

Supplemental Material

Data S1.

Supplemental Methods

Human induced pluripotent stem cell derivation and culture

Cells were routinely maintained in B8 medium⁶ on 1:800 diluted growth factor-reduced Matrigel (Corning, 356230) in 6-well plates (Greiner).(22) B8 was supplemented with 2 μ M thiazovivin (LC Labs, T-9753), hereby referred to as B8T, for the first 24 h after passage. Media was then changed daily with B8. Cells were passaged at a ratio of ~1:15-20 every 4 days using 0.5 mM EDTA (Gibco, 15575020) in DPBS^{-/-}, achieving ~80% confluence.

CRISPR/Cas9 gRNA design

DNA oligos (IDT) encoding each gRNA with BbsI ligation overhangs were annealed and inserted into the BbsI restriction site of a pSpCas9(BB)-2A-Puro (PX459, Addgene 62988) plasmid. The constructed gRNA expression plasmids were confirmed by Sanger sequencing (Eurofins) with the LK01_5_primer (5'-GACTATCATATGCTTACCG-3').

CRISPR/Cas9-mediated knockout of candidate genes

hiPSCs were cultured in B8 medium to ~80% confluence. Cells were harvested using 0.5 mM EDTA for 6 min at room temperature and resuspended in B8T medium; 5×10^6 cells were electroporated with 5 μ g of each gRNA expression vector. Cells were maintained for 48 h in B8T medium supplemented with 0.5 μ g/mL puromycin (Gibco, A1113802). Puromycin-resistant individual colonies were picked and expanded ~10 days after electroporation. Genomic DNA was extracted from the cell pellets using a Quick-DNA Miniprep Plus kit (Zymo, D4068). Clones with

indels were identified by Sanger sequencing (Eurofins) with primers outside of the targeting region. Indels were detected using an online tool (<https://benchling.com>).

Quantitative Real-time PCR to assess the success of the candidate genes Knock out

RNA was isolated using TRIzol reagent (Invitrogen, 15596026) and Direct-zol RNA microprep kit (Zymo, R2062) including on-column DNase digestion to remove genomic DNA. cDNA was produced from 2 µg of total RNA using a Maxima H Minus cDNA Synthesis Master Mix (Thermo Scientific, M1662). All PCR reactions were performed in triplicate in a 384-well plate format using TaqMan Gene Expression Master Mix (Applied Biosystems, 4444557) in a QuantStudio 5 Real-Time PCR System (Applied Biosystems, A28140). **Table S5** summarizes TaqMan probes. Relative quantification of gene expression was calculated using $2^{-\Delta\Delta C_t}$ method, normalized to the reference 18S and untreated control samples.

Cardiac differentiation

2-3 wells of hiPSC from a ~80% confluent 6-well plate were passaged using 0.5 mM EDTA in to Matrigel-coated 15 cm cell culture dishes, and grown in B8 medium for 4 days reaching ~80% confluence.

At the start of differentiation (day 0), B8 medium was changed to R6C, consisting of RPMI 1640 (Corning, 10-040-CM), supplemented with 6 µM of glycogen synthase kinase-3 inhibitor CHIR99021 (LC Labs, C-6556). On day 1, medium was changed to RPMI, and on day 2 medium was changed to RBA-C59, consisting of RPMI supplemented with 2 mg/mL fatty acid-free bovine serum albumin (GenDEPOT, A0100), 200 µg/mL L-ascorbic acid 2-phosphate (Wako, 321-44823) and 0.5 µM Wnt-C59 (Biorbyt, orb181132). Medium was then changed on day 4 and then

every other day with RBAI consisting of RPMI supplemented with 0.5 mg/mL fatty acid-free bovine serum albumin, 200 µg/mL L-ascorbic acid 2-phosphate and 1 µg/mL *E. coli*-derived recombinant human insulin (Gibco, A11382IJ). Contracting cells were noted from day 7, and differentiated cardiomyocytes were treated with 25 µg/mL of Zeocin from day 10 to day 14. On day 20 of differentiation, cardiomyocytes were dissociated using DPBS for 20 min at 37 °C followed by 1:200 Liberase TH (Roche, 5401151001) diluted in DPBS for 20 min at 37 °C, centrifuged at $300 \times g$ for 5 min, counted and 40,000 cells were plated onto Matrigel-coated 384 well plate for cell viability assay after doxorubicin treatment in RBAI supplemented with 10% Cosmic Calf Serum (Cytiva, SH30087.03) for 48 h. RBAI was then changed every other day until day 30.

Doxorubicin treatment and cell viability assay

Doxorubicin hydrochloride (HY-15142, MedChem Express) was resuspended to 10 mM in cell culture-grade water (Corning), and aliquots were stored at -20 °C. Day 30 hiPSC-CMs were treated for 72 h with doxorubicin (0.01-100 µM) diluted in RPMI 1640 medium (Corning) supplemented with 500 µg/mL fatty acid-free bovine serum albumin (BSA) (GenDEPOT, A0100). Cell viability was assessed after 72 h of doxorubicin (0.01-100 µM) using a resazurin assay. Resazurin sodium salt (Thermo, B2118703) was diluted to 5 mg/mL in sterile ultrapure water and 600 µL frozen aliquots were made. One aliquot was added to 14.4 mL of DPBS and then further diluted 1:10 in RPMI. This was added to the cells 25 µL/well and incubated at 37 °C for 2.5 h. Fluorescence was measured using a VarioSkan Lux Multi-Mode Reader (Thermo Scientific) using top read, an excitation wavelength of 560 nm, and an emission wavelength of 590 nm. Data were presented as mean \pm SEM. Comparisons were conducted via one way-ANOVA test, an unpaired two-tailed Student's t-test, or F-test. The experiments were not randomized, and the investigators were not

blinded to allocation during experiments and outcome assessment. Data were analyzed using Excel and graphed using Prism 7.0 software (GraphPad), depicting standard dose-response guidelines.

Table S1. List of Hallmark gene sets included and excluded from the analysis.

HALLMARK GENE SET NAME	ORIGINAL SIZE	AFTER RESTRICTING TO DATASET	STATUS
TNFA_SIGNALING_VIA_NFKB	200	169	
HYPOXIA	200	146	
CHOLESTEROL_HOMEOSTASIS	74	62	
MITOTIC_SPINDLE	199	187	
WNT_BETA_CATENIN_SIGNALING	42	36	
TGF_BETA_SIGNALING	54	45	
IL6_JAK_STAT3_SIGNALING	87	68	
DNA_REPAIR	150	144	
G2M_CHECKPOINT	200	180	
APOPTOSIS	161	138	
NOTCH_SIGNALING	32	27	
ADIPOGENESIS	200	168	
ESTROGEN_RESPONSE_EARLY	200	138	
ESTROGEN_RESPONSE_LATE	200	134	
ANDROGEN_RESPONSE	100	87	
MYOGENESIS	200	118	
PROTEIN_SECRETION	96	89	
INTERFERON_ALPHA_RESPONSE	97	94	
INTERFERON_GAMMA_RESPONSE	200	189	
APICAL_JUNCTION	200	132	
APICAL_SURFACE	44	28	
HEDGEHOG_SIGNALING	36	24	
COMPLEMENT	200	161	
UNFOLDED_PROTEIN_RESPONSE	113	108	
PI3K_AKT_MTOR_SIGNALING	105	92	
MTORC1_SIGNALING	200	192	
E2F_TARGETS	200	187	
MYC_TARGETS_V1	200	199	
MYC_TARGETS_V2	58	57	
EPITHELIAL_MESENCHYMAL_TRANSITION	200	103	
INFLAMMATORY_RESPONSE	200	148	
XENOBIOTIC_METABOLISM	200	136	
FATTY_ACID_METABOLISM	158	130	
OXIDATIVE_PHOSPHORYLATION	200	196	
GLYCOLYSIS	200	149	
REACTIVE_OXYGEN_SPECIES_PATHWAY	49	48	
P53_PATHWAY	200	173	
UV_RESPONSE_UP	158	125	

HALLMARK GENE SET NAME	ORIGINAL SIZE	AFTER RESTRICTING TO DATASET	STATUS
TNFA_SIGNALING_VIA_NFKB	200	169	
HYPOXIA	200	146	
CHOLESTEROL_HOMEOSTASIS	74	62	
MITOTIC_SPINDLE	199	187	
WNT_BETA_CATENIN_SIGNALING	42	36	
TGF_BETA_SIGNALING	54	45	
UV_RESPONSE_DN	144	104	
ANGIOGENESIS	36	21	
HEME_METABOLISM	200	186	
COAGULATION	138	82	
IL2_STAT5_SIGNALING	199	172	
BILE_ACID_METABOLISM	112	77	
PEROXISOME	104	89	
ALLOGRAFT_REJECTION	200	166	
SPERMATOGENESIS	135	64	
KRAS_SIGNALING_UP	200	134	
KRAS_SIGNALING_DN	200	81	
PANCREAS_BETA_CELLS	40	-	Rejected!

Table S2. List of Cardiomyopathy gene sets and their sizes included and excluded from the analysis.

CARDIOMYOPATHY GENE SET NAME	ORIGINAL SIZE	AFTER RESTRICTING TO DATASET	STATUS
CHEN_LVAD_SUPPORT_OF_FAILING_HEART_DN	42	25	
CHEN_LVAD_SUPPORT_OF_FAILING_HEART_UP	102	70	
HP_ASYMMETRIC_SEPTAL_HYPERTROPHY	11		Rejected!
HP_CONCENTRIC_HYPERTROPHIC_CARDIOMYOPATHY	16		Rejected!
HP_DILATED_CARDIOMYOPATHY	148	97	
HP_HYPERTROPHIC_CARDIOMYOPATHY	254	206	
HP_NONCOMPACTION_CARDIOMYOPATHY	9		Rejected!
HP_RESTRICTIVE_CARDIOMYOPATHY	15		Rejected!
HP_RIGHT_VENTRICULAR_CARDIOMYOPATHY	9		Rejected!
KAAB_FAILED_HEART_ATRIUM_DN	147	129	
KAAB_FAILED_HEART_ATRIUM_UP	36	23	
KAAB_FAILED_HEART_VENTRICLE_DN	44	34	
KAAB_HEART_ATRIUM_VS_VENTRICLE_DN	262	194	
KAAB_HEART_ATRIUM_VS_VENTRICLE_UP	256	174	
KEGG_ARRHYTHMOGENIC_RIGHT_VENTRICULAR_CARDIOMYOPATHY_ARVC	74	45	
KEGG_DILATED_CARDIOMYOPATHY	90	51	
KEGG_HYPERTROPHIC_CARDIOMYOPATHY_HCM	83	49	
KEGG_VIRAL_MYOCARDITIS	70	51	
WP_ARRHYTHMOGENIC_RIGHT_VENTRICULAR_CARDIOMYOPATHY	76	45	

Table S3. Prioritization of Differentially Expressed Genes.

Gene Symbol	Fold Change	Padj	Gene biotype	Heart disease association or biological function	Count of Matched pair upregulated (cases)/Total matched pairs	Expressed in Adult Heart (Y/N/L)	Expressed in hiPSC-CMs (Y/N/L)
<i>LDHA</i>	Leading Edge GSEA Analysis		protein_coding	Significantly increased in the heart under hemodynamic stress, and cardiomyocyte-specific deletion of <i>LDHA</i> in mice leads to severe cardiac dysfunction in response to pressure overload	24/40	Y	Y
<i>NKX3.1</i>	-2.04	3.25E-02	protein_coding	Transcription factors involved in regulation of cardiac gene transcription and expression or associated with the response of cardiac tissue to stress	24/40	Y	Y
<i>ANKRD9</i>	2.11	1.68E-03	protein_coding	Role in hypertension and myocardial repolarization. Involved in intracellular lipid accumulation	20/40	Y	Y
<i>RAP1GAP</i>	4.09	6.89E-04	protein_coding	Mediates Ang II-induced cardiomyocyte hypertrophy	20/40	L	Y
<i>FAM20A</i>	2.48	5.15E-06	protein_coding	FAM20A controls FAM20C localization. FAM20C protects against heart failure	16/40	Y	Y
<i>SLC6A9</i>	2.30	3.78E-03	protein_coding	Gene Variants associated with Human Essential Hypertension. DEG in Cardiomyocytes 2 Days Post Myocardial Infarction	12/40	Y	Y
<i>DAAM2</i>	2.03	2.93E-02	protein_coding	DAAM1 and DAAM2 are co-required for myocardial maturation and sarcomere assembly	4/40	Y	Y
<i>IFI27</i>	5.93	6.55E-06	protein_coding	Patented coronary heart disease diagnosis marker	21/40	Y	N
<i>KLC3</i>	2.01	1.25E-02	protein_coding	Gene Variants in Coronary Artery Disease	14/40	Y	N

Gene Symbol	Fold Change	Padj	Gene biotype	Heart disease association or biological function	Count of Matched pair upregulated (cases)/Total matched pairs	Expressed in Adult Heart (Y/N/L)	Expressed in hiPSC-CMs (Y/N/L)
<i>ALAS2</i>	2.29	7.42E-03	protein_coding	Increased heme accumulation (through cardiac overexpression of ALAS2) leads to increased oxidative stress and cell death in the heart	21/40	N	Y
<i>KLHDC8A</i>	2.06	3.09E-03	protein_coding	DEG in Cardiomyocytes 2 Days Post Myocardial Infarction and Paeoniflorin (PF) attenuated cardiac hypertrophy	15/40	N	Y
<i>ITLN1</i>	2.09	7.61E-03	protein_coding	Myocardial injury leads to a decrease in ITLN1 expression in the heart and a corresponding increase in plasma levels	12/40	N	Y
<i>HBG2</i>	4.00	1.20E-03	protein_coding	Associated with 40 diseases including cardiovascular diseases	23/40	N	N
<i>HBD</i>	3.43	2.36E-04	protein_coding	HBD activity a promising aid in the detection of myocardial infarction. Elevation of serum HBD occurred more frequently than a concurrent rise in serum GOT or LDH	25/40	N	N
<i>ARG1</i>	3.23	1.42E-05	protein_coding	Gene polymorphisms in idiopathic dilated cardiomyopathy. Role in AMI	20/40	N	N
<i>CD177</i>	2.70	7.67E-03	protein_coding	Abundance of CD177 transcript in acute Kawasaki Disease (acquired heart disease in children)	24/40	N	N
<i>GYPB</i>	2.69	7.92E-03	protein_coding	Differentially Expressed Gene in Coronary Heart Disease. Greatest Fold-Change in Expression During CVD Risk Factor Modification	21/40	N	N
<i>ORM1</i>	2.61	7.17E-04	protein_coding	Orosomuroid 1 Attenuates Doxorubicin-Induced Oxidative	21/40	N	N

Gene Symbol	Fold Change	Padj	Gene biotype	Heart disease association or biological function	Count of Matched pair upregulated (cases)/Total matched pairs	Expressed in Adult Heart (Y/N/L)	Expressed in hiPSC-CMs (Y/N/L)
				Stress and Apoptosis in Cardiomyocytes via Nrf2 Signaling			
<i>AHSP</i>	2.56	2.19E-03	protein_coding	α -hemoglobin–stabilizing protein regulates arteriolar contractility	25/40	N	N
<i>MCEMP1</i>	2.50	6.35E-06	protein_coding	MCEMP1 Gene Expression in cardiac cell lineage specific cardiac injury and repair	24/40	N	N
<i>IFIT1B</i>	2.36	4.40E-03	protein_coding	Upregulated genes for congenital heart block versus healthy flow-sorted cardiac fibroblasts. Biphasic and cardiomyocyte-specific IFIT activity protects cardiomyocytes from enteroviral infection	21/40	N	N
<i>CA1</i>	2.34	2.78E-02	protein_coding	Carbonic Anhydrase Activation Is Associated With Worsened Pathological Remodeling in Human Ischemic Diabetic Cardiomyopathy	24/40	N	N
<i>TSPO2</i>	2.31	3.78E-03	protein_coding	Involved in Cholesterol Redistribution. Key gene involved in myocardial infarction	11/40	N	N
<i>KLF1</i>	2.29	3.41E-03	protein_coding	KLF protein disorders are involved in the pathogenesis of cardiovascular disease, such as cardiac development, cardiac hypertrophy, and atherosclerosis. Krüppel-like factor 1 (KLF-1) as a mediator of a cytoprotective response that dictates longevity induced by reduced mitochondrial function	13/40	N	N

Gene Symbol	Fold Change	Padj	Gene biotype	Heart disease association or biological function	Count of Matched pair upregulated (cases)/Total matched pairs	Expressed in Adult Heart (Y/N/L)	Expressed in hiPSC-CMs (Y/N/L)
<i>MMP8</i>	2.24	1.75E-02	protein_coding	Indicator of Left Ventricular Remodeling and Cardiac Outcome in Patients after Acute Myocardial Infarction	17/40	N	N
<i>OLFM4</i>	2.19	4.32E-02	protein_coding	Greatest Fold-Change in Expression During CVD Risk Factor Modification		N	N
<i>HP</i>	2.17	1.67E-03	protein_coding	Inflammatory indicator in cardiovascular disease	25/40	N	N
<i>VSIG4</i>	2.16	5.24E-04	protein_coding	Right Ventricular Myocardial Biomarkers in Human Heart Failure	13/40	N	N
<i>S100A12</i>	2.14	4.91E-04	protein_coding	Biomarker for predicting cardiovascular events	23/40	N	N
<i>SPTA1</i>	2.14	4.40E-03	protein_coding	Spectrins regulates cardiac function	13/40	N	N
<i>KRT1</i>	2.04	2.60E-02	protein_coding	Keratin-1 is a novel binding protein for C-reactive protein. CRP correlates with cardiovascular disease and endothelial dysfunction	22/40	N	N
<i>CEACAM8</i>	2.01	5.12E-02	protein_coding	Dietary Pattern Specific Protein Biomarkers for Cardiovascular Disease	14/40	N	N
<i>ZDHHC19</i>	2.04	1.20E-03	protein_coding	ZDHHC19 promote STAT3 activation. STAT3 is involved in the protective mechanisms against different cardiac pathologies	9/40	N	N
<i>HLA-DRB6</i>	2.14	3.57E-02	transcribed_unprocessed_pseudogene		NA		
-	2.19	5.02E-03	lncRNA		NA		
<i>FCGR1CP</i>	2.17	3.57E-04	unprocessed_pseudogene		NA		

Gene Symbol	Fold Change	Padj	Gene biotype	Heart disease association or biological function	Count of Matched pair upregulated (cases)/Total matched pairs	Expressed in Adult Heart (Y/N/L)	Expressed in hiPSC-CMs (Y/N/L)
<i>IGKV1-27</i>	2.01	6.04E-03	IG_V_gene		NA		

Abbreviations: Y: Yes, N: N, L: Low

Table S4. List of primers used to validate CRISPR/Cas9-mediated genome editing using Sanger sequencing.

<i>LDHA</i> -KO	Exon2- F	5' TGAGGAAAGGCCAGCCCCACTT 3'
	Exon2- R	5' AGTGGGGGTAGAGGATGGGGTCA 3'

Table S5. List of TaqMan probes used for RT-PCR to verify successful CRISPR/Cas9-mediated genome editing.

Gene	TaqMan primers and probe
<i>LDHA</i>	Hs00855332 Applied Biosystems

Table S6. GSEA Heat Map list of genes.

NAME	SCORE	NAME	SCORE
<i>LDHA</i>	0.4979	<i>ZNF789</i>	-0.3589
<i>TP53I3</i>	0.4971	<i>C12orf42</i>	-0.3594
<i>GAPDH</i>	0.4730	<i>LMLN</i>	-0.3613
<i>SEMA6B</i>	0.4677	<i>DENND2C</i>	-0.3629
<i>LGALS1</i>	0.4630	<i>ZNF850</i>	-0.3638
<i>AP1S1</i>	0.4603	<i>RNF144A</i>	-0.3646
<i>ACAA1</i>	0.4469	<i>TRABD2A</i>	-0.3655
<i>METTL9</i>	0.4469	<i>RNF43</i>	-0.3664
<i>C19orf38</i>	0.4444	<i>NPIP3</i>	-0.3665
<i>FCGR1CP</i>	0.4410	<i>BCL11B</i>	-0.3665
<i>EXOSC4</i>	0.4408	<i>ZNF491</i>	-0.3674
<i>LAMTOR5</i>	0.4402	<i>HMGB3P32</i>	-0.3675
<i>TIMM13</i>	0.4388	<i>KLHL3</i>	-0.3680
<i>SLC39A1</i>	0.4296	<i>KAT6B</i>	-0.3681
<i>DUSP3</i>	0.4263	<i>ZNF891</i>	-0.3689
<i>PHETA2</i>	0.4240	<i>ZNF827</i>	-0.3695
<i>SMARCD3</i>	0.4223	<i>CROCCP3</i>	-0.3723
<i>MS4A4A</i>	0.4190	<i>ADGRF3</i>	-0.3724
<i>PCBD1</i>	0.4187	<i>CDHR3</i>	-0.3726
<i>MIIP</i>	0.4185	<i>HP1BP3</i>	-0.3737
<i>CD36</i>	0.4160	<i>RN7SL842P</i>	-0.3753
<i>ATP5MF</i>	0.4146	<i>AAK1</i>	-0.3764
<i>TMEM11</i>	0.4121	<i>EXOSC6</i>	-0.3779
<i>COX5A</i>	0.4115	<i>AKT3</i>	-0.3788
<i>MS4A6A</i>	0.4105	<i>LINC00299</i>	-0.3805
<i>DYNLL1</i>	0.4096	<i>SLC16A10</i>	-0.3810
<i>PLP2</i>	0.4086	<i>TRBJ1-6</i>	-0.3884
<i>RNF181</i>	0.4082	<i>RPS2P55</i>	-0.3903
<i>GBGT1</i>	0.4081	<i>FAM169A</i>	-0.3906
<i>SNAPIN</i>	0.4066	<i>RNF125</i>	-0.3909
<i>NOL3</i>	0.4063	<i>CEP126</i>	-0.3914
<i>TOMM40L</i>	0.4062	<i>TSPOAP1</i>	-0.3967
<i>PGK1</i>	0.4054	<i>TUBG1P</i>	-0.3972
<i>ECE2</i>	0.4049	<i>TDRKH</i>	-0.3974
<i>SERPINB1</i>	0.4045	<i>ABI2</i>	-0.4021
<i>HEIH</i>	0.4043	<i>ATM</i>	-0.4098
<i>LILRB4</i>	0.4041	<i>NINL</i>	-0.4098
<i>IDH1</i>	0.4033	<i>GABPB2</i>	-0.4115

NAME	SCORE	NAME	SCORE
<i>BLOC1S1</i>	0.4028	<i>TRBJ1-3</i>	-0.4128
<i>HK3</i>	0.4027	<i>SEPTIN7P2</i>	-0.4216
<i>CATSPER1</i>	0.4019	<i>TNRC6C</i>	-0.4238
<i>CTSH</i>	0.4011	<i>ARL10</i>	-0.4256
<i>MPDU1</i>	0.3997	<i>LRRC37A16P</i>	-0.4261
<i>SIL1</i>	0.3987	<i>NBPF15</i>	-0.4265
<i>MGST1</i>	0.3956	<i>MFSD13B</i>	-0.4276
<i>TUBA1B</i>	0.3950	<i>CARMIL1</i>	-0.4284
<i>ZG16B</i>	0.3941	<i>MAP3K9</i>	-0.4392
<i>CNTLN</i>	0.3938	<i>EPPK1</i>	-0.4404
<i>IFITM1</i>	0.3934	<i>KIF3A</i>	-0.4535

Table S7. Gene set (HALLMARK_ADIPOGENESIS) with genes up-regulated during adipocyte differentiation.

GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>CD36</i>	20	0.4160	0.0139	Yes
<i>IDH1</i>	37	0.4033	0.0275	Yes
<i>UQCR10</i>	117	0.3594	0.0349	Yes
<i>COX8A</i>	120	0.3583	0.0480	Yes
<i>CYC1</i>	147	0.3489	0.0589	Yes
<i>PIM3</i>	156	0.3469	0.0711	Yes
<i>COX6A1</i>	168	0.3438	0.0830	Yes
<i>ITGA7</i>	180	0.3415	0.0947	Yes
<i>SUCLG1</i>	288	0.3182	0.0985	Yes
<i>GPX4</i>	340	0.3111	0.1062	Yes
<i>CD151</i>	366	0.3070	0.1157	Yes
<i>IFNGR1</i>	377	0.3044	0.1262	Yes
<i>CDKN2C</i>	388	0.3025	0.1366	Yes
<i>STOM</i>	389	0.3022	0.1477	Yes
<i>MRPL15</i>	395	0.3015	0.1585	Yes
<i>UQCRC1</i>	408	0.3001	0.1686	Yes
<i>POR</i>	447	0.2948	0.1767	Yes
<i>NDUFB7</i>	489	0.2894	0.1843	Yes
<i>GADD45A</i>	514	0.2866	0.1931	Yes
<i>SQOR</i>	534	0.2845	0.2022	Yes
<i>ATP1B3</i>	536	0.2843	0.2126	Yes
<i>SDHB</i>	603	0.2767	0.2179	Yes
<i>ESRRA</i>	659	0.2706	0.2238	Yes
<i>DHRS7B</i>	661	0.2702	0.2337	Yes
<i>MTCH2</i>	810	0.2575	0.2322	Yes
<i>RAB34</i>	812	0.2574	0.2416	Yes
<i>MGST3</i>	827	0.2561	0.2500	Yes
<i>SLC1A5</i>	858	0.2538	0.2572	Yes
<i>RIOK3</i>	912	0.2503	0.2625	Yes
<i>JAGN1</i>	923	0.2492	0.2709	Yes
<i>ORM1</i>	950	0.2478	0.2781	Yes
<i>GHITM</i>	961	0.2468	0.2865	Yes
<i>FAH</i>	983	0.2451	0.2939	Yes
<i>CHCHD10</i>	984	0.2451	0.3030	Yes
<i>PREB</i>	1051	0.2411	0.3070	Yes
<i>TKT</i>	1071	0.2398	0.3144	Yes
<i>RETN</i>	1075	0.2397	0.3230	Yes

GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>UQCR11</i>	1079	0.2394	0.3316	Yes
<i>NDUFAB1</i>	1206	0.2330	0.3309	Yes
<i>BCL6</i>	1212	0.2326	0.3391	Yes
<i>ACADS</i>	1228	0.2316	0.3465	Yes
<i>NDUFS3</i>	1255	0.2298	0.3530	Yes
<i>ECH1</i>	1309	0.2271	0.3575	Yes
<i>ACAA2</i>	1347	0.2252	0.3631	Yes
<i>PFKFB3</i>	1350	0.2251	0.3712	Yes
<i>DRAM2</i>	1355	0.2248	0.3792	Yes
<i>REEP5</i>	1385	0.2233	0.3853	Yes
<i>ARL4A</i>	1455	0.2202	0.3883	Yes
<i>CRAT</i>	1568	0.2146	0.3879	Yes
<i>ME1</i>	1611	0.2121	0.3926	Yes
<i>COX7B</i>	1614	0.2120	0.4003	Yes
<i>UQCRQ</i>	1722	0.2062	0.3999	Yes
<i>ALDOA</i>	1752	0.2050	0.4054	Yes
<i>PRDX3</i>	1765	0.2045	0.4120	Yes
<i>CMBL</i>	1851	0.2003	0.4131	Yes
<i>UCK1</i>	1896	0.1988	0.4172	Yes
<i>IDH3G</i>	1935	0.1969	0.4216	Yes
<i>DECR1</i>	2016	0.1934	0.4228	Yes
<i>LPCAT3</i>	2066	0.1909	0.4262	Yes
<i>ETFB</i>	2116	0.1893	0.4296	Yes
<i>DGAT1</i>	2142	0.1881	0.4346	Yes
<i>UCP2</i>	2143	0.1881	0.4416	Yes
<i>UBC</i>	2196	0.1854	0.4446	Yes
<i>PGM1</i>	2274	0.1829	0.4456	Yes
<i>DHRS7</i>	2323	0.1807	0.4487	Yes
<i>ATP5PO</i>	2332	0.1804	0.4548	Yes
<i>DLD</i>	2414	0.1772	0.4553	Yes
<i>MGLL</i>	2504	0.1738	0.4551	Yes
<i>GPAT4</i>	2534	0.1726	0.4593	Yes
<i>DHCR7</i>	2535	0.1725	0.4657	Yes
<i>C3</i>	2561	0.1712	0.4701	Yes
<i>MDH2</i>	2562	0.1712	0.4764	Yes
<i>TALDO1</i>	2633	0.1688	0.4775	Yes
<i>RNF11</i>	2635	0.1687	0.4836	Yes
<i>UBQLN1</i>	2735	0.1650	0.4824	Yes
<i>COQ3</i>	2801	0.1625	0.4836	Yes

GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>GPD2</i>	2813	0.1620	0.4887	Yes
<i>SAMM50</i>	2834	0.1614	0.4932	Yes
<i>COQ5</i>	2887	0.1592	0.4952	Yes
<i>SOD1</i>	3000	0.1552	0.4926	Yes
<i>ITSN1</i>	3024	0.1545	0.4966	Yes
<i>PLIN2</i>	3033	0.1544	0.5017	Yes
<i>PEMT</i>	3379	0.1424	0.4814	No
<i>APLP2</i>	3487	0.1387	0.4786	No
<i>DNAJC15</i>	3538	0.1369	0.4799	No
<i>ALDH2</i>	3553	0.1364	0.4839	No
<i>QDPR</i>	3593	0.1350	0.4860	No
<i>ARAF</i>	3594	0.1349	0.4910	No
<i>NABP1</i>	3630	0.1340	0.4933	No
<i>COQ9</i>	3784	0.1291	0.4868	No
<i>TST</i>	3797	0.1287	0.4906	No
<i>GRPEL1</i>	3844	0.1273	0.4919	No
<i>SLC25A1</i>	3853	0.1269	0.4960	No
<i>PEX14</i>	3891	0.1258	0.4979	No
<i>ECHS1</i>	4233	0.1149	0.4769	No
<i>SULT1A1</i>	4238	0.1148	0.4808	No
<i>STAT5A</i>	4260	0.1142	0.4835	No
<i>RTN3</i>	4268	0.1140	0.4871	No
<i>TANK</i>	4289	0.1134	0.4898	No
<i>ABCA1</i>	4382	0.1107	0.4871	No
<i>ELOVL6</i>	4436	0.1086	0.4872	No
<i>PHYH</i>	4463	0.1074	0.4892	No
<i>DNAJB9</i>	4488	0.1065	0.4914	No
<i>GBE1</i>	4607	0.1018	0.4864	No
<i>RETSAT</i>	4696	0.0994	0.4835	No
<i>HADH</i>	4767	0.0972	0.4819	No
<i>AGPAT3</i>	4817	0.0956	0.4818	No
<i>CD302</i>	4820	0.0955	0.4852	No
<i>AK2</i>	4832	0.0952	0.4879	No
<i>SCP2</i>	4842	0.0949	0.4907	No
<i>ACO2</i>	4858	0.0942	0.4931	No
<i>SLC66A3</i>	4946	0.0912	0.4900	No
<i>NKIRAS1</i>	5028	0.0890	0.4873	No
<i>NDUFA5</i>	5235	0.0829	0.4751	No
<i>SLC19A1</i>	5365	0.0790	0.4684	No

GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>SLC27A1</i>	5366	0.0789	0.4713	No
<i>CAT</i>	5431	0.0767	0.4694	No
<i>ELMOD3</i>	5454	0.0762	0.4706	No
<i>BCL2L13</i>	5710	0.0679	0.4542	No
<i>IDH3A</i>	5861	0.0627	0.4454	No
<i>ACOX1</i>	5992	0.0582	0.4379	No
<i>CHUK</i>	6077	0.0555	0.4338	No
<i>SCARB1</i>	6213	0.0515	0.4257	No
<i>YWHAG</i>	6238	0.0507	0.4258	No
<i>MIGA2</i>	6258	0.0500	0.4262	No
<i>ADIPOR2</i>	6417	0.0454	0.4162	No
<i>AIFM1</i>	6485	0.0436	0.4128	No
<i>PFKL</i>	6510	0.0428	0.4126	No
<i>NMT1</i>	6720	0.0366	0.3985	No
<i>ENPP2</i>	6781	0.0345	0.3953	No
<i>ACADM</i>	7207	0.0213	0.3646	No
<i>REEP6</i>	7450	0.0138	0.3472	No
<i>IMMT</i>	7499	0.0124	0.3441	No
<i>ACLY</i>	7534	0.0112	0.3420	No
<i>RREB1</i>	7628	0.0082	0.3354	No
<i>CS</i>	8013	-0.0042	0.3071	No
<i>SDHC</i>	8388	-0.0153	0.2800	No
<i>HIBCH</i>	8585	-0.0217	0.2663	No
<i>MCCC1</i>	8670	-0.0244	0.2610	No
<i>MAP4K3</i>	8722	-0.0261	0.2581	No
<i>MYLK</i>	8740	-0.0266	0.2579	No
<i>ABCB8</i>	9158	-0.0401	0.2285	No
<i>DLAT</i>	9306	-0.0453	0.2192	No
<i>CPT2</i>	9472	-0.0498	0.2089	No
<i>SOWAHC</i>	9512	-0.0510	0.2079	No
<i>PTCD3</i>	9703	-0.0570	0.1959	No
<i>SLC5A6</i>	9794	-0.0610	0.1915	No
<i>RMDN3</i>	9804	-0.0615	0.1931	No
<i>ATL2</i>	9894	-0.0647	0.1889	No
<i>PPM1B</i>	10161	-0.0737	0.1719	No
<i>VEGFB</i>	10386	-0.0813	0.1583	No
<i>LIPE</i>	10463	-0.0840	0.1558	No
<i>G3BP2</i>	10565	-0.0882	0.1515	No
<i>GPX3</i>	10594	-0.0894	0.1527	No

GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>GPHN</i>	10615	-0.0902	0.1546	No
<i>PPP1R15B</i>	10727	-0.0940	0.1498	No
<i>GPAM</i>	10822	-0.0984	0.1465	No
<i>CAVIN2</i>	10850	-0.0997	0.1482	No
<i>SSPN</i>	10930	-0.1031	0.1461	No
<i>CMPK1</i>	11063	-0.1088	0.1404	No
<i>ANGPT1</i>	11332	-0.1207	0.1250	No
<i>TOB1</i>	11621	-0.1331	0.1085	No
<i>ESYT1</i>	11932	-0.1497	0.0911	No
<i>DBT</i>	12083	-0.1579	0.0858	No
<i>BAZ2A</i>	12346	-0.1736	0.0728	No
<i>CCNG2</i>	12597	-0.1918	0.0614	No
<i>EPHX2</i>	13023	-0.2314	0.0384	No
<i>PDCD4</i>	13231	-0.2559	0.0325	No

Table S8. Gene set (HALLMARK_OXIDATIVE_PHOSPHORYLATION) with genes encoding proteins involved in oxidative phosphorylation.

GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>LDHA</i>	0	0.4979	0.0137	Yes
<i>ACAA1</i>	6	0.4469	0.0257	Yes
<i>TIMM13</i>	12	0.4388	0.0374	Yes
<i>ATP5MF</i>	21	0.4146	0.0482	Yes
<i>COX5A</i>	23	0.4115	0.0595	Yes
<i>IDH1</i>	37	0.4033	0.0697	Yes
<i>NDUFS6</i>	71	0.3814	0.0777	Yes
<i>COX6B1</i>	88	0.3742	0.0869	Yes
<i>UQCR10</i>	117	0.3594	0.0947	Yes
<i>COX8A</i>	120	0.3583	0.1044	Yes
<i>ATP6V1C1</i>	121	0.3574	0.1143	Yes
<i>UQCRRS1</i>	129	0.3535	0.1235	Yes
<i>CYC1</i>	147	0.3489	0.1319	Yes
<i>ATP5PD</i>	150	0.3481	0.1413	Yes
<i>HSD17B10</i>	166	0.3442	0.1497	Yes
<i>COX6A1</i>	168	0.3438	0.1591	Yes
<i>HTRA2</i>	181	0.3415	0.1676	Yes
<i>ATP5F1B</i>	225	0.3296	0.1735	Yes
<i>ATP6V1F</i>	230	0.3287	0.1823	Yes
<i>SLC25A5</i>	267	0.3220	0.1885	Yes
<i>ETFA</i>	275	0.3203	0.1968	Yes
<i>SUCLG1</i>	288	0.3182	0.2047	Yes
<i>ATP5MC1</i>	291	0.3178	0.2133	Yes
<i>NDUFB4</i>	303	0.3160	0.2212	Yes
<i>MRPS15</i>	331	0.3128	0.2278	Yes
<i>GPX4</i>	340	0.3111	0.2358	Yes
<i>MRPL15</i>	395	0.3015	0.2401	Yes
<i>UQCRC1</i>	408	0.3001	0.2475	Yes
<i>POR</i>	447	0.2948	0.2528	Yes
<i>ECI1</i>	470	0.2911	0.2592	Yes
<i>NDUFA3</i>	482	0.2900	0.2664	Yes
<i>NDUFB7</i>	489	0.2894	0.2739	Yes
<i>ATP5F1A</i>	540	0.2836	0.2780	Yes
<i>ATP6V0E1</i>	551	0.2825	0.2851	Yes
<i>ATP5MC3</i>	555	0.2821	0.2926	Yes
<i>NDUFA8</i>	567	0.2812	0.2996	Yes
<i>RHOT1</i>	580	0.2797	0.3064	Yes

GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>SDHB</i>	603	0.2767	0.3124	Yes
<i>ATP5F1E</i>	660	0.2705	0.3157	Yes
<i>MRPS11</i>	663	0.2700	0.3230	Yes
<i>CYB5R3</i>	665	0.2698	0.3304	Yes
<i>TIMM8B</i>	684	0.2677	0.3364	Yes
<i>ATP5F1C</i>	716	0.2653	0.3414	Yes
<i>MRPS12</i>	730	0.2643	0.3477	Yes
<i>NDUFA2</i>	768	0.2608	0.3522	Yes
<i>MRPL11</i>	772	0.2606	0.3592	Yes
<i>NDUFA6</i>	777	0.2603	0.3660	Yes
<i>TIMM10</i>	798	0.2587	0.3717	Yes
<i>UQCRC2</i>	821	0.2565	0.3771	Yes
<i>MGST3</i>	827	0.2561	0.3838	Yes
<i>COX5B</i>	841	0.2552	0.3899	Yes
<i>SURF1</i>	853	0.2541	0.3961	Yes
<i>PHB2</i>	856	0.2539	0.4029	Yes
<i>ATP6V0B</i>	901	0.2507	0.4066	Yes
<i>SLC25A11</i>	924	0.2491	0.4118	Yes
<i>OXA1L</i>	960	0.2469	0.4160	Yes
<i>NDUFA4</i>	987	0.2449	0.4208	Yes
<i>HCCS</i>	1017	0.2436	0.4254	Yes
<i>ATP6V1D</i>	1031	0.2429	0.4311	Yes
<i>ATP5F1D</i>	1032	0.2428	0.4378	Yes
<i>ATP5MG</i>	1038	0.2420	0.4441	Yes
<i>NDUFC1</i>	1060	0.2406	0.4492	Yes
<i>UQCR11</i>	1079	0.2394	0.4545	Yes
<i>IDH2</i>	1110	0.2375	0.4588	Yes
<i>VDAC3</i>	1111	0.2375	0.4653	Yes
<i>ATP6V1E1</i>	1143	0.2361	0.4696	Yes
<i>BAX</i>	1164	0.2348	0.4745	Yes
<i>COX4I1</i>	1175	0.2345	0.4803	Yes
<i>ATP5ME</i>	1204	0.2330	0.4846	Yes
<i>NDUFAB1</i>	1206	0.2330	0.4910	Yes
<i>ATP5MC2</i>	1252	0.2299	0.4940	Yes
<i>NDUFS3</i>	1255	0.2298	0.5001	Yes
<i>NDUFS7</i>	1264	0.2294	0.5059	Yes
<i>UQCRH</i>	1295	0.2280	0.5099	Yes
<i>ECH1</i>	1309	0.2271	0.5152	Yes
<i>ACAA2</i>	1347	0.2252	0.5187	Yes

GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>NDUFB3</i>	1372	0.2236	0.5231	Yes
<i>ATP5PF</i>	1444	0.2207	0.5239	Yes
<i>NDUFA1</i>	1452	0.2204	0.5295	Yes
<i>COX7A2</i>	1458	0.2201	0.5352	Yes
<i>TCIRG1</i>	1492	0.2183	0.5387	Yes
<i>ATP1B1</i>	1502	0.2178	0.5441	Yes
<i>MRPS22</i>	1542	0.2159	0.5471	Yes
<i>FH</i>	1574	0.2141	0.5507	Yes
<i>COX7B</i>	1614	0.2120	0.5537	Yes
<i>ATP5PB</i>	1646	0.2106	0.5572	Yes
<i>NDUFS4</i>	1685	0.2081	0.5601	Yes
<i>UQCRCQ</i>	1722	0.2062	0.5631	Yes
<i>ACAT1</i>	1761	0.2046	0.5659	Yes
<i>PRDX3</i>	1765	0.2045	0.5714	Yes
<i>MRPL34</i>	1794	0.2030	0.5749	Yes
<i>HADHB</i>	1847	0.2005	0.5765	Yes
<i>NDUFS2</i>	1895	0.1989	0.5785	Yes
<i>IDH3G</i>	1935	0.1969	0.5811	Yes
<i>COX7C</i>	1953	0.1961	0.5852	Yes
<i>DECR1</i>	2016	0.1934	0.5860	Yes
<i>IDH3B</i>	2044	0.1922	0.5893	Yes
<i>MDH1</i>	2082	0.1903	0.5918	Yes
<i>ETFB</i>	2116	0.1893	0.5945	Yes
<i>ATP5PO</i>	2332	0.1804	0.5835	Yes
<i>TIMM9</i>	2334	0.1802	0.5884	Yes
<i>COX7A2L</i>	2353	0.1794	0.5920	Yes
<i>DLD</i>	2414	0.1772	0.5925	Yes
<i>OAT</i>	2448	0.1758	0.5949	Yes
<i>COX17</i>	2543	0.1721	0.5926	Yes
<i>NDUFB2</i>	2548	0.1719	0.5971	Yes
<i>MDH2</i>	2562	0.1712	0.6008	Yes
<i>HADHA</i>	2584	0.1702	0.6040	Yes
<i>GLUD1</i>	2776	0.1634	0.5943	Yes
<i>ISCA1</i>	2824	0.1617	0.5953	Yes
<i>VDAC1</i>	2938	0.1575	0.5912	Yes
<i>SLC25A12</i>	2997	0.1553	0.5912	Yes
<i>NQO2</i>	3026	0.1545	0.5934	Yes
<i>MTX2</i>	3031	0.1544	0.5974	Yes
<i>COX6C</i>	3039	0.1542	0.6011	Yes

GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>ISCU</i>	3084	0.1527	0.6020	Yes
<i>TOMM22</i>	3121	0.1516	0.6035	Yes
<i>NDUFB6</i>	3209	0.1486	0.6012	Yes
<i>SLC25A3</i>	3236	0.1475	0.6033	Yes
<i>ATP6AP1</i>	3312	0.1449	0.6018	Yes
<i>NDUFB1</i>	3320	0.1447	0.6052	Yes
<i>ATP6V1G1</i>	3349	0.1436	0.6071	Yes
<i>RHOT2</i>	3365	0.1430	0.6099	Yes
<i>PDHB</i>	3411	0.1413	0.6105	Yes
<i>COX15</i>	3452	0.1399	0.6114	Yes
<i>UQCRB</i>	3471	0.1392	0.6139	Yes
<i>TIMM17A</i>	3627	0.1341	0.6061	No
<i>TIMM50</i>	3790	0.1288	0.5976	No
<i>NDUFS8</i>	3814	0.1280	0.5994	No
<i>GRPEL1</i>	3844	0.1273	0.6008	No
<i>ACADVL</i>	3914	0.1248	0.5991	No
<i>CYB5A</i>	3925	0.1244	0.6018	No
<i>BDH2</i>	3990	0.1223	0.6004	No
<i>ABCB7</i>	4021	0.1212	0.6015	No
<i>ECHS1</i>	4233	0.1149	0.5890	No
<i>MFN2</i>	4355	0.1115	0.5831	No
<i>SUCLA2</i>	4441	0.1083	0.5798	No
<i>PHYH</i>	4463	0.1074	0.5812	No
<i>GPI</i>	4568	0.1036	0.5764	No
<i>NDUFB5</i>	4646	0.1007	0.5734	No
<i>VDAC2</i>	4672	0.1000	0.5743	No
<i>RETSAT</i>	4696	0.0994	0.5754	No
<i>ACO2</i>	4858	0.0942	0.5660	No
<i>ATP6V1H</i>	4901	0.0929	0.5655	No
<i>NDUFC2</i>	5001	0.0896	0.5606	No
<i>NDUFV1</i>	5020	0.0892	0.5617	No
<i>ATP6V0C</i>	5046	0.0884	0.5623	No
<i>NDUFA5</i>	5235	0.0829	0.5506	No
<i>MRPL35</i>	5702	0.0681	0.5179	No
<i>IDH3A</i>	5861	0.0627	0.5079	No
<i>ALAS1</i>	5912	0.0608	0.5059	No
<i>OPA1</i>	6014	0.0573	0.5000	No
<i>SDHA</i>	6043	0.0564	0.4994	No
<i>NDUFB8</i>	6162	0.0528	0.4921	No

GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>CYCS</i>	6352	0.0472	0.4794	No
<i>PDP1</i>	6484	0.0436	0.4709	No
<i>AIFM1</i>	6485	0.0436	0.4721	No
<i>NDUFV2</i>	6488	0.0435	0.4732	No
<i>PDHA1</i>	6493	0.0434	0.4741	No
<i>LDHB</i>	6540	0.0419	0.4718	No
<i>MPC1</i>	6631	0.0389	0.4662	No
<i>CASP7</i>	6696	0.0371	0.4625	No
<i>PMPCA</i>	6714	0.0366	0.4622	No
<i>PDHX</i>	6738	0.0359	0.4615	No
<i>COX10</i>	6761	0.0350	0.4608	No
<i>SLC25A20</i>	6908	0.0314	0.4509	No
<i>OGDH</i>	6923	0.0308	0.4507	No
<i>ETFDH</i>	6936	0.0304	0.4506	No
<i>LRPPRC</i>	7065	0.0260	0.4418	No
<i>SDHD</i>	7137	0.0235	0.4372	No
<i>ACADM</i>	7207	0.0213	0.4327	No
<i>AFG3L2</i>	7272	0.0193	0.4285	No
<i>FDX1</i>	7279	0.0192	0.4285	No
<i>IMMT</i>	7499	0.0124	0.4126	No
<i>CPT1A</i>	7618	0.0087	0.4041	No
<i>MRPS30</i>	7980	-0.0032	0.3774	No
<i>GOT2</i>	7996	-0.0037	0.3764	No
<i>CS</i>	8013	-0.0042	0.3753	No
<i>TOMM70</i>	8051	-0.0054	0.3727	No
<i>SDHC</i>	8388	-0.0153	0.3482	No
<i>DLST</i>	8430	-0.0167	0.3456	No
<i>HSPA9</i>	8755	-0.0272	0.3223	No
<i>NNT</i>	9074	-0.0374	0.2998	No
<i>MTRR</i>	9272	-0.0440	0.2864	No
<i>DLAT</i>	9306	-0.0453	0.2852	No
<i>PDK4</i>	9675	-0.0560	0.2594	No
<i>SUPV3L1</i>	10475	-0.0846	0.2024	No
<i>ACADSB</i>	10670	-0.0920	0.1906	No
<i>NDUFS1</i>	11054	-0.1086	0.1652	No
<i>FXN</i>	11279	-0.1185	0.1518	No
<i>ALDH6A1</i>	11340	-0.1209	0.1507	No
<i>NDUFA9</i>	11380	-0.1228	0.1512	No
<i>MTRF1</i>	12137	-0.1610	0.0995	No

GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>COX11</i>	12165	-0.1630	0.1020	No
<i>NDUFA7</i>	12198	-0.1652	0.1042	No
<i>SLC25A4</i>	12452	-0.1810	0.0904	No

Table S9. Gene Set (FAILED_HEART_ATRIUM_DN) with genes down-regulated in atria of failing hearts.

GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>LDHA</i>	0	0.4979	0.0253	Yes
<i>PGK1</i>	32	0.4054	0.0435	Yes
<i>IFITM1</i>	48	0.3934	0.0624	Yes
<i>LAPTM4A</i>	136	0.3521	0.0738	Yes
<i>PSMB4</i>	151	0.3481	0.0904	Yes
<i>COX6A1</i>	168	0.3438	0.1067	Yes
<i>PSMB5</i>	214	0.3314	0.1202	Yes
<i>SPTSSA</i>	232	0.3283	0.1356	Yes
<i>VTI1B</i>	236	0.3276	0.1520	Yes
<i>PRDX1</i>	273	0.3207	0.1656	Yes
<i>RRAGA</i>	295	0.3174	0.1801	Yes
<i>TMEM147</i>	312	0.3145	0.1949	Yes
<i>IFNGR1</i>	377	0.3044	0.2056	Yes
<i>CD59</i>	414	0.2996	0.2182	Yes
<i>MAD2L1BP</i>	472	0.2907	0.2287	Yes
<i>TXN</i>	487	0.2897	0.2424	Yes
<i>ACOT13</i>	528	0.2853	0.2539	Yes
<i>ATP6V0E1</i>	551	0.2825	0.2666	Yes
<i>EIF3I</i>	558	0.2817	0.2804	Yes
<i>GSTP1</i>	804	0.2583	0.2754	Yes
<i>NUTF2</i>	816	0.2566	0.2876	Yes
<i>NME2</i>	848	0.2546	0.2983	Yes
<i>MPST</i>	866	0.2532	0.3098	Yes
<i>PSMB3</i>	892	0.2512	0.3207	Yes
<i>SRI</i>	996	0.2445	0.3255	Yes
<i>YWHAE</i>	1009	0.2439	0.3370	Yes
<i>MPP1</i>	1034	0.2428	0.3476	Yes
<i>RAN</i>	1076	0.2396	0.3567	Yes
<i>BLVRB</i>	1096	0.2385	0.3674	Yes
<i>GDE1</i>	1296	0.2280	0.3643	Yes
<i>FKBP9</i>	1345	0.2253	0.3721	Yes
<i>PARVB</i>	1375	0.2236	0.3813	Yes
<i>GTF3A</i>	1377	0.2235	0.3926	Yes
<i>HDGF</i>	1431	0.2214	0.3999	Yes
<i>ELOC</i>	1512	0.2173	0.4050	Yes
<i>IFITM3</i>	1547	0.2157	0.4135	Yes

GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>LSM7</i>	1669	0.2092	0.4151	Yes
<i>SDF2</i>	1700	0.2073	0.4234	Yes
<i>PSMB1</i>	1730	0.2059	0.4318	Yes
<i>LAGE3</i>	1867	0.1997	0.4318	Yes
<i>RIT1</i>	2026	0.1931	0.4300	Yes
<i>ADRM1</i>	2040	0.1924	0.4388	Yes
<i>CTNNA1</i>	2161	0.1873	0.4394	Yes
<i>UBA3</i>	2174	0.1863	0.4480	Yes
<i>CLIC4</i>	2244	0.1838	0.4522	Yes
<i>PGM1</i>	2274	0.1829	0.4593	Yes
<i>OPTN</i>	2507	0.1737	0.4510	Yes
<i>STX4</i>	2519	0.1732	0.4590	Yes
<i>HINT1</i>	2614	0.1693	0.4606	Yes
<i>WARS1</i>	2654	0.1681	0.4663	Yes
<i>GLUD1</i>	2776	0.1634	0.4656	Yes
<i>PPM1A</i>	2829	0.1616	0.4700	Yes
<i>ACP1</i>	2913	0.1582	0.4719	Yes
<i>SUMO1</i>	2917	0.1581	0.4797	Yes
<i>ACVR1B</i>	2977	0.1559	0.4832	Yes
<i>RAB1A</i>	3063	0.1533	0.4847	Yes
<i>ZP3</i>	3245	0.1472	0.4788	Yes
<i>VAT1</i>	3247	0.1472	0.4862	Yes
<i>SLCO3A1</i>	3394	0.1418	0.4826	No
<i>PLEKHB2</i>	3572	0.1355	0.4764	No
<i>PSMD9</i>	3744	0.1303	0.4704	No
<i>TM9SF1</i>	3823	0.1278	0.4712	No
<i>FKBP1A</i>	3889	0.1259	0.4727	No
<i>SNU13</i>	4124	0.1180	0.4614	No
<i>CNIH1</i>	4277	0.1137	0.4560	No
<i>NPTN</i>	4392	0.1104	0.4532	No
<i>ACTB</i>	4442	0.1082	0.4550	No
<i>PSMA3</i>	4492	0.1063	0.4568	No
<i>DXO</i>	4506	0.1060	0.4612	No
<i>TMED10</i>	4697	0.0994	0.4522	No
<i>TAGLN</i>	4712	0.0988	0.4562	No
<i>PPP1CC</i>	5143	0.0855	0.4288	No
<i>LYPLA1</i>	5626	0.0707	0.3968	No
<i>MLEC</i>	5628	0.0706	0.4003	No
<i>APP</i>	5662	0.0697	0.4014	No

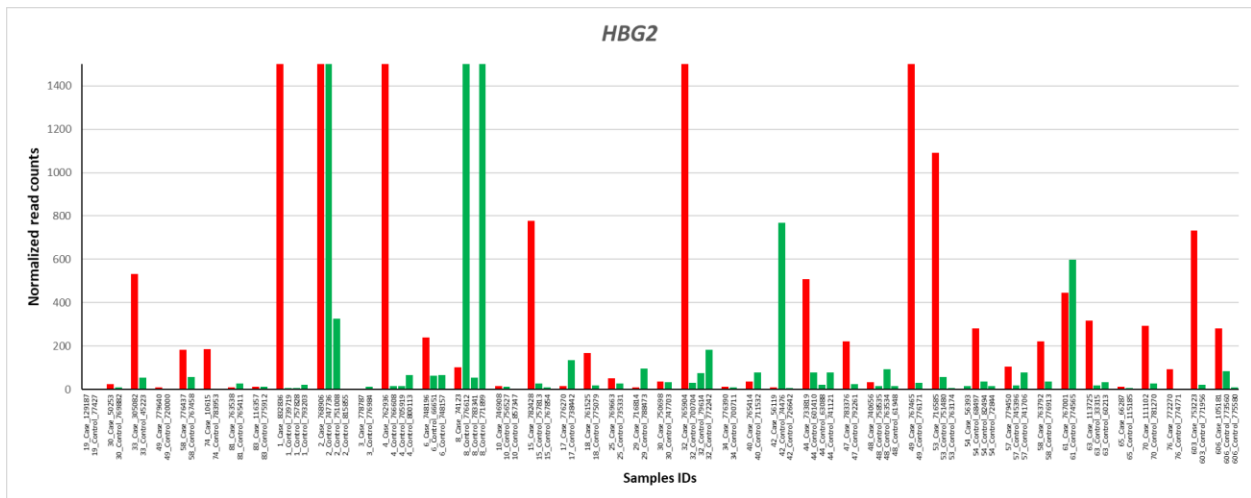
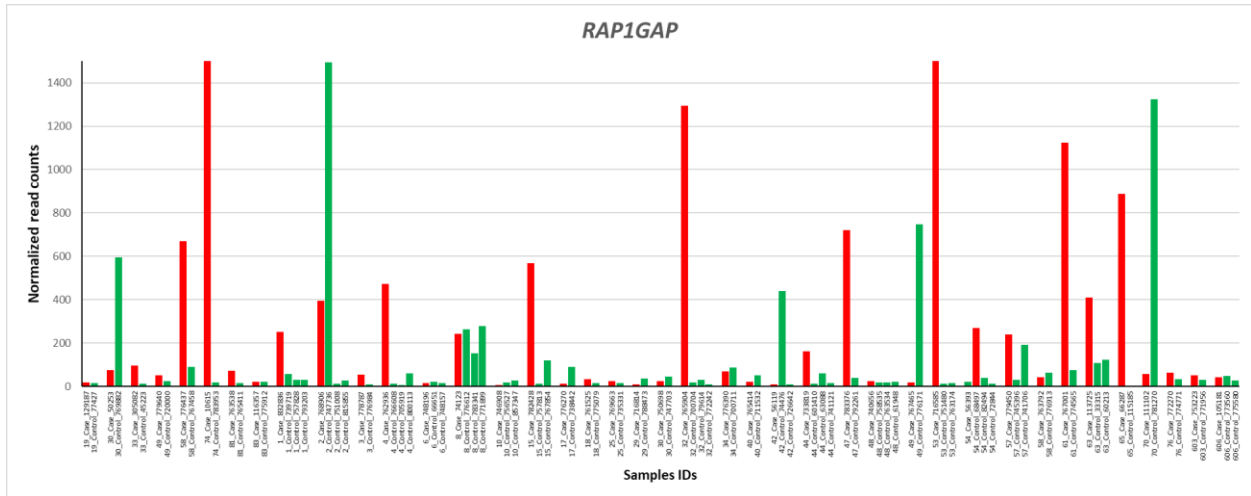
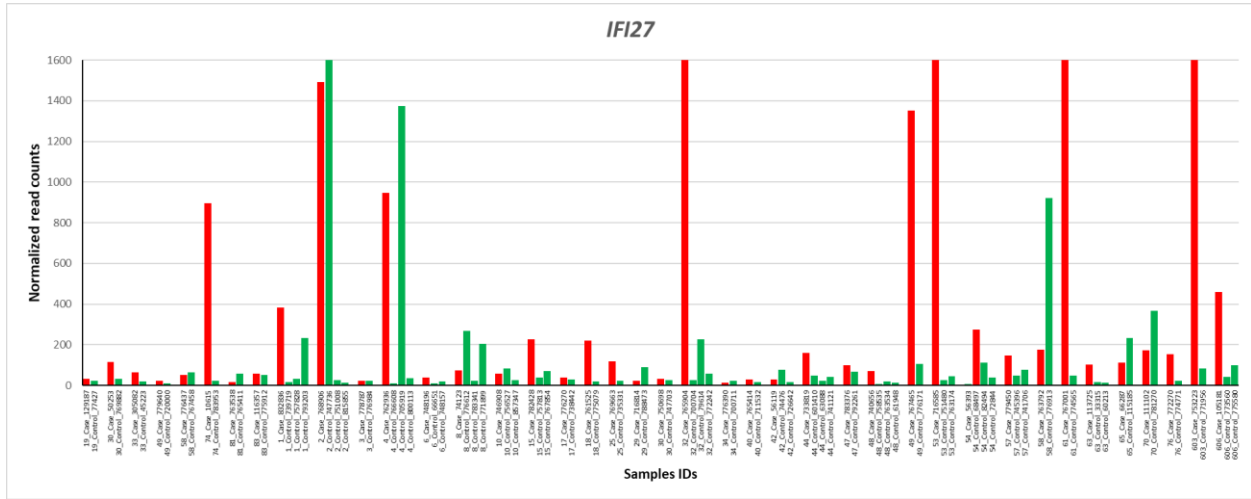
GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>GRB2</i>	5795	0.0649	0.3949	No
<i>CCZ1</i>	5809	0.0645	0.3973	No
<i>ITM2B</i>	5842	0.0635	0.3981	No
<i>SLC9A6</i>	6028	0.0569	0.3873	No
<i>EI24</i>	6051	0.0560	0.3886	No
<i>ACTN1</i>	6087	0.0553	0.3888	No
<i>DGUOK</i>	6106	0.0548	0.3902	No
<i>TNFAIP1</i>	6198	0.0518	0.3861	No
<i>ZNF22</i>	6271	0.0494	0.3833	No
<i>RAB9A</i>	6498	0.0433	0.3688	No
<i>NPRL2</i>	6584	0.0406	0.3646	No
<i>FAM131A</i>	6632	0.0389	0.3631	No
<i>STAT3</i>	6665	0.0381	0.3627	No
<i>YWHAZ</i>	6798	0.0340	0.3547	No
<i>MAP2K1</i>	7036	0.0269	0.3385	No
<i>PDCD6</i>	7055	0.0264	0.3385	No
<i>SS18</i>	7057	0.0263	0.3398	No
<i>PAFAH1B1</i>	7568	0.0102	0.3027	No
<i>PAPOLA</i>	7661	0.0074	0.2962	No
<i>MYH10</i>	8023	-0.0044	0.2698	No
<i>PIGH</i>	8156	-0.0090	0.2605	No
<i>MCM3</i>	8273	-0.0124	0.2526	No
<i>DDX21</i>	8409	-0.0159	0.2434	No
<i>CDC16</i>	8447	-0.0172	0.2416	No
<i>VAPB</i>	8555	-0.0206	0.2347	No
<i>GPR137B</i>	9256	-0.0435	0.1852	No
<i>TPM2</i>	9410	-0.0480	0.1763	No
<i>HNRNPL</i>	9446	-0.0490	0.1762	No
<i>TSC22D1</i>	9581	-0.0533	0.1691	No
<i>LRRN3</i>	9588	-0.0534	0.1713	No
<i>WASHC2C</i>	9754	-0.0595	0.1622	No
<i>CTTN</i>	9764	-0.0600	0.1645	No
<i>RPA1</i>	9829	-0.0623	0.1630	No
<i>PODXL</i>	10110	-0.0715	0.1459	No
<i>CAPN7</i>	10167	-0.0740	0.1455	No
<i>KPNA6</i>	10174	-0.0742	0.1489	No
<i>DAAM1</i>	10414	-0.0824	0.1354	No
<i>SLC39A14</i>	10434	-0.0832	0.1382	No
<i>G3BP2</i>	10565	-0.0882	0.1331	No

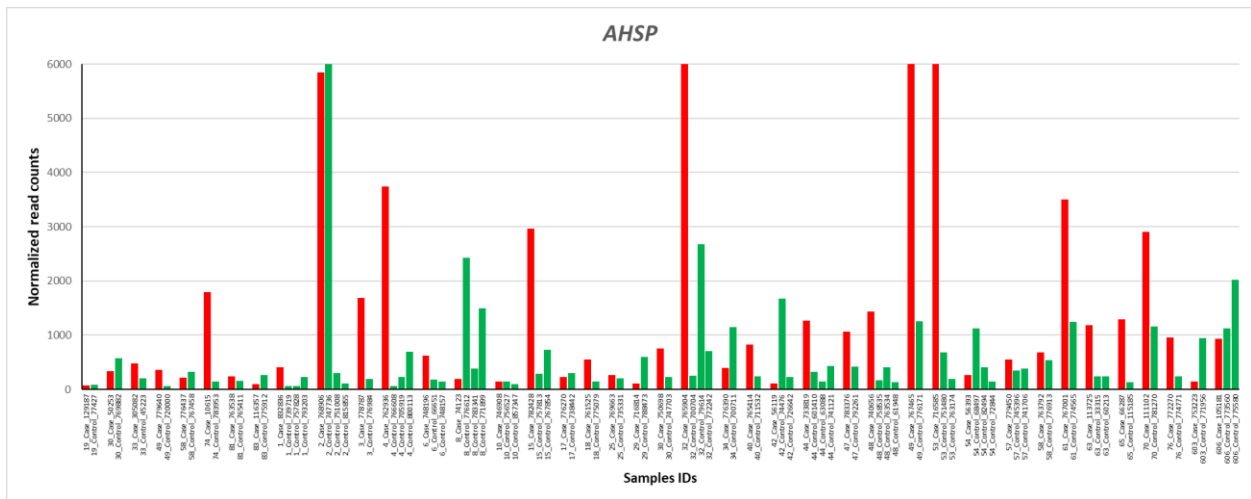
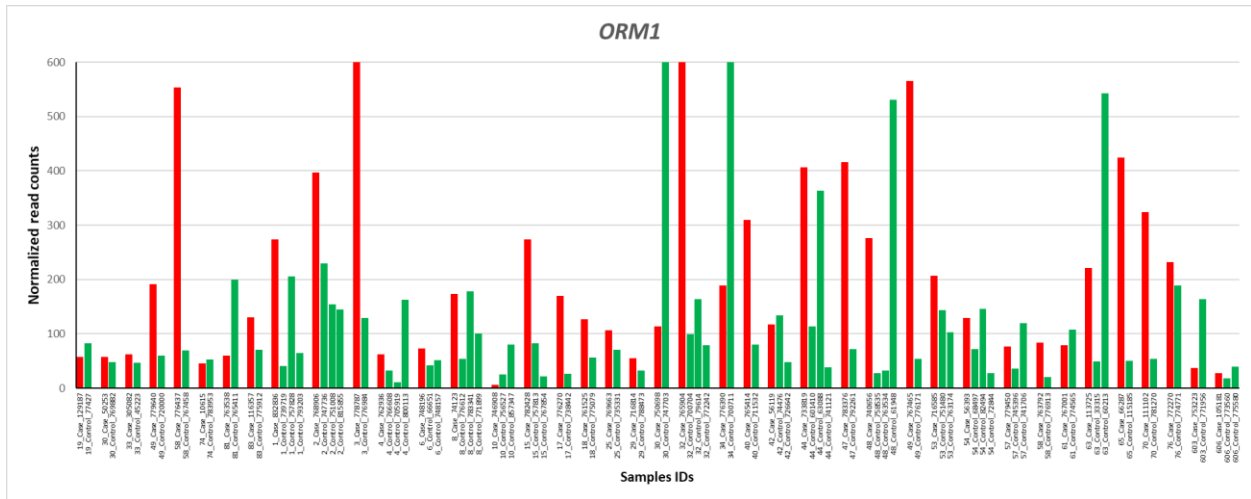
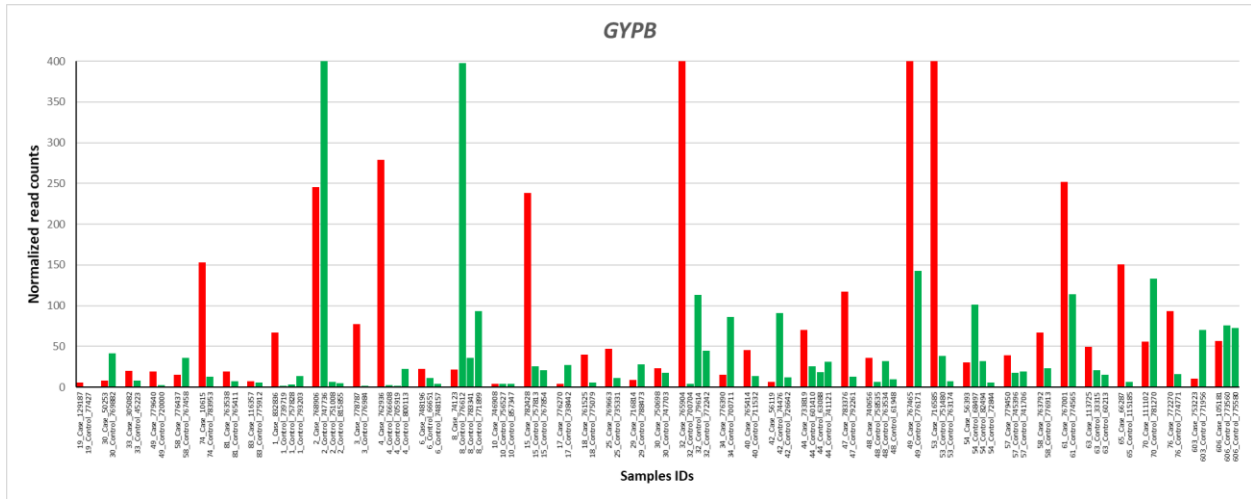
GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>LGMN</i>	10628	-0.0907	0.1331	No
<i>NUDT3</i>	10641	-0.0911	0.1368	No
<i>UBE2I</i>	10698	-0.0929	0.1374	No
<i>TGFBR3</i>	10714	-0.0934	0.1410	No
<i>ST3GAL1</i>	10719	-0.0936	0.1455	No
<i>UBE3C</i>	10820	-0.0983	0.1431	No
<i>LRBA</i>	10865	-0.1005	0.1449	No
<i>SMPD4</i>	11030	-0.1075	0.1383	No
<i>AMD1</i>	11417	-0.1242	0.1161	No
<i>RAD1</i>	11545	-0.1301	0.1133	No
<i>TGFBR2</i>	11613	-0.1327	0.1151	No
<i>GSTM3</i>	12178	-0.1637	0.0817	No
<i>CNN3</i>	12181	-0.1638	0.0899	No
<i>KHDC4</i>	12325	-0.1721	0.0881	No
<i>GSE1</i>	12915	-0.2202	0.0558	No

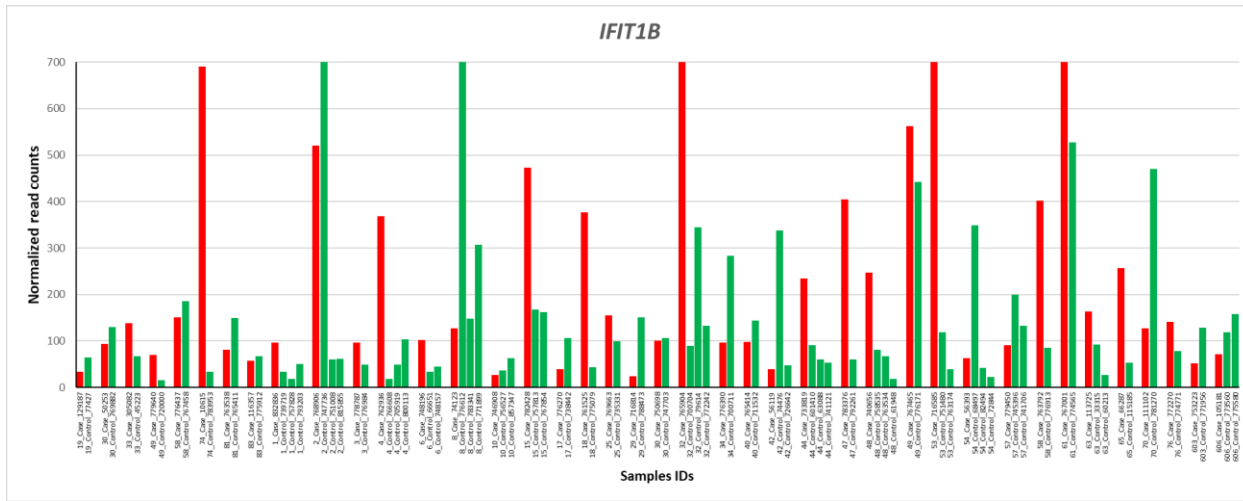
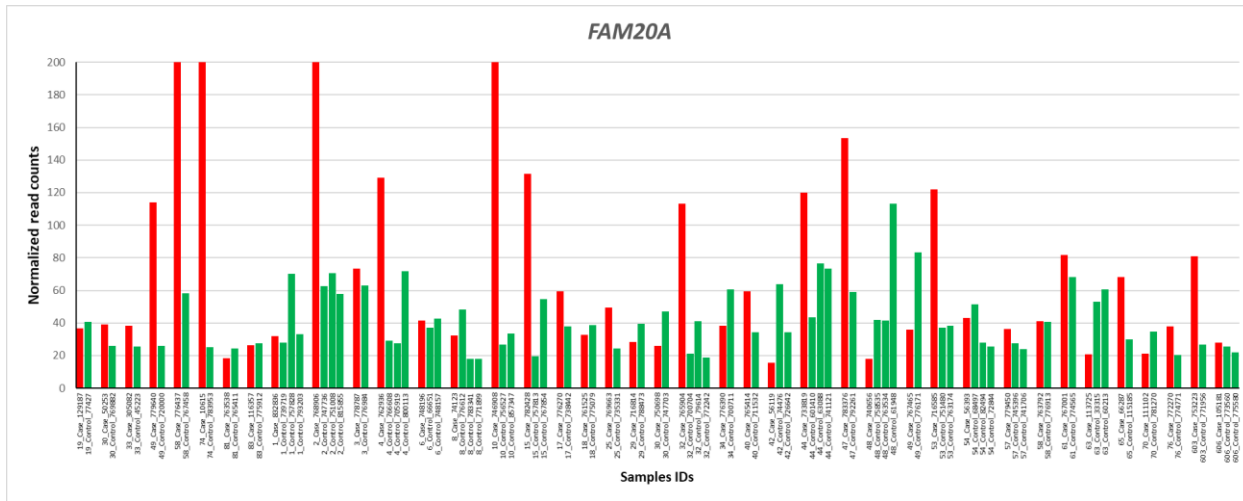
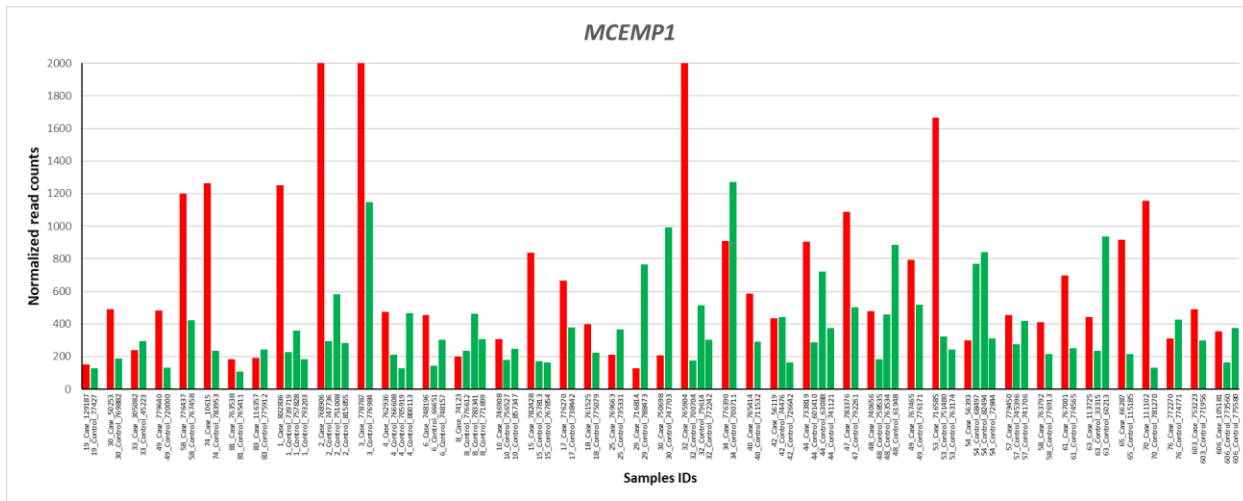
Table S10. Gene Set (KAAB_FAILED_HEART_VENTRICLE_DN) with genes down-regulated in the ventricles of failing hearts.

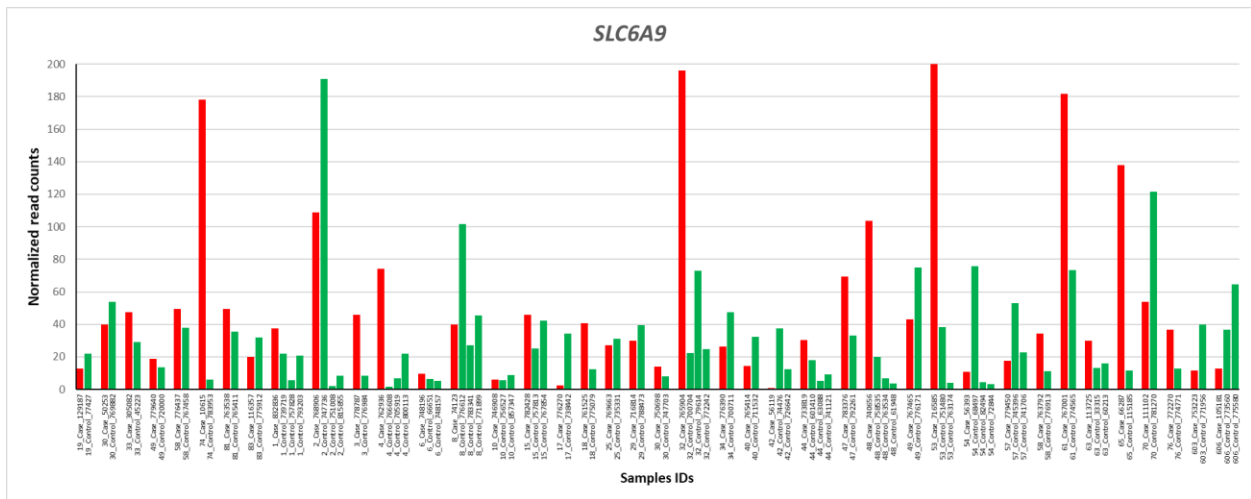
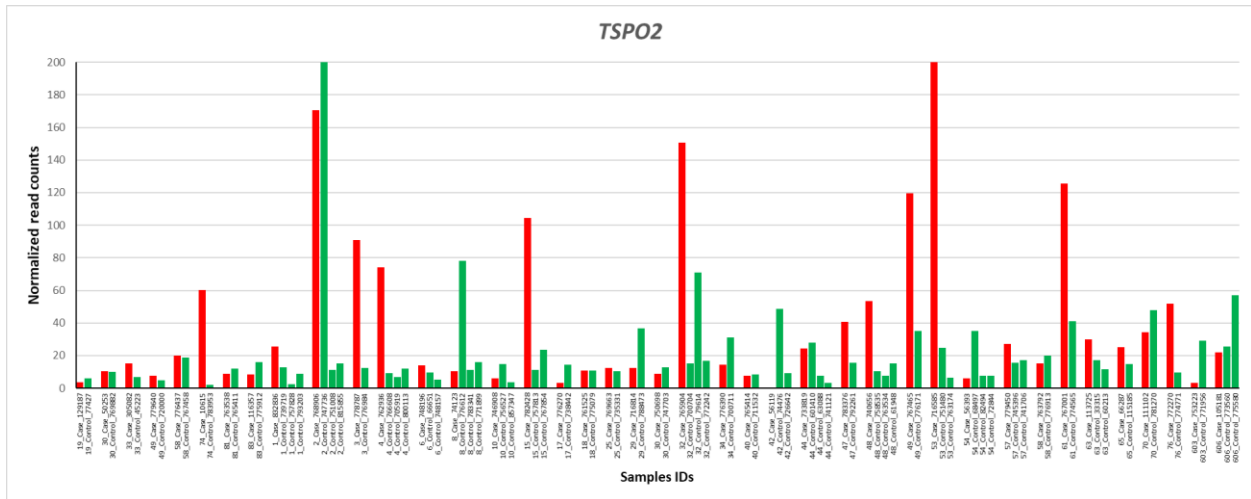
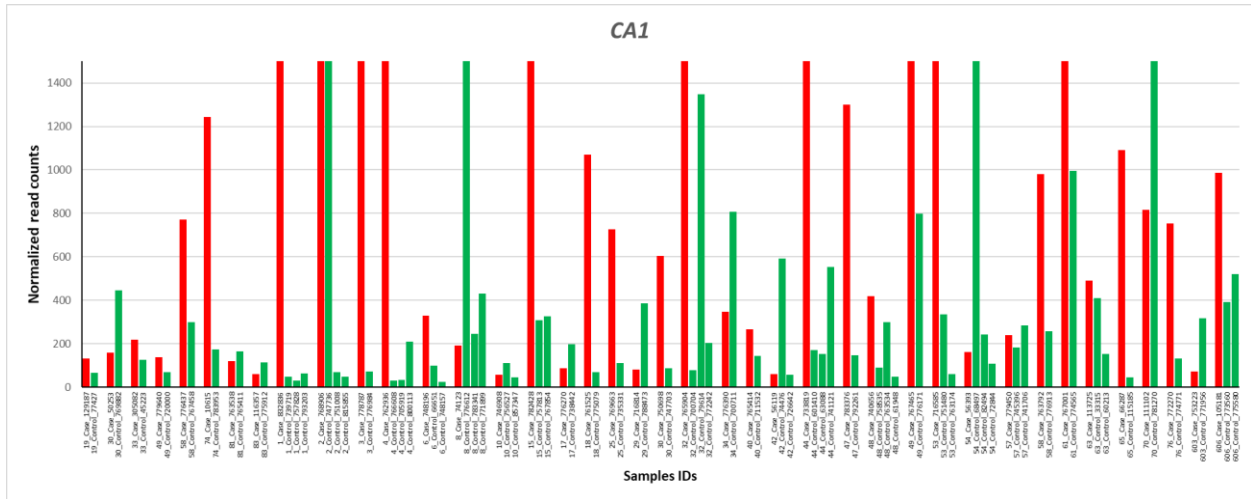
GENE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ENRICHMENT SCORE	CORE ENRICHMENT
<i>LDHA</i>	0	0.4979	0.0770	Yes
<i>SERPINB1</i>	34	0.4045	0.1372	Yes
<i>IFITM1</i>	48	0.3934	0.1971	Yes
<i>FCER1G</i>	93	0.3720	0.2514	Yes
<i>ATP5MC1</i>	291	0.3178	0.2861	Yes
<i>TMEM147</i>	312	0.3145	0.3333	Yes
<i>IFNGR1</i>	377	0.3044	0.3757	Yes
<i>C1QB</i>	471	0.2908	0.4138	Yes
<i>NME2</i>	848	0.2546	0.4256	Yes
<i>IFITM2</i>	939	0.2483	0.4574	Yes
<i>PSME2</i>	1191	0.2336	0.4752	Yes
<i>PQBP1</i>	1205	0.2330	0.5103	Yes
<i>GTF3A</i>	1377	0.2235	0.5323	Yes
<i>IFITM3</i>	1547	0.2157	0.5533	Yes
<i>CD14</i>	1744	0.2053	0.5706	Yes
<i>WARS1</i>	2654	0.1681	0.5300	Yes
<i>NQO2</i>	3026	0.1545	0.5267	Yes
<i>PTDSS1</i>	3206	0.1487	0.5366	Yes
<i>ZP3</i>	3245	0.1472	0.5565	Yes
<i>VAT1</i>	3247	0.1472	0.5792	Yes
<i>F13A1</i>	3581	0.1353	0.5758	Yes
<i>IRAK1</i>	3762	0.1298	0.5826	Yes
<i>SLC31A2</i>	4915	0.0924	0.5125	No
<i>EBP</i>	5542	0.0735	0.4779	No
<i>ISG15</i>	5851	0.0631	0.4651	No
<i>RAB9A</i>	6498	0.0433	0.4244	No
<i>STAT3</i>	6665	0.0381	0.4181	No
<i>LPCAT4</i>	9111	-0.0386	0.2448	No
<i>TSC22D1</i>	9581	-0.0533	0.2187	No
<i>DAAM1</i>	10414	-0.0824	0.1704	No
<i>SLC39A14</i>	10434	-0.0832	0.1819	No
<i>ATP2A2</i>	10823	-0.0984	0.1686	No
<i>AMD1</i>	11417	-0.1242	0.1444	No
<i>PPP2R5C</i>	11648	-0.1343	0.1483	No

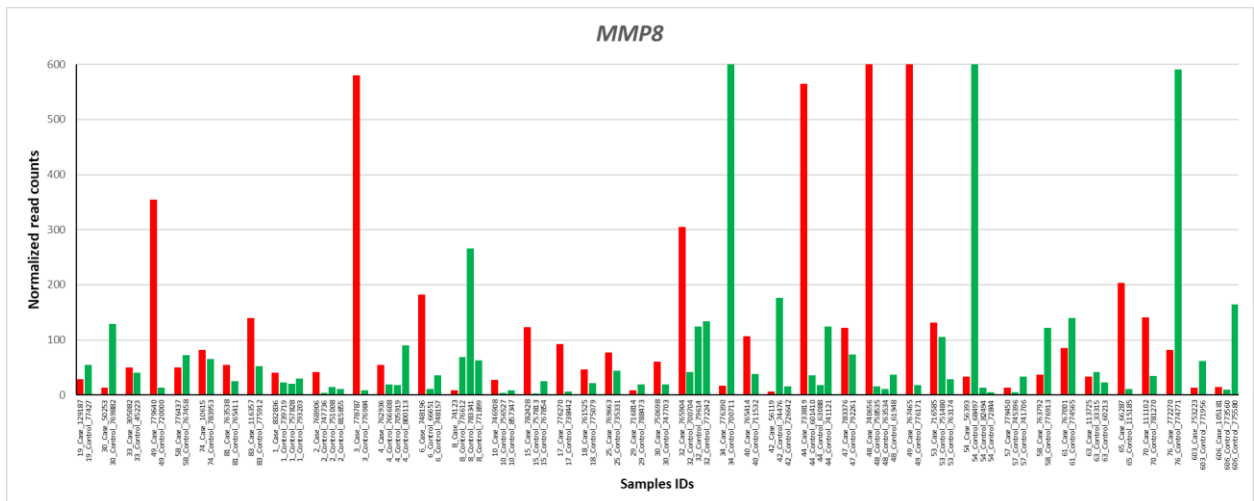
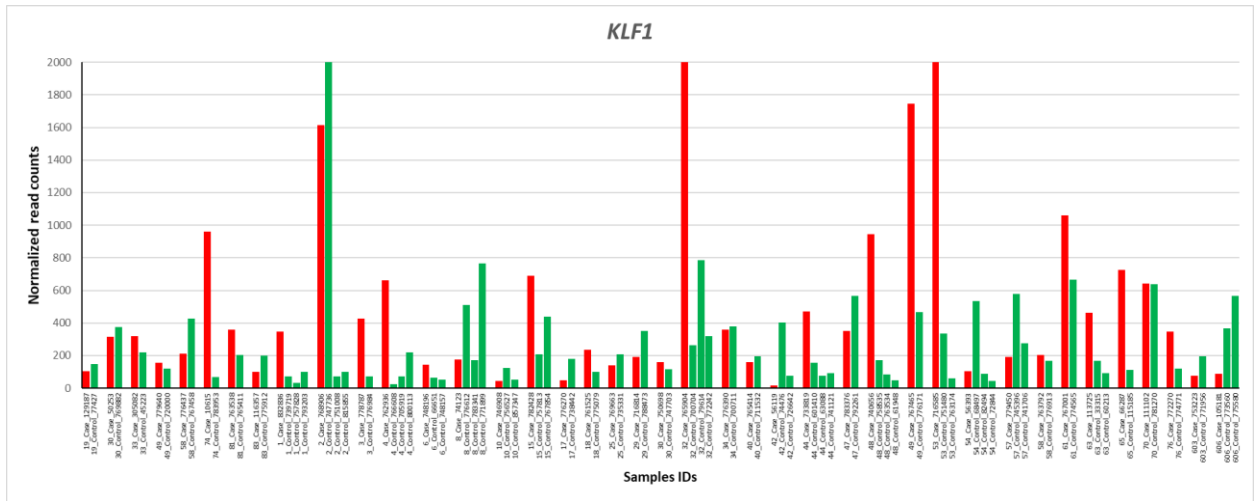
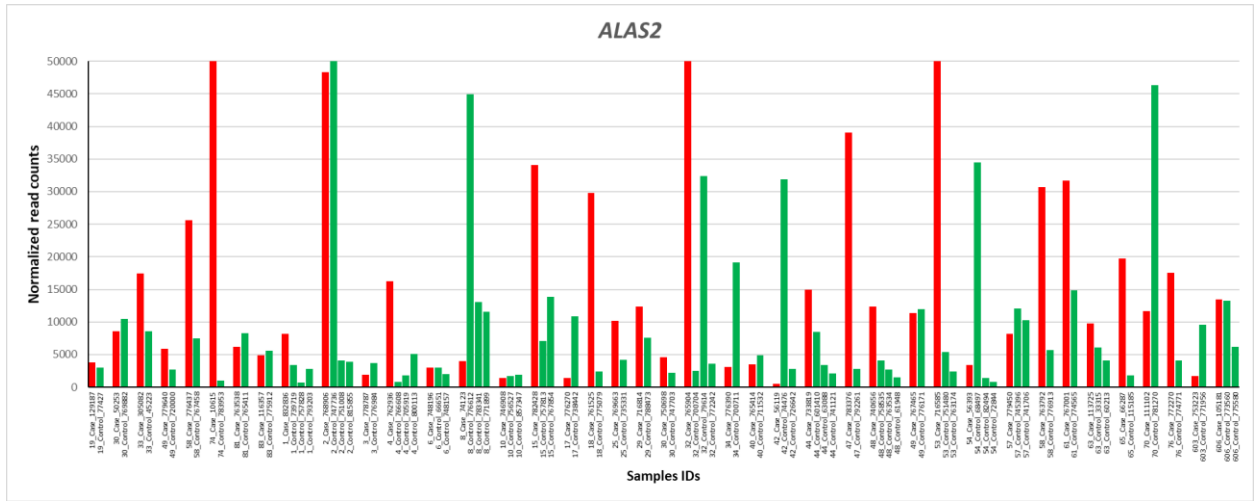
Figure S1. Gene expression plots for all Differentially Expressed Genes. The matched case-control sets are plotted side by side. Cases are indicated in red, and controls are indicated in green.

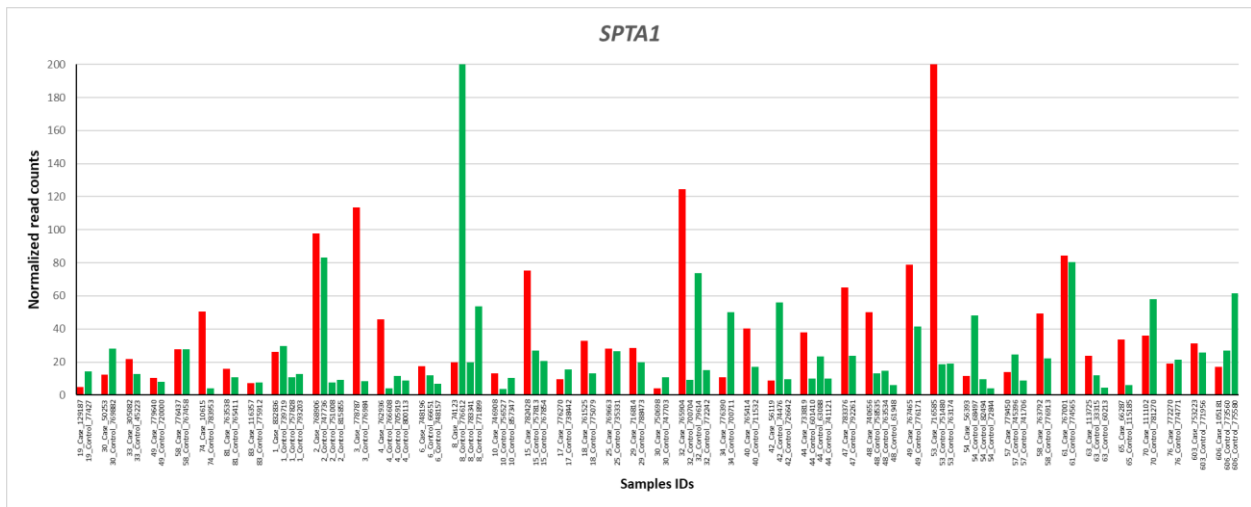
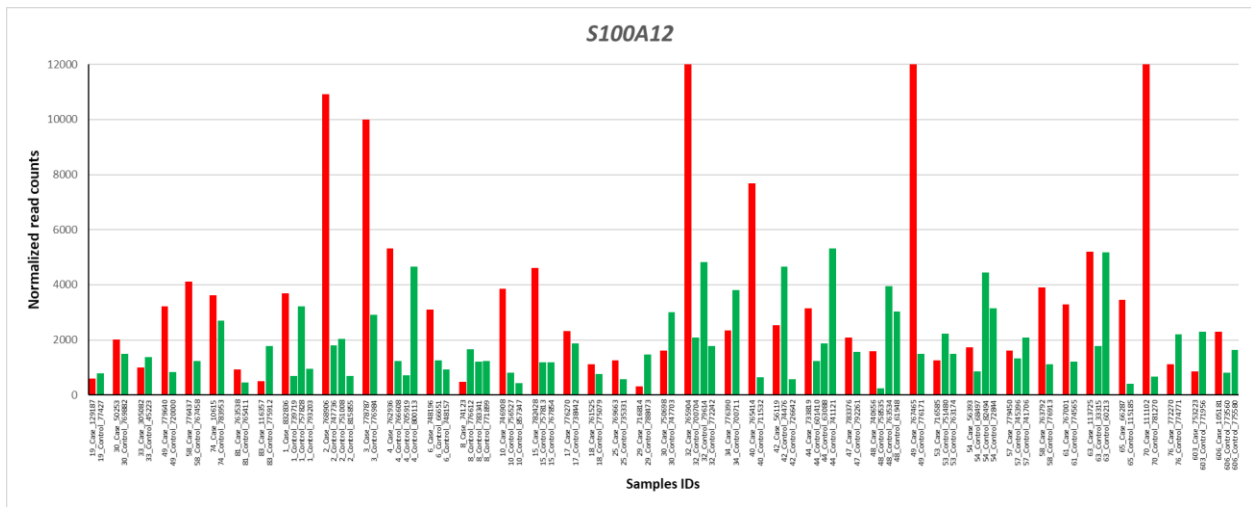
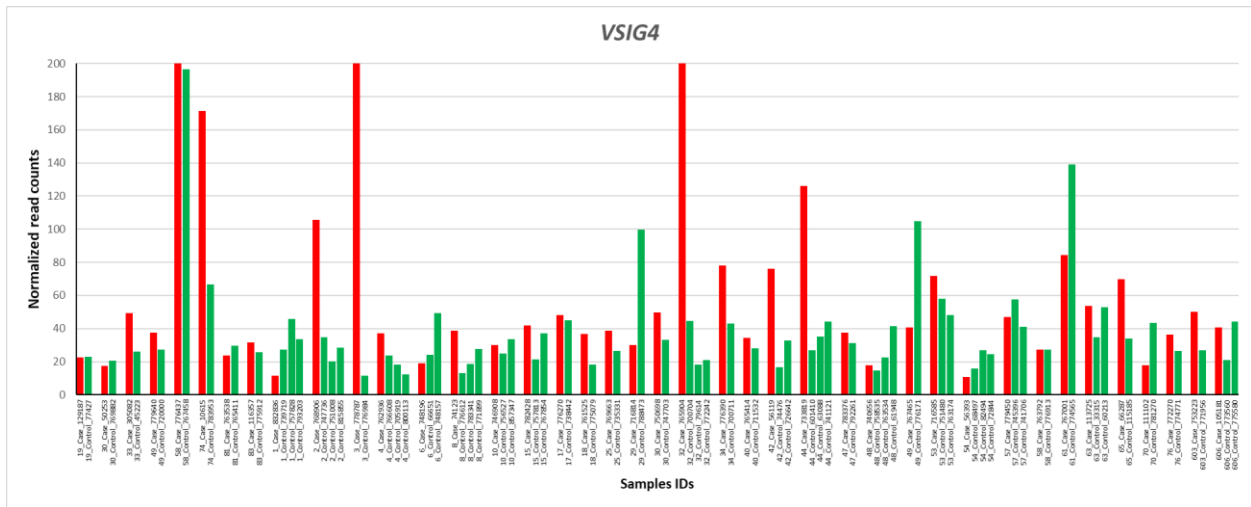


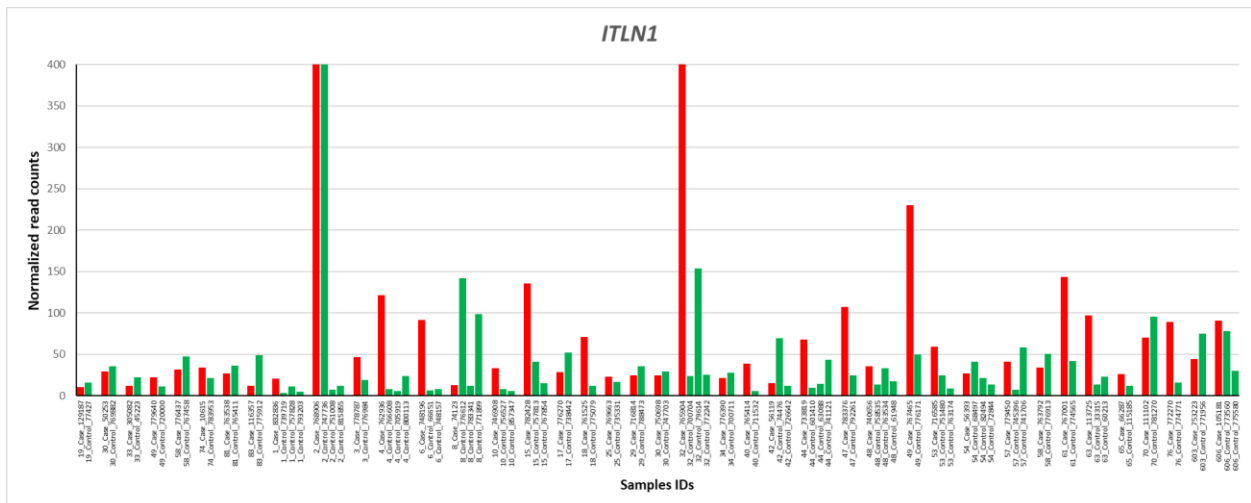
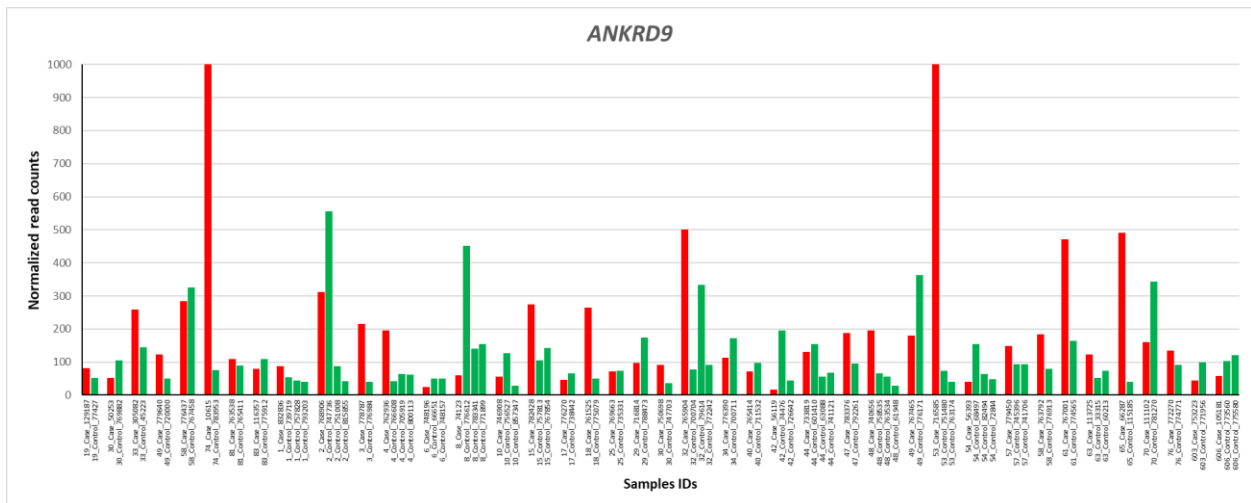
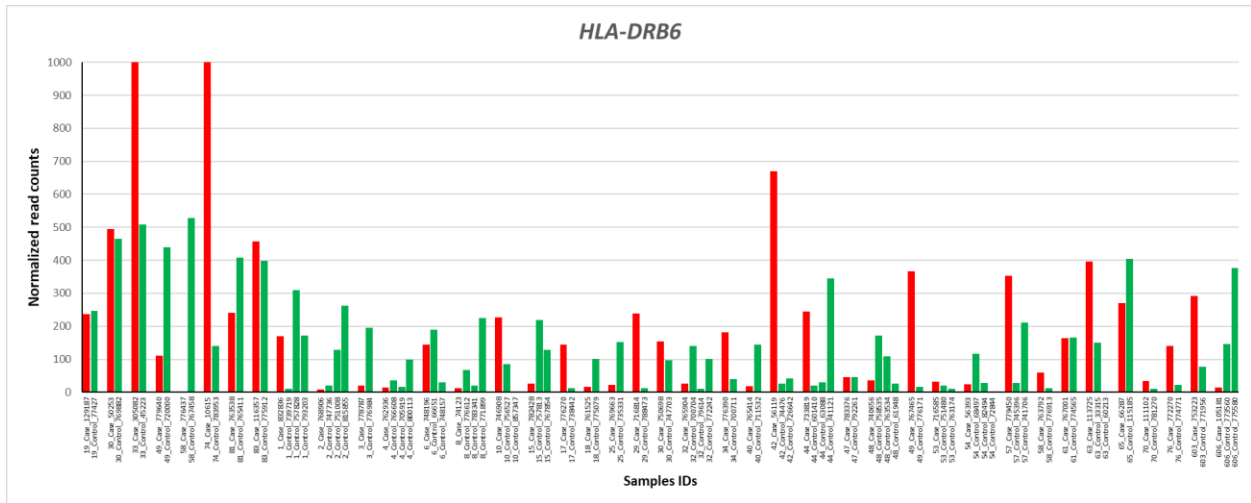




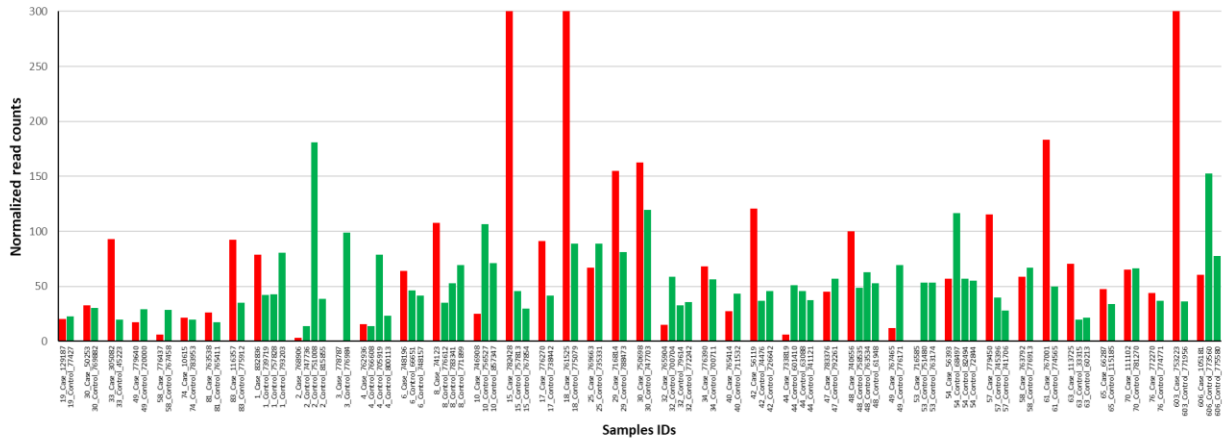








IGKV1-27



NKX3-1

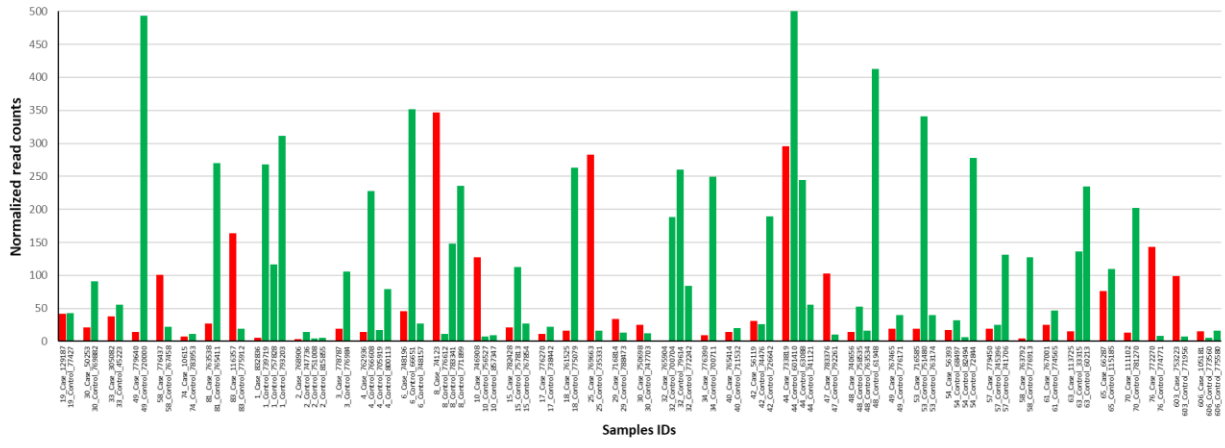


Figure S2. Validation of CRISPR/Cas9-mediated *LDHA* Knockout in an isogenic human induced pluripotent stem-cell line detected by Sanger sequencing. A 7-bp (Exon 2) deletion, confirmed by a qPCR of knockout by reverse transcription polymerase chain reaction.

