

1 **The effects of liraglutide and dapagliflozin on cardiac function and structure in a multi-hit**  
2 **mouse model of Heart Failure with Preserved Ejection Fraction**

3  
4 Coenraad Withaar<sup>1</sup>, Laura M.G. Meems<sup>1</sup>, George Markousis-Mavrogenis<sup>1</sup>, Cornelis J. Boogerd<sup>3</sup>,  
5 Herman H.W. Silljé<sup>1</sup>, E. Marloes Schouten<sup>1</sup>, Martin M. Dokter<sup>1</sup>, Adriaan A. Voors<sup>1</sup>, B. Daan  
6 Westenbrink<sup>1</sup>, Carolyn S.P. Lam<sup>2</sup>, Rudolf A. de Boer<sup>1</sup>

7  
8  
9 <sup>1</sup>Department of Cardiology, University Medical Center Groningen, University of Groningen, The  
10 Netherlands

11 <sup>2</sup>National University Heart Centre, Singapore

12 <sup>3</sup>Hubrecht Institute, Royal Netherlands Academy of Arts and Sciences and University Medical  
13 Center Utrecht, The Netherlands.

14  
15  
16 Short title: Liraglutide and dapagliflozin in a HFpEF mouse model

17  
18  
19  
20  
21 Corresponding author:

22 Prof. dr. R.A. de Boer

23 Department of Cardiology, University Medical Center Groningen

24 University of Groningen

25 Hanzeplein 1, 9713 GZ Groningen, The Netherlands

26 P.O. Box 30.001, 9700 RB Groningen, The Netherlands

27 Phone: +31-50-3612355 / +31-50-3615340

28 Fax: +31-50-3611347

29  
30 E-mail:

31 [r.a.de.boer@umcg.nl](mailto:r.a.de.boer@umcg.nl)

32  
33  
34  
35 **SUPPLEMENTARY DATA**  
36

	CTRL	HFD	CTRL+ ANGII	HFD+ ANGII
<b>Echocardiographic parameters</b>	n=9	n=8	n=7	n=11
FS (%)	32.7 ± 1.9	31.8 ± 2.7	28.3 ± 1.7	30.0 ± 2.2
EF (%)	61.2 ± 3.1	59.4 ± 3.7	59.4 ± 2.5	56.9 ± 2.9
LVIDs (mm)	2.6 ± 0.1	3.0 ± 0.2	2.7 ± 0.2	3.0 ± 0.1
LVIDd (mm)	4.0 ± 0.1	4.4 ± 0.1	3.7 ± 0.2	4.2 ± 0.1
LVPWs (mm)	1.4 ± 0.1	1.6 ± 0.0	1.5 ± 0.2	1.8 ± 0.1*
LVPWd (mm)	1.0 ± 0.1	1.14 ± 0.1	1.2 ± 0.2	1.3 ± 0.1*
LVAWs (mm)	1.4 ± 0.1	1.7 ± 0.1	1.8 ± 0.1*	1.8 ± 0.1*
LVAWd (mm)	1.0 ± 0.0	1.3 ± 0.1*	1.3 ± 0.1*	1.4 ± 0.1*
HR (bpm)	406 ± 11.4	429 ± 14.1	418 ± 18.4	406 ± 14.9
CO (L/min)	17.5 ± 2.0	22.6 ± 2.0	15.3 ± 1.5	18.1 ± 1.2
GLS	-21.4 ± 1.1	-17.9 ± 1.2	-16.9 ± 0.8*	-14.1 ± 0.6*
RPLSR	10.7 ± 0.8	9.4 ± 0.8	7.9 ± 0.9	7.5 ± 0.7*
<b>Aortic catheterization</b>	n=9	n=9	n=5	n=9
Pmax aorta	105 ± 2.1	117 ± 4.0*	120 ± 5.3*	128 ± 5.9*
Pmin aorta	66 ± 2.3	76 ± 3.0	79 ± 6.2	73 ± 6.6
Pmean aorta	84 ± 2.3	96 ± 3.3	99 ± 5.9	97 ± 6.5

38 **Supplemental table 1. Echocardiographic parameters and aortic catheterization**

39 FS = fractional shortening. EF = Ejection fraction. LVIDs = Left ventricular internal diameter in systole LVIDd = Left  
40 ventricular internal diameter in diastole. LVPWs = Left ventricular posterior wall thickness in systole. LVPWd = Left  
41 ventricular posterior wall thickness in diastole. LVAWs = Left ventricular anterior wall thickness in systole; LVAWd =  
42 Left ventricular anterior wall thickness in diastole. HR = Heart rate. CO = cardiac output. GLS = global longitudinal  
43 strain as marker of myocardial deformation RPLSR = Quantification of reverse peak longitudinal strain rate (RPLSR)  
44 as marker of diastolic function. Pmax = maximal aortic pressure. Pmin = minimal aortic pressure. Pmean = average  
45 aortic pressure.

46 CTRL = control chow. HFD = high fat diet. CTRL+ANGII = Angiotensin-II treated group on control chow. HFD+ANGII =  
47 Angiotensin-II treated group on high fat diet. Kruskal Wallis test followed by Mann-Witney-U. \* compared to CTRL.  
48 † compared to HFD. Data are presented as means ± standard error of the mean

49

	HFD+	HFD+	HFD+
	ANGII+	ANGII+	ANGII+
	SALINE	LIRA	DAPA
<b>A) Echocardiographic parameters</b>	n=13	n=13	n=13
FS (%)	29.8±2.4	36.3±2.6	31.4±1.8
EF (%)	61.3±2.7	65.8±3.3	59.6±2.6
LVIDs (mm)	2.5±0.1	2.3±0.2	2.6±0.2
LVIDd (mm)	3.7±0.1	3.5±0.1	3.7±0.2
LVPWs (mm)	1.9±0.1	1.7±0.1	1.7±0.1
LVPWd (mm)	1.5±0.1	1.2±0.1*	1.3±0.1
LVAWs (mm)	1.7±0.1	1.5±0.1*	1.8±0.1
LVAWd (mm)	1.3±0.03	1.1±0.1*	1.3±0.0
HR (bpm)	418±12.5	413±23.5	428±12.8
CO (L/min)	14.0±1.1	13.9±1.0	15.2±1.6
	n=10	n=9	n=13
GLS (%)	-15.8±0.6	-18.9±1.2*	-18.1±0.8*
RPLSR (1/s)	8.1±0.5	8.7±0.8	9.6±0.9
<b>B) Organ weights</b>	n=14	n=13	n=13
HW/tibia length (mg/mm)	9.9±0.3	8.4±0.3*	10.8±0.6
LV/tibia length (mg/mm)	8.1±0.3	6.6±0.2*	8.6±0.4
RV/tibia length (mg/mm)	1.4±0.1	1.3±0.1	1.6±0.1
Atria/tibia length (mg/mm)	0.6±0.0	0.4±0.0*	0.7±0.1
Lung/tibia length (mg/mm)	12.6±0.5	10.8±0.3*	13.2±0.7

51

52 **Supplemental table 2. Echocardiographic parameters and organ weights.**

53 **A) Echocardiographic parameters.** FS = fractional shortening. EF = ejection fraction. LVIDs = left ventricular internal  
54 diameter in systole LVIDd = Left ventricular internal diameter in diastole. LVPWs = Left ventricular posterior wall  
55 thickness in systole. LVPWd = Left ventricular posterior wall thickness in diastole. LVAWs = Left ventricular anterior  
56 wall thickness in systole. LVAWd = Left ventricular anterior wall thickness in diastole. HR = Heart rate. CO = Cardiac  
57 output. GLS = global longitudinal strain as marker of myocardial deformation. RPLSR = Quantification of reverse  
58 peak longitudinal strain rate (RPLSR) as marker of diastolic function.

59 **B) Organ weights.** HW = total heart weight. LV = Left ventricle. RV=right ventricle. All weights are corrected for tibia  
60 length.

61 HFD+ANGII+Lira = high fat diet + Angiotensin-II with daily liraglutide injection. HFD+ANGII+Dapa = high fat diet +  
62 Angiotensin-II with dapagliflozin treatment. Data are means ± standard error of the mean. \* = P<0.05 is considered  
63 significant compared to HFD+ANGII+Saline.

64

<b>Gene</b>	<b>Protein</b>	<b>5' - 3' forward</b>	<b>5' - 3' reverse</b>
<i>Nppa</i>	ANP	ATGGGCTCCTTCTCCATCAC	TCTACCGGCATCTTCTCCTC
<i>TIMP-1</i>	TIMP-1	CTGCTCAGCAAAGAGCTTTC	CTCCAGTTTGCAAGGGATAG
<i>Col1a1</i>	Col1a1	CTTCACCTACAGCACCCCTTGTG	CTTGGTGGTTTTGTATTCGATGAC
<i>Col3a1</i>	Col3a1	GCGATTCAAGGCTGAAG	GGGTGCGATATCTATGATGG
<i>Il-6</i>	IL-6	TCCCAACAGACCTGTCTATAC	CAGAATTGCCATTGCACAACCTC
<i>HAVCR1</i>	KIM-1	AAACCAGAGATTCCCACACG	GTCGTGGGTCTTCTGTAGC
<i>CLU</i>	Clusterin	GAAGATGAACGGGCCAGTGTG	TACTGCTCTGTCAGCCTCTC
<i>Rplp0</i>	36B4	AAGCGCGTCCTGGCATTGTC	GCAGCCGCAAATGCAGATGG

66 **Supplemental table 3. List of primers used in this study.**

Full name	protein	Uniprot code
Amlyloid beta A4 precursor protein-binding family B member, 1-interacting protein (Apbb1ip) Q8R5A3	apbb1ip	Q8R5A3
Appetite-regulating hormone (Ghr1) Q9EQX0	Ghr1	Q9EQX0
Aryl hydrocarbon receptor (Ahr) P30561	Ahr	P30561
Axin-1 (Axin1) O35625	Axin1	O35625
C-C motif chemokine 2 (Ccl2) P10148	Ccl2	P10148
C-C motif chemokine 20 (Ccl20) O89093	Ccl20	O89093
C-C motif chemokine 3 (Ccl3) P10855	Ccl3	P10855
C-C motif chemokine 5 (Ccl5) P30882	Ccl5	P30882
C-X-C motif chemokine 9 (Cxcl9) P18340	Cxcl9	P18340
Cadherin-6 (Cdh6) P97326	Cdh6	P97326
Calsynenin-2 (Clstn2) Q9ER65	Clstn2	Q9ER65
Carbonic anhydrase 13 (Ca13) Q9D6N1	Ca13	Q9D6N1
Carboxypeptidase E (Cpe) Q00493	Cpe	Q00493
Caspase-3 (Casp3) P70677	Casp3	P70677
Contactin-1 (Cntn1) P12960	Cntn1	P12960
Contactin-4 (Cntn4) Q69226	Cntn4	Q69226
CXADR-like membrane protein (Clmp) Q8R373	Clmp	Q8R373
Cysteine-rich motor neuron 1 protein (Crim1) Q9JL10	Crim1	Q9JL10
Cytosolic phospholipase A2 (Pla2g4a) P47713	Pla2g4a	P47713
Delta-like protein 1 (Dll1) Q61483	Dll1	Q61483
Dihydropteridine reductase (Qdpr) Q8BV14	Qdpr	Q8BV14
Disintegrin and metalloproteinase domain-containing protein 23 (Adam23) Q9R1V7	Adam23	Q9R1V7
Dual specificity mitogen-activated protein kinase kinase 6 (Map2k6) P70236	Map2k6	P70236
Dynactin subunit 2 (Dctn2) Q99KJ8	Dctn2	Q99KJ8
Epithelial cell adhesion molecule (Epcam) Q99JWS	Epcam	Q99JWS
Erythropoietin (Epo) P07321	Epo	P07321
Follistatin (Fst) P47931	Fst	P47931
Follistatin-related protein 3 (Fstl3) Q9EQC7	Fstl3	Q9EQC7
Forkhead box protein O1 (Foxo1) Q9R1E0	Foxo1	Q9R1E0
Friend leukemia integration 1 transcription factor (Flil1) P26323	Flil1	P26323
Gamma-enolase (Eno2) P17183	Eno2	P17183
GDNF family receptor alpha-1 (Gfra1) P97785	Gfra1	P97785
Glial cell line-derived neurotrophic factor (Gdnf) P48540	Gdnf	P48540
Glucagon (Gcg) P55095	Gcg	P55095
Granulocyte-macrophage colony-stimulating factor (Csf2) P01587	Csf2	P01587
Growth-regulated alpha protein (Cxcl1) P12850	Cxcl1	P12850
Hepatocyte growth factor (Hgf) Q08048	Hgf	Q08048
Immunoglobulin superfamily member 3 (Igsf3) Q6ZQA6	Igsf3	Q6ZQA6
Integrin beta-1-binding protein 2 (Itgb1bp2) Q9R000	Itgb1bp2	Q9R000
Integrin beta-6 (Itgb6) Q9Z0T9	Itgb6	Q9Z0T9
Interleukin-1 alpha (Il1a) P01582	Il1a	P01582
Interleukin-1 beta (Il1b) P10749	Il1b	P10749
Interleukin-10 (Il10) P18893	Il10	P18893
Interleukin-17A (Il17a) Q62386	Il17a	Q62386
Interleukin-17F (Il17f) Q7TNI7	Il17f	Q7TNI7
Interleukin-23 receptor (Il23r) Q8K4B4	Il23r	Q8K4B4
Interleukin-5 (Il5) P04401	Il5	P04401
Interleukin-6 (Il6) P08505	Il6	P08505
Kit ligand (Kitlg) P20826	Kitlg	P20826
Legumain (Lgmn) O89017	Lgmn	O89017
Leucine-rich repeat transmembrane protein FLRT2 (Flrt2) Q8BLUO	Flrt2	Q8BLUO
Lipoprotein lipase (Lpl) P11152	Lpl	P11152
Matrilin-2 (Matn2) O08746	Matn2	O08746
Melanoma-derived growth regulatory protein (Mia) Q61865	Mia	Q61865
N(G),N(G)-dimethylarginine dimethylaminohydrolase 1 (Odah1) Q9CWS0	ddah1	Q9CWS0
NAD kinase (Nadk) P58058	Nadk	P58058
Neurogenic locus notch homolog protein 3 (Notch3) Q61982	Notch3	Q61982
Neurotrophin-3 (Ntf3) P20181	Ntf3	P20181
Perilipin-1 (Plin1) Q8CGN5	Plin1	Q8CGN5
Peroxisredoxin-5, mitochondrial (Prdx5) P99029	Prdx5	P99029
Platelet-derived growth factor subunit B (Pdgfb) P31240	Pdgfb	P31240
Plexin-A4 (Plxna4) Q80UG2	Plxna4	Q80UG2
Poly [ADP-ribose] polymerase 1 (Parp1) P11103	Parp1	P11103
Protein CYR61 (Cyr61) P18406	Cyr61	P18406
Protein delta homolog 1 (Dlk1) Q09163	Dlk1	Q09163
Protein phosphatase inhibitor 2 (Ppp1r2) Q9DCL8	Ppp1r2	Q9DCL8
Protein S100-A4 (S100a4) P07091	S100a4	P07091
Protransforming growth factor alpha (Tgfa) P48030	Tgfa	P48030
Receptor tyrosine-protein kinase erbB-4 (Erbb4) Q61527	Erbb4	Q61527
Repulsive guidance molecule A (Rgma) Q6PCX7	Rgma	Q6PCX7
Ribosomal oxygenase 2 (Riox2) Q8CD15	Riox2	Q8CD15
Seizure 6-like protein 2 (Sez6l2) Q4V9Z5	Sez6l2	Q4V9Z5
Serine/threonine-protein kinase PAK 4 (Pak4) Q8BTW9	Pak4	Q8BTW9
Serine/threonine-protein kinase receptor R3 (Acvr1) Q61288	Acvr1	Q61288
Soluble calcium-activated nucleotidase 1 (Cant1) Q8VCF1	Cant1	Q8VCF1
Synaptosomal-associated protein 29 (Snap29) Q9ERB0	Snap29	Q9ERB0
Tenascin-R (Tnr) Q8BYI9	Tnr	Q8BYI9
Transforming growth factor beta receptor type 3 (Tgfb3) O88393	Tgfb3	O88393
Latency-associated peptide transforming growth factor beta-1 (Tgfb1) P04202	Tgfb1	P04202
Tripeptidyl-peptidase 1 (Tpp1) O89023	Tpp1	O89023
Troponin I, cardiac muscle (Tnni3) P48787	Tnni3	P48787
Tumor necrosis factor (Tnf) P06804	Tnf	P06804
Tumor necrosis factor ligand superfamily member 12 (Tnfsf12) O54907	Tnfsf12	O54907
Tumor necrosis factor receptor superfamily member 11B (Tnfrsf11b) O08712	Tnfrsf11b	O08712
Tumor necrosis factor receptor superfamily member 12A (Tnfrsf12a) Q9CR75	Tnfrsf12a	Q9CR75
Tumor necrosis factor receptor superfamily member 27 (Eda2r) Q8BX35	Eda2r	Q8BX35
Tumor necrosis factor receptor superfamily member 6 (Fas) P25446	Fas	P25446
Tyrosine-protein kinase Yes (Yes1) Q04736	Yes1	Q04736
V-set and immunoglobulin domain-containing protein 2 (Vsig2) Q9Z109	Vsig2	Q9Z109
Vascular endothelial growth factor D (Vegfd) P97946	Vegfd	P97946
WAP, Kazal, immunoglobulin, Kunitz and NTR domain-containing protein 2 (Wfikkn2) Q7TQN3	Wfikkn2	Q7TQN3
WNT1-inducible-signaling pathway protein 1 (Wisp1) O54775	Wisp1	O54775

Pathway	padj	NES	leadEdge
GO_EXTRACELLULAR_STRUCTURE_ORGANIZATION	<0.001	2,81	COL6A3, COL5A2, COL8A1, COL12A1, COL1A2, BGN, SPARC, MFAP5, COL4A1, COL4A2, COL1A1, TGFB2, COL5A1, COL6A2, COL16A1, VCAN, LOXL1, LOXL2, COL3A1, SULF1, POSTN, LAMC1, LOX, LTBP2, TNC, COL6A1, ITGA9, ADAMTS2, LUM, MFAP4, ELN, ADAMTS12, ITGB5, TIMP1, TGFB1, ANXA2, CAPG, COL4A4, FN1, LAMA2, MMP2, COL4A3, NID1, CD44, ITGB1, GPM6B, SPP1, ITGA6, COL4A5, ADAMTS5, ITGAV, LAMB1, CAPN2, APP, ADAM10, COL18A1, DCN, COMP, DDR2, CTSK, P4HA1, HSPG2, LAMA3, TNFRSF11B, ATXN1L, MMP14, RIPK1, HSD17B12, SERPINE1, CCDC80, PTK2, KDR, ACAN, ITGA5, FBLN5, ADAMTS20,
GO_COLLAGEN_FIBRIL_ORGANIZATION	<0.001	2,53	COL5A2, COL12A1, COL1A2, COL1A1, TGFB2, COL5A1, LOXL2, COL3A1, LOX, ADAMTS2, LUM, TGFB1, ANXA2, DDR2, P4HA1, CYP1B1, NF1, SFRP2, ATP7A
GO_MULTICELLULAR_ORGANISMAL_MACROMOLECULE_METABOLIC_PROCESS	<0.001	2,53	COL6A3, COL5A2, COL8A1, COL12A1, COL1A2, COL4A1, COL4A2, COL1A1, COL5A1, COL6A2, ACE, COL3A1, COL6A1, ADAMTS2, COL15A1, COL4A4, MMP2, COL4A3, COL4A5, COL18A1, CTSK, MMP14, HIF1A, COL8A2, CTSK, ADAM15
GO_MULTICELLULAR_ORGANISM_METABOLIC_PROCESS	<0.001	2,42	COL6A3, COL5A2, COL8A1, COL12A1, COL1A2, COL4A1, COL4A2, COL1A1, COL5A1, COL6A2, ACE, COL3A1, CLIC5, COL6A1, ADAMTS2, COL15A1, COL4A4, MMP2, COL4A3, COL4A5, COL18A1, CTSK, MMP14, HIF1A, COL8A2, CTSK, TRPV4, ADAM15
GO_CELLULAR_RESPONSE_TO_AMINO_ACID_STIMULUS	<0.001	2,34	COL5A2, COL1A2, COL4A1, COL1A1, COL16A1, COL3A1, COL6A1, MMP2, ZEB1, CAPN2, UBR1, HMGCS2, CPEB1, PDGFC, IPO5, EGFR, CPEB4
GO_CYTOSKELETON_DEPENDENT_CYTOKINESIS	<0.001	2,20	MYH10, APC, SPIRE1, RACGAP1, ANLN, ZNF365, KIF20A, CEP55, SPTBN1, ANK3, CKAP2, KIF4A, ACTR3, SPAST, USP8, ACTR2, RHOA, RASA1, AURKB, SNX18
GO_CYTOKINESIS	<0.001	2,18	MYH10, RHOC, ROCK2, APC, SPIRE1, RACGAP1, DIAPH2, MYH9, ANLN, ZNF365, BECN1, ECT2, KIF20A, KIF13A, NEK7, PRC1, CEP55, ZFYVE26, SEPT5, SPTBN1, ANK3, CKAP2, KIF4A, ACTR3, SPAST, USP8, RAB11FIP3, ACTR2, RHOA, RASA1, BIRC5, SEPT7, MAP9, AHCTF1, INCENP, AURKB, SNX18, NEK6
GO_REGULATION_OF_CELL_SUBSTRATE_ADHESION	<0.001	2,16	COL8A1, FBLN2, COL1A1, COL16A1, POSTN, ROCK2, FN1, NID1, ITGB1, GPM6B, SFRP1, PTK2B, BCL2, ACTN4, UTRN, FLNA, GSK3B, PTPRJ, PTEN, MMP14, HSD17B12, SERPINE1, CCDC80, JAK2, PTK2, FZD4, KDR, ITGA5, THBS1, EFNAS, DDR1, S100A10, PHLD2, FMN1, MACF1, ARPC2, GCNT2, KANK1, ADAM15, SLK, NF1, FZD7, NF2, RCC2, CD36, CDC42, NINJ1, TBCE, STG6A1, RASA1, CORO1C, ROCK1, SMOCC2, APOD, PLAU, RSU1, NPNT, APOA1, PIK3CB, LGALS1, ARHGEF7
GO_POSITIVE_REGULATION_OF_SMALL_GTPASE_MEDIATED_SIGNAL_TRANSDUCTION	<0.001	2,14	COL3A1, LPAR1, IGF1, F2R, AKAP13, F2RL1, SOS1, CDON, SHOC2, NOTCH2, RASGEF1A, RASGRP1, ABRA, ARRB1, ALS2, ROBO1, KITLG
GO_TISSUE_MIGRATION	<0.001	2,13	LOXL2, ACTA1, TGFB1, PTPN11, ITGB1, PTK2B, ZEB2, ARSB, PTEN, PKN1, MYH9, ANLN, PTK2, KDR, AMOT, CYP1B1, PKN3, SOX18, FGF2, PIK3CA, NANOS1, ROBO1, RHOA, PKN2, ACTG2, GPX1, APOA1
GO_TISSUE_REMODELING	<0.001	2,12	BGN, TGFB2, ACE, THBS4, TGFB3, ANXA1, F2R, PTK2B, NOX4, SEMA3C, LIPA, IGFBP5, CTSK, MMP14, JAG1, AXL, CSPG4, MEFC2, BMP2, HIF1A, NOTCH2, IL6, ATP7A, UF, CCR2, CTHRC1, BAK1, MDM2, TGFB1, LGR4
GO_MITOTIC_CYTOKINESIS	<0.001	2,11	MYH10, APC, RACGAP1, ANLN, ZNF365, KIF20A, CEP55, SPTBN1, ANK3, CKAP2, KIF4A, SPAST, USP8, RHOA, RASA1
GO_ENDODERM_DEVELOPMENT	<0.001	2,10	COL8A1, COL12A1, COL4A2, LAMC1, COL6A1, ITGB5, FN1, MMP2, ITGAV, LAMB1, EXT1, BMP1A, INHBA, LAMA3, SMAD4, TBX20, MMP14, ITGA5, ARC, BPTF, DUSP4
GO_RESPONSE_TO_TRANSFORMING_GROWTH_FACTOR_BETA	<0.001	2,10	COL1A2, COL4A2, COL1A1, TGFB2, COL3A1, STAR, POSTN, LTBP2, TGFB3, ANKRD1, ITGB5, ADAM9, TGFB1, CBL, SKIL, BAMBI, FN1, ITGB1, HIPK2, GDF15, SFRP1, NOX4, USP9X, CX3CR1, BMP1A, SMAD4, PTK2, MEFC2, MAP3K7, ACVR1, GCNT2, SOX9, FYN, USP15, KLF10, FKBP1A, TGFB2
GO_HEAD_MORPHOGENESIS	<0.001	2,09	COL1A1, TGFB2, TGFB3, PTPN11, MMP2, ARID5B, RAB3GAP1, PLEKHA1, NIPBL, CRISPLD1, ANKRD11, ASPH, RRAS, TGFB1, CRISPLD2, SGPL1, LRP6
GO_AMINOGLYCAN_CATABOLIC_PROCESS	<0.001	2,09	BGN, VCAN, SDC2, LUM, PRELP, CD44, DCN, HMMR, HSPG2, ARSB, GALNS, ACAN, CSPG4, FGF2, GPC6, IDS, TGFB1, CHI3L1, SDC3, SDC1, CTBS, CHID1, HYAL2, HEXB, FMOD, GUSB
GO_CELL_GROWTH	<0.001	2,08	EMP1, TGFB2, POSTN, SORBS2, TGFB3, ACTA1, NUPR1, MTPN, IQGAP1, ITGB1, SEMA3F, MTOR, ITGAV, USP9X, APP, BCL2, SPG11, ULK2, MAP1B, PDLIM5, ZEB2, RAPH1, EMP3, DCLK1, EFNAS, SEC61A1, CYFIP1, SOCS5, NOTCH2, DGDK, NPPA, SOX9, IL6, SEMA7A, NRP2, MEX3C, TGFB2, XRN2, TYMS, NOP58, SLIT3, SLC9A6, TGFB1
GO_CELL_JUNCTION_ORGANIZATION	<0.001	2,07	XIRP2, TGFB2, FLNC, LAMC1, TGFB3, ACTN1, DST, HEG1, RHOC, FN1, ITGB1, TLN1, APC, ITGA6, PTK2B, MTDH, STRN, PDPK1, BCL2, ACTN4, FLNA, DLG5, CTTN, LAMA3, PRKCA, SORBS1, ITGA5, AMOT, ECT2, MPP7, MPP5, DLG1, TRPV4, FSCN1, HIPK1, CDH4, LAMC2, CDH11, NUMBL, RAB8B, NF2, RCC2, TJP1, CDC42, DSP, THY1, TGFB1, PLEC, CTNND1, TBCE, VAMP1, RHOA, PKN2, CD151, CSF1R, NFASC, SMAD7, CADM3
GO_VASCULATURE_DEVELOPMENT	<0.001	2,07	COL8A1, COL1A2, COL4A1, COL4A2, COL1A1, TGFB2, COL5A1, LOXL1, LOXL2, MYH10, SRPX2, COL3A1, LOX, EREG, SYK, PDGFRA, COL15A1, CALCRL, TGFB1, PKD1, ANXA2, HEG1, PKD2, MFGE8, FN1, MMP2, ITGB1, CD34, LRP1, ITGAV, PTK2B, LUZP1, STK4, COL18A1, UNC5B, SEMA3C, CX3CL1, TNFRSF12A, RAPGEF1, SPHK1, EIF2AK3, HSPG2, TBX20, PTEN, MMP14, JAG1, SERPINE1, SOS1, MYH9, PTK2, FZD4, PRKCA, KDR, MIB1, ANGPTL4,
GO_EPIBOLY	<0.001	2,06	COL5A1, HBEGF, RHOC, FLNA, ITGA5, DDR1, ADAM17, LCP1, MMP12, RHOA
GO_ANGIOGENESIS	<0.001	2,05	COL8A1, COL4A1, COL4A2, TGFB2, LOXL2, SRPX2, EREG, SYK, PDGFRA, COL15A1, CALCRL, TGFB1, ANXA2, MFGE8, FN1, MMP2, ITGB1, CD34, ITGAV, PTK2B, STK4, COL18A1, UNC5B, CX3CL1, TNFRSF12A, EIF2AK3, HSPG2, TBX20, PTEN, MMP14, JAG1, SERPINE1, MYH9, PTK2, PRKCA, KDR, ANGPTL4, ITGA5, CSPG4, MED1, THBS1, CYP1B1, HIF1A, SOX18, COL8A2, THSD7A, FGFR1, FGF2, ACVR1, ARHGAP24, ADAM15, PIK3CA, GNA13, SFRP2, PTPRB, NUS1, NRP2, FMNL3, BAK1, TGFB2, SETD2, CDC42, HMOX1, NAA15, THY1, ROBO1, POFUT1, ECM1, AGGF1, NCL, VEZF1, PARVA, SPI1, C1GALT1, PIK3CG, FGF6, APOD, PLAU,
GO_ENDODERM_FORMATION	<0.001	2,04	COL8A1, COL12A1, COL4A2, COL6A1, ITGB5, FN1, MMP2, ITGAV, LAMB1, INHBA, LAMA3, TBX20, MMP14, ITGA5
GO_INTEGRIN_MEDIATED_SIGNALING_PATHWAY	<0.001	2,03	COL16A1, COL3A1, ITGA9, SYK, ITGB5, ADAM9, DST, PTPN11, ITGB1, NEDD9, ITGA6, ITGAV, PTK2B, ADAM10, DAB2, MYH9, PTK2, ITGA5, ITGB8, ITGA1, ADAM15, SEMA7A
GO_POSITIVE_REGULATION_OF_EPITHELIAL_TO_MESENCHYMAL_TRANSITION	<0.001	2,03	COL1A1, TGFB2, TGFB3, WWTR1, BAMBI, SMAD4, DAB2, SNAI1, GCNT2, SDCBP, TGFB2, TWIST1, TGFB1, BMP2, OLFM1, GLIPR2
GO_SKELETAL_SYSTEM_DEVELOPMENT	<0.001	2,03	COL5A2, COL12A1, COL1A2, SPARC, COL1A1, TGFB2, VCAN, COL3A1, SULF1, POSTN, FRZB, TGFB3, MGP, PDGFRA, LUM, TBX15, TIMP1, TGFB1, PTPN11, PKD1, ANXA2, NRP3, FAM20C, MMP2, ZEB1, PRELP, CD44, IGF1, CREB3L2, GLG1, SFRP1, AKAP13, CMKLR1, PLS3, EXT1, ANO6, COMP, ARID5B, BMP1A, FREM1, EXT1, TRPS1, EIF2AK3, WDR19, RPS6KA3, TNFRSF11B, STC1, MMP14, IMPAD1, FGFR3, SNAI1, PTHLH, PIP4K2A, ACAN, MEFC2,

70 **Supplemental table 5A**

71 Top 25 of enriched GO biological processes of upregulated genes in HFD+ANGII versus CTRL. Padj = P Value adjusted for multiple testing. NES = normalized  
72 enrichment score.

73

74

75

Pathway	padj	NES	leadEdge
GO_OXIDATIVE_PHOSPHORYLATION	0,0030	-3.49	UQCRC1, COX4I1, COX7B, NDUFS6, NDUFB11, NDUFV1, NDUFA9, NDUFS1, NDUFA5, NDUFS7, CYC1, UQCRCQ, COX6G, NDUFB8, NDUFA13, COX7C, UQCRC11, SDHC, NDUFB10, NDUFA6, NDUFS2, NDUFB9, UQCRCF51, COX8C, NDUFS3, NDUFB6, NDUFA11, NDUFA12, DLD, UQCRC2, NDUFA8, NDUFB7, COX5B, TAZ, UQCRCR, UQCRCR, COX6B1, NDUFV2, SURF1, COQ9, NDUFS8, NDUFA7, NDUFA4, UQCRCB, NDUFB5, NDUFA2, UQCRC10, NDUFS4, NDUFV3, AK2, NDUFC1.
GO_CELLULAR_RESPIRATION	0,0030	-3.48	SDHA, IDH3B, SUCLG2, UQCRC1, COX4I1, PINK1, COX7B, FH, NDUFS6, ETFA, ETFB, ALDH5A1, NDUFB11, NDUFV1, NDUFA9, NDUFS1, NDUFA5, NDUFS7, CYC1, UQCRCQ, IDH2, COX6G, OXA1L, NDUFB8, NDUFA13, COX7C, UQCRC11, SDHC, NDUFB10, NDUFA6, NDUFS2, MDH1, NDUFB9, SDHB, UQCRCF51, COX8C, MDH2, NDUFS3, NDUFB6, IDH3G, CS, NDUFA1, NDUFA12, DLD, UQCRC2, NDUFA10, SDHD, NDUFA8, SUCLG1, NNT, ME3, NDUFB7, COX5B, TAZ, UQCRCR, UQCRCR, COX6B1, NDUFV2, SURF1, COQ9, SIRT3, NDUFS8, OGDH, NDUFA7, NDUFA4, UQCRCB, NDUFB5, NDUFA2, UQCRC10, NDUFS4, NDUFV3, NDUFC1, NDUFC2-KCTD14, NDUFC2, NDUFB2, NDUFA1, NDUFA11, NDUFA12, NDUFA10, AIFM1, NDUFA8, NDUFB7, TAZ, NDUFV2, NDUFS8, NDUFA7, UQCRCB, NDUFB5, NDUFA2, UQCRC10, NDUFS4, NDUFV3, NDUFC1, NDUFC2, NDUFB2, NDUFA1, NDUFA11, IMMPL1, NDUFA3, FOXRED1, NDUFB4, BCS1L, NDUFAF3, NDUFS5, NDUFAF4
GO_ELECTRON_TRANSPORT_CHAIN	0,0030	-3.40	SDHA, UQCRC1, COX4I1, PINK1, COX7B, NDUFS6, ETFA, ETFB, ALDH5A1, NDUFB11, NDUFV1, NDUFA9, NDUFS1, NDUFA5, NDUFS7, CYC1, UQCRCQ, COX6G, NDUFB8, NDUFA13, COX7C, UQCRC11, SDHC, NDUFB10, NDUFA6, NDUFS2, NDUFB9, SDHB, UQCRCF51, COX8C, MDH2, NDUFS3, NDUFB6, IDH3G, CS, NDUFA1, NDUFA12, DLD, UQCRC2, NDUFA10, SDHD, NDUFA8, SUCLG1, NNT, ME3, NDUFB7, COX5B, TAZ, GNMT, UQCRCR, UQCRCR, COX6B1, NDUFV2, SURF1, COQ9, SIRT3, NDUFS8, OGDH, NDUFA7, NDUFA4, UQCRCB, AKT2, NDUFB5, PPP1CA, NDUFA2, UQCRC10, NDUFS4, NDUFV3, NDUFC1, NDUFC2-KCTD14, NDUFC2, NDUFB2, NDUFA1, COX10, NDUFA11
GO_ENERGY_DERIVATION_BY_OXIDATION_OF_ORGANIC_COMPOUNDS	0,0030	-3.12	SDHA, IDH3B, PFKM, SUCLG2, UQCRC1, COX4I1, PINK1, COX7B, AKT1, FH, NDUFS6, ETFA, ETFB, ALDH5A1, NDUFB11, NDUFV1, PYGM, NDUFA9, NDUFS1, NDUFA5, NDUFS7, CYC1, UQCRCQ, IDH2, COX6G, OXA1L, NDUFB8, NDUFA13, COX7C, UQCRC11, SDHC, NDUFB10, NDUFA6, NDUFS2, MDH1, NDUFB9, SDHB, UQCRCF51, COX8C, MDH2, NDUFS3, NDUFB6, IDH3G, CS, NDUFA1, NDUFA12, DLD, UQCRC2, NDUFA10, SDHD, NDUFA8, SUCLG1, NNT, ME3, NDUFB7, COX5B, TAZ, GNMT, UQCRCR, UQCRCR, COX6B1, NDUFV2, SURF1, COQ9, SIRT3, NDUFS8, OGDH, NDUFA7, NDUFA4, UQCRCB, AKT2, NDUFB5, PPP1CA, NDUFA2, UQCRC10, NDUFS4, NDUFV3, NDUFC1, NDUFC2-KCTD14, NDUFC2, NDUFB2, NDUFA1, NDUFA11, IMMPL1, NDUFA3, FOXRED1, NDUFB4, BCS1L, NDUFAF3, NDUFS5, NDUFAF4
GO_MITOCHONDRIAL_RESPIRATORY_CHAIN_COMPLEX_I_BIOGENESIS	0,0030	-3.07	NDUFS6, NDUFB11, NDUFV1, NDUFA9, NDUFS1, NDUFA5, NDUFS7, OXA1L, NDUFB8, NDUFA13, EC5IT, NDUFB10, NDUFA6, NDUFS2, NDUFB9, NDUFS3, NDUFB6, NDUFA1, NDUFA12, NDUFA10, AIFM1, NDUFA8, NDUFB7, TAZ, NDUFV2, NDUFS8, NDUFA7, UQCRCB, NDUFB5, NDUFA2, UQCRC10, NDUFS4, NDUFV3, NDUFC1, NDUFC2, NDUFB2, NDUFA1, NDUFA11, IMMPL1, NDUFA3, FOXRED1, NDUFB4, BCS1L, NDUFAF3, NDUFS5, NDUFAF4
GO_MITOCHONDRIAL_RESPIRATORY_CHAIN_COMPLEX_ASSEMBLY	0,0030	-3.05	NDUFS6, NDUFB11, NDUFV1, NDUFA9, NDUFS1, NDUFA5, SAMM50, NDUFS7, OXA1L, NDUFB8, NDUFA13, EC5IT, NDUFB10, NDUFA6, NDUFS2, NDUFB9, NDUFS3, NDUFB6, NDUFA1, NDUFA12, NDUFA10, AIFM1, NDUFA8, NDUFB7, TAZ, NDUFV2, NDUFS8, NDUFA7, UQCRCB, NDUFB5, NDUFA2, UQCRC10, NDUFS4, NDUFV3, NDUFC1, NDUFC2, NDUFB2, NDUFA1, NDUFA11, IMMPL1, NDUFA3, FOXRED1, NDUFB4, BCS1L, NDUFAF3, NDUFS5, IMMPL2L, SDHAF1, NDUFAF4
GO_GENERATION_OF_PRECURSOR_METABOLITES_AND_ENERGY	0,0030	-2.99	ENO3, SDHA, IDH3B, PFKM, SUCLG2, UQCRC1, COX4I1, PINK1, COX7B, AKT1, SLC25A3, FH, NDUFS6, ETFA, ETFB, ALDH5A1, NDUFB11, NDUFV1, PYGM, NDUFA9, NDUFS1, NDUFA5, NDUFS7, CYC1, UQCRCQ, IDH2, PKFBF1, COX6G, OXA1L, NDUFB8, NDUFA13, COX7C, UQCRC11, SDHC, NDUFB10, NDUFA6, NDUFS2, MDH1, NDUFB9, SDHB, UQCRCF51, COX8C, MDH2, NDUFS3, NDUFB6, IDH3G, CS, NDUFA1, SLC25A4, NDUFA12, DLD, UQCRC2, NDUFA10, SDHD, NDUFA8, SUCLG1, NNT, ME3, NDUFB7, COX5B, TAZ, GNMT, UQCRCR, UQCRCR, COX6B1, NDUFV2, SURF1, COQ9, SIRT3, NDUFS8, OGDH, NDUFA7, NDUFA4, UQCRCB, AKT2, NDUFB5, PPP1CA, NDUFA2, ,
GO_AEROBIC_RESPIRATION	0,0030	-2.90	SDHA, IDH3B, SUCLG2, UQCRC1, FH, NDUFV1, IDH2, OXA1L, SDHC, MDH1, SDHB, MDH2, IDH3G, CS, DLD, UQCRC2, SDHD, SUCLG1, NNT, ME3, UQCRCR, SURF1, SIRT3, OGDH, UQCRCB, UQCRC10, PDHA1, SUCLA2, MTFR1, COX10, ENO3, PFKM, UQCRC1, COX4I1, COX7B, NDUFS6, NDUFB11, NDUFV1, NDUFA9, NDUFS1, NDUFA5, NDUFS7, CYC1, UQCRCQ, PFKFB1, COX6G, NDUFB8, NDUFA13, COX7C, UQCRC11, SDHC, NDUFB10, NDUFA6, NDUFS2, ALDOB, NDUFB9, UQCRCF51, COX8C, NDUFS3, NDUFB6, NDUFA1, NDUFA12, DLD, UQCRC2, NDUFA10, ENTDP5, SUCLG1, NDUFB7, DGUOK, COX5B, TAZ, UQCRCR, UQCRCR, COX6B1, NDUFV2, SURF1, COQ9, NDUFS8, OGDH, NDUFA7, NDUFA4, UQCRCB, DUT, NDUFB5, NDUFA2, UQCRC10, NDUFS4, AK1, NDUFV3, AK2, NDUFC1, NDUFC2-KCTD14, NDUFC2, DCTPP1, NME6, NDUFB2, MYH6, NDUFA1, CHCHD10, NME4, COX10, NDUFA11, NFS1, MRPS15, MRPS35, MRPL39, MRPL42, MRPL44, MRPL45, HARS2, MRPS24, MRPS9, MRPL4, TUFM, MRPS28, MRPL28, MRPL38, MRPL51, MRPS11, MRPL41, MRPL18, GADD45GIP1, MRPL2, MRPL37, MRPS21, MRPL1, DAP3, MRPS31, MRPS30, MRPL30, MRPS26, MRPS7, AURKAIP1, MRPL24, MRPL23, CHCHD1, MRPL9, TSFM, MRPS12, MRPL12, MRPS16, MRPL11, MRPS18A, MRPS36, MRPL16, MRPS22, MRPL47, MRPS5, GATC, MRPL49, MRPL10, MRPL17, MRPS6, MRPL44, MRPL48, MRPS33, MRPS18C, MRPL21, MRPL27, MRPL50, MRPL46, QRSL1, MRPS14, MTFI2, EARS2, MRPL36, MRPS17, MRPL3, MRPL55, MRPS25
GO_NUCLEOSIDE_TRIPHOSPHATE_METABOLIC_PROCESS	0,0030	-2.87	ENO3, PFKM, UQCRC1, COX4I1, COX7B, NDUFS6, NDUFB11, NDUFV1, NDUFA9, NDUFS1, NDUFA5, NDUFS7, CYC1, UQCRCQ, PFKFB1, COX6G, NDUFB8, NDUFA13, COX7C, UQCRC11, SDHC, NDUFB10, NDUFA6, NDUFS2, ALDOB, NDUFB9, UQCRCF51, COX8C, NDUFS3, NDUFB6, NDUFA1, NDUFA12, DLD, UQCRC2, NDUFA10, ENTDP5, SUCLG1, NDUFB7, DGUOK, COX5B, TAZ, UQCRCR, UQCRCR, COX6B1, NDUFV2, SURF1, COQ9, NDUFS8, OGDH, NDUFA7, NDUFA4, UQCRCB, DUT, NDUFB5, NDUFA2, UQCRC10, GART, NDUFS4, AK1, NDUFV3, DHODH, AK2, NDUFC1, NDUFC2-KCTD14, NDUFC2, NDUFB2, MYH6, NDUFA1, CHCHD10, COX10, NDUFA11, MAGI3, GALK1, MSH2, LHPP, NDUFA3, PGAM2, FXN, PFAS
GO_MITOCHONDRIAL_TRANSLATION	0,0030	-2.84	MRPS15, MRPS35, MRPL39, MRPL42, MRPL44, MRPL45, HARS2, MRPS24, MRPS9, MRPL4, TUFM, MRPS28, MRPL28, MRPL38, MRPL51, MRPS11, MRPL41, MRPL18, GADD45GIP1, MRPL2, MRPL37, MRPS21, MRPL1, DAP3, MRPS31, MRPS30, MRPL30, MRPS26, MRPS7, AURKAIP1, MRPL24, MRPL23, CHCHD1, MRPL9, TSFM, MRPS12, MRPL12, MRPS16, MRPL11, MRPS18A, MRPS36, MRPL16, MRPS22, MRPL47, MRPS5, GATC, MRPL49, MRPL10, MRPL17, MRPS6, MRPL44, MRPL48, MRPS33, MRPS18C, MRPL21, MRPL27, MRPL50, MRPL46, QRSL1, MRPS14, MTFI2, EARS2, MRPL36, MRPS17, MRPL3, MRPL55, MRPS25
GO_NUCLEOSIDE_MONOPHOSPHATE_METABOLIC_PROCESS	0,0030	-2.81	ENO3, PFKM, UQCRC1, COX4I1, COX7B, NDUFS6, NDUFB11, NDUFV1, NDUFA9, NDUFS1, NDUFA5, NDUFS7, CYC1, UQCRCQ, PFKFB1, COX6G, NDUFB8, NDUFA13, COX7C, UQCRC11, SDHC, NDUFB10, NDUFA6, NDUFS2, ALDOB, NDUFB9, UQCRCF51, COX8C, NDUFS3, NDUFB6, NDUFA1, NDUFA12, DLD, UQCRC2, NDUFA10, ENTDP5, SUCLG1, NDUFB7, DGUOK, COX5B, TAZ, UQCRCR, UQCRCR, COX6B1, NDUFV2, SURF1, COQ9, NDUFS8, OGDH, NDUFA7, NDUFA4, UQCRCB, DUT, NDUFB5, NDUFA2, UQCRC10, GART, NDUFS4, AK1, NDUFV3, DHODH, AK2, NDUFC1, NDUFC2-KCTD14, NDUFC2, NDUFB2, MYH6, NDUFA1, CHCHD10, COX10, NDUFA11, MAGI3, GALK1, MSH2, LHPP, NDUFA3, PGAM2, FXN, PFAS
GO_TRANSLATIONAL_ELONGATION	0,0030	-2.78	MRPS15, MRPS35, MRPL39, MRPL42, MRPL44, MRPL45, MRPS24, MRPS9, MRPL4, TUFM, MRPS28, MRPL28, RPL2, GTPBB1, EEF1D, MRPL38, MRPL51, MRPS11, MRPL41, MRPL18, GADD45GIP1, MRPL2, MRPL37, MRPS21, MRPL1, DAP3, TRNAU1AP, MRPS31, MRPS30, MRPL30, MRPS26, EEF2, MRPS7, GTPBP2, AURKAIP1, MRPL24, MRPL23, CHCHD1, MRPL9, TSFM, MRPS12, MRPL12, MRPS16, MRPL11, MRPS18A, MRPS36, MRPL16, MRPS22, MRPL47, MRPS5, MRPL49, MRPL10, SECISBP2, MRPL17, MRPS6, MRPL44, MRPL48, MRPS33, MRPS18C, MRPL21, MRPL27, MRPL50, MRPL46, RPLP1, MRPS14, EIF5A1, EIF5A, MRPL36, MRPS17, EEFSEC, MRPL3, APTB1, MRPL55, MRPS25
GO_TRICARBOXYLIC_ACID_METABOLIC_PROCESS	0,0030	-2.71	SDHA, IDH3B, SUCLG2, FH, GHR, IDH2, SDHC, MDH1, SDHB, MDH2, IDH3G, CS, DLD, SDHD, SUCLG1, NNT, OGDH, PDHA1, SUCLA2, DLST, ACO2, IDH3A, DHTKD1, GLUD1
GO_TRANSLATIONAL_TERMINATION	0,0030	-2.67	MRPS15, MRPS35, MRPL39, MRPL42, MRPL44, MRPL45, MRPS24, MRPS9, MRPL4, MRPS28, MRPL28, MRPL38, MRPL51, MRPS11, MRPL41, MRPL18, GADD45GIP1, MRPL2, MRPL37, MRPS21, MRPL1, DAP3, MRPS31, MRPS30, MRPL30, MRPS26, MRPS7, AURKAIP1, MRPL24, MRPL23, CHCHD1, MRPL9, MRPS12, MRPL12, MRPS16, MRPL11, MRPS18A, MRPS36, MRPL16, MRPS22, MRPL47, MRPS5, MRPL49, MRPL10, MRPL17, MRPS6, MRPL44, MRPL48, MRPS33, MRPS18C, MRPL21, MRPL27, MRPL50, MRPL46, MRPS14, MRPL36, MRPS17, MRPL3, MRPL55, MRPS25
GO_BRANCHED_CHAIN_AMINO_ACID_METABOLIC_PROCESS	0,0030	-2.62	ACADS8, MCCC1, BCKDHB, MCCC2, IVD, PPM1K, HSD17B10, GHR, ALDH6A1, HIBADH, BCAT2, AUH, DLD, BCKDHA, DBT, ACAD8, HMGCL, BCKDK
GO_CELLULAR_AMINO_ACID_CATABOLIC_PROCESS	0,0030	-2.60	GPT, ACADS8, GCDH, ALDH4A1, MCCC1, CARNS1, BCKDHB, MCCC2, IVD, PPM1K, ALDH5A1, HSD17B10, OAT, HNMT, ALDH6A1, HIBADH, BCAT2, AUH, ALDH11, DLD, GCAT, BCKDHA, SHMT1, DBT, ACAD8, OGDH, QDPR, GOT2, HMGCL, GSTZ1, GOT1, BCKDK, DLST, ASPA, FAH, THNSL2, GLUD2, GLUD1
GO_ORGANIC_ACID_CATABOLIC_PROCESS	0,0030	-2.55	GPT, ACADS8, GCDH, ALDH4A1, SORD, MCCC1, CARNS1, BCKDHB, MCCC2, ECHS1, PCCA, ETFA, PCCB, ETFB, IVD, PPM1K, ALDH5A1, HSD17B10, OAT, HNMT, ALDH6A1, HIBADH, EC1, BCAT2, AUH, MCEE, PHYH, ALDH11, DLD, GCAT, BCKDHA, ACAA1, SHMT1, DBT, ECH1, ACADM, ACAD8, DCXR, OGDH, ACSF3, QDPR, HADH, AMACR, HADHA, GOT2, HMGCL, ACADVL, HADHB, GSTZ1, CYP26B1, PEX2, GOT1, BCKDK, DLST, ASPA, FAH, NUDT19, THNSL2, ACADS, PEX7, GLUD2, GLUD1
GO_GLYCOSYL_COMPOUND_METABOLIC_PROCESS	0,0030	-2.49	ENO3, MACROD1, PFKM, MCCC2, UQCRC1, COX4I1, COX7B, NDUFS6, NDUFB11, NDUFV1, NDUFA9, NDUFS1, NDUFA5, NDUFS7, CYC1, UQCRCQ, PFKFB1, COX6G, NDUFB8, NDUFA13, COX7C, UQCRC11, SDHC, NDUFB10, NDUFA6, NDUFS2, ALDOB, NDUFB9, APOBEC2, UQCRCF51, COX8C, MCEE, NDUFS3, NDUFB6, NDUFA1, NDUFA12, DLD, UQCRC2, AKR1B1, NDUFA10, ENTDP5, NDUFA8, DCAKD, ATP1A2, NDUFB7, DGUOK, COX5B, TAZ, GNMT, UQCRCR, UQCRCR, COX6B1, NDUFV2, SURF1, COQ9, NDUFS8, OGDH, NDUFA7, NDUFA4, UQCRCB, DUT, NDUFB5, NDUFA2, UQCRC10, GART, NDUFS4, AK1, NDUFV3, DHODH, AK2, NDUFC1, NDUFC2-KCTD14, NDUFC2, NME6, NDUFB2, PANK4, MYH6, NDUFA1, CHCHD10, NME4, COX10, NDUFA11, AKR1B10, ACOT7, NFS1, MAGI3, GALK1, MSH2, ACACB, GAMT, NDUFA3, PGAM2, FXN
O_MITOCHONDRION_ORGANIZATION	0,0030	-2.45	CAMK2A, RHOT2, PINK1, AKT1, NDUFS6, MRPS15, ADAMTS7, NDUFB11, NDUFV1, HSD17B10, RCL2L11, NDUFA9, NDUFS1, NDUFA5, MRPS35, SAMM50, SIVA1, NDUF57, MRPL39, OXA1L, NDUFB8, NDUFA13, EC5IT, NDUFB10, NDUFA6, NDUFS2, SLC22A3, MDH1, MRPL42, NDUFB9, MTFP1, MRPL14, RAB3A, MUL1, ACAA2, ASB2, ALKBH7, NDUFS3, NDUFB6, MRPL45, NDUFA1, SLC25A4, KCNK3, NDUFA12, HARS2, CHCHD3, NDUFA10, AIFM1, NDUFA8, PHB, MRPS24, NDUFB7, ESRRB, MRPS9, TAZ, MRPL4, NDUFV2, SIRT3, TUFM, NDUFS8, NDUFA7, TMEM70, UQCRCB, SNRBP, MRPS28, NDUFB5, YWHAE, NDUFA2, TOMM40, UQCRC10, NDUFS4, NDUFV3, PPIF, SOD2, TRMT5
GO_ALPHA_AMINO_ACID_CATABOLIC_PROCESS	0,0030	-2.41	GPT, GCDH, ALDH4A1, MCCC1, CARNS1, MCCC2, IVD, OAT, HNMT, ALDH6A1, HIBADH, AUH, ALDH11, DLD, GCAT, SHMT1, ACAD8, OGDH, QDPR, GOT2, HMGCL, GSTZ1, GOT1, DLST, ASPA, FAH, THNSL2, GLUD2, GLUD1
GO_PURINE_CONTAINING_COMPOUND_METABOLIC_PROCESS	0,0030	-2.39	ENO3, GMPR, MACROD1, PFKM, MCCC2, UQCRC1, COX4I1, COX7B, NDUFS6, NDUFB11, NDUFV1, NDUFA9, NDUFS1, NDUFA5, NDUFS7, CYC1, UQCRCQ, PFKFB1, COX6G, NDUFB8, NDUFA13, COX7C, UQCRC11, SDHC, NDUFB10, NDUFA6, PDE4A, NDUFS2, ALDOB, NDUFB9, UQCRCF51, COX8C, MCEE, NDUFS3, NDUFB6, NDUFA1, NDUFA12, DLD, UQCRC2, SHMT1, NDUFA10, ENTDP5, NDUFA8, DCAKD, ATP1A2, NDUFB7, DGUOK, COX5B, TAZ, GNMT, UQCRCR, UQCRCR, COX6B1, NDUFV2, SURF1, COQ9, NDUFS8, OGDH, NDUFA7, NDUFA4, UQCRCB, NDUFB5, NDUFA2, UQCRC10, GART, NDUFS4, AK1, NDUFV3, AK2, NDUFC1, NDUFC2-KCTD14, NDUFC2, NME6, NDUFB2, ,
GO_ESTABLISHMENT_OF_PROTEIN_LOCALIZATION_TO_ENDOPLASMIC_RETICULUM	0,0030	-2.39	RPL3L, RPS14, RPL8, RPS3, RPS9, RPS6, RPS23, RPS13, RPL38, RPL35A, RPS21, RPLP2, RPL36, RPS27, RPL11, RPL14, RPL18, RPLS17, RPS4X, RPL13, RPS15, RPL37A, RPL30, RPL23, RPS15A, RPL12, RPL34, RPL35, RPL36A, RPL28, RPL10A, RPL29, RPL19, RPL21, FAU, RPS24, RPS11, RPS16, RPS19, RPS5, SRP8B, SRP68, RPL39, RPLP1, RPL23A, RPL27
GO_NUCLEAR_TRANSCRIBED_MRNA_CATABOLIC_PROCESS_NONSENSE_MEDIATED_DECAY	0,0030	-2.36	RPL3L, RPS14, RPL8, RPS3, RPS9, RPS6, RPS23, RPS13, RPL38, RPL35A, RPS21, RPLP2, RPL36, RPS27, RPL11, RPL14, RPL18, RPLS17, RPS4X, RPL13, RPS15, RPL37A, RPL30, RPL23, PPS21A, RPS15A, EXOSC10, RPL12, RPL34, RPL35, RPL36A, RPL28, RPL10A, RPL29, RPL19, CAS3, RPL21, FAU, RPS24, RPS11, UPF1, RPS16, SMG5, RPS19, RPS5, UPF3B
GO_SMALL_MOLECULE_CATABOLIC_PROCESS	0,0030	-2.35	ENO3, GPT, ACADS8, GCDH, ALDH2, ALDH4A1, SORD, MCCC1, CARNS1, PFKM, BCKDHB, MCCC2, ECHS1, PCCA, ETFA, PCCB, ETFB, IVD, PPM1K, ALDH5A1, HSD17B10, ENPP2, OAT, HNMT, ALDH6A1, PFKFB1, HIBADH, EC1, ALDOB, BCAT2, AUH, INPP5E, OXCT1, NUDT3, MCEE, KHK, PHYH, ALDH11, DLD, GCAT, BCKDHA, ACAA1, SHMT1, DBT, ECH1, GALT, ACADM, ACAD8, DCXR, SCARF1, OGDH, ACSF3, QDPR, HADH, AMACR, HADHA, GOT2, HMGCL, PNKD, ACADVL, HADHB, GSTZ1, CYP26B1, AKR1B10, PEX2, GALK1, GOT1, PGAM2, BCKDK, DLST, ASPA, FAH, NUDT19, THNSL2, IMPA2, ADHS, ACADS, ALDH1B1, PEX7, GLUD2, GLUD1, INPP5K, DHODH, CRYL1, ABHD10
GO_MONOCARBOXYLIC_ACID_CATABOLIC_PROCESS	0,0030	-2.32	ACADS8, GCDH, ALDH4A1, SORD, ECHS1, PCCA, ETFA, PCCB, ETFB, IVD, ALDH5A1, EC1, MCEE, PHYH, ACAA1, ECH1, ACADM, ACAD8, DCXR, HADH, AMACR, HADHA, GOT2, ACADVL, HADHB, CYP26B1, PEX2

77 Top 25 of enriched GO biological processes of downregulated genes in HFD+ANGII versus CTRL. Padj = P Value adjusted for multiple testing. NES= normalized  
 78 enrichment score.

Pathway	padj	NES	leadEdge
KEGG_ECM_RECEPTOR_INTERACTION	0,00175	2,455631	COL6A3, COL5A2, COL1A2, COL4A1, COL4A2, COL1A1, COL5A1, COL6A2, COL3A1, LAMC1, THBS4, TNC, COL6A1, SDC2, ITGA9, ITGB5, COL4A4, FN1, LAMA2, CD44, ITGB1, SPP1, ITGA6, ITGAV, LAMB1, COMP, HMMR, HSPG2, LAMA3, ITGA5, THBS1, ITGB8
KEGG_FOCAL_ADHESION	0,00175	2,352287	COL6A3, COL5A2, COL1A2, COL4A1, COL4A2, COL1A1, COL5A1, COL6A2, FLNC, COL3A1, LAMC1, THBS4, TNC, COL6A1, ITGA9, ACTN1, PDGFRA, PIK3R3, ITGB5, MYL12A, AKT3, ROCK2, COL4A4, FN1, LAMA2, IGF1, ITGB1, IGF1R, SPP1, TLN1, ITGA6, ITGAV, LAMB1, CAPN2, PPP1R12A, PDPK1, COMP, BCL2, ACTN4, FLNA, MET, GSK3B, CRK, RAGAP1, LAMA3, FLNB, PTEN, ARHGAP5, SOS1, PTK2, PRKCA, KDR, ITGA5, THBS1, ITGB8, ITGA1, ARHGAP35, PDGFC, PIK3CA, PAK6, FYN, MYLK2, EGFR, LAMC2, PIK3R5, PRKCB
KEGG_TGF_BETA_SIGNALING_PATHWAY	0,00175	2,116799	TGFB2, THBS4, TGFβ3, GDF6, TGFβR1, ROCK2, SMURF2, DCN, COMP, BMPRIA, INHBB, INHBA, SMAD4, THBS1, PPP2CA, BMPR2, SP1, ACVR1, RPS6KB1, ID2, FST, EP300, TGFB2, TGFβ1, BMP2, RHOA, TFDP1, ROCK1, THBS3, SMAD7, RBL1, CDKN2B, MYC, ACVR2B, ACVR2A, SMAD5
KEGG_REGULATION_OF_ACTIN_CYTOSKELETON	0,00175	1,971689	ENAH, MYH10, MSN, ARHGEF12, ITGA9, ACTN1, PDGFRA, PIK3R3, NCKAP1, ITGB5, MYL12A, ROCK2, FN1, IQGAP1, ITGB1, F2R, APC, ITGA6, ITGAV, PPP1R12A, ACTN4, RRAS2, DIAPH2, CRK, PIKFYVE, NRAS, FGFR3, SOS1, MYH9, PTK2, PIP4K2A, ITGA5, IQGAP3, ITGB8, FGD3, SSH2, ARPC2, CYFIP1, ARPC5L, FGFR1, FGF2, ITGA1, ARPC1B, ARHGAP35, ARHGEF6, PDGFC, PIK3CA, GNAI3, PAK6, GNG12, MYLK2, CFL2, LIMK1, EGFR, PIK3R5, NCKAP1L, CDC42, RRAS, CD14, DIAPH3, DOCK1, RHOA, TIAM2, PIK3CG, ROCK1, FGF6, ARPC5, CFL1, VAV1, PIK3CB, ARHGEF7, VAV3, PAK1, PAK3, F2, PDGFRB, PFN2, MAP2K1, DIAPH1, PAK2, ARPC4, ARHGEF4, FGFR2
KEGG_ADHERENS_JUNCTION	0,002724	1,856705	ACTN1, TGFβR1, IQGAP1, IGF1R, ACTN4, MET, PTPRF, PTPRJ, SMAD4, SNAI1, SORBS1, MAP3K7, FGFR1, FYN, PTPRB, EP300, EGFR, TGFB2, TJP1, CDC42, CTNND1, RHOA, YES1
KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY	0,002724	1,7938	SYK, PIK3R3, PTPN11, IFNGR1, PTK2B, NRAS, ULBP2, RAET1L, RAET1G, ULBP1, ULBP3, SOS1, PRKCA, LCP2, TNFRSF10C, TNFRSF10D, TNFRSF10B, PIK3CA, NFAT5, FYN, PIK3R5, PRKCB, TNFSF10, PIK3CG, VAV1, PIK3CB, VAV3, PAK1, SH3BP2, NFATC3, TYROBP, PTPN6, MAP2K1, NFATC2, KRAS, CD48, SOS2
KEGG_PATHOGENIC_ESCHERICHIA_COLI_INFECTION	0,005828	1,789319	TLR4, ROCK2, ITGB1, TUBB6, CTTN, TUBB3, TUBA1A, PRKCA, TUBB, TUBA1C, ARHGEF2, TUBB2A, ARPC2, ARPC5L, ARPC1B, FYN, HCLS1, CDC42, CD14, NCL, RHOA, ROCK1, ARPC5, TUBB4A, YWHAQ, ARPC4, TUBB4B
KEGG_N_GLYCAN_BIOSYNTHESIS	0,007785	1,786919	MGAT5B, ALG10B, ALG10, MAN1A2, ALG14, STT3A, MGAT5, MGAT4A, STT3B, MGAT2, MAN1A1, MAN2A1
KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS	0,002724	1,74136	SYK, PLA2G4A, PIK3R3, AKT3, GAB2, ASAP2, ASAP1, CRK, SPHK1, PIKFYVE, DNMI1, PRKCA, PLD1, ARPC2, ARPC5L, ARPC1B, PIK3CA, RPS6KB1, CFL2, LIMK1, PIK3R5, PRKCB, CDC42, INPP5D, ARF6, PRKCD, DNMI1, PIK3CG, PTPRC, ARPC5, CFL1, VAV1, PIK3CB, VAV3, PAK1, FCGR1A
KEGG_PROSTATE_CANCER	0,006622	1,692087	PDGFRA, PIK3R3, AKT3, IGF1, IGF1R, CREB5, MTOR, CREB3L2, PDPK1, BCL2, E2F3, GSK3B, NRAS, PTEN, SOS1, CREB3, RB1, FGFR1, PDGFC, PIK3CA, IKBKG, HSP90AA1, EP300, EGFR, PIK3R5, E2F1
KEGG_DORSO_VENTRAL_AXIS_FORMATION	0,04558	1,685633	SPIRE1, ETV6, SOS1, CPEB1, NOTCH2, EGFR, ETS1, MAP2K1, KRAS, SOS2
KEGG_ENDOCYTOSIS	0,00175	1,666435	RAB31, PDGFRA, CBL, GRK5, CLTC, F2R, IGF1R, EHD4, HSPA1L, SMURF2, ASAP2, EPS15, MET, ARFGAP3, ITCH, ASAP1, EEA1, CCR5, PIKFYVE, DNMI1, DAB2, RABEP1, FGFR3, VPS4B, CHMP3, KDR, PLD1, ACAP2, CLTB, SMAPB1, AP2B1, CHMP5, EGFR, CBLB, TFR3, CDC42, ARF6, ARRB1, MDM2, USP8, RAB11FIP3, ARAP1, RAB11FIP5, DNMI1, CSF1R
KEGG_PATHWAYS_IN_CANCER	0,00175	1,622301	COL4A1, COL4A2, TGFβ2, LAMC1, TGFβ3, PDGFRA, PIK3R3, TGFβR1, CBL, AKT3, FZD1, COL4A4, FN1, LAMA2, MMP2, IGF1, ITGB1, IGF1R, APC, MTOR, ITGA6, ITGAV, TRAF3, LAMB1, STK4, BCL2, MET, E2F3, DAPK2, GSK3B, CRK, NRAS, LAMA3, SMAD4, PTEN, FGFR3, SOS1, PTK2, FZD4, PRKCA, WNT9B, PLD1, HIF1A, FZD2, PTC1, RB1, FGFR1, FGF2, RUNX1, PIK3CA, IKBKG, TPR, HSP90AA1, IL6, EGN3, EP300, EGFR, FZD7, ARNT, RAD51, WNT9A, LAMC2, PIK3R5, E2F1, CBLB, PRKCB, GIL3, TGFB2, CDC42, APPL1, MDM2, TGFβ1, BMP2, KITLG, RHOA, STK36, SPI1, CCND1, CSF1R, LAMA4, BIRC5, PIK3CG, FGF6, CASP8, PTGS2, ETS1, CDKN2B
KEGG_LEUKOCYTE_TRANSENDOHELIAL_MIGRATION	0,007785	1,616086	MSN, ACTN1, PIK3R3, PTPN11, MYL12A, ROCK2, MMP2, ITGB1, PTK2B, ACTN4, ARHGAP5, PTK2, PRKCA, ARHGAP35, PIK3CA, GNAI3, PIK3R5, PRKCB, CDC42, RAP1B, THY1, CLDN15, CTNND1, CLDN23, RHOA, CYBB, PIK3CG, ROCK1, PECAM1, VAV1, PIK3CB, VAV3
KEGG_GLYCOSAMINOGLYCAN_BIOSYNTHESIS_CHONDROITIN_SULFATE	0,074749	1,593241	CHPF, CSGALNACT2, DSE, XYLT1, CHSY1, CHPF2, CHST3, CHST11, CHST14, CHST15, CSGALNACT1, CHSY3
KEGG_CHRONIC_MYELOID_LEUKEMIA	0,026755	1,580176	TGFB2, TGFβ3, PIK3R3, TGFβR1, PTPN11, CBL, AKT3, GAB2, E2F3, CRK, NRAS, SMAD4, SOS1, RB1, RUNX1, PIK3CA, IKBKG, PIK3R5, E2F1, CBLB, TGFB2, MDM2, TGFβ1, CCND1, PIK3CG, PIK3CB, MYC, MECOM, MAP2K1, CDK6, NFKB1, CRKL, KRAS, SOS2
KEGG_PHOSPHATIDYLINOSITOL_SIGNALING_SYSTEM	0,027644	1,56528	PIK3R3, INPP5J, PLCB4, INPP4B, PIKFYVE, PTEN, PLCB1, PLCE1, PRKCA, PIP4K2A, DGKD, PIK3CA, ITPR1, PIK3R5, PRKCB, INPP5D, CALM1, ITPR2, PI4KA, INPP1, DGKH, INPP5B, PIK3CG, CALM2, PIK3CA, PIK3CB, INPP4A, ITPK1, CDIPT, IPPK, SYNJ1
KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	0,022818	1,563511	TLR4, PIK3R3, AKT3, SPP1, TRAF3, LBP, MAP2K3, CTSK, RIPK1, CD80, TLR8, MAP3K7, TLR2, PIK3CA, IKBKG, IL6, PIK3R5, TLR7, TBK1, CD14, CD40, TLR1, IRAK4, MAP3K8, PIK3CG, CASP8, PIK3CB, CXCL9, IKBKE, TLR3, MAP2K1, TRAF6, NFKB1, CD86
KEGG_SMALL_CELL_LUNG_CANCER	0,025809	1,55903	COL4A1, COL4A2, LAMC1, PIK3R3, AKT3, COL4A4, FN1, LAMA2, ITGB1, ITGA6, ITGAV, TRAF3, LAMB1, BCL2, E2F3, LAMA3, PTEN, PTK2, RB1, PIK3CA, IKBKG, LAMC2, PIK3R5, E2F1
KEGG_AMINOACYL_TRNA_BIOSYNTHESIS	0,055456	1,553188	NARS, GARS, EPRS, IARS, LARS, AARS, SARS, MARS, TARS, CARS, YARS
KEGG_LONG_TERM_DEPRESSION	0,047663	1,536031	GNAO1, PLA2G4A, IGF1, PRKG1, IGF1R, GRIA3, PLCB4, NRAS, PLCB1, PRKCA, PPP2CA, GNAI3, GNAI3, ITPR1, PRKCB, ITPR2
KEGG_CELL_ADHESION_MOLECULES_CAMS	0,036473	1,513535	VCAN, SDC2, ITGA9, ITGB1, CD34, ITGA6, GLG1, ITGAV, PTPRF, CD80, ITGB8, CDH4, CLDN15, CD40, CLDN23, SDC3, NFASC, SDC1, CADM3, PTPRC, PECAM1, ALCAM
KEGG_GAP_JUNCTION	0,042086	1,503137	ADCY7, PDGFRA, LPAR1, PRKG1, TUBB6, PLCB4, NRAS, TUBB3, CDK1, TUBA1A, SOS1, PLCB1, PRKCA, TUBB, TUBA1C, TUBB2A, DRD1, PDGFC, GNAI3, EGFR, ITPR1, PRKCB, TJP1, ITPR2
KEGG_HYPERTROPHIC_CARDIOMYOPATHY_HCM	0,056371	1,472137	TGFB2, ACE, TGFβ3, ITGA9, DMD, ITGB5, DES, LAMA2, IGF1, ITGB1, PRKAB2, ITGA6, ITGAV, TPM4, ITGA5, LMNA, ITGB8, ITGA1, SGCD, IL6, PRKAA1, SLC8A1, PRKAG3, CACNB3, TGFβ1, CACNA2D1, PRKAA2
KEGG_PANCREATIC_CANCER	0,096156	1,414621	TGFB2, TGFβ3, PIK3R3, TGFβR1, AKT3, E2F3, SMAD4, PLD1, RB1, ARHGEF6, PIK3CA, IKBKG, EGFR, RAD51, PIK3R5, E2F1, TGFB2, CDC42

79 Supplemental table 5C.

80 Top 25 of enriched KEGG cellular processes of upregulated genes in HFD+ANGII versus CTRL. Padj = P Value adjusted for multiple testing. NES= normalized  
 81 enrichment score.



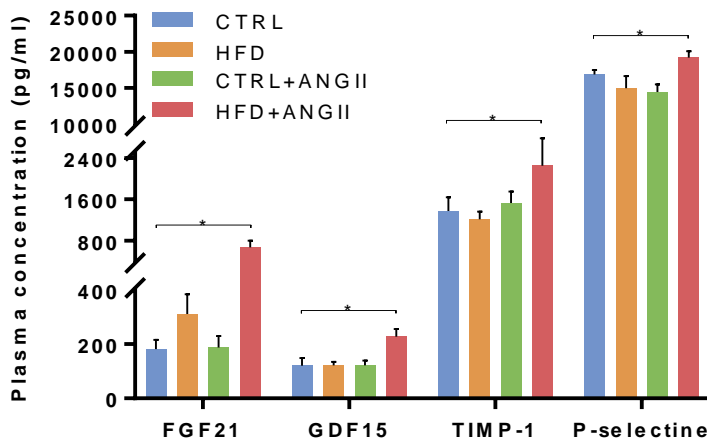
pathway	padj	NES	leadEdge
KEGG_PARKINSONS_DISEASE	0,00175	-3,23364	SDHA, UQCRC1, COX4I1, PINK1, COX7B, NDUFS6, NDUFV1, NDUFA9, NDUFS1, NDUFA5, NDUFS7, CYC1, UQCRCQ, COX6C, NDUFB8, COX7C, UQCRC1, SDHC, NDUFB10, NDUFA6, NDUFS2, COX7A1, NDUFB9, SDHB, UQCRFS1, COX8C, NDUFS3, NDUFB6, COX6A2, NDUFA1, SLC25A4, UQCRC2, NDUFA10, SDHD, VDAC1, NDUFA8, NDUFB7, COX5B, UQCRHL, UQCRH, COX6B1, NDUFV2, NDUFS8, NDUFA7, NDUFA4, UQCRB, NDUFB5, NDUFA2, NDUFAZ, UQCRC10, NDUFS4, NDUFV3, COX7A2, NDUFC1, NDUFC2, NDUFB2, NDUFAB1, HTRAZ, VDAC2, NDUFA3, COX6B2
KEGG_OXIDATIVE_PHOSPHORYLATION	0,00175	-3,08635	SDHA, UQCRC1, COX4I1, COX7B, NDUFS6, NDUFV1, NDUFA9, NDUFS1, NDUFA5, NDUFS7, CYC1, UQCRCQ, COX6C, NDUFB8, COX7C, UQCRC1, SDHC, NDUFB10, NDUFA6, NDUFS2, COX7A1, NDUFB9, SDHB, PPA2, UQCRFS1, COX8C, NDUFS3, NDUFB6, COX6A2, NDUFA1, UQCRC2, NDUFA10, SDHD, NDUFA8, NDUFB7, COX5B, UQCRHL, UQCRH, COX6B1, NDUFV2, NDUFS8, NDUFA7, NDUFA4, UQCRB, NDUFB5, NDUFA2, UQCRC10, NDUFS4, NDUFV3, COX7A2, NDUFC1, NDUFC2, NDUFB2, NDUFAB1, ATP6V1F, COX10, NDUFA11, LHPP, NDUFA3, COX6B2
KEGG_ALZHEIMERS_DISEASE	0,00175	-2,8459	SDHA, UQCRC1, COX4I1, COX7B, NDUFS6, ATP2A2, CACNA1S, LPL, NDUFV1, HSD17B10, NDUFA9, NDUFS1, NDUFA5, NDUFS7, CYC1, UQCRCQ, COX6C, NDUFB8, COX7C, UQCRC1, SDHC, NDUFB10, NDUFA6, NDUFS2, COX7A1, NDUFB9, SDHB, UQCRFS1, COX8C, NDUFS3, NDUFB6, COX6A2, NDUFA1, UQCRC2, NDUFA10, SDHD, NDUFA8, NDUFB7, COX5B, UQCRHL, UQCRH, COX6B1, NDUFV2, NDUFS8, NDUFA7, NDUFA4, UQCRB, NDUFB5, NDUFA2, UQCRC10, NDUFS4, NDUFV3, COX7A2, NDUFC1, NDUFC2, NDUFB2, NDUFAB1
KEGG_CARDIAC_MUSCLE_CONTRACTION	0,00175	-2,82662	TNNT2, UQCRC1, COX4I1, COX7B, ATP2A2, MYL2, CACNA1S, MYL3, CYC1, UQCRCQ, COX6C, COX7C, UQCRC1, COX7A1, UQCRFS1, COX8C, COX6A2, UQCRC2, ATP1A2, COX5B, UQCRHL, UQCRH, COX6B1, UQCRB, UQCRC10, COX7A2, MYH6, TPM1, CACNB2, COX6B2, CACNB1, CACNG6, ATP1B2
KEGG_VALINE_LEUCINE_AND_Isoleucine_DEGRADATION	0,00175	-2,82063	ACADSB, ALDH2, MCCC1, BCKDHB, MCCC2, ECHS1, PCCA, PCCB, IVD, HSD17B10, ALDH6A1, HIBADH, BCAT2, AUH, OXCT1, ACAA2, MCEE, DLD, BCKDHA, ACAA1, DBT, ACADM, ACAD8, ALDH9A1, HADH, HADHA, HMGCL, HADHB
KEGG_RIBOSOME	0,00175	-2,75329	RPL3L, RPL8, RPS3, RPS9, RPS6, RPS23, RPS13, RPL38, RPL35A, RPS21, RPLP2, RPL36, RPS27, RPL11, RPL14, RPL18, RPS17, RPS4X, RPL13, RPS15, RPL37A, RPL30, RPL23, RPS15A, RPL12, RPL34, RPL35, RPL36A, RPL28, RPL10A, RPL29, RPL19, RPL21, FAU, RPS24, RPS11, RPS16, RPS19, RPS5, RPL22L1, RPL39, RPLP1, RPL23A, RPL27
KEGG_HUNTINGTONS_DISEASE	0,00175	-2,74057	SDHA, UQCRC1, COX4I1, COX7B, NDUFS6, NDUFV1, NDUFA9, NDUFS1, NDUFA5, NDUFS7, CYC1, UQCRCQ, COX6C, NDUFB8, COX7C, UQCRC1, SDHC, NDUFB10, NDUFA6, NDUFS2, COX7A1, NDUFB9, SDHB, UQCRFS1, COX8C, NDUFS3, NDUFB6, COX6A2, NDUFA1, SLC25A4, UQCRC2, NDUFA10, SDHD, VDAC1, NDUFA8, NDUFB7, COX5B, UQCRHL, UQCRH, COX6B1, NDUFV2, NDUFS8, NDUFA7, NDUFA4, UQCRB, NDUFB5, NDUFA2, UQCRC10, TAF4, NDUFS4, NDUFV3, SOD2, COX7A2, NDUFC1, NDUFC2, NDUFB2, NDUFAB1, POLR2E, POLR2C, SOD1, VDAC2, NDUFA3, COX6B2, POLR2F, NDUFB4, PPARGC1A, VDAC3, HDAC2, POLR2I, AP251
KEGG_CITRATE_CYCLE_TCA_CYCLE	0,00175	-2,73007	SDHA, IDH3B, SUCLG2, FH, IDH2, SDHC, MDH1, SDHB, MDH2, IDH3G, CS, DLD, SDHD, SUCLG1, OGDH, PDHA1, SUCLA2, DLST, ACO2, IDH3A, PC
KEGG_PROPANOATE_METABOLISM	0,00175	-2,48861	ALDH2, LDHB, SUCLG2, ECHS1, PCCA, PCCB, ALDH6A1, MCEE, SUCLG1, ACADM, ACSS1, ALDH9A1, HADHA, SUCLA2, ACACB, ALDH1B1, MLYCD, EHHADH, ACSS3, ACAT2
KEGG_BUTANOATE_METABOLISM	0,00175	-2,18783	ALDH2, ECHS1, ALDH5A1, L2HGDI, OXCT1, ALDH9A1, HADH, HADHA, HMGCL, PDHA1, AKR1B10, ACSM5, ACADS, ALDH1B1, EHHADH, ACAT2
KEGG_FATTY_ACID_METABOLISM	0,00175	-2,17514	ACADSB, GCDH, ALDH2, ECHS1, ECI1, ACAA2, ACAA1, ACADM, ALDH9A1, HADH, HADHA, ACADVL, HADHB, ADH5, ACSL6, ACADS, ALDH1B1, ADH1B, ADH1A, ADH1C, EHHADH, ACAT2, ECI2
KEGG_PYRUVATE_METABOLISM	0,00175	-2,13167	ALDH2, LDHB, LDHD, MDH1, MDH2, DLD, AKR1B1, ME3, ACSS1, ALDH9A1, PDHA1, ACACB, PC, ALDH1B1, ACYP2
KEGG_DRUG_METABOLISM_CYTOCHROME_P450	0,002775	-2,02132	GSTK1, MAOB, GSTP1, GSTM2, CYP2D6, GSTZ1, GSTM3, MGST3, GSTA5, FMO1, ADH5, ADH1B, ADH1A, ADH1C, GSTT2, GSTO2, FMO2, GSTM4
KEGG_BETA_ALANINE_METABOLISM	0,006874	-1,90986	ALDH2, ECHS1, ACADM, ALDH9A1, HADHA, ALDH1B1, DPYD, MLYCD, EHHADH, UPB1
KEGG_PEROXISOME	0,00175	-1,90387	GSTK1, PRDX5, IDH2, PHYH, PMVK, ACAA1, ECH1, PXMP2, PEX6, DHRS4, SOD2, AMACR, HMGCL, SOD1, PXMP4, PEX2, GNPAT, NUDT19, ACSL6, PEX7, PEX5, MLYCD, CRAT, EHHADH, PRDX1, ECI2, PIPOX
KEGG_METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450	0,005138	-1,87385	GSTK1, GSTP1, GSTM2, GSTZ1, GSTM3, MGST3, GSTA5, ADH5, ADH1B, ADH1A, ADH1C, GSTT2, DHDH
KEGG_GLYCOLYSIS_GLUONEOGENESIS	0,007758	-1,84159	ENO3, ALDH2, LDHB, PFKM, ALDOB, DLD, ACSS1, ALDH9A1, FBP2, PDHA1, PGAM2, ADH5, ALDH1B1, ADH1B, ADH1A, ADH1C, GALM
KEGG_TRYPTOPHAN_METABOLISM	0,014614	-1,76949	GCDH, ALDH2, MAOB, ECHS1, INMT, OGDH, ALDH9A1, HADH, HADHA
KEGG_SPLICEOSOME	0,002775	-1,76178	PPI1L, RBMX, SNRPB, PRPF40B, PRPF19, DDX5, BCAS2, SRSF2, NAA38, SF3B2, SNRNP70, HSPA2, SRSF5, DDX39B, ACIN1, TRA2A, CHERP, SF3A2, SART1, HSPA1A, HSPA1B, SRSF3, NCBP2, THOC3, PUF60, TXNL4A, SF3B5, LSM3, SRSF6, DDX23, SYF2, CDC40, HNRNP1A1, SNRPC, SRSF4, SNRPD3, HNRNPM, SRSF7, MAGOHB, SNRNP27, U2AF2, SF3A1, PIRG1, RBM22, LSM7, PCBP1, MAGOH, SRSF1, HNRNPU, PQBP1, CCDC12, PRPF31, SNW1, SNRNP40, XAB2, DHX16, ISY1, TRA2B, LSM6, CWC15, SNRPA1, SNRPF, LSM2
KEGG_LYSINE_DEGRADATION	0,014614	-1,75798	GCDH, ALDH2, ECHS1, OGDH, ALDH9A1, HADH, HADHA, DLST, DOT1L, ALDH1B1, AASDH, EHHADH, AASDH, SETD1B, ACAT2, PIPOX, EHM2
KEGG_ALANINE ASPARTATE AND GLUTAMATE METABOLISM	0,026117	-1,72474	GPT, ALDH4A1, ALDH5A1, ACY3, GOT2, NIT2, GOT1, ASPA, GLUD2, GLUD1, GPT2, AD5L
KEGG_HISTIDINE_METABOLISM	0,024828	-1,7212	ALDH2, MAOB, HNMT, ACY3, ALDH9A1, ASPA, HEMK1, ALDH1B1, DDC, LCM2
KEGG_ARGININE_AND_PROLINE_METABOLISM	0,035521	-1,64213	ALDH2, ALDH4A1, MAOB, CKM, OAT, ACY1, ALDH9A1, GOT2, CKMT2, GAMT, GOT1, ALDH1B1, GLUD2, GLUD1
KEGG_CYSSTEINE_AND_METHIONINE_METABOLISM	0,062935	-1,58533	ADI1, LDHB, MPST, GOT2, GOT1, MAT2B, APIP
KEGG_FRUCTOSE_AND_MANNANOSE_METABOLISM	0,092066	-1,52163	SORD, PFKM, PFKFB1, ALDOB, KHK, AKR1B1, FBP2, AKR1B10, GMPPA, MPI

82

## 83 Supplemental table 5D

84 Top 25 of enriched KEGG cellular processes of downregulated genes in HFD+ANGII versus CTRL. Padj = P Value adjusted for multiple testing. NES= normalized  
85 enrichment score.

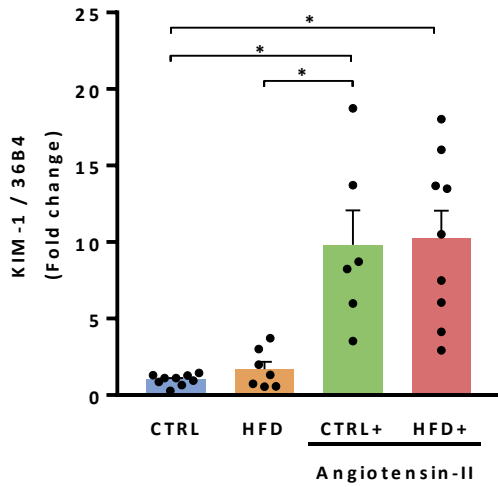
86



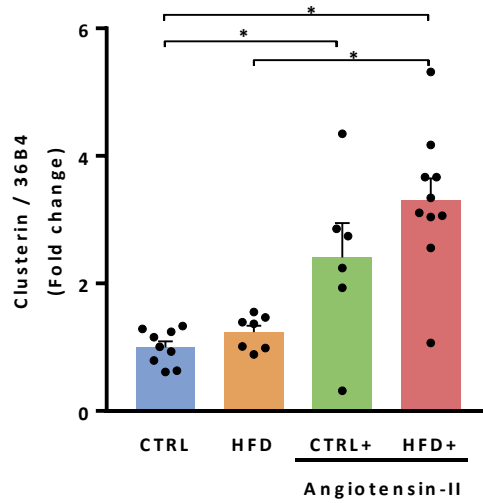
87  
 88 **Supplemental figure 1. Plasma concentrations determined with Luminex.**  
 89 Fibroblast growth factor 21 (FGF-21), Growth differentiation factor 15 (GDF-15), Tissue inhibitor metalloprotease-1  
 90 (TIMP-1), P-selectine.  
 91 CTRL = control diet. HFD = high fat diet. CTRL+ANGII = Angiotensin-II treated group on control chow. HFD+ANGII =  
 92 Angiotensin-II treated group on high fat diet. Data are presented as means. Error bars represent standard error of  
 93 the mean. Statistical testing was performed with Kruskal Wallis test followed by Mann-Witney-U.

94  
 95  
 96  
 97  
 98  
 99  
 100  
 101  
 102  
 103  
 104  
 105  
 106  
 107  
 108  
 109  
 110  
 111

**A**

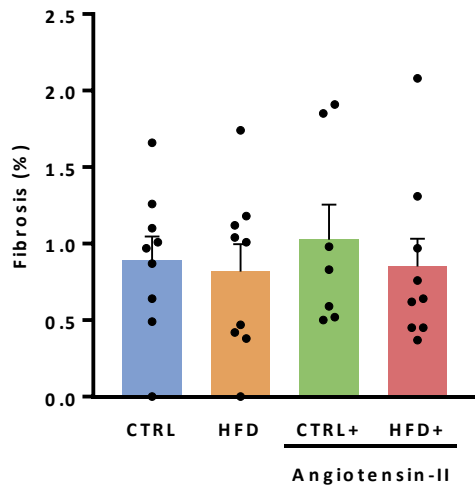


**B**

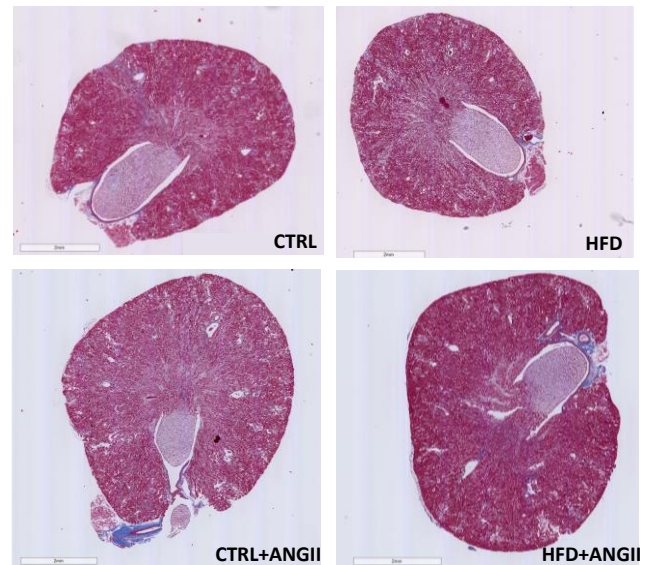


112

**C**



**D**



113

114

115

116 **Supplemental figure 2. Kidney injury and fibrosis markers**

117 A) LV mRNA expression levels of kidney injury marker (KIM-1). B) LV mRNA expression of Clusterin. C) Histological

118 analysis of kidney fibrosis, expressed in fold-change compared to reference control values (n=7-9 mice per group.

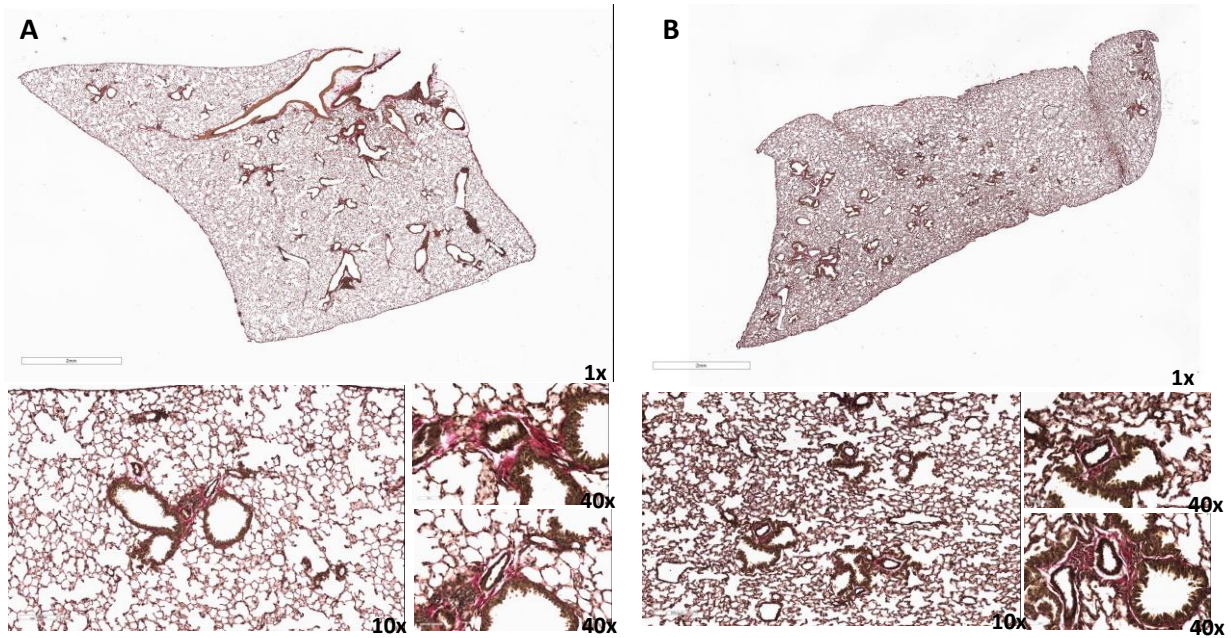
119 D) Images of histologic staining depicting kidney fibrosis (Masson). CTRL = control chow. HFD = high fat diet.

120 CTRL+ANGII = Angiotensin-II treated group on control chow. HFD+ANGII = Angiotensin-II treated group on high fat

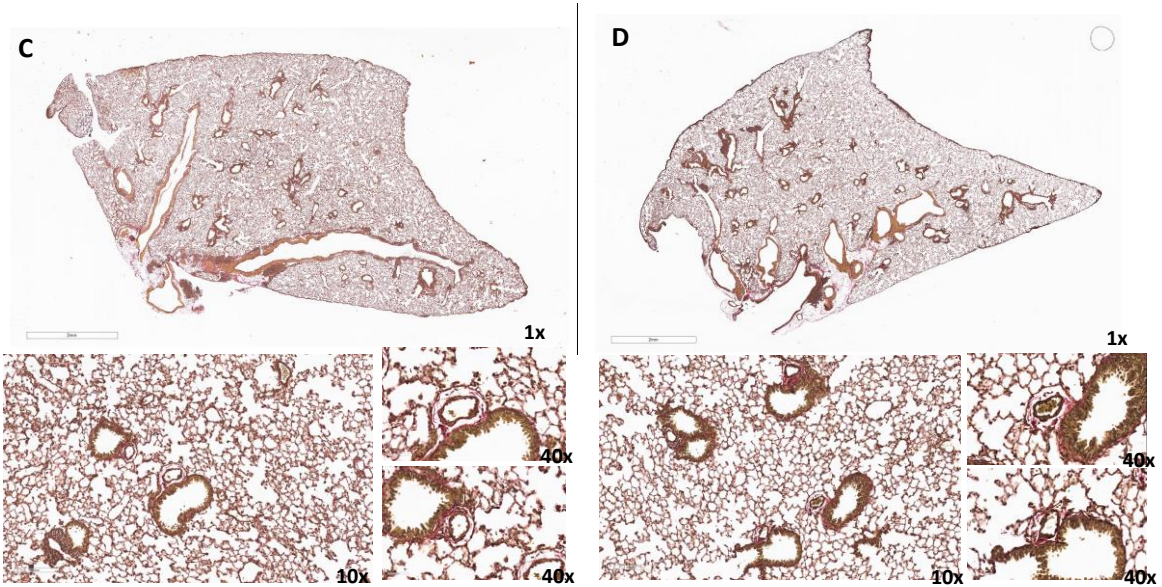
121 diet. Data are presented as mean + SEM. \* = Kruskal Wallis test followed by Mann-Whitney-U P<0.05 is considered

122 significant.

123



124



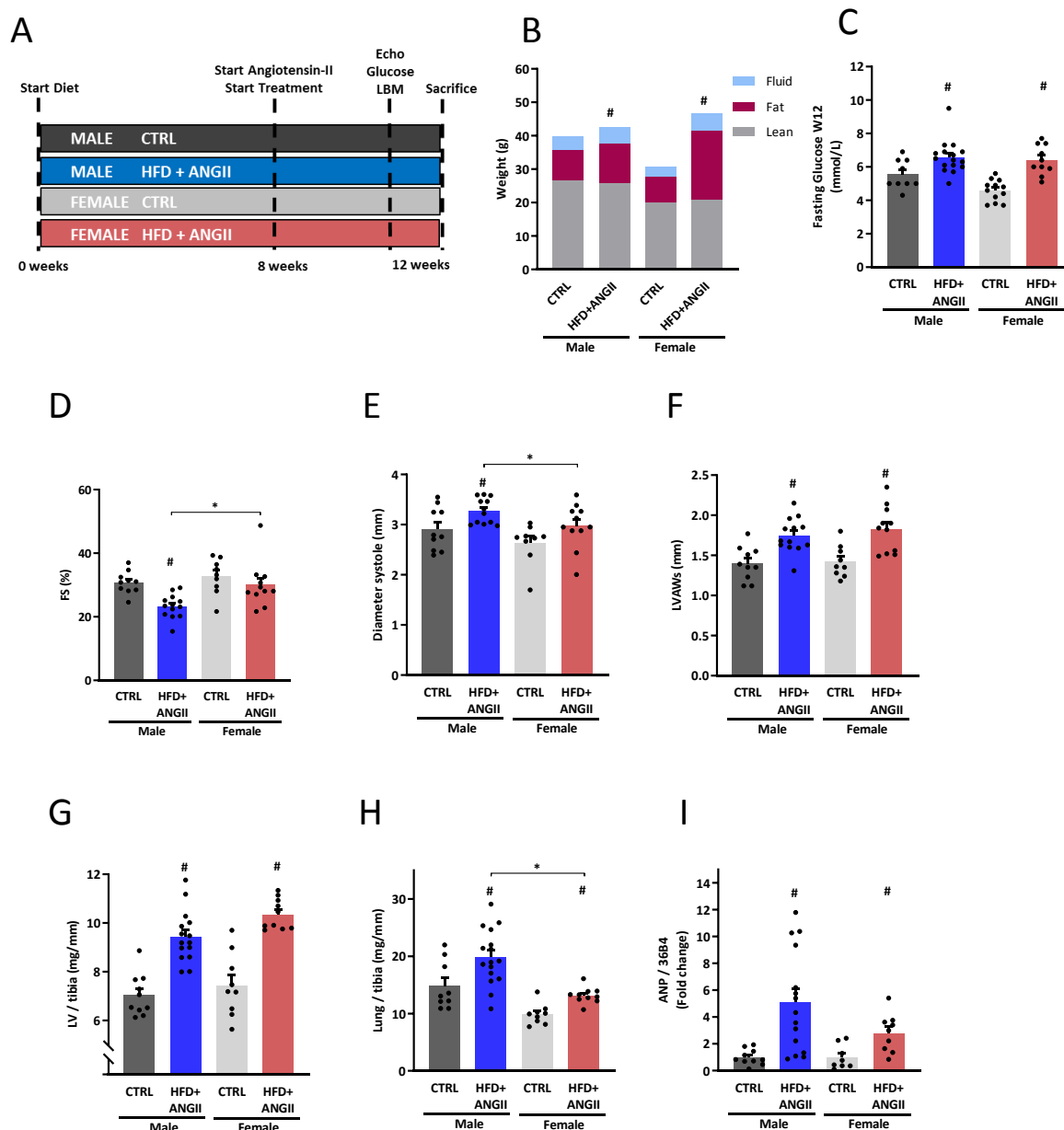
125

126 **Supplemental figure 3. Representative images of the Verhoeff-Van Gieson staining.**

127 A and B) representative image of CTRL animals. C and D) representative images of HFD+ANGII animals. Elastin in

128 black, collagen in red, endothelial cells in brown and blood cells in gold.

129



130  
 131 **Supplemental figure 3. Old male and female mice subjected to HFD+ANGII develop different phenotypes.**  
 132 A) Overview of experimental design. B) Body mass composition (fluid, fat, and lean mass) measured by minispec  
 133 LF90II body composition analyser (n=9-15 mice per group). C) Fasting glucose (n=9-15 mice per group). D)  
 134 Fractional shortening (FS, systolic function) (n=9-13 mice per group) E) LV end-systolic diameter (n=9-13 mice per  
 135 group). F) LVAWs = left ventricle anterior wall thickness in systole (n=9-13 mice per group). G) LV/tibia = left  
 136 ventricle weight corrected for tibia length (n=9-15 mice). H) Lung weight/tibia length (n=9-15 mice). I) LV mRNA  
 137 expression levels of Atrial Natriuretic Peptide (ANP) fold change compared to sex-matched controls (n=8-13 mice  
 138 per group).

139 CTRL = control chow. HFD+ANGII = Angiotensin-II treated group on high fat diet. Data are presented as means +  
140 SEM. # = compared to sex-matched controls \*= Male HFD +ANGII compared to Female HFD + ANGII. Kruskal Wallis  
141 test followed by Mann-Witney-U  $P < 0.05$  is considered significant.  
142