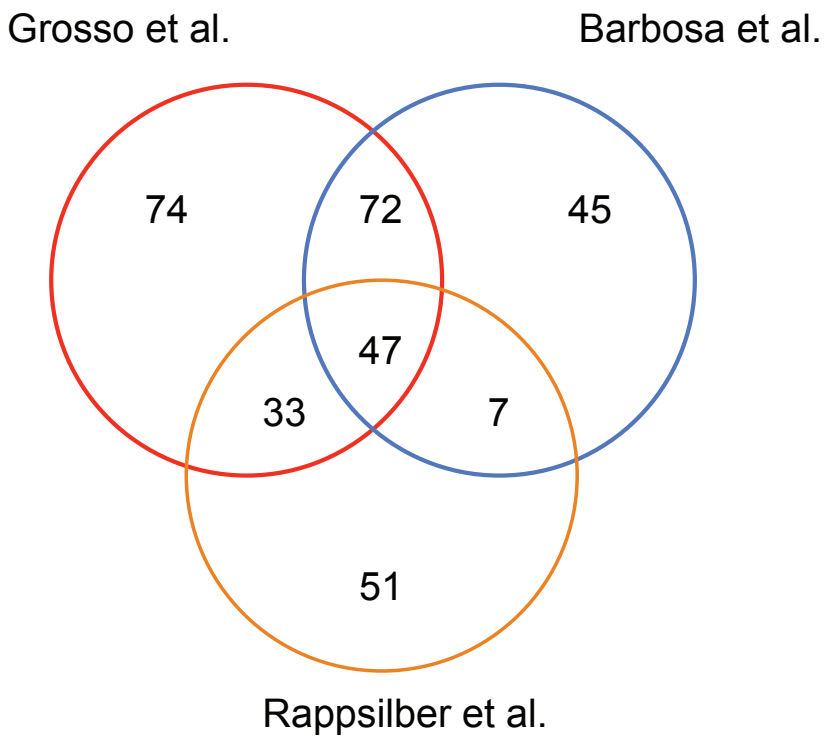
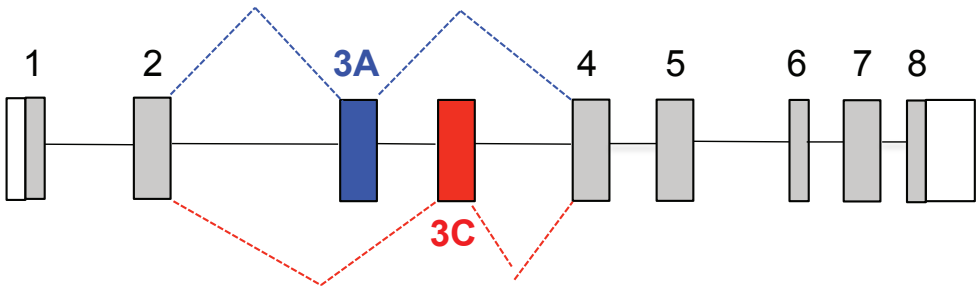
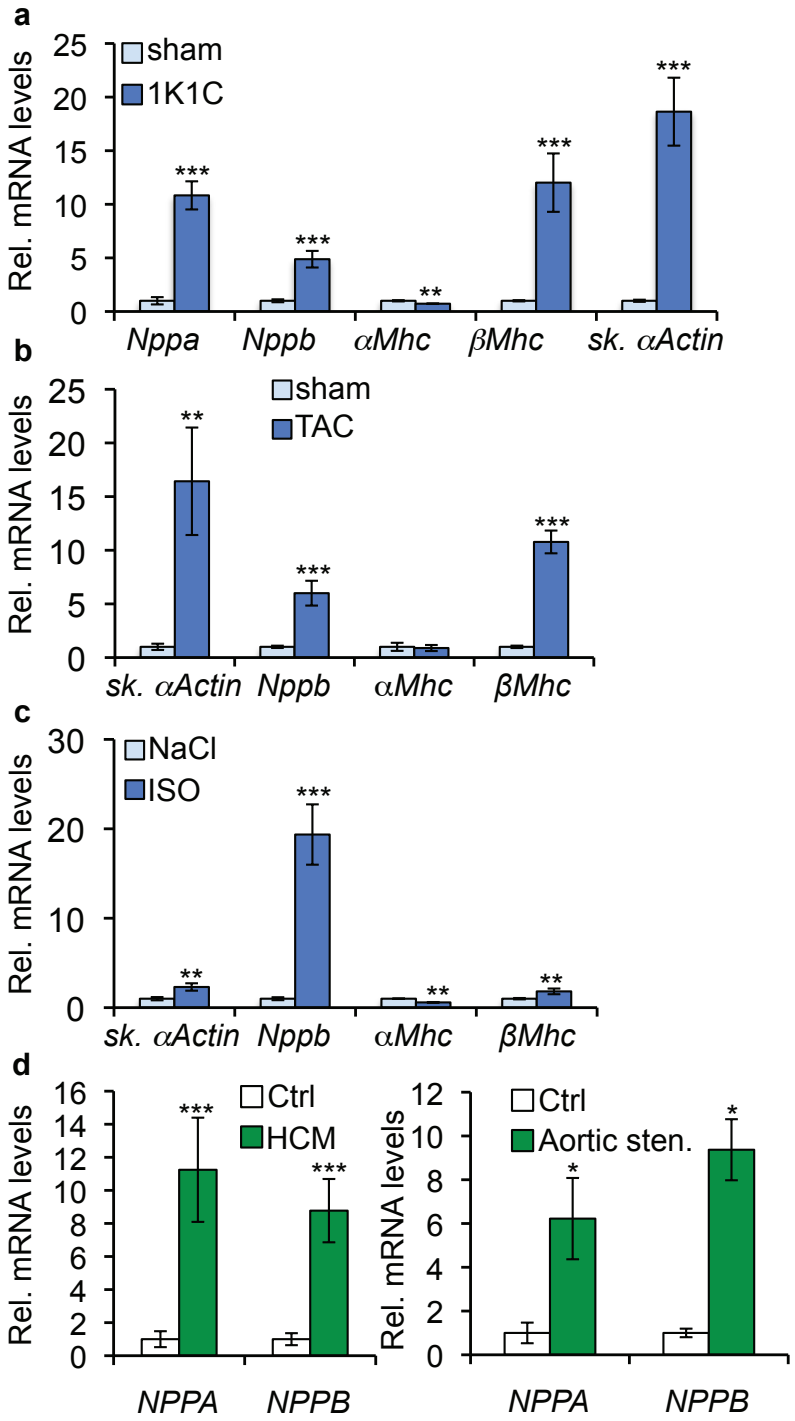
doi:10.1038/nature14508



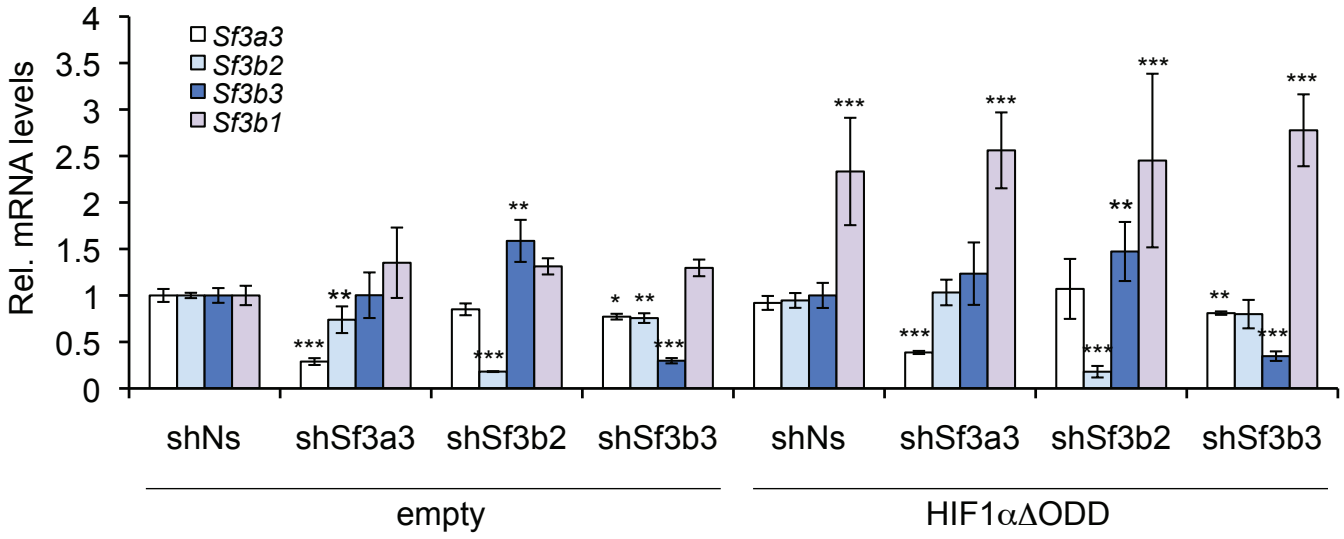
Supplementary Figure 1 | a, Venn-Diagram of identified splice factors in the work of Barbossa et al., Grosso et al. and Rappsilber et al. A total number of 329 genes were indentified.



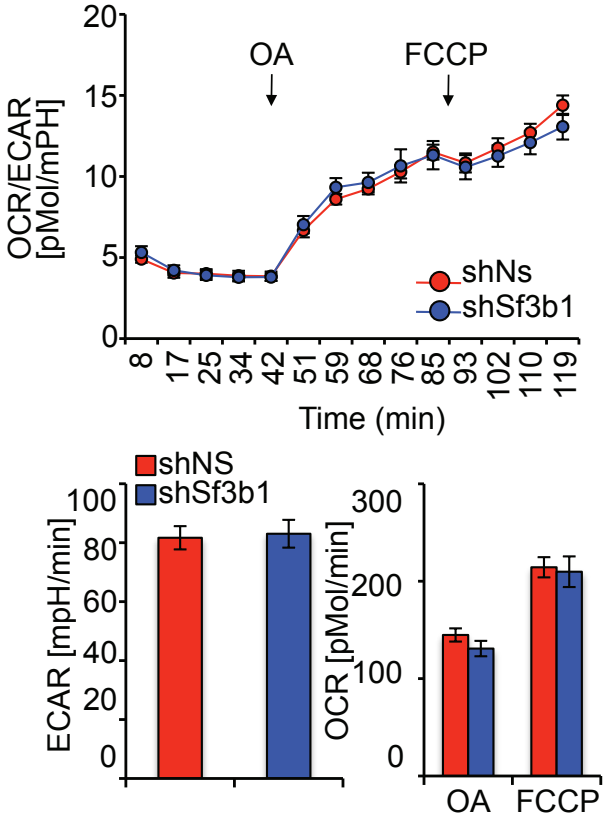
Supplementary Figure 2 | Schematic representation of *KHK* pre-mRNA. Alternative spliced exons 3A and 3C leading to expression of either KHK-A or KHK-C protein are highlighted in blue (exon 3A) and red (exon 3C).



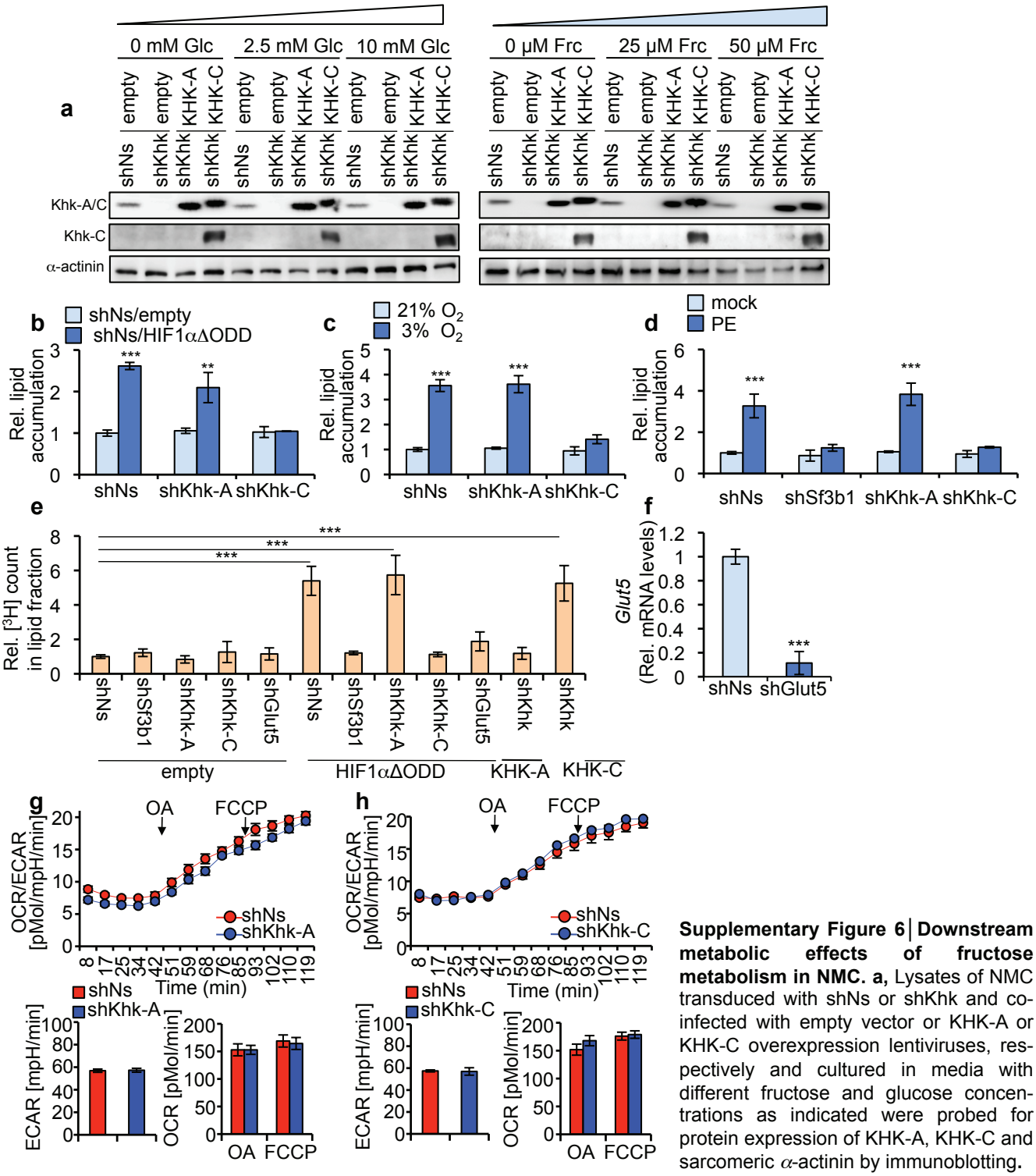
Supplementary Figure 3 | Gene expression of hypertrophic markers in mouse models of cardiac hypertrophy or heart disease patients and their corresponding controls, presented in Extended Data Fig. 1. a, b, Probes from left ventricles of 1K1C, TAC or ISO-treated mice and their corresponding controls were analyzed for mRNA hypertrophic markers. All values were presented in relation to sham-operated controls set as 1.0 (n = 6; shown is mean ± SEM; *p<0.05; **p< 0.01; ***p < 0.001; two-tailed unpaired t-test). **c, d,** Leftventricular biopsies of hypertrophic cardiomyopathy (HCM) patients and healthy controls were analysed for mRNA expression hypertrophic markers (**t**). All values are presented in relation to healthy controls set as 1.0 (n = 6 for controls and n = 16 for patient samples; shown is mean ± SEM; *p< 0.05; ***p< 0.001; two-tailed unpaired t-test).



Supplementary Figure 4 | Depletion of U2-snRNP components in NMC in the presence or absence of HIF1αΔODD. NMC were transduced with either scrambled shRNA or shSf3a3, shSf3b2 or shSf3b3 were co-transduced with empty vector or HIF1αΔODD. Gene expression was evaluated by qRT-PCR. Values were normalised to shNs/empty infected NMC (n = 3; shown is mean ± SD; *p < 0.05; **p < 0.01; ***p < 0.001; one-way ANOVA followed by Dunnett's multiple comparison post-test).

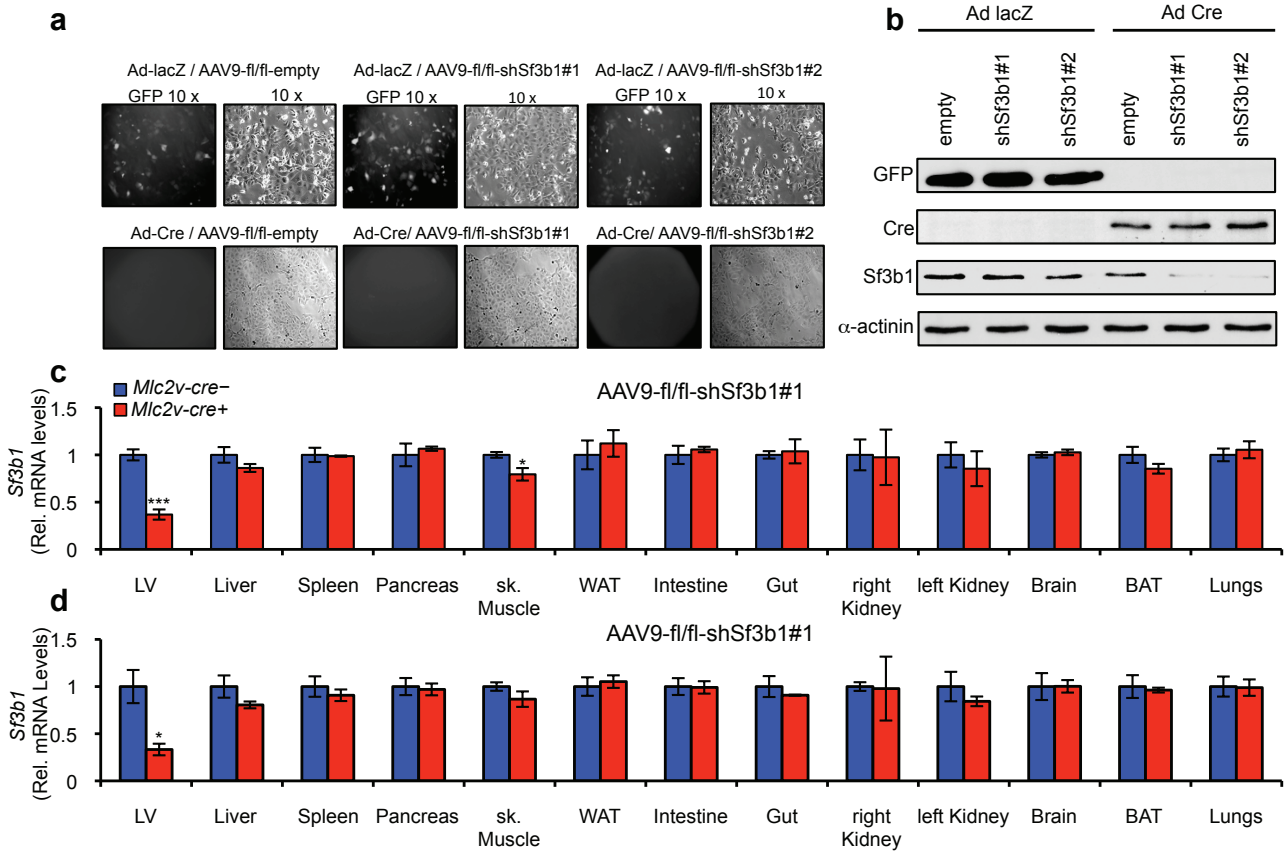


Supplementary Figure 5 | Assessment of extracellular acidification rate (ECAR), and oleic acid and FCCP-induced oxygen consumption rate (OCR) in NMC transduced with shNs and shSf3b1 lentiviruses. Highlighted ECAR measurements were done at baseline. All data are compared to shNs-transduced NMC. (n = 9 per condition)



Supplementary Figure 6 | Downstream metabolic effects of fructose metabolism in NMC. a, Lysates of NMC transduced with shNs or shKhk and co-infected with empty vector or KHK-A or KHK-C overexpression lentiviruses, respectively and cultured in media with different fructose and glucose concentrations as indicated were probed for protein expression of KHK-A, KHK-C and sarcomeric α-actinin by immunoblotting.

B–d, NMC transduced and treated as indicated were incubated overnight with OA and stained with Nile Red. Stainings were quantified using a plate reader with 485/535 nm excitation/emission filters. Values were compared to control set as 1.0. (n = 3; shown is mean ± SD; ***p > 0.001; one-way ANOVA followed by Dunnett's multiple comparison post-test).**e,** NMC infected as denoted were incubated with oleic acid (OA) and [^{3}H]fructose. A lipid extraction was done to assess incorporation of [^{3}H] into lipids (n = 4; shown is mean ± SD; ***p > 0.001; one-way ANOVA followed by Dunnett's multiple comparison post-test). **f,** shRNA against Glut5 was evaluated by qPCR for its potential to inhibit *Glut5* expression. Data are shown in relation to shNs NMC (set to 1.0), (n = 3; shown is mean ± SD; ***p > 0.001; two-tailed unpaired t-test). **g, h,** Assessment of ECAR and OA and FCCP-induced OCR in NMC infected with shNs or shKhk-A lentiviruses (**g**) and shNs or shKhk-C lentiviruses (**h**), Highlighted ECAR measurements were done at baseline. All data are compared to shNs-transduced NMC (n = 9; shown is mean ± SEM; ***p > 0.001; two-tailed unpaired t-test).



Supplementary Figure 7 | ***In vitro* and *in vivo* validation of modified AAV9.** **a, b,** NMC transduced with AAV9-fl/fl-empty, AAV9-fl/fl-shSf3b1#1 and AAV9-fl/fl-shSf3b1#2 viruses in NMC were investigated for removal of the CMV-GFP/stop reporter cassette by Adeno-Cre-mediated recombination using immunofluorescent microscopy (**a**) and immunoblot detection for indicated proteins (**b**) As a control served transductions with Adeno-lacZ viruses, where the GFP/stop reporter cassette is retained. **c, d,** *Sf3b1* mRNA expression was assessed using qPCR in different organs of *Mlc2v-cre*− and *Mlc2v-cre*+ mice injected as in **m**. Data represent mean ± SEM; (n = 4 for *Mlc2v-cre*− AAV9-fl/fl-shSf3b1#1 or *Mlc2v-cre*+ AAV9-fl/fl-shSf3b1#1 mice and n = 3 for for *Mlc2v-cre*− AAV9-fl/fl-shSf3b1#2 or *Mlc2v-cre*+ AAV9-fl/fl-shSf3b1#2 mice; shown is mean ± SEM; ***p < 0.001; two-tailed unpaired t-test).

Sample ID	Sex	Type	age	AVA (cm^2)	MPG (mmHg)	PWD (mm)	IVSD (mm)	Antihyp. Drugs	EF (%)	Type 2 Diabetes
LV 1J	male	Aortic stenosis	0.8	0.8	54	–	–	yes	–	yes
LV 2J	female	Aortic stenosis	0.6	0.6	45	–	–	yes	75	no
LV 3J	female	Aortic stenosis	0.7	0.7	52	–	–	yes	74	yes
LV 26	female	Aortic stenosis	80	–	47	–	14	yes	60	yes
LV 29	male	Aortic stenosis	74	0.8	47	–	–	yes	75	no
LV 30	female	Aortic stenosis	77	0.77	44	12	13	yes	55	no
LV 34	female	Aortic stenosis	58	n.a.	–	–	–	yes	65	yes
LV 39	female	Aortic stenosis	72	0.9	43	15	16	yes	70	yes
LV 41	female	Aortic stenosis	83	0.7	50	12	13	yes	70	yes
LV 43	male	Aortic stenosis	77	0.6	67	14	16	yes	60	–
LV 48	male	Aortic stenosis	77	0.6	70	15	17	yes	60	no
LV 33	male	Aortic stenosis	77	0.9	43	15	15	yes	60	–
LV 61	female	Aortic stenosis	79	0.5	50	17	15	yes	60	–
LV 62	female	Aortic stenosis	74	0.7	38	19	19	yes	60	–
LV 90	female	Aortic stenosis	57	0.6	52	–	–	yes	60	–
LV 92	female	Aortic stenosis	78	0.4	53	17	21	yes	60	–
LV101	male	Aortic stenosis	52	0.7	74	14	19	yes	60	–

Sample ID	Sex	Type	Age	PCWP (mmHg)	CI (l/min/m^3)	pMean (mmHg)	IVSD (mm)	Hypertension	EF (%)	LVEDD (mm)
LV 77	female	HCM	77	0.7	40	40	–	yes	65	–
LV 91	female	HCM	50	–	–	–	–	yes	30	–
LV115	female	HCM	56	–	68	68	26	yes	60	–
LV496	male	HCM	42	16	1.80	–	20	yes	60	76
LV535	male	HCM	45	19	1.98	–	13	yes	18	61
LV552	female	HCM	55	12	1.67	–	20	yes	46	43
LV624	female	HCM	66	25	1.56	–	31	yes	65	35
LV679	female	HCM	53	11	2.30	–	20	yes	39	40
LV703	male	HCM	48	23	2.25	–	–	yes	30	–
LV712	female	HCM	55	14	2.00	–	17	yes	40	53
LV007	male	HCM	–	33	1.37	–	–	yes	20	–

Supplementary Table 4 | Demographic and clinical data of patients with Aortic stenosis and hypertrophic cardiomyopathy.
LV = left ventricle; AVA = aortic valve area; MPG = mean pressure gradient; PWD = posterior wall diameter; IVSD = interventricular septum diameter; EF = ejection fraction; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; pMean = mean pressure; LVEDD = left ventricular end-diastolic diameter.

The protein coding sequence of (mouse) codon optimised *Sf3b1*

```
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```

Translation of the protein coding sequence of (mouse) codon optimised *Sf3b1*

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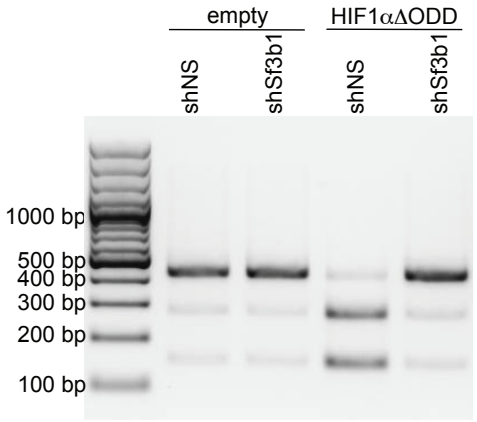
Supplementary Data 1 | Coding and amino acid sequence of (mouse) codon optimised *Sf3b1*.

Agarose gel referring to Fig. 1c



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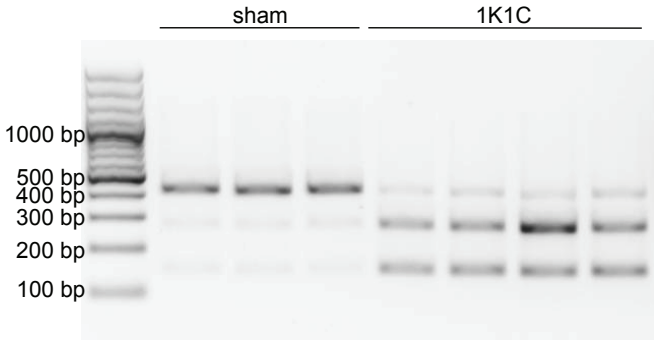
Agarose gel referring to Fig. 1d



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Agarose gels referring to Fig. 1g

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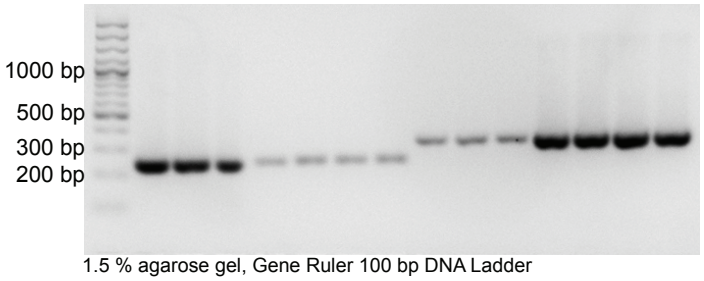

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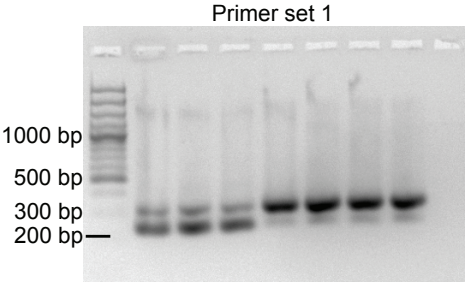
Primer set 1



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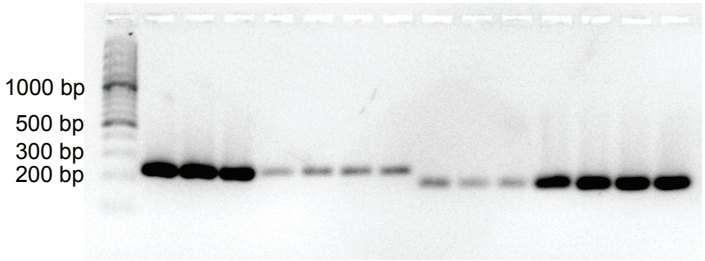

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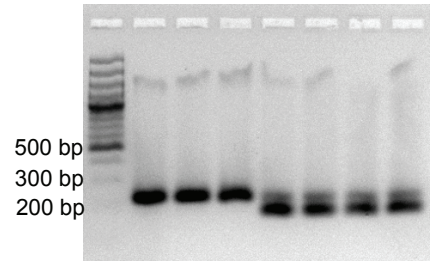

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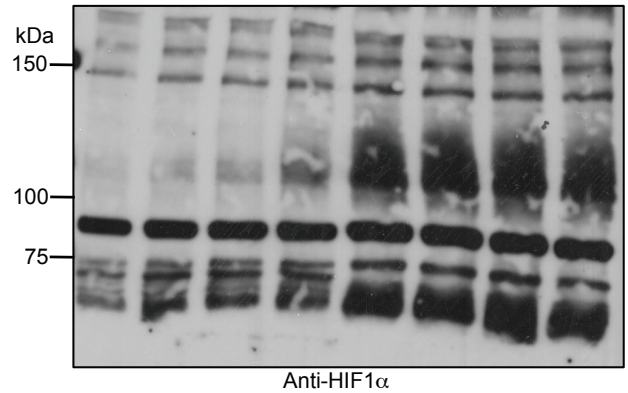
Immunoblots Figure 1e



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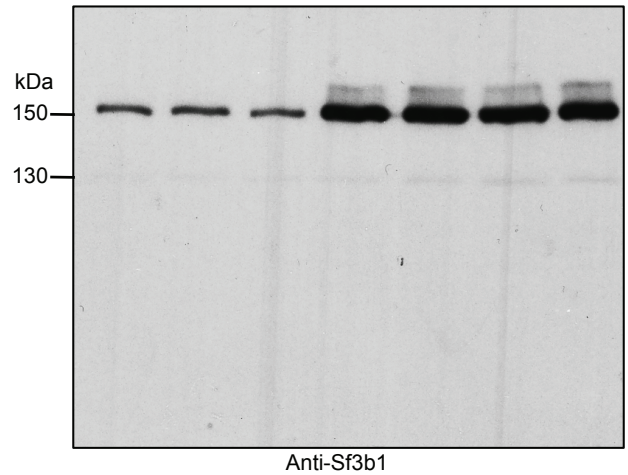

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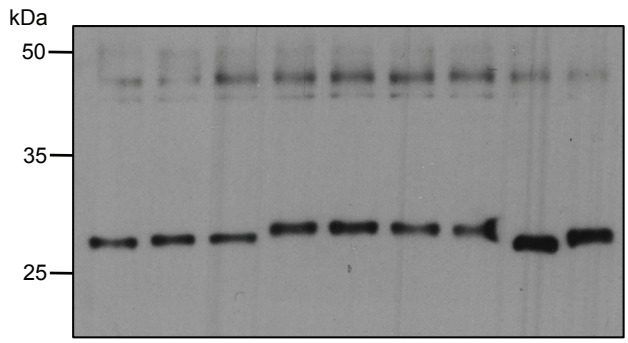
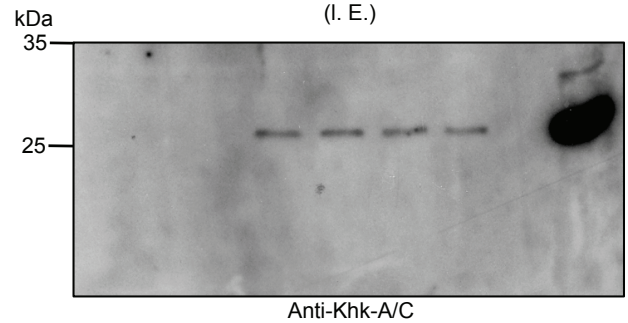


Anti-Khk-A/C
(I. E.)



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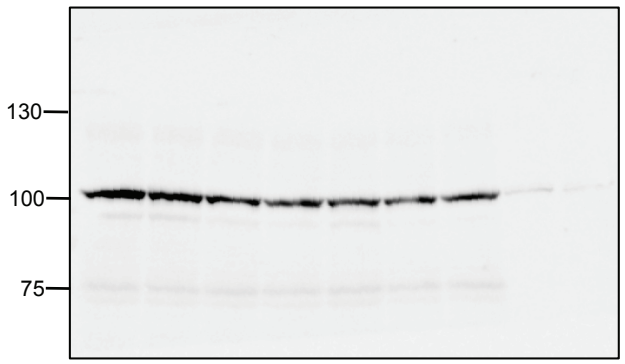
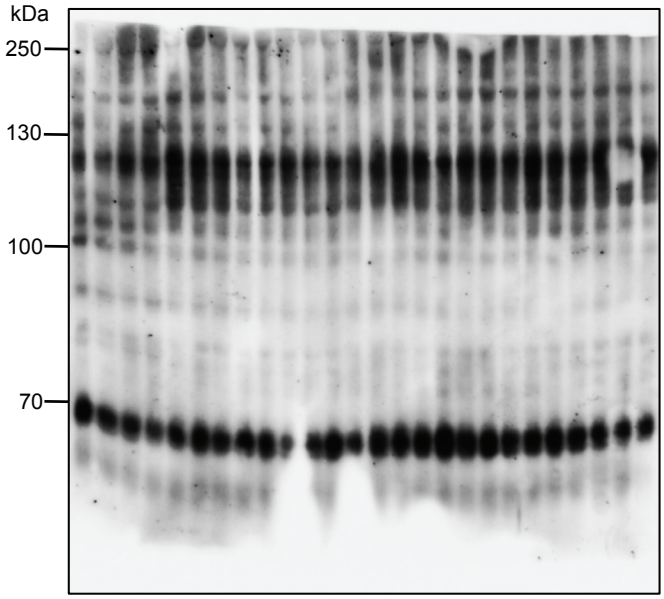


Anti-αActinin

Immunoblots Figure 1h



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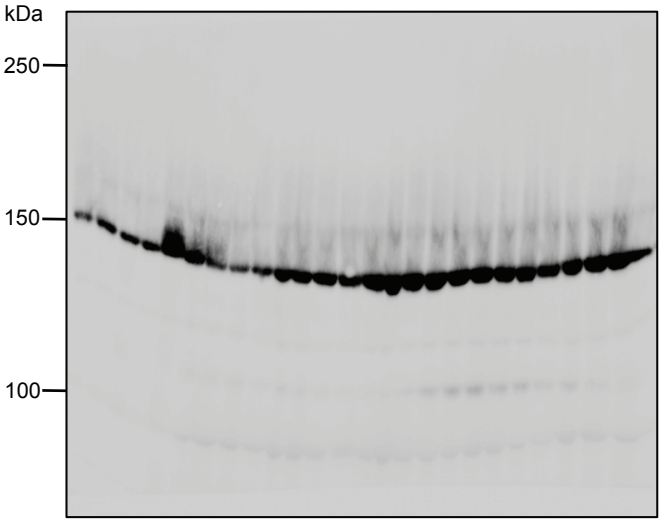
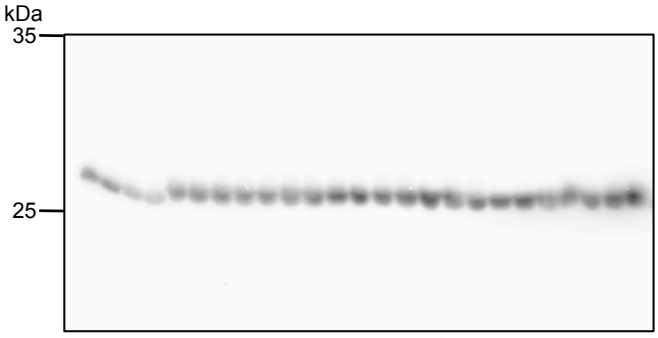
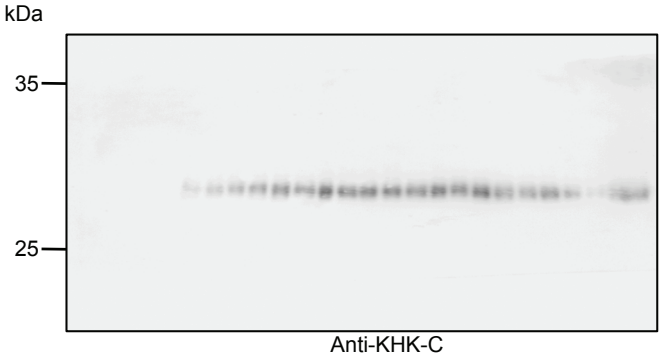


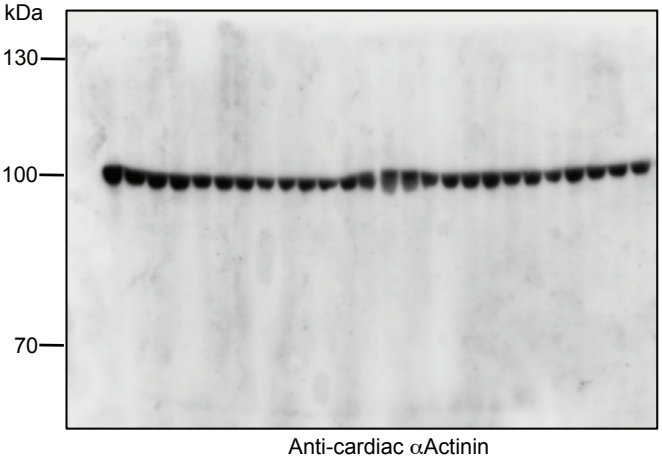
Anti-SF3B1



Anti-KHK-A/C

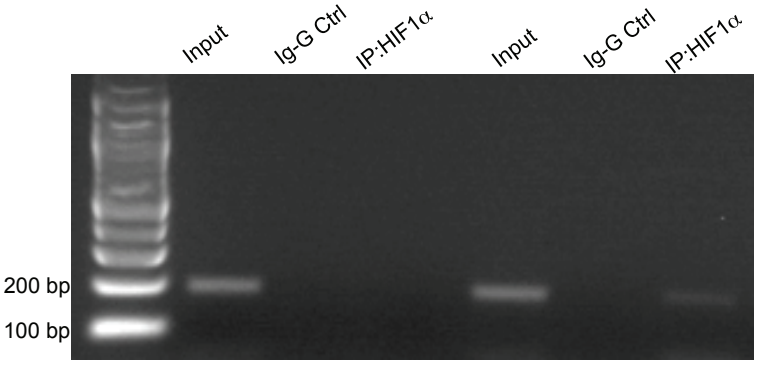


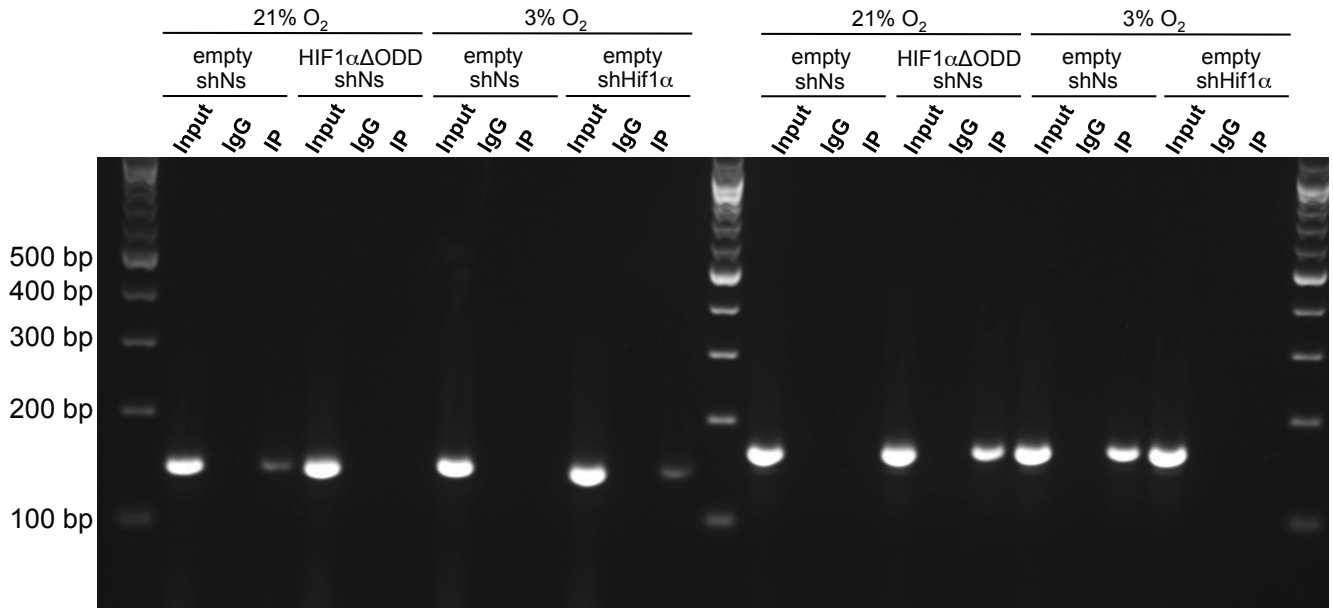
Anti-KHK-C



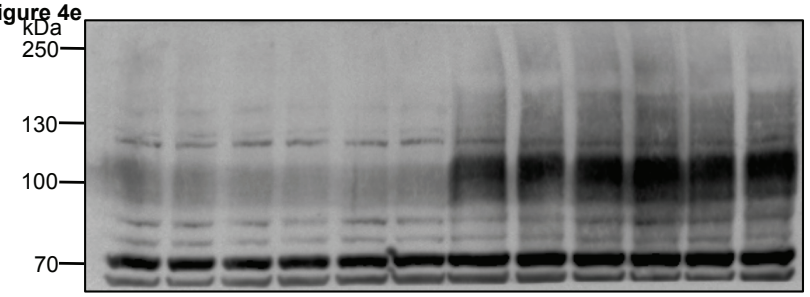
Anti-cardiac αActinin

ChIP Fig. 2b


Input
Ig-G Ctrl
IP:HIF1α
Input
Ig-G Ctrl
IP:HIF1α
200 bp
100 bp


21% O2
3% O2
21% O2
3% O2
empty shNs
HIF1αΔODD shNs
empty shNs
empty shHif1α
empty shNs
HIF1αΔODD shNs
empty shNs
empty shHif1α
Input
IgG
IP
500 bp
400 bp
300 bp
200 bp
100 bp

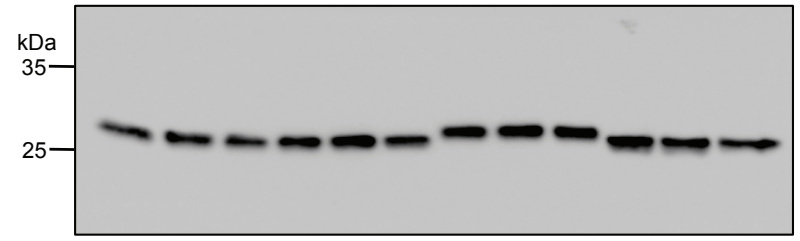
Immunoblots Figure 4e



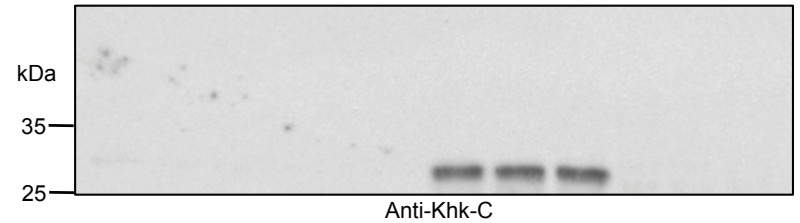
Anti-Hif1α

Anti-Sf3b1

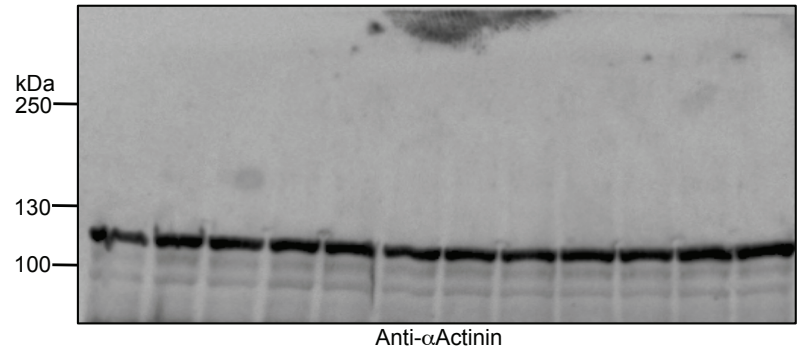
Anti-GFP



Anti-Khk-A/C

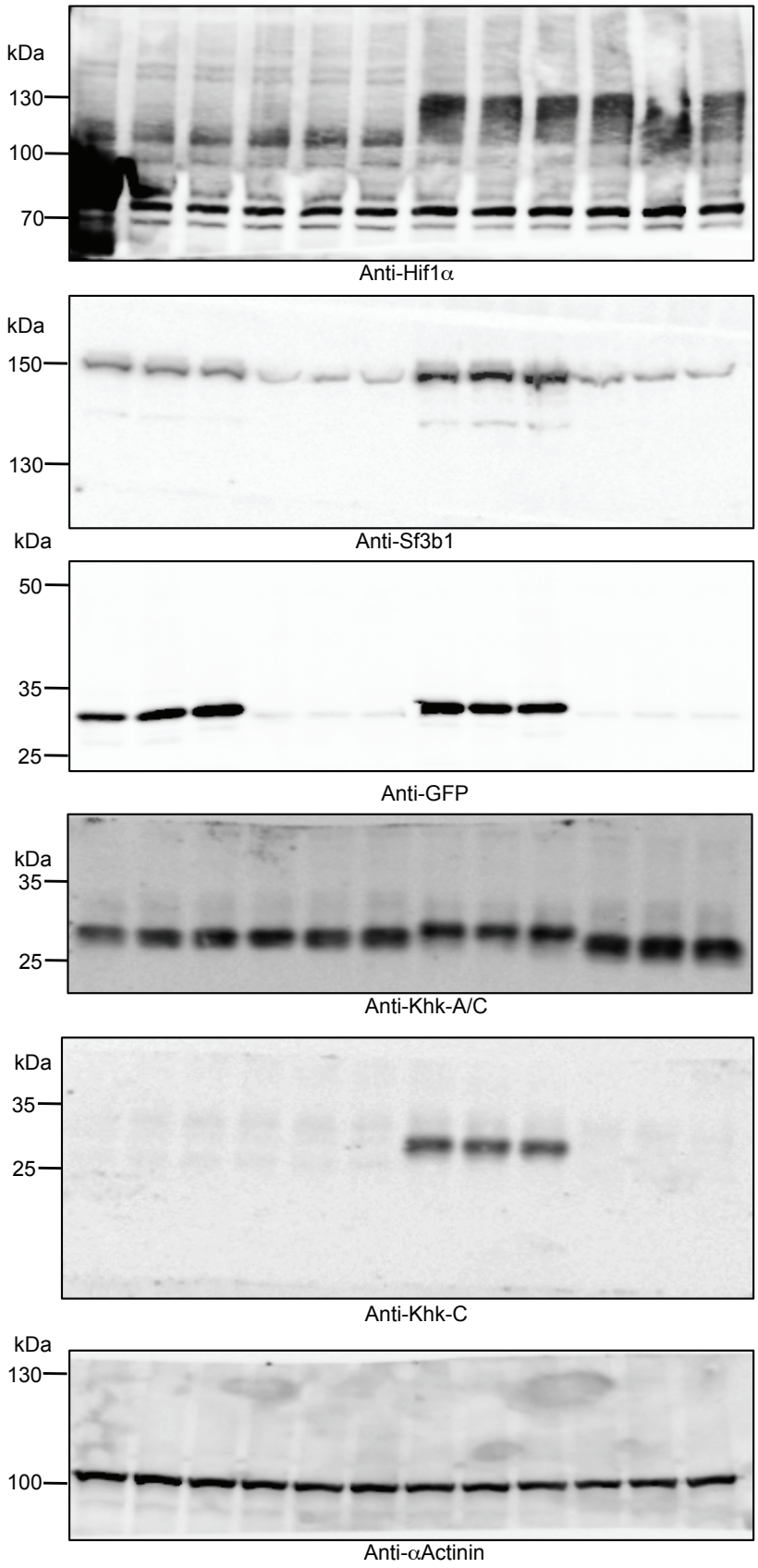


Anti-Khk-C

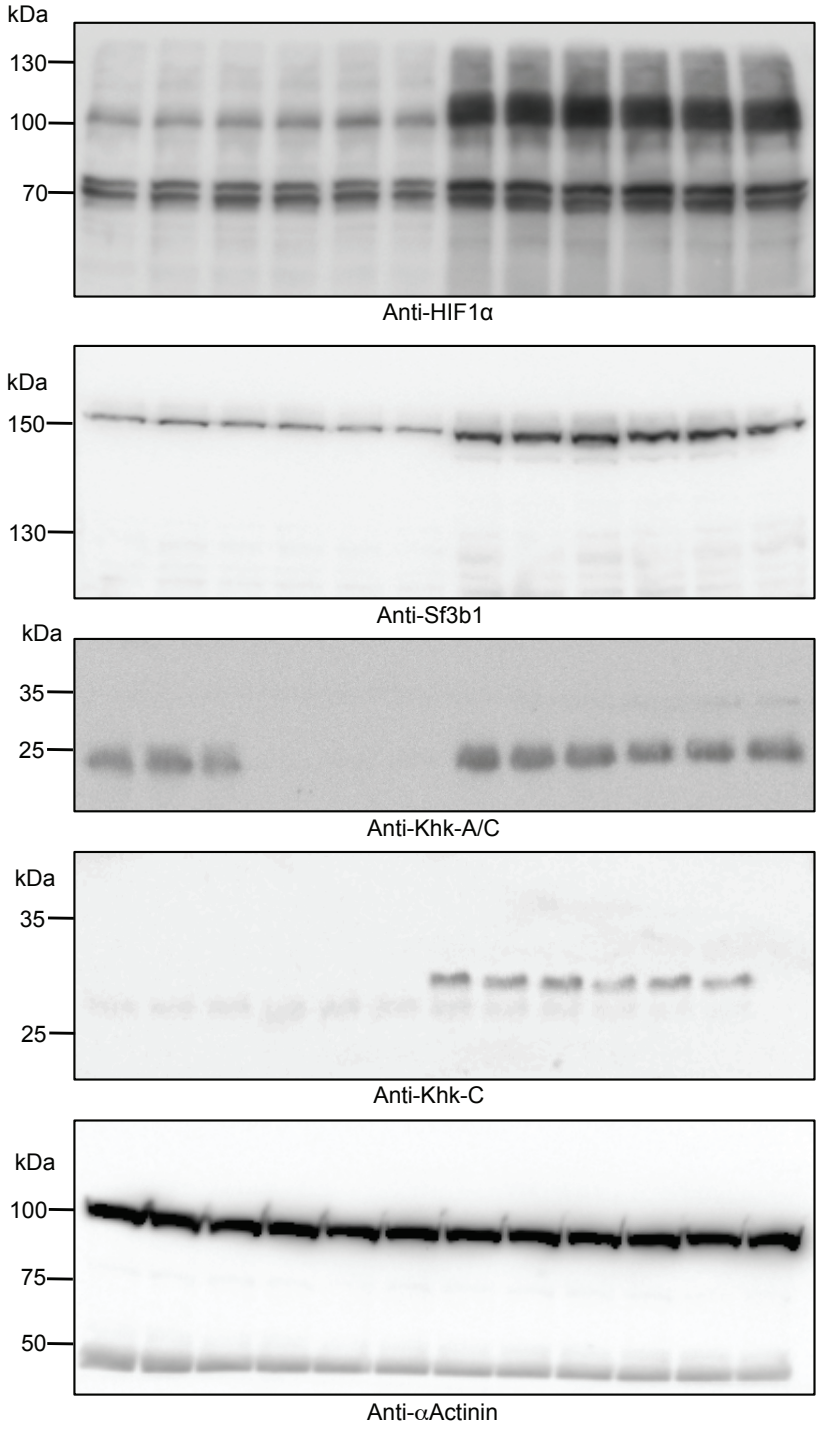


Anti-αActinin

Immunoblots Figure 4h



Immunoblots Figure 5d



Immunoblots Figure 5h