENSMUSG00000033294	0.621598922	
1246	Rnd3	ENSMUSG00000017144	0.619969972	
1247	Rps26-ps1	ENSMUSG00000059775	0.619435377	
1248	Hinfp	ENSMUSG00000032119	0.618940271	
1249	Rnf4	ENSMUSG00000029110	0.618481098	
1250	Gadd45a	ENSMUSG00000036390	0.617931993	
1251	Cdc42se2	ENSMUSG00000052298	0.61765282	
1252	Tusc2	ENSMUSG00000010054	0.614390119	
1253	Nup205	ENSMUSG00000038759	0.61390988	
1254	Hras	ENSMUSG00000025499	0.613823609	
1255	H2afz	ENSMUSG00000037894	0.613687268	
1256	Crls1	ENSMUSG00000027357	0.613582286	
1257	1810022K09Rik	ENSMUSG00000078784	0.61310472	
1258	Prdm4	ENSMUSG00000035529	0.612345211	
1259	Utp23	ENSMUSG00000022313	0.612224386	
1260	Abca7	ENSMUSG00000035722	0.610961443	
1261	Slc43a2	ENSMUSG00000038178	0.609567402	
1262	Arhgap1	ENSMUSG00000027247	0.609348442	
1263	1110065P20Rik	ENSMUSG00000078570	0.608295661	
1264	Mlec	ENSMUSG00000048578	0.607575492	
1265	Ctgf	ENSMUSG00000019997	0.607389662	

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1267	Fstl1	ENSMUSG00000022816	0.606903738	
1268	Cript	ENSMUSG00000024146	0.606393596	
1269	Cdkn2d	ENSMUSG00000096472	0.606364933	
1270	Slc38a1	ENSMUSG00000023169	0.606175017	
1271	Snrnp40	ENSMUSG00000074088	0.606046247	
1272	Rpl37rt	ENSMUSG00000072692	0.605870647	
1273	Ticam1	ENSMUSG00000047123	0.605515294	
1274	Mknk1	ENSMUSG00000028708	0.605372644	
1275	Zpr1	ENSMUSG00000032078	0.605301172	
1276	Ptov1	ENSMUSG00000038502	0.605065096	
1277	Borcs6	ENSMUSG00000045176	0.603991584	
1278	Pwp2	ENSMUSG00000032834	0.603470513	
1279	Cd302	ENSMUSG00000060703	0.602227963	
1280	Col4a5	ENSMUSG00000031274	0.601840054	
1281	Dcun1d3	ENSMUSG00000048787	0.601495354	
1282	Tmem41b	ENSMUSG00000047554	0.601304134	
1283	Ak6	ENSMUSG00000078941	0.600480642	
1284	Abhd17c	ENSMUSG00000038459	0.6004754	
1285	Adam9	ENSMUSG00000031555	0.598811296	
1286	Tspan9	ENSMUSG00000030352	0.597732982	
1287	Tmbim6	ENSMUSG00000023010	0.597709731	
1288	Evi5l	ENSMUSG00000011832	0.597197721	
1289	Mcm6	ENSMUSG00000026355	0.596849969	
1290	Hspa8	ENSMUSG00000015656	0.596785008	
1291	Myo9a	ENSMUSG00000039585	0.595772587	
1292	Cdv3	ENSMUSG00000032803	0.594391759	
1293	Rps5	ENSMUSG00000012848	0.59352121	
1294	Gpr108	ENSMUSG00000005823	0.592814952	
1295	Wsb1	ENSMUSG00000017677	0.592735969	
1296	Rps19	ENSMUSG00000040952	0.592580642	
1297	Hmg20b	ENSMUSG00000020232	0.5917954	
1298	Flna	ENSMUSG00000031328	0.590876496	
1299	Ccdc25	ENSMUSG00000022035	0.588484211	
1300	Maea	ENSMUSG00000079562	0.588459912	
1301	Ap3m1	ENSMUSG00000021824	0.588426438	
1302	Leprot	ENSMUSG00000035212	0.587584642	
1303	Rpl14	ENSMUSG00000025794	0.587384075	
1304	Pbdc1	ENSMUSG00000031226	0.587199446	
1305	Itm2c	ENSMUSG00000026223	0.586300683	
1306	Klf2	ENSMUSG00000055148	0.586213082	
1307	Yars	ENSMUSG00000028811	0.585805997	
1308	Ctnnal1	ENSMUSG00000038816	0.585104715	
1309	Anxa2	ENSMUSG00000032231	0.584881521	
1310	Tomm70a	ENSMUSG00000022752	0.584741477	
1311	Sds1	ENSMUSG00000029596	0.584574705	
1312	9930021J03Rik	ENSMUSG00000046138	0.58445531	

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1315	Sbf1	ENSMUSG00000036529	0.582653681	
1316	Fam174a	ENSMUSG00000051185	0.582472213	
1317	Taldo1	ENSMUSG00000025503	0.582320022	
1318	D930016D06Rik	ENSMUSG00000097392	0.581637646	
1319	Dcaf13	ENSMUSG00000022300	0.581585018	
1320	Exoc1	ENSMUSG00000036435	0.581250128	
1321	Ltbr	ENSMUSG00000030339	0.581166184	
1322	Ppp2r5a	ENSMUSG00000026626	0.581147697	
1323	Ttc37	ENSMUSG00000033991	0.580241398	
1324	Ipo4	ENSMUSG00000002319	0.580236941	
1325	Bag2	ENSMUSG00000042215	0.579701437	
1326	Dse	ENSMUSG00000039497	0.579658773	
1327	Rhbdd1	ENSMUSG00000026142	0.578566976	
1328	Fam208b	ENSMUSG00000033799	0.578445914	
1329	Rpl12	ENSMUSG00000038900	0.575352258	
1330	Tmem208	ENSMUSG00000014856	0.575008895	
1331	Cyb5b	ENSMUSG00000031924	0.574780909	
1332	Trove2	ENSMUSG00000018199	0.573184709	
1333	Ddx10	ENSMUSG00000053289	0.573045385	
1334	Fat1	ENSMUSG00000070047	0.572118107	
1335	Fbn1	ENSMUSG00000027204	0.571995332	
1336	B3gat3	ENSMUSG00000071649	0.571481092	
1337	Nlk	ENSMUSG00000017376	0.57134959	
1338	Dnajc2	ENSMUSG00000029014	0.571336165	
1339	Gm37084	ENSMUSG00000102856	0.5710928	
1340	Pspc1	ENSMUSG00000021938	0.57058026	
1341	Btaf1	ENSMUSG00000040565	0.569496277	
1342	Loxl1	ENSMUSG00000032334	0.568574626	
1343	Hand2	ENSMUSG00000038193	0.568356416	
1344	Cfap36	ENSMUSG00000020462	0.567957448	
1345	Emp2	ENSMUSG00000022505	0.567116638	
1346	Tmem160	ENSMUSG00000019158	0.566839725	
1347	Rala	ENSMUSG00000008859	0.566565194	
1348	Gba	ENSMUSG00000028048	0.566345276	
1349	Sec23b	ENSMUSG00000027429	0.565988723	
1350	Bud31	ENSMUSG00000038722	0.56464418	
1351	Pno1	ENSMUSG00000020116	0.563941008	
1352	Gm15459	ENSMUSG00000100801	0.562548494	
1353	Rpe	ENSMUSG00000026005	0.56228236	
1354	Pdlim1	ENSMUSG00000055044	0.562234977	
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1356	Sf3b6	ENSMUSG00000037361	0.561260446	
1357	L2hgdh	ENSMUSG00000020988	0.561232297	
1358	Rps27a	ENSMUSG00000020460	0.561222534	
1359	Mpp6	ENSMUSG00000038388	0.560892157	

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1361	Rack1	ENSMUSG00000020372	0.560178981	
1362	Rab5a	ENSMUSG00000017831	0.55994017	
1363	Slc11a2	ENSMUSG00000023030	0.559739773	
1364	Blvra	ENSMUSG0000001999	0.559022061	
1365	Lnpk	ENSMUSG00000009207	0.558561254	
1366	Sumf1	ENSMUSG00000030101	0.558050627	
1367	Dusp27	ENSMUSG00000026564	0.557232968	
1368	Zfp330	ENSMUSG00000031711	0.556388189	
1369	Tasp1	ENSMUSG00000039033	0.555967599	
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1374	Ppip5k1	ENSMUSG00000033526	0.553921651	
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1376	Ddost	ENSMUSG00000028757	0.552975811	
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1379	Rnft1	ENSMUSG00000020521	0.549530386	
1380	Gm15500	ENSMUSG00000086583	0.549512492	
1381	Cct2	ENSMUSG00000034024	0.549296809	
1382	Esyt2	ENSMUSG00000021171	0.549186355	
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1384	Gfpt1	ENSMUSG00000029992	0.548423544	
1385	Ufm1	ENSMUSG00000027746	0.547345291	
1386	Rps12	ENSMUSG00000061983	0.547126738	
1387	Wbscr22	ENSMUSG00000005378	0.546905029	
1388	Plekh01	ENSMUSG00000015745	0.546833989	
1389	Jund	ENSMUSG00000071076	0.546304886	
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1391	Tesk1	ENSMUSG00000028458	0.545899804	
1392	Eif2s1	ENSMUSG00000021116	0.545643719	
1393	Mtr	ENSMUSG00000021311	0.544752927	
1394	Fam192a	ENSMUSG00000031774	0.544488305	
1395	Cacul1	ENSMUSG00000033417	0.54428689	
1396	Ran	ENSMUSG00000029430	0.542801135	
1397	Commd4	ENSMUSG00000032299	0.542503083	
1398	Pcdhgc3	ENSMUSG00000102918	0.541874673	
1399	Gsr	ENSMUSG00000031584	0.541721894	
1400	Ascc2	ENSMUSG00000020412	0.540838018	
1401	Edem3	ENSMUSG00000043019	0.540722206	
1402	Scamp2	ENSMUSG00000040188	0.540442832	
1403	Gyg	ENSMUSG00000019528	0.539156464	
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1407	Uba5	ENSMUSG00000032557	0.536745484	
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1415	Anxa7	ENSMUSG00000021814	0.532414861	
1416	Gm6136	ENSMUSG00000084106	0.532066705	
1417	Maged2	ENSMUSG00000025268	0.531469614	
1418	Rpl13	ENSMUSG00000000740	0.531304063	
1419	Txndc17	ENSMUSG00000020803	0.530715324	
1420	Polr1b	ENSMUSG00000027395	0.530455322	
1421	Pgrmc2	ENSMUSG00000049940	0.528930034	
1422	Sec61a1	ENSMUSG00000030082	0.528825325	
1423	Selenok	ENSMUSG00000042682	0.528515985	
1424	Mettl2	ENSMUSG00000020691	0.52787577	
1425	Nedd4l	ENSMUSG00000024589	0.527241157	
1426	Hspa14	ENSMUSG00000109865	0.526804674	
1427	Rpl4	ENSMUSG00000032399	0.526427875	
1428	Timm17b	ENSMUSG00000031158	0.526378283	
1429	Ogfrl1	ENSMUSG00000026158	0.525974161	
1430	Twf2	ENSMUSG00000023277	0.524151338	
1431	Qars	ENSMUSG00000032604	0.52410875	
1432	Zcchc7	ENSMUSG00000035649	0.523261157	
1433	Sec24a	ENSMUSG00000036391	0.523249415	
1434	Gm9794	ENSMUSG00000107176	0.522853865	
1435	Vapa	ENSMUSG00000024091	0.521932574	
1436	Cct5	ENSMUSG00000022234	0.521632792	
1437	Ythdc2	ENSMUSG00000034653	0.521246085	
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1439	Gtf3c6	ENSMUSG00000019837	0.520981546	
1440	Imp4	ENSMUSG00000026127	0.520974461	
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1442	Eef1d	ENSMUSG00000055762	0.520926659	
1443	Pabpc1	ENSMUSG00000022283	0.520114387	
1444	Usp9x	ENSMUSG00000031010	0.520076771	
1445	Mtmr9	ENSMUSG00000035078	0.519041252	
1446	Uap1	ENSMUSG00000026670	0.518762823	
1447	Lmna	ENSMUSG00000028063	0.518272094	
1448	Msn	ENSMUSG00000031207	0.51705165	
1449	Rpl37	ENSMUSG00000041841	0.516447015	
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1460	Scfd1	ENSMUSG00000020952	0.511947739	
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1462	Pnp	ENSMUSG00000021871	0.510733136	
1463	Adamts2	ENSMUSG00000036545	0.510538921	
1464	Ralgps1	ENSMUSG00000038831	0.510487815	
1465	Exosc9	ENSMUSG00000027714	0.509835303	
1466	Abce1	ENSMUSG00000058355	0.509233442	
1467	Dyrk2	ENSMUSG00000028630	0.508790477	
1468	Dis3	ENSMUSG00000033166	0.508518208	
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1470	Ccdc6	ENSMUSG00000048701	0.507225369	
1471	Hspa13	ENSMUSG00000032932	0.507138892	
1472	Wdr43	ENSMUSG00000041057	0.506417679	
1473	Epb41	ENSMUSG00000028906	0.505875092	
1474	Mtpn	ENSMUSG00000029840	0.505665596	
1475	Atr	ENSMUSG00000032409	0.505648778	
1476	Nupl1	ENSMUSG00000063895	0.505096689	
1477	Traf7	ENSMUSG00000052752	0.504886147	
1478	Ptges3-ps	ENSMUSG00000040078	0.504635487	
1479	Rps20	ENSMUSG00000028234	0.504393132	
1480	Eif5a	ENSMUSG00000078812	0.502601419	
1481	Tbce	ENSMUSG00000039233	0.502541866	
1482	Psme2	ENSMUSG00000079197	0.502236661	
1483	Plaa	ENSMUSG00000028577	0.501379027	
1484	Mtdh	ENSMUSG00000022255	0.501300669	
1485	Rpl15	ENSMUSG00000012405	0.50108021	
1486	Rps23	ENSMUSG00000049517	0.50065545	
1487	Larp1	ENSMUSG00000037331	0.500420423	
1488	Eif2a	ENSMUSG00000027810	0.500170125	
1489	1110008F13Rik	ENSMUSG00000027637	0.499021313	
1490	Ap2b1	ENSMUSG00000035152	0.498820397	
1491	Pes1	ENSMUSG00000020430	0.498363938	
1492	Pigm	ENSMUSG00000050229	0.498275869	
1493	Nmt1	ENSMUSG00000020936	0.498171532	
1494	Set	ENSMUSG00000054766	0.498097334	
1495	Ttc13	ENSMUSG00000037300	0.498063021	
1496	Utp11	ENSMUSG00000028907	0.497994406	
1497	Naa25	ENSMUSG00000042719	0.497062382	
1498	Twf1	ENSMUSG00000022451	0.496746642	
1499	Nacc1	ENSMUSG0000001910	0.496606494	
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1504	Dhx29	ENSMUSG00000042426	0.494292892	
1505	Nelfe	ENSMUSG00000024369	0.494029333	
1506	Snx4	ENSMUSG00000022808	0.492311794	
1507	Dnajb2	ENSMUSG00000026203	0.491360664	
1508	Rrp36	ENSMUSG00000023971	0.490777527	
1509	Vcip1	ENSMUSG00000045210	0.489566213	
1510	Btf3	ENSMUSG00000021660	0.488985218	
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1516	Kdelr2	ENSMUSG00000079111	0.484165692	
1517	Zfp809	ENSMUSG00000057982	0.483616479	
1518	Wnk1	ENSMUSG00000045962	0.482921099	
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1520	Rpain	ENSMUSG00000018449	0.482469071	
1521	Ifnar1	ENSMUSG00000022967	0.481257099	
1522	Capza1	ENSMUSG00000070372	0.48085383	
1523	Pex2	ENSMUSG00000040374	0.480696842	
1524	Usp22	ENSMUSG00000042506	0.480619961	
1525	Ap1s1	ENSMUSG0000004849	0.480458595	
1526	Ank3	ENSMUSG00000069601	0.480387379	
1527	BC017643	ENSMUSG00000039294	0.480156834	
1528	Nrd1	ENSMUSG00000053510	0.479951824	
1529	Atp6v1a	ENSMUSG00000052459	0.479716457	
1530	Cpeb2	ENSMUSG00000039782	0.479321725	
1531	Rpl27a	ENSMUSG00000046364	0.478058747	
1532	Rplp0	ENSMUSG00000067274	0.477678845	
1533	Tmem57	ENSMUSG00000028826	0.477620117	
1534	Aspscr1	ENSMUSG00000025142	0.476714939	
1535	Rpl35a	ENSMUSG00000060636	0.476592185	
1536	Eif3c	ENSMUSG00000030738	0.476556054	
1537	Fer	ENSMUSG00000000127	0.475780649	
1538	Nsun2	ENSMUSG00000021595	0.475446391	
1539	Tmem159	ENSMUSG00000030917	0.474912436	
1540	Pikfyve	ENSMUSG00000025949	0.474014519	
1541	Rap1a	ENSMUSG00000068798	0.47161947	
1542	Zfp277	ENSMUSG00000055917	0.471340675	
1543	Kras	ENSMUSG00000030265	0.47105097	
1544	Prrc1	ENSMUSG00000024594	0.46918257	
1545	Meis1	ENSMUSG00000020160	0.468645237	
1546	Tatdn2	ENSMUSG00000056952	0.468427648	
1547	Rpl18	ENSMUSG00000059070	0.468298467	

1548	Apobec2	ENSMUSG00000040694	0.467918891	
1549	Nop9	ENSMUSG00000019297	0.467913558	
1550	Ppme1	ENSMUSG00000030718	0.467808746	
1551	Hnrnpab	ENSMUSG00000020358	0.467596901	
1552	Rps7	ENSMUSG00000061477	0.467217561	
1553	Polr3d	ENSMUSG00000000776	0.466640189	
1554	Tmem131	ENSMUSG00000026116	0.466395694	
1555	Rprd1a	ENSMUSG00000040446	0.46630709	
1556	Large1	ENSMUSG0000004383	0.465827982	
1557	Ppm1a	ENSMUSG00000021096	0.465810417	
1558	Impdh2	ENSMUSG00000062867	0.464314265	
1559	Foxk2	ENSMUSG00000039275	0.464100051	
1560	Slc39a1	ENSMUSG00000052310	0.463241415	
1561	Sec22b	ENSMUSG00000027879	0.462370633	
1562	Rnf220	ENSMUSG00000028677	0.462087496	
1563	Hprt	ENSMUSG00000025630	0.461867288	
1564	Stt3a	ENSMUSG00000032116	0.460882392	
1565	Rusc2	ENSMUSG00000035969	0.460422338	
1566	Fbxo30	ENSMUSG00000047648	0.459889961	
1567	Ptbp1	ENSMUSG0000006498	0.459552879	
1568	Pcd6ip	ENSMUSG00000032504	0.459538872	
1569	Pak1ip1	ENSMUSG00000038683	0.45920386	
1570	Rpl5	ENSMUSG00000058558	0.45759172	
1571	Gclc	ENSMUSG00000032350	0.457365506	
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1573	Tspo	ENSMUSG00000041736	0.455357739	
1574	Rngtt	ENSMUSG00000028274	0.45518463	
1575	Arpc5	ENSMUSG0000008475	0.455169113	
1576	Vta1	ENSMUSG00000019868	0.455165181	
1577	Nup153	ENSMUSG00000021374	0.452302113	
1578	Rpl19-ps11	ENSMUSG00000081094	0.451845185	
1579	Sdc2	ENSMUSG00000022261	0.451375996	
1580	Kpna2	ENSMUSG00000018362	0.451108853	
1581	Cct7	ENSMUSG00000030007	0.451064726	
1582	Plekha3	ENSMUSG00000002733	0.450449321	
1583	Trim47	ENSMUSG00000020773	0.450051423	
1584	Eli2	ENSMUSG00000001542	0.449405846	
1585	Psmd13	ENSMUSG00000025487	0.449189383	
1586	Ube2s	ENSMUSG00000060860	0.448979167	
1587	Nclin	ENSMUSG00000020238	0.448881513	
1588	Tprgl	ENSMUSG00000029030	0.447808781	
1589	Anxa5	ENSMUSG00000027712	0.447580481	
1590	C1galt1	ENSMUSG00000042460	0.447490504	
1591	Otud6b	ENSMUSG00000040550	0.447360687	
1592	Gpr89	ENSMUSG00000028096	0.446185855	
1593	Rpl6	ENSMUSG00000029614	0.445430246	
1594	Creb3	ENSMUSG00000028466	0.444868288	

1595	Acbd3	ENSMUSG00000026499	0.444834976	
1596	Myl6	ENSMUSG00000090841	0.44477446	
1597	Celf2	ENSMUSG0000002107	0.443389626	
1598	Stk4	ENSMUSG00000018209	0.44306901	
1599	Stam2	ENSMUSG00000055371	0.442407482	
1600	Bcl10	ENSMUSG00000028191	0.441448134	
1601	Ankrd13a	ENSMUSG00000041870	0.441141247	
1602	Ubxn4	ENSMUSG00000026353	0.440828321	
1603	Txn1	ENSMUSG00000028367	0.440760263	
1604	Nt5c2	ENSMUSG00000025041	0.440499317	
1605	Vim	ENSMUSG00000026728	0.440447875	
1606	Tnpo2	ENSMUSG00000031691	0.440413941	
1607	Actl6a	ENSMUSG00000027671	0.439581209	
1608	Apc	ENSMUSG00000005871	0.438561537	
1609	Ipo7	ENSMUSG00000066232	0.438287864	
1610	Atxn10	ENSMUSG00000016541	0.438244785	
1611	Clec16a	ENSMUSG00000068663	0.438069619	
1612	Hspb2	ENSMUSG00000038086	0.437749757	
1613	Klh128	ENSMUSG00000020948	0.436341544	
1614	Tapt1	ENSMUSG00000046985	0.4344988	
1615	Lnx2	ENSMUSG00000016520	0.433632558	
1616	Raph1	ENSMUSG00000026014	0.433568542	
1617	Rab8a	ENSMUSG0000003037	0.433239524	
1618	Dnajc14	ENSMUSG00000025354	0.432367351	
1619	Lig3	ENSMUSG00000020697	0.43221014	
1620	Ppp1r10	ENSMUSG00000039220	0.432036417	
1621	Golgb1	ENSMUSG00000034243	0.431179617	
1622	Agps	ENSMUSG00000042410	0.429622442	
1623	2410004B18Rik	ENSMUSG00000036873	0.429123234	
1624	Polr1d	ENSMUSG00000029642	0.429083038	
1625	Ifit2	ENSMUSG00000045932	0.428185087	
1626	Pdpk1	ENSMUSG00000024122	0.427992282	
1627	Shc1	ENSMUSG00000042626	0.427736386	
1628	Rpl11	ENSMUSG00000059291	0.427510886	
1629	Psen1	ENSMUSG00000019969	0.425337299	
1630	Mob1b	ENSMUSG0000006262	0.424911449	
1631	Dnajb14	ENSMUSG00000074212	0.424691855	
1632	Pdcl	ENSMUSG00000009030	0.423479042	
1633	Nfe2l1	ENSMUSG00000038615	0.423458423	
1634	Cerk	ENSMUSG00000035891	0.422612544	
1635	Usp11	ENSMUSG00000041264	0.422298345	
1636	Zfr	ENSMUSG00000022201	0.422083471	
1637	Zzef1	ENSMUSG00000055670	0.421255634	
1638	Arhgap35	ENSMUSG00000058230	0.421243693	
1639	Cpsf2	ENSMUSG00000041781	0.421154457	
1640	Senp2	ENSMUSG00000022855	0.420867142	
1641	Vkorc1l1	ENSMUSG00000066735	0.419948769	

1642	Tor1aip2	ENSMUSG00000050565	0.419690379	
1643	Gopc	ENSMUSG00000019861	0.418279038	
1644	Rpl19	ENSMUSG00000017404	0.417853569	
1645	Ormdl3	ENSMUSG00000038150	0.41609523	
1646	Vps50	ENSMUSG00000001376	0.416003245	
1647	Tmem167b	ENSMUSG00000068732	0.4141696	
1648	Atp2b1	ENSMUSG00000019943	0.413375903	
1649	Ctr9	ENSMUSG00000005609	0.411103842	
1650	Rpl32	ENSMUSG00000057841	0.410686893	
1651	Shmt2	ENSMUSG00000025403	0.410606786	
1652	Nfu1	ENSMUSG00000029993	0.410467612	
1653	Rtdc1	ENSMUSG00000027502	0.409129447	
1654	Rpl36a	ENSMUSG00000079435	0.406900204	
1655	Arhgap44	ENSMUSG00000033389	0.406653807	
1656	Mapkap1	ENSMUSG00000038696	0.403232633	
1657	Cdc27	ENSMUSG00000020687	0.397319585	
1658	Rpl38	ENSMUSG00000057322	0.395963629	
1659	Rps28	ENSMUSG00000067288	0.395527258	
1660	Agpat5	ENSMUSG00000031467	0.395433606	
1661	Usp16	ENSMUSG00000025616	0.394837266	
1662	Kmt2c	ENSMUSG00000038056	0.393548682	
1663	Rps11	ENSMUSG00000003429	0.390542775	
1664	Nckap1	ENSMUSG00000027002	0.39046974	
1665	Rps6	ENSMUSG00000028495	0.389588619	
1666	Rpl23	ENSMUSG00000071415	0.388202902	
1667	Spcs1	ENSMUSG00000021917	0.388074753	
1668	Rer1	ENSMUSG00000029048	0.387121349	
1669	Rpl21	ENSMUSG00000041453	0.387085901	
1670	Herpud2	ENSMUSG00000008429	0.387057779	
1671	Tex2	ENSMUSG00000040548	0.387042778	
1672	Rpl34	ENSMUSG00000062006	0.384011235	
1673	Rad23b	ENSMUSG00000028426	0.382016811	
1674	Smurf2	ENSMUSG00000018363	0.381844884	
1675	Ssu72	ENSMUSG00000029038	0.378402997	
1676	Actr2	ENSMUSG00000020152	0.372350328	
1677	Sec16a	ENSMUSG00000026924	0.368718913	
1678	Vcl	ENSMUSG00000021823	0.367809184	
1679	Kcmf1	ENSMUSG00000055239	0.366537133	
1680	Hist1h2bc	ENSMUSG00000018102	0.366213554	
1681	Ap3d1	ENSMUSG00000020198	0.365877498	
1682	Gspt1	ENSMUSG00000062203	0.362498791	
1683	Emg1	ENSMUSG0000004268	0.36048787	
1684	Rpl26	ENSMUSG00000060938	0.358523171	
1685	Papola	ENSMUSG00000021111	0.353600692	
1686	Ltn1	ENSMUSG00000052299	0.346780688	
1687	Zbtb18	ENSMUSG00000063659	0.345898917	
1688	Dync1i2	ENSMUSG00000027012	0.343053737	

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1690	Stard13	ENSMUSG00000016128	-0.33002037	
1691	Mcur1	ENSMUSG00000021371	-0.331018492	
1692	Anapc16	ENSMUSG00000020107	-0.334941423	
1693	Ctcf	ENSMUSG00000005698	-0.340043238	
1694	Gid4	ENSMUSG00000018415	-0.341031179	
1695	Suclg1	ENSMUSG00000052738	-0.344632806	
1696	Phkb	ENSMUSG00000036879	-0.345880192	
1697	Mrpl16	ENSMUSG00000024683	-0.347104116	
1698	Nt5c3	ENSMUSG00000029780	-0.347197258	
1699	Ndufa4	ENSMUSG00000029632	-0.347321075	
1700	Dld	ENSMUSG00000020664	-0.348359566	
1701	Ndufs5	ENSMUSG00000028648	-0.349959395	
1702	Mtif2	ENSMUSG00000020459	-0.351120021	
1703	Mrpl41	ENSMUSG00000036850	-0.351442806	
1704	Flcn	ENSMUSG00000032633	-0.353979766	
1705	Apoo	ENSMUSG00000079508	-0.354620094	
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1709	Ktn1	ENSMUSG00000021843	-0.35553506	
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1711	Ghr	ENSMUSG00000055737	-0.356919536	
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1717	Tfb2m	ENSMUSG00000026492	-0.368367894	
1718	Bola3	ENSMUSG00000045160	-0.368409315	
1719	Al314180	ENSMUSG00000050812	-0.370341583	
1720	Pkig	ENSMUSG00000035268	-0.370865955	
1721	Gfm1	ENSMUSG00000027774	-0.372045633	
1722	Rfc1	ENSMUSG00000029191	-0.373279742	
1723	Mrps7	ENSMUSG00000046756	-0.373571505	
1724	Tmem70	ENSMUSG00000025940	-0.373700669	
1725	Rgl2	ENSMUSG00000041354	-0.374237516	
1726	Comt	ENSMUSG00000000326	-0.374500043	
1727	Ttc3	ENSMUSG00000040785	-0.375445622	
1728	Slc2a4	ENSMUSG00000018566	-0.376367489	
1729	Apbb2	ENSMUSG00000029207	-0.376437254	
1730	Slc29a1	ENSMUSG00000023942	-0.377334309	
1731	Ephb4	ENSMUSG00000029710	-0.378476259	
1732	Podxl	ENSMUSG00000025608	-0.378840206	
1733	Acad8	ENSMUSG00000031969	-0.380084657	
1734	Nfs1	ENSMUSG00000027618	-0.380273806	
1735	Mov10l1	ENSMUSG00000015365	-0.380571431	

1736	Rbfa	ENSMUSG00000024570	-0.380868045	
1737	Vdac1	ENSMUSG00000020402	-0.38107449	
1738	Cmtm4	ENSMUSG00000096188	-0.381093678	
1739	Gns	ENSMUSG00000034707	-0.382467044	
1740	Vezf1	ENSMUSG00000018377	-0.382484952	
1741	Ahcyl1	ENSMUSG00000027893	-0.383608464	
1742	Ppp2r3a	ENSMUSG00000043154	-0.383720923	
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1744	Adh5	ENSMUSG00000028138	-0.385524887	
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1746	Palld	ENSMUSG00000058056	-0.38674525	
1747	Hibch	ENSMUSG00000041426	-0.386842623	
1748	Mrpl45	ENSMUSG00000018882	-0.386998359	
1749	Irak1	ENSMUSG00000031392	-0.388013884	
1750	Etfb	ENSMUSG00000004610	-0.388530487	
1751	Shroom4	ENSMUSG00000068270	-0.38858819	
1752	Palmd	ENSMUSG00000033377	-0.38982511	
1753	Prex2	ENSMUSG00000048960	-0.389829878	
1754	Ank	ENSMUSG00000022265	-0.390274588	
1755	Bves	ENSMUSG00000071317	-0.39070521	
1756	Spin1	ENSMUSG00000021395	-0.391893133	
1757	Uqcc1	ENSMUSG0000005882	-0.392293332	
1758	Mlip	ENSMUSG00000032355	-0.393328936	
1759	Adgre5	ENSMUSG00000002885	-0.39416034	
1760	5730455P16Rik	ENSMUSG00000057181	-0.394775112	
1761	Uaca	ENSMUSG00000034485	-0.395337858	
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1763	P4ha2	ENSMUSG00000018906	-0.396374056	
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1767	Xdh	ENSMUSG00000024066	-0.397427326	
1768	Mrps31	ENSMUSG00000031533	-0.399327557	
1769	Mrpl42	ENSMUSG00000062981	-0.400101018	
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1772	Prdx2	ENSMUSG00000005161	-0.401256028	
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1774	Plekha2	ENSMUSG00000031557	-0.402065752	
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1781	Filip1	ENSMUSG00000034898	-0.404808973	
1782	Man2a2	ENSMUSG00000038886	-0.404907511	

1783	Csnk1e	ENSMUSG00000022433	-0.405508405	
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1789	Ptprg	ENSMUSG00000021745	-0.40686054	
1790	Rad23a	ENSMUSG00000003813	-0.406870035	
1791	Vegfa	ENSMUSG00000023951	-0.407265505	
1792	Cox5a	ENSMUSG00000000088	-0.4082817	
1793	Eid1	ENSMUSG00000091337	-0.408287989	
1794	St3gal6	ENSMUSG00000022747	-0.408502881	
1795	Cenpb	ENSMUSG00000068267	-0.409653595	
1796	Atp5o	ENSMUSG00000022956	-0.412328593	
1797	Cox6c	ENSMUSG00000014313	-0.412378508	
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1802	Zfp106	ENSMUSG00000027288	-0.413933106	
1803	Atp5l	ENSMUSG00000038717	-0.415039908	
1804	Rev1	ENSMUSG00000026082	-0.416685113	
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1806	Cbr4	ENSMUSG00000031641	-0.417802571	
1807	Mrps16	ENSMUSG00000049960	-0.418700587	
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1813	Ctnnbip1	ENSMUSG00000028988	-0.422896573	
1814	Smarcc2	ENSMUSG00000025369	-0.423145415	
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1828	Tek	ENSMUSG0000006386	-0.429972944	
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1832	Selenoo	ENSMUSG00000035757	-0.431788726	
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1853	Lrba	ENSMUSG00000028080	-0.445188289	
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1861	Thbd	ENSMUSG00000074743	-0.450155336	
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1869	Mpc1	ENSMUSG00000023861	-0.454010318	
1870	Arap3	ENSMUSG00000024451	-0.454430577	
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1893	Rxra	ENSMUSG00000015846	-0.46390427	
1894	Plxna2	ENSMUSG00000026640	-0.464090077	
1895	Tfpi	ENSMUSG00000027082	-0.464151348	
1896	Nectin2	ENSMUSG00000062300	-0.464518076	
1897	Id1	ENSMUSG00000042745	-0.465373756	
1898	Atp5k	ENSMUSG00000050856	-0.465861938	
1899	Fgd4	ENSMUSG00000022788	-0.465947898	
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1901	Gdi1	ENSMUSG00000015291	-0.466500275	
1902	Cyth1	ENSMUSG00000017132	-0.466603943	
1903	Rdh14	ENSMUSG00000020621	-0.467924562	
1904	Man2b1	ENSMUSG00000005142	-0.467970752	
1905	Cebpzos	ENSMUSG00000062691	-0.468072836	
1906	Cox10	ENSMUSG00000042148	-0.46855685	
1907	Lamb1	ENSMUSG0000002900	-0.468698685	
1908	Sdhb	ENSMUSG00000009863	-0.469939549	
1909	Smim8	ENSMUSG00000028295	-0.470234616	
1910	Rora	ENSMUSG00000032238	-0.470431033	
1911	Sash1	ENSMUSG00000015305	-0.471569521	
1912	Ndufa10	ENSMUSG00000026260	-0.471907212	
1913	Inpp1l	ENSMUSG00000032737	-0.471926812	
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1915	Abca8b	ENSMUSG00000020620	-0.472167165	
1916	Pfkl	ENSMUSG00000020277	-0.472372865	
1917	Fbxo3	ENSMUSG00000027180	-0.472386005	
1918	Epha2	ENSMUSG0000006445	-0.472681309	
1919	Lsm3	ENSMUSG00000034192	-0.472934874	
1920	Mcu	ENSMUSG00000009647	-0.47390754	
1921	Zfp46	ENSMUSG00000051351	-0.474136595	
1922	Mylk3	ENSMUSG00000031698	-0.47469853	
1923	Hexim1	ENSMUSG00000048878	-0.474915967	

1924	Reep5	ENSMUSG0000005873	-0.475325833	
1925	Phldb2	ENSMUSG00000033149	-0.475769131	
1926	Tor1aip1	ENSMUSG0000026466	-0.475785048	
1927	Gm14539	ENSMUSG0000084830	-0.476505704	
1928	Npr2	ENSMUSG0000028469	-0.476959568	
1929	Ndufa13	ENSMUSG0000036199	-0.477006508	
1930	Tnni3k	ENSMUSG0000040086	-0.47721625	
1931	Meox2	ENSMUSG0000036144	-0.477585602	
1932	Sptb	ENSMUSG0000021061	-0.477789659	
1933	Dgke	ENSMUSG0000000276	-0.477813778	
1934	Mhrt	ENSMUSG0000097652	-0.478564073	
1935	Timp3	ENSMUSG0000020044	-0.479300268	
1936	Clip1	ENSMUSG0000049550	-0.479458231	
1937	Cry2	ENSMUSG0000068742	-0.479977792	
1938	Tmed4	ENSMUSG000004394	-0.480344669	
1939	Taf9b	ENSMUSG0000047242	-0.480447869	
1940	Bbs2	ENSMUSG0000031755	-0.480648668	
1941	Dnajc30	ENSMUSG0000061118	-0.482118886	
1942	Sqor	ENSMUSG000005803	-0.48252714	
1943	Got2	ENSMUSG0000031672	-0.482837514	
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1945	Ipo13	ENSMUSG0000033365	-0.483853739	
1946	Msh3	ENSMUSG0000014850	-0.484420729	
1947	Lama5	ENSMUSG0000015647	-0.484493385	
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1949	Smim20	ENSMUSG0000061461	-0.48501137	
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1951	Dtx3	ENSMUSG0000040415	-0.485346335	
1952	BC002163	ENSMUSG0000081824	-0.48553041	
1953	Myl2	ENSMUSG0000013936	-0.485587731	
1954	Coq10a	ENSMUSG0000039914	-0.485795885	
1955	Cipc	ENSMUSG0000034157	-0.485832112	
1956	Usmg5	ENSMUSG0000071528	-0.485849192	
1957	Lpgat1	ENSMUSG0000026623	-0.485877902	
1958	Fabp5	ENSMUSG0000027533	-0.486619568	
1959	Bcl2l13	ENSMUSG0000009112	-0.487594302	
1960	Jcad	ENSMUSG0000033960	-0.487967018	
1961	Dsp	ENSMUSG0000054889	-0.488635126	
1962	Rsad1	ENSMUSG0000039096	-0.490113874	
1963	Ptprs	ENSMUSG0000013236	-0.491214759	
1964	Tmem60	ENSMUSG0000045435	-0.491417203	
1965	Dhrs1	ENSMUSG0000002332	-0.491445875	
1966	Pex6	ENSMUSG0000002763	-0.492441239	
1967	Uros	ENSMUSG0000030979	-0.493265423	
1968	Plekha6	ENSMUSG0000041757	-0.493672018	
1969	Coq7	ENSMUSG0000030652	-0.493836532	
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1974	Ndufa5	ENSMUSG00000023089	-0.494981118	
1975	Fmo1	ENSMUSG00000040181	-0.495617612	
1976	Msh2	ENSMUSG00000024151	-0.495685067	
1977	A630072M18Rik	ENSMUSG00000101013	-0.495706507	
1978	Uqcrc2	ENSMUSG00000030884	-0.496340757	
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1983	Itprkb	ENSMUSG00000038855	-0.498209082	
1984	Ndufb4	ENSMUSG00000022820	-0.498355141	
1985	Hsd17b10	ENSMUSG00000025260	-0.498427365	
1986	Pter	ENSMUSG00000026730	-0.498531238	
1987	Sgk1	ENSMUSG00000019970	-0.49854871	
1988	Spry1	ENSMUSG00000037211	-0.498721526	
1989	Rgs3	ENSMUSG00000059810	-0.498745317	
1990	Trip10	ENSMUSG00000019487	-0.499011963	
1991	Stap2	ENSMUSG00000038781	-0.499049928	
1992	Scp2	ENSMUSG00000028603	-0.499407896	
1993	Asb8	ENSMUSG00000048175	-0.499712609	
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1999	Lrpprc	ENSMUSG00000024120	-0.502034908	
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2001	Eef1a2	ENSMUSG00000016349	-0.502163664	
2002	Mapk14	ENSMUSG00000053436	-0.50273589	
2003	Synpo2	ENSMUSG00000050315	-0.503117568	
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2007	Rarb	ENSMUSG00000017491	-0.504450356	
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2009	Agl	ENSMUSG00000033400	-0.505072435	
2010	Ctsh	ENSMUSG00000032359	-0.505149262	
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2013	Agpat2	ENSMUSG00000026922	-0.506377875	
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2144	Trib2	ENSMUSG00000020601	-0.550737716	
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2146	Tmem126a	ENSMUSG00000030615	-0.551399718	
2147	Appl2	ENSMUSG00000020263	-0.551485075	
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2149	Ogfod3	ENSMUSG00000025169	-0.551923838	
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2152	Pde4d	ENSMUSG00000021699	-0.554099419	
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2193	Med12l	ENSMUSG00000056476	-0.567943216	
2194	Plcg1	ENSMUSG00000016933	-0.568154692	
2195	Tfp1	ENSMUSG0000006335	-0.568414535	
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2212	2510002D24Rik	ENSMUSG00000071632	-0.575631521	
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2214	Dcaf8	ENSMUSG00000026554	-0.575800509	
2215	Adck1	ENSMUSG00000021044	-0.576037786	
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2535	Crat	ENSMUSG00000026853	-0.716422069	
2536	Adgrf5	ENSMUSG00000056492	-0.717033467	
2537	Coq3	ENSMUSG00000028247	-0.717122404	
2538	Cox8b	ENSMUSG00000025488	-0.717363717	
2539	Scamp5	ENSMUSG00000040722	-0.718445314	
2540	Alad	ENSMUSG00000028393	-0.718929217	
2541	Mrps34	ENSMUSG00000038880	-0.719143077	
2542	Aldh5a1	ENSMUSG00000035936	-0.720139965	
2543	mt-Tt	ENSMUSG00000064371	-0.720428493	
2544	Sgcb	ENSMUSG00000029156	-0.720594515	
2545	Pomgnt2	ENSMUSG00000066235	-0.720795206	
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2547	Acbd4	ENSMUSG00000056938	-0.720929778	
2548	1010001N08Rik	ENSMUSG00000097222	-0.72110946	
2549	Fuz	ENSMUSG00000011658	-0.72122837	
2550	Suox	ENSMUSG00000049858	-0.722112765	
2551	Bbs10	ENSMUSG00000035759	-0.722258322	
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2553	Mrpl14	ENSMUSG00000023939	-0.722528921	
2554	Dll4	ENSMUSG00000027314	-0.722648159	
2555	Card10	ENSMUSG00000033170	-0.723010669	
2556	Gm10925	ENSMUSG00000100862	-0.7230275	
2557	Tmem110	ENSMUSG0000006526	-0.724584545	
2558	Clasp2	ENSMUSG00000033392	-0.725169753	
2559	Smarca2	ENSMUSG00000024921	-0.726387329	
2560	Ptgr2	ENSMUSG00000072946	-0.726456441	
2561	Mgll	ENSMUSG00000033174	-0.726791001	
2562	Podxl2	ENSMUSG00000033152	-0.727560053	
2563	Chmp4c	ENSMUSG00000027536	-0.729854121	
2564	Pnpla7	ENSMUSG00000036833	-0.730157453	
2565	D830050J10Rik	ENSMUSG00000107994	-0.73086899	
2566	Nudt16l1	ENSMUSG00000022516	-0.731272383	
2567	Macrod1	ENSMUSG00000036278	-0.731557102	
2568	Glt28d2	ENSMUSG00000031286	-0.732389934	
2569	Pyurf	ENSMUSG00000043162	-0.733408675	
2570	Abat	ENSMUSG00000057880	-0.73374244	
2571	Rasgrp2	ENSMUSG00000032946	-0.733785494	
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2574	Dok7	ENSMUSG00000044716	-0.734943827	
2575	Dsg2	ENSMUSG00000044393	-0.735091546	
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2590	Snrk	ENSMUSG0000038145	-0.739884033	
2591	mt-Atp6	ENSMUSG0000064357	-0.740257904	
2592	Cnst	ENSMUSG0000038949	-0.740503336	
2593	Npc1	ENSMUSG0000024413	-0.741679415	
2594	Crocc	ENSMUSG0000040860	-0.743405824	
2595	Cdk5rap1	ENSMUSG0000027487	-0.743471282	
2596	Vldlr	ENSMUSG0000024924	-0.743540465	
2597	Trabd2b	ENSMUSG0000070867	-0.744158503	
2598	Cpeb3	ENSMUSG0000039652	-0.74449319	
2599	Prpf19	ENSMUSG0000024735	-0.744666247	
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2604	Nmnat3	ENSMUSG0000032456	-0.745655725	
2605	Ric8b	ENSMUSG0000035620	-0.746236414	
2606	Dcaf4	ENSMUSG0000021222	-0.746482309	
2607	Cenpp	ENSMUSG0000021391	-0.746913297	
2608	Akap7	ENSMUSG0000039166	-0.747518484	
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2610	Tmc7	ENSMUSG0000042246	-0.749229475	
2611	0610009O20Rik	ENSMUSG0000024442	-0.750003149	
2612	Cd36	ENSMUSG0000002944	-0.750182522	
2613	Prag1	ENSMUSG0000050271	-0.750503491	
2614	Sox18	ENSMUSG0000046470	-0.751310502	
2615	BC026585	ENSMUSG0000033488	-0.751508003	
2616	Lpos	ENSMUSG0000097867	-0.751539192	
2617	Vwa7	ENSMUSG0000007030	-0.751719346	
2618	Smpd2	ENSMUSG0000019822	-0.753299005	
2619	Cc2d2a	ENSMUSG0000039765	-0.754129807	
2620	BC029722	ENSMUSG0000074649	-0.754307684	
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2622	Abcb4	ENSMUSG0000042476	-0.755115237	
2623	Casp6	ENSMUSG0000027997	-0.755830956	
2624	Smim26	ENSMUSG0000074754	-0.756716004	
2625	Gm9755	ENSMUSG0000030735	-0.757322821	
2626	Art3	ENSMUSG0000034842	-0.758317218	
2627	Auh	ENSMUSG0000021460	-0.758686888	
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2629	Bend5	ENSMUSG00000028545	-0.759702467	
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2636	Klhl32	ENSMUSG00000040387	-0.763651741	
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2706	Esrrg	ENSMUSG00000026610	-0.808884554	
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2722	Scarna17	ENSMUSG00000088689	-0.817632297	

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2743	Rhot2	ENSMUSG00000025733	-0.827671361	
2744	Acad10	ENSMUSG00000029456	-0.82818379	
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2748	Gm6652	ENSMUSG00000099858	-0.830246173	
2749	Prickle3	ENSMUSG00000031145	-0.83071083	
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2760	Slc26a10	ENSMUSG00000040441	-0.841428669	
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2779	Sord	ENSMUSG00000027227	-0.853819145	
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2782	Sdr39u1	ENSMUSG00000022223	-0.858542837	
2783	Epm2a	ENSMUSG00000055493	-0.858822742	
2784	Mettl26	ENSMUSG00000025731	-0.859351403	
2785	Nlrx1	ENSMUSG00000032109	-0.859781875	
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2787	Tstd3	ENSMUSG00000028251	-0.863467016	
2788	Acads	ENSMUSG00000029545	-0.86371654	
2789	Gm23119	ENSMUSG00000089235	-0.864298007	
2790	Hadhb	ENSMUSG00000059447	-0.866526662	
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2816	Prickle1	ENSMUSG00000036158	-0.881386132	

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2819	Grhpr	ENSMUSG00000035637	-0.887265881	
2820	Mmp15	ENSMUSG00000031790	-0.887919234	
2821	Rhobtb2	ENSMUSG00000022075	-0.888230243	
2822	Txlnb	ENSMUSG00000039891	-0.88964442	
2823	Timp4	ENSMUSG00000030317	-0.890229159	
2824	Hopx	ENSMUSG00000059325	-0.892712081	
2825	Ppif	ENSMUSG00000021868	-0.892765578	
2826	Setd6	ENSMUSG00000031671	-0.892962604	
2827	Cdk18	ENSMUSG00000026437	-0.893020603	
2828	Per3	ENSMUSG00000028957	-0.895496834	
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2844	Stmn2	ENSMUSG00000027500	-0.909480017	
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2846	Gm10461	ENSMUSG00000107277	-0.909824707	
2847	Colec11	ENSMUSG00000036655	-0.91027753	
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2849	Pde4c	ENSMUSG00000031842	-0.911589434	
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2851	Inca1	ENSMUSG00000057054	-0.913738658	
2852	Plet1os	ENSMUSG00000101304	-0.915336161	
2853	Hlf	ENSMUSG0000003949	-0.915557847	
2854	Slc40a1	ENSMUSG00000025993	-0.918664253	
2855	Cpt1b	ENSMUSG00000078937	-0.919775589	
2856	Mme	ENSMUSG00000027820	-0.922523877	
2857	Jam2	ENSMUSG00000053062	-0.923211756	
2858	Gsta4	ENSMUSG00000032348	-0.925528534	
2859	Rnf144b	ENSMUSG00000038068	-0.927869013	
2860	Etfa	ENSMUSG00000032314	-0.928447357	
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2863	mt-Nd6	ENSMUSG00000064368	-0.931104975	

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2865	Lmo2	ENSMUSG00000032698	-0.932777063	
2866	Sobp	ENSMUSG00000038248	-0.933063875	
2867	Ldhd	ENSMUSG00000031958	-0.933350141	
2868	Atp1b2	ENSMUSG00000041329	-0.934700712	
2869	AU021092	ENSMUSG00000051669	-0.937918233	
2870	Ckm	ENSMUSG00000030399	-0.93816446	
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2872	Fam228b	ENSMUSG00000050545	-0.940775714	
2873	Fam81a	ENSMUSG00000032224	-0.941465985	
2874	5430431A17Rik	ENSMUSG00000108322	-0.941737365	
2875	Il2ra	ENSMUSG00000026770	-0.942288619	
2876	Tarsl2	ENSMUSG00000030515	-0.943537175	
2877	4632428C04Rik	ENSMUSG00000097184	-0.945595775	
2878	Unc119	ENSMUSG00000002058	-0.949090283	
2879	Sv2a	ENSMUSG00000038486	-0.950702636	
2880	Acot11	ENSMUSG00000034853	-0.950965714	
2881	Tmem71	ENSMUSG00000036944	-0.951169612	
2882	Acadvl	ENSMUSG00000018574	-0.951280633	
2883	Gm33609	ENSMUSG00000104736	-0.951720598	
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2885	Ptpn3	ENSMUSG00000038764	-0.952770283	
2886	Art5	ENSMUSG00000070424	-0.953880012	
2887	Adi1	ENSMUSG00000020629	-0.954935021	
2888	Adamts7	ENSMUSG00000032363	-0.956271344	
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2890	Acad11	ENSMUSG00000090150	-0.957106991	
2891	Nampt	ENSMUSG00000020572	-0.957162533	
2892	Neil2	ENSMUSG00000035121	-0.957934306	
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2897	Nat8l	ENSMUSG00000048142	-0.964304504	
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2899	Tnip3	ENSMUSG00000044162	-0.965612186	
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2904	Ttc38	ENSMUSG00000035944	-0.973692559	
2905	Exoc3l4	ENSMUSG00000021280	-0.97422634	
2906	Glul	ENSMUSG00000026473	-0.974400932	
2907	L3hypdh	ENSMUSG00000019718	-0.974488828	
2908	Optn	ENSMUSG00000026672	-0.974648007	
2909	Sh3d21	ENSMUSG00000073758	-0.976004393	
2910	2310040G24Rik	ENSMUSG00000101655	-0.9776137	

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2912	Impa2	ENSMUSG00000024525	-0.979310612	
2913	Akr1b10	ENSMUSG00000061758	-0.979513983	
2914	Apc2	ENSMUSG00000020135	-0.979782053	
2915	Slc22a3	ENSMUSG00000023828	-0.98242249	
2916	Hdac11	ENSMUSG00000034245	-0.982675759	
2917	Retreg1	ENSMUSG00000022270	-0.983179656	
2918	2310039L15Rik	ENSMUSG00000100550	-0.983477268	
2919	Btnl9	ENSMUSG00000040283	-0.984495261	
2920	Mitf	ENSMUSG00000035158	-0.985274263	
2921	Gm43288	ENSMUSG00000106220	-0.986173465	
2922	Gm37691	ENSMUSG00000104348	-0.987647578	
2923	Nrg2	ENSMUSG00000060275	-0.9878458	
2924	Cep128	ENSMUSG00000061533	-0.988840525	
2925	Scara5	ENSMUSG00000022032	-0.990524464	
2926	Plin3	ENSMUSG00000024197	-0.991344724	
2927	Gpr157	ENSMUSG00000047875	-0.991543849	
2928	Scn4a	ENSMUSG0000001027	-0.992162729	
2929	Mtfp1	ENSMUSG0000004748	-0.992563111	
2930	Gm20712	ENSMUSG00000093677	-0.992852849	
2931	Cpxm2	ENSMUSG00000030862	-0.995825171	
2932	Ankrd35	ENSMUSG00000038354	-0.995973091	
2933	Whrn	ENSMUSG00000039137	-0.996383244	
2934	Oxld1	ENSMUSG00000039670	-0.996621904	
2935	2310069G16Rik	ENSMUSG00000097102	-0.996914287	
2936	Gm11899	ENSMUSG00000087399	-0.99920021	
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2938	Gm43050	ENSMUSG00000106795	-1.00051903	
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2940	Cxx1c	ENSMUSG00000051851	-1.003518841	
2941	Fstl4	ENSMUSG00000036264	-1.004906968	
2942	Tef	ENSMUSG00000022389	-1.007327474	
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2946	Adam11	ENSMUSG00000020926	-1.012923867	
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2948	D630003M21Rik	ENSMUSG00000037813	-1.013110658	
2949	Gstt2	ENSMUSG00000033318	-1.013144454	
2950	Hadha	ENSMUSG00000025745	-1.013688305	
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2953	Pm20d2	ENSMUSG00000054659	-1.014437199	
2954	Gnmt	ENSMUSG0000002769	-1.014646858	
2955	1110034G24Rik	ENSMUSG00000044991	-1.015035925	
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2958	Vwa8	ENSMUSG00000058997	-1.019871529	
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2962	Gm45203	ENSMUSG00000108494	-1.022852343	
2963	Zfp934	ENSMUSG0000074865	-1.022913935	
2964	Bri3	ENSMUSG0000047843	-1.023056606	
2965	Gm14403	ENSMUSG0000094786	-1.025311153	
2966	Gper1	ENSMUSG0000053647	-1.02689718	
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2968	Fsd2	ENSMUSG0000038663	-1.028381935	
2969	Acadl	ENSMUSG0000026003	-1.02937998	
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2971	Galm	ENSMUSG0000035473	-1.029656305	
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2977	Rasl2-9	ENSMUSG0000083649	-1.04519485	
2978	Dut	ENSMUSG0000027203	-1.045216758	
2979	0610040J01Rik	ENSMUSG0000060512	-1.046029335	
2980	Gm5532	ENSMUSG0000073535	-1.046366906	
2981	Fam69b	ENSMUSG0000036186	-1.046657605	
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2983	Ggnbp1	ENSMUSG0000048731	-1.048886547	
2984	Hsdl2	ENSMUSG0000028383	-1.052403212	
2985	Tcf15	ENSMUSG0000068079	-1.054316753	
2986	Gck	ENSMUSG0000041798	-1.054429563	
2987	Nudt7	ENSMUSG0000031767	-1.054560606	
2988	Vamp5	ENSMUSG0000073002	-1.055082504	
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2990	Tmem266	ENSMUSG0000032313	-1.056874166	
2991	Zfp612	ENSMUSG0000044676	-1.058287295	
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2993	Gm14327	ENSMUSG0000074521	-1.063729109	
2994	mt-Tp	ENSMUSG0000064372	-1.064094033	
2995	Mlycd	ENSMUSG0000074064	-1.064314435	
2996	Klhl38	ENSMUSG0000022357	-1.066499302	
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3002	Kyat1	ENSMUSG0000039648	-1.072370642	
3003	A530013C23Rik	ENSMUSG000006462	-1.072410593	
3004	Myzap	ENSMUSG0000041361	-1.073298516	

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3008	Naprt	ENSMUSG00000022574	-1.077579958	
3009	A430046D13Rik	ENSMUSG00000097353	-1.07782994	
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3014	Fahd2a	ENSMUSG00000027371	-1.081780336	
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3017	Sema3b	ENSMUSG00000057969	-1.083197213	
3018	Tcap	ENSMUSG0000007877	-1.083463945	
3019	Idh2	ENSMUSG00000030541	-1.084701281	
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3021	Acaa2	ENSMUSG00000036880	-1.088062756	
3022	Gm3646	ENSMUSG00000091937	-1.089192401	
3023	Ace2	ENSMUSG00000015405	-1.089199488	
3024	Hhatl	ENSMUSG00000032523	-1.090321835	
3025	Tesc	ENSMUSG00000029359	-1.091053216	
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3027	3425401B19Rik	ENSMUSG00000071540	-1.095134825	
3028	PIn	ENSMUSG00000038583	-1.095582809	
3029	Hs3st5	ENSMUSG00000044499	-1.096291803	
3030	Retsat	ENSMUSG00000056666	-1.099116341	
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3032	Dpysl4	ENSMUSG00000025478	-1.102956308	
3033	Car4	ENSMUSG00000000805	-1.104007528	
3034	Mb	ENSMUSG00000018893	-1.105490432	
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3037	Pfkm	ENSMUSG00000033065	-1.109724719	
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3046	Rxrg	ENSMUSG00000015843	-1.118586113	
3047	Myot	ENSMUSG00000024471	-1.119671173	
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3054	Itgb1bp2	ENSMUSG00000031312	-1.129564361	
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3061	Bcl11b	ENSMUSG00000048251	-1.137896146	
3062	Prodh	ENSMUSG0000003526	-1.139746748	
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3065	Slc25a42	ENSMUSG0000002346	-1.143080285	
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3076	Gm37829	ENSMUSG00000104453	-1.153922176	
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3090	Decr1	ENSMUSG00000028223	-1.170808345	
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3093	Fam131a	ENSMUSG00000050821	-1.177724473	
3094	Adssl1	ENSMUSG00000011148	-1.178539024	
3095	Masp1	ENSMUSG00000022887	-1.181926604	
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3097	Prr29	ENSMUSG0000009210	-1.183153469	
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3099	Perm1	ENSMUSG00000078486	-1.184081299	
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3105	Cutc	ENSMUSG00000025193	-1.191014933	
3106	Dhtkd1	ENSMUSG00000025815	-1.193470072	
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3115	Frem2	ENSMUSG00000037016	-1.201861415	
3116	Rnf207	ENSMUSG00000058498	-1.204774423	
3117	Rbp7	ENSMUSG00000028996	-1.204832761	
3118	Slc7a4	ENSMUSG00000022756	-1.205300042	
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3123	Mterf2	ENSMUSG00000049038	-1.215741322	
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3126	Asb14	ENSMUSG00000021898	-1.22249016	
3127	1700040L02Rik	ENSMUSG00000019945	-1.226527603	
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3129	Paqr7	ENSMUSG00000037348	-1.227742628	
3130	Efnb3	ENSMUSG00000003934	-1.229266384	
3131	Gm45163	ENSMUSG00000109419	-1.230381694	
3132	Pfkfb1	ENSMUSG00000025271	-1.231363939	
3133	2010107G23Rik	ENSMUSG00000020083	-1.23169514	
3134	Rhobtb1	ENSMUSG00000019944	-1.235028161	
3135	1810034E14Rik	ENSMUSG00000097101	-1.239581107	
3136	mt-Ta	ENSMUSG00000064347	-1.242281225	
3137	Ldhb	ENSMUSG00000030246	-1.248140182	
3138	Gm2011	ENSMUSG00000107741	-1.249105324	
3139	Pkd2l2	ENSMUSG00000014503	-1.250439434	
3140	Ces1d	ENSMUSG00000056973	-1.251442559	
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3146	Wipf3	ENSMUSG00000086040	-1.256386079	
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3151	Rom1	ENSMUSG00000071648	-1.26486349	
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3154	Gm11734	ENSMUSG00000085419	-1.266503712	
3155	Lrp1b	ENSMUSG00000049252	-1.266856005	
3156	Gm572	ENSMUSG00000070577	-1.268319908	
3157	Gm43672	ENSMUSG00000106019	-1.268807853	
3158	Rbfox1	ENSMUSG0000008658	-1.269620216	
3159	Gm20522	ENSMUSG00000092241	-1.272304916	
3160	Kcnk2	ENSMUSG00000037624	-1.273199588	
3161	BC037032	ENSMUSG00000087221	-1.282525456	
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3163	Fabp3-ps1	ENSMUSG00000056366	-1.287005673	
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3165	Glns-ps1	ENSMUSG00000082100	-1.28951477	
3166	Alox12	ENSMUSG00000000320	-1.292683326	
3167	Plekhh1	ENSMUSG00000060716	-1.294707791	
3168	Srrm4	ENSMUSG00000063919	-1.297778461	
3169	Arhgef19	ENSMUSG00000028919	-1.306615492	
3170	Myom2	ENSMUSG00000031461	-1.307139947	
3171	Slc25a20	ENSMUSG00000032602	-1.307349159	
3172	Kcnv2	ENSMUSG00000047298	-1.307793653	
3173	Sh2d4a	ENSMUSG00000053886	-1.311358263	
3174	Csdc2	ENSMUSG00000042109	-1.311590607	
3175	Smco1	ENSMUSG00000046345	-1.331318384	
3176	Fabp3	ENSMUSG00000028773	-1.335957877	
3177	Ptpn	ENSMUSG00000026204	-1.341673166	
3178	Map3k21	ENSMUSG00000031853	-1.348702929	
3179	Cacna1s	ENSMUSG00000026407	-1.356885022	
3180	Krt222	ENSMUSG00000035849	-1.357991658	
3181	Acad12	ENSMUSG00000042647	-1.36229579	
3182	Mfsd4b1	ENSMUSG00000038522	-1.362817899	
3183	Ccrl2	ENSMUSG00000043953	-1.365266828	
3184	Magix	ENSMUSG00000031147	-1.366433446	
3185	Mir208a	ENSMUSG00000065432	-1.369653349	
3186	Mccc1os	ENSMUSG00000086392	-1.373886049	
3187	Unc13a	ENSMUSG00000034799	-1.376024873	
3188	4930458D05Rik	ENSMUSG00000087611	-1.383346548	
3189	Plin5	ENSMUSG00000011305	-1.392322443	
3190	Pfn4	ENSMUSG00000020639	-1.394021192	
3191	Spata2l	ENSMUSG00000033594	-1.401642039	
3192	Plxbn3	ENSMUSG00000031385	-1.402146155	

3193	Capn3	ENSMUSG00000079110	-1.402187838	
3194	Ptgds	ENSMUSG00000015090	-1.405537765	
3195	Cmtm8	ENSMUSG00000041012	-1.405711428	
3196	Gfra4	ENSMUSG00000027316	-1.408922551	
3197	Nrn1	ENSMUSG00000039114	-1.417394585	
3198	E330011O21Rik	ENSMUSG00000109841	-1.424155483	
3199	Tmem25	ENSMUSG0000002032	-1.424395886	
3200	Gm34302	ENSMUSG00000103476	-1.428462909	
3201	Gm10699	ENSMUSG00000074461	-1.430274418	
3202	Lrrc52	ENSMUSG00000040485	-1.432298226	
3203	Agbl2	ENSMUSG00000040812	-1.439180094	
3204	Tmod4	ENSMUSG00000005628	-1.440979157	
3205	Lrtm1	ENSMUSG00000045776	-1.452630127	
3206	Lgi3	ENSMUSG00000033595	-1.456746041	
3207	Foxred2	ENSMUSG00000016552	-1.457388753	
3208	Gm12519	ENSMUSG00000085643	-1.459198157	
3209	Nrb	ENSMUSG00000025723	-1.459632991	
3210	9030612E09Rik	ENSMUSG00000045008	-1.462111853	
3211	Ccdc189	ENSMUSG00000057176	-1.466492114	
3212	Gm20619	ENSMUSG00000093482	-1.470913864	
3213	P2ry1	ENSMUSG00000027765	-1.478547649	
3214	Dhrs3	ENSMUSG00000066026	-1.485480146	
3215	Rasd2	ENSMUSG00000034472	-1.502500427	
3216	Dcaf12l1	ENSMUSG00000045284	-1.50295348	
3217	Acy3	ENSMUSG00000024866	-1.505525483	
3218	Paqr9	ENSMUSG00000064225	-1.507219972	
3219	Kcna7	ENSMUSG00000038201	-1.51962661	
3220	Ky	ENSMUSG00000035606	-1.521105304	
3221	Cpt2	ENSMUSG00000028607	-1.546700563	
3222	Ociad2	ENSMUSG00000029153	-1.54931381	
3223	Klhl33	ENSMUSG00000090799	-1.551297275	
3224	P2rx6	ENSMUSG00000022758	-1.551666095	
3225	Hmgcs2	ENSMUSG00000027875	-1.555810995	
3226	Fah	ENSMUSG00000030630	-1.557877241	
3227	Tmem196	ENSMUSG00000048004	-1.557902735	
3228	Cyp1a1	ENSMUSG00000032315	-1.563510036	
3229	Gm5069	ENSMUSG00000055676	-1.583367073	
3230	1500026H17Rik	ENSMUSG00000097383	-1.595989867	
3231	Poln	ENSMUSG00000045102	-1.605717186	
3232	Ttll1	ENSMUSG00000022442	-1.618000571	
3233	Lrrc4b	ENSMUSG00000047085	-1.620767358	
3234	Pdp2	ENSMUSG00000048371	-1.622674208	
3235	Acsm5	ENSMUSG00000030972	-1.623060194	
3236	Lix1	ENSMUSG00000047786	-1.650475797	
3237	Rtn4r	ENSMUSG00000043811	-1.656677431	
3238	Tpd52l1	ENSMUSG00000000296	-1.677962008	
3239	Echdc3	ENSMUSG00000039063	-1.680348036	

3240	Armc2	ENSMUSG00000071324	-1.689499242	
3241	Mylk4	ENSMUSG00000044951	-1.713399449	
3242	Esrrb	ENSMUSG00000021255	-1.724388138	
3243	Gm20594	ENSMUSG00000096887	-1.729589199	
3244	Fn3k	ENSMUSG00000025175	-1.770367777	
3245	Pnck	ENSMUSG0000002012	-1.79339723	
3246	D7Ert443e	ENSMUSG00000030994	-1.794174424	
3247	A530016L24Rik	ENSMUSG00000043122	-1.814446005	
3248	Uckl1os	ENSMUSG00000010492	-1.823225698	
3249	Nudt17	ENSMUSG00000028100	-1.833632626	
3250	Scgb1c1	ENSMUSG00000038801	-1.866522579	
3251	Scd4	ENSMUSG00000050195	-1.885374552	
3252	Ripor2	ENSMUSG00000036006	-1.906096489	
3253	Tmem82	ENSMUSG00000043085	-1.943550535	
3254	9430062P05Rik	ENSMUSG00000104263	-1.950562933	
3255	Bmp7	ENSMUSG0000008999	-1.951083338	
3256	Bdh1	ENSMUSG00000046598	-1.96275389	
3257	Igfals	ENSMUSG00000046070	-1.995145669	
3258	Ogdhl	ENSMUSG00000021913	-2.024478749	
3259	Gm45670	ENSMUSG0000109635	-2.027657599	
3260	Fbp2	ENSMUSG0000021456	-2.035397682	
3261	Myh7b	ENSMUSG0000074652	-2.05635109	
3262	Ucp3	ENSMUSG0000032942	-2.089765907	
3263	Gchfr	ENSMUSG0000046814	-2.106077278	
3264	Slc25a34	ENSMUSG0000040740	-2.121871686	
3265	Snai3	ENSMUSG0000006587	-2.140545121	
3266	B430212C06Rik	ENSMUSG0000046415	-2.212029917	
3267	Lars2	ENSMUSG0000035202	-2.220350519	
3268	Angptl3	ENSMUSG0000028553	-2.261570039	
3269	Ano5	ENSMUSG0000055489	-2.265706879	
3270	Gm36670	ENSMUSG0000109696	-2.289250624	
3271	Clec18a	ENSMUSG0000033633	-2.41653806	
3272	Cngb3	ENSMUSG0000056494	-2.495569712	
3273	Aldob	ENSMUSG0000028307	-2.533973922	
3274	Lgals4	ENSMUSG0000053964	-2.549164923	
3275	Acot1	ENSMUSG0000072949	-2.630300791	
3276	Pde11a	ENSMUSG0000075270	-2.650558147	
3277	Slc15a2	ENSMUSG0000022899	-3.106933705	

**Table IV: 7-day TAC echocardiographic parameters**

	Con Sham (n = 5)	Con+Rheb Sham (n = 5)	ATF6 cKO Sham (n = 5)	ATF6 cKO+Rheb Sham (n = 5)
FS (%)	31.47±4.07	33.63±1.68	28.61±2.54	28.28±1.67
EF (%)	59.40±5.61	63.18±2.30	55.60±4.07	54.94±2.72
LVEDV (µl)	55.61±9.30	56.30±2.97	59.41±3.99	75.90±6.83
LVESV (µl)	23.61±2.83	20.84±2.03	26.91±4.19	34.54±4.42
LVIDD (mm)	3.59±0.24	3.65±0.08	3.73±0.10	4.12±0.16
LVIDS (mm)	2.48±0.27	2.42±0.10	2.67±0.16	2.96±0.15
PWTD (mm)	0.72±0.06	0.68±0.05	0.93±0.08	0.72±0.08
PWTS (mm)	1.03±0.11	1.02±0.06	1.15±0.14	0.94±0.08
AWTD (mm)	0.91±0.07	0.87±0.02	0.92±0.08	0.83±0.03
AWTS (mm)	1.21±0.05	1.16±0.08	1.21±0.08	1.12±0.05
HR (bpm)	488±18.43	516±16.48	464±33.55	504±35.34
HW (mg)	138.60±7.91	134.75±2.55	137.73±3.05	161.60±8.84
BW (g)	26.14±0.97	26.64±0.43	27.13±0.26	28.05±0.65
TL (mm)	19.00±0.37	18.50±0.26	19.67±0.26	22.00±0.37
HW/BW (mg/g)	5.29±0.13	5.07±0.15	5.08±0.13	5.75±0.21
HW/TL (mg/mm)	7.28±0.29	7.29±0.19	7.00±0.07	7.34±0.32

	Con TAC (n = 7)	Con+Rheb TAC (n = 8)	ATF6 cKO TAC (n = 7)	ATF6 cKO+Rheb TAC (n = 8)
FS (%)	29.73±2.25	31.60±1.08	17.71±2.20 <sup>1,2</sup>	26.25±1.07
EF (%)	57.77±1.54	60.57±1.54	37.25±4.15 <sup>1,2</sup>	52.41±1.88
LVEDV (µl)	46.54±4.61	50.55±2.03	61.26±4.53 <sup>2</sup>	52.73±5.77 <sup>1</sup>
LVESV (µl)	19.71±1.81	19.92±1.08	38.91±4.66 <sup>1,2</sup>	25.46±3.78 <sup>2</sup>
LVIDD (mm)	3.36±0.15	3.49±0.06 <sup>1</sup>	3.77±0.12 <sup>2</sup>	3.53±0.16 <sup>1</sup>
LVIDS (mm)	2.36±0.13	2.39±0.05	3.11±0.16 <sup>1,2</sup>	2.61±0.15 <sup>1</sup>
PWTD (mm)	1.78±0.12 <sup>1</sup>	1.54±0.08 <sup>1</sup>	1.03±0.04 <sup>2</sup>	1.45±0.14 <sup>1</sup>
PWTS (mm)	1.99±0.11 <sup>1</sup>	1.66±0.14 <sup>1</sup>	1.07±0.08 <sup>2</sup>	1.68±0.13 <sup>1</sup>
AWTD (mm)	1.28±0.05 <sup>1</sup>	1.23±0.08 <sup>1</sup>	0.91±0.12 <sup>2</sup>	1.27±0.13 <sup>1</sup>
AWTS (mm)	1.49±0.09 <sup>1</sup>	1.61±0.06 <sup>1</sup>	1.28±0.13 <sup>2</sup>	1.62±0.13 <sup>1</sup>
HR (bpm)	523±9.02	519±13.29	505±13.20	514±22.54
HW (mg)	212.44±3.89 <sup>1</sup>	217.20±14.08 <sup>1</sup>	176.89±7.44 <sup>1,2</sup>	232.95±9.99 <sup>1,2</sup>
BW (g)	24.34±0.66	23.99±0.51 <sup>1</sup>	25.63±0.47	25.52±0.73 <sup>1</sup>
TL (mm)	19.60±0.40	19.00±0.31	20.86±0.32	20.17±0.44
HW/BW (mg/g)	8.75±0.24 <sup>1</sup>	9.10±0.69 <sup>1</sup>	6.90±0.27 <sup>1,2</sup>	9.15±0.39 <sup>1</sup>
HW/TL (mg/mm)	10.86±0.22 <sup>1</sup>	11.39±0.56 <sup>1</sup>	8.50±0.41 <sup>1,2</sup>	11.54±0.33 <sup>1</sup>

FS = fractional shortening

EF = ejection fraction

LVEDV = left ventricular end diastolic volume

LVESV = left ventricular end systolic volume

LVIDD = left ventricular inner diameter in diastole

LVIDS = left ventricular inner diameter in systole

PWTD = left ventricular posterior wall thickness in diastole

PWTS = left ventricular posterior wall thickness in systole

AWTD = left ventricular anterior wall thickness in diastole

AWTS = left ventricular anterior wall thickness in systole

HR = heart rate in beats per minute

HW = heart weight

BW = body weight

TL = tibia length

HW/BW = heart weight/body weight

HW/TL = heart weight/tibia length

Statistical analyses used a one-way ANOVA with a Newman-Keuls post-hoc analysis.

<sup>1</sup> = p ≤ 0.05 different from respective Sham<sup>2</sup> = p ≤ 0.05 different from Con TAC

**Table V: TAC time course echocardiographic parameters for Wild-Type mice**

	Sham (n = 4)	3-Hours TAC (n = 4)	2-Days TAC (n = 4)	7-Days TAC (n = 4)
FS (%)	30.76±1.69	32.27±1.83	28.32±3.21	25.36±1.85
EF (%)	59.11±2.58	61.40±2.64	54.95±4.98	50.51±3.00 <sup>1</sup>
LVEDV ( $\mu$ l)	55.18±3.16	50.76±3.82	58.16±1.60	62.66±1.32 <sup>1</sup>
LVESV ( $\mu$ l)	22.82±2.74	19.94±2.60	26.38±3.44	30.87±1.67 <sup>1</sup>
LVIDD (mm)	3.62±0.08	3.49±0.11	3.70±0.04	3.82±0.03 <sup>1</sup>
LVIDS (mm)	2.51±0.11	2.37±0.13	2.65±0.14	2.85±0.06 <sup>1</sup>
PWTD (mm)	0.70±0.04	0.78±0.03	0.91±0.12	1.30±0.05 <sup>1</sup>
PWTS (mm)	1.03±0.04	1.12±0.06	1.22±0.09	1.69±0.06 <sup>1</sup>
AWTD (mm)	0.79±0.04	0.93±0.05	1.03±0.05 <sup>1</sup>	1.50±0.04 <sup>1</sup>
AWTS (mm)	1.10±0.04	1.22±0.06	1.25±0.04	1.78±0.05 <sup>1</sup>
HR (bpm)	517±11.32	503±13.78	509±11.75	517±7.18
HW (mg)	121.05±5.23	158.95±4.05 <sup>1</sup>	162.90±3.39 <sup>1</sup>	208.50±10.04 <sup>1</sup>
BW (g)	23.09±0.28	31.00±0.85 <sup>1</sup>	27.94±1.56 <sup>1</sup>	29.06±0.37 <sup>1</sup>
TL (mm)	18.50±0.29	23.50±0.29 <sup>1</sup>	21.50±0.50 <sup>1</sup>	22.75±0.25 <sup>1</sup>
HW/BW (mg/g)	5.24±0.22	5.13±0.06	5.85±0.43	7.19±0.42 <sup>1</sup>
HW/TL (mg/mm)	6.54±0.21	6.76±0.10	7.56±0.51 <sup>1</sup>	9.15±0.35 <sup>1</sup>

FS = fractional shortening

EF = ejection fraction

LVEDV = left ventricular end diastolic volume

LVESV = left ventricular end systolic volume

LVIDD = left ventricular inner diameter in diastole

LVIDS = left ventricular inner diameter in systole

PWTD = left ventricular posterior wall thickness in diastole

PWTS = left ventricular posterior wall thickness in systole

AWTD = left ventricular anterior wall thickness in diastole

AWTS = left ventricular anterior wall thickness in systole

HR = heart rate in beats per minute

HW = heart weight

BW = body weight

TL = tibia length

HW/BW = heart weight/body weight

HW/TL = heart weight/tibia length

Statistical analyses used a one-way ANOVA with a Newman-Keuls post-hoc analysis.

<sup>1</sup> = p ≤ 0.05 different from Sham

**Table VI: 3-hour TAC echocardiographic parameters for Con and ATF6 cKO mice**

	Con Sham (n = 5)	ATF6 cKO Sham (n = 4)	Con TAC (n = 5)	ATF6 cKO TAC (n = 4)
FS (%)	34.06±2.95	33.88±3.13	31.91±1.57	31.59±3.66
EF (%)	63.57±3.78	63.18±4.30	60.66±2.26	59.72±5.30
LVEDV ( $\mu$ l)	51.52±3.83	58.55±2.44	61.47±4.92	63.15±5.20
LVESV ( $\mu$ l)	18.28±1.23	21.79±3.28	24.33±2.86	26.21±5.31
LVIDD (mm)	3.51±0.11	3.71±0.07	3.78±0.12	3.82±0.13
LVIDS (mm)	2.30±0.06	2.46±0.15	2.57±0.12	2.63±0.23
PWTD (mm)	0.84±0.08	0.76±0.07	0.72±0.05	0.81±0.06
PWTS (mm)	0.90±0.23	1.16±0.18	1.08±0.05	1.16±0.07
AWTD (mm)	0.86±0.10	0.90±0.09	0.88±0.04	0.93±0.04
AWTS (mm)	1.77±0.16	1.24±0.08	1.21±0.04	1.22±0.04
HR (bpm)	493±19.31	517±10.09	510±10.16	512±14.34
HW (mg)	128.88±5.32	137.30±6.35	148.00±2.16 <sup>1</sup>	152.78±6.37 <sup>1</sup>
BW (g)	24.58±0.88	25.88±1.04	26.58±0.40	28.16±0.65 <sup>1</sup>
TL (mm)	19.40±0.51	19.00±0.41	21.00±0.32	21.75±0.48 <sup>1</sup>
HW/BW (mg/g)	5.24±0.11	5.31±0.16	5.58±0.15	5.42±0.14
HW/TL (mg/mm)	6.65±0.25	7.23±0.23	7.06±0.16	7.02±0.22

FS = fractional shortening

EF = ejection fraction

LVEDV = left ventricular end diastolic volume

LVESV = left ventricular end systolic volume

LVIDD = left ventricular inner diameter in diastole

LVIDS = left ventricular inner diameter in systole

PWTD = left ventricular posterior wall thickness in diastole

PWTS = left ventricular posterior wall thickness in systole

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HR = heart rate in beats per minute

HW = heart weight

BW = body weight

TL = tibia length

HW/BW = heart weight/body weight

HW/TL = heart weight/tibia length

Statistical analyses used a one-way ANOVA with a Newman-Keuls post-hoc analysis.

<sup>1</sup> = p ≤ 0.05 different from respective Sham

<sup>2</sup> = p ≤ 0.05 different from Con TAC