Supplemental Table 1: Gene up-regulated in remnant kidneys of the lesion-prone FVB/N mice as compared to the resistant B6D2F1 animals 2 months after 75% nephron reduction.

Gene Symbol	Gene Name	FC	FDR	Accession number
Lcn2	lipocalin 2	9.95	0.008	NM_008491
Hmgb3	high-mobility group box 3	3.94	0.034	NM_008253
Fgb	fibrinogen beta chain	3.38	0.021	NM_181849
Csf1	colony stimulating factor 1 (macrophage)	3.29	0.037	NM_007778
Kras	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	2.79	0.013	NM_021284
Pea15a	phosphoprotein enriched in astrocytes 15	2.66	0.040	NM_011063
myc	myelocytomatosis oncogene	2.65	0.013	NM_010849
Col4a1	collagen, type IV, alpha 1	2.59	0.015	NM_009931
Cp	ceruloplasmin (ferroxidase)	2.46	0.020	NM_001042611
Socs2	suppressor of cytokine signaling 2	2.42	0.037	NM_007706
Fn1	fibronectin 1	2.39	0.034	NM_010233
Clock	clock homolog (mouse)	2.32	0.011	NM_007715
Ucp2	uncoupling protein 2 (mitochondrial, proton carrier)	2.31	0.048	NM_011671
Col1a1	collagen, type I, alpha 1	2.31	0.013	NM_007742
Col15a1	collagen, type XV, alpha 1	2.29	0.013	NM_009928
Ly6e	lymphocyte antigen 6 complex, locus E	2.26	0.040	NM_008529
Flna	filamin A, alpha (actin binding protein 280)	2.24	0.021	NM_010227
Col1a2	collagen, type I, alpha 2	2.16	0.021	NM_007743
Serping1	serpin peptidase inhibitor, clade G (C1 inhibitor), member 1	2.10	0.016	NM_009776
Sirpa	signal-regulatory protein alpha	2.07	0.041	NM_007547
Col4a2	collagen, type IV, alpha 2	2.04	0.034	NM_009932
H2-K1	histocompatibility 2, K1, K region	2.03	0.023	NM_001001892
F3	coagulation factor III (thromboplastin, tissue factor)	1.97	0.000	NM_010171
Clu	clusterin	1.95	0.037	NM_013492
3930401B19Rik	RIKEN cDNA 3930401B19 gene	1.93	0.044	
Plau	plasminogen activator, urokinase	1.89	0.041	NM_008873
Ywhah	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein	1.88	0.024	NM_011738
Tmsb10	thymosin beta 10	1.86	0.032	NM_001039392
Cstb	cystatin B (stefin B)	1.80	0.041	NM_007793
Tgif1	TGFB-induced factor homeobox 1	1.76	0.011	NM_009372
Amd1	adenosylmethionine decarboxylase 1	1.73	0.029	NM_009665
Gale	UDP-galactose-4-epimerase	1.73	0.011	NM_178389
Flnc	filamin C, gamma (actin binding protein 280)	1.70	0.033	NM_001081185
Gnb1	guanine nucleotide binding protein (G protein), beta polypeptide 1	1.70	0.029	NM_008142
Hn1	hematological and neurological expressed 1	1.65	0.013	NM_008258
Tsc22d3	TSC22 domain family, member 3	1.63	0.048	NM_001077364
Mcl1	myeloid cell leukemia sequence 1 (BCL2-related)	1.59	0.048	NM_008562
Map3k1	mitogen-activated protein kinase kinase kinase 1	1.56	0.021	NM_011945
Eif6	eukaryotic translation initiation factor 6	1.56	0.044	NM_010579
Irf1	interferon regulatory factor 1	1.55	0.012	NM_008390
Mad2l1	MAD2 mitotic arrest deficient-like 1 (yeast)	1.53	0.048	NM_019499
Hmgn2	high-mobility group nucleosomal binding domain 2	1.51	0.032	NM_016957
Tuba1a	tubulin, alpha 1a	1.51	0.015	NM_011653
Hsp90b1	heat shock protein 90kDa beta (Grp94), member 1	1.51	0.014	NM_011631

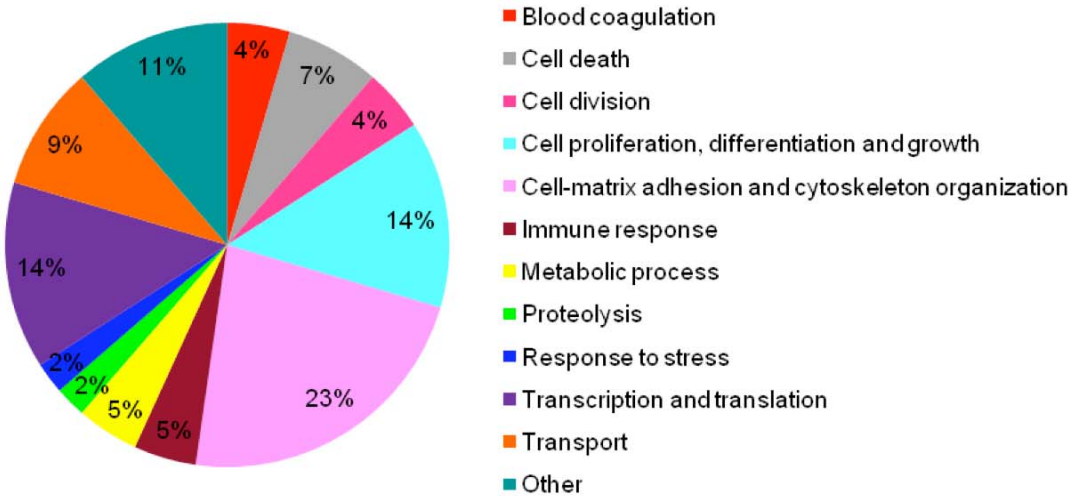
Genes with more than 1.5-fold change (FC) and a false-discovery rate (FDR) < 0.05 (using the Benjamini-Hochberg procedure) were considered significant.

Supplemental Table 2: Genes down-regulated in remnant kidneys of the lesion-prone FVB/N mice as compared to the resistant B6D2F1 animals 2 months after 75% nephron reduction.

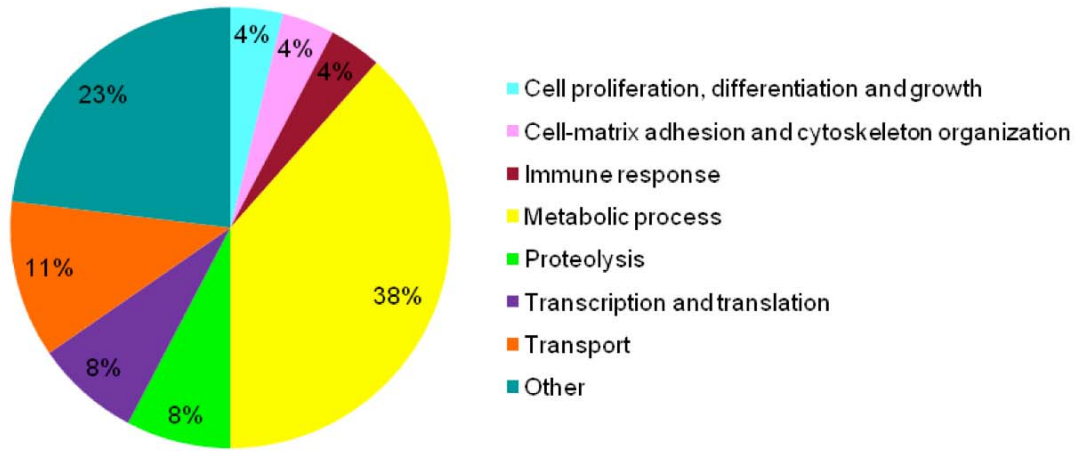
Gene Symbol	Gene Name	FC	FDR	Accession number
Ttr	transthyretin	-12.78	0.016	NM_013697
Inmt	indolethylamine N-methyltransferase	-8.03	0.035	NM_009349
Selenbp1	selenium binding protein 1	-5.92	0.016	NM_009150
Fgf6	fibroblast growth factor 6	-5.50	0.011	NM_010204
MyoD1	myogenic differentiation 1	-4.47	0.011	NM_010866
St3gal6	ST3 beta-galactoside alpha-2,3-sialyltransferase 6	-3.42	0.004	NM_018784
Pgam2	phosphoglycerate mutase 2	-3.28	0.030	NM_018870
Metapl1	methionine aminopeptidase 1D	-2.75	0.009	NM_025633
Klk1	kallikrein 1	-2.56	0.020	NM_010639
Ass1	argininosuccinate synthetase 1	-2.46	0.015	NM_007494
H2-Eb1	histocompatibility 2, class II antigen E beta	-2.38	0.015	NM_010382
Enpp2	ectonucleotide pyrophosphatase/phosphodiesterase 2	-2.37	0.021	NM_015744
Bcat2	branched chain aminotransferase 2, mitochondrial	-2.12	0.017	NM_009737
Slc2a4	solute carrier family 2 (facilitated glucose transporter), member 4	-2.12	0.039	NM_009204
Des	desmin	-2.09	0.017	NM_010043
Cyp2a4	cytochrome P450, family 2, subfamily A, polypeptide 13	-1.92	0.015	NM_009997
Folh1	folate hydrolase (prostate-specific membrane antigen) 1	-1.88	0.013	NM_016770
Tctex1	dynein, light chain, Tctex-type 1	-1.79	0.036	NM_009342
Tcea3	transcription elongation factor A (SII), 3	-1.75	0.010	NM_011542
Rgs5	regulator of G-protein signaling 5	-1.65	0.030	NM_009063
Nudt19	nudix (nucleoside diphosphate linked moiety X)-type motif 19	-1.61	0.023	NM_033080
Ephb2	EPH receptor B2	-1.59	0.044	NM_010142
Gstt1	glutathione S-transferase theta 1	-1.58	0.029	NM_008185
Rdh7	retinol dehydrogenase 7	-1.53	0.035	NM_017473
Angptl3	angiopoietin-like 3	-1.52	0.033	NM_013913
Mthfd1	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1, methenyltetrahydrofolate cyclohydrolase, formyltetrahydrofolate synthetase	-1.51	0.014	NM_138745

Genes with more than 1.5-fold change (FC) and a false-discovery rate (FDR) < 0.05 (using the Benjamini-Hochberg procedure) were considered significant.

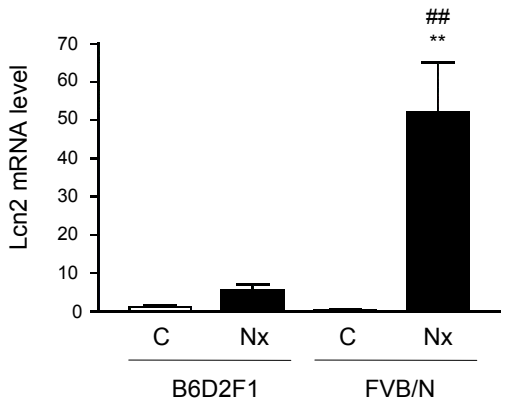
A



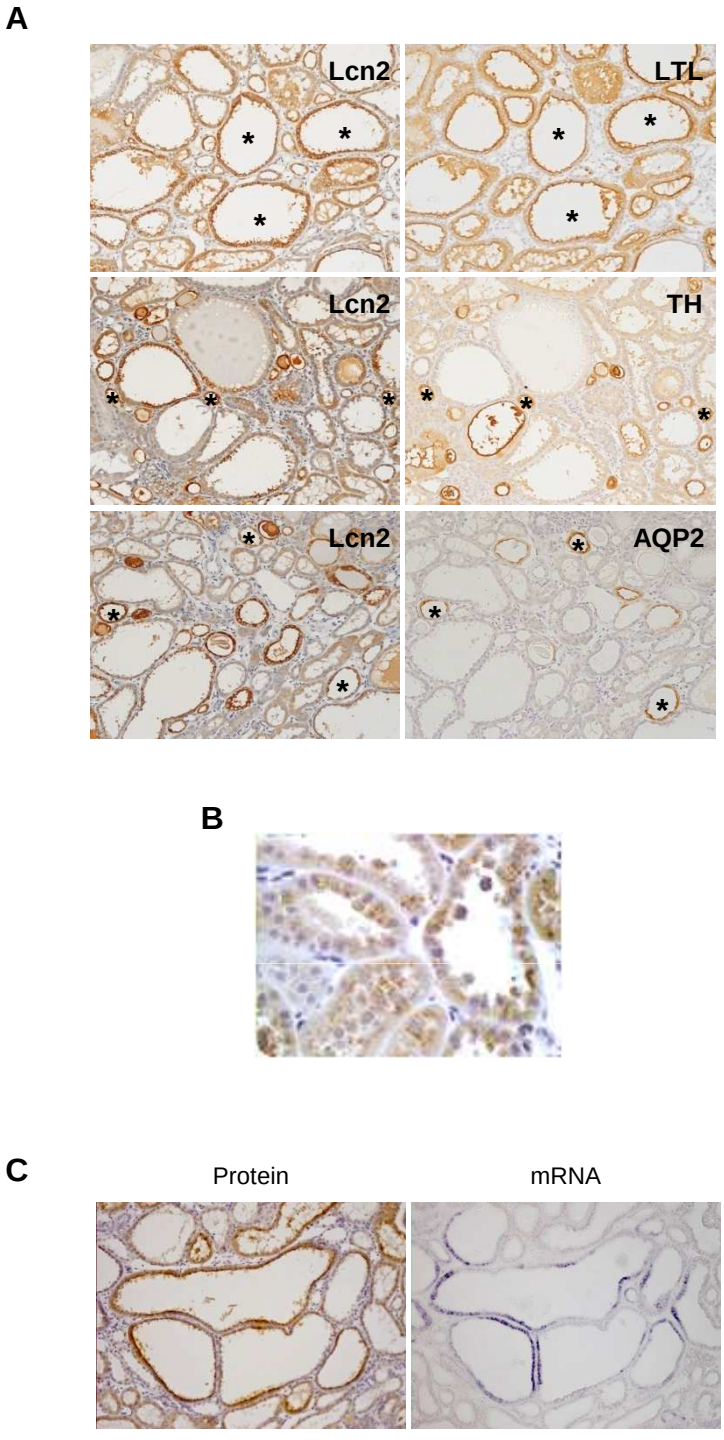
B



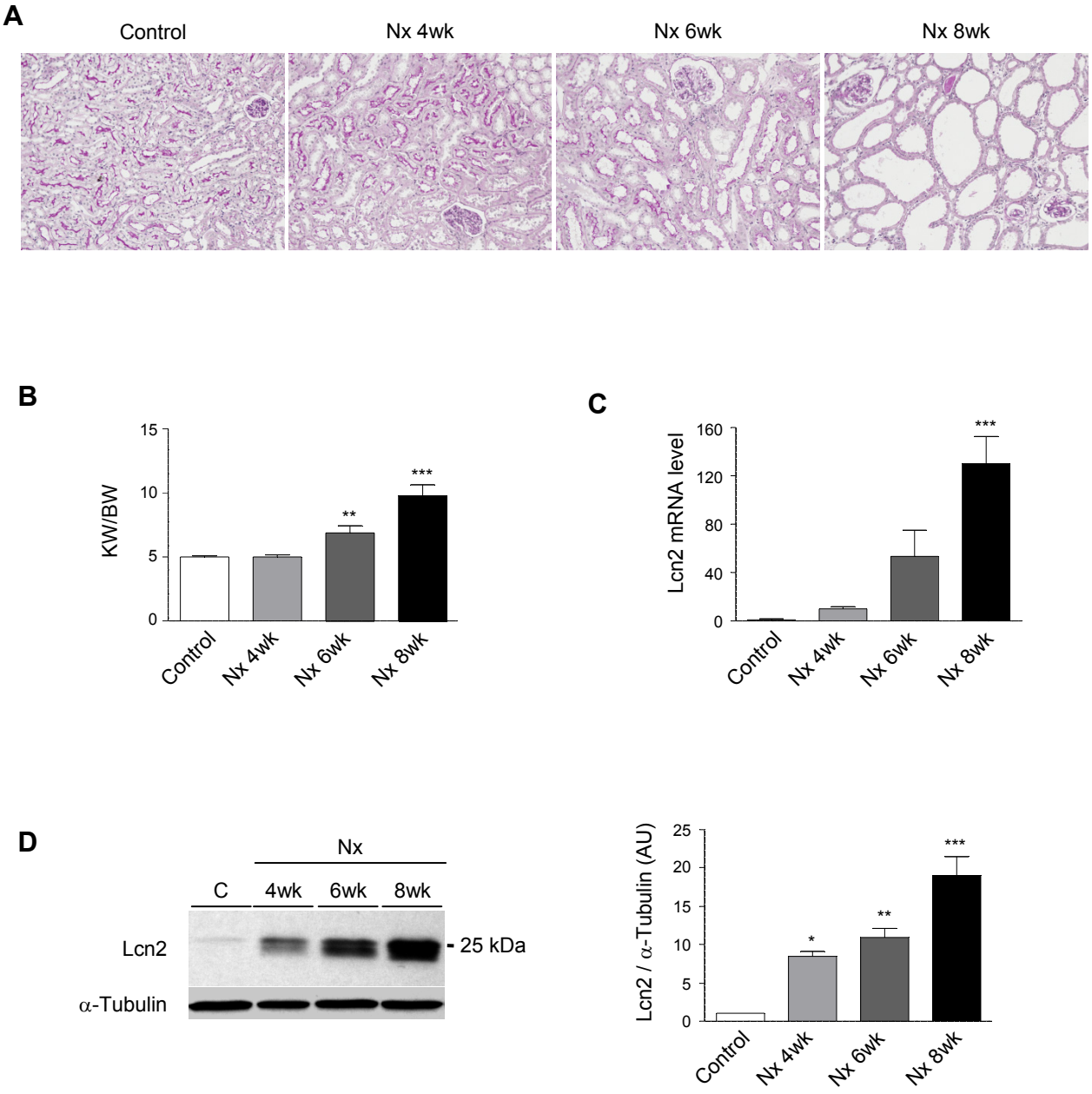
Supplemental Figure 1: Hierarchical clustering analysis of the 70 differentially expressed mRNAs between FVB/N and B6D2F1 strains. **(A-B)** Schematic representation of the transcripts up-regulated (A) and down-regulated (B) in remnant kidneys of FVB/N mice as compared to B6D2F1 animals, 2 months after nephron reduction.



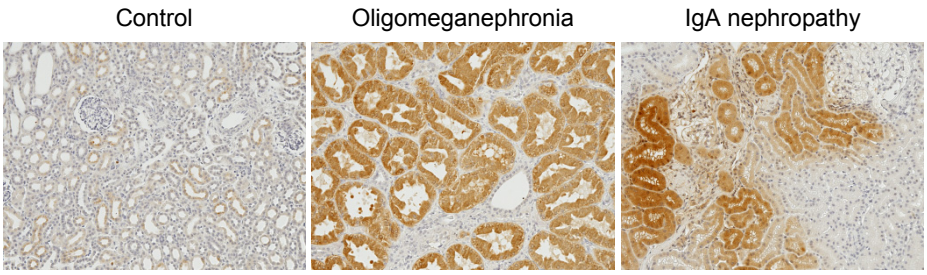
Supplemental Figure 2: Lcn2 is overexpressed in kidneys of FVB/N mice. Lcn2 mRNA expression evaluated by real-time RT-PCR in control (C) and 75% nephrectomized (Nx) B6D2F1 and FVB/N mice, 2 months after surgery. Data are means ± SEM; n = 6 and 10-11 for control and Nx mice, respectively. ANOVA followed by Tukey-Kramer test; control versus Nx mice: ** $P < 0.01$ and B6D2F1 versus FVB/N mice: ## $P < 0.01$.



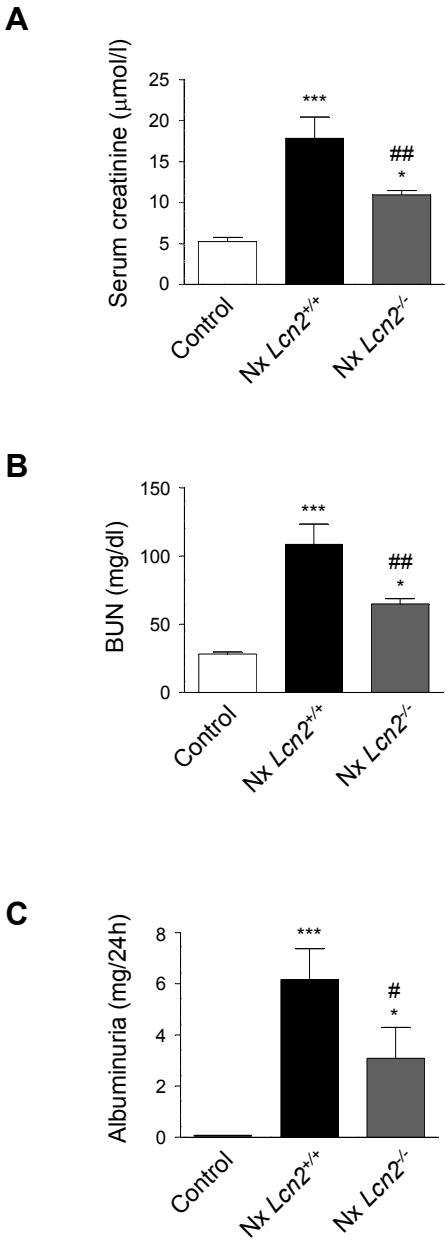
Supplemental Figure 3: Lcn2 protein and mRNA localization in remnant kidneys of FVB/N mice, 2 months after nephron reduction. (A) Lcn2 is predominantly expressed in proximal tubules. Colocalization experiments in kidneys from 75% nephrectomized (Nx) FVB/N mice, 2 months after surgery. Upper panels: serial sections stained for Lcn2 (left) and Lotus Tetragonolobus Lectin (LTL, right), a marker of proximal tubules. Middle panels: serial sections stained for Lcn2 (left) and Tamm Horsfall (TH, right), a marker of ascending limbs of loops of Henle. Lower panels: serial sections stained for Lcn2 (left) and Aquaporin 2 (AQP2, right), a marker of collecting ducts. Asterisks show some of the tubules in which Lcn2 colocalizes. Magnification: X200. **(B)** Lcn2 is found in a punctuate cytoplasmic distribution. Lcn2 immunohistochemistry in kidneys from Nx FVB/N mice, 2 months after surgery. Magnification: X600. **(C)** Colocalization experiments in kidneys from Nx FVB/N mice, 2 months after surgery. Serial sections stained for Lcn2 protein (left) and mRNA (right). Magnification: X200.



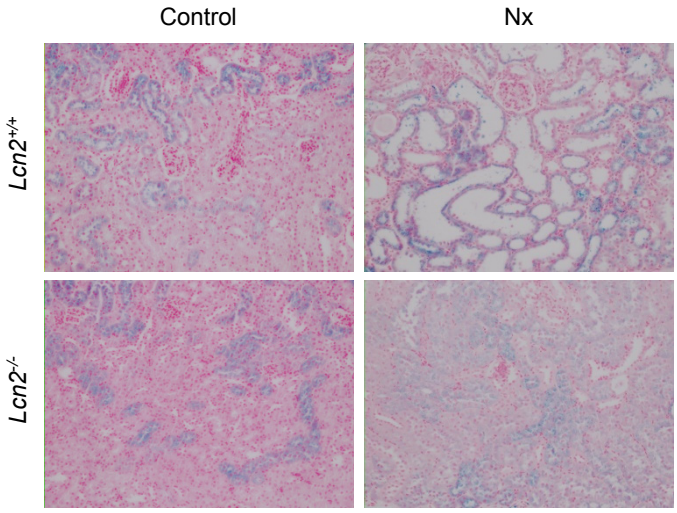
Supplemental Figure 4: Lcn2 overexpression precedes the development of renal lesions. (A) Morphology of kidneys from sham-operated (control) and 75% nephrectomized (Nx) FVB/N mice, 4 (4wk), 6 (6wk) and 8 (8wk) weeks after surgery. Magnification: X200. **(B)** Kidney weight (KW) to body weight (BW) ratio in control and Nx mice, 4, 6 and 8 weeks after surgery. **(C-D)** Lcn2 expression evaluated by (C) real-time RT-PCR and (D) western blot in kidneys from control (C) and Nx mice, 4, 6 and 8 weeks after surgery. Because no differences were detected between controls at the various time points, only one group is shown. Data are means ± SEM; *n* = 4-11. ANOVA followed by Tukey-Kramer test; control versus Nx mice: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.



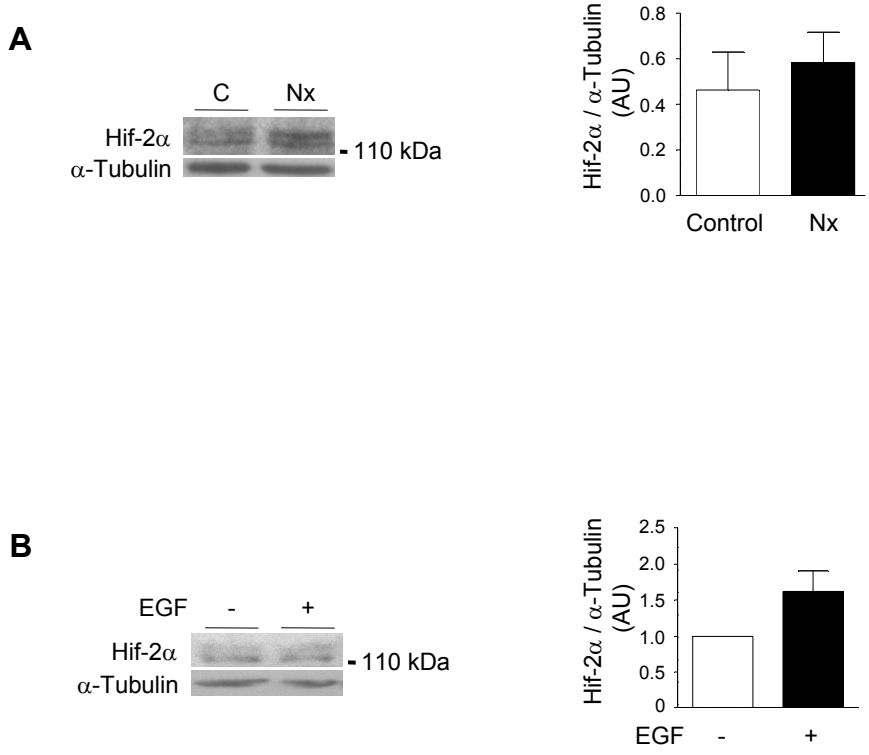
Supplemental Figure 5: LCN2 is overexpressed in kidneys of patients with chronic kidney disease. LCN2 staining in kidneys from controls (*n* = 9) and patients with oligomeganephronia (*n* = 11) and IgA nephropathy (*n* = 12). Magnification: X200.



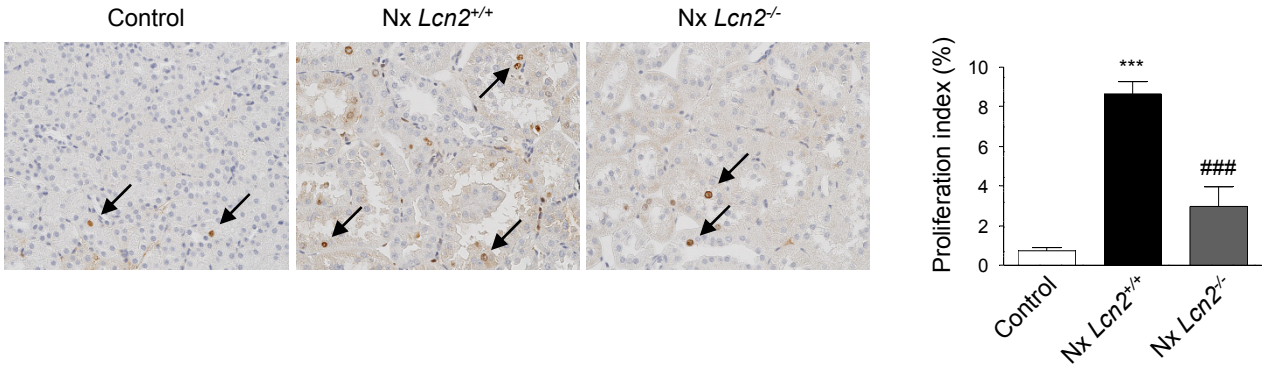
Supplemental Figure 6: *Lcn2* deficiency improves renal function and albuminuria after nephron reduction. (A-B) Serum creatinine (A), blood urea nitrogen (BUN) (B) and daily urinary albumin excretion (C) were measured in control and 75% nephrectomized (Nx) wild-type (*Lcn2*$^{+/+}$) or mutant (*Lcn2*$^{-/-}$) mice, 2 months after nephron reduction. Because no differences were detected between wild-type and mutant control mice, only one group is shown. Data are means ± SEM; n = 4-6 and 5-11 for control and Nx, respectively. ANOVA followed by Tukey-Kramer test; control versus Nx mice: * $P < 0.05$, *** $P < 0.001$ and *Lcn2*$^{+/+}$ versus *Lcn2*$^{-/-}$: # $P < 0.05$, ## $P < 0.01$.



Supplemental Figure 7: Lcn2 is not required for iron deposits in proximal tubules. Perls staining of kidneys from control and 75% nephrectomized (Nx) wild-type (*Lcn2*$^{+/+}$, upper panels) or mutant (*Lcn2*$^{-/-}$, lower panels) mice, 2 months after nephron reduction. Magnification: X200. *n* = 4-6 and 10-12 for control and Nx mice, respectively.



Supplemental Figure 8: Hypoxia Inducible Factor-2α (Hif-2α) expression does not change upon EGF activation. (A) Hif-2α protein expression and quantification in control (C) and 75% nephrectomized (Nx) mice, 2 months after surgery. **(B)** Hif-2α protein expression and quantification in mIMCD-3 cells, 24 hours after EGF treatment. Data are means ± SEM; *n* = 5 and 6-10 for in vitro and in vivo experiments, respectively.



Supplemental Figure 9: *Lcn2* deficiency prevents the increase of cell proliferation after nephron reduction. Ki-67 staining (black arrow) and quantification of tubular cell proliferation in kidneys from control, 75% nephrectomized (Nx) *Lcn2*$^{+/+}$ and *Lcn2*$^{-/-}$ mice, 2 months after surgery. Magnification: X400. Because no differences were detected between wild-type and mutant control mice, only one group is shown. Data are means ± SEM; *n* = 4-5. ANOVA followed by Tukey-Kramer test; control versus Nx mice: *** $P < 0.001$ and Nx *Lcn2*$^{+/+}$ versus Nx *Lcn2*$^{-/-}$ mice: ### $P < 0.001$.