ORIGINAL RESEARCH

Acute Decompensated Heart Failure and the Kidney: Physiological, Histological and Transcriptomic Responses to Development and Recovery

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BACKGROUND: Acute decompensated heart failure (ADHF) is associated with deterioration in renal function—an important risk factor for poor outcomes. Whether ADHF results in permanent kidney damage/dysfunction is unknown.

METHODS AND RESULTS: We investigated for the first time the renal responses to the development of, and recovery from, ADHF using an ovine model. ADHF development induced pronounced hemodynamic changes, neurohormonal activation, and decline in renal function, including decreased urine, sodium and urea excretion, and creatinine clearance. Following ADHF recovery (25 days), creatinine clearance reductions persisted. Kidney biopsies taken during ADHF and following recovery showed widespread mesangial cell prominence, early mild acute tubular injury, and medullary/interstitial fibrosis. Renal transcriptomes identified altered expression of 270 genes following ADHF development and 631 genes following recovery. A total of 47 genes remained altered post-recovery. Pathway analysis suggested gene expression changes, driven by a network of inflammatory cytokines centered on IL-1β (interleukin 1β), lead to repression of reno-protective eNOS (endothelial nitric oxide synthase) signaling during ADHF development, and following recovery, activation of glomerulosclerosis and reno-protective pathways and repression of proinflammatory/fibrotic pathways. A total of 31 dysregulated genes encoding proteins detectable in urine, serum, and plasma identified potential candidate markers for kidney repair (including *CNGA3* [cyclic nucleotide gated channel subunit alpha 3] and *OIT3* [oncoprotein induced transcript 3]) or long-term renal impairment in ADHF (including *ACTG2* [actin gamma 2, smooth muscle] and *ANGPTL4* [angiopoietin like 4]).

CONCLUSIONS: In an ovine model, we provide the first direct evidence that an episode of ADHF leads to an immediate decline in kidney function that failed to fully resolve after ≈4 weeks and is associated with persistent functional/structural kidney injury. We identified molecular pathways underlying kidney injury and repair in ADHF and highlighted 31 novel candidate biomarkers for acute kidney injury in this setting.

Key Words: acute decompensated heart failure ■ acute kidney injury ■ kidney function ■ transcriptome

Heart failure (HF) is a leading cause of morbidity and mortality worldwide. Approximately 20% of currently middle-aged people will develop HF in their remaining lifetime,[1] with ≈20% of patients dying in the first year after diagnosis and >50% after 5 years.[2] HF is a progressive syndrome characterized by recurrent episodes of acute worsening or decompensation and frequently accompanied by acute

CLINICAL PERSPECTIVE

What Is New?

- Characterization of serial functional and histological data during the development and resolution of acute decompensated heart failure (ADHF; using an ovine model) provides the first direct evidence that a single episode of ADHF can cause acute kidney injury (AKI), as demonstrated by cellular necrosis, tubular injury, and glomerular scarring, which is associated with a decline in kidney function that fails to fully resolve after ≈4 weeks.
- Renal gene expression profiling of pathways associated with kidney injury and repair in ADHF suggest changes in expression may be driven by a network of inflammatory cytokines centered on IL-1β (interleukin 1β).

What Are the Clinical Implications?

- These data suggest that an episode of ADHF on a background of previously normal kidneys represents a significant event that can result in acute kidney injury and lead to permanent kidney injury and decrement in renal function.
- Recognition and awareness of the significance of acute kidney injury is critical in clinical ADHF management to prevent unintended adverse renal effects and associated poor outcomes.
- Inhibition of IL-1β may have therapeutic potential in cardiorenal disease, including acute kidney injury in ADHF.

Nonstandard Abbreviations and Acronyms

ADHF	acute decompensated heart failure
AKI	acute kidney injury
AngII	angiotensin II
AVP	arginine vasopressin
CVP	central venous pressure
eNOS	endothelial nitric oxide synthase
GP6	glycoprotein VI
IPA	Ingenuity Pathway Analysis
MCs	mesangial cells
PDGF	platelet-derived growth factor
PPAR	peroxisome proliferator-activated receptor
RNA-seq	RNA sequencing
TGF-β	transforming growth factor-β
WRF	worsening renal function

renal dysfunction—1 of the most important risk factors for poor clinical outcomes and death.[3] Indeed, the majority of individuals hospitalized with acute decompensated HF (ADHF) exhibit at least some degree of existing renal insufficiency, with perhaps as many as two thirds manifesting moderate to severe impairment.[4] Furthermore, a considerable number of patients incur acute worsening of kidney function, which if sustained, is associated with increased short-term and long-term mortality.[5]

With both background impairment and additional decrements in renal function portending a worse prognosis in HF,[3–5] there is a need to better understand the pathophysiological mechanisms linking the failing heart and the kidney. Although kidney dysfunction in HF has traditionally been considered a result of impaired renal blood flow in the setting of depressed cardiac function, increasing evidence suggests contributory mechanisms are more complex and multifactorial. Putative contributors also include central venous congestion (and therefore renal venous hypertension), anemia, oxidative stress, inflammation, neurohormonal activation, and renal sympathetic overactivity.[6,7] However, despite considerable prior research, the pathophysiology of kidney dysfunction in HF remains incompletely understood. This is in a large part attributed to poor renal characterization. Importantly, it is not known whether acutely reduced kidney function secondary to ADHF leads to persistent kidney injury and repair by scarring—resulting in permanent kidney injury and dysfunction—or whether kidney structure and function recovers fully to predecompensated levels following successful HF treatment. Answers to these questions and a deeper understanding of molecular alterations in the kidney during development and resolution of ADHF may inform the management of patients with HF and point to therapeutic targets for renal preservation in HF.

We therefore investigated serial physiological (hemodynamic, neurohumoral, renal) and kidney histological and transcriptome (RNA sequencing [RNA-seq]) responses during the development and resolution of ADHF using an ovine model of ADHF induced by rapid left ventricular (LV) pacing.[8]

METHODS

RNA-seq data have been deposited in the National Center for Biotechnology Information Gene Expression Omnibus database (www.ncbi.nlm.nih.gov/geo; Accession No. GSE180502). All other data and supporting materials/methods are either available within the article (and its online supplementary files) or from the corresponding author upon reasonable request.

Sheep Instrumentation

Studies were approved by the Animal Ethics Committee of the University of Otago–Christchurch (No. C23/10;

in accordance with the New Zealand Animal Welfare Act 1999 and Amendment No. 2 [2015]) and conform to current National Institute of Health guidelines (8th edition).

A total of 9 adult Coopworth ewes (4–6 years; 47–69 kg; Lincoln University Farm, Canterbury, New Zealand) were instrumented via a left lateral thoracotomy as previously described[8] under general anesthesia (induced by intravenous diazepam [1×0.5 mg/kg]/intravenous ketamine [1×4 mg/kg]; maintained with 2% isoflurane/2 L per minute nitrous oxide/2 L per minute oxygen) and using approved perioperative/postoperative analgesia (intravenous carprofen [4 mg/kg once a day for ≥3 days], intravenous buprenorphine [0.005–0.01 mg/kg once a day for ≥3 days], intercostal bupivacaine [1×25 mg]/intercostal lignocaine [1×100 mg]), and antibiotics (intravenous cephazolin [2×20 mg/kg], intravenous enrofloxacin [1×2.5 mg/kg]). Briefly, catheters were placed via the jugular vein and in the left atrium for blood sampling and measurement of central venous pressure (CVP) and left atrial pressure; Konigsberg pressure-tip transducers were inserted in the aorta to record mean arterial pressure (MAP) and into the apex of the left ventricle to obtain heart rate, LV pressures, and derivatives of pressure over time (dP/dt[max]); a Swan-Ganz thermodilution catheter (American Edwards) was placed in the pulmonary artery for measurement of cardiac output; and a 7-French His-bundle electrode was stitched subepicardially to the left ventricle for subsequent cardiac pacing. A bladder catheter was inserted per urethra to allow timed urine collections. Adequacy of anesthesia was monitored via serial measurements of heart rate, blood pressure, capillary refill time, mucous membrane color, palpable blink response, jaw tone, anesthetic gas analysis, oxygen saturation, and end-tidal CO_2 levels.

Animals recovered for at least 14 days before commencing the study protocol, and throughout the study they were held in metabolic cages and received a diet of Lucerne chaff and food pellets (providing ≈75 mmol sodium/day, ≈150 mmol potassium/day) with free access to water.

Note that only ewes have been used in the current study because of practical issues with having an indwelling bladder catheter in a conscious male sheep within a metabolic crate. In addition, it is difficult to source male animals as male lambs are typically castrated within weeks of birth and sent off to the meat works before they are a year old.

Study Protocol

The study followed a longitudinal repeated-measures design with sampling conducted during a 5-day baseline period (days −4 to 0) followed by 14 days of rapid LV pacing at 220 bpm to induce ADHF (days 1 to 14, pace), and then termination of pacing and 25 days of recovery (days 1 to 25, recovery).

Hemodynamic measurements (CVP, left atrial pressure, MAP, heart rate, cardiac output, dP/dt[max]) were recorded using an online data acquisition system (PowerLab Systems; ADInstruments) and made before the commencement of pacing (baseline; days −4, −2, 0), during pacing (ADHF; days 1–4, 7–9, 10, 11, 14) and following the cessation of pacing (recovery; days 15–18, 21, 23, 25, 28, 30, 32, 35, 37, 39).

Blood samples were drawn following each hemodynamic measurement. Samples were taken into EDTA tubes on ice, centrifuged at 4 °C, and stored at either −20 °C or −80 °C before assay for ANP (atrial natriuretic peptide), BNP (B-type natriuretic peptide), PRA (plasma renin activity), aldosterone, endothelin-1, AVP (arginine vasopressin), and catecholamines.[8] For each analyte, all samples from individual animals were measured in the same assay to avoid interassay variability. Plasma sodium, potassium, creatinine, urea, albumin, and hematocrit were measured with every blood sample taken.

Water intake and urine collections for the measurement of volume and excretion of sodium, potassium, creatinine, and urea were made daily during the first 26 days of study and then every 2 to 3 days until protocol completion. Creatinine clearance was calculated as urine creatinine×volume/plasma creatinine.

Serial kidney biopsies were performed in duplicate before pacing (baseline), on day 14 of pacing (HF), and after 25 days (nonpacing) recovery. For the first 2 procedures, the sheep were anesthetized (as described previously), and 2 adjacent percutaneous kidney biopsies were taken under ultrasonic guidance (Philips iE33; Philips Ultrasound) using a 14 g spring-loaded automated biopsy gun (BARD Peripheral Vascular, Inc.). Final kidney samples were collected at study end immediately following euthanasia (intravenous Pentobarb300 100 mg/kg). On each occasion, 1 of the biopsies was fixed in 10% formalin (4 °C overnight) for histological analysis, and the other snap frozen in liquid nitrogen and stored at −80 °C for subsequent RNA extraction and RNA-seq analysis.

Histological Analysis

Formalin-fixed kidney biopsy samples were dehydrated in ethanol, embedded in paraffin, and cut into longitudinal 7-μm sections before mounting. Sections were stained with hematoxylin–eosin or Masson's trichrome and examined under light microscopy by a specialist pathologist. Specimens from 7×baseline, 9×HF, and 8×recovery biopsies were found to be acceptable for further evaluation. Presence of fibrosis (collagen deposition) was analyzed in digital images of Masson's trichrome-stained kidney sections (×10

objective magnification) by an image processing program (ImageJ) employing color-based thresholding to determine percentage blue-staining collagen.

RNA-Seq and Bioinformatic Analysis

Full details of RNA extraction, library preparation, and bioinformatic analysis are provided in Data S1. Briefly, total RNA was extracted from frozen kidney biopsy samples and purified with RNeasy Midi Columns (Qiagen). To maximize statistical power, the 5×baseline, 6×HF, and 5×recovery serial samples were supplemented with kidney samples collected postmortem from animals euthanized before, during, or after the same pacing protocol. This provided a total of 14×baseline, 13×HF, and 8×recovery samples for RNA-seq analysis. RNA-seq libraries were prepared using total RNA and TruSeq stranded mRNA library prep kits (Illumina).

Statistical Analysis
Physiological Data Analysis

Changes during pacing and postpacing recovery were assessed by 1-way repeated ANOVA (SPSS version 11.022). Where significant time effects were identified by ANOVA, level of significance at individual time points versus baseline (mean of samples taken before pacing) was determined by Fisher's protected least-significant difference tests. Results of baseline versus day 14 pacing and day 39 recovery are provided in the text. Significance was assumed at $P<0.05$.

Transcriptome Analysis

To confirm all biopsy samples were of kidney origin (ie, not contaminated with other tissue), the 1000 most abundant genes in each sample were tested for enrichment of tissue-specific genes across 35 human tissues using the Tissue Enrich package[9] in R.[10] Kidney origin was confirmed for all but 3 samples (Figure S1), which were excluded, leaving a total of 11×baseline, 13×HF, and 8×recovery samples for differential expression analysis.

Gene expression was compared between time points (baseline to HF, HF to recovery, and baseline to recovery) using negative binomial generalized linear models with DESeq2[11] using a false discovery rate α=0.05. As not all animals underwent serial sampling, samples were treated as independent samples. Data for individual genes are presented as normalized read counts and corrected for library size using DESeq2 normalization.[11]

Genes that differed between baseline and HF, HF and recovery, and baseline and recovery ($P<0.01$ after adjustment for multiple comparisons, fold change >1.2 or <0.83) were compared with 884 genes associated with acute kidney injury (AKI) as documented

in 2 large databases: Harmonizome[12] and Ingenuity Pathway Analysis (IPA) knowledgebase (https://qiagenbioinformatics.com/products/ingenuity-pathway-analysis)[13] (Table S1). Enrichment for canonical pathways and nephrotoxicity networks was tested with Core and Comparative gene set enrichment analysis workflows using IPA software. The net effect of individual gene expression changes on the network/pathway (ie, whether the combined effect of individual gene expression changes predicted activation or inhibition of the network/pathway) was determined using Z scores (scores >2 indicate pathway activation, <−2 indicate pathway inhibition). Potential circulating or urinary biomarkers were identified using the IPA Biomarker Filter workflow and Protein Atlas secretome (www.proteinatlas.org).[14] A P value of $P<0.01$ after correction for multiple comparisons was used for all IPA analyses. Associations between candidate kidney biomarkers, selected neurohormones, and hemodynamic indexes were assessed with Pearson correlation (after ln-transformation of data) and visualized on correlation matrices using the Corrplot package[15] in R.[10]

RESULTS

Physiological Results

A total of 14 days of rapid LV pacing produced the hemodynamic deterioration, multifaceted hormonal activation, and sodium-retaining hallmarks of human ADHF. Significant reductions were observed in cardiac output, dP/dt(max), and MAP together with increases in CVP, left atrial pressure, and calculated total peripheral resistance (calculated total peripheral resistance=MAP/CO), resulting in a halving of (calculated) renal perfusion pressure (MAP-CVP; all $P<0.001$; Figure 1; Figure S2). Attendant neuroendocrine changes included marked rises in plasma ANP ($P<0.001$), BNP ($P<0.01$), PRA ($P<0.05$), aldosterone ($P<0.01$), endothelin-1 ($P<0.001$), AVP ($P<0.01$), epinephrine ($P<0.05$), and norepinephrine ($P<0.05$; Figure S3). Renal function was adversely affected as evidenced by a halving in urine output and significant declines in urine sodium, potassium, urea, and creatinine excretion (all $P<0.001$; Figure 1; Figure S4). In addition, plasma creatinine levels rose ($P<0.01$; Table S2) and creatinine clearance was markedly reduced ($P<0.001$; Figure 1).

Following termination of rapid pacing and 25 days of recovery, most measurements returned to prepacing baseline levels. Exceptions included left atrial pressure ($P<0.01$) and the natriuretic peptides (ANP, $P<0.01$; BNP, $P<0.05$), which remained slightly but significantly elevated relative to baseline. Importantly, urine creatinine excretion ($P<0.001$) and creatinine clearance ($P<0.001$) remained significantly decreased compared
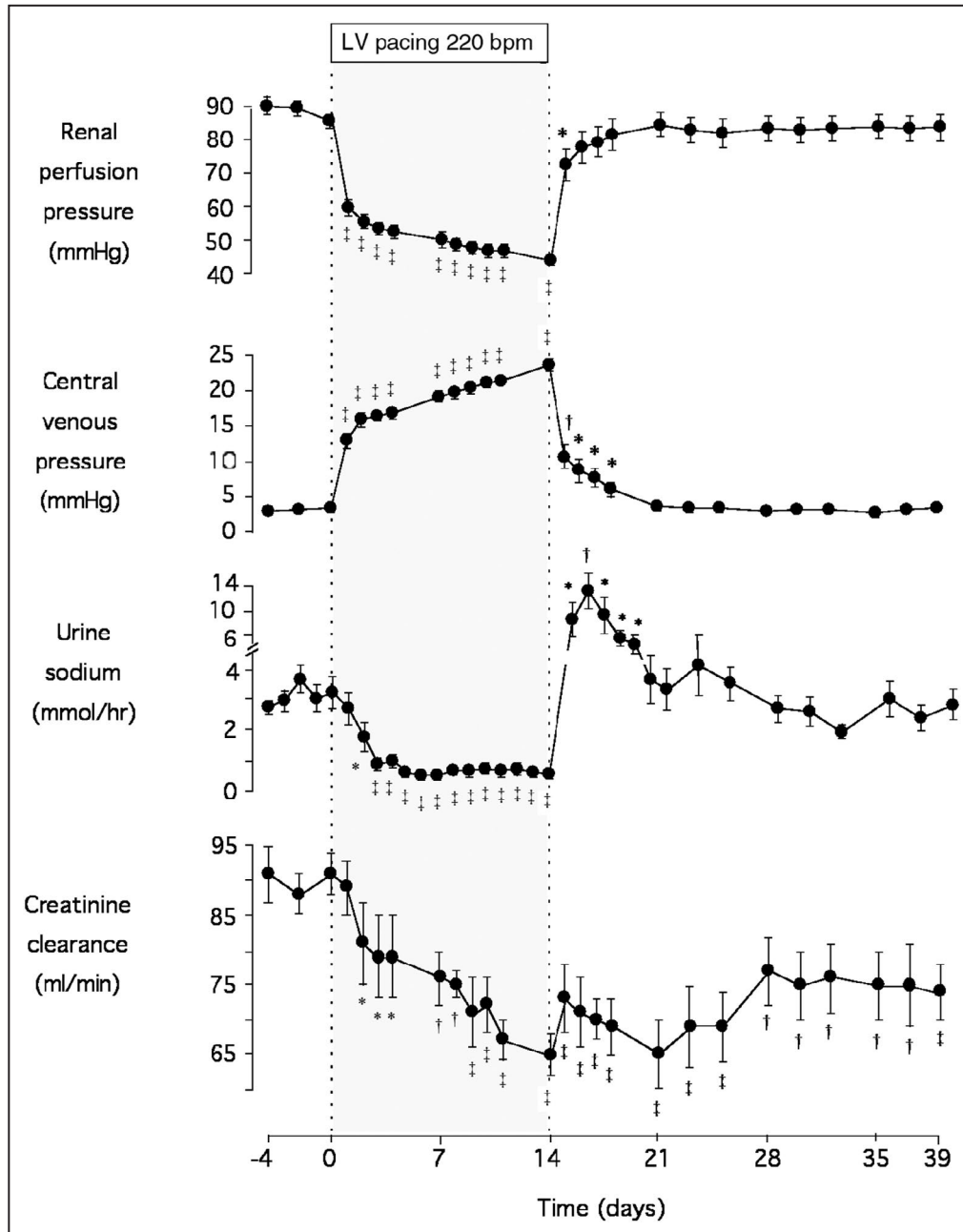
Figure 1. Mean±SEM serial physiological responses in 9 sheep before (baseline) and during development of acute decompensated heart failure (induced by left ventricular pacing at 220 bpm for 14 days) and during 25 days of recovery following termination of pacing.

Significant differences from prepacing baseline levels are shown by the following: *$P<0.05$, †$P<0.05$, and ‡$P<0.001$ by 1-way ANOVA. bpm indicates beats per minute; and LV, left ventricular.

with baseline even after 25 days of recovery, with plasma creatinine concentrations also tending to remain raised ($P=0.075$; Figure 1; Table S2; Figures S2 through S4).

With respect to the consistency of renal dysfunction evident with ADHF development, it should be noted that all sheep demonstrated rises in plasma creatinine (range, 6–28 µmol/L) and falls in creatinine excretion (range, −0.04 to −0.16 mmol/h) and clearance (range, −5.4 to −40.5 mL/min) during ADHF compared with baseline. Following 25 days of recovery, creatinine excretion remained reduced in all animals (range, −0.003 to −0.094 mmol/h) along with creatinine clearance (range, −5.1 to −28.5 mL/min).

Histological Results

The majority of kidney biopsies taken before pacing (baseline) had no significant histological abnormalities (5/7 samples [72%]; Figure 2A). In contrast, more than half of the samples taken during fully developed ADHF (day 14 of LV pacing) showed evidence of early mild acute tubular injury (5/9 samples [56%]), and most exhibited a prominence of glomerular mesangial cells (MCs; 7/9 samples [78%]). The same was true of biopsies taken after 25 days of ADHF recovery (63% showing both MC prominence and tubular injury). These also demonstrated some mild chronic inflammation (2/8 samples) as well as focal/patchy dystrophic calcification and medullary/interstitial fibrosis in nearly half of the specimens (3/8 samples for both; Figure 2A). Development of fibrosis is further supported by digital analysis (ImageJ) showing increased collagen deposition in all animals but 1 following development/recovery of ADHF, with levels increasing from 36±4.2% at baseline to 44.8±1.6% at HF ($P<0.05$) and 42.5±3.8% at recovery ($1.0 > P>0.05$) and can be visualized in representative serial kidney samples from the 3 states (baseline, HF, recovery) showing increased blue-staining collagen (Figure 2B).

Transcriptome Results

RNA-seq generated a mean±SD of $22.0±2.1×10^6$ high-quality read pairs per sample, which mapped to 31 553 unique genes in the sheep genome. Gene expression levels were compared between kidney biopsies collected at baseline (n=11), HF (n=13), and recovery (n=8). A total of 270 genes differed between baseline and HF ($P<0.01$ after adjustment for multiple comparisons, fold change >1.2 or <0.83, 47% upregulated in HF; Figure 3, Figure 4A, Table S3), 631 genes differed between HF and recovery (41% upregulated at recovery; Figure 3, Figure 4B, Table S3), and 47 genes differed between baseline and recovery (21% upregulated at recovery; Figure 3, Table S3). Of 827 unique genes that differed between time points, 152 (17%) had no known human homolog (most were in silico predicted transcripts) and were not analyzed further. The remaining 675 genes included 85 genes previously implicated in AKI (including mediators of fibrosis, inflammation and apoptosis, and components of the extracellular matrix), but not genes encoding early markers for AKI (including *LCN2* [lipocalin 2]; *IGFBP7* [insulin-like growth factor-binding protein 7] or *TIMP2* [tissue inhibitor of metalloproteinases 2]) (Figure S5). The vast majority of differentially expressed genes (590 of 675 genes, 87%) had no prior reported association with AKI.

Cell Signaling Pathways

To investigate the molecular pathways altered in the kidney in response to ADHF development and recovery, comparative pathway analysis was performed for 675 genes altered between baseline and HF, HF and recovery, and baseline and recovery. Genes altered across these time points were enriched for a network of genes that regulate glomerulosclerosis and 8 molecular pathways (absolute Z score >2 and $P<0.01$ after adjustment for multiple comparisons; Figure 5A, Table S3). These were eNOS (endothelial nitric oxide synthase) signaling (repressed during ADHF development; Figure S6A); cholesterol biosynthesis and PPAR (peroxisome proliferator-activated receptor) signaling (activated during recovery; Figure S6B and S6C); and GP6 (glycoprotein VI), PDGF (platelet-derived growth factor), oncostatin M, acute phase response, and "hepatic" fibrosis signaling (all repressed during recovery; Figure S6D through S6H). The "hepatic" fibrosis pathway likely represents renal fibrosis given that the IPA knowledgebase lacks an annotated pathway for renal fibrosis and many genes/proteins are shared. All of these pathways have established roles in AKI. Among the 85 differentially expressed genes mapping to these pathways, 59 (69%) had not previously been implicated in AKI, and only 2 remained altered after recovery from ADHF. None of the identified pathways remained significantly activated or repressed after recovery.

Predicted Upstream Regulators

To identify potential upstream regulators, a statistical approach was used to identify regulator genes that may alter gene expression during ADHF development and recovery with a directionality consistent with the observed expression changes. The top-predicted upstream regulator gene (ie, gene that promotes the development of ADHF and represses recovery) was the proinflammatory cytokine IL-1β (interleukin 1β), a known regulator of kidney pathology (baseline to HF and HF to recovery, $P<0.001$ after adjustment for multiple comparisons; absolute Z score >3.5). A mechanistic network generated for IL-1β indicated that the cytokine may activate a network of coregulators, including tumour necrosis factor, to alter the expression of 74 (27%) genes from baseline to HF and 263 (42%) genes from HF to recovery (Figure S7). Of these, 27 and 54 genes, respectively, may be regulated directly by IL-1β (data not shown).

Candidate Plasma/Serum and Urinary Biomarkers for AKI in ADHF

To identify potential novel biomarkers of kidney injury and recovery in ADHF, the following 2 sets of genes were selected: (1) those that differed between baseline and recovery (termed *HF-sustained* genes; n=47, 21% upregulated at recovery) and (2) those that differed from baseline to HF and from HF to recovery, but not from
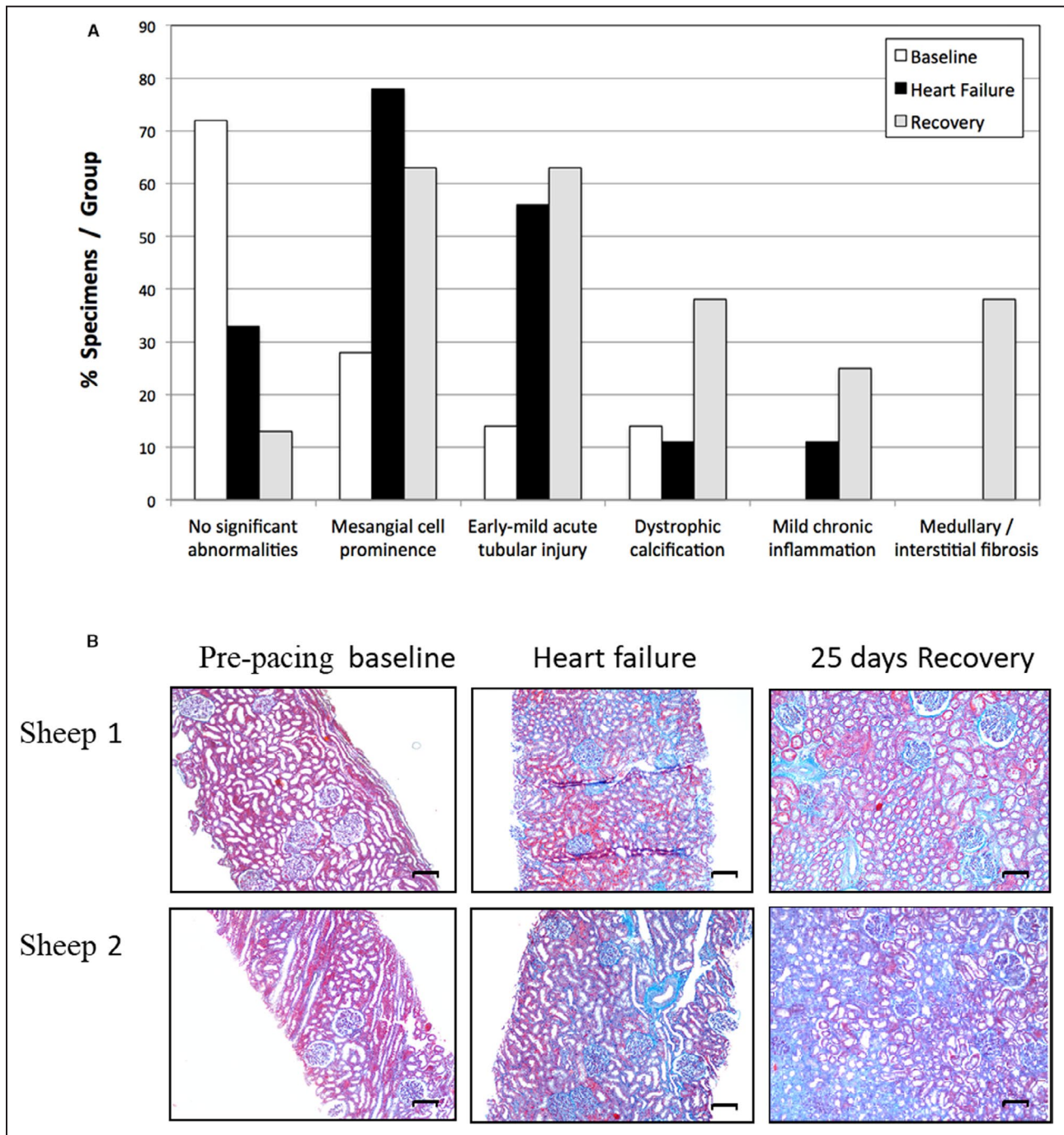
Figure 2.   Serial histological responses in sheep during development of, and recovery from, acute decompensated heart failure.

A, Principal histological findings in serial kidney biopsies taken in 9 sheep before (baseline, n=7), after development of acute decompensated heart failure (induced by left ventricular pacing at 220 bpm for 14 days; n=9), and after 25 days of recovery following termination of pacing (recovery, n=8). (Note that mesangial cell prominence is not included here as a significant histologic abnormality.). **B**, Masson's trichrome staining of representative serial kidney biopsies taken before (baseline) and after development of acute decompensated heart failure (induced by left ventricular pacing at 220 bpm for 14 days) and after 25 days of recovery following termination of pacing (recovery). Blue staining indicates collagen deposition. Scale bar=100 μmol/L.

baseline to recovery (termed *HF-responsive* genes; n=93, 47% upregulated at HF compared with baseline). From these, genes encoding proteins detectable in plasma, serum, or urine were selected as identifiers of potential candidate circulating or urinary markers and ranked based on their fold change in expression between time points. Of the 32 protein-encoding genes identified (Figure 6), 13 were HF-sustained
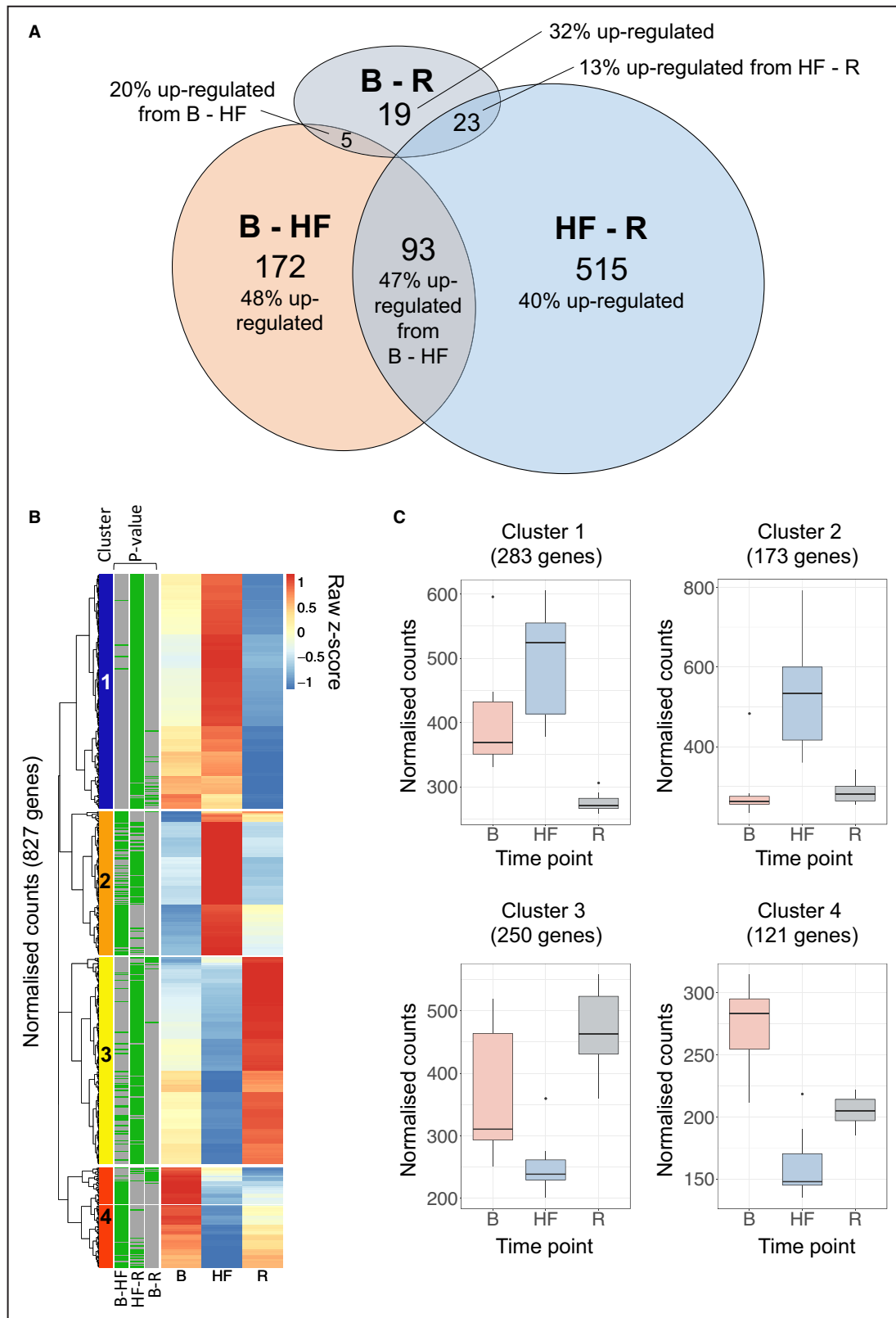
genes, representing potential persistent markers of kidney damage or dysfunction in ADHF (Table 1), and 19 were HF-responsive genes, representing potential markers for kidney repair in ADHF (Table 2). Although 5 HF-sustained and 8 HF-responsive genes had previously been implicated in AKI (42%; Tables 1 and 2, Figure 6), only 1 gene, *REN* (renin), had been investigated in patients with AKI and ADHF previously.[16]

Figure 3. **Genes altered in the kidney after development of, and following recovery from, acute decompensated HF; n=827; *P*<0.01 after adjustment for multiple comparisons, fold change >1.2 or <0.83).**

A, A total of 270 genes differed between B and HF and 631 genes differed between HF and R, of which 93 genes were altered across both data sets and were termed HF-responsive genes. A total of 47 genes differed between B and R and were termed HF-sustained genes. Percentages indicate the number of genes upregulated in the latter of the 2 time points. **B**, Heatmap showing median gene expression levels at B, HF, and R for genes differentially expressed between time points. Gene expression was scaled using *Z* scores to enable genes expressed at high and low abundance to be visualized on the same graph. For each gene, the color scale indicates high (red) or low (blue) expression relative to the other time points. Green bars (**left**) indicate differential expression between time points. Unsupervised hierarchical clustering identified four broad clusters of genes with similar patterns of expression across time points (clusters 1–4, **far left**). **C**, Box plots summarizing gene expressions for genes in each cluster in **B** (geometric mean) shown for all samples at each time point. B indicates baseline; HF, heart failure; and R, recovery.

Consequently, the remaining 31 genes were prioritized as identifying potential novel markers for AKI in ADHF.

Lastly, to explore the relationship between each of the genes that potentially translate to protein biomarkers with neurohormones and with hemodynamic measurements, correlation matrices were generated with data from 5 sheep for whom full serial measurements were available (Figures S8 and S9). Comparing changes from baseline to HF, HF-responsive candidate biomarker generating genes clustered into 6 groups with similar profiles. These were (1) *MUC20* (mucin 20) with urine urea and creatinine concentrations; (2) *IGFBP3* (insulin like growth factor binding protein 3) and *HPCA* (hippocalcin) with fluid balance; (3) *REN* and *LARP1B* (La ribonucleoprotein domain family member 1B) with urine volume; (4) *NGFR* (nerve growth factor receptor), *STAT3* (signal transducer and activator of transcription 3), *PDE5A* (phosphodiesterase 5A), *CAPN1* (calpain 1), *SIPA1L1* (signal induced proliferation associated 1 like 1), *GLTP* (glycolipid transfer protein), *SLC5A1* (solute carrier family 5 member 1), and *TXNDC16* (thioredoxin domain containing 16) with plasma urea and creatinine concentrations; (5) *CNGA3* (cyclic nucleotide gated channel subunit alpha

3) and *OIT3* (oncoprotein induced transcript 3) with MAP and renal perfusion pressure; and (6) *HSP90AA1* (heat shock protein 90 alpha family class A member 1), *KLF7* (Kruppel like factor 7), *FSTL3* (follistatin like 3), and *HSP90B1* (heat shock protein 90 beta family member 1) with PRA and plasma BNP concentrations (Figure S8A). In general, these relationships were not preserved from HF to recovery, suggesting a dynamic shift in relationships between gene expression, neurohormones, and hemodynamic responses as the model moves from developing ADHF through to recovery (Figure S8B). Similarly, comparing changes from baseline to recovery, HF-sustained biomarkers clustered into 4 groups with similar profiles. These were (1) *PDGFRB* (platelet derived growth factor receptor beta) and *SLC52A3* (solute carrier family 52 member 3) with urine sodium concentrations; (2) *FLT4* (Fms related tyrosine kinase 4), *PLEKHA8* (pleckstrin homology domain containing A8), *CFI* (complement factor I), and *CA2* (carbonic anhydrase 2) with urine urea and creatinine concentrations; (3) *ACADVL* (acyl-CoA dehydrogenase very long chain), *PCOLCE2* (procollagen C-endopeptidase enhancer 2), *ACTG2* (actin gamma 2, smooth muscle), *DES* (desmin), *ADIPOQ* (adiponectin,
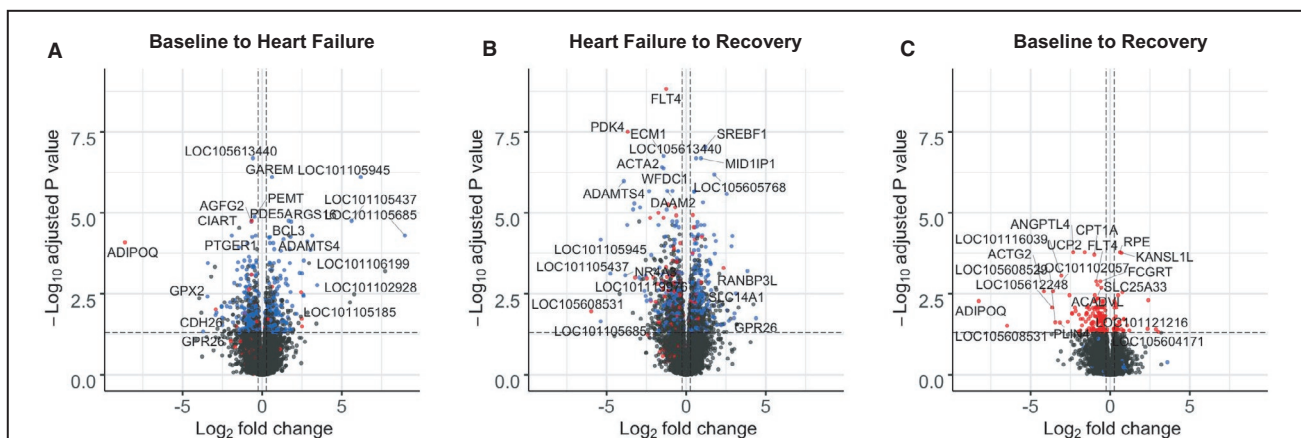
Figure 4. **Volcano plots showing genes altered from (A) baseline to heart failure, (B) heart failure to recovery, and (C) baseline to recovery.**

Genes to the right of the vertical dashed lines have a >1.2-fold increase in expression; those to the left of the vertical dashed lines have a >1.2-fold decrease in expression (ie, <0.83-fold change) between time points. The horizontal dashed line indicates the threshold for statistical significance (*P*<0.01 after adjustment for multiple comparisons). Blue dots indicate HF-responsive genes and red dots indicate HF-sustained genes. Full gene names available from https://www.ncbi.nlm.nih.gov/gene/.
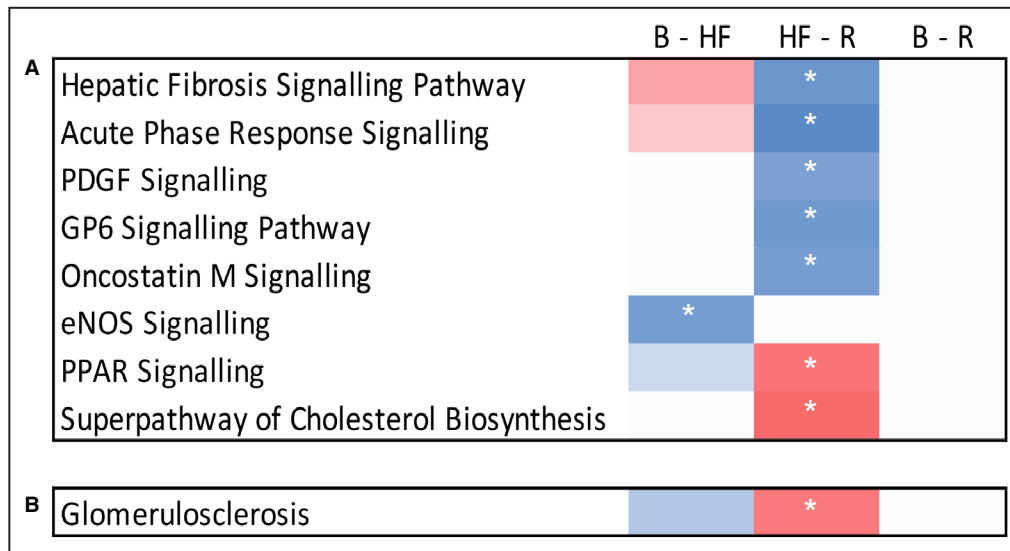
Figure 5. Cell signaling pathways (A) and nephrotoxicity networks significantly enriched during HF and/or recovery (R) (B). (*P*<0.01 after correction for multiple comparisons.)

Pathways are clustered according to their pattern of activation at each time point. Pathways were considered activated (red boxes) if the activation *Z* score was >2 or repressed (blue boxes) if the activation *Z* score was <−2 (indicated by white asterisks). None of these pathways remained altered after recovery. Note that the pathway described as "hepatic" fibrosis likely represents renal fibrosis given that renal gene expression was measured, the Ingenuity Pathway Analysis knowledgebase lacks an annotated pathway for renal fibrosis, and many components of these pathways are shared. B indicates baseline; eNOS, endothelial nitric oxide synthase; GP6, glycoprotein VI; HF, heart failure; PDGF, platelet-derived growth factor; PPAR, peroxisome proliferator-activated receptor; and R, recovery.

C1Q, and collagen domain containing), and *ANGPTL4* (angiopoietin like 4) with plasma creatinine concentrations; and (4) *BGN* (biglycan) with PRA and plasma BNP concentrations (Figure S9).

DISCUSSION

The present study exploits the unique advantages of a large, comprehensively instrumented, animal model in which ADHF can be reproducibly induced and then resolved. Serial physiological and kidney responses during ADHF induction and recovery showed that the pacing-induced impairments in systemic/regional hemodynamics and widespread neurohumoral activation were associated with a decline in renal function as evidenced by avid sodium and volume retention, elevation of plasma creatinine concentrations, and reductions in creatinine excretion and clearance. Importantly, following pacing cessation and 25 days of recovery from ADHF while hemodynamic and hormonal indexes essentially returned to prepacing baseline levels, a degree of renal dysfunction persisted. These data suggest that an episode of ADHF on a background of previously normal kidneys can result in AKI that fails to fully resolve after ≈4 weeks recovery, leading to a permanent decrement in renal function.

This suggestion is supported by serial kidney histology. Whereas prepacing kidney biopsies were generally noted as having no significant abnormalities, this was not the case for specimens taken either during ADHF or after 25 days of recovery. More than half of the ADHF samples showed evidence of early mild acute tubular injury, as did recovery specimens. Furthermore, nearly half of the recovery biopsies exhibited focal or scattered dystrophic calcification—a deposition of calcium salts that commonly occurs in degenerated or necrotic cells/tissue as a result of damage or injury[17] and can also indicate the presence of ongoing organ dysfunction. A conspicuous histopathological feature of the majority of biopsies taken following ADHF development was the prominence of glomerular MCs, an anomaly that generally still presents after 4 weeks of ADHF recovery. MC proliferation is a nonspecific response to assorted forms of glomerular insult and is a feature of many human and experimental kidney diseases.[18] Stimulation of MC replication is reported to occur via multiple mechanisms including hypoxia, inflammation, podocyte injury[19] and a large number of chemical mediators that encompass cytokines, growth factors, and hormones, with the latter including AngII (angiotensin II), aldosterone, endothelin-1, and AVP[20]—all of which were elevated during ADHF in the current study (with increments in

RNA-Seq in 14 'Baseline', 13 'Heart Failure' and 8 'Recovery' kidney biopsy/tissue samples

⬇

827 differentially expressed genes across time points (p.adj<0.01, fold-change >1.2 or <-1.2)

47 ADHF 'sustained' genes

B - R 19 — 23

5

B - HF 172

HF - R 515

93

93 ADHF 'responsive' genes

Selected genes encoding proteins detectable in plasma or urine

13 potential markers of long-term renal impairment: ***ADIPOQ***, *ACTG2*, ***ANGPTL4***, ***DES***, *PCOLCE2*, *SLC52A3*, <u>*FLT4*</u>, *BGN*, *CFI*, ***PDGFRB***, *ACADVL*, ***CA2***, *PLEKHA8*

19 potential markers of kidney repair: <u>***REN***</u>, <u>***NGFR***</u>, <u>*CNGA3*</u>, *SLC5A1*, *OIT3*, *HPCA*, *FSTL3*, *MUC20*, ***IGFBP3***, ***STAT3***, *TXNDC16*, <u>***HSP90AA1***</u>, *LARP1B*, *GLTP*, *SIPA1L1*, ***CAPN1***, *KLF7*, ***PDE5A***, <u>***HSP90B1***</u>

⬇

675 differentially expressed genes with human homologs

⬇

Pathway analysis

- Enriched for 9 pathways/networks associated with known roles in AKI (acute phase response signaling, hepatic fibrosis, oncostatin M signaling, eNOS signaling, PPAR signaling, cholesterol biosynthesis, PDGF signaling, GP6 signaling, glomerulosclerosis, p.adj<0.01, z-score >2 or <-2)
- Gene expression regulated by a network of cytokines centered on IL-1β

➡ 85 genes mapped to enriched pathways (31% previously associated with AKI)

➡ 590 genes did not map to enriched pathways (10% previously associated with AKI)

Figure 6. Transcriptome summary.
Kidney samples from animals that underwent serial sampling were supplemented with kidney samples collected postmortem from animals having undergone a similar pacing/recovery protocol, giving a total of 14×B, 13×HF, and 8×R samples for RNA sequencing analysis. Expression of 827 unique genes differed across the time course: B to HF, HF to R, and B to R. Of these, 675 genes had a human homolog and progressed to pathway analysis. Of 47 HF-sustained genes (those that remained altered after 4 weeks of recovery), 13 genes encoded proteins detectable in plasma or urine and may represent markers of long-term renal impairment in ADHF. Of 93 HF-responsive genes (those that increased during ADHF development and decreased during recovery or vice versa), 19 genes encoded proteins detectable in plasma or urine and may represent markers of kidney repair in ADHF. Genes denoted in bold text indicate genes previously associated with AKI, genes that are underlined indicate genes that mapped to pathways shown to be enriched in pathway analysis. *ACADVL* indicates acyl-CoA dehydrogenase very long chain; *ACTG2*, actin gamma 2, smooth muscle; ADHF, acute decompensated heart failure; *ADIPOQ*, adiponectin, C1Q, and collagen domain containing; AKI, acute kidney injury; *ANGPTL4*, angiopoietin like 4; B, baseline; *BGN*, biglycan CA2, carbonic anhydrase 2; *CAPN1*, calpain 1; *CFI*, complement factor I; *CNGA3*, cyclic nucleotide gated channel subunit alpha 3; *DES*, desmin; eNOS, endothelial nitric oxide synthase; *FLT4*, Fms related tyrosine kinase 4; *FSTL3*, follistatin like 3; *GLTP*, glycolipid transfer protein; GP6, glycoprotein VI; HF, heart failure; *HPCA*, hippocalcin; *HSP90AA1*, heat shock protein 90 alpha family class A member 1; *HSP90B1*, heat shock protein 90 beta family member 1; *IGFBP3*, insulin like growth factor binding protein 3; IL1β, interleukin 1β; *KLF7*, Kruppel like factor 7; *LARP1B*, La ribonucleoprotein domain family member 1B; *MUC20*, mucin 20; *NGFR*, nerve growth factor receptor; *OIT3*, oncoprotein induced transcript 3; p-adj, p-value adjusted for multiple comparisons; *PCOLCE2*, procollagen C-endopeptidase enhancer 2; *PDE5A*, phosphodiesterase 5A; PDGF, platelet-derived growth factor; *PDGFRB*, platelet derived growth factor receptor beta; *PLEKHA8*, pleckstrin homology domain containing A8; PPAR, peroxisome proliferator-activated receptor; R, recovery; *REN*, renin; *SIPA1L1*, signal induced proliferation associated 1 like 1; *SLC5A1*, solute carrier family 5 member 1; *SLC52A3*, solute carrier family 52 member 3; *STAT3*, signal transducer and activator of transcription 3; and *TXNDC16*, thioredoxin domain containing 16.

Table 1. Dysregulated Genes Encoding Candidate Responsive Biomarkers for AKI and Recovery in Acute Decompensated Heart Failure

Symbol	Name	Cellular location	Plasma/ serum	Urine	Known drug target*	Previous association with AKI†	Normalized read counts at B‡	Fold change B-HF§¶	Fold change HF-R§¶	Fold change B-R§¶
REN‖	Renin	ES	Yes	No	Yes	Yes	53 (48–102)	7.1††	−10.1††	…
NGFR	Nerve growth factor receptor	PM	No	Yes	Yes	Yes	86 (51–98)	−2.7**	2.6**	…
CNGA3	Cyclic nucleotide gated channel subunit alpha 3	PM	Yes	No	No	No	93 (85–126)	2.6**	−3.3††	…
SLC5A1	Solute carrier family 5 member 1	PM	Yes	No	No	No	358 (197–574)	−2.4#	2.5#	…
OIT3	Oncoprotein induced transcript 3	N	Yes	No	No	No	29 (15–33)	2.2**	2.6#	…
HPCA	Hippocalcin	C	Yes	Yes	No	No	50 (40–59)	−2.2**	1.9#	…
FSTL3	Follistatin like 3	ES	Yes	No	No	No	103 (91–126)	2.1**	−1.9#	…
MUC20	Mucin 20, cell surface associated	PM	No	Yes	No	No	1280 (889–1441)	−2.0**	1.9#	…
IGFBP3	Insulin like growth factor binding protein 3	ES	Yes	Yes	No	Yes	495 (373–668)	−2.0#	2.0#	…
STAT3	Signal transducer and activator of transcription 3	N	Yes	No	Yes	Yes	1182 (1060–1274)	2.0#	−1.9#	…
TXNDC16	Thioredoxin domain containing 16	ES	Yes	No	No	No	255 (220–352)	−1.9††	1.7#	…
HSP90AA1	Heat shock protein 90 alpha family class A member 1	C	No	Yes	Yes	Yes	10 647 (9601–11 011)	1.7**	−1.5#	…
LARP1B	La ribonucleoprotein domain family member 1B	ES	Yes	No	No	No	159 (153–195)	1.6**	−1.5#	…
GLTP	Glycolipid transfer protein	C	No	Yes	No	No	798 (734–914)	−1.5††	1.6††	…
SIPA1L1	Signal induced proliferation associated 1 like 1	C	Yes	No	No	No	820 (762–1283)	−1.5#	1.7#	…
CAPN1	Calpain 1	C	No	Yes	No	Yes	1448 (1204–1595)	−1.5**	1.4#	…
KLF7	Kruppel like factor 7	N	Yes	No	No	No	567 (524–625)	1.4††	−1.3#	…
PDE5A	Phosphodiesterase 5A	C	Yes	No	Yes	Yes	2088 (1901–2231)	−1.4††	1.4††	…
HSP90B1	Heat shock protein 90 beta family member 1	C	Yes	Yes	Yes	Yes	8974 (8708–9585)	1.4#	−1.4#	…

AKI indicates acute kidney injury; B, baseline; C, cytoplasm; ES, extracellular space; HF, heart failure; N, nucleus; PM, plasma membrane; and R, recovery.

*Gene/protein product targeted by 1 or more pharmaceutical drugs.

†Genes associated with AKI in the Harmonizome database[12] and Ingenuity Pathway Analysis knowledgebase.[13]

‡Normalized RNA sequencing read counts at B expressed as median (interquartile range).

§Expression fold changes between B, HF, and R.

‖Genes enriched, or specifically expressed in, kidney (www.proteinatlas.org).[14]

¶P<0.05, #P<0.01, **P<0.001, and ††P<0.0001 after adjustment for multiple comparisons.

PRA implying concurrent elevation of AngII). Although a transient increase in MCs is thought to occur in response to glomerular injury as part of the process of tissue repair or "wound healing," persistent MC proliferation caused by repetitive or more sustained glomerular injury is believed to precede, as well as promote, irreversible glomerular scarring and subsequent loss of renal function.[18] Indeed, abnormally proliferative MCs are themselves able to release mediators of proliferation, inflammation, and fibrosis (eg, AngII)[21] and to increase mesangial extracellular matrix accumulation, leading to progressive glomerulosclerosis and interstitial fibrosis.[22] Of particular significance, this process of

tissue remodeling, mesangial expansion, and glomerular scarring progresses even after termination of the initial noxious stimulus, regardless of the type of glomerular injury.[23]

Consistent with a process of progressive reparative glomerular fibrosis/scarring, the present study observed evidence of renal fibrosis subsequent to ADHF-induced AKI, with histological signs of interstitial medullary fibrosis (mild focal or patchy) noted only in recovery biopsies. The continued renal impairment (ie, persistent reductions in creatinine excretion and clearance) seen in recovery is congruent with the loss of function typically resulting from the excess

Table 2. Dysregulated Genes Encoding Candidate-Sustained Biomarkers of Kidney Damage or Dysfunction in Acute Decompensated Heart Failure

Symbol	Name	Cellular location	Plasma/ serum	Urine	Known drug target*	Previous association with AKI†	Normalized read counts at baseline‡	Fold change B-HF§‖	Fold change HF-R§‖	Fold change B-R§‖
ADIPOQ	Adiponectin, C1Q, and collagen domain containing	ES	Yes	No	No	Yes	1 (0–182)	−394**		−307¶
ACTG2	Actin gamma 2, smooth muscle	C	No	Yes	No	No	45 (12–241)	−7.6¶		−17.9¶
ANGPTL4	Angiopoietin like 4	ES	Yes	No	No	Yes	193 (121–273)		−4.8**	−5.0#
DES	Desmin	C	Yes	No	No	Yes	378 (266–882)			−4.6¶
PCOLCE2	Procollagen C-endopeptidase enhancer 2	ES	No	Yes	No	No	45 (26–87)			−2.7¶
SLC52A3	Solute carrier family 52 member 3	PM	Yes	No	No	No	260 (195–428)		−3.4**	−2.6¶
FLT4	Fms related tyrosine kinase 4	PM	Yes	No	Yes	No	401 (280–510)		−2.4**	−1.8¶
BGN	Biglycan	ES	No	Yes	No	No	1720 (1430–2272)			−1.8¶
CFI	Complement factor I	ES	Yes	Yes	No	No	1882 (1783–2191)	1.5¶		1.7¶
PDGFRB	Platelet derived growth factor receptor beta	PM	No	Yes	Yes	Yes	1324 (1105–1676)			−1.6¶
ACADVL	Acyl-CoA dehydrogenase very long chain	C	Yes	No	No	No	5918 (5389–6703)		−1.5**	−1.5¶
CA2	Carbonic anhydrase 2	C	Yes	Yes	Yes	Yes	12 771 (10 670–14 644)			−1.4¶
PLEKHA8	Pleckstrin homology domain containing A8	ES	Yes	No	No	No	499 (473–532)			1.4¶

AKI indicates acute kidney injury; B, baseline; C, cytoplasm; ES, extracellular space; HF, heart failure; PM, plasma membrane; and R, recovery.

*Gene/protein product is targeted by 1 or more pharmaceutical drugs.

†Genes associated with AKI in the Harmonizome database[12] and Ingenuity Pathway Analysis knowledgebase.[13]

‡Normalized RNA sequencing read counts at B expressed as median (interquartile range).

§Expression fold changes between B, HF, and R.

‖$P < 0.05$, ¶$P < 0.01$, #$P < 0.001$, and **$P < 0.0001$ after adjustment for multiple comparisons.

accumulation of the extracellular matrix and fibrosis as normal tissue architecture is replaced with scar tissue. In agreement with our findings, work from experimental studies of AKI in mice support the notion that fibrosis is ongoing after the initial AKI, with activated fibroblasts failing to return to their resting state.[24] Our results are also in keeping with the clinical observation that renal interstitial fibrosis is the strongest indicator of progression of chronic kidney disease (even if the primary disease is glomerular).[25]

Although findings from multiple experimental and clinical studies have demonstrated that extended periods of chronic HF result in progressive renal pathology,[26] conclusions regarding the impact of ADHF on kidney structure/function are far less definitive. Observational studies in several patient groups, including those hospitalized for acute myocardial infarction and/or percutaneous coronary revascularization, have found that those patients diagnosed with an episode of AKI were more likely to develop end-stage renal disease or chronic kidney disease,[27] with the severity, duration, and frequency of AKI appearing to

be important predictors of outcomes. Furthermore, the development of chronic kidney disease in patients with idiopathic dilated cardiomyopathy without renal insufficiency at initial diagnosis was independently related to the frequency of HF admissions,[28] and the likelihood of patients hospitalized for ADHF developing worsening renal function increased in those presenting with renal dysfunction at baseline.[29] In other studies looking at acute worsening of kidney function in patients hospitalized with HF, a prospective, multicenter cohort registry[30] reported that of a total of 5625 patients, worsening renal function (WRF) occurred in 55.1% of patients and was an independent predictor of in-hospital, short-term (3-month) and long-term (1-year) mortality. Among those patients with WRF, 61.9% showed transient WRF (recovery of serum creatinine level at discharge; mean hospitalization, 14.0±17.6 days) and 38.1% showed persistent WRF (nonrecovered creatinine level at discharge). Importantly, even transient WRF was shown to be a risk factor for 1-year mortality compared with no WRF, with persistent WRF according no additive risk compared

Figure 7.   Summary of physiological and kidney histological and transcriptomic responses to development of, and recovery from, ADHF.

ACADVL indicates acyl-CoA dehydrogenase very long chain; *ACTG2*, actin gamma 2, smooth muscle; ADHF, acute decompensated heart failure; *ADIPOQ*, adiponectin, C1Q, and collagen domain containing; *ANGPTL4*, angiopoietin like 4; *BGN*, biglycan *CA2*, carbonic anhydrase 2; *CAPN1*, calpain 1; *CFI*, complement factor I; *CNGA3*, cyclic nucleotide gated channel subunit alpha 3; *DES*, desmin; eNOS, endothelial nitric oxide synthase; *FLT4*, Fms related tyrosine kinase 4; *FSTL3*, follistatin like 3; *GLTP*, glycolipid transfer protein; *HPCA*, hippocalcin; *HSP90AA1*, heat shock protein 90 alpha family class A member 1; *HSP90B1*, heat shock protein 90 beta family member 1; *IGFBP3*, insulin like growth factor binding protein 3; IL1β, interleukin 1β; *KLF7*, Kruppel like factor 7; *LARP1B*, La ribonucleoprotein domain family member 1B; *MUC20*, mucin 20; *NGFR*, nerve growth factor receptor; *OIT3*, oncoprotein induced transcript 3; *PCOLCE2*, procollagen C-endopeptidase enhancer 2; *PDE5A*, phosphodiesterase 5A; PDGF, platelet-derived growth factor; *PDGFRB*, platelet derived growth factor receptor beta; *PLEKHA8*, pleckstrin homology domain containing A8; PPAR, peroxisome proliferator-activated receptor; *REN*, renin; *SIPA1L1*, signal induced proliferation associated 1 like 1; *SLC5A1*, solute carrier family 5 member 1; *SLC52A3*, solute carrier family 52 member 3; *STAT3*, signal transducer and activator of transcription 3; and *TXNDC16*, thioredoxin domain containing 16.

with transient WRF (despite this patient group being overall "sicker"). In another cohort of 27 309 patients from ADHERE (Acute Decompensated Heart Failure National Registry),[31] both transient (11.7%) and persistent (20.3%) WRF were associated with higher risks of 90-day postadmission mortality compared with those without WRF (68.0%), although in this study persistent WRF was associated with a higher risk relative to transient WRF. These data suggest that WRF, whether transient or persistent, represents a significant event during acute HF that, even despite measurable recovery, has significant consequences beyond the initial episode. Although all of these works provide anecdotal evidence that episodes of acute exacerbation of HF are associated with the occurrence of AKI and development/progression of renal impairment, the current study presents direct serial functional and histological data showing that a single episode of ADHF can cause AKI, which has consequences and implications beyond the acute event—with tubular injury, cellular necrosis (as indicated by dystrophic calcifications), and glomerular scarring accompanied by a permanent loss of renal function. Of note, this loss of function, although relatively minor, was consistently demonstrated across all animals studied.

Many of the triggers/processes believed to contribute to the initial renal injury following an episode of HF decompensation, as well as promote subsequent progressive renal pathology and functional decline, were evident in the current study. These include reductions in renal perfusion pressure (resulting in low-grade ischemia, hypoxia, and loss of kidney autoregulation),[32] increases in CVP (causing renal congestion and leading to increased renal interstitial pressure, tubular compression, and stimulation of inflammatory mediators),[33] and maladaptive neurohormonal activation. Notably, this includes increased sympathetic nervous traffic (which increases renal vascular resistance, augments renal renin release, and induces oxidative stress[34]), endothelin-1 (a potent renal vasoconstrictor that also possesses inflammatory and mitogenic properties and stimulates MC contraction and extracellular matrix production[35]), AVP (stimulates MC proliferation and renin

secretion and alters renal hemodynamics[36]), and the renin-angiotensin-aldosterone system. Activation of the renin-angiotensin-aldosterone system axis and its main effector AngII, in particular, is considered pivotal to the pathogenesis of much renal disease,[37] with the peptide shown to exacerbate the initial injury and promote fibrosis both directly and indirectly via stimulation of aldosterone (promotes renal inflammatory and fibrotic processes, podocyte injury, and MC proliferation[20]) and upregulation of numerous reactive oxygen species, chemokines, growth factors, and cytokines, most especially TGF-β (transforming growth factor β)—a central regulator/mediator of fibrosis following AKI.[38]

In an effort to elucidate the pathways involved in the development and recovery of AKI in ADHF, we performed RNA-seq in sequential kidney biopsies (baseline, HF, recovery), identifying altered expression of >800 genes. Changes in gene expression were consistent with repression of the reno-protective eNOS signaling pathway during ADHF development and activation of glomerulosclerosis and reno-protective pathways and repression of proinflammatory and profibrotic pathways during ADHF recovery. Three observations can be made from these data. First, renal inflammation and ischemia (as a consequence of ADHF) markedly altered renal gene expression, potentially leading to a reduction in local generation of nitric oxide—an established process in the "injury phase" of AKI that can promote further tissue damage and initiate an adaptive or maladaptive repair response.[39] Second, recovery from ADHF was associated with a further substantial shift in renal gene expression involving more than twice the number of genes associated with ADHF development. These gene expression changes may simultaneously serve to (1) restore the expression of many genes altered during ADHF development to baseline levels, (2) promote glomerulosclerosis (consistent with histological analysis), and (3) mediate the switch toward healing and repair (consistent with the partial improvement in renal function during recovery), as evidenced by activation of reno-protective pathways (cholesterol biosynthesis[40] and

ADHF DEVELOPMENT

Cardiovascular
- ↓ Cardiac output
- ↓ Arterial pressure
- ↓ Left atrial pressure
- ↑ Natriuretic peptides
- ↓ Central venous pressure

ADHF RECOVERY

Cardiovascular
- - Cardiac output
- - Arterial pressure
- ↓ Left atrial pressure
- ↑ Natriuretic peptides
- - Central venous pressure

Haemodynamic
- ↓ Renal perfusion pressure
- ↓ Creatinine Clearance
- ↓ Urinary volume/sodium

Haemodynamic
- - Renal perfusion pressure
- ↓ Creatinine Clearance
- - Urinary volume/sodium

Histology
- ↑ Mesangial prominence
- ↑ Acute tubular Injury
- ↑ Inflammation

Histology
- ↑ Mesangial prominence
- ↑ Acute tubular Injury
- ↑ Inflammation
- ↑ Dystrophic calcification
- ↑ Collagen / Fibrosis

RNASeq
270 genes altered

RNASeq
631 genes altered

Gene expression changes may be driven by network of inflammatory cytokines centred on IL1

Signaling pathways:
- ↑ 'Hepatic' fibrosis
- ↑ Acute phase response
- ↓ PPAR
- ↓ eNOS
- ↓ Glomerulosclerosis network

Signaling pathways:
- ↓ 'Hepatic' fibrosis
- ↓ Acute phase response
- ↑ PPAR
- ↓ PDGF
- ↓ Glycoprotein VI
- ↓ Oncostatin M
- ↑ Cholesterol biosynthesis
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Selected genes encoding proteins detectable in plasma or urine

93 ADHF 'responsive' genes -
Potential markers of kidney repair:
REN, NGFR, CNGA3, SLC5A1, OIT3, HPCA, FSTL3, MUC20, IGFBP3, STAT3, TXNDC16, HSP90AA1, LARP1B, GLTP, SIPA1L1, CAPN1, KLF7, PDE5A, HSP90B1

47 ADHF 'sustained' genes -
Potential markers of long-term renal impairment:
ADIPOQ, ACTG2, ANGPTL4, DES, PCOLCE2, SLC52A3, FLT4, BGN, CFI, PDGFRB, ACADVL, CA2, PLEKHA8

PPAR[41] signaling) and repression of proinflammatory (acute phase response[42] and oncostatin M[43] signaling), platelet activation (GP6 signaling[44]), and profibrotic pathways (PDGF signaling[45] and "hepatic" fibrosis[39]). Third, although most gene expression changes were transient, the expression of 47 genes remained altered

(relative to baseline) after 4 weeks of recovery, suggesting that ADHF promotes a persistent shift in renal gene expression. These long-term alterations may be associated with incomplete resolution of injury or maladaptive changes in kidney structure and potentially predispose to long-term renal impairment.[39] Although all pathways have established roles in AKI, this study is the first to suggest their direct involvement in kidney injury and repair in ADHF.

Consistent with previous studies of AKI,[46] our data suggest that changes in renal gene expression during ADHF development and recovery may be driven by a network of inflammatory cytokines centred on IL-1β. A recent post hoc analysis of CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study)[47] suggested that selective targeting of IL-1β improves cardiovascular outcomes in patients with chronic kidney disease and a history of myocardial infarction and systemic inflammation over a median of 3.7 years of follow-up.[48] Although the precise mechanism of action was not described and there was no overall benefit on renal outcomes in this trial, these findings suggest that inhibition of IL-1β may have therapeutic potential in cardiorenal disease, including AKI in ADHF.

Our data provide the first mechanistic insights into the molecular changes associated with AKI during the development of, and recovery from, ADHF. These data add to work by Pleasant et al,[49] who used RNA sequencing to investigate renal gene expression in murine pre-symptomatic HF. In kidney tissue collected at 24 weeks, Pleasant et al identified 6 genes that differed by >1.5-fold between transgenic mice that develop cardiomyopathy and later progress to HF (after 24 weeks) and matched wild-type controls. We confirmed the involvement of 3 of the 6 genes (renin, arginase 2, α-1 antitrypsin), supporting the idea that a small number of genes associated with AKI in established ADHF may also be altered before the onset of overt symptomatic HF and promote susceptibility to AKI. Beyond ADHF, we observed a number of genes in common with studies investigating early transcriptional responses to kidney injury and repair (<24 hours) in rodent models of renal ischemia/reperfusion.[50–52] Together these data suggest that AKI is associated with activation and repression of hundreds of renal genes, each with its own temporal profile, of which a small proportion may represent common pathways shared by multiple AKI etiologies.

To prioritize candidate markers for AKI in ADHF, we identified 32 genes encoding proteins detectable in urine or blood that were strongly responsive to ADHF (n=19) or showed a persistent change in expression (n=13). Of these, 13 have previously been implicated in AKI, but only 1, REN, was previously investigated in clinical studies of AKI in ADHF.[16] The HF-responsive biomarkers showed a very similar magnitude and opposite direction of fold change between baseline and HF and HF and recovery, indicating a strong relationship with kidney injury/repair and highlighting their potential as markers for kidney repair in ADHF. Among these, CNGA3 (required for normal vision and olfactory signal transduction[14]) and OIT3 (potentially involved in liver development and function[14]) had large fold changes in expression and were correlated with renal perfusion pressure, an important determinant of renal function. Similarly, 2 of the HF-sustained biomarkers, ACTG2 (a component of the cytoskeleton that mediates cell motility[14]) and ANGPTL4 (a multifunctional protein that regulates lipid metabolism and apoptosis[14]), showed consistent large decreases in expression across more than 1 time point. These sustained changes in gene expression may reflect incomplete resolution of injury or maladaptive changes in kidney structure that persist beyond other indexes of kidney injury, suggesting that they may be markers of long-term renal impairment in ADHF.

Our study has several limitations. First, we were unable to obtain serial kidney biopsies at >3 time points owing to the invasive and highly technically demanding nature of sampling. Second, we did not detect altered expression of genes encoding emerging markers of AKI, such as LCN2 (which encodes NGAL [neutrophil gelatinase-associated lipocalin]), IGFBP7 (insulin-like growth factor-binding protein 7), and TIMP2 (tissue inhibitor of metalloproteinases 2). Thus, although our data provide exciting novel mechanistic insights into the molecular changes associated with AKI in ADHF, we may have missed early events. Third, pathway analysis could only be performed for sheep genes for which there is an established human or rodent homologue. Consequently, several predicted protein-coding genes displaying the greatest differences in expression between time points (potentially representing novel pathways and biomarkers of AKI in ADHF) were excluded from our analysis. Future work will investigate whether changes in renal gene expression can be detected at the protein level, and if these changes are detectable in circulation.

In summary (see Figure 7), we have characterized the events leading to kidney injury and repair during the development of, and recovery from, ADHF (using an ovine model). By assessing changes in hormonal, hemodynamic, biochemical, and urine measures of cardio-renal injury and repair, we provide the first direct evidence that an episode of ADHF leads to a decline in kidney function that fails to fully resolve after ≈4 weeks and is associated with important, potentially lasting, kidney injury. Renal gene expression profiling provides the first insight into the pathways associated with kidney injury and repair in ADHF, highlighting the potential importance of inflammatory mediators in regulating these processes. We have prioritized 31 novel

candidates as biomarkers for AKI in the setting of ADHF.

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SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

RNA Sequencing and Bioinformatics Analysis

RNA extraction and RNA-Seq library preparation:

Frozen kidney biopsy samples (<100mg) were placed in pre-chilled tubes with TRIzol™ reagent (Invitrogen, Carlsbad, CA) and subjected to automated grinding at 30Hz for 10minutes in a MM301 tissue mill (Retsch, Haan, Germany). Total RNA was purified with RNeasy Midi Columns (Qiagen, Hilden, Germany) according to manufacturer's instructions. RNA yield and integrity were assessed with a 2200 TapeStation system (Agilent Technologies, Waldbronn, Germany). Of the total biopsies collected, 5xBaseline, 6xHF and 5xRecovery serial samples had an RNA integrity number equivalent (RINe) >6.0 (mean 6.7, range 6.0-8.2) and a mean concentration of 246ng/μL (range 55-817ng/μL). To maximise statistical power, additional kidney samples were collected post-mortem from animals having undergone a similar pacing/recovery protocol, with tissues obtained from an additional 9xNormal sheep (Baseline), 7xHF sheep and 3xRecovery sheep. Total RNA was isolated, purified and analysed as above. RNA integrity was similar to serially biopsied samples (mean RINe 7.1, range 5.8-8.5). All RNA samples (n=14xBaseline, 13xHF, 8xRecovery) were submitted to library construction, sequencing and bioinformatics (Otago Genomics and Bioinformatics, University of Otago, New Zealand). RNA libraries were prepared using 500ng input total RNA and TruSeq stranded mRNA library prep kits (Illumina, San Diego, CA) according to the manufacturer's instructions. To minimize lane effects, all libraries were normalised, and equimolarly pooled before being paired-end sequenced across two lanes of HiSeq 2500 flowcell, V4 chemistry (Illumina), generating 125bp reads.

Bioinformatics analysis:

Individual libraries were separated from multiplexed sequencing data (total yield=93.9Gb), adapter- and quality-trimmed and converted to FASTQ format with fastq-mcf [https://expressionanalysis.github.io/ea-utils/]. Paired-end reads <50 nucleotides were removed with the SolexaQA package and the quality of the remaining reads verified using fastqc tools [https://www.bioinformatics.babraham.ac.uk/projects/fastqc/] (mean quality score/base=35.8, mean percentage of bases ≥Q30=94.8%). Sequence reads for all samples were aligned to the *Ovis aries* genome (assembly version-3.1, http://www.ncbi.nlm.nih.gov/genome/83) using Bowtie 2 and TopHat2. Sequencing produced a relatively even level of coverage for all samples (mean±standard deviation number of paired mapped reads per sample=$22.0\pm2.1\times10^{\cdot}$). Read counts for each transcript based on RefSeq and Ensembl annotations were extracted with Bedtools. Those mapping to different isoforms of the same gene were combined to provide gene-level counts for comparative analysis.

Table S1. Dysregulated genes compared with 884 genes associated with acute kidney injury as documented in databases Harmonizome and Ingenuity Pathway Analysis (IPA) Knowledgebase (https://qiagenbioinformatics.com/products/ ingenuity-pathway-analysis).

Gene	Harmonizome database	IPA knowledgbase
A2M	Y	
ABAT		Y
ABCA1	Y	
ABCB1	Y	
ABCB11	Y	
ABCB4	Y	
ABCC1	Y	
ABCC2	Y	
ABCC3	Y	
ABCC4	Y	
ABCC6	Y	
ABCG2	Y	
ACACA	Y	
ACACB	Y	
ACADM	Y	
ACAT1	Y	
ACE	Y	
ACHE	Y	
ACO2	Y	
ACOX1	Y	
ACSL1	Y	
ACSL6	Y	
ACTA2	Y	
ACTB	Y	
ADIPOQ	Y	
ADIPOR2	Y	
ADM	Y	
ADORA1		Y
ADORA2A		Y
ADRA2A		Y
ADRA2B		Y
ADRA2C		Y
ADRB1	Y	
ADRB2	Y	
AGER	Y	
AGPAT9	Y	
AGT	Y	
AGTR1	Y	
AGTR2	Y	
AHR	Y	
AHSG		Y
AIFM1	Y	
AK4	Y	
AKAP12	Y	
AKR1A1		Y
AKR1B1	Y	
AKT1	Y	
AKT2	Y	
ALAD	Y	
ALAS1	Y	
ALAS2	Y	
ALB	Y	Y
ALDH1A1	Y	
ALDH2	Y	
ALDH3A1	Y	
ALDH5A1		Y
ALDOA	Y	
ALDOC	Y	
ALOX5AP	Y	
ALPL	Y	
AMBP	Y	Y
AMN	Y	
AMY2A		Y
AMY2B		Y
ANGPT1	Y	
ANGPTL4	Y	
ANPEP		Y
ANXA1	Y	
ANXA2	Y	
ANXA3	Y	
ANXA5	Y	
APAF1	Y	
APEX1	Y	
APOA1	Y	
APOA4	Y	
APOB	Y	
APOE	Y	
APP	Y	
AQP1	Y	
AQP2	Y	Y
AQP3	Y	
AQP4	Y	
AR	Y	Y
ARC	Y	
ARG1	Y	
ARG2	Y	
ARL6IP5	Y	
ARNT	Y	
ARNTL	Y	
ASAH1	Y	
ASL	Y	
ASNS	Y	
ASS1	Y	
ATF3	Y	
ATF4	Y	
ATF5	Y	
ATF6	Y	
ATG5		Y
ATM	Y	
ATP1A1	Y	Y
ATP1B1	Y	Y
ATP2A2	Y	
ATP4A		Y
ATP4B		Y
ATP5A1	Y	
AURKA	Y	
AVP	Y	
AVPR3		Y
B2M	Y	Y
BAD	Y	
BAG3	Y	
BAK1	Y	
BAX	Y	
BBC3	Y	
BCL2	Y	
BCL2L1	Y	
BCL2L11	Y	
BCL2L2	Y	
BCL6	Y	
BDNF	Y	
BECN1	Y	
BGLAP	Y	
BHLHE40	Y	
BHMT	Y	
BID	Y	
BIRC2	Y	
BIRC3	Y	
BIRC5	Y	
BNIP3	Y	
BNIP3L	Y	
BRCA1	Y	
BTG2	Y	
C1QA	Y	
C1QB	Y	
C3	Y	
CA2	Y	
CACNA1B		Y
CALB1	Y	
CALCA	Y	
CALD1	Y	
CALR	Y	
CAMK2A	Y	
CAMK4		Y
CANX	Y	
CAPN1	Y	
CAPN2	Y	
CASP1	Y	
CASP12	Y	
CASP2	Y	
CASP3	Y	
EPHX2	Y	
EPO	Y	
EPOR		Y
ERN1	Y	
ERP29	Y	
ESR1	Y	
ETS2	Y	
F2	Y	
F2R	Y	
F3	Y	
FABP1	Y	Y
FABP3	Y	
FABP4	Y	
FADD	Y	
FADS1	Y	
FADS2	Y	
FAS	Y	
FASLG	Y	
FASN	Y	
FAT1	Y	
FBP1	Y	
FBXO32	Y	
FDFT1	Y	
FDPS	Y	
FGA	Y	
FGB	Y	
FGF1	Y	
FGF2	Y	
FKBP5	Y	
FLT1	Y	
FMO5	Y	
FN1	Y	
FOS	Y	
FOSB	Y	
FOSL1	Y	
FOSL2	Y	
FOXO1	Y	
FOXO3	Y	
FSHB	Y	
FSTL1	Y	
FTH1	Y	
FYB1		Y
FYN	Y	
G0S2	Y	
G6PC	Y	
G6PD	Y	
GABRA1		Y
GABRA2		Y
GABRA3		Y
GABRA4		Y
GABRA5		Y
GABRA6		Y
GABRB1		Y
GABRB2		Y
GABRB3		Y
GABRD		Y
GABRE		Y
GABRG1		Y
GABRG2		Y
GABRG3		Y
GABRP		Y
GAD1	Y	
GAD2		Y
GADD45A	Y	
GADD45B	Y	
GADD45G	Y	
GAPDH	Y	
GAS6	Y	
GCLC	Y	
GCLM	Y	
GDF15	Y	
GFAP	Y	
GFER	Y	
GGT1		Y
GH1	Y	
GHR	Y	
GJA1	Y	
GLDC	Y	
GLUL	Y	
GM2A	Y	
GNAI2	Y	
GNAS	Y	
GPAM	Y	
GPNMB	Y	
GPRC5B		Y
GPT	Y	
GPX1	Y	
GPX2	Y	
GPX3	Y	
GPX4	Y	
GRIN1		Y
GRIN2A		Y
GRIN2B	Y	Y
GRIN2C		Y
GRIN2D		Y
GRIN3A		Y
GRIN3B		Y
GSK3B	Y	
GSN	Y	
GSR	Y	
GSS		Y
GSTA1	Y	
GSTA2	Y	
GSTA3	Y	
GSTA4	Y	
GSTM1	Y	
GSTM2	Y	
GSTM3	Y	
GSTP1	Y	
GSTT1	Y	
GUCY1B3	Y	
GUSB	Y	
H2AFX	Y	
HADH	Y	
HAVCR1	Y	Y
HBEGF	Y	
HBG2	Y	
HDAC1	Y	
HERPUD1	Y	
HES1	Y	
HEXB	Y	
HGF	Y	
HIF1A	Y	
HLA-DRB1	Y	
HLA-DRB3	Y	
HLA-DRB4	Y	
HLA-DRB5	Y	
HMGB1	Y	
HMGB2	Y	
HMGCR	Y	Y
HMGCS1	Y	
HMGCS2	Y	
HMOX1	Y	Y
HNF4A	Y	
HPCAL1	Y	
HPGD	Y	
HPN	Y	
HRAS	Y	
HSD11B1	Y	
HSD11B2	Y	
HSF1	Y	
HSP90AA1	Y	
HSP90AB1	Y	
HSP90B1	Y	
HSPA1A	Y	
HSPA1B	Y	
HSPA4L	Y	
HSPA5	Y	
HSPA8	Y	
HSPA9	Y	
NPPA	Y	
NPPB	Y	
NPY	Y	
NQO1	Y	
NR0B2	Y	
NR1D1	Y	
NR1H3	Y	
NR1I2	Y	
NR1I3	Y	
NR3C1	Y	
NR3C2		Y
NR4A1	Y	
NRP1	Y	
NT5E	Y	
NUPR1	Y	
OCLN	Y	
ODC1	Y	
OLR1	Y	
P4HA1	Y	
PARP1	Y	
PCK1	Y	
PCNA	Y	
PDE11A		Y
PDE3A		Y
PDE3B		Y
PDE4A		Y
PDE4B	Y	Y
PDE4C		Y
PDE4D		Y
PDE5A		Y
PDE7A		Y
PDE7B		Y
PDE8A		Y
PDGFA	Y	
PDGFB	Y	
PDGFRB	Y	
PDIA3	Y	
PDIA4	Y	
PDIA6	Y	
PDK4	Y	
PDLIM7	Y	
PECAM1	Y	
PER2	Y	
PFKFB3	Y	
PGD	Y	
PGK1	Y	
PHGDH	Y	
PHYH	Y	
PIGA	Y	
PIK3R1	Y	
PIR	Y	
PKLR	Y	
PKM	Y	Y
PLA2G2A	Y	
PLA2G4A	Y	
PLAT	Y	
PLAU	Y	
PLAUR	Y	
PLG	Y	
PLIN2	Y	
PLK1	Y	
PLSCR1	Y	
PLTP	Y	
PMAIP1	Y	
PNMT	Y	
POMC	Y	
PON1	Y	
POR	Y	
POU5F1	Y	
PPARA	Y	
PPARD	Y	
PPARG	Y	
PPARGC1A	Y	
PPP1CB	Y	
PPP1R15A	Y	
PPP2CA	Y	
PPP3CA	Y	
PRDX1	Y	
PRDX2	Y	
PRDX3	Y	
PRDX6	Y	
PRKAA1	Y	
PRKCA	Y	
PRKCB	Y	
PRKCD	Y	
PRKCE	Y	
PRL	Y	
PRLR	Y	
PRNP	Y	
PSAT1	Y	
PTEN	Y	
PTGIS	Y	
PTGS1	Y	
PTGS2	Y	
PTK2	Y	
RAC1	Y	
RAD50	Y	
RAF1	Y	
RAMP2	Y	
RAPGEF3	Y	
RB1	Y	
RBP1	Y	
REL	Y	
RELA	Y	
RELB	Y	
RELN	Y	
REN	Y	
RGMB		Y
RGS16	Y	
RGS2	Y	
RGS4	Y	
RHOA	Y	
RPS6	Y	
RPS6KB1	Y	
RPSA	Y	
RRM2	Y	
RXRA	Y	
S100A10	Y	
S100A11	Y	
S100A4	Y	
S100A6	Y	
S100A8	Y	
S100A9	Y	
S100B	Y	
SAT1	Y	
SCARB1	Y	
SCD	Y	
SCN10A		Y
SCN1A		Y
SCN1B		Y
SCN5A		Y
SCNN1A	Y	
SDC2	Y	
SELE	Y	
SELL	Y	
SELP	Y	
SERPINA4	Y	
SERPINB2	Y	
SERPINE1	Y	
SERPINH1	Y	
SESN2	Y	
SFTPB	Y	
SGK1	Y	
SHMT1	Y	
SIRT1	Y	Y
SLC11A1	Y	
SLC12A1		Y
SLC16A1	Y	
SLC1A2	Y	
SLC20A1	Y	

Gene				Gene				Gene			
CASP4	Y			HSPB1	Y			SLC22A1	Y		
CASP6	Y			HSPD1	Y			SLC22A12	Y		
CASP7	Y			HSPE1	Y			SLC22A2	Y		
CASP8	Y			HSPH1	Y			SLC22A24	Y		
CASP9	Y			ICAM1	Y			SLC22A3	Y		
CAT	Y			ID2	Y			SLC22A5	Y		
CAV1	Y			ID3	Y			SLC22A6	Y		
CBR1	Y			IDI1	Y			SLC22A7	Y		
CCL2	Y			IER3	Y			SLC22A8	Y		
CCL20	Y			IFNA2	Y			SLC22A9	Y		
CCL3	Y			IFNG	Y		Y	SLC27A2	Y		
CCL5	Y			IFRD1	Y			SLC29A1	Y		
CCN1			Y	IGF1	Y			SLC2A1	Y		
CCNA2	Y			IGF1R	Y			SLC2A2	Y		
CCNB1	Y			IGFBP1	Y			SLC2A3	Y		
CCNB2	Y			IGFBP2	Y			SLC2A4	Y		
CCND1	Y			IGFBP3	Y			SLC30A1	Y		
CCND2	Y			IGFBP4	Y			SLC3A2	Y		
CCND3	Y			IGFBP5	Y			SLC40A1	Y		
CCNE1	Y			IKBKB	Y			SLC7A11	Y		Y
CCNE2	Y			IL10	Y			SLC9A3			Y
CCNG1	Y			IL12A	Y			SMAD2	Y		
CD14	Y			IL12B	Y			SMAD3	Y		
CD36	Y			IL13	Y			SNCA	Y		
CD38	Y			IL18	Y		Y	SOCS3	Y		
CD40	Y			IL1A	Y			SOD1	Y		
CD44	Y			IL1B	Y			SOD2	Y		
CD55	Y			IL1RN	Y			SOD3	Y		
CD5L			Y	IL2	Y			SP1	Y		
CD74	Y			IL20	Y			SPARC	Y		
CD86	Y			IL23A	Y			SPHK1	Y		
CD9	Y			IL2RA	Y			SPON1	Y		
CDC25B	Y			IL4	Y			SPP1	Y		Y
CDC42	Y			IL5	Y			SQSTM1	Y		
CDC6	Y			IL6	Y			SRC	Y		
CDH1	Y			ILK	Y			SREBF1	Y		
CDK1	Y			INHBA	Y			SRGN	Y		
CDK2	Y			INHBE	Y			SRXN1	Y		
CDK4	Y			INS	Y			STAR	Y		
CDK5	Y			INSIG1	Y			STAT1	Y		
CDKN1A	Y			IRS1	Y			STAT3	Y		
CDKN1B	Y			ITGAM	Y			STAT6	Y		
CDKN1C	Y			ITGB1	Y			STIP1	Y		
CDKN2A	Y			JAK1	Y			STMN1	Y		
CEBPA	Y			JAK2	Y			SUFU	Y		
CEBPB	Y			JUN	Y			SULT1A1	Y		
CEBPD	Y			JUNB	Y			SV2A			Y
CES2	Y			JUND	Y			TAC1	Y		
CFD	Y			KCNH2	Y			TAGLN	Y		
CFLAR	Y			KDR	Y			TDO2	Y		
CFTR	Y			KEAP1	Y			TF	Y		
CHAC1	Y			KLF2	Y			TFF3	Y		
CHEK1	Y			KLF4	Y			TFRC	Y		
CHEK2	Y			KLF5	Y			TGFA	Y		
CHUK	Y			KLF6	Y			TGFB1	Y		
CITED2	Y			KLF9	Y			TGFB2	Y		
CKB	Y			KLK1	Y			TGFBR2	Y		
CKM	Y			KNG1	Y			TGIF1	Y		
CKS2	Y			KRAS	Y			TH	Y		
CLDN1	Y			KRT18	Y			THBS1	Y		
CLU	Y		Y	KRT8	Y			THRSP	Y		
COL18A1	Y			LAMC2	Y			TIMM17A	Y		
COL1A1	Y			LBP	Y			TIMP1	Y		
COL1A2	Y			LCN2	Y		Y	TIMP2	Y		
COL3A1	Y			LCP2			Y	TIMP3	Y		
COL4A1	Y			LDHB	Y			TJP1	Y		
COMT	Y			LDLR	Y			TK1	Y		
CP	Y			LEP	Y			TKT	Y		
CPS1	Y			LGALS1	Y			TLR2	Y		
CPT1A	Y			LGALS3	Y			TLR4	Y		
CREB1	Y			LHB	Y			TNC	Y		
CREBBP	Y			LIF	Y			TNF	Y		
CREM	Y			LIPC	Y			TNFAIP3	Y		
CRP	Y			LITAF	Y			TNFRSF10B	Y		
CRYAB	Y			LMCD1	Y			TNFRSF11B	Y		
CSF1	Y			LMNA	Y			TNFRSF12A	Y		
CSF2	Y			LOX	Y			TNFRSF1A	Y		
CST3	Y		Y	LPIN1	Y			TNFSF10	Y		
CTGF	Y			LPL	Y			TNFSF11	Y		
CTH	Y			LSS	Y			TNFSF9	Y		
CTNNB1	Y			LTA	Y			TNNC1			Y
CTSB	Y			LYZ			Y	TOP2A	Y		
CTSD	Y			MAFF	Y			TP53	Y		
CTSL	Y			MAOA	Y			TPI1	Y		
CX3CL1	Y			MAOB	Y			TPM1	Y		
CXCL1	Y			MAP1LC3B	Y			TRAF2	Y		
CXCL10	Y			MAP2K1	Y			TRIB3	Y		
CXCL12	Y			MAP2K2	Y			TSC22D3	Y		
CXCL2	Y			MAP2K3	Y			TTR	Y		
CXCL8	Y			MAP2K6	Y			TUBA1A	Y		
CXCR4	Y			MAP3K5	Y			TUBB	Y		
CYB5A	Y			MAPK1	Y			TXN	Y		
CYBA	Y			MAPK14	Y			TXNIP	Y		
CYBB	Y			MAPK3	Y			TXNRD1	Y		
CYCS	Y			MAPK8	Y			TYMP	Y		
CYP11A1	Y			MAPK9	Y			TYMS	Y		
CYP1A1	Y			MAPKAPK2	Y			UBC	Y		
CYP1A2	Y			MARCKS	Y			UBE2C	Y		
CYP1B1	Y			MBP	Y			UCHL1	Y		
CYP24A1	Y			MCL1	Y			UCP1	Y		
CYP2B6	Y			MCM2	Y			UCP2	Y		
CYP2C19	Y			MCM7	Y			UGCG	Y		
CYP2C8	Y			MDM2	Y			UGT1A1	Y		
CYP2C9	Y			ME1	Y			UGT1A10	Y		
CYP2D6	Y			MGLL	Y			UGT1A3	Y		
CYP2E1	Y			MGMT	Y			UGT1A6	Y		
CYP3A4	Y			MGP	Y			UGT1A9	Y		
CYP3A5	Y			MGST1	Y			UGT2B7	Y		
CYP4A11	Y			MIF	Y			UNG	Y		
CYP7A1	Y			MKI67	Y			UOX	Y		
CYR61	Y			MME	Y		Y	VCAM1	Y		
DDIT3	Y			MMP1	Y			VCAN	Y		
DDIT4	Y			MMP13	Y			VCL	Y		
DES	Y			MMP2	Y			VDAC1	Y		
DFFA	Y			MMP3	Y			VDR	Y		
DGAT1	Y			MMP7	Y			VEGFA	Y		
DGKE	Y			MMP9	Y			VIM	Y		
DHCR7	Y			MPO	Y			VLDLR	Y		
DHFR	Y			MSMO1	Y			VNN1	Y		
DIABLO	Y			MT1A	Y			WEE1	Y		
DNAJA1	Y			MT2A	Y			WIPI1	Y		
DNAJB1	Y			MT3	Y			XBP1	Y		
DNAJB9	Y			MTHFD2	Y			XDH	Y		
DNMT1	Y			MTHFR	Y			XIAP	Y		
DRD1	Y			MTOR	Y						
DRD2	Y			MVP	Y						
DUSP1	Y			MYC	Y						
DUSP6	Y			MYH6	Y						
E2F1	Y			MYH7	Y						
ECH1	Y			MYL9	Y						
ECHS1	Y			NAGLU			Y				
ECI1	Y			NBN	Y						
EDN1	Y			NCF1	Y						
EDNRA	Y			NCF2	Y						
EDNRB	Y			NDRG1	Y						
EEF1A1	Y			NEDD9	Y						
EEF2	Y			NEFH	Y						
EGF	Y			NFAT5	Y						
EGFR	Y			NFATC4	Y						
EGLN3	Y			NFE2L1	Y						
EGR1	Y			NFE2L2	Y						
EGR2	Y			NFKB1	Y						
EIF2A	Y			NFKB2	Y						
EIF2AK3	Y			NFKBIA	Y						
EIF2S1	Y			NFKBIZ	Y						
EIF4EBP1	Y			NGF	Y						
EIF5	Y			NGFR	Y						
ELOVL6	Y			NME1	Y						
EMP1	Y			NOS1	Y						
EMP3	Y			NOS2	Y						
ENC1	Y			NOS3	Y		Y				
ENO1	Y			NOX1	Y						
ENTPD5	Y			NOX4	Y						
EPAS1	Y			NPHS1	Y						
EPHX1	Y			NPHS2	Y						

Table S2. Responses during development and recovery from acute heart failure induced by 2 weeks of rapid left ventricular pacing.

Day: Pacing Rate:	Baseline No pacing	D7-Pace 220bpm	D14-Pace 220bpm	D1-Recovery No pacing	D7-Recovery No pacing	D25-Recovery No pacing
Heart rate (beats/min)	88±5	220±0 ‡	220±0 ‡	130±14 *	100±6	86±5
Cardiac Output (L/min)	7.49±0.41	4.11±0.29 ‡	3.75±0.22 ‡	6.38±0.52 *	7.24±0.41	7.38±0.39
Mean Arterial Pressure (mmHg)	88.6±2.5	69.1±2.5 ‡	67.4±2.1 ‡	82.8±4.0	88.0±4.3	87.0±4.5
Left atrial Pressure (mmHg)	4.6±0.5	24.2±1.1 ‡	28.7±21.5‡	17.1±3.5 †	7.7±1.1 *	5.9±0.6 *
CTPR (mmHg/L/min)	12.0±0.8	17.1±0.9 ‡	18.3±1.1 ‡	13.3±0.9	12.3±0.7	12.2±0.7
Plasma ANP (pmol/L)	20±2	225±33 ‡	348±38 ‡	116±40 *	39±7 *	24±2 †
Plasma BNP (pmol/L)	1.5±0.5	34.3±8.3 †	47.9±6.5 ‡	30.9±7.6 †	6.3±1.6 *	2.4±0.6 *
Plasma renin activity (nmol/L/hr)	0.17±0.03	1.78±0.51 *	2.01±0.56 *	0.69±0.35	0.16±0.02	0.20±0.04
Plasma aldosterone (pmol/L)	218±30	2314±989 *	4644±1624 *	1570±797	257±71	383±114
Plasma endothelin-1 (pmol/L)	2.01±0.12	3.30±0.32 †	4.41±0.44 ‡	3.00±0.60	2.02±0.08	1.94±0.10
Plasma vasopressin (mmol/L)	1.6±0.1	2.4±0.4 *	2.7±0.5 *	2.2±0.6	1.9±0.1	1.7±0.2
Plasma epinephrine (pmol/L)	621±96	1325±244 *	1554±182 *	1375±585	496±173	602±145
Plasma norepinephrine (nmol/L)	7.6±1.7	21.2±4.6 *	26.7±9.2 *	20.9±6.2	9.1±2.3	9.7±3.1
Plasma sodium (mmol/L)	146.0±1.1	144.3±1.6	144.0±1.7	144.6±0.8	147.5±0.7	146.1±0.5
Plasma potassium (mmol/L)	4.2±0.1	4.4±0.1	4.5±0.1	4.4±0.1	4.5±0.1	4.2±0.1
Plasma creatinine (umol/L)	75.3±1.5	82.4±3.5 †	87.6±4.5 †	81.3±6.0	84.5±4.1 *	80.6±2.8
Hematocrit (%)	26.0±1.6	25.9±1.8	24.8±2.0	24.1±1.8	25.0±1.3	23.8±1.4 *
Urine output (ml/24hrs)	1436±163	689±201 †	674±89 ‡	2748±470 †	1850±298	1772±252
Urine potassium (mmol/hr)	14.4±1.6	6.1±1.2 ‡	5.3±1.2 ‡	11.1±2.5	12.4±1.6	15.7±1.5
Urine creatinine (umol/hr)	0.41±0.02	0.38±0.02 *	0.34±0.02 †	0.35±0.3 *	0.32±0.3 †	0.36±0.3 †
Drinking (ml/hr)	3091±454	2363±557	2001±406 †	2889±598	4535±348 †	3746±424 *

Values are mean ± SEM. Calculated total peripheral resistance (CTPR) Atrial natriuretic peptide (ANP); B-type natriuretic peptide (BNP). Significant differences between baseline (mean of samples taken over the 5 days prior to pacing) and pacing and post-pacing recovery time-points were determined by paired student's t-tests and shown by: * $p<0.05$, † $p<0.01$, ‡ $p<0.001$, by 1-way ANOVA.

Table S3. Genes differing between Baseline (B) and heart failure (HF) and Recovery (R).

Gene	Median Normalised Counts at Baseline	Kidney Enriched Genes	B-HF Fold Change	B-HF Direction	B-HF Adjusted P-value	HF-R Fold Change	HF-R Direction	HF-R Adjusted P-value	B-R Fold Change	B-R Direction	B-R Adjusted P-value	HF Responsive Genes	HF Sustained Genes	Potential Biomarker for AKI in ADHF	Present in at least one canonical pathway or network	Acute Phase Response Signalling	eNOS Signalling	Hepatic Fibrosis Signalling Pathway	PPAR Signalling	Superpathway of Cholesterol Biosynthesis	Oncostatin M Signalling	GP6 Signalling Pathway	PDGF Signalling	Glomerulosclerosis Network
ADIPOQ	1	N	394.17	Down	7.76E-05				306.61	Down	5.30E-03	N	Y	Y	N	Y	N	N	N	N	N	N	N	Y
REN	53	Y	7.14	Up	7.21E-05	10.10	Down	7.89E-06				Y	N	Y	Y	Y	Y	N	Y	N	N	N	Y	N
FOS	187	N	5.98	Up	3.23E-03	7.79	Down	9.92E-04				Y	N		Y	Y	N	Y	N	Y	N	N	Y	N
HSPA6	16	N	5.43	Up	2.66E-03							N	N		Y	N	Y	N	N	N	N	N	N	N
WNT9B	20	Y	4.02	Down	7.94E-03	7.19	Up	1.08E-04				Y	N		Y	N	N	Y	N	N	N	N	N	Y
PTGER1	48	Y	3.76	Down	4.80E-05	2.95	Up	2.45E-03				Y	N		Y	N	N	N	N	N	N	N	N	Y
SCTR	87	N	3.44	Up	5.21E-05							N	N		Y	N	N	Y	N	N	N	N	N	Y
RND1	47	N	3.07	Up	9.93E-03							N	N		Y	N	N	Y	N	N	N	N	N	N
NGFR	86	N	2.75	Down	1.10E-04	2.56	Up	8.65E-04				Y	N	Y	Y	Y	N	Y	N	Y	N	N	N	N
CNGA3	93	N	2.61	Up	5.51E-04	3.34	Down	2.36E-05				Y	N	Y	Y	N	Y	N	N	N	N	N	N	N
SERPING1	4833	N	2.53	Up	6.16E-05							N	N		Y	Y	N	N	N	N	N	N	N	N
HSPA1L	5038	N	2.39	Up	4.79E-03							N	N		Y	N	Y	N	Y	N	N	N	N	N
STAT3	1182	N	1.95	Down	1.25E-03	1.92	Down	3.10E-03				Y	N	Y	Y	Y	N	Y	N	Y	N	Y	N	Y
SREBF1	446	N	1.78	Down	2.16E-04	2.31	Up	9.48E-08				Y	N		Y	N	N	N	N	N	N	N	N	Y
HSP90AA1	10647	N	1.66	Up	3.38E-04	1.51	Down	8.82E-03				Y	N	Y	Y	N	Y	N	Y	N	N	N	N	N
SKIL	458	N	1.49	Up	5.89E-04							N	N		Y	N	N	N	N	N	N	N	N	Y
RIPK1	1153	N	1.39	Up	3.28E-04	1.43	Down	1.54E-04				Y	N		Y	Y	N	N	N	N	N	N	N	N
MRAS	180	N	1.37	Down	5.75E-04							N	N		Y	Y	N	Y	N	Y	N	N	N	N
HSP90B1	8974	N	1.37	Up	5.71E-03	1.42	Down	2.39E-03				Y	N	Y	Y	N	Y	N	Y	N	Y	N	N	N
IRAK2	219	N	1.35	Up	1.42E-03	1.51	Down	1.85E-03				Y	N		Y	N	N	Y	N	N	N	N	N	N
PRKAG2	830	N	1.33	Down	4.80E-05	1.41	Up	2.24E-06				Y	N		Y	N	Y	Y	Y	N	N	N	N	N
TRAF6	435	N	1.32	Up	3.78E-04							N	N		Y	Y	N	Y	N	Y	N	N	Y	N
IL11RA	520	N	1.31	Down	2.41E-03							N	N		Y	N	N	N	N	N	Y	N	N	N
SMAD4	633	N	1.24	Up	6.41E-03							N	N		Y	N	N	N	N	N	N	N	N	Y
ACVR1	783	N	1.23	Up	5.29E-03							N	N		Y	N	N	Y	N	N	N	N	N	N
WNT7B	17	N				9.75	Up	8.44E-03				N	N		Y	N	N	Y	N	N	N	N	N	N
SNAI1	43	N				3.56	Down	2.55E-03				N	N		Y	N	N	Y	N	N	N	N	N	Y
CREB3L3	135	N				3.47	Down	7.38E-04				N	N		Y	N	N	N	N	N	N	N	N	N
COL1A1	707	N				3.04	Down	6.69E-03				N	N		Y	N	N	Y	N	N	N	Y	N	N
RASD1	100	N				2.97	Down	1.03E-03				N	N		Y	Y	N	Y	N	Y	N	Y	N	N
ACTA2	2569	N				2.86	Down	3.90E-07				N	N		Y	N	N	Y	N	N	N	N	N	N
CEBPB	41	N				2.72	Down	6.48E-04				N	N		Y	Y	N	N	N	N	N	N	N	N
FLT4	401	N				2.39	Down	1.50E-09	1.84	Down	1.30E-03	N	Y	Y	Y	N	N	Y	N	N	N	N	N	N
OSMR	692	N				2.38	Down	2.91E-03				N	N		Y	N	N	N	N	N	Y	N	N	N
COL6A3	754	N				2.31	Down	9.47E-04				N	N		Y	N	N	N	N	N	N	Y	N	N
VWF	407	N				2.15	Down	6.55E-03				N	N		Y	N	Y	N	N	N	N	N	N	N
TM7SF2	143	N				1.98	Up	5.50E-03				N	N		Y	N	N	N	N	Y	N	N	N	N
STAB2	45	N				1.95	Down	6.36E-03				N	N		Y	N	N	N	N	N	N	N	N	Y
JAK3	148	N				1.93	Down	2.63E-03				N	N		Y	N	N	N	N	N	Y	N	N	N
CACNA1C	96	N				1.93	Down	1.46E-03				N	N		Y	N	N	Y	N	N	N	N	N	N
SQLE	165	N				1.90	Up	1.36E-03				N	N		Y	N	N	N	N	Y	N	N	N	N
F8	464	N				1.87	Down	5.25E-04				N	N		Y	N	Y	N	N	N	N	N	N	N
COL4A1	3404	N				1.86	Down	3.79E-03				N	N		Y	N	N	Y	N	N	N	Y	N	N
COL6A1	1520	N				1.85	Down	9.46E-03				N	N		Y	N	N	N	N	N	N	Y	N	N
STAB1	503	N				1.84	Down	5.75E-04				N	N		Y	N	N	N	N	N	N	N	N	Y
COL27A1	471	N				1.83	Down	2.36E-05				N	N		Y	N	N	N	N	N	N	Y	N	N
WNT2B	180	N				1.78	Up	2.07E-04				N	N		Y	N	N	Y	N	N	N	N	N	N
MYLK	3705	N				1.75	Down	6.79E-05				N	N		Y	N	Y	N	N	N	N	N	N	N
F2RL1	392	N				1.70	Up	1.40E-04				N	N		Y	N	N	N	N	N	N	N	N	Y
WFDC2	2511	N				1.69	Down	1.46E-03				N	N		Y	N	N	N	N	N	N	N	N	N
TNFRSF1B	526	N				1.65	Down	1.37E-03				N	N		Y	Y	N	Y	N	N	Y	N	N	N
HADHB	7895	N				1.62	Down	5.87E-03				N	N		Y	N	N	N	Y	N	N	N	N	N
MVD	283	N				1.60	Up	6.16E-05				N	N		Y	N	N	N	N	Y	N	N	N	N
RASGRP2	183	N				1.60	Down	1.82E-03				N	N		Y	N	N	N	N	N	N	Y	N	N
DHCR24	3050	N				1.60	Up	3.28E-03				N	N		Y	N	N	N	N	Y	N	N	N	N
DHCR7	192	N				1.55	Up	5.30E-04				N	N		Y	N	N	N	N	Y	N	N	N	N
PRKCB	367	N				1.54	Down	3.28E-03				N	N		Y	N	N	Y	N	N	N	Y	Y	N
KDR	2574	N				1.52	Down	3.75E-03				N	N		Y	N	Y	N	N	N	N	N	N	N
INPP5D	275	N				1.52	Down	3.08E-03				N	N		Y	N	N	N	N	N	N	Y	N	N
VEGFC	211	N				1.51	Down	5.57E-04				N	N		Y	N	Y	N	N	N	N	N	N	N
EBP	381	N				1.50	Up	9.21E-03				N	N		Y	N	N	N	N	Y	N	N	N	N
MSMO1	1123	N				1.50	Up	3.55E-03				N	N		Y	N	N	N	N	Y	N	N	N	N
FDFT1	789	N				1.47	Up	1.50E-03				N	N		Y	N	N	N	N	Y	N	N	N	N
EPAS1	4940	N				1.45	Down	6.97E-04				N	N		Y	N	N	N	Y	N	Y	N	N	N
LAMA5	2363	N				1.44	Down	2.58E-03				N	N		Y	N	N	Y	N	N	N	Y	N	N
TGFBR2	832	N				1.44	Down	4.87E-03				N	N		Y	N	N	Y	N	N	N	N	N	Y
LCAT	448	N				1.43	Down	7.68E-03				N	N		Y	N	N	N	N	N	N	N	N	Y
HADHA	5399	N				1.41	Down	7.39E-04				N	N		Y	N	N	N	Y	N	N	N	N	N
HMGCS1	1025	N				1.41	Up	3.44E-03				N	N		Y	N	N	N	N	Y	N	N	N	N
ATP1B1	27825	N				1.39	Up	4.65E-03				N	N		Y	N	N	N	N	N	N	N	N	Y
FDPS	309	N				1.39	Up	4.48E-03				N	N		Y	N	N	N	N	Y	N	N	N	N
MAP3K14	265	N				1.38	Down	1.38E-03				N	N		Y	Y	N	N	N	N	Y	N	N	N
SHC1	1762	N				1.38	Down	2.80E-03				N	N		Y	Y	N	N	N	Y	N	Y	Y	Y
MYH9	3960	N				1.37	Down	4.92E-03				N	N		Y	N	N	N	N	N	N	N	N	Y
VEGFB	514	N				1.35	Up	4.55E-03				N	N		Y	N	Y	N	N	N	N	N	N	N
FOXO1	742	N				1.35	Down	6.74E-04				N	N		Y	N	N	N	N	N	Y	N	N	N
PIK3R2	387	N				1.34	Up	1.73E-03				N	N		Y	Y	N	Y	N	N	N	Y	Y	N
ACTN4	3200	N				1.34	Down	4.68E-03				N	N		Y	N	N	N	N	N	N	N	N	Y
PLCG1	1217	N				1.31	Down	5.79E-03				N	N		Y	N	N	Y	N	N	N	Y	N	N
STAT5A	307	N				1.28	Down	4.06E-03				N	N		Y	N	N	N	N	N	Y	N	Y	N
WIPF1	622	N				1.25	Down	2.80E-03				N	N		Y	N	N	N	N	N	N	N	N	N
GHR	1640	N				1.25	Down	8.30E-03				N	N		Y	N	N	N	N	N	Y	N	N	N
HSPA1A	9798	N	2.37	Up	4.79E-03							N	N		Y	N	Y	N	Y	N	N	N	N	N
FIGF	95	N	1.92	Down	3.30E-03							N	N		Y	N	Y	N	N	N	N	N	N	N
CTGF	474	N				2.60	Down	1.54E-04				N	N		Y	N	N	Y	N	N	N	N	N	Y
OC10110568	1	N	499.76	Up	4.80E-05							N	N		N	N	N	N	N	N	N	N	N	N
OC10110619	0	N	210.91	Up	6.00E-04							N	N		N	N	N	N	N	N	N	N	N	N
OC10110594	2	N	72.97	Up	7.54E-07	41.44	Down	6.79E-05				Y	N		N	N	N	N	N	N	N	N	N	N
OC10110543	11	N	49.02	Up	1.68E-05	27.21	Down	7.53E-04				Y	N		N	N	N	N	N	N	N	N	N	N
GPX2	3	N	15.53	Up	4.12E-03							N	N		N	N	N	N	N	N	N	N	N	N
NR4A3	7	N	10.94	Up	1.63E-03	14.18	Down	8.48E-04				Y	N		N	N	N	N	N	N	N	N	N	N
FCGBP	32	N	10.85	Down	3.68E-03							N	N		N	N	N	N	N	N	N	N	N	N
GREM1	641	N	10.68	Down	3.37E-04							N	N		N	N	N	N	N	N	N	N	N	N
OC10111802	8	N	9.23	Down	8.81E-04							N	N		N	N	N	N	N	N	N	N	N	N
ADAMTS4	15	N	8.83	Up	4.80E-05	15.14	Down	1.05E-06				Y	N		N	N	N	N	N	N	N	N	N	N
MX2	132	N	8.17	Up	1.30E-04	6.18	Down	2.58E-03				Y	N		N	N	N	N	N	N	N	N	N	N
MYO1A	45	N	7.85	Down	4.42E-04							N	N		N	N	N	N	N	N	N	N	N	N
OC10110466	133	N	7.68	Up	3.41E-04							N	N		N	N	N	N	N	N	N	N	N	N
ACTG2	45	N	7.57	Down	9.17E-03	5.85	Down	8.65E-04	17.94	Down	2.66E-03	N	Y	Y	N	N	N	N	N	N	N	N	N	N
OC10561552	21	N	6.11	Up	2.84E-04							N	N		N	N	N	N	N	N	N	N	N	N
NR4A1	144	N	6.04	Up	3.51E-03	13.06	Down	2.36E-05				Y	N		N	N	N	N	N	N	N	N	N	N
SCGB3A2	19	N	5.86	Down	7.36E-03							N	N		N	N	N	N	N	N	N	N	N	N
OC10560449	15	N	5.84	Down	7.58E-03							N	N		N	N	N	N	N	N	N	N	N	N
SMTNL1	10	N	5.65	Up	7.02E-04	4.75	Down	4.80E-03				N	N		N	N	N	N	N	N	N	N	N	N
SELP	34	N	5.12	Up	6.81E-04							N	N		N	N	N	N	N	N	N	N	N	N
OC10560598	14	N	4.67	Down	7.29E-03							N	N		N	N	N	N	N	N	N	N	N	N
SLC14A2	152	Y	4.05	Down	5.53E-03	7.45	Up	5.17E-05				Y	N		N	N	N	N	N	N	N	N	N	N
ATF3	280	N	3.70	Up	7.23E-03							N	N		N	N	N	N	N	N	N	N	N	N
TM4SF20	20	N	3.58	Down	4.71E-03							N	N		N	N	N	N	N	N	N	N	N	N
AJAP1	14	N	3.56	Down	7.70E-03							N	N		N	N	N	N	N	N	N	N	N	N
RGS16	33	N	3.53	Up	1.76E-05							N	N		N	N	N	N	N	N	N	N	N	N
TNFAIP3	138	N	3.48	Up	9.96E-03							N	N		N	N	N	N	N	N	N	N	N	N
ICAM1	437	N	3.43	Up	2.64E-03							N	N		N	N	N	N	N	N	N	N	N	N
RASAL1	76	N	3.38	Down	1.39E-03	5.83	Up	2.62E-06				Y	N		N	N	N	N	N	N	N	N	N	N
LOXL4	156	N	3.33	Up	3.37E-04	5.03	Down	2.16E-06				Y	N		N	N	N	N	N	N	N	N	N	N
JUNB	160	N	3.32	Up	1.25E-04	2.73	Down	3.68E-03				Y	N		N	N	N	N	N	N	N	N	N	N
CA8	120	N	3.31	Up	4.79E-03	3.32	Up	6.97E-03				Y	N		N	N	N	N	N	N	N	N	N	N
SULT6B1	36	N	3.20	Up	4.80E-05							N	N		N	N	N	N	N	N	N	N	N	N
BCL3	83	N	3.16	Up	1.68E-03	2.22	Down	7.97E-03				Y	N		N	N	N	N	N	N	N	N	N	N
OC10561312	25	N	3.03	Up	1.63E-03							N	N		N	N	N	N	N	N	N	N	N	N
PI16	47	N	3.03	Down	5.53E-03							N	N		N	N	N	N	N	N	N	N	N	N
RDH12	82	N	2.99	Down	5.42E-04	3.62	Up	7.41E-05				Y	N		N	N	N	N	N	N	N	N	N	N
OC10561015	18	N	2.97	Down	7.04E-03							N	N		N	N	N	N	N	N	N	N	N	N
OC10112009	235	N	2.95	Up	5.21E-03							N	N		N	N	N	N	N	N	N	N	N	N
CPXM1	74	N	2.94	Down	1.63E-03							N	N		N	N	N	N	N	N	N	N	N	N
OC10560652	150	N	2.93	Down	3.99E-03							N	N		N	N	N	N	N	N	N	N	N	N
MISP	49	N	2.93	Down	8.35E-03							N	N		N	N	N	N	N	N	N	N	N	N
CKAP2L	78	N	2.85	Up	3.20E-04	2.71	Up	1.35E-03				Y	N		N	N	N	N	N	N	N	N	N	N
MAP3K7CL	37	N	2.83	Up	1.04E-03	3.20	Down	4.90E-04				Y	N		N	N	N	N	N	N	N	N	N	N
OC10111734	42	N	2.79	Up	1.41E-03							N	N		N	N	N	N	N	N	N	N	N	N
CIART	139	N	2.72	Down	2.76E-05							N	N		N	N	N	N	N	N	N	N	N	N
CYSLTR2	23	N	2.64	Down	1.63E-03							N	N		N	N	N	N	N	N	N	N	N	N
OC10111140	37	N	2.62	Down	4.71E-03							N	N		N	N	N	N	N	N	N	N	N	N
PPP1R1A	1175	N	2.53	Down	1.03E-03	2.58	Up	1.51E-03				Y	N		N	N	N	N	N	N	N	N	N	N
C14H19orf33	127	N	2.47	Down	8.08E-03	2.66	Up	5.39E-03				Y	N		N	N	N	N	N	N	N	N	N	N
SLC5A1	358	N	2.44	Down	7.36E-03	2.54	Up	7.03E-03				Y	N		N	N	N	N	N	N	N	N	N	N
HRH3	31	N	2.39	Down	5.30E-03							N	N		N	N	N	N	N	N	N	N	N	N
OC10560576	212	N	2.37	Down	4.42E-04	3.40	Down	6.58E-07				Y	N		N	N	N	N	N	N	N	N	N	N
LOC494436	4916	N	2.37	Up	4.91E-03							N	N		N	N	N	N	N	N	N	N	N	N
LSMEM1	33	N	2.36	Up	6.20E-03							N	N		N	N	N	N	N	N	N	N	N	N
SLC13A4	43	N	2.30	Up	6.96E-03	2.85	Down	7.85E-04				Y	N		N	N	N	N	N	N	N	N	N	N
CEBPD	54	N	2.26	Up	4.77E-03	2.24	Down	7.89E-03				Y	N		N	N	N	N	N	N	N	N	N	N
NFIL3	257	N	2.26	Up	1.43E-04							N	N		N	N	N	N	N	N	N	N	N	N
OC10560866	125	N	2.25	Up	7.27E-03							N	N		N	N	N	N	N	N	N	N	N	N
ERRFI1	808	N	2.23	Up	9.97E-04	2.01	Down	8.47E-03				Y	N		N	N	N	N	N	N	N	N	N	N
OIT3	29	N	2.21	Up	8.20E-04	2.61	Down	1.08E-04				Y	N	Y	N	N	N	N	N	N	N	N	N	N
OC10111612	126	N	2.20	Down	2.66E-03	2.25	Up	3.28E-03				Y	N		N	N	N	N	N	N	N	N	N	N
OC10560443	22	N	2.18	Down	8.34E-03							N	N		N	N	N	N	N	N	N	N	N	N
HPCA	50	N	2.18	Down	2.84E-04	1.86	Up	9.03E-03				Y	N		N	N	N	N	N	N	N	N	N	N
CLDN19	159	N	2.17	Down	8.90E-03							N	N		N	N	N	N	N	N	N	N	N	N
CAPN6	3922	N	2.10	Down	2.76E-03	2.16	Up	3.17E-03				Y	N		N	N	N	N	N	N	N	N	N	N
MEI1	54	N	2.07	Down	3.99E-03	2.33	Up	9.92E-04				Y	N		N	N	N	N	N	N	N	N	N	N
HSPH1	923	N	2.07	Up	1.75E-03							N	N		N	N	N	N	N	N	N	N	N	N
MUC15	1929	N	2.06	Down	1.81E-03	2.04	Up	3.68E-03				Y	N		N	N	N	N	N	N	N	N	N	N
FSTL3	103	N	2.06	Up	2.93E-04	1.92	Down	7.89E-03				Y	N		N	N	N	N	N	N	N	N	N	N
KLF4	83	N	2.04	Up	4.71E-03							N	N		N	N	N	N	N	N	N	N	N	N
MUC20	1280	N	2.01	Down	8.20E-04	1.93	Up	3.39E-03				Y	N		N	N	N	N	N	N	N	N	N	N
IGFBP3	495	N	2.00	Down	1.81E-03	1.95	Up	4.68E-03				Y	N		N	N	N	N	N	N	N	N	N	N
CCDC68	101	N	1.97	Down	5.33E-04							N	N		N	N	N	N	N	N	N	N	N	N
ANO3	2176	N	1.97	Down	9.97E-03	1.94	Up	2.64E-03				Y	N		N	N	N	N	N	N	N	N	N	N
ELF5	694	Y	1.94	Down	2.35E-03	2.33	Up	1.12E-04				Y	N		N	N	N	N	N	N	N	N	N	N

Gene	Num	Flag	Ratio A	Dir A	P A	Ratio B	Dir B	P B	Ratio C	Dir C	P C	F1	F2	F3																	
CH25H	79	N	1.93	Up	3.09E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
RELB	152	N	1.91	Up	2.08E-03	2.07	Down	8.30E-04				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NFKBIZ	793	N	1.91	Up	9.97E-04							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
INHA	51	N	1.90	Down	7.64E-04							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TXNDC16	255	N	1.90	Down	8.37E-05	1.67	Up	4.95E-03			Y	N			N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
RIMS3	38	N	1.89	Up	9.09E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10560587	293	N	1.89	Up	7.23E-03	2.08	Down	2.53E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10560496	58	N	1.88	Down	3.13E-03	1.85	Up	6.30E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MMP24	114	Y	1.85	Down	4.73E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10560391	31	N	1.85	Down	4.38E-04							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
DNASE1L3	677	N	1.84	Down	1.03E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SBNO2	708	N	1.83	Down	8.73E-03	1.98	Down	3.97E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ASB9	569	N	1.82	Down	1.23E-03	2.20	Up	2.36E-05				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
IGSF9	43	N	1.82	Down	8.43E-03	1.85	Up	8.88E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HTATIP2	285	N	1.81	Down	1.81E-03	1.93	Up	8.31E-04				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SMIM6	31	N	1.81	Down	2.82E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
BVES	53	N	1.81	Up	7.38E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
C12H1orf101	81	N	1.80	Down	4.27E-03	1.85	Up	3.71E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TMEM54	166	N	1.79	Down	6.96E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CHST3	40	N	1.79	Up	2.50E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
L1CAM	1757	N	1.78	Down	3.63E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TNXB	542	N	1.78	Down	2.19E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10561328	23	N	1.77	Up	6.20E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADRA2B	238	N	1.76	Down	5.96E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
EPHA2	203	N	1.75	Up	1.06E-03	1.69	Down	4.68E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CDKL2	746	N	1.74	Down	3.99E-04	2.08	Up	4.74E-06				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10111498	473	N	1.74	Up	4.73E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SH3TC1	519	N	1.73	Up	2.63E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ELOVL6	348	N	1.72	Down	1.63E-03	2.02	Up	4.92E-05				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
UBE2L6	525	N	1.72	Up	1.35E-03	1.64	Down	6.44E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
POF1B	160	N	1.70	Down	2.86E-04							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SNX16	670	N	1.69	Down	1.25E-04	1.53	Down	5.18E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TMEM139	103	Y	1.68	Down	5.16E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
YPEL2	1464	N	1.67	Up	3.93E-03	1.70	Down	4.31E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FBP2	951	N	1.67	Up	3.30E-03	1.96	Down	1.08E-04				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
KIAA0040	289	N	1.67	Down	6.41E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADIRF	138	N	1.66	Down	9.93E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LARP1B	159	N	1.65	Up	9.74E-04	1.54	Down	9.46E-03				Y	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ANKS6	356	N	1.65	Up	3.13E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TBC1D16	944	N	1.65	Down	3.23E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10561178	67	N	1.64	Down	7.03E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MMP15	97	N	1.63	Down	2.95E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10561222	203	N	1.63	Down	7.03E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FGF7	73	N	1.63	Up	6.96E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10561173	147	N	1.62	Up	3.99E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10112015	887	N	1.62	Up	3.27E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
RAB19	61	N	1.62	Down	7.73E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SERPINH1	1564	N	1.62	Up	8.15E-05	1.53	Down	1.46E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MAD2L1	107	N	1.61	Down	1.97E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ESRP2	836	N	1.61	Down	8.53E-03	1.76	Up	2.07E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10111235	374	N	1.61	Up	7.29E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
AGFG2	917	N	1.61	Down	1.76E-05	1.61	Up	5.37E-05				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10111044	1224	N	1.60	Up	3.99E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OCA2	702	N	1.59	Down	7.94E-03	1.82	Up	6.45E-04				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CEACAM20	1235	N	1.59	Up	4.40E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PEMT	128	N	1.58	Down	1.68E-05							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SLC25A33	397	N	1.58	Down	7.64E-04				1.73	Down	1.70E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10560596	1228	N	1.58	Up	4.79E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
KLHL25	192	N	1.57	Down	9.27E-03	1.73	Down	1.86E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FAM89A	38	N	1.57	Up	4.79E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SMC2	430	N	1.57	Down	8.08E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10110648	1579	N	1.56	Up	5.74E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
COL7A1	71	N	1.56	Down	9.48E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CHORDC1	1097	N	1.56	Up	2.66E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10110192	1621	N	1.56	Up	5.30E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NRP2	827	N	1.55	Down	5.39E-04	1.67	Down	8.81E-05				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MID1IP1	238	N	1.55	Down	4.42E-04	1.90	Up	2.09E-07				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
GLTP	798	N	1.55	Down	5.21E-05	1.61	Up	2.59E-05				Y	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CFI	1882	N	1.54	Up	1.79E-03				1.70	Up	2.81E-03	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
KLHL29	272	N	1.54	Down	2.82E-03	1.58	Down	2.58E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MOB3B	348	N	1.54	Up	4.18E-04							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SIPA1L1	820	N	1.53	Down	8.08E-03	1.69	Up	1.41E-03				Y	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
GAREM	439	N	1.53	Up	7.54E-07							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
GAS8	1179	N	1.53	Down	4.77E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
DNAJA1	1193	N	1.52	Up	4.85E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
RAB25	157	N	1.50	Down	5.65E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10561344	1520	N	1.50	Down	1.98E-07	1.53	Up	2.09E-07				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10111628	252	N	1.49	Up	6.28E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PMEPA1	591	N	1.49	Up	6.41E-03	1.52	Down	5.68E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10561521	419	N	1.48	Down	7.58E-03	1.50	Up	8.48E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ARL8A	87	N	1.47	Up	5.53E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CAPN1	1448	N	1.46	Down	3.99E-04	1.37	Up	7.43E-03				Y	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CIRBP	2515	N	1.46	Down	4.43E-04							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TMEM79	245	N	1.45	Down	3.98E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
AHSA2	173	N	1.44	Up	3.17E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
GPR137B	1833	N	1.44	Up	7.80E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PFKM	717	N	1.44	Down	3.99E-03	1.41	Up	9.30E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
RAD18	169	N	1.44	Down	5.53E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10560459	137	N	1.44	Down	3.99E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FRS3	91	N	1.43	Down	9.04E-03	1.49	Up	4.48E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TBC1D30	162	N	1.43	Up	2.14E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PTGES3	962	N	1.43	Up	1.78E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ZNF281	426	N	1.42	Up	3.47E-04							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
DPCD	196	N	1.42	Down	1.19E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
GRB10	1114	N	1.42	Up	8.08E-03	1.82	Down	2.11E-06				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10560872	1248	N	1.41	Up	2.76E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10560632	517	N	1.41	Down	5.39E-04	1.37	Down	3.52E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SLC6A8	987	N	1.41	Up	6.41E-03	1.41	Down	9.72E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PFDN4	354	N	1.41	Up	5.53E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SPRY1	1376	N	1.41	Up	4.91E-03	1.43	Down	4.08E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
KLF7	567	N	1.40	Up	8.18E-05	1.30	Down	5.87E-03				Y	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CCT6A	996	N	1.40	Up	5.21E-05							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
DSG2	759	N	1.40	Down	6.81E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TMEM180	159	N	1.40	Down	1.81E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
BCAM	1592	N	1.40	Down	9.04E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ACSL3	1078	N	1.40	Down	7.40E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PGP	446	N	1.39	Up	4.65E-03	1.42	Up	4.80E-04				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TSHZ2	283	N	1.39	Up	6.05E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PDE5A	2088	N	1.39	Up	1.27E-05	1.44	Up	2.16E-06				Y	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
RUSC2	360	N	1.39	Down	4.79E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
GCNT7	173	N	1.39	Down	2.33E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HYAL1	321	N	1.38	Down	6.96E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NUDT16L1	179	N	1.38	Down	4.77E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MOB3C	161	N	1.37	Up	5.53E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TBCEL	443	N	1.37	Down	1.81E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
BBS12	156	N	1.37	Up	9.49E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
P4HA1	700	N	1.37	Up	3.60E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ZNF800	230	N	1.36	Up	5.12E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CUEDC1	321	N	1.36	Down	7.99E-04							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
RBM15	446	N	1.36	Down	4.24E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ZNF346	318	N	1.35	Down	3.91E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
GYG1	444	N	1.35	Down	4.07E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NUDT18	212	N	1.35	Down	5.53E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TCP11L2	525	N	1.34	Down	1.36E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PAWR	1702	N	1.34	Up	5.52E-05							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CHPF2	425	N	1.34	Up	6.20E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HOMER2	694	N	1.34	Up	9.96E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MAL2	2528	N	1.33	Down	3.56E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PPP1R13B	552	N	1.32	Up	4.95E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
STK11IP	408	N	1.32	Down	4.40E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NCAPD3	163	N	1.32	Down	6.20E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10560341	2198	N	1.31	Up	8.08E-04							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ABHD12	878	N	1.31	Down	8.63E-04							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ZCCHC2	340	N	1.31	Up	2.80E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ZNF672	665	N	1.31	Down	7.19E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PRRG2	419	N	1.30	Down	5.75E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LZIC	687	N	1.30	Up	6.76E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10560656	557	N	1.29	Down	2.84E-04							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MTG2	641	N	1.29	Down	7.03E-03				1.39	Down	6.25E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10560360	219	N	1.29	Down	7.36E-03	1.30	Up	7.35E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
GGCX	2370	N	1.29	Up	7.03E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TMEM201	514	N	1.29	Down	7.36E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
C2H9orf89	483	N	1.29	Down	8.89E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FBXO7	1041	N	1.28	Down	3.28E-04	1.31	Up	1.89E-04				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TAF9	365	N	1.28	Up	7.94E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TMEM39A	367	N	1.28	Up	1.19E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
RAB9A	792	N	1.27	Down	1.35E-03	1.36	Up	5.37E-05				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TFE3	745	N	1.26	Up	7.55E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
EFNA1	996	N	1.26	Up	7.29E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
GKAP1	414	N	1.26	Up	9.59E-04							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10111589	1064	N	1.26	Down	9.96E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
EID1	997	N	1.26	Down	8.89E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CERS2	3696	N	1.26	Up	7.36E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
RTFDC1	601	N	1.26	Down	1.25E-04							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SHC4	1094	N	1.25	Down	6.78E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
RMND5B	438	N	1.25	Down	1.63E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SKIV2L2	2292	N	1.25	Down	9.09E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
RP9	593	N	1.24	Up	7.03E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10110598	445	N	1.24	Up	1.93E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LGR4	1642	N	1.24	Down	9.96E-03	1.31	Up	1.33E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
INO80C	483	N	1.23	Down	7.21E-04							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
BCAR1	1867	N	1.23	Up	9.83E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
UBL7	478	N	1.23	Down	5.14E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ANKRD13A	772	N	1.22	Down	2.57E-03	1.22	Up	3.68E-03				Y	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10111102	1730	N	1.21	Down	2.83E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANK4	807	N	1.20	Down	9.83E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
UBE2E1	595	N	1.20	Down	5.20E-03							N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SLC14A1	11	N				18.64	Up	6.65E-03				N	N		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

ID	Value	Flag	FC	Dir	p-value	FC2	Dir2	p-value2	A	B	C										
OC10111997	7	N	18.17	Down	3.19E-03				N	N		N	N	N	N	N	N	N	N	N	N
RANBP3L	15	Y	14.38	Up	6.26E-06				N	N		N	N	N	N	N	N	N	N	N	N
PDK4	2008	N	12.81	Down	3.18E-08	5.90	Down	3.49E-03	N	Y		N	N	N	N	N	N	N	N	N	N
OC10111718	1570	N	9.59	Down	5.16E-06				N	N		N	N	N	N	N	N	N	N	N	N
OC10110205	15	N	9.29	Down	9.98E-04	12.06	Down	2.65E-03	N	Y		N	N	N	N	N	N	N	N	N	N
OC10111981	41	Y	8.71	Up	3.06E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10111744	1491	N	7.76	Down	3.85E-05				N	N		N	N	N	N	N	N	N	N	N	N
OC10111795	1351	N	7.46	Down	6.78E-06				N	N		N	N	N	N	N	N	N	N	N	N
CCL24	10	N	7.00	Down	1.15E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10111196	153	N	6.77	Up	4.79E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10561003	13	N	6.52	Down	1.09E-03				N	N		N	N	N	N	N	N	N	N	N	N
EGR1	246	N	5.83	Down	3.72E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10111769	4128	N	5.83	Down	2.87E-04				N	N		N	N	N	N	N	N	N	N	N	N
EGR3	10	N	5.58	Down	5.18E-03				N	N		N	N	N	N	N	N	N	N	N	N
NNMT	18	N	5.55	Down	1.05E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560648	77	N	5.09	Up	5.07E-04	5.25	Up	4.98E-03	N	Y		N	N	N	N	N	N	N	N	N	N
OC10560903	429	N	4.90	Up	6.41E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10110754	434	N	4.88	Up	6.75E-03				N	N		N	N	N	N	N	N	N	N	N	N
ANGPTL4	193	N	4.80	Down	1.43E-05	5.01	Down	1.64E-04	N	Y	Y	N	N	N	N	N	N	N	N	N	N
ASGR1	175	N	4.69	Down	3.17E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10111603	905	N	4.66	Down	5.18E-03	8.40	Down	8.65E-04	N	Y		N	N	N	N	N	N	N	N	N	N
OC10560196	428	N	4.60	Up	2.97E-03				N	N		N	N	N	N	N	N	N	N	N	N
RNF183	90	Y	4.58	Down	2.01E-04				N	N		N	N	N	N	N	N	N	N	N	N
C8H6orf118	20	N	4.51	Up	7.26E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10561003	13	N	4.24	Down	9.82E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10561166	30	N	4.22	Up	7.58E-04				N	N		N	N	N	N	N	N	N	N	N	N
OC10110780	282	N	4.21	Up	5.34E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560673	23	N	4.16	Down	9.98E-04				N	N		N	N	N	N	N	N	N	N	N	N
GLP1R	199	N	4.13	Up	7.67E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10561632	18	N	4.09	Down	2.56E-04				N	N		N	N	N	N	N	N	N	N	N	N
OC10560839	20	N	3.98	Down	7.48E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10112013	778	Y	3.97	Down	5.57E-04				N	N		N	N	N	N	N	N	N	N	N	N
ARMC12	134	N	3.92	Down	2.87E-04				N	N		N	N	N	N	N	N	N	N	N	N
OC10110227	14	N	3.88	Down	1.42E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10110711	1775	N	3.84	Up	5.76E-03				N	N		N	N	N	N	N	N	N	N	N	N
SULT1C3	42	N	3.84	Down	1.11E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560416	94	N	3.82	Down	8.00E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560460	34	N	3.77	Down	5.60E-03				N	N		N	N	N	N	N	N	N	N	N	N
GALR3	12	N	3.72	Up	2.32E-03				N	N		N	N	N	N	N	N	N	N	N	N
BTG2	367	N	3.62	Down	6.36E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560938	75	N	3.61	Up	2.03E-03				N	N		N	N	N	N	N	N	N	N	N	N
ARRDC2	795	N	3.49	Down	1.56E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10561483	87	N	3.49	Up	1.80E-04				N	N		N	N	N	N	N	N	N	N	N	N
CDKN1A	257	N	3.47	Down	6.27E-03				N	N		N	N	N	N	N	N	N	N	N	N
VWA2	139	N	3.37	Up	7.48E-03				N	N		N	N	N	N	N	N	N	N	N	N
SOSTDC1	186	N	3.37	Up	4.78E-05				N	N		N	N	N	N	N	N	N	N	N	N
SLC52A3	260	N	3.35	Down	9.96E-06	2.63	Down	7.65E-03	N	Y	Y	N	N	N	N	N	N	N	N	N	N
ECEL1	53	N	3.27	Down	5.12E-03				N	N		N	N	N	N	N	N	N	N	N	N
ZFP36	308	N	3.26	Down	2.44E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560642	23	N	3.23	Down	3.69E-03				N	N		N	N	N	N	N	N	N	N	N	N
MCTP1	353	N	3.21	Up	3.68E-03				N	N		N	N	N	N	N	N	N	N	N	N
LMOD1	123	N	3.08	Down	2.87E-04				N	N		N	N	N	N	N	N	N	N	N	N
SCUBE1	8	N	3.08	Down	3.73E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560224	29	N	3.06	Down	2.93E-04				N	N		N	N	N	N	N	N	N	N	N	N
DTX4	32	N	3.06	Up	7.26E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10110531	46	N	3.01	Down	8.70E-03				N	N		N	N	N	N	N	N	N	N	N	N
PGLYRP4	18	N	2.96	Down	1.46E-03				N	N		N	N	N	N	N	N	N	N	N	N
ACOX2	1910	N	2.95	Down	3.12E-04				N	N		N	N	N	N	N	N	N	N	N	N
OMD	84	N	2.95	Down	1.03E-04				N	N		N	N	N	N	N	N	N	N	N	N
RGS9BP	22	N	2.91	Up	3.85E-04				N	N		N	N	N	N	N	N	N	N	N	N
MAPK4	332	N	2.88	Down	1.22E-03				N	N		N	N	N	N	N	N	N	N	N	N
SLC47A1	24	Y	2.88	Down	5.44E-03				N	N		N	N	N	N	N	N	N	N	N	N
RAB17	647	N	2.84	Up	3.38E-04				N	N		N	N	N	N	N	N	N	N	N	N
OC10112367	1585	N	2.84	Down	4.79E-03				N	N		N	N	N	N	N	N	N	N	N	N
GAL3ST3	193	N	2.84	Up	3.59E-04				N	N		N	N	N	N	N	N	N	N	N	N
OC10112341	1158	N	2.84	Down	4.44E-03				N	N		N	N	N	N	N	N	N	N	N	N
GSTT2	150	N	2.77	Up	9.23E-03				N	N		N	N	N	N	N	N	N	N	N	N
NT5C1A	28	N	2.74	Down	9.33E-03				N	N		N	N	N	N	N	N	N	N	N	N
BCL2L15	363	N	2.74	Down	1.42E-03				N	N		N	N	N	N	N	N	N	N	N	N
RAPGEFL1	68	N	2.73	Up	2.87E-04				N	N		N	N	N	N	N	N	N	N	N	N
TGM2	861	N	2.72	Down	2.13E-03				N	N		N	N	N	N	N	N	N	N	N	N
APOLD1	173	N	2.71	Down	2.32E-03				N	N		N	N	N	N	N	N	N	N	N	N
RARRES1	61	N	2.69	Down	7.40E-03				N	N		N	N	N	N	N	N	N	N	N	N
PM20D1	2265	N	2.69	Down	1.43E-05				N	N		N	N	N	N	N	N	N	N	N	N
WFDC1	811	N	2.68	Down	4.21E-07				N	N		N	N	N	N	N	N	N	N	N	N
ECM1	472	N	2.68	Down	1.77E-07				N	N		N	N	N	N	N	N	N	N	N	N
DHX58	166	N	2.63	Down	7.41E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10561515	107	N	2.63	Down	1.06E-04				N	N		N	N	N	N	N	N	N	N	N	N
CDS1	388	N	2.63	Up	8.09E-04				N	N		N	N	N	N	N	N	N	N	N	N
OC10112315	1355	N	2.63	Down	1.27E-03				N	N		N	N	N	N	N	N	N	N	N	N
BLNK	141	N	2.61	Down	7.48E-03				N	N		N	N	N	N	N	N	N	N	N	N
AEBP1	1413	N	2.59	Down	5.50E-05				N	N		N	N	N	N	N	N	N	N	N	N
OC10560688	506	N	2.56	Down	3.85E-03				N	N		N	N	N	N	N	N	N	N	N	N
KCNE3	28	N	2.53	Down	1.34E-03				N	N		N	N	N	N	N	N	N	N	N	N
PROX1	551	N	2.51	Up	6.04E-04				N	N		N	N	N	N	N	N	N	N	N	N
RAB1FIP4	172	N	2.51	Up	3.68E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560605	34	N	2.50	Down	5.83E-03				N	N		N	N	N	N	N	N	N	N	N	N
TAGLN	1264	N	2.47	Down	8.81E-05				N	N		N	N	N	N	N	N	N	N	N	N
NDST3	69	N	2.46	Up	4.65E-03				N	N		N	N	N	N	N	N	N	N	N	N
TNFSF13B	159	N	2.46	Down	5.37E-05				N	N		N	N	N	N	N	N	N	N	N	N
MEIOB	152	N	2.45	Up	6.79E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10111289	377	N	2.44	Down	3.79E-03				N	N		N	N	N	N	N	N	N	N	N	N
SLC2A10	29	N	2.43	Down	2.42E-04				N	N		N	N	N	N	N	N	N	N	N	N
KIF21B	39	N	2.42	Down	1.37E-03				N	N		N	N	N	N	N	N	N	N	N	N
SIM2	543	Y	2.42	Up	3.28E-03				N	N		N	N	N	N	N	N	N	N	N	N
ZBTB16	364	N	2.42	Down	9.64E-03				N	N		N	N	N	N	N	N	N	N	N	N
GADD45G	139	N	2.41	Down	1.47E-03				N	N		N	N	N	N	N	N	N	N	N	N
SCD	299	N	2.41	Up	3.09E-04				N	N		N	N	N	N	N	N	N	N	N	N
LIPE	276	N	2.40	Down	4.70E-04				N	N		N	N	N	N	N	N	N	N	N	N
OC10110743	1228	N	2.38	Down	7.86E-03				N	N		N	N	N	N	N	N	N	N	N	N
RELT	15	N	2.38	Down	6.27E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560335	37	N	2.38	Down	9.67E-03				N	N		N	N	N	N	N	N	N	N	N	N
GSTA4	1013	N	2.37	Up	9.08E-03				N	N		N	N	N	N	N	N	N	N	N	N
CLNK	36	Y	2.35	Down	1.85E-03				N	N		N	N	N	N	N	N	N	N	N	N
SLC47A2	11838	Y	2.35	Down	7.93E-06				N	N		N	N	N	N	N	N	N	N	N	N
PROSER2	229	N	2.34	Up	1.29E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10110281	26	N	2.33	Up	8.44E-03				N	N		N	N	N	N	N	N	N	N	N	N
MICAL2	108	N	2.31	Down	5.97E-04				N	N		N	N	N	N	N	N	N	N	N	N
OC10560265	45	N	2.30	Down	9.72E-03				N	N		N	N	N	N	N	N	N	N	N	N
DAAM2	1211	N	2.28	Down	2.11E-06				N	N		N	N	N	N	N	N	N	N	N	N
ATP10A	164	N	2.27	Down	8.71E-03				N	N		N	N	N	N	N	N	N	N	N	N
SERPINE2	219	N	2.27	Down	6.36E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560226	30	N	2.27	Up	6.70E-05				N	N		N	N	N	N	N	N	N	N	N	N
STAC	44	N	2.26	Down	5.86E-03				N	N		N	N	N	N	N	N	N	N	N	N
TMEM100	48	N	2.26	Down	4.70E-04				N	N		N	N	N	N	N	N	N	N	N	N
UPP1	141	N	2.25	Down	6.61E-03				N	N		N	N	N	N	N	N	N	N	N	N
KCNMB1	115	N	2.23	Down	1.60E-03				N	N		N	N	N	N	N	N	N	N	N	N
FXYD7	17	N	2.23	Down	7.26E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10110879	115	N	2.23	Down	7.35E-03				N	N		N	N	N	N	N	N	N	N	N	N
RAMP3	79	N	2.21	Down	5.37E-05				N	N		N	N	N	N	N	N	N	N	N	N
EHD3	370	N	2.21	Down	5.46E-06				N	N		N	N	N	N	N	N	N	N	N	N
OC10561247	69	N	2.21	Up	4.41E-03				N	N		N	N	N	N	N	N	N	N	N	N
ARID5A	30	N	2.20	Down	9.38E-03				N	N		N	N	N	N	N	N	N	N	N	N
ADAM19	181	N	2.20	Down	5.18E-03				N	N		N	N	N	N	N	N	N	N	N	N
UCP2	449	N	2.20	Down	2.58E-03	3.03	Down	1.64E-04	N	Y		N	N	N	N	N	N	N	N	N	N
WISP1	103	N	2.18	Down	1.59E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10561657	36	N	2.17	Up	2.07E-03				N	N		N	N	N	N	N	N	N	N	N	N
SLC26A8	18	N	2.16	Up	9.82E-03				N	N		N	N	N	N	N	N	N	N	N	N
DBP	978	N	2.14	Up	5.17E-03				N	N		N	N	N	N	N	N	N	N	N	N
FHL1	785	N	2.13	Down	1.59E-03				N	N		N	N	N	N	N	N	N	N	N	N
MYO3B	449	Y	2.13	Up	3.06E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560322	31	N	2.13	Down	5.84E-03				N	N		N	N	N	N	N	N	N	N	N	N
IRF9	730	N	2.13	Down	2.07E-03				N	N		N	N	N	N	N	N	N	N	N	N
GPR182	48	N	2.12	Up	1.27E-03				N	N		N	N	N	N	N	N	N	N	N	N
SLC16A6	797	N	2.12	Down	3.44E-03				N	N		N	N	N	N	N	N	N	N	N	N
ANGPT4	118	N	2.10	Down	7.53E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560603	30	N	2.08	Down	3.68E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560576	82	N	2.07	Down	8.88E-03				N	N		N	N	N	N	N	N	N	N	N	N
AZIN2	24	N	2.06	Up	3.20E-03				N	N		N	N	N	N	N	N	N	N	N	N
SLC44A4	2838	N	2.05	Down	7.16E-04				N	N		N	N	N	N	N	N	N	N	N	N
TPM2	749	N	2.05	Down	3.79E-03				N	N		N	N	N	N	N	N	N	N	N	N
SIGLEC5	26	N	2.05	Down	5.10E-03				N	N		N	N	N	N	N	N	N	N	N	N
ADAMTSL4	408	N	2.04	Down	6.79E-05				N	N		N	N	N	N	N	N	N	N	N	N
TLN2	391	Y	2.04	Up	3.36E-03				N	N		N	N	N	N	N	N	N	N	N	N
TMEM37	453	N	2.03	Down	5.04E-03				N	N		N	N	N	N	N	N	N	N	N	N
RNF207	155	N	2.03	Up	8.88E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560611	107	N	2.02	Down	6.56E-04				N	N		N	N	N	N	N	N	N	N	N	N
VNN1	1300	N	2.02	Down	5.46E-03				N	N		N	N	N	N	N	N	N	N	N	N
CD248	102	N	2.01	Down	9.67E-03				N	N		N	N	N	N	N	N	N	N	N	N
PPP1R14A	104	N	2.00	Down	4.65E-03				N	N		N	N	N	N	N	N	N	N	N	N
GCNT3	168	N	1.99	Down	1.53E-03				N	N		N	N	N	N	N	N	N	N	N	N
PDE10A	265	N	1.99	Down	3.45E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10561010	145	N	1.99	Up	2.73E-03				N	N		N	N	N	N	N	N	N	N	N	N
EPPK1	176	N	1.99	Up	5.87E-03				N	N		N	N	N	N	N	N	N	N	N	N
GJA5	734	N	1.99	Down	1.09E-03				N	N		N	N	N	N	N	N	N	N	N	N
FA2H	285	N	1.97	Up	3.85E-03				N	N		N	N	N	N	N	N	N	N	N	N
KLHL14	480	N	1.96	Up	5.75E-04				N	N		N	N	N	N	N	N	N	N	N	N
NREP	294	N	1.95	Up	3.95E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10110910	89	N	1.95	Up	1.44E-03				N	N		N	N	N	N	N	N	N	N	N	N
ITGA8	721	N	1.95	Down	1.06E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560446	58	Y	1.95	Down	4.52E-03				N	N		N	N	N	N	N	N	N	N	N	N
C19H3orf14	46	N	1.94	Down	8.31E-04				N	N		N	N	N	N	N	N	N	N	N	N
PLCB2	95	N	1.94	Down	2.48E-03				N	N		N	N	N	N	N	N	N	N	N	N
OC10560841	814	N	1.94	Up	1.08E-04				N	N		N	N	N	N	N	N	N	N	N	N
ARHGEF16	558	N	1.92	Down	3.63E-04				N	N		N	N	N	N	N	N	N	N	N	N
CSRNP1	320	N	1.92	Down	3.52E-03				N	N		N	N	N	N	N	N	N	N	N	N
USP27X	642	N	1.91	Up	2.11E-03				N	N		N	N	N	N	N	N	N	N	N	N
TTC21A	703	N	1.91	Down	4.31E-03				N	N		N	N	N	N	N	N	N	N	N	N

Gene	Count					FC1	Dir1	P1	FC2	Dir2	P2													
OC10561175	129	N				1.91	Down	3.85E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
SMPD3	93	N				1.89	Down	6.79E-03	2.12	Down	8.64E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
ACVRL1	474	N				1.89	Down	1.85E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
C15H11orf52	106	N				1.89	Up	2.36E-05				N	N		N	N	N	N	N	N	N	N	N	N	N
C3H12orf75	688	N				1.89	Up	6.46E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
CSRP2	1635	N				1.89	Down	5.75E-04	1.96	Down	3.49E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
OC10111358	488	N				1.88	Up	1.51E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
Mar-03	77	N				1.88	Down	1.68E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
MCAM	351	N				1.88	Down	5.96E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
MMP16	102	N				1.87	Up	7.38E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
DUSP4	56	N				1.85	Down	8.71E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
MRVI1	533	N				1.84	Down	7.27E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
ACTN1	822	N				1.83	Down	1.85E-05				N	N		N	N	N	N	N	N	N	N	N	N	N
SDC3	71	N				1.83	Down	8.87E-04	1.89	Down	5.30E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
OC10561062	104	N				1.83	Up	3.65E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
CMKLR1	168	N				1.83	Down	7.26E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
SBSPON	314	N				1.83	Up	5.17E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
ICK	554	N				1.82	Up	5.63E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
ZFAT	1235	Y				1.82	Down	9.09E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10560724	173	N				1.81	Down	6.86E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
KCNJ1	3872	Y				1.80	Up	7.47E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10111233	510	N				1.80	Down	6.33E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
ACSL1	11903	N				1.79	Down	3.03E-04	1.74	Down	7.90E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
LMO2	414	N				1.79	Up	7.44E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10561500	29	N				1.79	Up	9.20E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
CCDC64	734	Y				1.79	Up	3.75E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10560354	90	N				1.79	Down	1.51E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10111566	4260	N				1.78	Up	7.03E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
INSIG1	509	N				1.78	Up	3.09E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
NXPH2	69	Y				1.78	Down	1.82E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
ROBO4	564	N				1.78	Down	4.41E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
PREX1	370	N				1.78	Down	1.06E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
TRNAW-CCA	386	N				1.78	Up	6.79E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
SLC4A10	221	N				1.78	Up	4.12E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
AQP2	40207	Y				1.77	Up	6.65E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
HOPX	100	N				1.76	Down	2.73E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
PVRL4	51	N				1.76	Up	5.90E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
GCA	312	N				1.76	Up	4.25E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
CPT1A	1794	N				1.76	Down	5.93E-04	2.00	Down	1.96E-04	N	Y		N	N	N	N	N	N	N	N	N	N	N
SLC16A5	634	N				1.76	Down	6.94E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
ATP2A3	683	N				1.75	Up	4.99E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
ZDHHC14	194	N				1.75	Down	7.57E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
AGPAT2	1018	N				1.75	Down	1.05E-04	1.70	Down	4.35E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
KIT	378	N				1.75	Down	8.09E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10561528	366	N				1.74	Down	5.90E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
CD24	4267	N				1.74	Up	3.80E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
SLC22A5	4981	N				1.74	Down	9.32E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
WDR4	81	N				1.74	Down	5.86E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
FLNA	4913	N				1.73	Down	1.52E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
GRIN2D	128	N				1.73	Up	5.10E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10112226	278	N				1.72	Down	8.31E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
PLS1	999	N				1.72	Up	1.22E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
KIRREL	243	N				1.72	Down	2.32E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
ERMP1	1503	N				1.72	Up	3.40E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
DSC2	216	N				1.72	Up	5.33E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
FASN	617	N				1.71	Up	4.20E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10560569	505	N				1.71	Down	1.45E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
SLC25A20	889	N				1.71	Down	1.28E-04	1.61	Down	8.41E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
WDFY4	139	N				1.71	Down	9.36E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
ADGRF3	356	Y				1.71	Down	3.12E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
MOCS1	2898	N				1.70	Down	1.97E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
LPAR6	232	N				1.70	Up	4.68E-05				N	N		N	N	N	N	N	N	N	N	N	N	N
HOXB5	180	N				1.70	Up	3.45E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
CCDC8	766	N				1.70	Up	2.98E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10561585	4685	N				1.70	Up	3.28E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
KLF11	994	N				1.69	Down	8.30E-03	1.90	Down	8.41E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
GALNT16	356	N				1.69	Down	6.61E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10111315	83	N				1.69	Up	3.29E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
DTX1	236	N				1.69	Down	9.59E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
CLEC1A	191	N				1.69	Down	4.15E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
PAPSS2	118	N				1.69	Down	9.78E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
GATA6	89	N				1.68	Down	6.88E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
PPM1K	2738	N				1.68	Up	9.15E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
KLF10	695	N				1.68	Down	2.58E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
PAK3	278	N				1.67	Up	2.87E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10560659	128	N				1.67	Up	5.23E-05				N	N		N	N	N	N	N	N	N	N	N	N	N
UGT8	189	N				1.66	Up	8.82E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
RNASEH2A	179	N				1.66	Up	1.67E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
DOC2B	134	N				1.66	Down	3.95E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
PKDCC	679	N				1.65	Down	1.40E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
S1PR1	637	N				1.65	Down	2.65E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
BPIFC	64	N				1.64	Up	5.96E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
ARNTL	276	N				1.64	Down	3.08E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
GAL3ST1	124	N				1.64	Up	3.36E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
ARHGEF25	232	N				1.64	Down	6.77E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
POR	2389	N				1.64	Down	2.55E-05				N	N		N	N	N	N	N	N	N	N	N	N	N
NT5DC3	666	N				1.64	Down	6.80E-05				N	N		N	N	N	N	N	N	N	N	N	N	N
HOXB6	3292	Y				1.63	Up	1.93E-05				N	N		N	N	N	N	N	N	N	N	N	N	N
RFTN1	301	N				1.63	Down	2.07E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
RASA3	649	N				1.63	Down	9.15E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
CXCL16	465	N				1.62	Down	3.50E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
ENC1	200	N				1.62	Down	1.42E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
DPYSL3	591	N				1.61	Down	2.44E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
FCGRT	3193	N				1.61	Down	6.74E-06	1.54	Down	1.30E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
CHST2	128	N				1.61	Down	7.42E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
GGT5	1820	N				1.61	Down	5.96E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
CAB39L	305	N				1.61	Up	2.40E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
LMNA	520	N				1.61	Down	9.98E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
ZYX	1031	N				1.60	Down	6.97E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
NEDD9	1833	N				1.60	Down	2.04E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
COTL1	569	N				1.59	Down	1.50E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
LVRN	109	N				1.59	Up	9.75E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
CCDC86	123	N				1.59	Up	3.45E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
MAP3K6	338	N				1.59	Down	4.44E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
CCDC88C	568	N				1.59	Down	4.48E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
C7H15orf62	172	N				1.59	Down	3.68E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
ADRA1A	101	N				1.59	Down	6.53E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10560423	171	N				1.58	Down	4.79E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
CCDC92	184	N				1.58	Up	7.93E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10560823	90	N				1.57	Up	9.46E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
PPP1R3C	379	N				1.57	Up	4.29E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
IGF2R	4755	N				1.57	Down	8.82E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
ABHD2	1560	N				1.57	Down	5.18E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
TMEM206	688	N				1.56	Down	9.72E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
NETO2	1259	N				1.56	Up	1.51E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
IFT27	559	N				1.56	Up	8.81E-05				N	N		N	N	N	N	N	N	N	N	N	N	N
EFEMP1	3113	N				1.56	Down	7.73E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
SH2D4A	298	N				1.56	Up	4.04E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
LDB2	525	N				1.56	Down	2.36E-05				N	N		N	N	N	N	N	N	N	N	N	N	N
RCN3	326	N				1.56	Down	8.32E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
DZIP1	696	N				1.56	Up	1.67E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
KCNJ3	391	N				1.55	Down	7.38E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
EPCAM	2721	N				1.55	Up	6.29E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
DLL4	279	N				1.55	Down	3.20E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
TEF	373	N				1.55	Up	2.18E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
ACADVL	5918	N				1.55	Down	1.21E-05	1.48	Down	2.04E-03	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N
SMOX	126	N				1.54	Down	7.42E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
TSPAN15	611	N				1.54	Up	9.59E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
SHISA5	715	N				1.53	Down	3.38E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
GALNT18	1084	N				1.53	Up	4.52E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10560905	323	N				1.53	Up	5.96E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
GJA1	263	N				1.53	Down	9.78E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
CNTNAP1	85	N				1.52	Up	4.68E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
IL4R	958	N				1.52	Up	2.98E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
ERICH2	172	N				1.51	Up	7.38E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
NPR1	884	N				1.51	Down	3.22E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
MESDC1	211	N				1.50	Down	3.75E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10111997	2235	N				1.50	Down	2.49E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10112318	179	N				1.50	Up	4.04E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
RRP9	214	N				1.50	Down	1.94E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10112241	1126	N				1.50	Down	8.30E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
SMARCA2	1134	N				1.49	Up	7.44E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
LOC443104	2811	N				1.49	Down	3.45E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
PDE3A	568	N				1.48	Down	2.91E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
GSTP1	1176	N				1.48	Up	8.00E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
MCL1	4048	N				1.47	Down	8.30E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
EMC10	360	N				1.47	Up	9.93E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
TMEM107	103	N				1.47	Up	1.59E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
SLAIN1	122	N				1.47	Up	5.65E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
DMTN	1398	N				1.47	Up	4.68E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10560304	201	N				1.46	Up	2.80E-05				N	N		N	N	N	N	N	N	N	N	N	N	N
PLCL1	1458	N				1.46	Up	3.72E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
VSIG10	408	N				1.46	Up	8.08E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
AASS	656	N				1.46	Up	9.78E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
CYTIP	550	N				1.46	Up	6.83E-05				N	N		N	N	N	N	N	N	N	N	N	N	N
CLUH	1524	N				1.46	Down	2.80E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
N4BP2L1	659	N				1.46	Down	4.65E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
ZNF214	209	N				1.46	Up	2.95E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
TMEM2	443	N				1.46	Down	2.46E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
SYNPO	354	N				1.46	Down	9.25E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
MKNK2	850	N				1.45	Up	8.81E-05				N	N		N	N	N	N	N	N	N	N	N	N	N
OC10560288	463	N				1.45	Up	4.12E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
EGFL7	523	N				1.45	Down	5.44E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
TMEM125	397	N				1.45	Up	2.01E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
MTHFD2	149	N				1.45	Down	8.92E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
VCL	2070	N				1.45	Down	4.57E-03				N	N		N	N	N	N	N	N	N	N	N	N	N
LRRC42	282	N				1.45	Up	5.60E-04				N	N		N	N	N	N	N	N	N	N	N	N	N
NEIL2	965	N				1.44	Up	2.95E-04				N	N		N	N	N	N	N	N	N	N	N	N	N

Gene	ID	Flag	Ratio	Dir	p-value	Ratio2	Dir2	p-value2															
GGTA2P	1273	N	1.43	Down	4.31E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
NME7	8829	N	1.43	Up	7.35E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CLYBL	1153	N	1.43	Up	2.46E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10561572	75	N	1.43	Up	3.28E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
NUDT5	476	N	1.43	Up	8.74E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10560702	175	N	1.43	Up	7.48E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
DLG3	648	N	1.43	Up	1.50E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CALML4	1029	N	1.42	Up	6.94E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10110322	267	N	1.42	Down	3.20E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
APBA3	487	N	1.42	Down	6.74E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
C7H14orf105	923	Y	1.42	Up	7.44E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10112291	290	N	1.42	Down	1.05E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CALR	6173	N	1.42	Down	3.38E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
ARG2	621	Y	1.42	Up	5.75E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
SREBF2	1880	N	1.42	Up	4.80E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PSEN2	388	N	1.42	Down	3.16E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
SLC50A1	164	N	1.42	Down	9.82E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10111347	394	N	1.41	Down	3.68E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
NHP2	231	N	1.41	Down	2.12E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
MAST2	380	N	1.41	Down	1.52E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
LRRC75A	144	N	1.41	Up	6.38E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CRY2	421	N	1.41	Up	2.80E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
RPGRIP1L	311	N	1.41	Up	9.09E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
MAN1C1	1336	N	1.41	Down	6.74E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10112139	1354	N	1.41	Down	9.98E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
ZNF710	649	N	1.40	Up	1.43E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CALCOCO2	5136	N	1.40	Down	2.45E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PLVAP	3993	N	1.39	Down	9.09E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
RAB3IP	942	N	1.39	Up	2.06E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PERP	904	N	1.39	Up	5.06E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
RRP12	438	N	1.39	Down	3.30E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OPTN	927	N	1.38	Up	2.80E-05				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PKD2	2435	N	1.38	Up	1.11E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
MYO10	1964	N	1.38	Down	1.21E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CDSL	272	N	1.38	Up	1.64E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
MPC1	2962	N	1.38	Up	5.90E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
ATG4C	780	N	1.38	Up	5.96E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
LRRC8A	515	N	1.38	Down	8.20E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PRKACB	579	N	1.38	Down	4.79E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
RTKN	664	N	1.37	Up	3.75E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
HOXB7	344	N	1.37	Up	8.57E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CNTLN	602	N	1.37	Up	3.72E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
NFYC	1645	N	1.37	Up	1.44E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10560496	227	N	1.36	Up	4.98E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
TMEM185B	230	N	1.36	Down	7.43E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
TMEM106B	1417	N	1.36	Up	3.72E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
FMNL3	943	N	1.36	Down	3.12E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
FSD1L	235	N	1.36	Up	1.57E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
IMP4	501	N	1.36	Down	4.48E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
SESTD1	1088	N	1.36	Up	9.72E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
NCLN	288	N	1.36	Down	8.92E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
MAPRE2	598	N	1.35	Down	4.41E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sep-09	1450	N	1.35	Down	4.31E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
SNAP29	395	N	1.35	Down	5.59E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10111360	367	N	1.35	Up	7.97E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
KCNJ16	4930	Y	1.34	Down	3.95E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10111455	162	N	1.34	Up	8.74E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
FLNB	2961	N	1.34	Down	4.25E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
DDR1	2492	N	1.33	Up	4.65E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CDC37L1	1194	N	1.33	Up	1.18E-05	1.26	Up	6.89E-03	N	Y	N	N	N	N	N	N	N	N	N	N	N	N
HOXD3	1422	N	1.33	Up	2.20E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
SUMO3	986	N	1.33	Up	1.49E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
BOP1	195	N	1.33	Down	2.98E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
SNX25	754	N	1.33	Up	1.73E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
KCNIP2	291	N	1.33	Up	8.82E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
DYNC2H1	378	N	1.32	Up	9.09E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
ZNF652	618	N	1.32	Up	2.73E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
INTS1	289	N	1.32	Down	7.18E-03	1.40	Down	7.65E-03	N	Y	N	N	N	N	N	N	N	N	N	N	N	N
NACC1	172	N	1.32	Down	8.20E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
TSPAN18	578	N	1.32	Down	8.32E-03	1.40	Down	8.41E-03	N	Y	N	N	N	N	N	N	N	N	N	N	N	N
SMURF1	903	N	1.32	Down	9.72E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
RAMP2	502	N	1.32	Down	9.30E-03	1.42	Down	5.30E-03	N	Y	N	N	N	N	N	N	N	N	N	N	N	N
EPM2AIP1	2272	N	1.31	Up	1.82E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PDIA4	1598	N	1.31	Down	7.48E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PUS1	383	N	1.31	Down	7.42E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
DENND1A	1167	N	1.31	Up	2.32E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
STIM1	734	N	1.30	Down	3.36E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
ACTB	9042	N	1.30	Down	5.86E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
AKIP1	202	N	1.30	Down	7.89E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
SPAG1	268	N	1.30	Down	9.15E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
ETFB	2319	N	1.30	Down	3.47E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
HGH1	225	N	1.30	Down	1.43E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CCT5	1251	N	1.30	Down	2.44E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
SMC3	1330	N	1.30	Up	1.07E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
SESN1	681	N	1.30	Down	6.93E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10560369	9028	N	1.29	Down	5.87E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
POMT2	369	N	1.29	Down	8.73E-05				N	N	N	N	N	N	N	N	N	N	N	N	N	N
AGK	425	N	1.29	Down	7.92E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
MCC	856	N	1.29	Down	1.22E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
B3GAT3	419	N	1.29	Down	2.11E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
ABCB8	401	N	1.29	Down	7.20E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
ZBTB4	1487	N	1.29	Up	4.26E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
RSRC1	9280	N	1.28	Down	5.60E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CRELD1	674	N	1.28	Down	9.75E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PDXK	4783	N	1.28	Down	4.51E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PHLDB2	2207	N	1.28	Up	7.11E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CRYZL1	801	N	1.28	Up	5.90E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PTPN23	391	N	1.27	Down	1.09E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
WBSCR16	344	N	1.27	Down	6.49E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
EIF4G1	3708	N	1.27	Down	3.71E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
RARS2	1434	N	1.27	Up	5.87E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PCMTD1	3230	N	1.27	Up	5.51E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
MAN1B1	217	N	1.26	Down	7.35E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CAPN12	775	N	1.26	Down	3.67E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10110276	259	N	1.26	Down	3.28E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
KAT2A	402	N	1.26	Down	6.70E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CCM2	427	N	1.25	Down	9.59E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
AIMP2	293	N	1.25	Down	6.59E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
FANCE	260	N	1.25	Up	5.87E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
LETMD1	397	N	1.25	Down	1.71E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PEA15	1240	N	1.25	Down	6.41E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
RB1	595	N	1.25	Up	1.81E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
FTSJ1	349	N	1.25	Down	3.72E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CNOT8	631	N	1.25	Up	4.68E-05				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10560286	2292	N	1.25	Up	3.28E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
CDS8	1472	N	1.24	Down	1.42E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
LASP1	3114	N	1.24	Down	5.74E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
MIER3	524	N	1.24	Up	8.82E-03	1.30	Up	8.41E-03	N	Y	N	N	N	N	N	N	N	N	N	N	N	N
FAM92A1	774	N	1.24	Up	1.46E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
TP53BP2	993	N	1.24	Up	6.66E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
NUCKS1	1239	N	1.24	Up	8.70E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
IGIP	357	N	1.23	Up	6.61E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
GOLT1B	275	N	1.23	Down	4.46E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10561648	1217	N	1.23	Up	9.41E-04				N	N	N	N	N	N	N	N	N	N	N	N	N	N
MARS	720	N	1.23	Down	3.28E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PSMD11	885	N	1.23	Down	4.59E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
ECHDC1	1137	N	1.23	Up	2.11E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
RAD17	464	N	1.23	Up	8.00E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
FUNDC1	369	N	1.22	Up	6.28E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PHF11	905	N	1.22	Down	6.79E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
RUFY2	595	N	1.22	Up	5.58E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
FANCA	644	N	1.22	Down	2.63E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
DSTYK	940	N	1.22	Up	3.54E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
PREP	503	N	1.22	Down	1.53E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
SURF2	648	N	1.22	Down	9.23E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
AKTIP	551	N	1.22	Up	6.69E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
DCAF6	773	N	1.21	Up	4.50E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
POLR2A	2244	N	1.20	Up	7.31E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
ZNF384	584	N	1.20	Down	1.94E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
KHSRP	1020	N	1.20	Down	5.87E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
EXOC8	748	N	1.20	Up	7.23E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
RNF13	1694	N	1.20	Up	1.11E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
ZNF276	564	N	1.20	Down	8.83E-03				N	N	N	N	N	N	N	N	N	N	N	N	N	N
OC10561224	23	N				12.53	Down	8.41E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
DES	378	N				4.65	Down	8.41E-03	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N
PCOLCE2	45	N				2.74	Down	8.41E-03	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N
OC10112000	22	N				2.48	Down	9.53E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
OC10560932	47	N				2.00	Down	9.65E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
GATSL3	438	N				1.98	Down	5.30E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
CPT1B	184	N				1.87	Down	8.41E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
OC10560554	406	N				1.79	Down	8.64E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
BGN	1720	N				1.76	Down	4.41E-03	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N
KANSL1L	2139	N				1.63	Up	1.73E-04	N	Y		N	N	N	N	N	N	N	N	N	N	N
PDGFRB	1324	N				1.60	Up	8.47E-03	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N
RPE	1379	N				1.53	Up	1.64E-04	N	Y		N	N	N	N	N	N	N	N	N	N	N
CA2	12771	N				1.44	Down	8.41E-03	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N
PLEKHA8	499	N				1.41	Up	3.49E-03	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N
PEX16	492	N				1.34	Up	5.30E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
USE1	429	N				1.28	Down	8.41E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
SLTM	1416	N				1.24	Up	6.07E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
CSTF3	1122	N				1.21	Up	8.47E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N
EIF4ENIF1	1212	N				1.20	Up	5.30E-03	N	Y		N	N	N	N	N	N	N	N	N	N	N

Figure S1A. **Tissue composition of kidney biopsy samples collected at (A) Baseline, (B) Heart Failure and (C) Recovery.**

Gene expression profiles of all but three samples, collected at Baseline, were consistent with kidney tissue. Expression profiles of these three, matching skeletal muscle, adrenal gland and esophagus, were excluded, leaving a total of 11xBaseline, 13xHF and 8xRecovery samples for differential expression analysis.

Figure S1B. Tissue composition of kidney biopsy samples collected at (A) Baseline, (B) Heart Failure and (C) Recovery.

Gene expression profiles of all but three samples, collected at Baseline, were consistent with kidney tissue. Expression profiles of these three, matching skeletal muscle, adrenal gland and esophagus, were excluded, leaving a total of 11xBaseline, 13xHF and 8xRecovery samples for differential expression analysis.

Figure S1C. Tissue composition of kidney biopsy samples collected at (A) Baseline, (B) Heart Failure and (C) Recovery.

Gene expression profiles of all but three samples, collected at Baseline, were consistent with kidney tissue. Expression profiles of these three, matching skeletal muscle, adrenal gland and esophagus, were excluded, leaving a total of 11xBaseline, 13xHF and 8xRecovery samples for differential expression analysis.

Figure S2. Serial hemodynamic responses in sheep during development of, and recovery from, acute decompensated heart failure.

Data represent mean+SEM responses in nine sheep before (Baseline) and during the development of acute decompensated heart failure (induced by left-ventricular [LV] pacing @220bpm for 14 days), and following recovery over 25-days termination of pacing. Significant differences from pre-pacing baseline are shown by: * $p<0.05$, † $p<0.05$, ‡ $p<0.001$, by 1-way ANOVA.

Figure S3. Serial hormone responses in sheep during development of, and recovery from, acute decompensated heart failure.
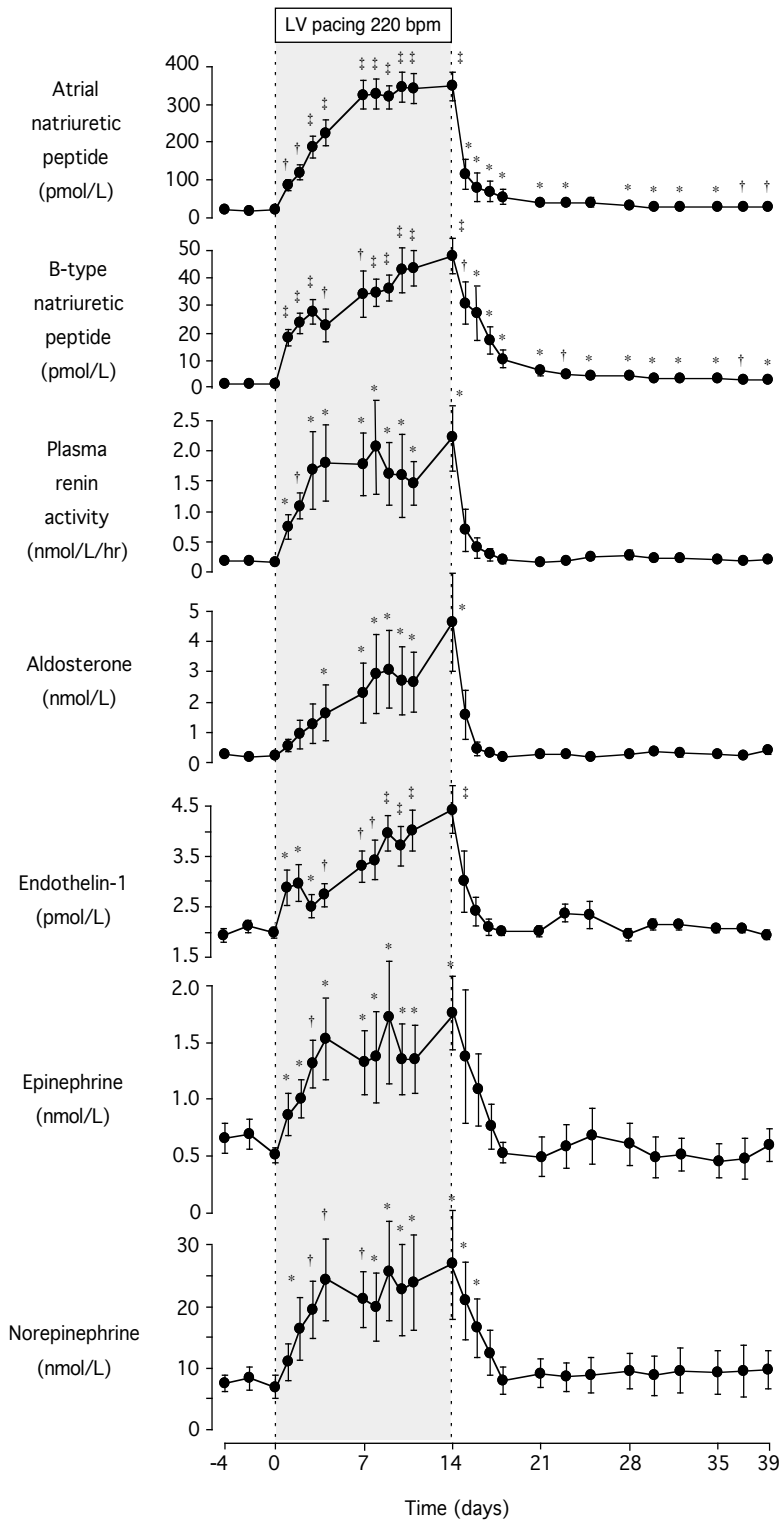
Data represent mean+SEM responses in nine sheep before (Baseline) and during the development of acute decompensated heart failure (induced by left-ventricular [LV] pacing @220bpm for 14 days), and following recovery over 25-days termination of pacing. Significant differences from pre-pacing baseline levels are shown by: * $p<0.05$, † $p<0.05$, ‡ $p<0.001$, by 1-way ANOVA.

Figure S4. Serial renal responses in sheep during development of, recovery from, acute and decompensated heart failure.
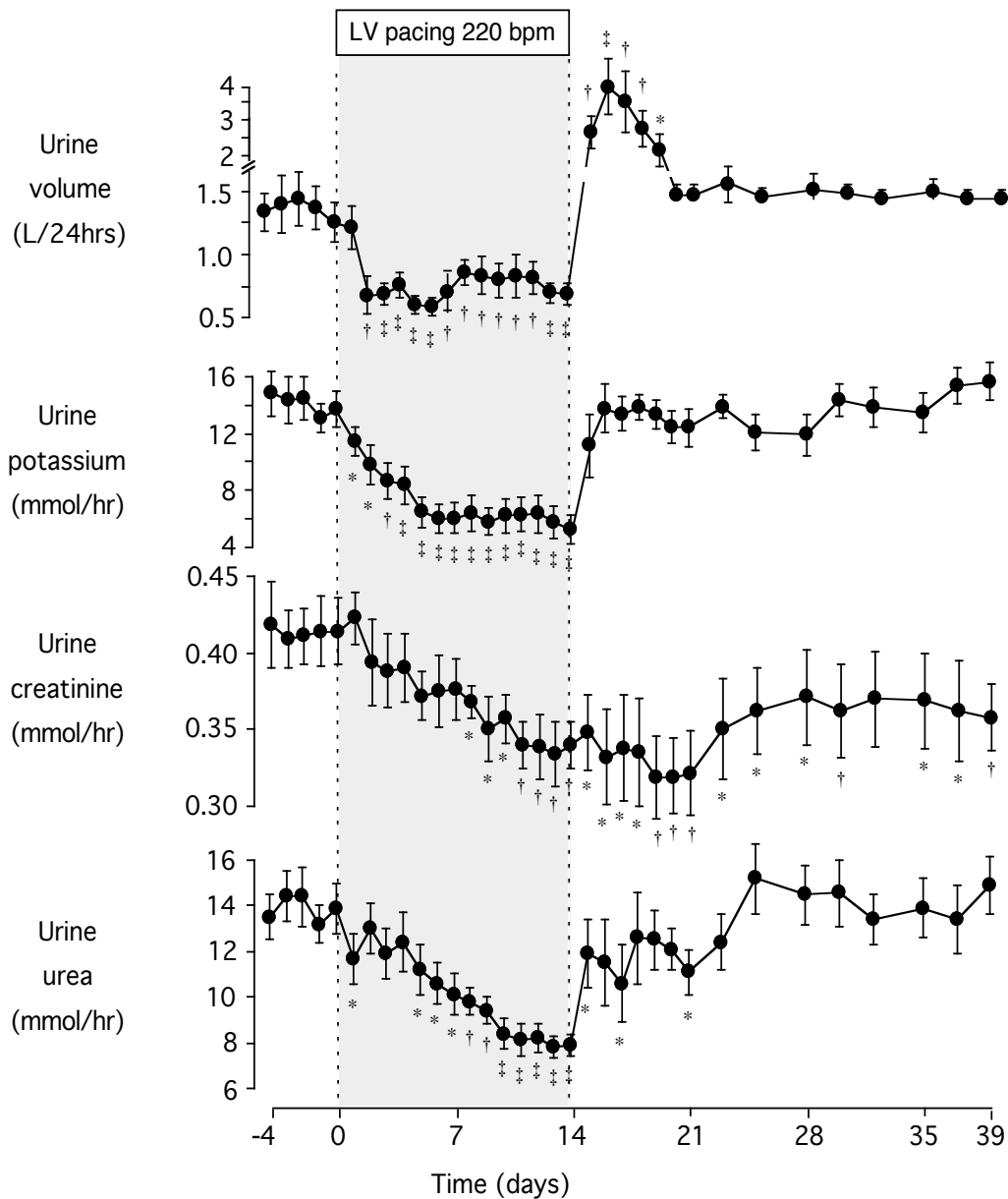
Data represent mean±SEM responses in nine sheep before (Baseline) and during the development of acute decompensated heart failure (induced by left-ventricular [LV] pacing @220bpm for 14 days), and following recovery over 25-days termination of pacing. Significant differences from pre-pacing baseline levels are shown by: * p<0.05, † p<0.05, ‡ p<0.001, by 1-way ANOVA.

Figure S5. Heatmap showing median expression levels at Baseline (B, n=11), heart failure (HF, n=13) and Recovery (R, n=8) for 85 genes differentially expressed between timepoints and previously associated with acute kidney injury.
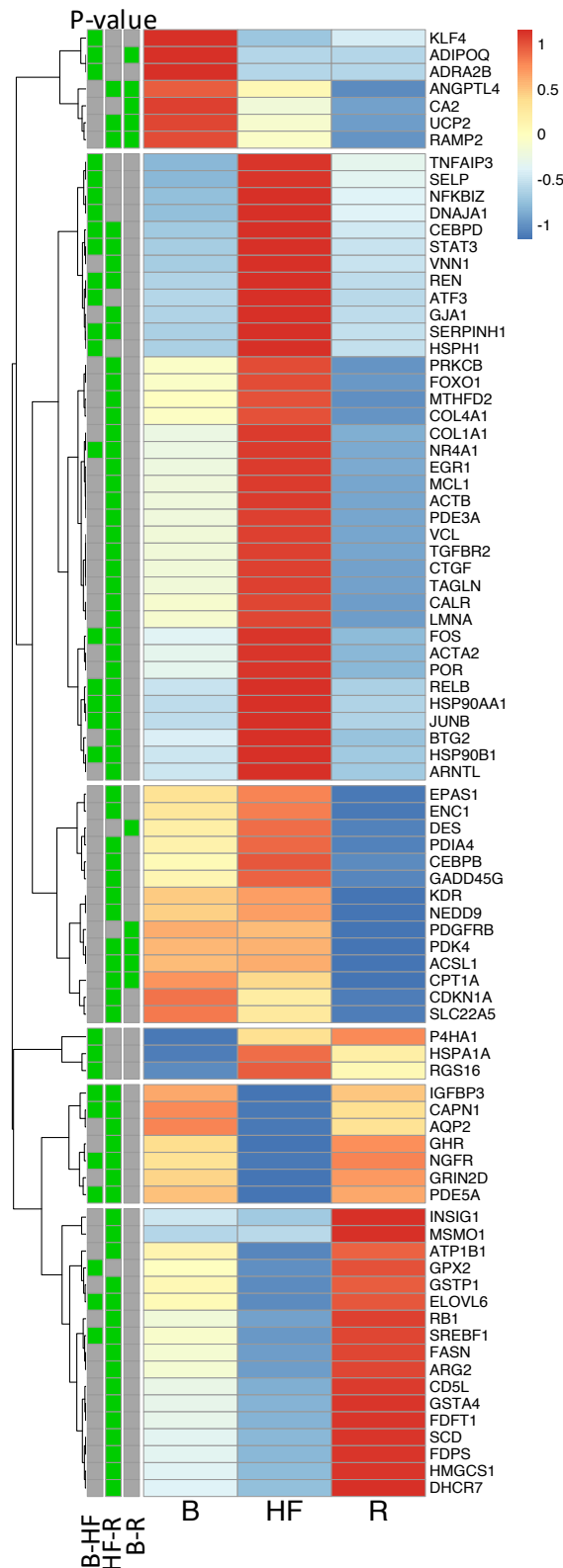
Median gene expression was scaled using z-scores so expression at high and low abundance to be visualised on the same graph. For each gene, the colour scale indicates high (red) or low (blue) expression relative to the other time points. Green boxes (left panel) indicate differential expression between time points (p<0.01 after adjustment for multiple comparisons, fold change >1.2 or <0.83). Genes formed six broad clusters with similar patterns of expression across time points.

Figure S6A. Endothelial nitric oxide synthase (eNOS) signalling pathway illustrating altered expression of individual genes from Baseline to Heart failure (HF) and from HF to Recovery.

A
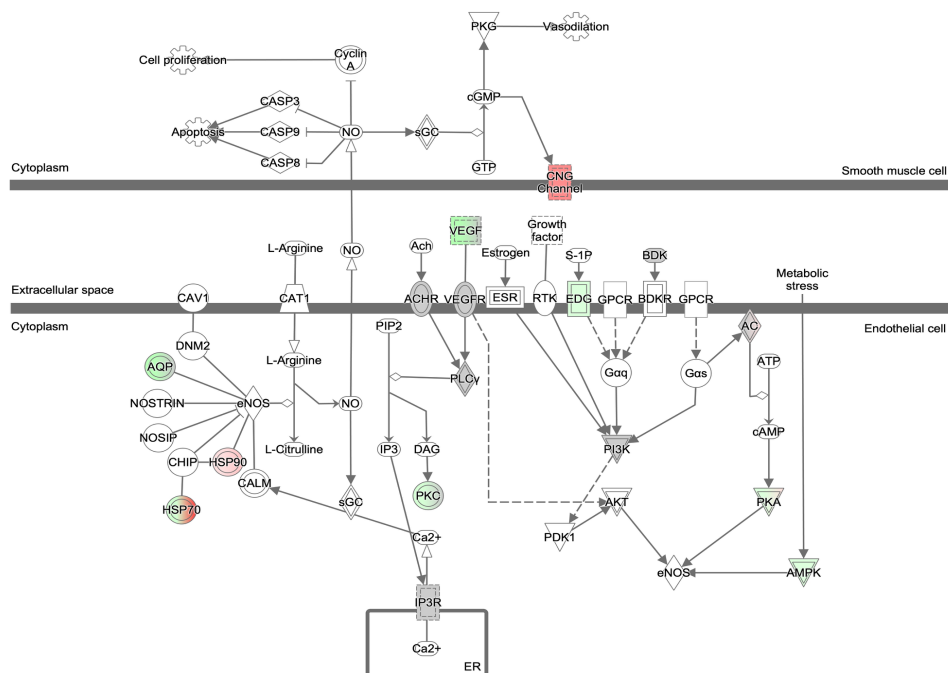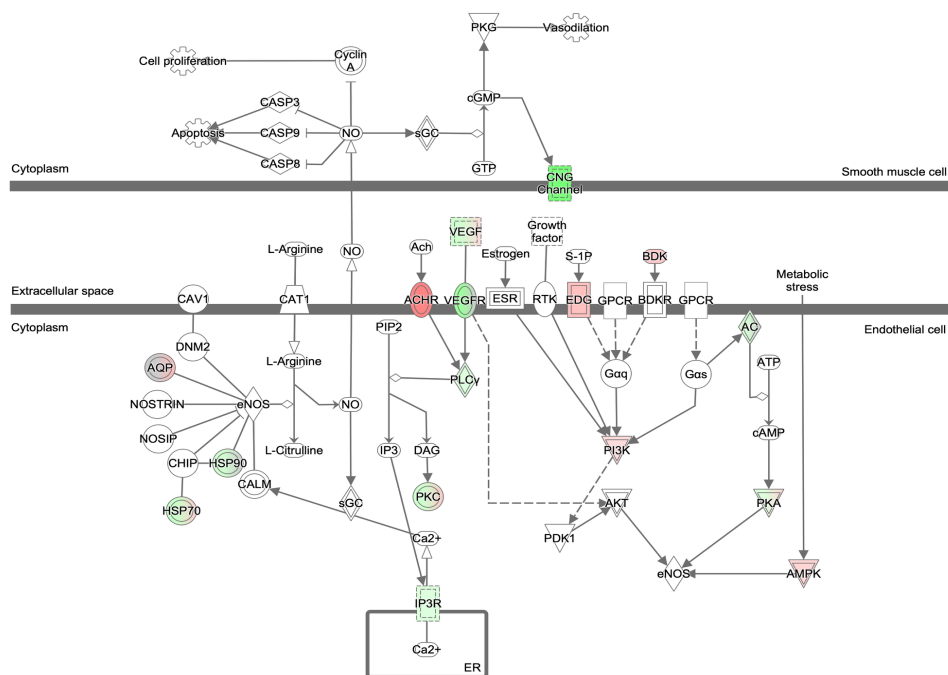
Red indicates increased expression; green indicates decreased expression.

Figure S6B. Cholesterol Biosynthesis signalling pathway illustrating altered expression of individual genes from Baseline to Heart failure (HF) and from HF to Recovery.

B

Superpathway of Cholesterol Biosynthesis

Baseline to HF   HF to Recovery

Red indicates increased expression; green indicates decreased expression.

Figure S6C. Peroxisome proliferator-activated receptor (PPAR) signalling pathway illustrating altered expression of individual genes from Baseline to Heart failure (HF) and from HF to Recovery.
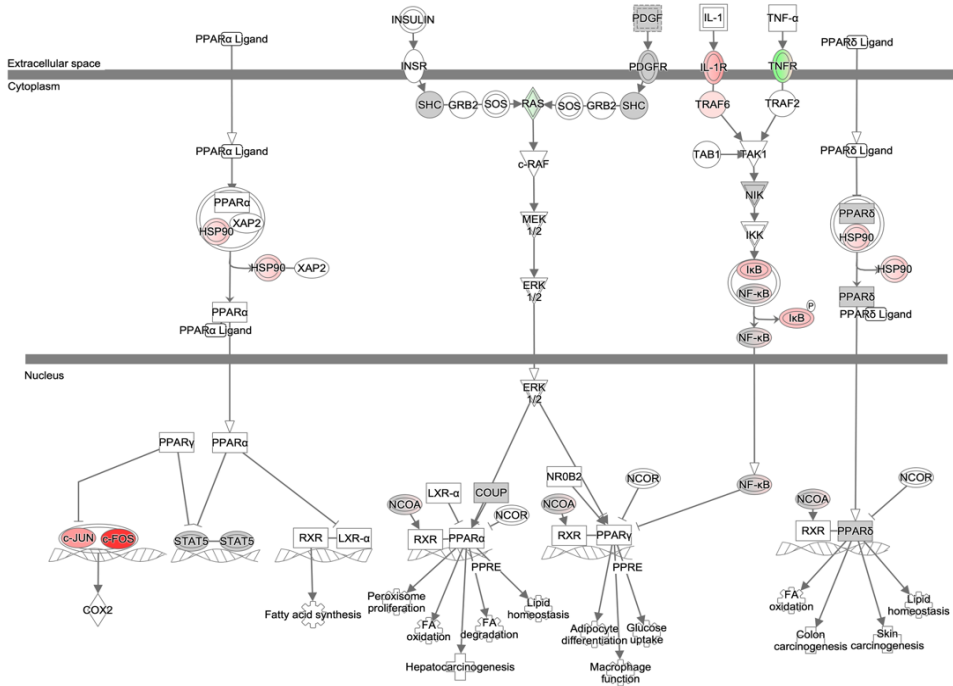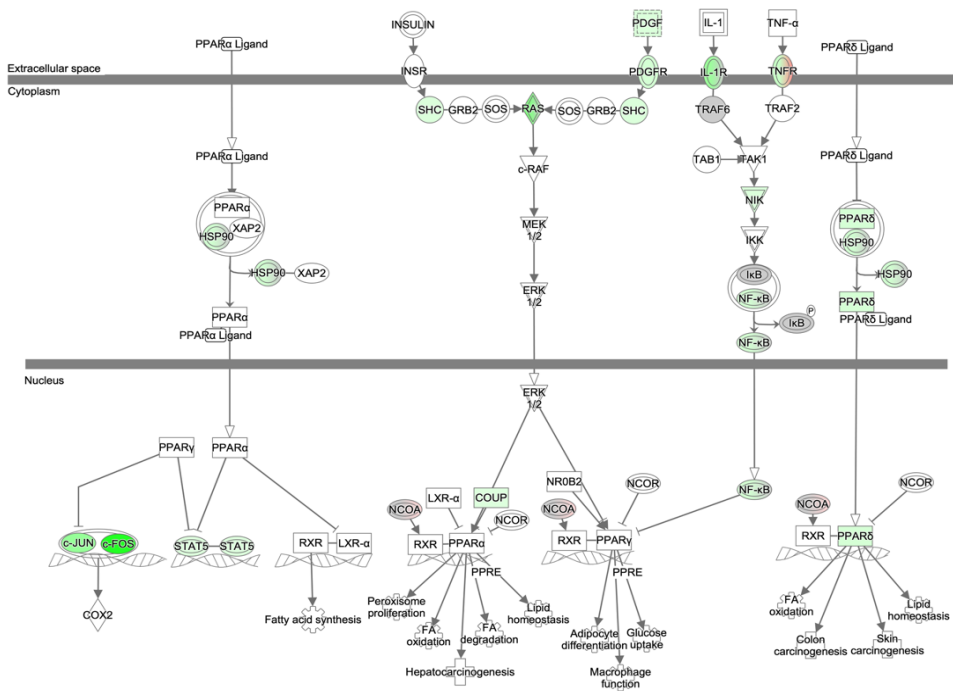
Red indicates increased expression; green indicates decreased expression.

Figure S6D. Glycoprotein VI (GP6) signalling pathway illustrating altered expression of individual genes from Baseline to Heart failure (HF) and from HF to Recovery.

Red indicates increased expression; green indicates decreased expression.

Figure S6E. Platelet-derived growth factor (PGDF) signalling pathway illustrating altered expression of individual genes from Baseline to Heart failure (HF) and from HF to Recovery.

E
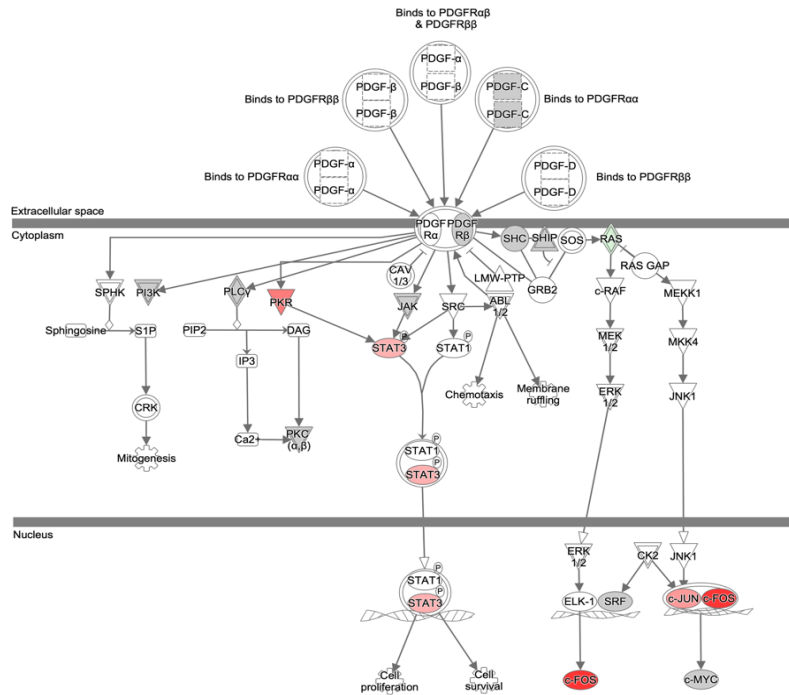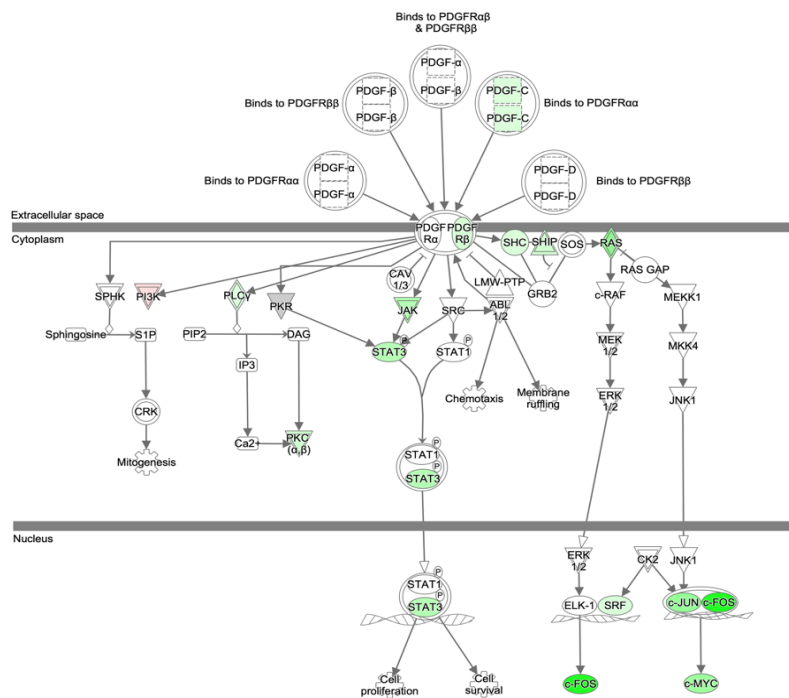
Red indicates increased expression; green indicates decreased expression.

Figure S6F. Oncostatin M signalling pathway illustrating altered expression of individual genes from Baseline to Heart failure (HF) and from HF to Recovery.

Red indicates increased expression; green indicates decreased expression.

Figure S6G. Acute Phase Response signalling pathway illustrating altered expression of individual genes from Baseline to Heart failure (HF) and from HF to Recovery.

G

Acute Phase Response
Baseline to HF
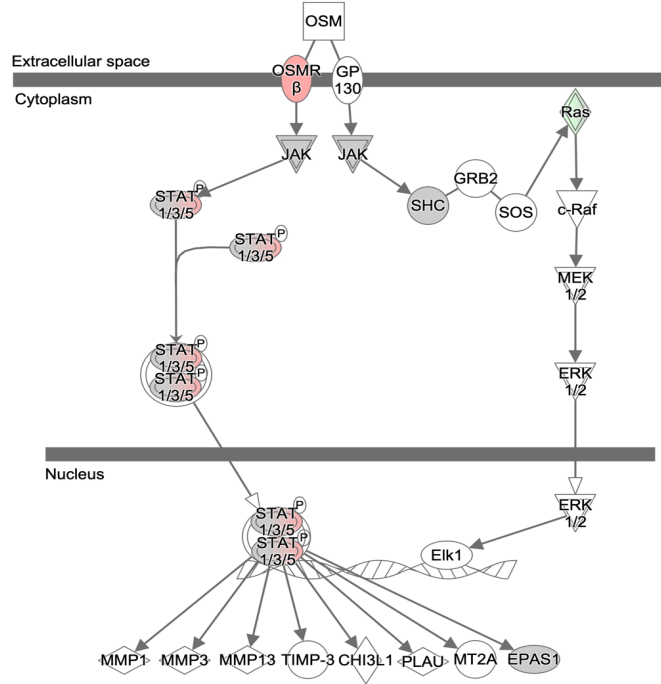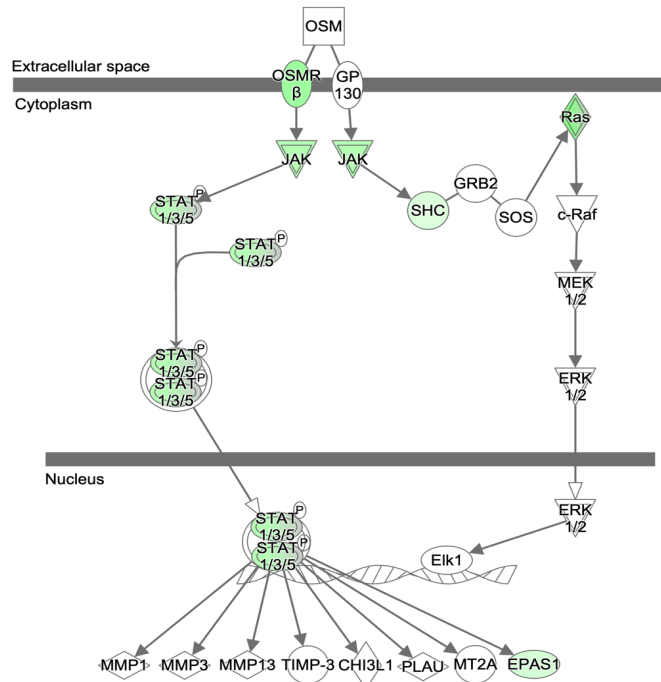
HF to Recovery

Red indicates increased expression; green indicates decreased expression.

Figure S6H. Hepatic Fibrosis signalling pathway illustrating altered expression of individual genes from Baseline to Heart failure (HF) and from HF to Recovery.

H

Hepatic Fibrosis Signalling Pathway

Baseline to HF
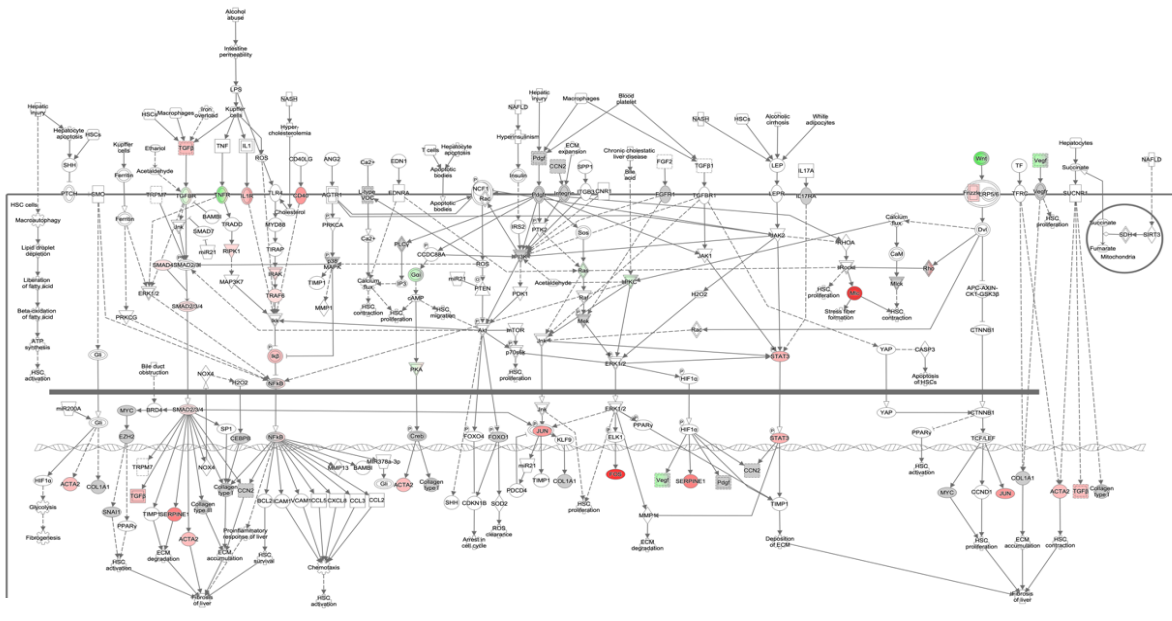
HF to Recovery
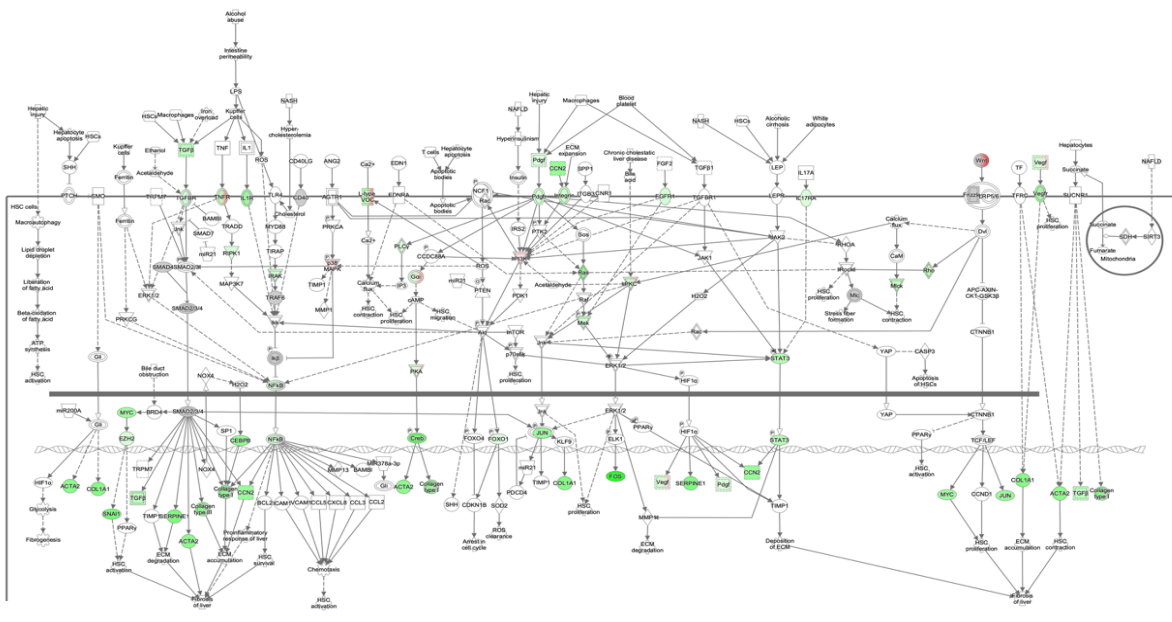
Red indicates increased expression; green indicates decreased expression.
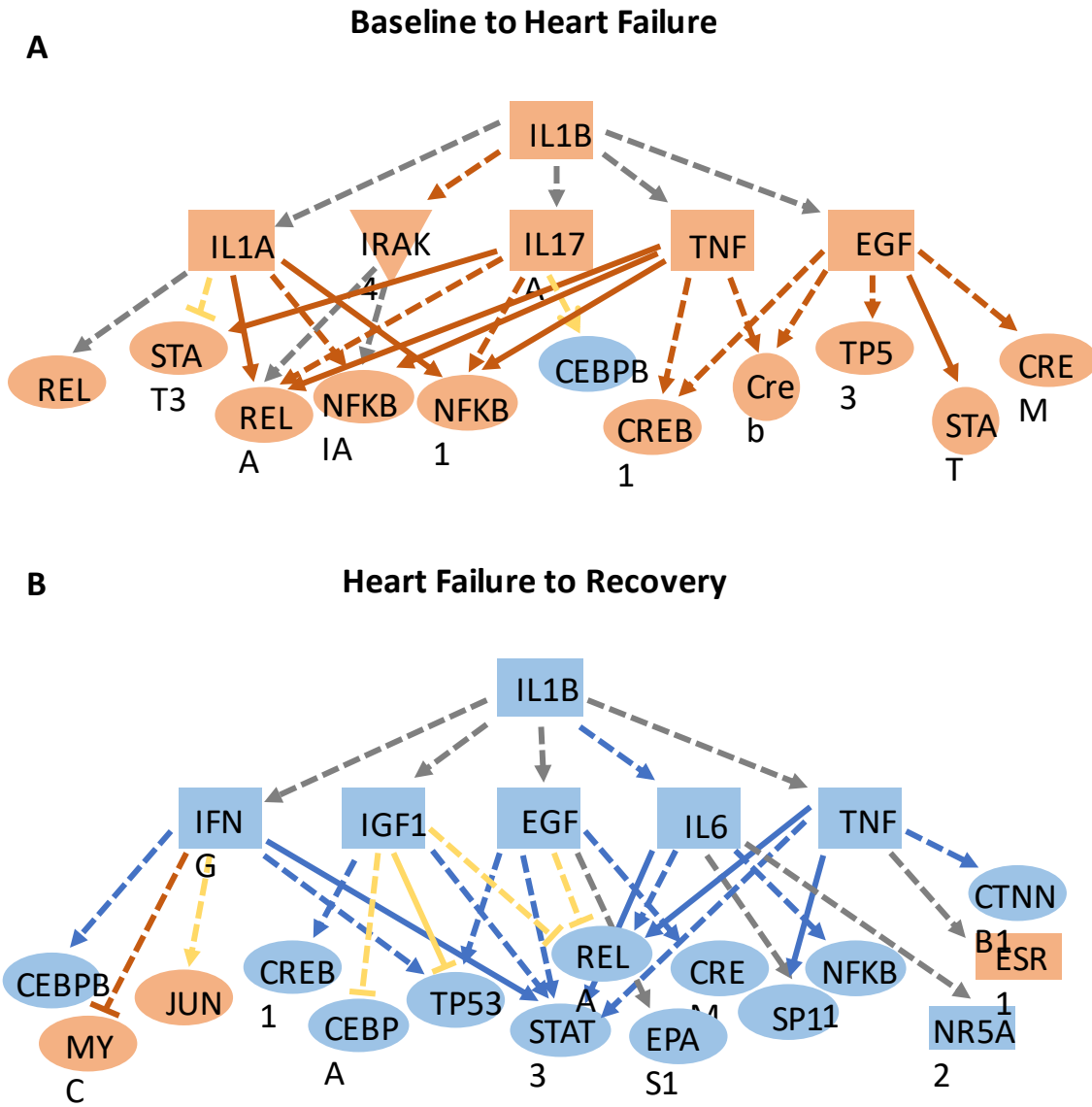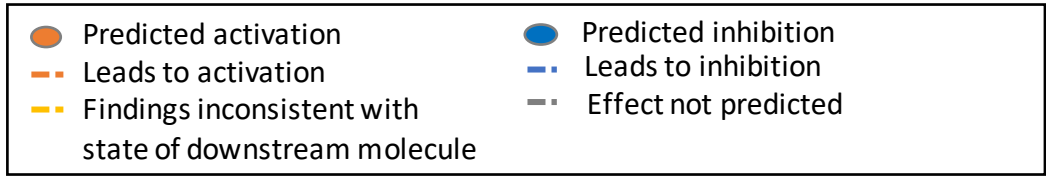
Suppl-Fig 7: Predicted mechanistic regulatory network for the pro-inflammatory cytokine, Interleukin 1 beta (IL1β). (**A**) IL1β is predicted to be activated in heart failure (HF) and (**B**) repressed during Recovery based on altered expression of 74 (27%) genes altered from Baseline to HF and 263 (42%) genes altered from HF to Recovery. IL1β would be predicted to influence the expression of genes in the dataset directly or indirectly via this network of closely connected regulatory molecules with similar predicted patterns of activation and inhibition. Red/blue lines indicate activating/inhibiting connections between regulators that are consistent with the predicted direction of activation of both regulators. Yellow connecting lines indicate connections that are inconsistent with the predicted state of the downstream molecule. Grey lines indicate effects that are not predicted in the IPA knowledgebase.

Figure S8. Correlation matrices comparing changes from (A) Baseline to heart failure (HF) and from (B) HF to Recovery between 19 'HF-responsive' candidate kidney biomarkers and neurohormone/hemodynamic measurements.
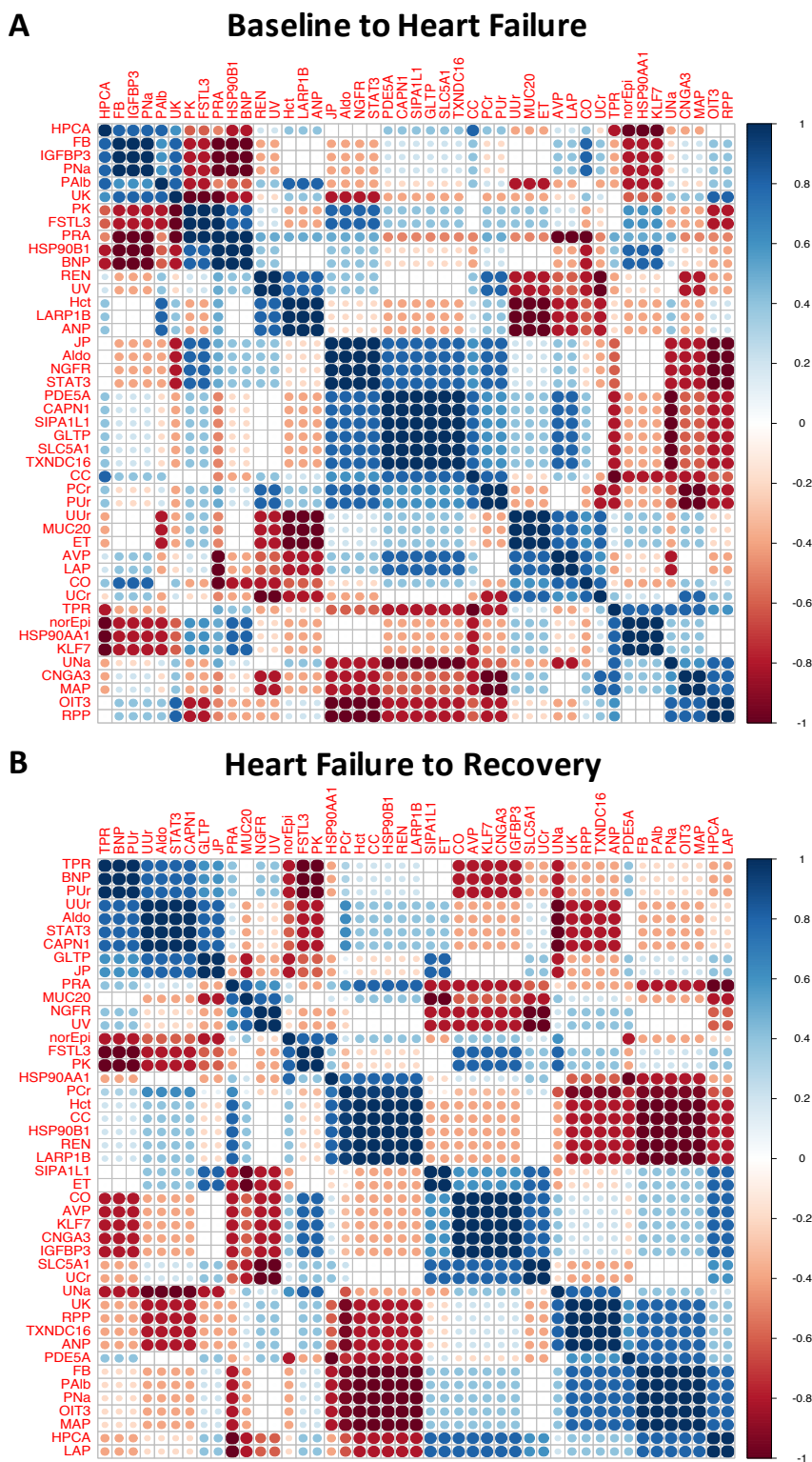
Hierarchical clustering identifies candidate kidney biomarkers that change with a similar pattern to key neurohormone / hemodynamic indices of cardiac and renal function. Data are shown for 5 sheep for whom serial measurements were available Baseline (n=4), HF (n=5) and Recovery (n=5). The strength and direction of each association is indicated by circle size (larger circles=stronger correlation), blue indicates +ve correlations; red indicates -ve correlations.

Figure S9. Correlation matrices comparing changes from Baseline to Recovery between 13 'HF-sustained' candidate kidney biomarkers and neurohormone / hemodynamic measurements.
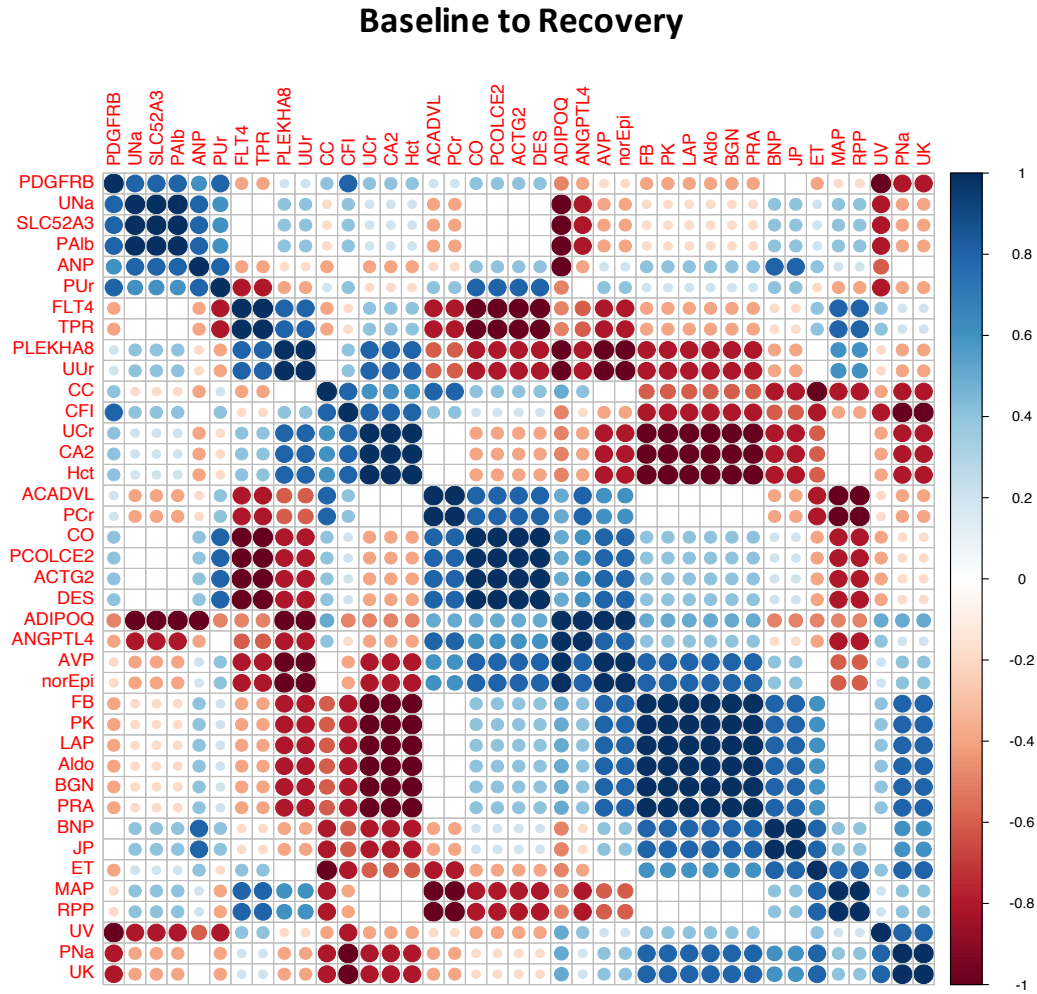
Baseline to Recovery

Hierarchical clustering identifies candidate kidney biomarkers that change with a similar pattern to key neurohormone and hemodynamic indices of cardiac and renal function. Data are shown for 5 sheep for whom serial measurements were available Baseline (n=4) Recovery (n=5). The strength and direction of each association is indicated by circle size (larger circles = stronger correlations), blue indicates positive correlations; red indicates negative correlations.