Supplemental Material

The Renin Cell Baroreceptor, a Nuclear Mechanotransducer Central for Homeostasis

Hirofumi Watanabe, Brian C. Belyea, Robert L. Paxton, Minghong Li,
Bette J. Dzamba, Douglas W. DeSimone, R. Ariel Gomez,
Maria Luisa S. Sequeira-Lopez.

Expanded Materials & Methods
Online Figures I–XV
Online Tables I–VII
References 47–65

Methods

Animals

All animals were maintained in a room with controlled temperature and humidity under a 12-hour light/dark cycle. All animals were handled following the National Institutes of Health guidelines for the care and use of experimental animals. The study was approved by the Institutional Animal Care and Use Committee of the University of Virginia. C57Bl/6 mice were obtained from the Jackson Laboratory (Bar Harbor, ME). To perform the transcriptome analysis of renin cells, we used the *$Ren1^{c}$-YFP* mice[4]. To generate Mice with conditional deletion of the *Itgb1* gene in cells of the renin lineage *(Itgb1cKO* mice)[25], we used the *$Ren1^{dCre}$* mice[31] and the *$Itgb1^{flox}$* mice (Jackson laboratory: 004605). After a few generations, we generated *$Ren1^{dCre/+}$; $Itgb1^{flox/flox}$* conditional knockout mice and *$Ren1^{d+/+}$; $Itgb1^{flox/flox}$* as control mice. *Lmna* floxed mice were provided by Dr. Yixian Zheng (Department of Embryology, Carnegie Institution for Science, Stanford, CA)[32]. We generated *$Ren1^{dCre/+}$; $Lmna^{flox/flox}$* conditional knockout (*LmnacKO*) mice and *$Ren1^{d+/+}$; $Lmna^{flox/flox}$* as control mice. Genotyping of the mice was performed by Transnetyx (Cordova, TN). Both male and female mice were used in the experiments.

Aortic coarctation

Mice were anesthetized with 2.5% isoflurane. The left side of the back of the mouse was opened, and the abdominal aorta at the suprarenal level was exposed and carefully detached from the vena cava between the left and right renal arteries and freed of the surrounding adventitial adipose tissue by gentle dissection. Then, the aorta was gently constricted between the left and right renal arteries. The aorta was ligated with the 6-0 silk suture, including steel wire, and the wire was removed quickly after the ligation. Then, the constricted part of the aorta became the diameter of the wire. For RNA-seq of renin cells, we used *$Ren1^{c}$-YFP* mice at 8 to 12 weeks of age with 0.30 mm wire. *Itgb1cKO* and their control mice at 4 weeks of age were subjected to the aortic coarctation (AoCo) with 0.25 mm wire. For other experiments, we used mice at 2 to 4 months of age with 0.35 mm and 0.30 mm wires, for males and females, respectively. Sham-treated mice underwent the same procedure, with the exception of exposing the aorta and AoCo. Then, the muscle layer was sutured, and the skin incision closed. Buprenorphine (0.1–0.2 mg/kg) was used for pain management. Seventy-two hours after surgeries, mice were anesthetized by tribromoethanol (300 mg/kg). After blood collection, the kidneys were dissected, and the animals were euthanized.

We used only the mice that were alive at the time to be harvested. We excluded the mice that died during and within 72 hours after the AoCo surgeries.

Blood pressure measurement from both carotid and femoral arteries

Seventy-two hours after the AoCo surgery, mice were anesthetized with 1.5% isoflurane and kept at 37.5°C. Polyethylene catheters (PE10, Becton Dickinson; internal diameter, 0.28 mm) pre-filled with heparinized saline were inserted into the right carotid artery and left femoral artery. Arterial pressure was continuously recorded from both catheters simultaneously by an RX104A transducer with AcqKnowledge software (BIOPAC Systems Inc., Goleta, CA). Mean arterial pressure and systolic and diastolic blood pressure (BP) were measured for 10 minutes[24].

BP measurement from right carotid arteries was performed on *Itgb1cKO* and control mice 72 hours after the AoCo surgery with the same recording method described above.

Histological analysis
Mice were anesthetized with tribromoethanol. Kidneys were removed, fixed in 4% paraformaldehyde (PFA), 10% formalin, or Bouin's solution overnight, and embedded in paraffin.
For frozen sections to observe YFP positive cells, kidneys were fixed in 4% PFA for 1 hour. After washing in PBS, the kidneys were placed in 30% sucrose overnight and then frozen in O.C.T (Thermo Fisher Scientific, Waltham, MA). The frozen blocks were sectioned at 20 µm thickness and washed in PBS. Staining for nuclei was performed with Hoechst 33342 (Thermo Fisher Scientific). Sections were covered with cover glasses with PBS.
Periodic acid–Schiff (PAS) staining was performed on 5 µm paraffin sections from kidneys fixed with Bouin's solution. Sections were deparaffinized in xylenes, rehydrated with sequential incubations in ethanol (100%, 95%, and 70%), washed with deionized water, and incubated with 0.5% periodic acid (Millipore-Sigma, Burlington, MA) for 10 minutes. Then sections were stained with Schiff's reagent (Millipore-Sigma) for 20 minutes. After washing with running water, the sections were counterstained with hematoxylin (Millipore-Sigma), differentiated in saturated lithium carbonate solution (Millipore-Sigma), dehydrated in graded ethanols and xylenes, and mounted with Cytoseal XYL (Thermo Fisher Scientific).

RNA extraction and quantitative RT-PCR
Renal cortices were removed and placed in RNAlater Stabilization Solution (Thermo Fisher Scientific) overnight at 4°C and then stored at −20°C. RNA was extracted from renal cortices or cultured cells using TRIzol reagent (Thermo Fisher Scientific) and RNeasy Mini Kit (Qiagen, Dusseldorf, Germany). Reverse transcription (RT) was performed using oligo(dT) primer and M-MLV Reverse Transcriptase (Promega, Madison, WI) at 42 ˚C for 1 hour according to the manufacturer's instructions. Quantitative PCR was performed with SYBR Green I (Thermo Fisher Scientific) in a CFX Connect system (Bio-Rad Laboratories, Hercules, CA). Primers are listed in Online Table VI. The optimized program was 95 ˚C for 3 min, followed by 40 cycles of denaturation at 95 ˚C for 30 seconds, annealing for 30 seconds, and extension at 72 ˚C for 30 seconds. The annealing temperature for *Ren1*, *Lmna*, and *Rps14* mRNA was 57 ˚C, 55 ˚C, and 61 ˚C, respectively. The mRNA expression of *Ren1* and *Lmna* was normalized to *Rps14* expression, and the changes in expression were determined by the $\Delta\Delta$Ct method and were reported as relative expression compared to control mice[38].

Synthesis of probes for *in situ* hybridization
To develop the probes specific for *Ren1, Akr1b7, Atp6v1g3, and Aldh7a1* mRNA, DNA fragments were synthesized by PCR using cDNA from wild type C57BL/6 mouse kidneys with a 3' T3 promoter and a 5' T7 promoter. Primers are listed in Online Table VII. After purification and confirmation of DNA sequences, digoxigenin (DIG)-labeled RNA sense and antisense probes were generated by *in vitro* transcription using DIG RNA Labelling Mix and T3 or T7 Polymerase (Millipore-Sigma)[47].

In situ hybridization

In situ hybridization (ISH) was performed with 4% paraformaldehyde fixed-paraffin-embedded kidney tissues. The tissues were sectioned at 7 μm thickness, deparaffinized in xylenes, rehydrated with sequential incubations in ethanol (100%, 95%, and 70%), washed with PBS, and post-fixed with 4% PFA at room temperature for 30 minutes, followed by acetylation (0.375% acetic anhydride) for 10 minutes and permeabilization with Proteinase K (10 μg/mL) for 30 minutes at 37 ˚C. After the-preincubation with the hybridization buffer (500 ng/mL in hybridization buffer of 50% formamide, 5x SSC, 50 μg/mL yeast transfer RNA, 1% SDS, 50 μg/mL heparin) for 1 hour at 37 ˚C, slides were incubated with the DIG-labeled sense or antisense riboprobes at 55 °C overnight. The slides then received stringency washes in 0.2x SSC at 65 ˚C for 30 minutes 3 times and blocking with 10% heat-inactivated sheep serum for 1 hour, and they were incubated with anti–digoxigenin-alkaline phosphatase antibody (1:4,000, 11093274910 [Millipore-Sigma]) overnight at 4°C. After washing, slides were treated with NTMT solution (100 mmol/L NaCl, 100 mmol/L Tris pH 9.5, 50 mmol/L $MgCl_2$, 0.1% Tween-20, 2 mmol/L levamisole) for 10 minutes. Sections were incubated with BM Purple (Millipore-Sigma) for 3 hours for *Ren1* mRNA, 2 days for *Akr1b 7* mRNA, 3 days for *Atp6v1g3* mRNA, and 7 days for *Aldh7a1* mRNA, respectively. The reactions were terminated, and the sections were fixed by 0.2% glutaraldehyde + 4% paraformaldehyde and mounted with Glycergel Mounting Medium (Agilent Technologies, Santa Clara, CA). We confirmed the specificity of ISH by comparing antisense probes generated with T7 polymerase and sense probes generated with T3 polymerase. The ISH signals were observed with antisense probes, and there was no signal with sense probes for all genes we targeted. To compare the intensity of the signals, we placed the kidney sections of both the right and left kidneys from the same mice on the same slides and treated the sections equally during the whole procedure[47].

Blood chemistry

Animals were anesthetized by tribromoethanol (300 mg/kg). Blood was collected by cardiac puncture and placed into tubes containing EDTA or heparinized plasma separator tubes (BD Microtainer [Becton Dickinson). Tests of the basic metabolic panel were performed by the University of Virginia Hospital clinical laboratory[5].

ELISA for renin in plasma and cell culture medium

Plasma specimens were obtained from blood after centrifugation at 1,000 g at 4 ˚C for 15 minutes. The cell culture medium was centrifuged at 2,000 rpm at 4 ˚C for 10 minutes, and the supernatant was collected. Renin concentration was determined using ELISA (ELM-Renin1-1 [RayBiotech, Norcross, GA])[48].

Isolation of renin cells and mRNA sequencing

Renin cells were isolated from the kidney from *Ren1^c-YFP* mice at 8 to 12 weeks of age after 72 hours of AoCo or sham surgeries using fluorescence-activated cell sorting (FACS), as described previously[5,24]. Renal cortices were dissected, minced with razor blades, and transferred into 15 mL tubes with 5 mL of enzymatic solution (0.3% collagenase A [Millipore-Sigma], 0.25% trypsin [Millipore-Sigma], and 0.0021% DNase I

[Millipore-Sigma]). The tubes were placed flat inside a shaking incubator (80 RPM) for 15 minutes at 37°C. The solution was then pipetted up/down ten times and settled for 2 minutes, and the supernatant with single cells was collected. The enzymatic solution was added to the 15 mL tube containing the remaining undigested cortices, and the digestion procedure was repeated a total 3 times. The supernatants collected from the 3 digestions were pooled and centrifuged at 1,100 g for 4 minutes at 4°C using a Sorvall RT7 refrigerated centrifuge (Sorvall, Newtown, CT). The cell pellet was resuspended with fresh buffer 1 (130 mmol/L NaCl, 5 mmol/L KCl, 2 mmol/L $CaCl_2$, 10 mmol/L glucose, 20 mmol/L sucrose, 10 mmol/L HEPES, pH 7.4), and the suspension was poured through a 100 μm nylon cell strainer (Corning Inc., Corning, NY) and washed with the buffer 1. The flow-through was poured through a 40 μm nylon cell strainer (Corning Inc.) and washed with buffer 1. The flow-through was centrifuged at 1,100 g for 4 minutes at 4°C. The cell pellet was resuspended in 1.5 mL of resuspension buffer [PBS, 1% FBS, 1 mmol/L EDTA, DNAase I (Millipore-Sigma)]. The dead cells were labeled with DAPI (Millipore-Sigma). Cells were analyzed and sorted by FACS using the Influx Cell Sorter (Becton Dickinson, Franklin Lakes, NJ). The YFP-positive cells not staining positive with DAPI were sorted, directly collected into the 1x Reaction buffer of SMART-Seq v4 Ultra Low Input RNA Kit for Sequencing (Takara Bio USA, Mountain View, CA), and used to generate cDNA libraries. One thousand cells from each kidney were used. The cDNA was amplified with 13 cycles of PCR. cDNA was isolated using the Agencourt AMPure XP Kit (Beckman Coulter, Brea, CA) and eluted in the Fluidigm dilution reagent (Takara Bio USA). Samples were quantified using a Qubit 3.0 Fluorometer (Thermo Fisher Scientific) and qualified using the High Sensitivity D5000 ScreenTape System (Agilent Technologies, Santa Clara, CA). Nextera DNA Library Prep Kit (Illumina, San Diego, CA) was used to make cDNA libraries tagmented and indexed with unique barcodes suitable for Illumina sequencing. Libraries were sequenced on an Illumina HiSeq 2500/4000 platform (150-bp paired-end reads).

RNA-seq data analysis

The cDNA libraries of renin cells from right and left kidneys from 3 mice with AoCo and 2 mice with sham surgeries were sequenced. Sequencing data was initially quality-checked using FastQC with the FASTQ file reads. Prior to alignment, we removed low-quality reads and adapter sequences using Trimmomatic. We aligned FASTQ reads to the GRCm38/ENSEMBL mouse genome using Salmon, and transcript-level estimates of expression were scaled up to gene-level estimates using the Tximport R package, with the 'lengthScaledTPM' argument for abundance estimation[49]. R version 3.6.3 was used for graphical and statistical analysis. The R package DESeq2[50] was used for count normalization and paired differential gene expression analysis of the data from the right and left kidneys subjected to the AoCo and differential gene expression analysis to compare renin cells that received high perfusion pressure and normal perfusion pressure and renin cells that received normal perfusion pressure and low perfusion pressure. We excluded genes of which no sequence read was detected in any samples from the DESeq2 analysis. The volcano plot and MA plot were generated with ggplot2 in R. The heatmap of the AoCo group was generated with ggplot2 and ggdendro in R. The heatmap and clustering analysis and principal component analysis for all the samples, including cells from sham surgeries, were done with transcripts per million (TPM) values with

differentially expressed genes (DEGs) between the right and left kidneys using packages in R (pheatmap, ggplot2, and ggfortify). GO[51] of gene sets were obtained using Metascape[52]. Pathway enrichment analysis (GO biological processes) was performed with the DEGs. The AutoAnnotate function in Cytoscape[53] was used to perform network analyses to visualize pathways related to the gene sets. R codes are available on Zenodo at https://doi.org/10.5281/zenodo.4672146.

Cell culture

We used a cell line of arteriolar smooth muscle cells of the renin lineage[4]. Cells were maintained in Dulbecco's minimal essential medium/Ham's F12 (DMEM/F12) (Thermo Fisher Scientific) supplemented with 10% fetal bovine serum (Thermo Fisher Scientific) at 37˚C. We used cells at 10 to 20 passages. To stimulate the renin phenotype, 1 mmol/L of cAMP and 0.1 mmol/L of IBMX were applied to the cell culture medium. We applied the cAMP + IBMX again 48 hours after the first application of them.

Pneumatic pressure experiment

Cells were plated on the 6-well plates on the day before the treatment. After the treatment of cAMP + IBMX, the culture plates were placed in a gas-pressurized cell culture chamber (AGP-1000 [Strex USA, San Diego, California]) connected to pre-mixed gas, which in turn is placed inside an incubator[54]. The air pressure was applied to the culture continuously at 80 mmHg or 250 mmHg. Gas exchange by releasing pressure and re-pressurizing the chamber was done every 3 hours.

Magnetic force experiment

Spherical magnetic beads of 2.8-µm diameter (Dynabeads M-280 Tosylactivated [Thermo Fisher Scientific])[55,56] were washed with PBS and incubated with 100 µg/mL fibronectin (Millipore-Sigma) at 37°C for 24 hours. Then the fibronectin-coated beads were washed three times with PBS containing 0.1% bovine serum albumin, dissociated by sonication with Bioruptor Pico (Diagenode, Denville, NJ), and stored at 4˚ C before use. Cells were plated on 6-well plates with the growth medium on the day before the treatment. Cells were subjected to low serum medium (0.1% serum/DMEM/F12) for 8 hours and then incubated in PBS for 5 minutes twice, followed by DMEM/F12 with penicillin-streptomycin (Thermo Fisher) without serum. The fibronectin-coated magnetic beads (3 mg/well) were applied to the cells and incubated for 1 hour. After adhering the beads to the cells, the medium was changed to the growth medium with penicillin-streptomycin. Treatment of cAMP + IBMX was performed as described above. Then we applied force by the magnets attached to the lid of the 6-well plates. Permanent neodymium magnets (stacked 3 disc magnets of N52 grade with diameter 32 mm x thickness 3 mm) were used to generate perpendicular forces on beads attached to the dorsal surface of cells. The pole face of the magnets was parallel with and 10 mm from the culture plate surface.

Immunoprecipitation and Western blot

The cultured arteriolar smooth muscle cells of the renin lineage were rinsed three times with ice-cold TBS, then solubilized with 1 mL lysis buffer (1% NP40, 150 mM NaCl, 25 mM Tris pH7.4, 100 mM PMSF, and protease inhibitor cocktail [Millipore-Sigma]) per T25

flask. Lysates were centrifuged at 16,100 g at 4 ˚C for 10 minutes, and the supernatant was removed to a fresh tube. A sample (50 µL per flask) of lysate was reserved for Western analysis, and the rest was precleared by incubating for 1 hour at 4 ˚C with 100 µL protein A-Sepharose CL-4B (GE Healthcare, Chicago, IL). The cleared lysate was then incubated with end-over-end rotation for an hour with 4 µL/mL of antiserum directed against a synthetic peptide from the β1 cytoplasmic tail[57] then for 1 hour with the addition of 100 µl protein A-Sepharose. The beads (both preclear and immunoprecipitates) were washed 3 times with lysis buffer then eluted by boiling for 5 minutes in 2X Laemmli buffer containing β-mercaptoethanol. Lysate, preclear, and immunoprecipitated samples were resolved on 7% SDS polyacrylamide gels and transferred to nitrocellulose. Membranes were blocked for 1 hour in TBS containing .1% tween (TBST) and 10% non-fat dry milk, then incubated overnight at 4 ˚C in TBST, 5% non-fat dry milk containing either a 1:5,000 dilution of the anti-β1 antiserum, a 1:1,000 dilution of an antiserum raised against a synthetic peptide from the extracellular domain of the α5 subunit[58], or a 1:1,000 dilution of a rabbit monoclonal antibody to the αV subunit (D2N5H [Cell Signaling, Danvers, MA]). Membranes were washed in TBST then incubated for 1 hour at room temperature with a 1:20,000 dilution of anti-Rabbit IgG conjugated to Alexa Flour 790 (711-655-152 [Jackson ImmunoResearch, West Grove, PA]) in TBST containing 5% non-fat dry milk, washed 3 times with TBST then imaged with an Odyssey scanner (Licor, Lincoln, NE).

Fluorescence ISH

Fluorescence ISH was performed with paraffin-embedded 10 % formalin-fixed kidney sections at 5 µm thickness and cultured renin cells using RNAScope Multiplex Fluorescent V2 Assay (Advanced Cell Diagnostics, Hayward, CA, USA). Kidney sections were deparaffinized in xylenes, rehydrated in 100% ethanol, dried for 5 minutes at 60 ˚C, and then treated with hydrogen peroxide (Advanced Cell Diagnostics) at room temperature for 10 minutes, RNAscope Target Retrieval Reagents (Advanced Cell Diagnostics) at 100 ˚C for 15 minutes, and RNAscope Protease Plus (Advanced Cell Diagnostics) at 40 ˚C for 30 minutes. The renin cells cultured on the cover glasses were washed, fixed in 4% PFA for 30 minutes, dehydrated with sequential incubations in ethanol (50%, 70%, and 100%), and treated with hydrogen peroxide (Advanced Cell Diagnostics) for 10 minutes at room temperature and RNAscope Protease III (Advanced Cell Diagnostics) for 10 minutes at room temperature. The hybridization was performed with probes for *Kiss1* mRNA (RNAscope Probe- Mm-Kiss1, 500141 [Advanced Cell Diagnostics]), *Vtn* mRNA (RNAscope Probe- Mm-Vtn, 443601 [Advanced Cell Diagnostics]), *Sdf2l1* mRNA (RNAscope Probe- Mm-Sdf2l1, 562401 [Advanced Cell Diagnostics]), *E2f3* mRNA (RNAscope Probe- Mm-E2f3, 437821 [Advanced Cell Diagnostics]), *Lmna* mRNA (RNAscope Probe-Mm-Lmna, 314811 [Advanced Cell Diagnostics]), and *Ren1* mRNA (RNAscope Probe Mm-Ren1-C2, 433461-C2 [Advanced Cell Diagnostics]), as manufacturer's instructions. As the fluorophores to detect the signals, Cy3 Amplification Reagent and Fluorescein Amplification Reagent (PerkinElmer, Waltham, MA) were used for *Kiss1, Vtn, Sdf2l1,* and *E2f3,* and *Lmna* mRNA and *Ren1* mRNA, respectively. After the assay, samples were counterstained with DAPI (Advanced Cell Diagnostics) and mounted in ProLong Gold Antifade Mountant (Thermo Fisher Scientific).

Immunohistochemistry, immunocytochemistry, and immunofluorescence staining. For staining for renin and α-smooth muscle actin (α-SMA), kidney sections from paraffin blocks fixed with Bouin's solution were deparaffinized in xylenes, rehydrated with sequential incubations in ethanol (100%, 95%, and 70%), and washed with PBS. Then, sections were treated with 0.3% hydrogen peroxide in methanol for 10 minutes. After washing with PBS and blocking with 3% BSA and 2% goat serum or horse serum for 1 hour at room temperature, sections were incubated with an anti-renin antibody (rabbit polyclonal anti-mouse antibody; diluted at 1:500)[59] or an anti-α-SMA antibody (A2547 [Millipore-Sigma]; diluted at 1:10,000)[60] at 4 ˚C overnight. After the washing with PBS, sections were incubated with biotinylated secondary antibody, goat anti-rabbit IgG (BA-1000 [Vector Laboratories, Burlingame, CA]; diluted at 1:200) or horse anti-mouse IgG (BA-2000 [Vector Laboratories]; diluted at 1:200) for renin or α-SMA, respectively, at room temperature for 30 minutes. Staining was amplified using the Vectastain ABC kit (Vector Laboratories) and developed with 3,3'-diaminobenzidine (Millipore-Sigma)[61]. The sections were counterstained with hematoxylin (Millipore-Sigma), dehydrated in graded ethanol and xylenes, and mounted with Cytoseal XYL (Thermo Fisher Scientific). For the staining for renin and lamin A/C on the consecutive sections, tissue sections from paraffin blocks fixed with 10% formalin were used. The recombinant anti-lamin A + lamin C antibody (ab133256 [Abcam, Cambridge, MA]; diluted at 1:400) as a primary antibody and goat anti-rabbit IgG as a secondary antibody were used.

Kidney sections at 5 µm fixed with 10% formalin were deparaffinized in xylenes, rehydrated with sequential incubations in ethanol (100%, 95%, and 70%), washed in PBS, and microwave-treated with 10 mmol/L sodium citrate buffer for 10 minutes. After blocking with 3% BSA, 5% donkey serum, 0.04 % cold fish skin gelatin, and 0.05 % Triton X-100 in PBS for 1 hour at room temperature, sections were incubated with the primary antibodies at room temperature for 90 minutes. As the primary antibodies, the anti-rat renin antibody (diluted at 1:200)[49] and the recombinant anti-lamin A + lamin C antibody (ab133256 [Abcam]; diluted at 1:400) were used. Then sections were washed in PBS, blocked again, and incubated with Alexa Fluor 488–conjugated donkey anti-goat antibody (A11055 [Thermo Fisher Scientific]; diluted at 1:500) and Alexa Fluor 568–conjugated donkey anti-rabbit antibody (A10042 [Thermo Fisher Scientific]; diluted at 1:500) for 1 hour at room temperature. After washes in PBS, nuclei were stained with Hoechst 33342 (Thermo Fisher Scientific). Sections were mounted in ProLong Gold Antifade Mountant (Thermo Fisher Scientific).

The renin cells cultured on the cover glasses were washed and fixed in 4% PFA for 10 minutes. After washing in PBS, cells were permeabilized with 0.3% Triton X-100 for 5 minutes. After washing in PBS and blocking with 3% BSA, 5% donkey serum, 0.04 % cold fish skin gelatin, and 0.05 % Triton X-100 in PBS, cells were incubated with primary antibodies at room temperature for 90 minutes. After the washing, cells were incubated with Alexa Fluor 568–conjugated donkey anti-rabbit antibody (A10042 [Thermo Fisher Scientific]; diluted at 1:500) or Alexa Fluor 568–conjugated donkey anti-mouse antibody (A10037 [Thermo Fisher Scientific]; diluted at 1:500) for 1 hour at room temperature. After washes in PBS, nuclei were stained with Hoechst 33342 (Thermo Fisher Scientific). Cells were mounted in ProLong Gold Antifade Mountant (Thermo Fisher Scientific). As primary antibodies, the anti-α-SMA antibody (A2547 [Millipore-Sigma]; diluted at 1:10,000), the anti-lamin A + lamin C antibody (ab133256 [Abcam]; diluted at 1:400), the anti-lamin A/C

antibody (39288 [Active Motif, Carlsbad, CA]; diluted at 1:1,000), the anti-H3K4me1 antibody (710795 [Thermo Fisher Scientific]; diluted at 1:1,000), the anti-H3K4me2 antibody (ab7766 [Abcam]; diluted at 1:1,000), the anti-H3K4me3 antibody (39060 [Active Motif]; diluted at 1:1,000), the anti-H3K9me2 antibody (ab1220 [Abcam]; diluted at 1:1,000), the anti-H3K9me3 antibody (39162 [Active Motif]; diluted at 1:1,000), the anti-H3K27ac antibody (ab4729 [Abcam]; diluted at 1:2,000), and the anti-H3K27me3 antibody (9733 [Cell Signaling]; diluted at 1:1,600) were used. Staining for F-actin was performed using Acti-Stain 488 Phalloidin (PHDG1 [Cytoskeleton, Inc, Denver, CO]) before the nuclei staining.

We confirmed the specificity of the staining with the same procedures using secondary antibody-only controls, which failed to stain the tissue sections or cells. The anti-renin antibody was validated with the kidney sections from renin knockout mice[5].

CRISPR knockout of the *Lmna* gene

Lmna knockout in cultured renin cells (*LmnaKO*) was performed using CRISPR-Cas9 ribonucleoproteins (RNPs)[62] with Alt-R CRISPR-Cas9 system (Integrated DNA Technologies [IDT], Coralville, IA) and the Amaxa Nucleofector System (Lonza, Basel, Switzerland). We designed 2 guide RNAs (gRNAs) targeting exon 2 of the mouse *Lmna* gene: gRNA 1: 5’ – TTCTAGCAACACCAAGAAGG – 3’; gRNA 2: 5’–GCGAGCTCCATGACCTGCGG–3’ (Online Figure X). The Cas9 protein (Alt-R S.p. HiFi Cas9 Nuclease V3 [IDT]) and gRNA (IDT) were incubated at room temperature for 15 minutes to generate RNP. One million cells were resuspended in 100 µL of Nucleofector solution SE (SE Cell Line 4D-NucleofectorTM X Kit [Lonza]) containing 1 µmol/L of RNP 1 and 1µmol/L of RNP 2, and 1 µmol/L of Alt-R Cas9 Electroporation Enhancer (IDT). Cells were electroporated using the 4D-Nucleofector system (Lonza) under the program CM-130. As a control, the cells treated in the same way except for RNPs were used. After nucleofection, the cells were cultured in the growth medium, and after 7 days from nucleofection with one passage, cells were used for further experiments.

DNA extraction from cells and confirmation of the *LmnaKO*

The fractions remaining after RNA extraction with TRIzol reagent were subjected to DNA extraction. After the DNA was precipitated with 100% ethanol, the DNA pellet was washed with 0.1 mol/L sodium citrate/10% ethanol. The pellet was then rinsed with 75% ethanol. DNA pellets were dissolved in nuclease-free water. To detect the *Lmna* gene knockout, PCR was performed with the following primers: forward: 5’–GACTGGAGAAGTGAAGGTGAGC–3’, reverse: 5’–TCATGGAAGGGTAGAGAAGAA–3’. After the PCR, 1.5% agarose gel electrophoresis was performed. Then the PCR products from the control and cell pool of *LmnaKO* were purified and received Sanger sequencing using the PCR primers.

ATAC-seq in cultured renin cells

We performed ATAC-seq (Assay for Transposase-Accessible Chromatin using sequencing) with 2 replicates of control cells and 2 replicates of *LmnaKO* cells. Cells were harvested and frozen in culture media containing FBS and 5% DMSO. Cryopreserved cells were sent to Active Motif to perform the ATAC-seq assay. The cells were then thawed in a 37 ˚C water bath, pelleted, washed with cold PBS, and tagmented as

previously described[63], with some modifications[64]. Briefly, cell pellets were resuspended in lysis buffer, pelleted, and tagmented using the enzyme and buffer provided in the Nextera DNA Library Prep Kit (Illumina). Tagmented DNA was then purified using the MinElute PCR purification kit (Qiagen), amplified with 10 cycles of PCR, and purified using Agencourt AMPure SPRI beads (Beckman Coulter). The resulting material was quantified using the KAPA Library Quantification Kit for Illumina platforms (KAPA Biosystems, Wilmington, MA) and sequenced with paired-end 42-nt sequencing on the NextSeq 500 sequencer (Illumina).

ATAC-seq data analysis

Reads from ATAC-seq were aligned using the BWA algorithm (mem mode; default settings). Duplicate reads were removed, only reads mapping as matched pairs and only uniquely mapped reads (mapping quality >= 1) were used for further analysis. Alignments were extended in silico at their 3'-ends to a length of 200 bp and assigned to 32-nt bins along the genome. The resulting histograms (genomic "signal maps") were stored in bigWig files. Peaks were identified using the MACS 2.1.0 algorithm at a cutoff of *P*-value 1e-7, without control file, and with the –nomodel option. Peaks that were on the ENCODE blacklist of known false ChIP-Seq peaks were removed. For differential accessibility analysis, reads were counted in all merged peak regions, and the replicates for each condition were compared using DESeq2[50]. GO biological processes enrichment analysis was performed with GREAT[65] and Metascape[52] with the peaks with adjusted *P*-value less than 0.1 by the differential accessible analysis.

Microscopy

The images were visualized using a Zeiss Imager M2 microscope equipped with an ApoTome-2 fitted with the AxioCam 305 color and AxioCam 506 mono camera (Carl Zeiss Microscopy, Oberkochen, Germany).

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 8.4.3 (GraphPad Software, La Jolla, CA). The data were analyzed for normal distribution using the Shapiro-Wilk test. Data were considered normally distributed if the *P*-value was not less than 0.05. Normally distributed data are shown as means ± standard deviation. According to test requirements, Student's two-tailed t-test, paired t-test, one-way ANOVA with Tukey's multiple comparison test, or two-way ANOVA with Sidak's multiple comparison test was used. $P<0.05$ was considered significant.

The numbers of replicates and repeats of individual experiments and statistical tests used are shown in the figure legends.

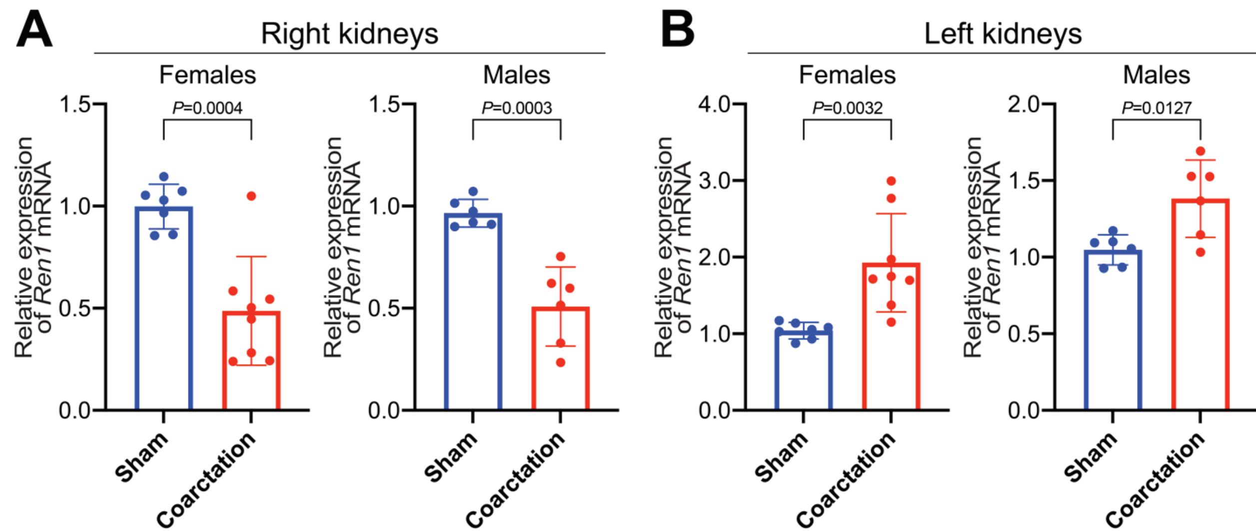
For *in vivo* experiments, sample sizes were determined based on the numbers required to achieve statistical significance.

Data availability

The RNA-seq and ATAC-seq data sets generated in this study can be accessed at the GEO public repository using the accession number GSE157699 and GSE167522, respectively.

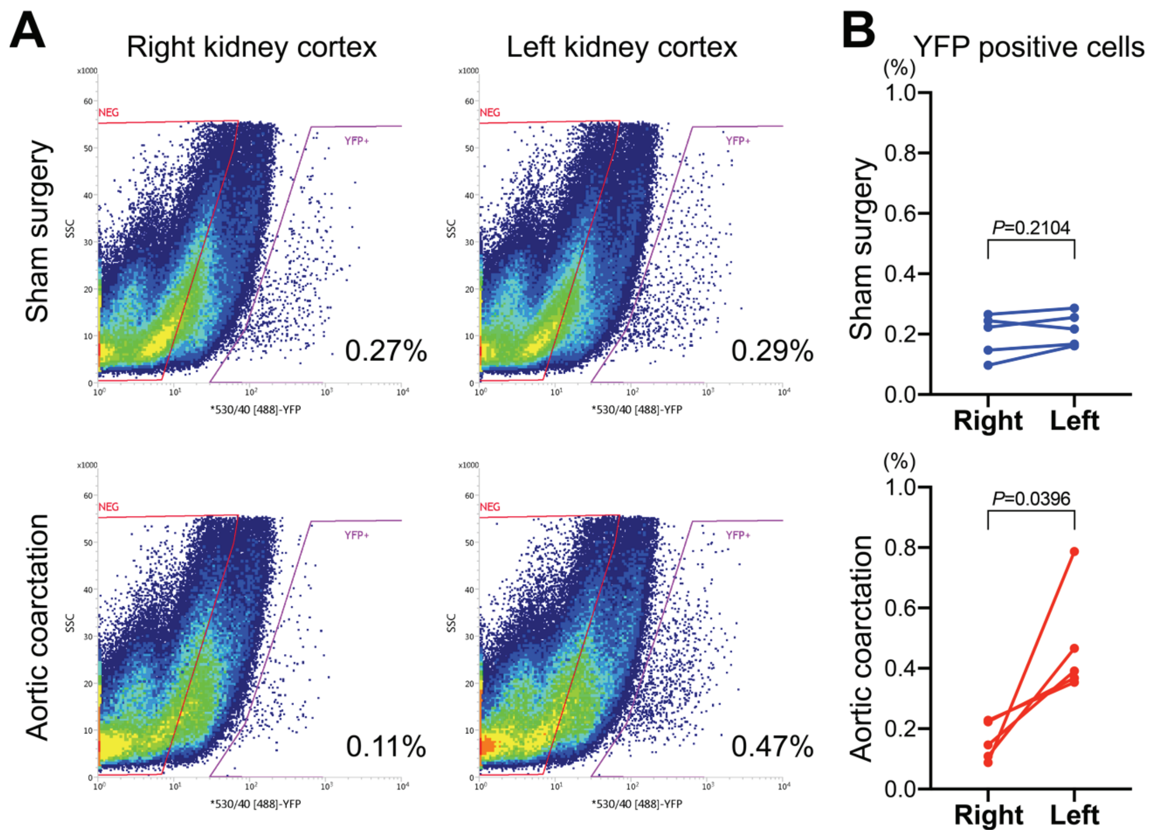
R codes are available on Zenodo at https://doi.org/10.5281/zenodo.4672146.
Additional information will be available upon request to the corresponding authors.

Online Figure I



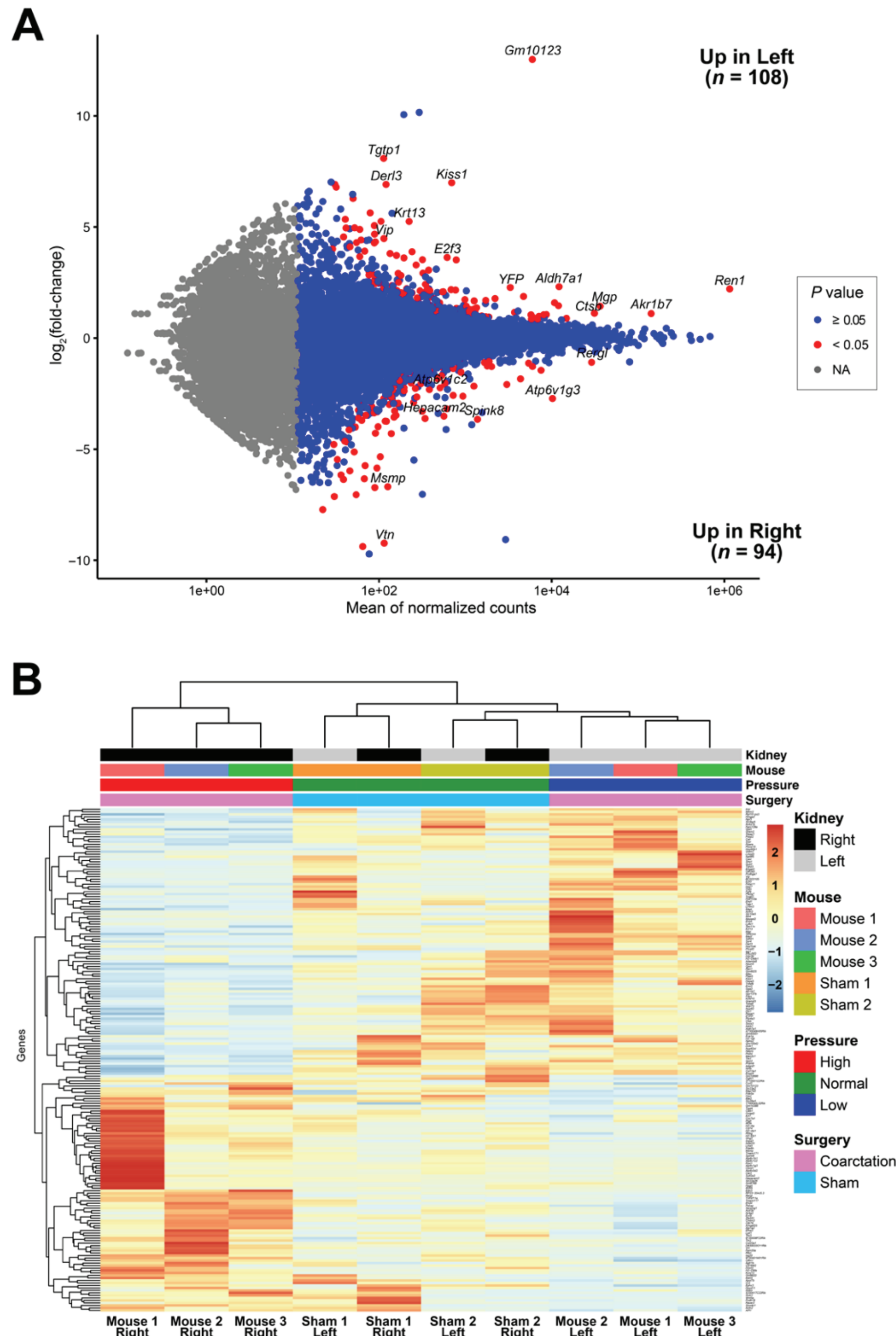
Online Figure I. Aortic coarctation induces changes in *Ren1* expression. A, Comparison of *Ren1* expression between right renal cortices subjected to sham surgeries and aortic coarctation (AoCo) by quantitative reverse transcription PCR (qRT-PCR). The expression of *Ren1* mRNA was significantly lower with AoCo in female ($n \geq 7$, Student's t-test) and male mice ($n=6$, Student's t-test). **B,** Comparison of *Ren1* expression between left renal cortices subjected to sham surgeries and AoCo by qRT-PCR. The expression of *Ren1* mRNA was significantly higher with AoCo in female ($n \geq 7$, Student's t-test) and male mice ($n=6$, Student's t-test). All data are reported as means ± standard deviation.

Online Figure II



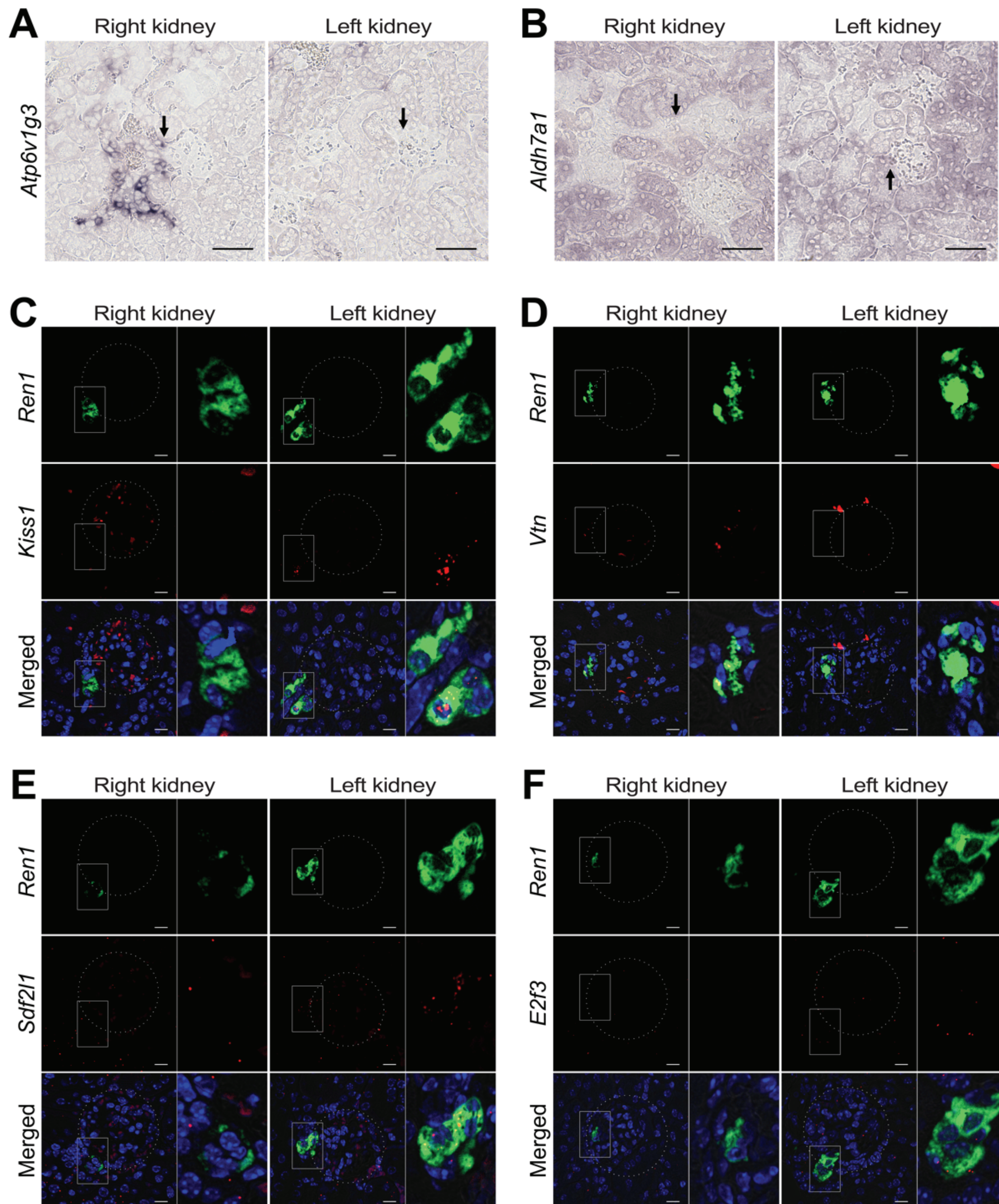
Online Figure II. Isolation of renin cells from kidneys subjected to aortic coarctation surgeries. A, Representative results of fluorescence-activated cell sorting using kidneys from *Ren1^{c}-YFP* mice. The graphs show the percentage of YFP-positive cells in all single cells in each kidney. **B,** Percentage of the YFP-positive cells detected by fluorescence-activated cell sorting. There was no difference in the percentage of YFP positive cells between the right and left kidneys subjected to the sham surgeries (*n*=5, paired t-test). With aortic coarctation, the percentage of YFP-positive cells in the left kidneys was significantly higher than in the right kidneys (*n*=5, paired t-test).

Online Figure III



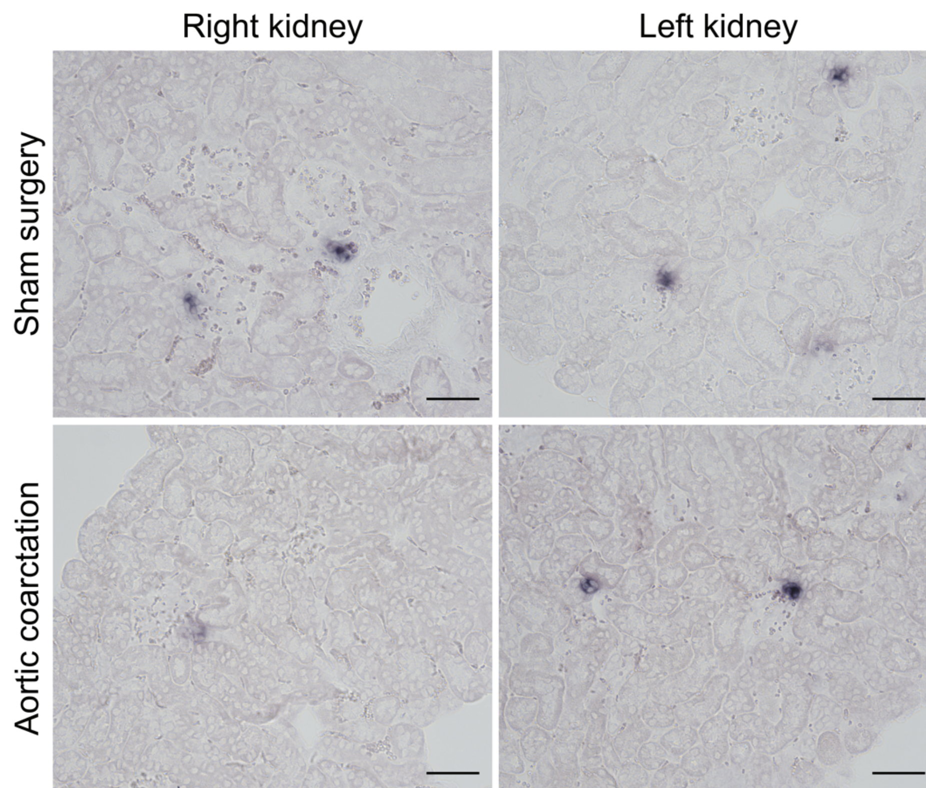
Online Figure III. RNA-seq analysis of renin cells with aortic coarctation. A, MA plot of RNA-seq analysis. The 202 differentially expressed genes (DEGs) between renin cells in the right kidneys and left kidneys were shown in red. Expression of the 94 genes and 108 genes were higher in the right and left kidneys, respectively. **B,** Heatmap using the expression levels of DEGs across all the samples, including renin cells from mice with sham surgeries. The transcripts per million values of the gene expression from the samples were used. The renin cells with high pressure (Mouse 1-3 Right), normal pressure (Sham 1-2 Right and Left), and low pressure (Mouse 1-3 Left) were clearly separated. The expression pattern in the sham group is in between the right kidneys (high pressure) and left kidneys (low pressure) from the AoCo group.

Online Figure IV



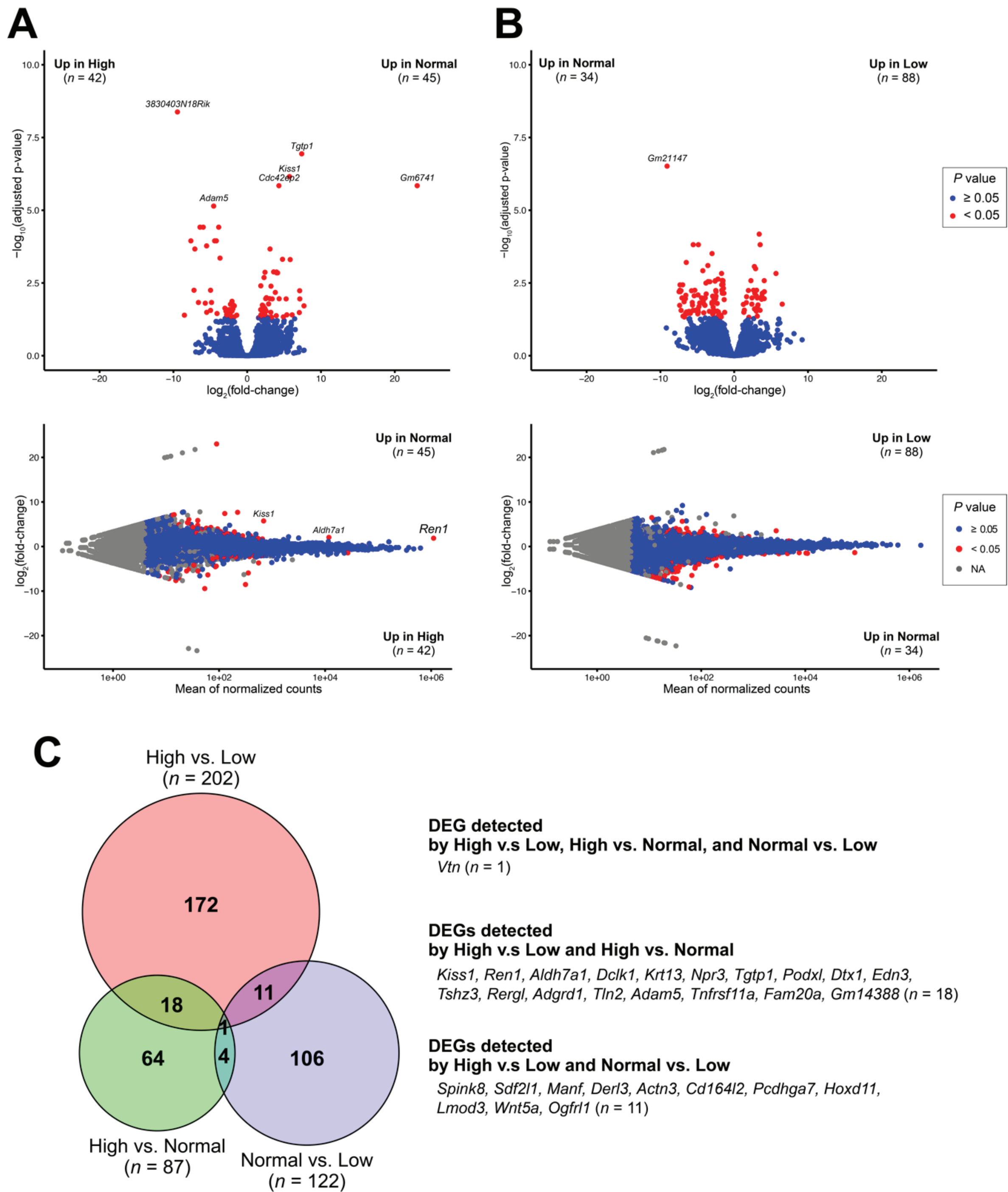
Online Figure IV. *In situ* hybridization for differentially expressed genes detected by RNA-seq on kidneys subjected to aortic coarctation. A, *Atp6v1g3* mRNA showed higher expression at the juxtaglomerular (JG) area (arrows) of the right kidneys than in the left ones. Scale bar, 50 µm. **B,** *Aldh7a1* mRNA showed higher expression in the JG area (arrows) of left kidneys than in the right ones. Scale bar, 50 µm. **C,** Fluorescence *in situ* hybridization (ISH) for *Ren1* mRNA (green), *Kiss1* mRNA (red), and DAPI (blue). *Kiss1* was expressed in the renin-expressing cells at a higher level in the left kidneys than the right kidneys. Scale bar,10 µm. **D,** Fluorescence ISH for *Ren1* mRNA (green), *Vtn* mRNA (red), and DAPI (blue). *Vtn* was expressed in the renin-expressing cells at a higher level in the right kidneys than the left kidneys. Scale bar, 10 µm. **E,** Fluorescence ISH for *Ren1* mRNA (green), *Sdf2l1* mRNA (red), and DAPI (blue). *Sdf2l1* was expressed in the renin-expressing cells at a higher level in the left kidneys than the right kidneys. Scale bar,10 µm. F**,** Fluorescence ISH for *Ren1* mRNA (green), *E2f3* mRNA (red), and DAPI (blue). *E2f3* was expressed in the renin-expressing cells at a higher level in the left kidneys than the right kidneys. Scale bar,10 µm. Dashed circles indicate glomeruli.

Online Figure V



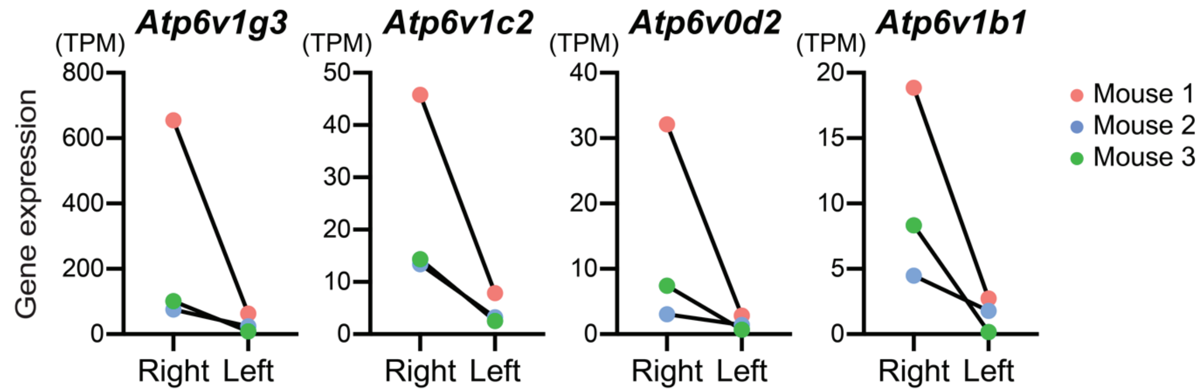
Online Figure V. *In situ* hybridization for *Akr1b7* mRNA in the kidneys subjected to the aortic coarctation. The intensity and extension of the signals at the juxtaglomerular areas were not different between the right and left kidneys from mice with sham surgery. With aortic coarctation, signals of *Akr1b7* mRNA in the right kidneys were decreased, and signals in left kidneys were significantly increased, compared to sham surgeries. Scale bar, 50 µm.

Online Figure VI



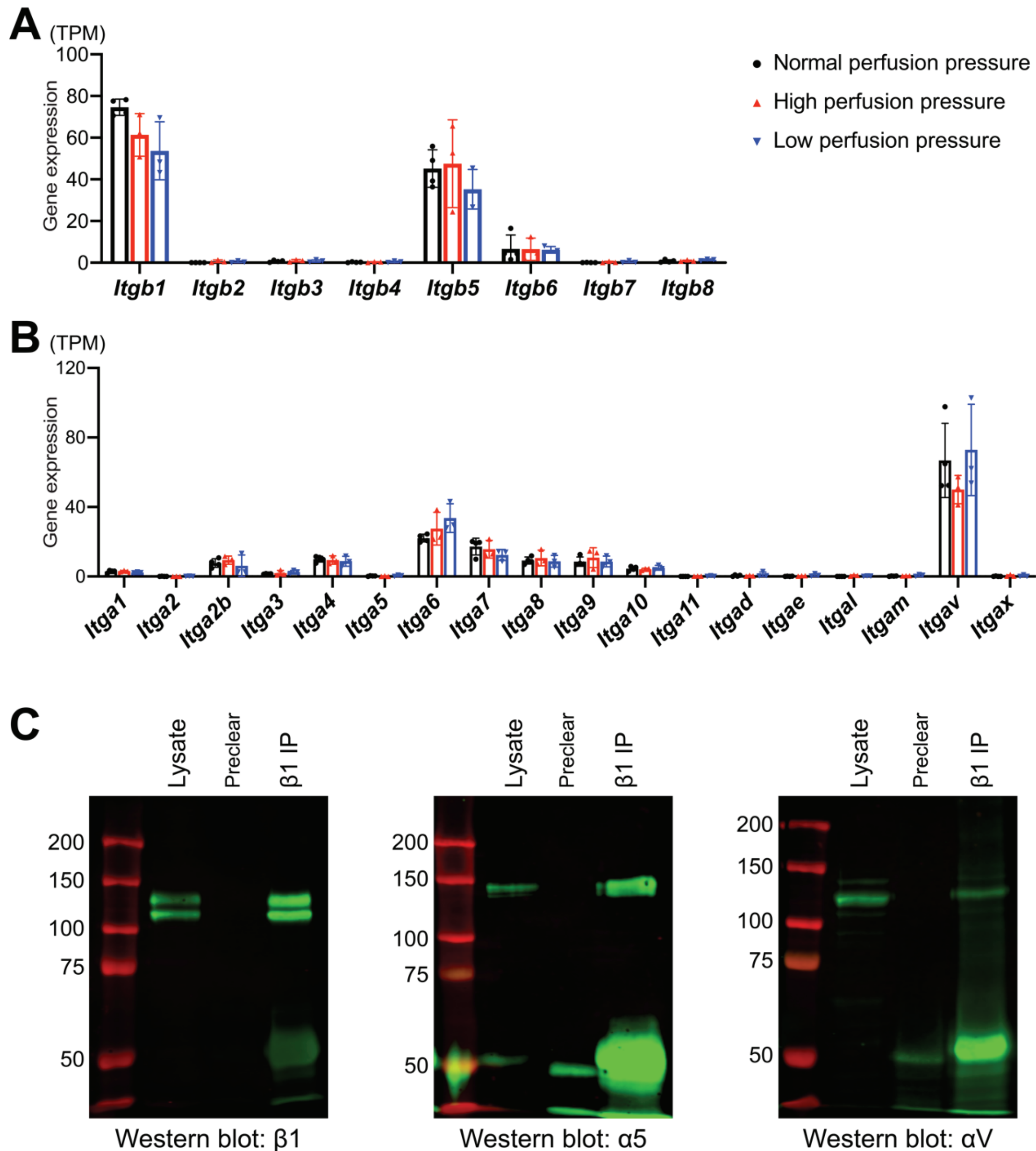
Online Figure VI. RNA-seq analysis of renin cells with different perfusion pressure. A, Volcano plot and MA plot of RNA-seq analysis of renin cells with high and normal perfusion pressure. The 87 differentially expressed genes (DEGs) were shown in red. **B,** Volcano plot and MA plot of RNA-seq analysis of renin cells with high and normal perfusion pressure. The 122 DEGs were shown in red. **C,** DEGs detected by each analysis of the RNA-seq data.

Online Figure VII



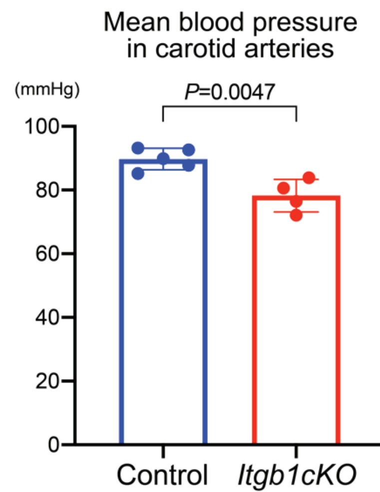
Online Figure VII. Expression of the vacuolar ATPase genes by RNA-seq in renin cells. Expression of the vacuolar ATPase genes that showed differential expression between the renin cells in the right and left kidneys from the mice with aortic coarctation. Data are shown in transcripts per million (TPM).

Online Figure VIII



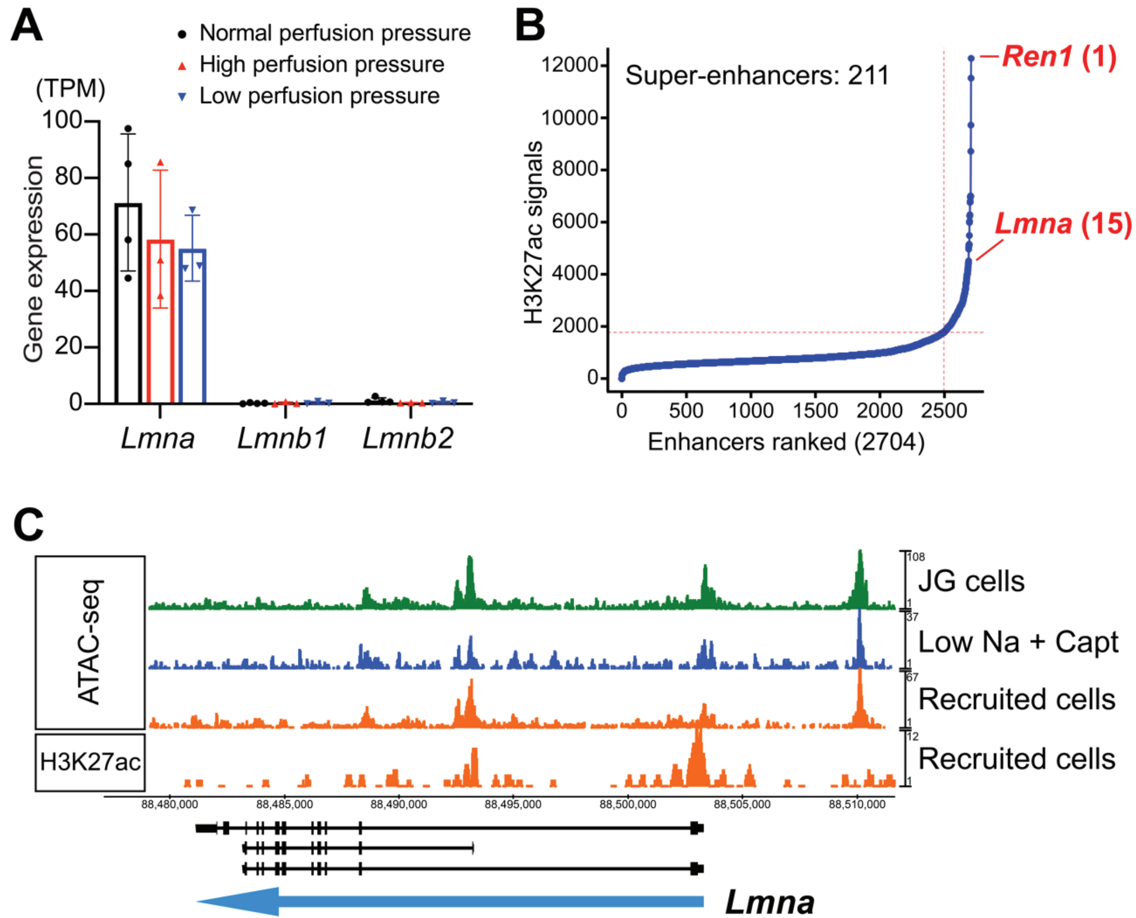
Online Figure VIII. The expression of integrins in renin cells. A, Expression of the β integrin family genes examined by the RNA-seq. *Itgb1* was the highest gene of the β integrin family genes in renin cells (*n*=10, *P*<0.0001, two-way ANOVA followed by Tukey's multiple comparison test). The expression of *Itgb1* was not different between renin cells with high and low perfusion pressure (*n*= 3, *P*=0.18, paired t-test). **B,** Expression of the α integrin family genes examined by the RNA-seq. *ItgaV* was the highest gene of the α integrin family genes in renin cells (*n*=10, *P*<0.0001, two-way ANOVA followed by Tukey's multiple comparison test). **C,** Western blot detection of β1 integrin heterodimers immunoprecipitated from cultured renin cells. β1 integrins were immunoprecipitated from renin cell lysates using an antiserum directed against a conserved peptide sequence in the cytoplasmic tail. Western blotting was used to detect the β1 subunit and the associated α subunits α5 and αV. Lysates were precleared with protein A prior to immunoprecipitation. The band detected at 50 kDa is IgG heavy chain. Data are shown in transcripts per million (TPM) as means ± standard deviation.

Online Figure IX



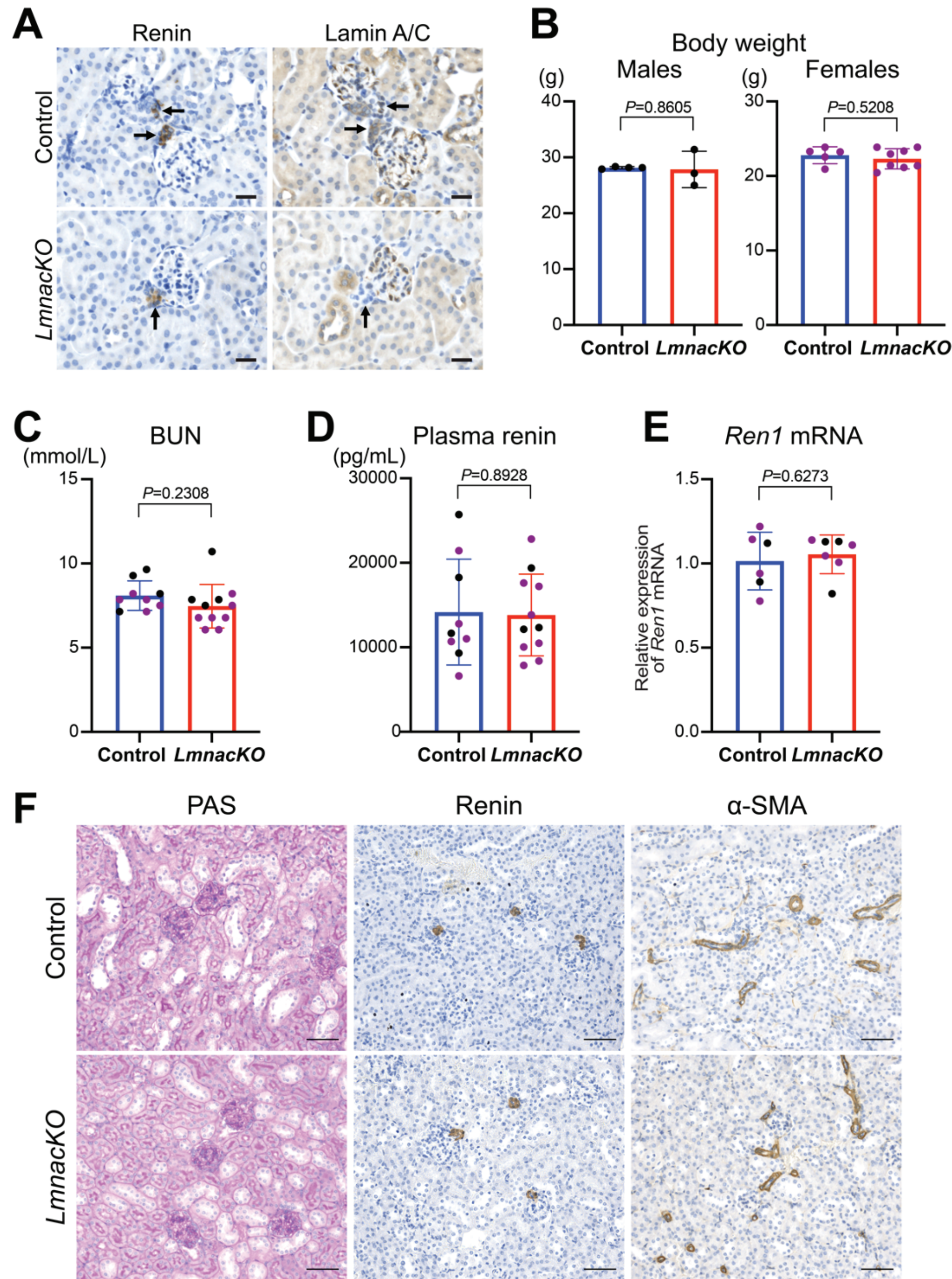
Online Figure IX. Blood pressure in mice with conditional deletion of *Itgb1* with aortic coarctation. Blood pressure (BP) measurement under anesthesia from the carotid arteries of control mice and mice with the *Itgb1* gene knockout in cells of the renin lineage (*Itgb1cKO*) three days after aortic coarctation. The BP in the *Itgb1cKO* (*n*=4) was significantly lower than the control mice (*n*=5, Student's t-test). Data are reported as means ± standard deviation.

Online Figure X



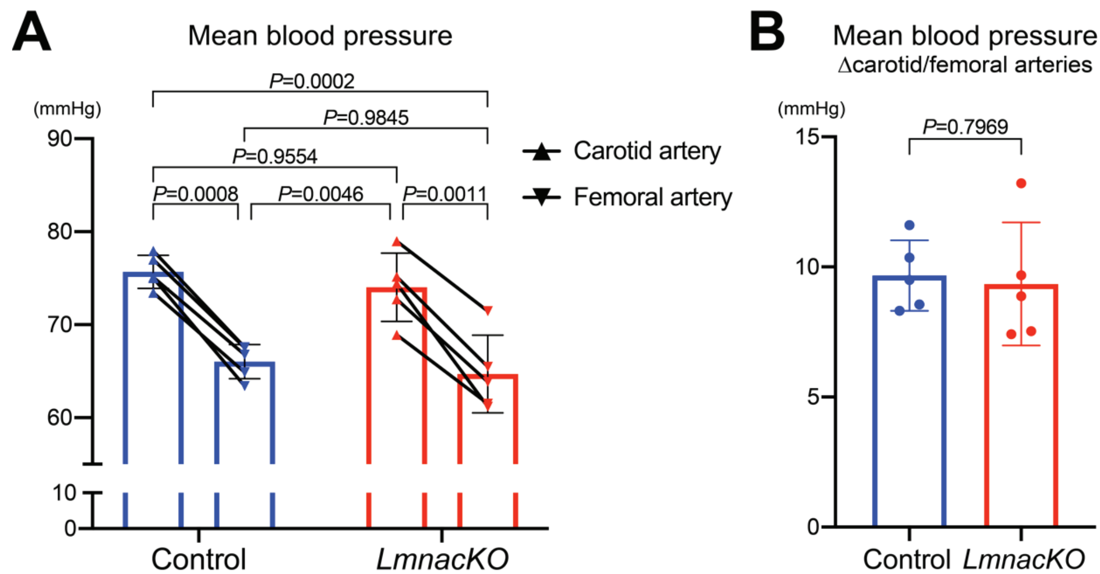
Online Figure X. The *Lmna* gene locus in renin cells is epigenetically active. A, Expression of the lamin protein family genes examined by the RNA-seq. *Lmna* was the highest gene in the renin cells (*n*=10, *P*<0.0001, two-way ANOVA followed by Tukey's multiple comparison test). The expression of *Lmna* was not different between renin cells with high and low perfusion pressure (*n*=3, *P*=0.85, paired t-test). Data are shown in transcripts per million (TPM) as means ± standard deviation. **B,** Renin cells have a super-enhancer at the *Lmna* gene locus. The previous report identified 211 super-enhancers out of 2,704 total enhancers, based on the signal strength for H3K27ac in the recruited native renin cells. The super-enhancer at the *Lmna* gene locus ranked in the fifteenth position for H3K27ac enrichment in renin cells. **C,** The *Lmna* gene locus in renin cells has open chromatin and H3K27ac. The ATAC-Seq (Assay for Transposase-Accessible Chromatin using sequencing) profile shows overlaps of the signals among the juxtaglomerular (JG) cells (green), acutely stimulated renin cells by a low sodium diet plus captopril for 7 days (Low Na + Capt, blue), and the chronically recruited renin cells (orange) at the *Lmna* gene locus. The signals of H3K27ac were observed at the open chromatin regions of the *Lmna* gene locus in the recruited renin cells (orange). Data were obtained from the previously published paper (Martinez MF *et al. J Clin Invest* 2018).

Online Figure XI



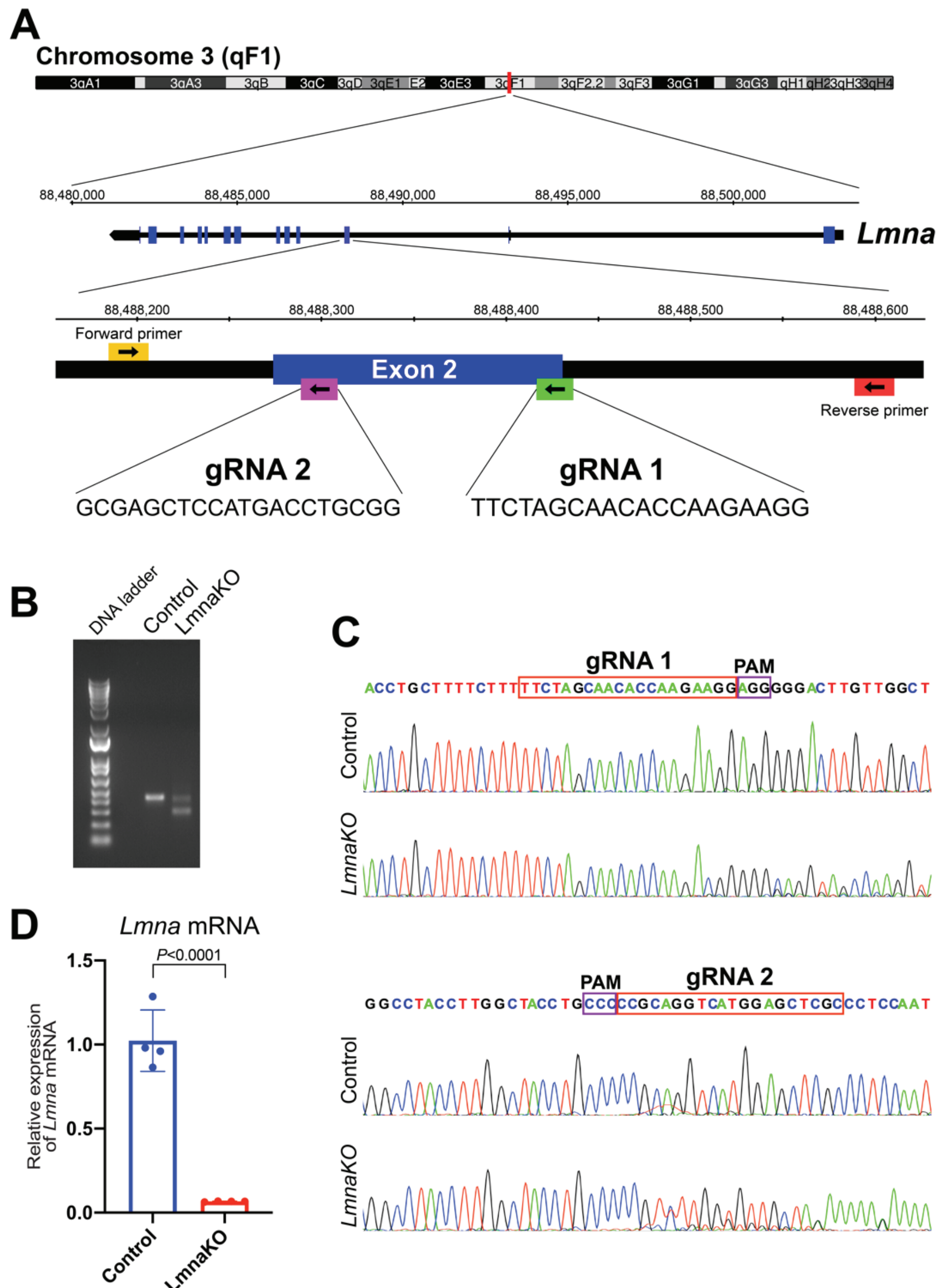
Online Figure XI. The *Lmna* gene knockout in cells of the renin lineage did not show any phenotypes without stimulation. A, Immunohistochemistry for renin and lamin A/C on the consecutive sections. Lamin A/C was detected in the renin-positive cells in control mice. However, mice with conditional deletion *of the Lmna* gene in cells of the renin lineage *(LmnacKO)* showed no signal of lamin A/C at the juxtaglomerular (JG) area and the renin-positive cells. Arrows indicate the cells at the JG area. Scale bar, 20 μm. **B,** There was no difference in the body weight between the *LmnacKO* and control in both male ($n \geq 3$) and female mice ($n \geq 4$) (Student's t-test). The blood urea nitrogen (BUN) ($n \geq 9$) (**C**), plasma renin concentration ($n \geq 9$) (**D**), and *Ren1* mRNA in the kidneys ($n \geq 6$) (**E**) from *LmnacKO* mice at normal states did not show any difference compared to the controls (Student's t-test). **F,** PAS staining and immunohistochemistry for renin and α-smooth muscle actin (α-SMA) did not show any abnormality of the kidneys from *LmnacKO* mice. Scale bar, 50 μm. All data are reported as means ± standard deviation. Black dots show male samples, and purple dots show female samples.

Online Figure XII



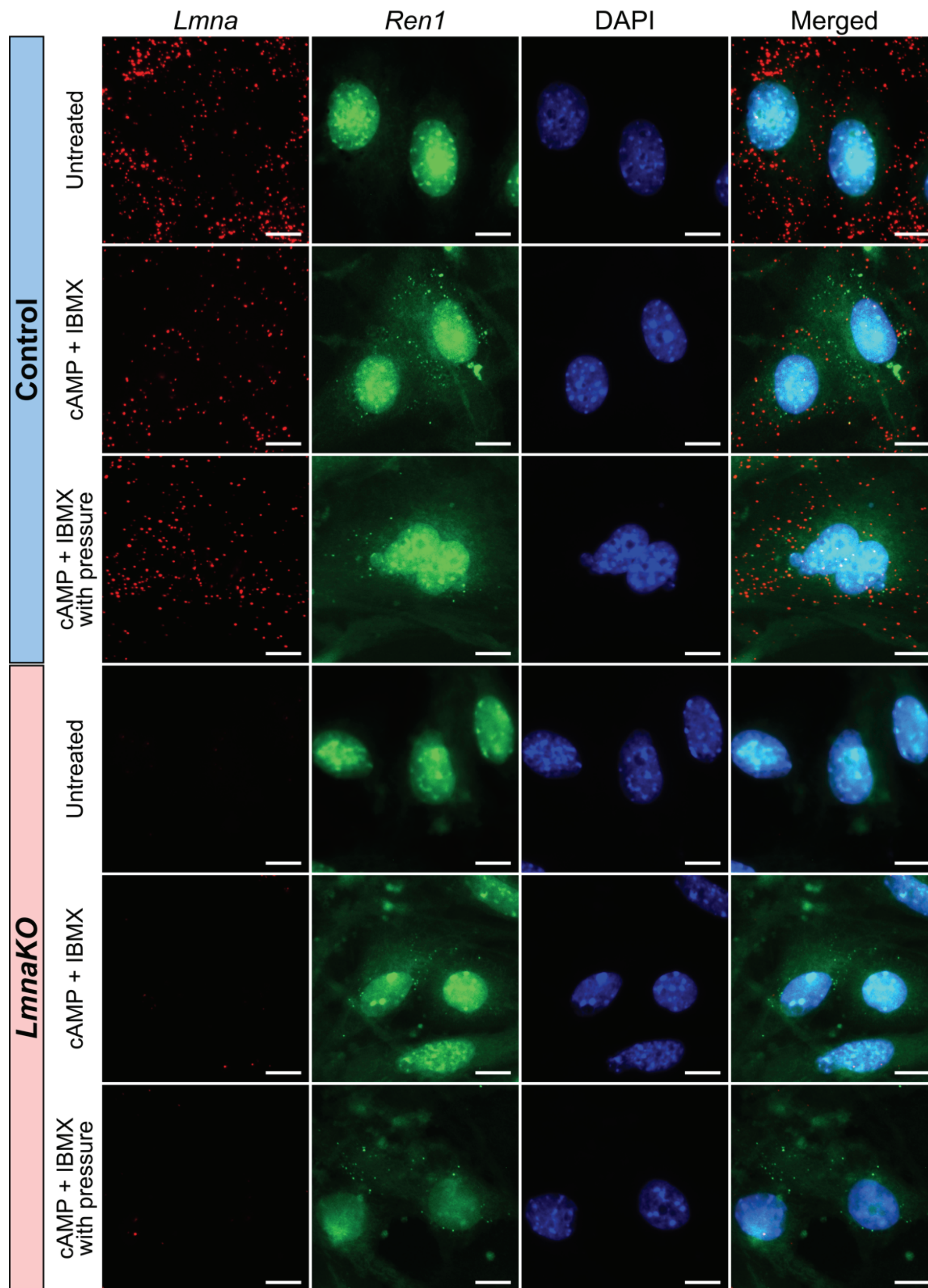
Online Figure XII. Blood pressure in the mice with conditional deletion of *Lmna* with aortic coarctation. A, Simultaneous blood pressure (BP) measurement under anesthesia from the carotid and femoral arteries of control mice and mice with the *Lmna* gene knockout in cells of the renin lineage (*LmnacKO*) three days after aortic coarctation. The BP was significantly different between carotid and femoral arteries in both groups, and there was no difference in carotid and femoral arteries between control and *LmnacKO* mice (n=5, two-way ANOVA followed by Sidak's multiple comparison test). **B,** There was no significant difference in the delta BP between carotid and femoral arteries between control and *LmnacKO* mice. Data are reported as means ± standard deviation.

Online Figure XIII



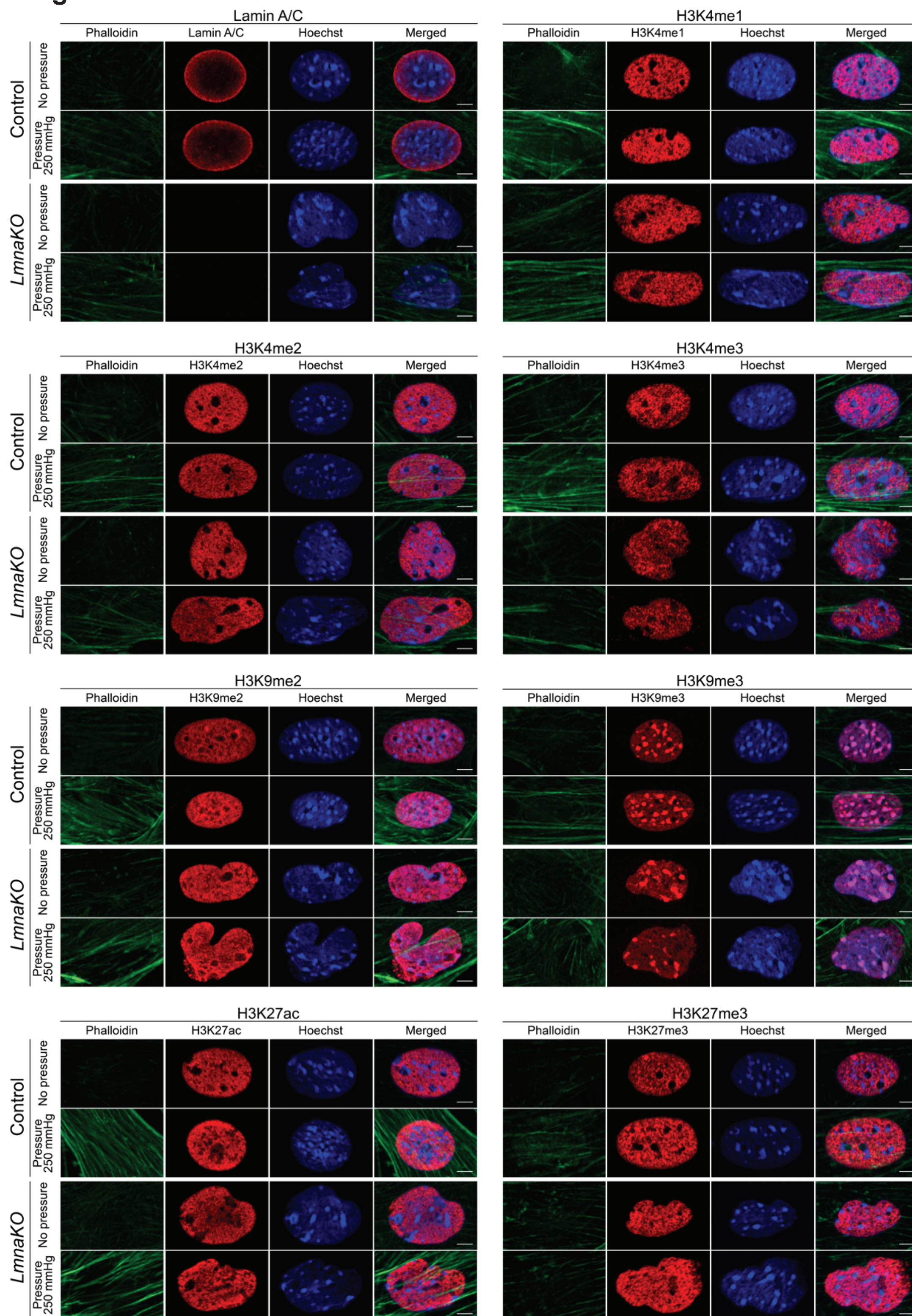
Online Figure XIII. *Lmna* gene knockout in cultured renin cells using CRISPR-Cas9. A, Schematic showing the guide RNA (gRNA) targeting sites on the exon 2 of the *Lmna* gene. Two gRNAs were designed for the knockout of the *Lmna* gene (*LmnaKO*) in the cultured renin cells. A primer pair (shown in yellow and red) was designed to confirm *LmnaKO*. **B,** Agarose gel electrophoresis of the PCR product using the genomic DNA from *LmnaKO* renin cells showed two DNA fragments. **C,** Analysis of CRISPR-mediated mutations by Sanger sequencing. The sequencing of PCR products showed the mutations of the genome at two expected sites. Target sites and PAM sequences were indicated in red and purple, respectively. **D,** Quantitative reverse transcription PCR showed a significant decrease in *Lmna* mRNA in *LmnaKO* renin cells (n=4, Student's t-test). The data are representative of three independent repetitions. Data are reported as means ± standard deviation.

Online Figure XIV



Online Figure XIV. Fluorescence *in situ* hybridization in renin cells with pneumatic pressure. Detailed pictures of the fluorescence *in situ* hybridization in the cultured renin cells for *Lmna* mRNA (red), *Ren1* mRNA (green), and DAPI (blue) that are shown in Figure 6E. The *Ren1* expression (shown as green dots) was induced by cAMP + IBMX, and it was lower in cells with the knockout of the *Lmna* gene (*LmnaKO*) compared to control cells. The control renin cells showed a decrease in the *Ren1* expression by the pneumatic pressure. The reduction of *Ren1* mRNA by pressure was not significant in *LmnaKO* renin cells. Scale bar, 10 μm.

Online Figure XV



Online Figure XV. Immunocytochemistry for lamin A/C and histone marks in renin cells with pneumatic pressure. Detailed pictures of the immunocytochemistry in the cultured renin cells with or without the knockout of the *Lmna* gene (*LmnaKO*) for lamin A/C or histone marks (red), F-actin stained by phalloidin (green), and Hoechst (blue) that are shown in Figure 7E. Scale bar, 5 μm.

Online Table I: Differentially expressed genes higher in renin cells from right kidneys (high perfusion pressure) when compared to left kidneys (low perfusion pressure).

	Symbol	log2FoldChange	Adjusted *P* value
1	*Spink8*	-3.655777562	2.75E-18
2	*Hepacam2*	-3.516497768	3.49E-15
3	*Vtn*	-9.231679908	3.07E-09
4	*Atp6v1g3*	-2.720025752	3.07E-09
5	*Ckmt1*	-2.162928088	3.42E-09
6	*Msmp*	-6.688954396	3.44E-08
7	*RP23-354J5.3*	-9.380145361	1.70E-07
8	*Atp6v1c2*	-2.239652583	2.35E-07
9	*Slc26a4*	-3.619705643	4.79E-07
10	*Tmem117*	-3.477407675	7.08E-07
11	*Pde6h*	-3.296269851	8.04E-05
12	*Rhbg*	-3.559604851	0.000111281
13	*Atp6v0d2*	-2.579210462	0.000114083
14	*Aif1l*	-2.072466009	0.000153427
15	*Impa2*	-3.277691617	0.000158182
16	*Serping1*	-1.277771223	0.000161697
17	*H2-Ab1*	-2.085919987	0.000308739
18	*Cd74*	-1.834143169	0.000309708
19	*Pakap*	-6.726551933	0.000389529
20	*Edn3*	-5.739677207	0.000389529
21	*H2-Eb1*	-3.184446978	0.000475672
22	*Actr3b*	-2.889283845	0.000497878
23	*Cox7a1*	-1.258616166	0.000544087
24	*Ifit3b*	-3.367347706	0.000718842
25	*Kcnj13*	-4.298711263	0.000763891
26	*Ociad2*	-2.014704201	0.000763891
27	*Olfr78*	-1.282383392	0.000950711
28	*Mal2*	-2.652637325	0.000986038
29	*Ephx3*	-1.541162241	0.001222119
30	*Rtkn*	-2.890554472	0.001242678
31	*Cd164l2*	-6.159945848	0.001515467
32	*Krt7*	-2.267921543	0.001732579
33	*H2-Aa*	-2.61625816	0.00181841
34	*Ptgfr*	-1.831006588	0.002259173
35	*Slco4c1*	-4.640747806	0.002266353
36	*Col22a1*	-2.986414509	0.002841412
37	*Isg20*	-4.002960736	0.003026037
38	*Evi5l*	-2.635458786	0.003026037
39	*Hoxd11*	-2.723034405	0.003083709
40	*Rergl*	-1.089999458	0.003311608
41	*Raver2*	-3.475298053	0.003757048
42	*Efna3*	-5.848818302	0.004100046
43	*Agtr1b*	-2.020399317	0.00452895
44	*Gng2*	-2.931401419	0.004757526
45	*Gvin1*	-7.71766638	0.006352035
46	*H2-DMa*	-1.850719721	0.006366551
47	*Tln2*	-1.371307572	0.006704756
48	*Atp1a2*	-1.098612176	0.006704756
49	*Ccrl2*	-1.689199937	0.00774981
50	*Adam5*	-3.317408781	0.007766964
51	*Pde5a*	-1.477813298	0.007766964
52	*Olfm1*	-1.949968503	0.007880538
53	*Calb1*	-1.44848998	0.008191234
54	*D630033O11Rik*	-2.104065787	0.008826704
55	*Wnt5a*	-3.599317287	0.009131606
56	*Msh5*	-3.07666371	0.009632883
57	*Aldoc*	-7.048406637	0.010236011
58	*Tnfrsf11a*	-1.916529819	0.010236011
59	*Ehd4*	-1.288707648	0.010812176
60	*Gm6768*	-6.332408252	0.012132627
61	*Atp6v1b1*	-2.995835748	0.012893353
62	*Fam20a*	-2.050356206	0.012893353
63	*Sult2a3*	-5.124294586	0.013432317
64	*Ifi205*	-5.341611653	0.013448529
65	*Slc23a2*	-2.317671051	0.016651831
66	*5330417C22Rik*	-4.670576392	0.017231883
67	*Nr4a2*	-1.043982892	0.01751799
68	*Tmem171*	-3.745289002	0.018915366
69	*Lipt1*	-4.282596716	0.021737433
70	*Map7d2*	-1.088224371	0.02230613
71	*3110001I22Rik*	-3.703598016	0.024157943
72	*Dmrt2*	-3.148972836	0.02495406
73	*Ogfrl1*	-2.345241269	0.025697066
74	*Gm14388*	-5.977520392	0.0258456
75	*Hpgd*	-3.738357261	0.028010795
76	*Gm9920*	-2.893861674	0.028945803
77	*Tox3*	-6.362976867	0.030571187
78	*9130401M01Rik*	-1.689900644	0.031377448
79	*9130008F23Rik*	-1.354604126	0.033850023
80	*Foxi1*	-2.233995129	0.034109297
81	*Zfp551*	-4.787241419	0.034360824
82	*Lilra5*	-5.464547368	0.036028882
83	*Pcdh18*	-1.324332368	0.036028882
84	*Actn2*	-2.128597553	0.036039751
85	*Car2*	-1.128248625	0.037089806
86	*Apol7b*	-3.243293894	0.037564044
87	*Gm10698*	-7.130095796	0.043434006
88	*Arhgef25*	-1.015976248	0.044438676
89	*Cmtm3*	-1.649911069	0.045049015
90	*Tigd4*	-2.377839584	0.047105662
91	*Cpvl*	-3.985379673	0.048317576
92	*Slc22a26*	-4.132216882	0.048450879
93	*Cr2*	-3.041563515	0.049398085
94	*1700040L02Rik*	-1.211444656	0.049410857

Online Table II: Differentially expressed genes higher in renin cells from left kidneys (low perfusion pressure) when compared to right kidneys (high perfusion pressure).

	Symbol	log2FoldChange	Adjusted *P* value
1	*Kiss1*	6.990194654	2.25E-22
2	*Ren1*	2.209732695	8.43E-16
3	*Sdf2l1*	3.521647933	2.63E-13
4	*Hmga2*	3.884926068	9.89E-12
5	*Manf*	1.874692498	1.90E-11
6	*Derl3*	6.912957376	9.67E-10
7	*Aldh7a1*	2.312898159	3.07E-09
8	*Vip*	4.483501124	1.21E-08
9	*Dclk1*	2.922082461	1.21E-08
10	*E2f3*	3.630148668	1.83E-08
11	*YFP*	2.277496744	7.68E-08
12	*Krt13*	5.248698385	1.54E-07
13	*Qpct*	2.177225977	2.66E-07
14	*Plpp5*	1.698040933	2.66E-07
15	*Npr3*	2.160520226	8.26E-07
16	*Olfr282*	5.252366383	2.33E-06
17	*B3gat2*	3.720662477	2.34E-06
18	*Nup62cl*	3.28998545	2.34E-06
19	*Hspa5*	1.590156729	2.81E-06
20	*Anks1b*	2.9111401	7.61E-06
21	*Eno3*	1.677019711	8.60E-06
22	*Grem2*	2.191144118	9.29E-06
23	*Fkbp11*	2.209454985	9.70E-06
24	*Tgtp1*	8.087029097	9.80E-06
25	*Ostn*	4.889278401	1.59E-05
26	*Fbxw15*	5.635138455	1.63E-05
27	*Ly6c1*	2.077935531	5.10E-05
28	*Ptp4a3*	1.457067136	9.83E-05
29	*Shq1*	2.817056756	0.000111281
30	*Podxl*	3.806337573	0.000118468
31	*Dtx1*	2.420173488	0.000177301
32	*Mpped2*	5.060111115	0.000279299
33	*Tshz3*	3.91253619	0.000521292
34	*Ehd1*	2.218990483	0.000556265
35	*Actn3*	4.414514528	0.000721845
36	*Sh3bp5*	1.305830906	0.000879097
37	*Calr*	1.15730428	0.000896126
38	*Enpp4*	2.036980347	0.001163445
39	*Mgp*	1.435567296	0.001222119
40	*Gys2*	4.332261232	0.001360893
41	*Pla2g7*	3.609789865	0.001454472
42	*Pcdhga7*	5.346440825	0.001585983
43	*Mapt*	1.780773572	0.00181841
44	*Ctsb*	1.116021714	0.002054859
45	*Gpr137b*	1.047296537	0.002094886
46	*Itih4*	3.52928298	0.002234647
47	*Akr1b7*	1.102454427	0.00225728
48	*Gramd3*	1.366122422	0.002266353
49	*Nphs2*	3.055843547	0.002531712
50	*Fkbp2*	1.058042658	0.002576125
51	*Casr*	4.296979438	0.004378285
52	*BC023105*	6.907445485	0.005461947
53	*Lmod3*	4.955494093	0.005461947
54	*Adgrd1*	2.365086423	0.005877673
55	*Sugp2*	1.953537076	0.005928739
56	*Lrrtm3*	2.085095412	0.007344721
57	*Ppara*	2.511053773	0.008667051
58	*Fgf9*	2.98624752	0.009206918
59	*Socs3*	1.219135572	0.009364965
60	*Rasal1*	1.437595766	0.009370483
61	*Pou5f2*	6.791414567	0.009705558
62	*Ssr4*	0.939042049	0.009946124
63	*Slc10a5*	2.507615746	0.010117144
64	*Tle2*	1.807296052	0.010236011
65	*Exo5*	2.632004926	0.01050771
66	*Gpn2*	2.839264456	0.011032739
67	*Fam129a*	1.277835805	0.011745102
68	*Nsun5*	2.036981236	0.011748699
69	*Adrb1*	1.79626057	0.011788575
70	*Ing1*	1.343927543	0.011788575
71	*Mlec*	1.234120284	0.011788575
72	*Gm15542*	6.283105526	0.011897189
73	*Rpl10-ps3*	1.04989562	0.012132627
74	*Hsp90b1*	0.889769927	0.012297999
75	*Man2c1*	1.770569224	0.014406989
76	*Plcxd2*	3.670664372	0.014810965
77	*Kctd10*	1.216485795	0.016588277
78	*Nepro*	2.439087838	0.017231883
79	*Gm10123*	12.53958935	0.018480955
80	*Steap1*	4.280458854	0.018480955
81	*Gga2*	1.093252516	0.018480955
82	*Ddx39*	1.178968408	0.02092255
83	*Nat8f5*	4.677227435	0.021836127
84	*Hist1h3e*	4.554206935	0.023963346
85	*Prdm6*	4.108455428	0.025469264
86	*Tuba8*	1.113451443	0.026762945
87	*Gm45551*	0.978635836	0.027327599
88	*Adamts8*	2.69031943	0.028010795
89	*H2-DMb1*	2.042419574	0.028010795
90	*Insr*	0.948515914	0.028010795
91	*Gstm7*	2.128715131	0.029541061
92	*Srpr*	0.961273248	0.030888747
93	*Nup62*	2.141206699	0.031131312
94	*Gja5*	1.278996942	0.032336164
95	*Hist1h4i*	4.9628794	0.033055088
96	*Mtmr2*	1.521825567	0.033809204
97	*Fdps*	0.995338524	0.033850023
98	*Dpp7*	1.584170957	0.034522281
99	*Sec11c*	0.858381545	0.034672587
100	*Wdr73*	1.208283905	0.036745266
101	*Selenos*	0.855575079	0.037384746
102	*Nmb*	2.139271001	0.044438676
103	*A730049H05Rik*	1.640184472	0.044438676
104	*Gm4925*	4.012017274	0.045049015
105	*Eva1a*	2.837610707	0.046258977
106	*H2-Q6*	2.259898396	0.046258977
107	*Tnfsf9*	1.732058278	0.049398085
108	*Col12a1*	1.487642229	0.049398085

Online Table III: Differentially expressed genes between renin cells exposed to high perfusion pressure and normal perfusion pressure.

Genes higher in renin cells with high perfusion pressure			
	Symbol	log2FoldChange	Adjusted *P* value
1	*3830403N18Rik*	-9.448134435	4.19E-09
2	*Slc7a12*	-8.510929529	0.040450903
3	*Gm42672*	-7.633638367	0.000113195
4	*Gm15206*	-7.212192495	0.005667963
5	*Gm15530*	-7.094174995	0.000214406
6	*Gm10273*	-6.607227588	0.014902441
7	*Gpbar1*	-6.38697549	3.81E-05
8	*Ccl6*	-5.955127058	3.81E-05
9	*Gm5979*	-5.67172777	0.015695506
10	*Tnmd*	-5.501900122	0.000168031
11	*Nxnl2*	-5.481738396	0.03241203
12	*Gm11962*	-4.972170916	0.027716391
13	*Cxcr6*	-4.966256366	0.005667963
14	*Gm14388*	-4.835503564	0.014902441
15	*Adam5*	-4.539981832	7.16E-06
16	*Trac*	-4.406893129	0.000113195
17	*Plek2*	-4.195726728	0.000113195
18	*Gm12504*	-4.096212734	0.03545743
19	*Edn3*	-3.850692221	3.81E-05
20	*Col3a1*	-3.681114496	0.00044166
21	*Gm17177*	-3.030235514	0.023382742
22	*Mettl4*	-2.888805864	0.029428744
23	*Zik1*	-2.789418082	0.039182282
24	*Kcns3*	-2.788245837	0.026363216
25	*Vtn*	-2.779809772	0.039928917
26	*Rad51ap1*	-2.582605084	0.032466898
27	*Dcdc2b*	-2.526228317	0.034301248
28	*Htr1b*	-2.481587087	0.032466898
29	*Zfp661*	-2.412838968	0.026363216
30	*Tigar*	-2.322370324	0.027716391
31	*Ifit3*	-2.276346101	0.017123859
32	*RP23-438P19.11*	-2.245840641	0.041976393
33	*Zfp874a*	-2.18562711	0.04415696
34	*Tnfrsf11a*	-2.059799095	0.013554138
35	*D230025D16Rik*	-2.055335471	0.029321434
36	*Fam20a*	-2.009193292	0.024824271
37	*Cep19*	-1.990524749	0.024824271
38	*Tln2*	-1.950492383	0.024824271
39	*Map9*	-1.881121191	0.018155232
40	*G2e3*	-1.766235379	0.046226691
41	*Abca5*	-1.752803576	0.019460737
42	*Rergl*	-1.425680166	0.040450903

Genes higher in renin cells with normal perfusion pressure			
	Symbol	log2FoldChange	Adjusted *P* value
1	*Gm6741*	23.0334358	1.44E-06
2	*Clic3*	7.691613842	0.019460737
3	*Tgtp1*	7.389451261	1.16E-07
4	*AC202135.1*	7.119954298	0.011140351
5	*4930556J24Rik*	7.106758317	0.005839742
6	*Gm13303*	7.049370527	0.032676503
7	*Magix*	6.07109784	0.039426916
8	*Krt19*	5.829697626	0.000497893
9	*Kiss1*	5.727172568	6.96E-07
10	*Gm28308*	5.372862974	0.039426916
11	*Ugt1a8*	5.281357711	0.011186463
12	*Spin4*	4.898207045	0.046662667
13	*Bbc3*	4.787584032	0.000489455
14	*Mmp2*	4.324123917	0.011071143
15	*Cdc42ep2*	4.299845491	1.44E-06
16	*Dusp15*	4.119777194	0.001421037
17	*Satb2*	4.011408719	0.001421037
18	*Ccdc81*	3.978238162	0.001330471
19	*Mrgprh*	3.941713251	0.042111678
20	*Adamtsl3*	3.817584023	0.006643223
21	*Adgrb2*	3.591233579	0.001320918
22	*Krt13*	3.388833172	0.011124821
23	*Podxl*	3.28858121	0.047492652
24	*Srgap1*	3.225049353	0.004109296
25	*Hyal3*	3.195172382	0.032466898
26	*Bcorl1*	3.092161861	0.000214644
27	*Tshz3*	3.056354616	0.010971843
28	*Ppp1r13b*	2.886032632	0.016563331
29	*Gpatch3*	2.773118352	0.047492652
30	*Ankrd27*	2.61276718	0.01016414
31	*Cntnap1*	2.557612958	0.029321434
32	*Rab42*	2.500815476	0.010971843
33	*Ccdc134*	2.457195604	0.026303353
34	*Dtx1*	2.420466245	0.001346516
35	*Dclk1*	2.387596767	0.023382742
36	*Fer1l5*	2.363596781	0.037133642
37	*Adgrd1*	2.27838194	0.00206425
38	*Mrc2*	2.166092112	0.027716391
39	*Akna*	2.146183562	0.019124771
40	*Pclo*	2.120774078	0.046662667
41	*Aldh7a1*	2.053967881	0.018155232
42	*Ren1*	1.860642696	0.039426916
43	*Pnpla6*	1.8410485	0.003972023
44	*Tenm4*	1.837967242	0.026363216
45	*Npr3*	1.701883651	0.048674316

Online Table IV: Differentially expressed genes between renin cells exposed to low perfusion pressure and normal perfusion pressure.

Genes higher in renin cells with normal perfusion pressure

	Symbol	log2FoldChange	Adjusted *P* value
1	*Gm21147*	-9.083409	3.05E-07
2	*Majin*	-7.478356	0.006321704
3	*Gm20708*	-7.389405	0.01871818
4	*Krt23*	-7.355237	0.005642718
5	*Msantd1*	-7.330993	0.003674176
6	*Dnajb3*	-7.297478	0.006321704
7	*Pcdhb6*	-7.207255	0.005859825
8	*Tmem52*	-7.195839	0.02772246
9	*Sbspon*	-7.088111	0.01032268
10	*Nodal*	-6.993279	0.003674176
11	*Gm13303*	-6.930182	0.0434434
12	*Gm29586*	-6.779997	0.01406489
13	*Pnliprp2*	-6.754256	0.04675797
14	*Gm14766*	-6.608354	0.01086641
15	*4930507D05Rik*	-6.590079394	0.035640389
16	*Vtn*	-6.560569	0.008440506
17	*Fhdc1*	-6.489657	0.000621793
18	*AA413626*	-6.457030709	0.031378758
19	*Mettl21c*	-6.355847	0.03583105
20	*Cnr1*	-6.121457334	0.029837276
21	*Cyp7a1*	-5.951595	0.03467663
22	*Cd164l2*	-5.789632499	0.005859825
23	*Gm17815*	-5.678888	0.01481287
24	*Fxyd6*	-5.659695	0.01840815
25	*Gm9785*	-5.583356	0.02772246
26	*Prtg*	-5.550147	0.000152894
27	*Gm15737*	-5.423891	0.008752487
28	*Itgax*	-5.341684	0.005605175
29	*Bcl6b*	-5.296580789	0.02786683
30	*Chil1*	-5.025984651	0.029837276
31	*Pm20d2*	-4.923396	0.03646896
32	*Pik3cg*	-4.900999	0.008169995
33	*Gm9573*	-4.894406	0.02474592
34	*Trp73*	-4.857358	0.03137876
35	*Arhgef38*	-4.853300217	0.000152894
36	*Ccdc64b*	-4.776312817	0.020513983
37	*St6galnac5*	-4.684536	0.01529165
38	*Elf3*	-4.429872	0.01032268
39	*Tmod2*	-4.260167	0.001200025
40	*Lct*	-4.192586	0.01275272
41	*Melk*	-4.125101	0.03346586
42	*Padi2*	-4.081116	0.01684036
43	*Clcf1*	-4.040149022	0.010322682
44	*Wnt5a*	-3.971742	0.01863315
45	*Cpa2*	-3.931687	0.01032268
46	*Tnn*	-3.817644	0.003164407
47	*Hyal3*	-3.798105	0.007547861
48	*Serpinb8*	-3.568984	0.000803116
49	*Spn*	-3.536936	0.002852158
50	*Selplg*	-3.3729	0.02983728
51	*Gpatch3*	-3.310255	0.00287011
52	*Knstrn*	-3.024607	0.01492315
53	*Ephb2*	-3.010992	0.0163581
54	*Csrnp3*	-2.997179	0.000306594
55	*Cd38*	-2.919792361	0.029911231
56	*Hoxd11*	-2.912331	0.008984049
57	*Galnt15*	-2.903366	0.03740696
58	*Mctp2*	-2.850866	0.02145237
59	*Mpst*	-2.781458	0.01463569
60	*Slc35g2*	-2.752349	0.0108818
61	*Caln1*	-2.744771927	0.027722462
62	*Usp49*	-2.590604	0.002738249
63	*Tspan18*	-2.570687	0.00263612
64	*Ogfrl1*	-2.536861	0.02983728
65	*Exo1*	-2.520634	0.01097133
66	*Urb1*	-2.50516	0.005724045
67	*Kit*	-2.463634	0.008984049
68	*Neb*	-2.458965	0.006321704
69	*Usp42*	-2.308038	0.0159651
70	*Mfsd4a*	-2.29612	0.02952566
71	*Cbl*	-2.203442755	0.002332324
72	*Exoc3l4*	-2.191536	0.04389447
73	*Spink8*	-2.149669	0.03137876
74	*Olfr1167*	-2.075358	0.04541952
75	*Sass6*	-1.815663	0.04060771
76	*Sipa1l3*	-1.752922	0.04665706
77	*Gm10715*	-1.717369	0.001484198
78	*Gm10720*	-1.701779	0.003674176
79	*Gm17535*	-1.685645	0.005642718
80	*Gm10801*	-1.630071	0.002599085
81	*Gm21738*	-1.602018	0.007135205
82	*Gm11168*	-1.561444	0.002963444
83	*Gm10719*	-1.516287	0.00263612
84	*Gm10717*	-1.51042	0.003589522
85	*Gm10718*	-1.458523	0.004804036
86	*Gm10721*	-1.397257	0.007135205
87	*Gm10800*	-1.367633	0.01185884
88	*Gm10722*	-1.303218	0.032094

Genes higher in renin cells with low perfusion pressure

	Symbol	log2FoldChange	Adjusted *P* value
1	*Vmn1r3*	6.507975	0.01693951
2	*Olfr33*	5.655881	0.001484198
3	*Dusp27*	4.082679	0.006321704
4	*Derl3*	4.078048	0.01097133
5	*Gm527*	4.068382	0.00263612
6	*Polh*	3.817434	0.007135205
7	*Lmod3*	3.732097	0.008984049
8	*Gm13212*	3.706813	0.0114841
9	*Ogn*	3.516016	0.000152894
10	*Per2*	3.498772	0.02745776
11	*Ccdc146*	3.379771543	6.66E-05
12	*Actn3*	3.22381419	0.017875454
13	*Frzb*	3.146664	0.02441585
14	*Gm13689*	3.144816	0.02142878
15	*Neu2*	3.12083	0.04379041
16	*Pcdhga7*	3.118613	0.01032268
17	*Gimap4*	3.030153	0.005643789
18	*Cyp4a14*	2.995132	0.02952566
19	*Tspan33*	2.98502	0.008801357
20	*Cdh11*	2.890250413	0.001020709
21	*Ccl2*	2.797275958	0.007218691
22	*Kif22*	2.752518	0.02474592
23	*Sgcg*	2.741186	0.000855751
24	*Pcdhb17*	2.624157	0.005642718
25	*Abca5*	2.403302292	0.010322682
26	*Nuak2*	2.392145	0.01689004
27	*Hbb-bt*	2.260945	0.00263612
28	*Cyp4a31*	1.988463	0.04773108
29	*Sdf2l1*	1.920853	0.005724045
30	*Pgm3*	1.682577	0.009467839
31	*Casp12*	1.644154425	0.014957068
32	*Col4a3*	1.383124	0.02708684
33	*Glt28d2*	1.302152	0.032094
34	*Manf*	1.24091	0.01717914

Online Table V: Differentially accessible regions between *LmnaKO* cells and control cells.

Peaks higher in control cells					
	Chromosome	Start	End	log2FoldChange	Adjusted *P* value
1	17	29,824,862	29,825,423	-0.76	9.86E-03
2	8	71,476,213	71,477,006	-0.73	0.027385963
3	9	61,778,460	61,779,233	-0.71	0.035325116
4	5	113,098,604	113,099,404	-0.7	1.74879E-05
5	9	63,516,862	63,517,298	-0.66	0.07695201
6	19	45,548,139	45,548,821	-0.64	0.052581961
7	17	13,305,841	13,306,363	-0.64	7.70E-02
8	8	70,713,192	70,713,764	-0.63	1.64E-02
9	9	98,633,771	98,634,235	-0.63	0.07695201
10	12	71,546,791	71,547,258	-0.62	0.083045181
11	9	21,417,758	21,418,252	-0.61	0.083045181
12	13	32,707,810	32,708,350	-0.61	0.09300862
13	16	13,405,259	13,405,877	-0.59	0.013142066
14	6	49,641,235	49,641,727	-0.59	0.022292243
15	12	17,338,322	17,338,916	-0.59	8.30E-02
16	10	18,076,885	18,077,521	-0.58	0.016280042
17	14	25,231,834	25,232,299	-0.58	0.077296967
18	15	36,489,694	36,490,186	-0.57	0.022573453
19	7	19,010,560	19,011,083	-0.57	9.00E-02
20	11	74,862,037	74,862,605	-0.55	0.054549386
21	16	93,220,386	93,220,952	-0.55	0.09300862
22	1	64,790,753	64,791,149	-0.55	0.095296027
23	10	60,571,173	60,571,658	-0.54	0.099442895
24	4	119,118,617	119,119,112	-0.53	0.083045181
25	11	96,863,623	96,864,048	-0.53	0.089958343
26	4	149,550,841	149,551,341	-0.52	0.056088199
27	8	25,159,984	25,160,488	-0.52	0.089958343
28	2	166,356,010	166,356,460	-0.52	0.09300862
29	15	103,145,533	103,146,139	-0.51	0.089958343
30	8	124,181,934	124,182,710	-0.5	0.039007166
31	19	58,288,097	58,288,880	-0.5	0.044216699
32	7	49,907,925	49,908,559	-0.5	0.044216699
33	11	76,911,214	76,911,780	-0.48	0.053744509
34	15	78,960,049	78,960,510	-0.48	0.089958343
35	5	136,094,185	136,095,370	-0.47	0.034437147
36	10	61,374,775	61,375,486	-0.47	0.035116307
37	13	46,955,663	46,956,173	-0.47	0.083045181
38	8	122,147,632	122,148,043	-0.45	0.097818098
39	13	55,483,136	55,483,840	-0.44	0.043855716
40	5	139,794,859	139,795,376	-0.44	0.055147552
41	6	53,337,232	53,338,199	-0.44	0.089958343
42	12	84,190,087	84,190,663	-0.43	0.089958343
43	6	100,218,390	100,218,971	-0.43	0.095296027
44	15	82,932,824	82,933,375	-0.43	0.099066001
45	8	126,881,661	126,882,220	-0.42	0.059776768
46	15	66,968,315	66,969,229	-0.41	0.039073688
47	8	12,662,335	12,663,343	-0.41	0.07695201
48	8	126,685,440	126,685,914	-0.41	0.09300862
49	15	77,928,617	77,929,359	-0.4	0.043855716
50	2	71,542,524	71,543,382	-0.4	0.09300862
51	11	102,465,553	102,466,489	-0.39	0.083045181
52	17	27,131,134	27,131,902	-0.39	0.083045181
53	7	25,707,471	25,708,156	-0.39	0.094376407
54	11	84,179,199	84,180,550	-0.39	0.095296027
55	11	87,591,644	87,592,462	-0.38	0.033528785
56	8	84,125,483	84,126,207	-0.38	0.052581961
57	8	95,012,333	95,013,133	-0.34	0.051069513
58	15	38,384,195	38,385,174	-0.34	0.09300862
59	7	80,715,162	80,715,960	-0.33	0.083045181
60	8	121,901,776	121,902,387	-0.33	0.089507749
61	12	70,890,797	70,891,953	-0.31	0.09300862
62	8	34,224,912	34,225,732	-0.3	0.083865994

Peaks higher in *LmnaKO* cells					
	Chromosome	Start	End	log2FoldChange	Adjusted *P* value
1	1	20,653,707	20,654,559	0.73	1.31E-02
2	10	126,601,123	126,601,845	0.71	0.016280042
3	16	85,792,774	85,793,747	0.7	0.035325116
4	2	89,920,832	89,921,502	0.7	0.040943305
5	2	39,295,436	39,295,993	0.7	0.044216699
6	12	67,993,427	67,993,894	0.69	0.052581961
7	2	9,481,604	9,482,444	0.67	1.31E-02
8	11	86,580,218	86,580,953	0.66	2.29E-05
9	9	57,292,003	57,292,745	0.66	0.077296967
10	15	98,178,997	98,179,724	0.65	0.005626793
11	6	65,606,820	65,607,393	0.64	0.023490291
12	12	35,283,857	35,284,383	0.64	0.083045181
13	19	12,005,862	12,006,234	0.63	0.071453278
14	7	106,236,236	106,237,353	0.62	1.75E-05
15	18	3,382,759	3,383,674	0.62	0.059776768
16	11	50,376,967	50,378,214	0.61	0.010491646
17	19	18,811,286	18,811,970	0.61	0.026868459
18	1	168,598,085	168,598,898	0.61	7.73E-02
19	1	90,973,199	90,973,682	0.6	0.078008742
20	11	68,092,027	68,092,745	0.6	0.083045181
21	5	106,964,131	106,964,958	0.6	0.092140195
22	4	71,968,695	71,969,605	0.59	0.077296967
23	19	16,558,359	16,559,008	0.59	0.09300862
24	11	94,954,272	94,954,910	0.59	0.094376407
25	1	125,516,606	125,517,406	0.58	0.023490291
26	1	166,002,466	166,003,603	0.58	0.052581961
27	9	6,430,442	6,431,255	0.58	0.055147552
28	10	34,071,004	34,071,895	0.58	0.09300862
29	2	106,991,215	106,991,873	0.57	0.089507749
30	19	5,802,422	5,802,788	0.57	0.099349557
31	19	5,839,457	5,840,105	0.56	0.01364034
32	19	5,840,525	5,840,924	0.56	0.027385963
33	15	42,369,491	42,370,425	0.56	0.046733889
34	18	78,577,216	78,577,912	0.56	0.052581961
35	13	108,402,882	108,403,612	0.56	0.077296967
36	6	43,247,337	43,247,888	0.56	0.092374022
37	4	139,310,453	139,311,210	0.56	0.09300862
38	5	75,416,576	75,417,309	0.55	0.039073688
39	12	35,220,085	35,220,774	0.55	0.071453278
40	2	9,791,877	9,792,606	0.55	0.083045181
41	1	69,507,631	69,508,806	0.55	0.09300862
42	10	102,622,524	102,623,336	0.54	0.017596836
43	15	53,001,676	53,002,317	0.54	0.085290122
44	17	42,301,202	42,301,900	0.54	0.089958343
45	4	47,504,780	47,505,571	0.53	0.083045181
46	19	5,793,795	5,795,610	0.52	4.94256E-08
47	9	95,511,616	95,512,382	0.52	0.095296027
48	17	63,677,914	63,678,768	0.51	0.023490291
49	2	148,371,894	148,372,595	0.5	0.089958343
50	X	17,026,096	17,026,784	0.49	0.09300862
51	11	69,124,078	69,124,745	0.48	0.083045181
52	11	48,856,186	48,857,127	0.46	0.035325116
53	8	92,008,703	92,009,756	0.45	0.043374471
54	9	41,950,314	41,951,874	0.45	0.044216699
55	10	17,722,684	17,723,697	0.45	0.049444416
56	9	65,201,118	65,201,936	0.45	0.051520138
57	13	23,570,989	23,571,574	0.45	0.059776768
58	11	86,581,165	86,581,779	0.45	0.071453278
59	1	72,226,135	72,227,337	0.44	0.040943305
60	2	13,583,422	13,584,195	0.42	0.07695201
61	10	71,198,675	71,199,517	0.42	0.083045181
62	13	6,192,997	6,194,062	0.42	0.083045181
63	11	120,343,256	120,344,730	0.41	0.035325116
64	11	86,581,988	86,583,000	0.39	0.059776768
65	14	55,014,745	55,015,733	0.38	0.099349557
66	1	72,243,675	72,245,047	0.37	0.07695201
67	19	12,011,343	12,012,625	0.37	0.07695201
68	1	171,501,604	171,503,988	0.33	0.044216699

Online Table VI: Primers for quantitative reverse transcription PCR.

Gene	Forward sequence (5' to 3')	Reverse sequence (5' to 3')
Ren1	ACAGTATCCCAACAGGAGAGACAAG	GCACCCAGGACCCAGACA
Lmna	TGGAGATCGATAACGGGAAG	ATTATCCAGCTTGGCGGAGT
Rps14	CAGGACCAAGACCCCTGGA	ATCTTCATCCCAGAGCGAGC

Online Table VII: Primers to generate probes for *in situ* hybridization.

Gene	Primer	Sequence (5' to 3')
Ren1	T3 (Forward)	AATTAACCCTCACTAAAGGGACAGCTCTTAGAAAGCCTTG
	T7 (Reverse)	TAATACGACTCACTATAGGGAAAGGTCTGTGTCACAGTGA
Akr1b7	T3 (Forward)	AATTAACCCTCACTAAAGGGTGACCAACCAGATTGAGAGC
	T7 (Reverse)	TAATACGACTCACTATAGGGCAGTATTCCTCGTGGAAAGGAT
Atp6v1g3	T3 (Forward)	AATTAACCCTCACTAAAGGGCAGTCTCAGGGGATCCAACAG
	T7 (Reverse)	TAATACGACTCACTATAGGGTGGACTTCTGGTTTCATGTCG
Aldh7a1	T3 (Forward)	AATTAACCCTCACTAAAGGGCCAACTACTGGGAAGACTGGTG
	T7 (Reverse)	TAATACGACTCACTATAGGGCAGTGAAGGACAGCAGGTTCA

References

47. Watanabe H, Paxton RL, Tolerico MR, et al. Expression of Acsm2, a kidney-specific gene, parallels the function and maturation of proximal tubular cells. *Am J Physiol Renal Physiol.* 2020;319:F603-F611.

48. Martinez MF, Martini AG, Sequeira-Lopez MLS, Gomez RA. Ctcf is required for renin expression and maintenance of the structural integrity of the kidney. *Clin Sci (Lond).* 2020;134:1763-1774.

49. Guessoum O, Zainab M, Sequeira-Lopez MLS, Gomez RA. Proliferation does not contribute to murine models of renin cell recruitment. *Acta Physiol (Oxf).* 2020; 2020:e13532.

50. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biol.* 2014;15:550.

51. Ashburner M, Ball CA, Blake JA, et al. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. *Nat Genet.* 2000;25:25-29.

52. Zhou Y, Zhou B, Pache L, Chang M, Khodabakhshi AH, Tanaseichuk O, Benner C, Chanda SK. Metascape provides a biologist-oriented resource for the analysis of systems-level datasets. *Nat Commun.* 2019;10:1523.

53. Kucera M, Isserlin R, Arkhangorodsky A, Bader GD. AutoAnnotate: A Cytoscape app for summarizing networks with semantic annotations. *F1000Res.* 2016;5:1717.

54. Nagamatsu G, Shimamoto S, Hamazaki N, Nishimura Y, Hayashi K. Mechanical stress accompanied with nuclear rotation is involved in the dormant state of mouse oocytes. *Sci Adv.* 2019;5:eaav9960.

55. Guilluy C, Swaminathan V, Garcia-Mata R, O'Brien ET, Superfine R, Burridge K. The Rho GEFs LARG and GEF-H1 regulate the mechanical response to force on integrins. *Nat Cell Biol.* 2011;13:722-727.

56. Fujiwara S, Ohashi K, Mashiko T, Kondo H, Mizuno K. Interplay between Solo and keratin filaments is crucial for mechanical force-induced stress fiber reinforcement. *Mol Biol Cell.* 2016;27:954-966.

57. Marcantonio EE, Hynes RO. Antibodies to the conserved cytoplasmic domain of the integrin beta 1 subunit react with proteins in vertebrates, invertebrates, and fungi. *J Cell Biol.* 1988;106:1765-1772.

58. Joos TO, Whittaker CA, Meng F, DeSimone DW, Gnau V, Hausen P. Integrin alpha 5 during early development of Xenopus laevis. *Mech Dev.* 1995;50:1871-99.

59. Gomez RA, Pentz ES, Jin X, Cordaillat M, Sequeira Lopez ML. CBP and p300 are essential for renin cell identity and morphological integrity of the kidney. *Am J Physiol Heart Circ Physiol.* 2009;296:H1255-62.

60. Sequeira-Lopez ML, Lin EE, Li M, Hu Y, Sigmund CD, Gomez RA. The earliest metanephric arteriolar progenitors and their role in kidney vascular development. *Am J Physiol Regul Integr Comp Physiol.* 2015;308:R138-49.

61. Lin EE, Sequeira-Lopez ML, Gomez RA. RBP-J in FOXD1+ renal stromal progenitors is crucial for the proper development and assembly of the kidney vasculature and glomerular mesangial cells. *Am J Physiol Renal Physiol.* 2014;306:F249-F258.

62. Zuris JA, Thompson DB, Shu Y, et al. Cationic lipid-mediated delivery of proteins enables efficient protein-based genome editing in vitro and in vivo. *Nat Biotechnol.* 2015;33:73-80.

63. Buenrostro JD, Giresi PG, Zaba LC, Chang HY, Greenleaf WJ. Transposition of native chromatin for fast and sensitive epigenomic profiling of open chromatin, DNA-binding proteins and nucleosome position. *Nat Methods.* 2013;10:1213-1218.

64. Corces MR, Trevino AE, Hamilton EG, et al. An improved ATAC-seq protocol reduces background and enables interrogation of frozen tissues. *Nat Methods.* 2017;14:959-962.

65. McLean CY, Bristor D, Hiller M, Clarke SL, Schaar BT, Lowe CB, Wenger AM, Bejerano G. GREAT improves functional interpretation of cis-regulatory regions. *Nat Biotechnol.* 2010;28:495-501.