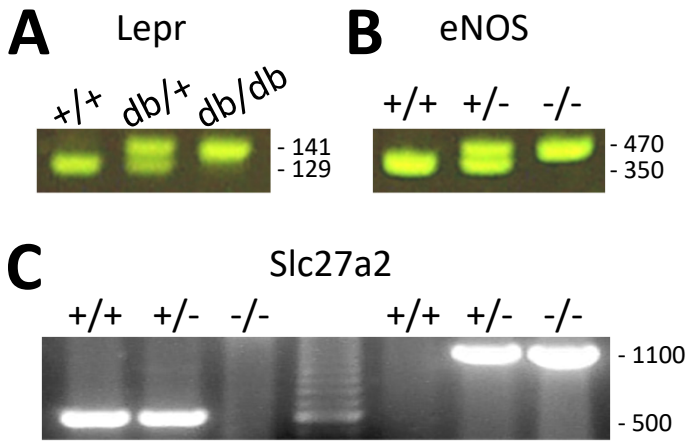
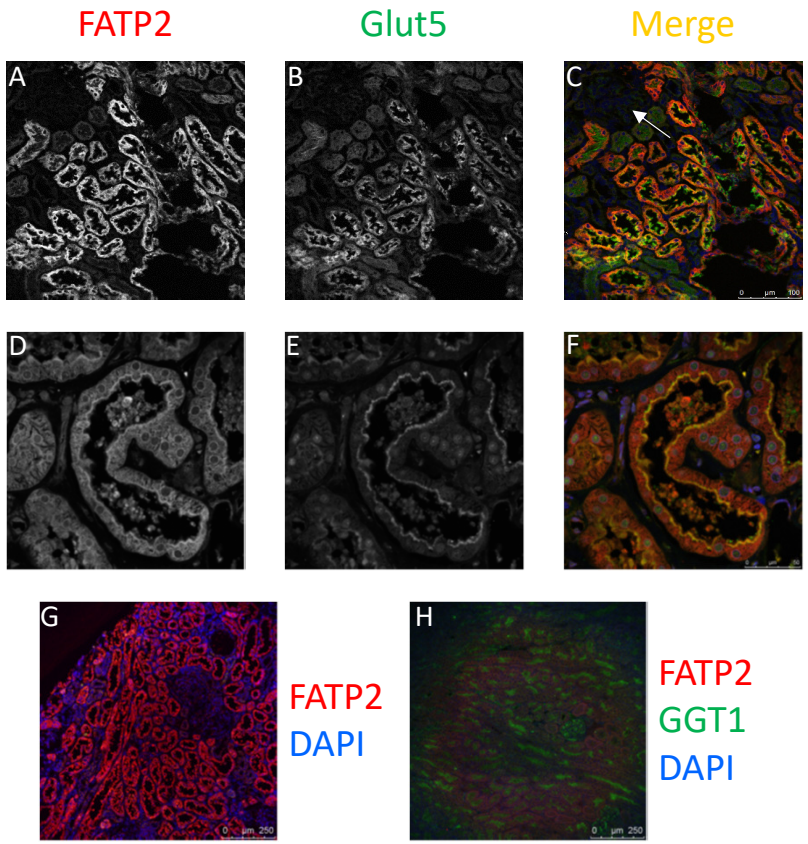
Supplemental Table 1. Summary phenotype data

Genotype			Intervention		Phenotype								
Slc27a2	Lepr	eNOS	Diet	STZ	GFR	Albuminuria	IFTA	NAFLD	FBS	Insulin	Islet size	Obesity	Mortality
+/+	+/+	+/+	Normal	No	+++	+	0	0	+	++	++	0	+
+/+	db/db	+/+	Normal	No	++++	++	0	+	++++	+	+	+++	++
+/+	db/db	-/-	Normal	No	+	++++	+++	1/2+	++++	+	+	+++	++++
+/-	db/db	-/-	Normal	No	++	ND	++	++	+++	ND	ND	++++	ND
-/-	db/db	-/-	Normal	No	+++	+++	+	++	++	+++	++++	++++	+++
+/+	+/+	+/+	High fat	No	+++	+	0	ND	+	+++	ND	+++	ND
+/+	+/+	+/+	High fat	Yes	++	++	++	ND	+++	+	ND	++	ND
-/-	+/+	+/+	High fat	No	+++	+	0	ND	++	++	ND	+++	ND
-/-	+/+	+/+	High fat	Yes	+++	+	+	ND	++	++	ND	++	ND

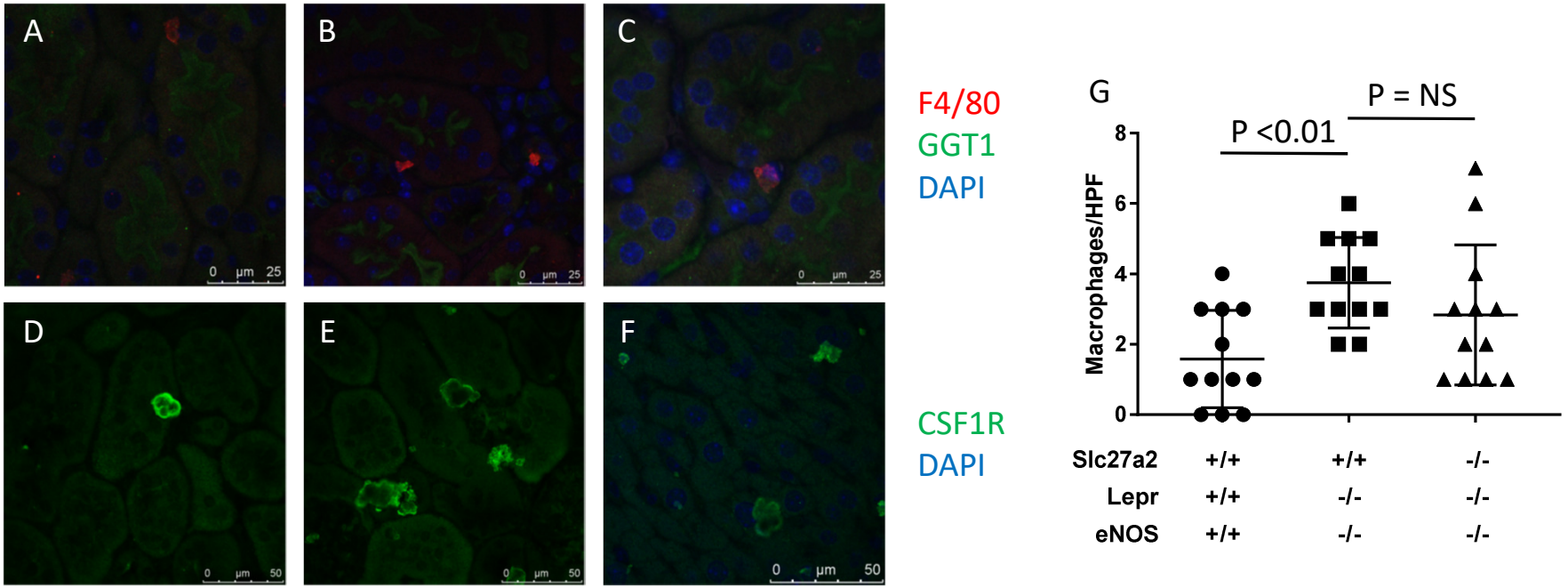
Abbreviations: FBS, fasting blood sugar; GFR, glomerular filtration rate; IFTA, interstitial fibrosis and tubular atrophy; NAFLD, non-alcoholic fatty liver disease; ND, not done



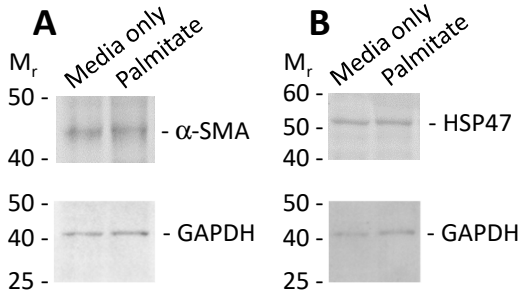
Supplemental Figure 1. Representative genotyping gels. RT-PCR for 30 cycles for amplification of A, leptin receptor gene (Lepr), forward primer for both alleles: 5'-AGAACGGACACTCTTTGAAGTCTC-3', reverse wild-type: 5'-AACCATAGTTTAGGTTTGTTTC-3', reverse db: 5'-CAATTCAGTGTAAACCATAGTTTAGGTTTGTTT-3'. B, endothelial nitric oxide synthase gene (eNOS), both alleles forward: 5'-CTCCAACTTAGTGCAGGTCT-3', reverse wild-type: 5'-ATGGTTGCCTTCACACGCTT-3', reverse $eNOS^{-/-}$: 5,-CTTCCTCGTGCTTTACGGTA-3'. C, fatty acid transporter-2 gene (Slc27a2), both alleles forward: 5'-CTCCCTGCATTGGTGTGAGAGAATTTTG -3', wild-type reverse: 5'-TTAGTCAGATGCCAACCATAGGCAAGCT-3'; $Slc27a2^{-/-}$ reverse: GAAGAACTCGTCAAGAAGGCG-3'.



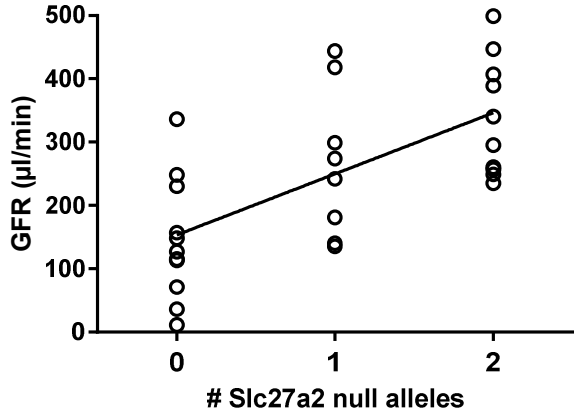
Supplemental Figure 2. Proximal tubule FATP2 expression. Paraffin-embedded human kidney was labeled for FATP2 (red), Glut5 (green) or merged (yellow) and viewed at 100X (A-C) and 400X (D-F) magnification. Arrow depicts a glomerulus. Wild-type (G) and *Slc27a2*$^{-/-}$(H) mouse kidney frozen sections were labeled for FATP2 (red), and nuclei were counterstained with DAPI (blue) and viewed at 100X magnification. Proximal tubules were counterstained with anti-GGT1 IgG in H.



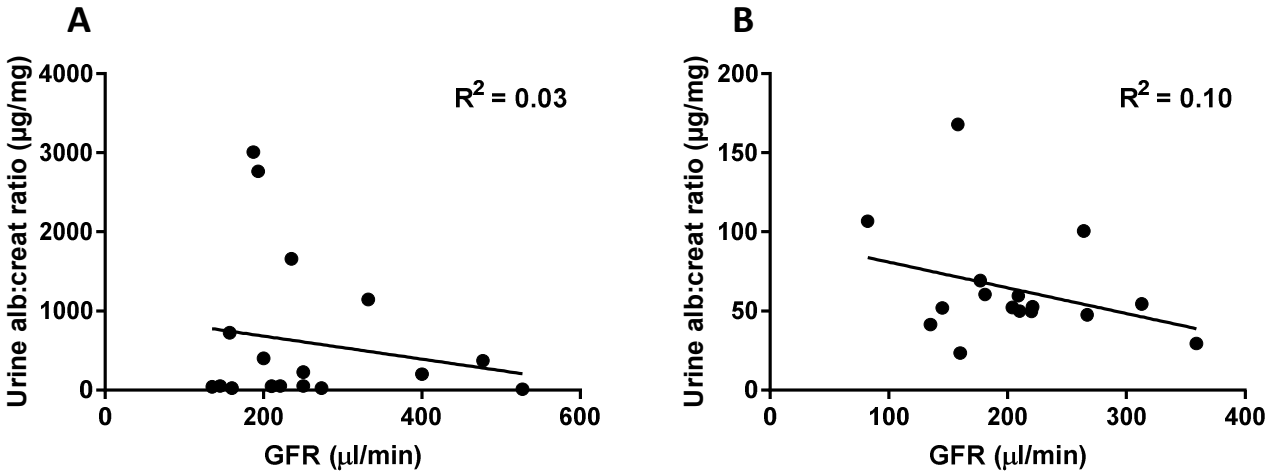
Supplemental Figure 3. Paraffin sections from *Slc27a2*$^{+/+}$ *Lepr*$^{+/+}$ *eNOS*$^{+/+}$ (A and D), *Slc27a2*$^{+/+}$ *Lepr*$^{db/db}$ *eNOS*$^{-/-}$ (B and E) and Slc27a2$^{-/-}$ Lepr$^{db/db}$ eNOS$^{-/-}$ (C and F) mouse kidneys were labeled for macrophages with anti-F4/80 (A-C, 400X magnification) or anti-CSF1R (D-F, 630X magnification) IgG. Macrophages from CSF1R-labeled slides were quantified from four randomly selected sections in three mice per genotype by an observer blinded to experimental condition. Data are shown in panel G. Groups were compared by ANOVA and Tukey's multiple comparisons test.



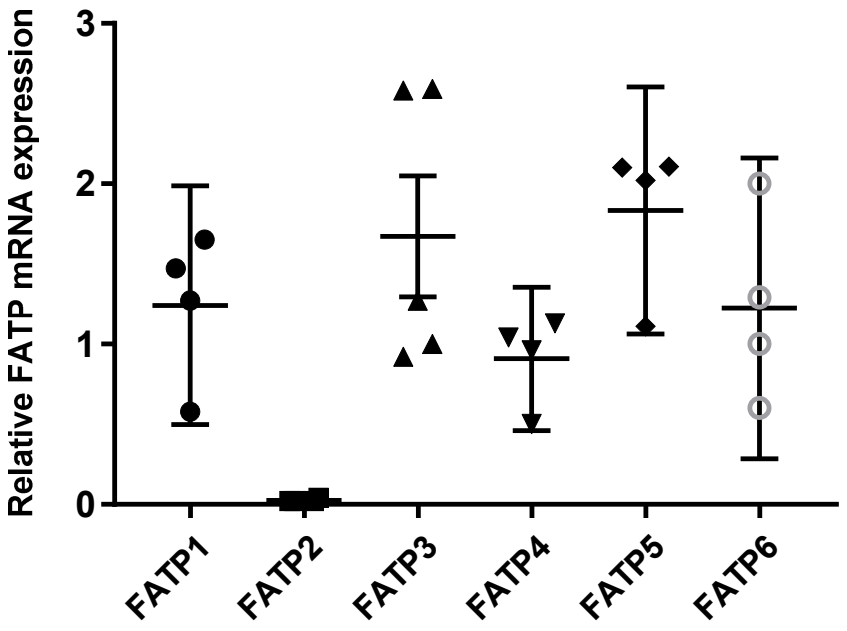
Supplemental Figure 4. Fatty acids do not stimulate EMT. HK2 human proximal tubule cells were serum starved for 24 hrs, and then incubated ± palmitate (100 μM complexed with 0.2% albumin) for 24 hrs at 37^{o} C. Cell lysates were resolved by SDS-PAGE and probed for α-smooth muscle actin (A) or heat shock protein-47 (B). Blots were then stripped and re-probed for GAPDH as a loading control.



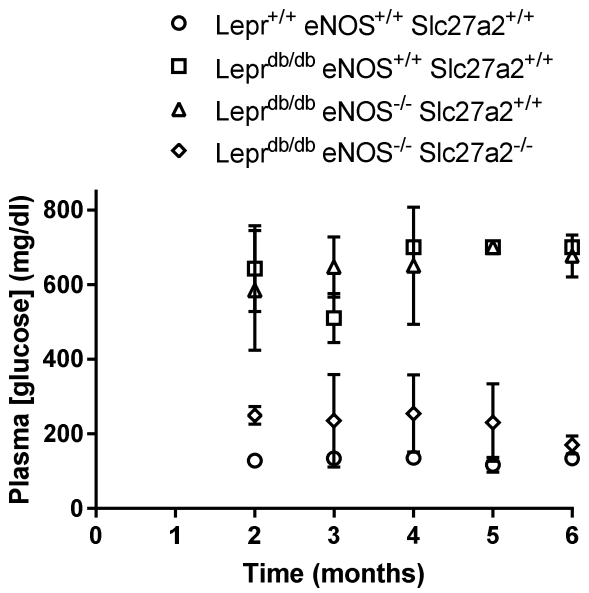
Supplemental Figure 5. Correlation of GFR with Slc27a2 null allele number. GFR data from Lepr$^{db/db}$ eNOS$^{-/-}$ mice in Figure 3A were re-analyzed according to Scl27a2$^{-/-}$ allele number, i.e., Scl27a2$^{+/+}$ Lepr$^{db/db}$ eNOS$^{-/-}$ = 0, Scl27a2$^{+/-}$ Lepr$^{db/db}$ eNOS$^{-/-}$ = 1, Scl27a2$^{-/-}$ Lepr$^{db/db}$ eNOS$^{-/-}$ = 2 . Linear regression analysis revealed R^2 = 0.98, p = 0.10 for slope differing from zero.



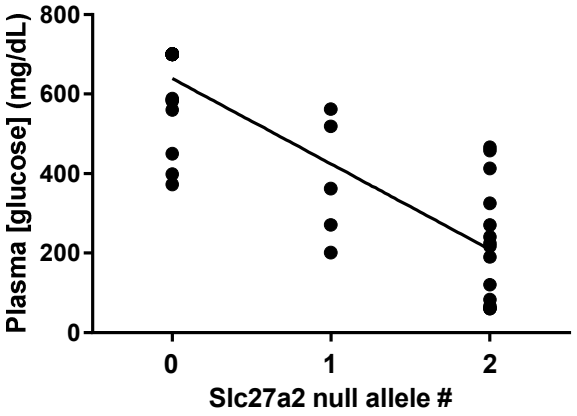
Supplemental Figure 6. Correlation of albuminuria with GFR. The relationship between albuminuria and GFR is plotted for the genetic model of DKD (all genotypes) in A, and the HFD ± STZ inducible model (all treatment groups) in B. There was an inverse correlation in both groups, though the slope of the linear regression lines was not significant from zero in either graph (P = 0.50 in A, P = 0.23 in B).



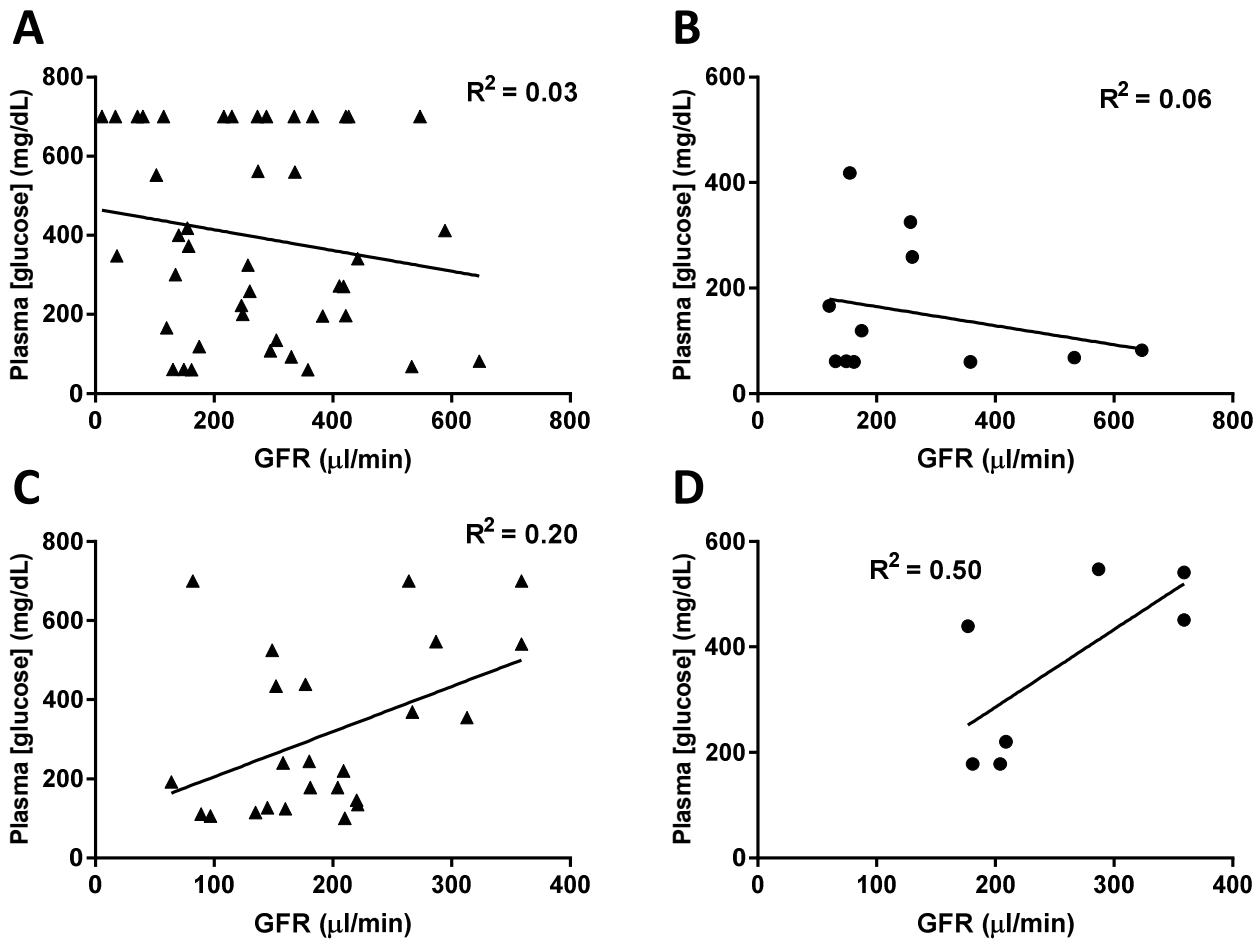
Supplemental Figure 7. Compensatory expression of FATP isoforms in Slc27a2$^{-/-}$ kidney. FATP isoform mRNA expression in whole kidneys was determined by quantitative RT-PCR, as described in Methods. Oligonucleotide primers with proprietary sequence identities were purchased from TaqMan with catalogue numbers for Fatp1: Mm00449511_m1, Fatp2: Mm00449517_m1, Fatp3: Mm01220017_m1, Fatp4: Mm01327405_m1, Fatp5: Mm00447768_m1, Fatp6: Mm01258609_m1, GAPDH: Hs02758991_g1. The FATP isoform:GAPDH ratio was determined in samples from Slc27a2$^{+/+}$ and Slc27a2$^{-/-}$ mouse kidneys, and normalized to 1.0 in the Slc27a2$^{+/+}$ sample in each experiment. Data are expressed as mean ± SEM.



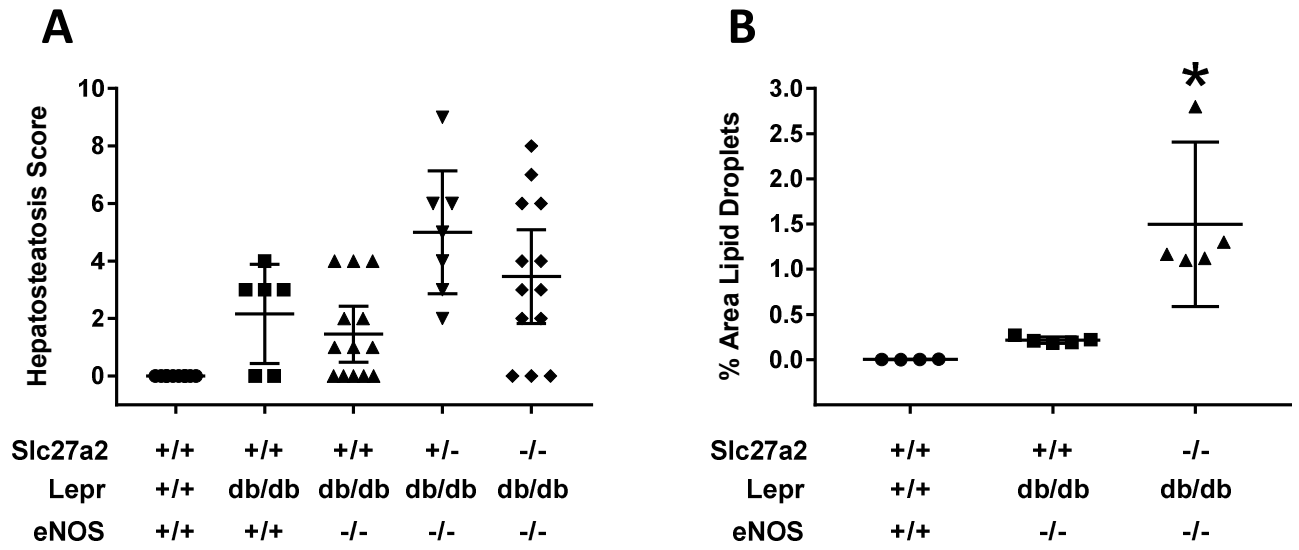
Supplemental Figure 8. Glycemia by genotype over time. Fasting plasma samples were obtained monthly for each genotype. Glucose concentrations were determined by glucometer. Plasma glucose values >600 mg/dl were assigned a value of 700. Data are plotted as mean ± SEM.



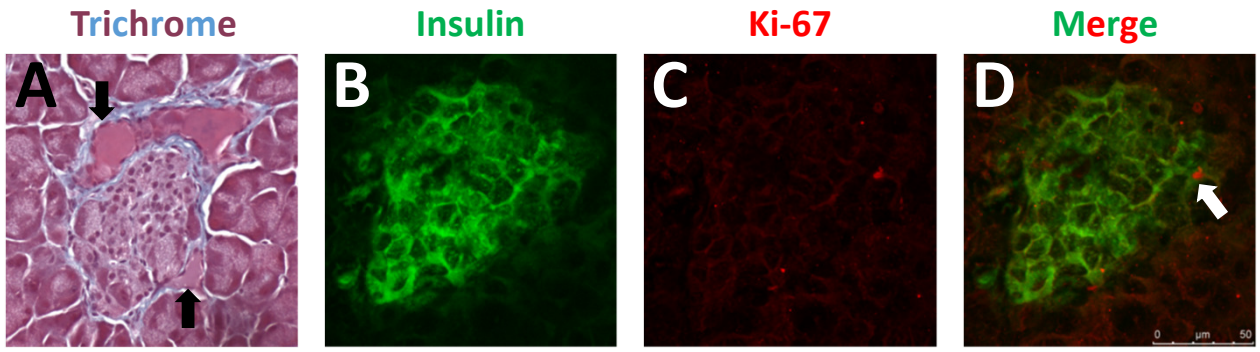
Supplemental Figure 9. Correlation between glycemia and Slc27a2 null allele number. Fasting plasma glucose concentrations were determined by glucometer in $Lepr^{db/db}$ $eNOS^{-/-}$ mice with 0, 1 or 2 Slc27a2 null alleles. Plasma glucose values >600 mg/dl were assigned a value of 700. Linear regression analysis revealed $R^2 = 0.996$, $p < 0.05$ for slope differing from zero.



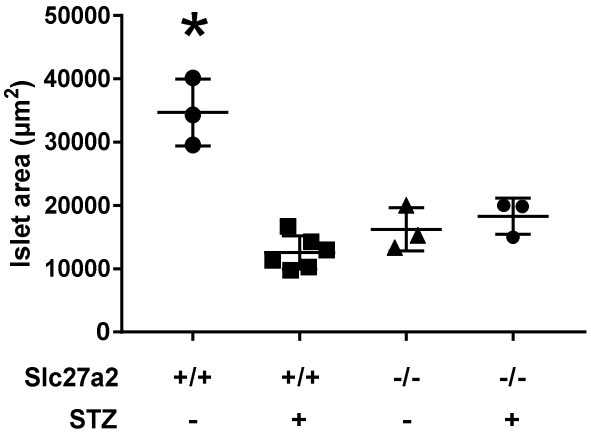
Supplemental Figure 10. Correlation between glycemia and GFR. Fasting plasma glucose concentrations were plotted vs. corresponding GFR values for A. All genotypes, B. Slc27a2$^{-/-}$ Lepr$^{db/db}$ eNOS$^{-/-}$ cohort only. C. HFD ± STZ, all mice. D. HFD + STZ-treated Slc27a2$^{-/-}$ cohort only. Linear regression and R2 values were calculated with GraphPad Prism software.



Supplemental Figure 11. No correlation between FATP2 genotype and hepatosteatosis. Hepatosteatosis was scored on a scale specifically designed for mice, as described in Methods. *P <0.05 compared to other two groups by ANOVA and Tukey's test for multiple comparisons.



Supplemental Figure 12. Pancreas immunohistology. A, Masson's trichrome stain from Slc27a2$^{+/+}$ Lepr$^{db/db}$ eNOS$^{-/-}$ pancreas. Black arrows demarcate hyaline cysts. B-D, Pancreatic islet from two-month old Slc27a2$^{-/-}$ Lepr$^{db/db}$ eNOS$^{-/-}$. β-cell cytoplasmic insulin label (green); proliferating β-cell nuclear label (red, demarcated by white arrow).



Supplemental Figure 13. Preserved insulin secretion is associated with islet size and FATP2 gene deletion. Islet area was measured as described in Methods. Each symbol represents mean area of all islets from one section per mouse. * P <0.001 compared to other groups by ANOVA and Tukey's multiple comparisons test.