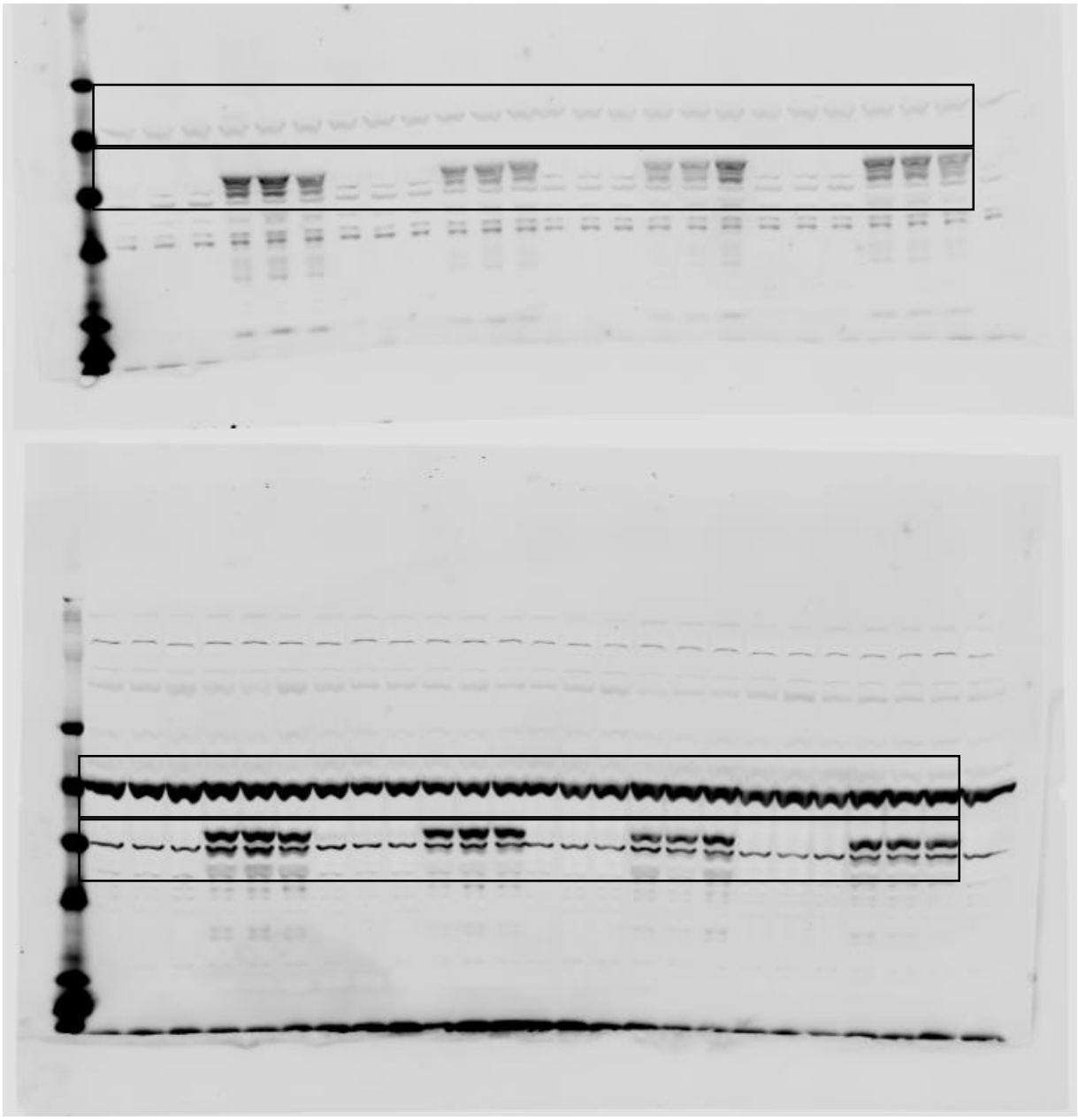
Full unedited gels for Supplemental Figure 1



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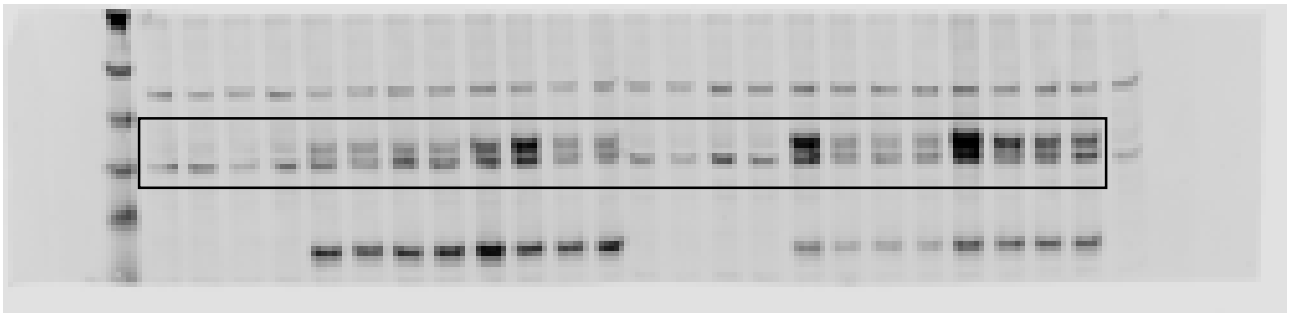
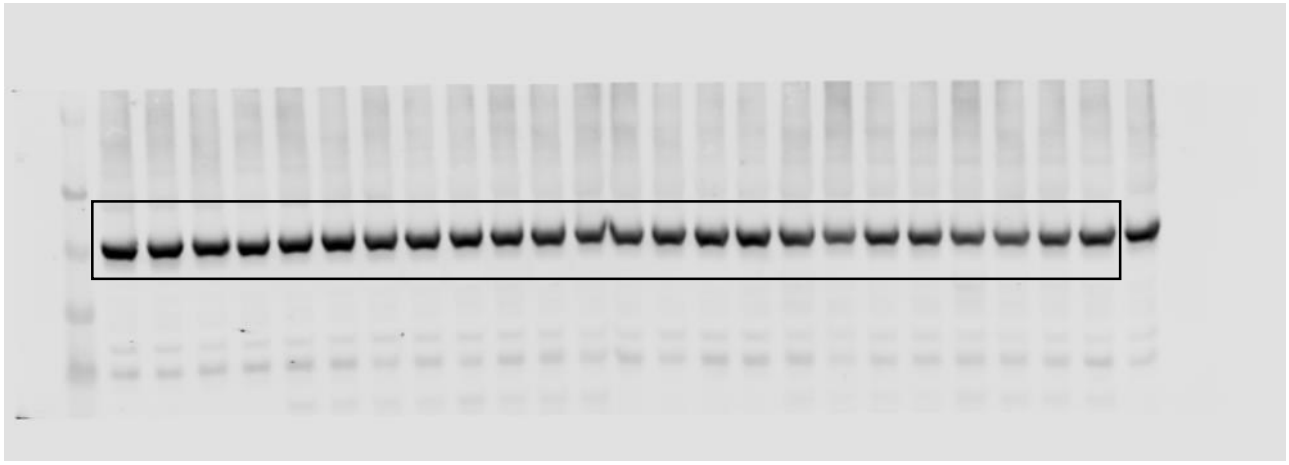
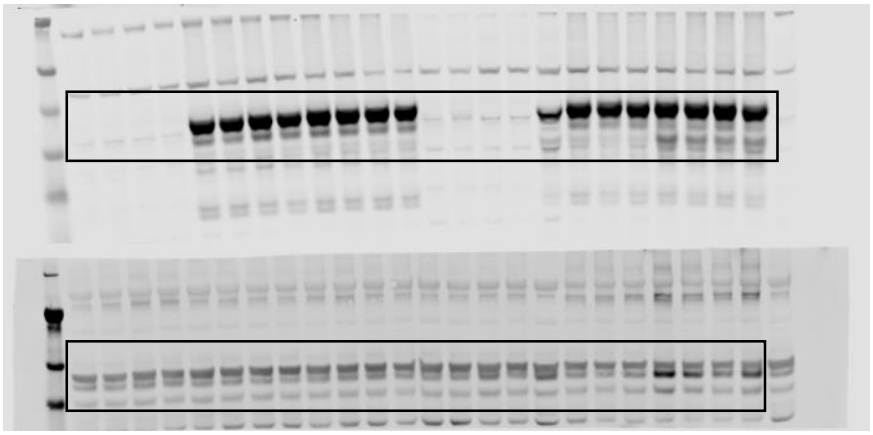


APOL1



α-tub

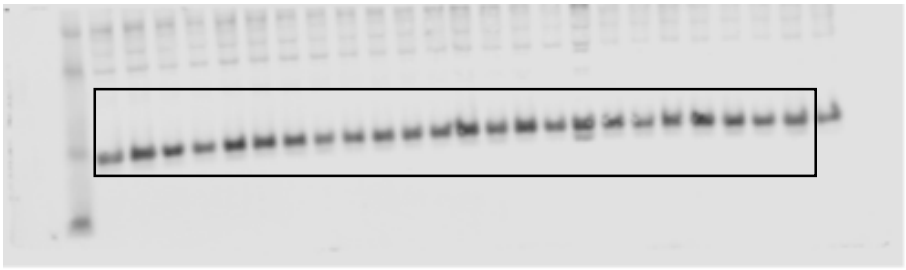
Full unedited gels for Supplemental Figure 10



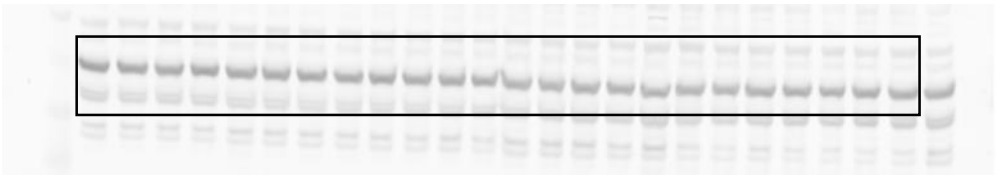
APOL1

Liver

p62



LC3B



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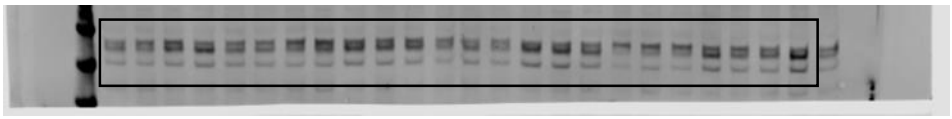

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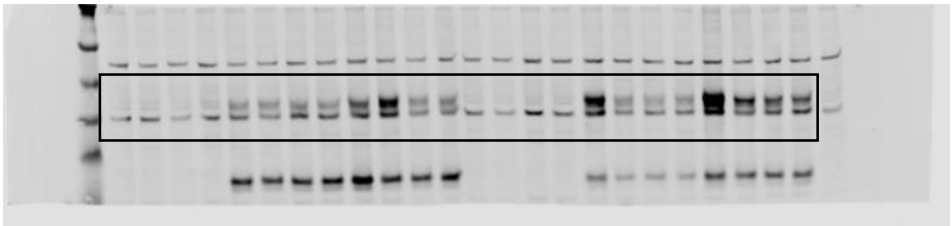
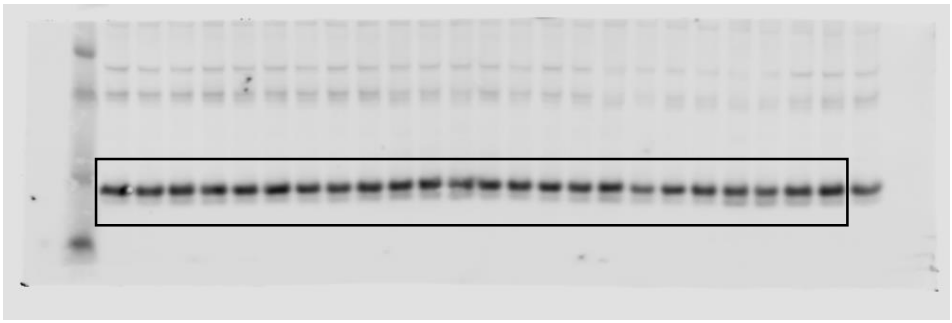


Kidney

APOL1



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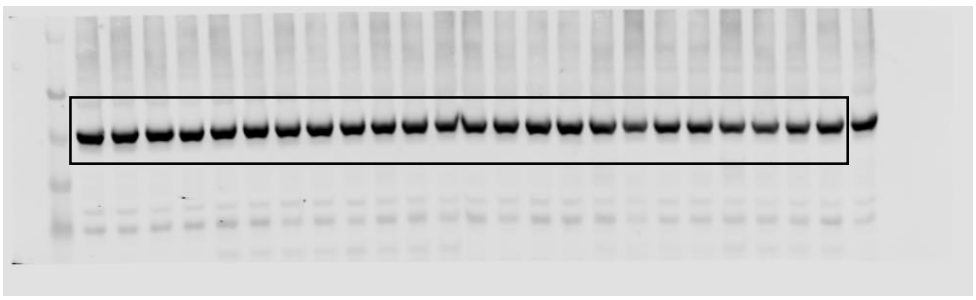
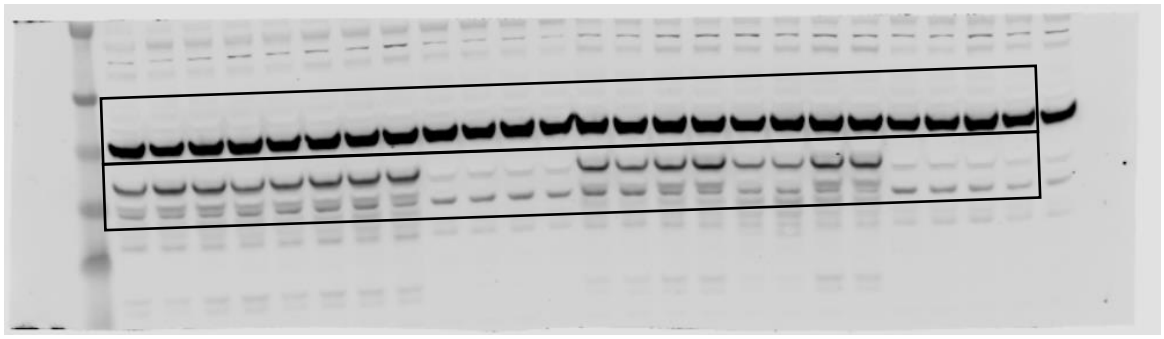


α-tub

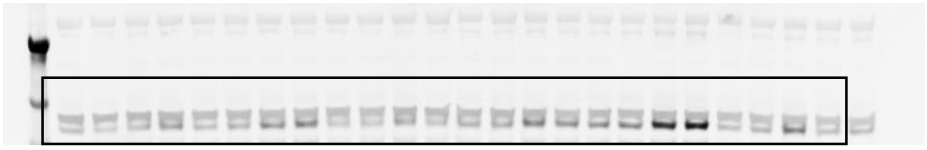
Full unedited gels for Supplemental Figure 11



α-tub

APOL1

Liver



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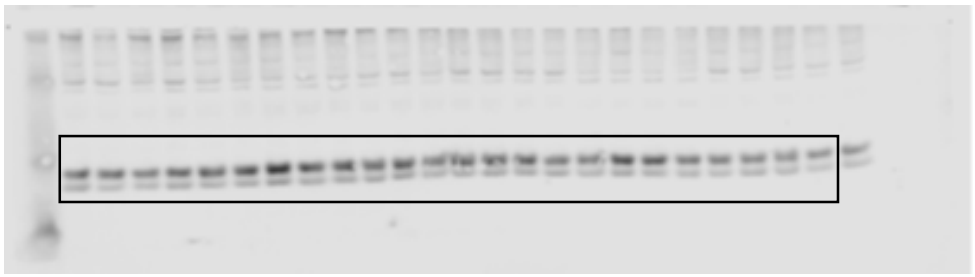

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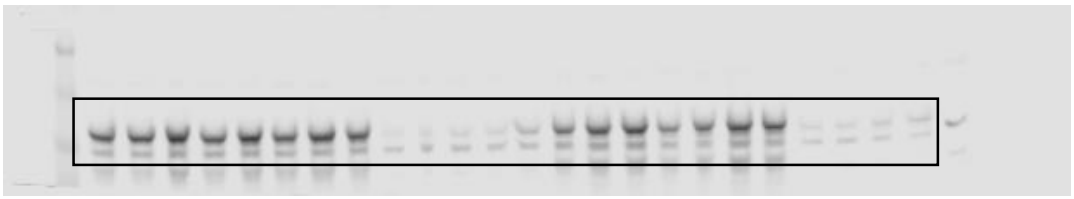
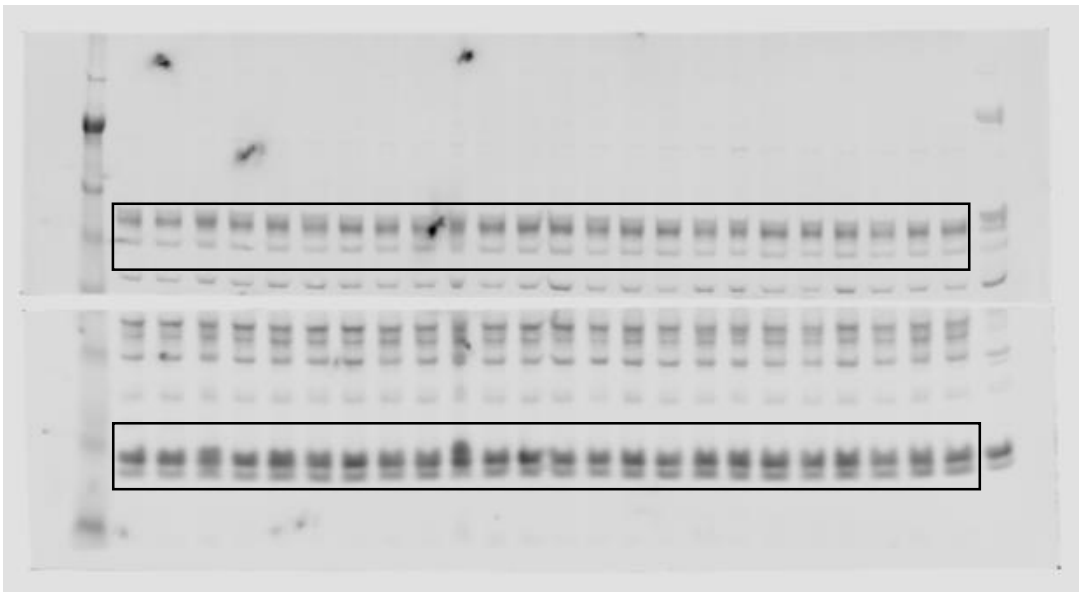


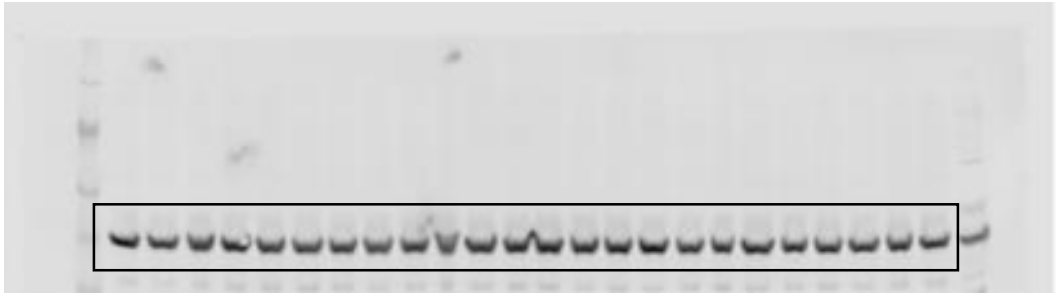
APOL1



p62

Kidney

LC3B



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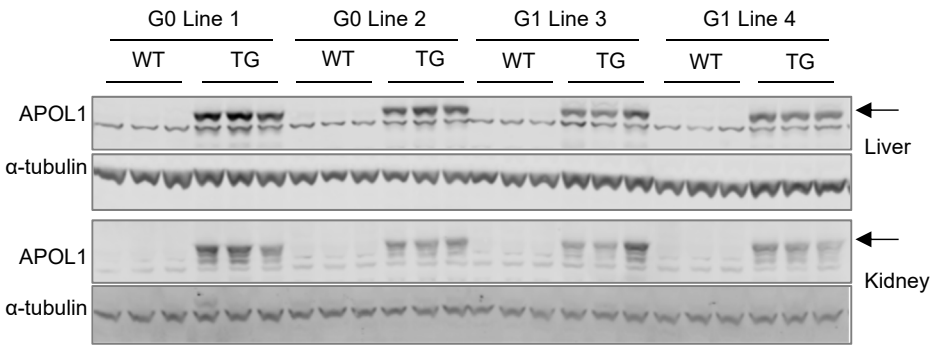
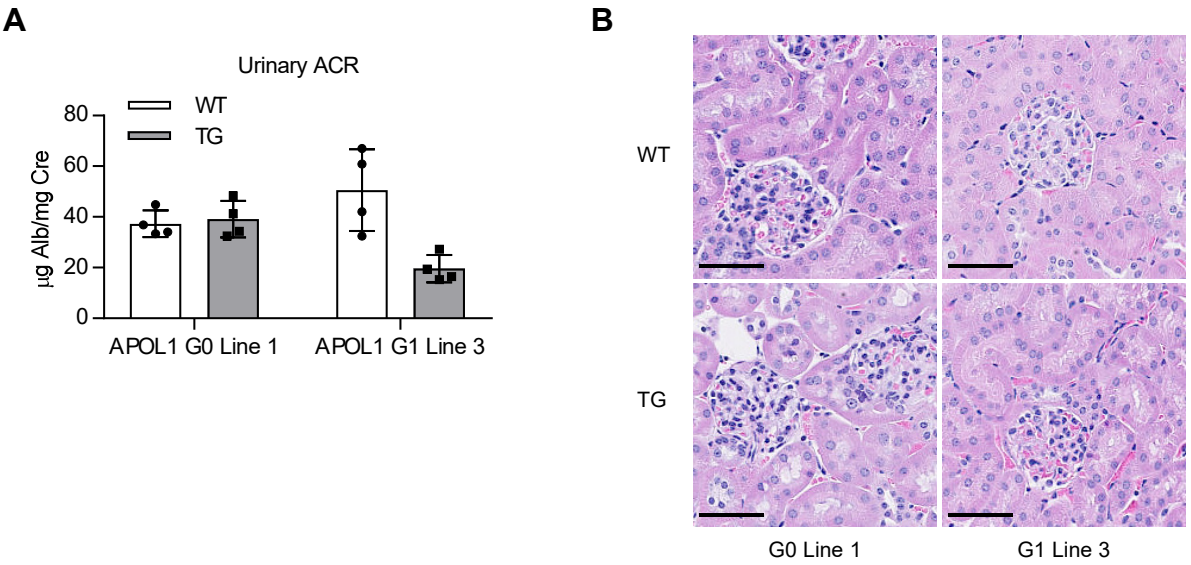
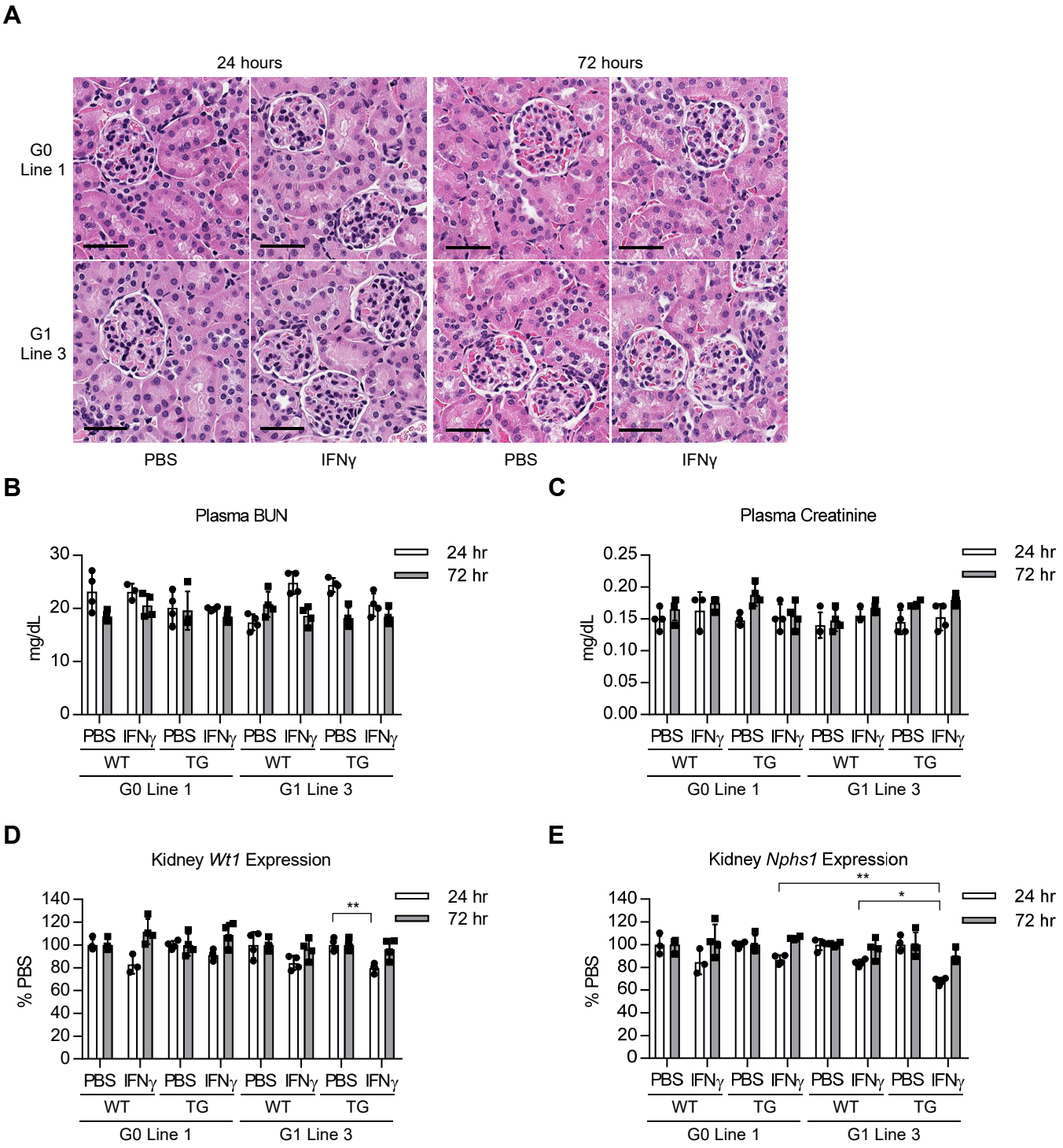


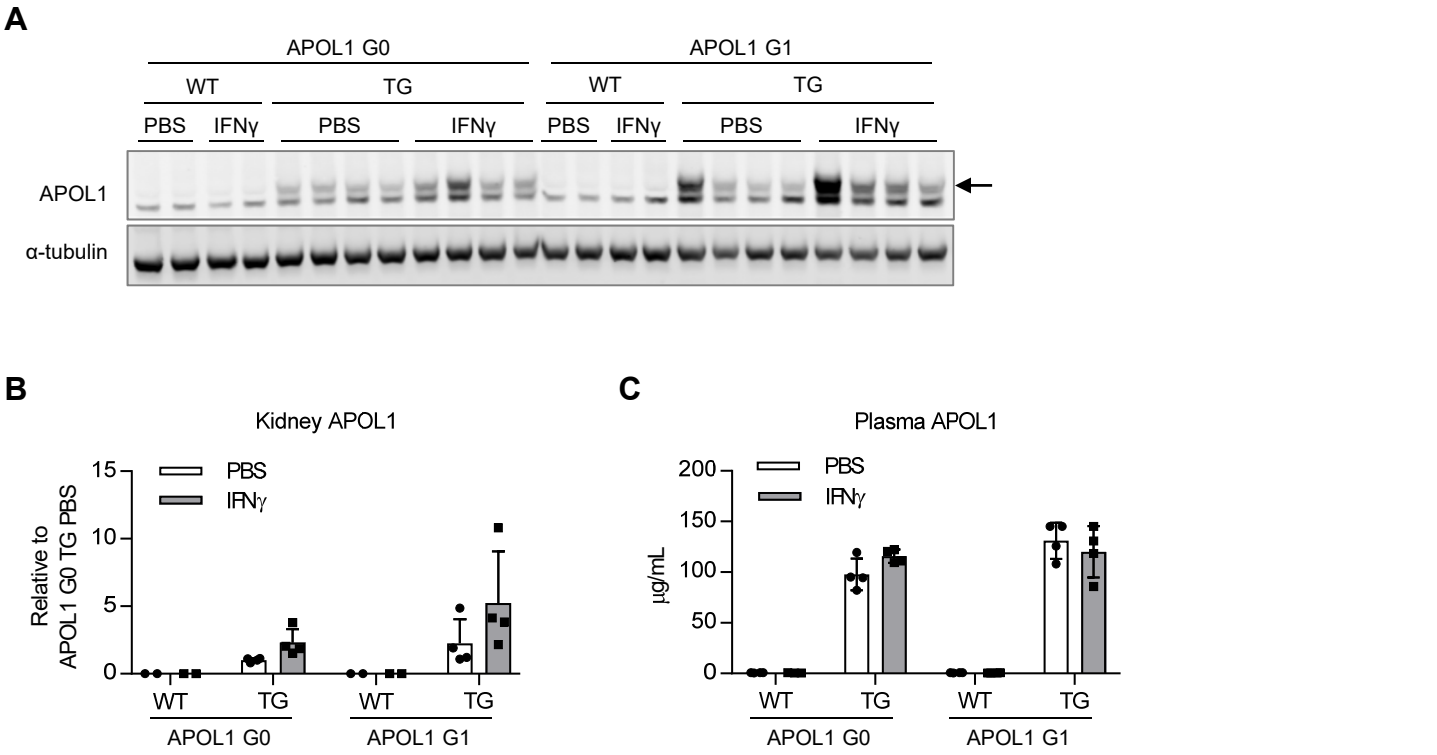
Supplemental Figure 1 Genomic *APOL1* transgenic mice express APOL1 protein in liver and kidney. Western blot analysis of APOL1 expression in liver and kidney of transgenic mice (*n*=3). Each lane represents an individual animal.



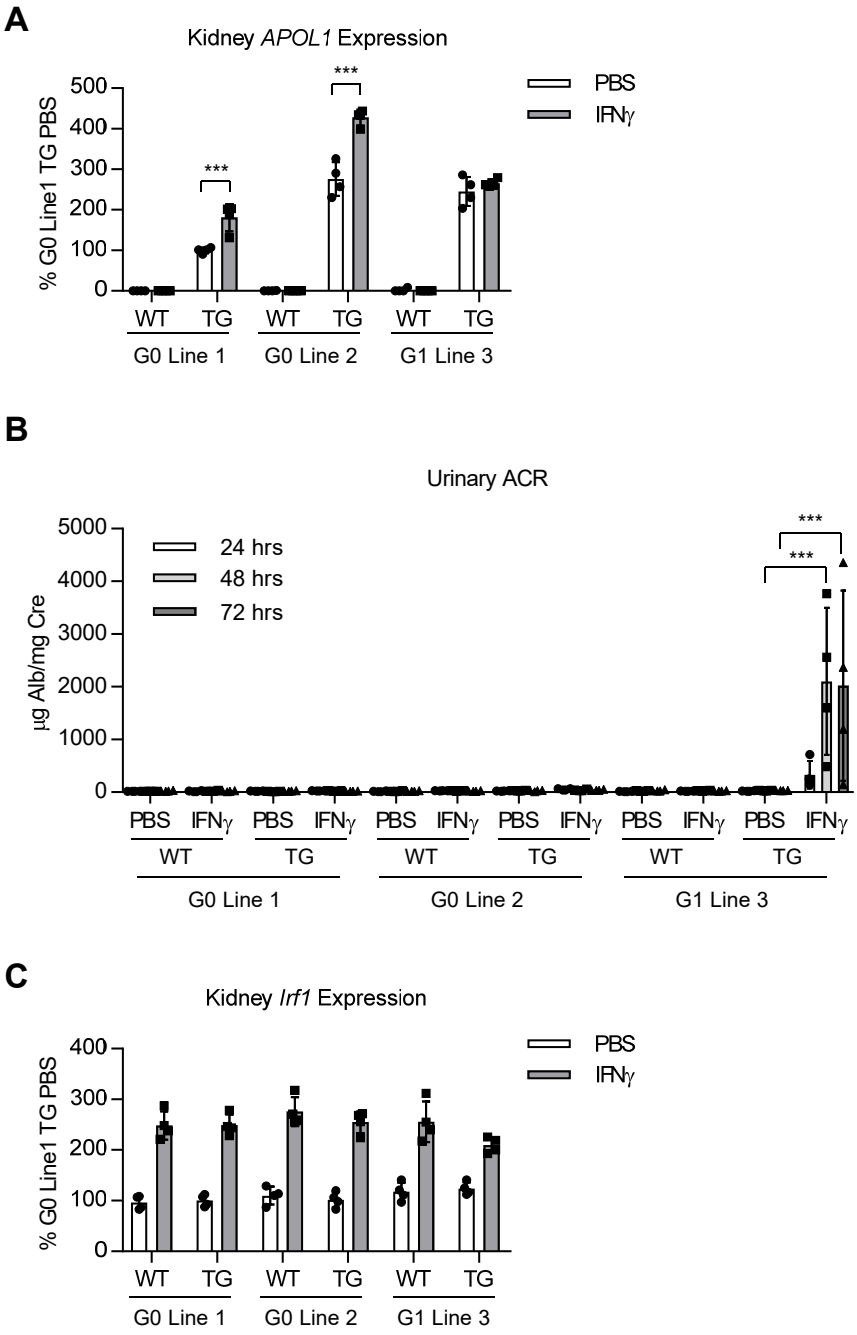
Supplemental Figure 2 Genomic *APOL1* G0 and G1 transgenic mice do not exhibit a renal phenotype. (**A**) Urine albumin levels of 32-week-old *APOL1* transgenic and WT littermate mice (*n*=4) were measured by Albumin ELISA and normalized to urine creatinine levels. (**B**) Representative H&E-stained kidney images from 32-week-old *APOL1* G0 and G1 transgenic mice and their WT littermates. *n*=4; Scale bar, 50 µm.



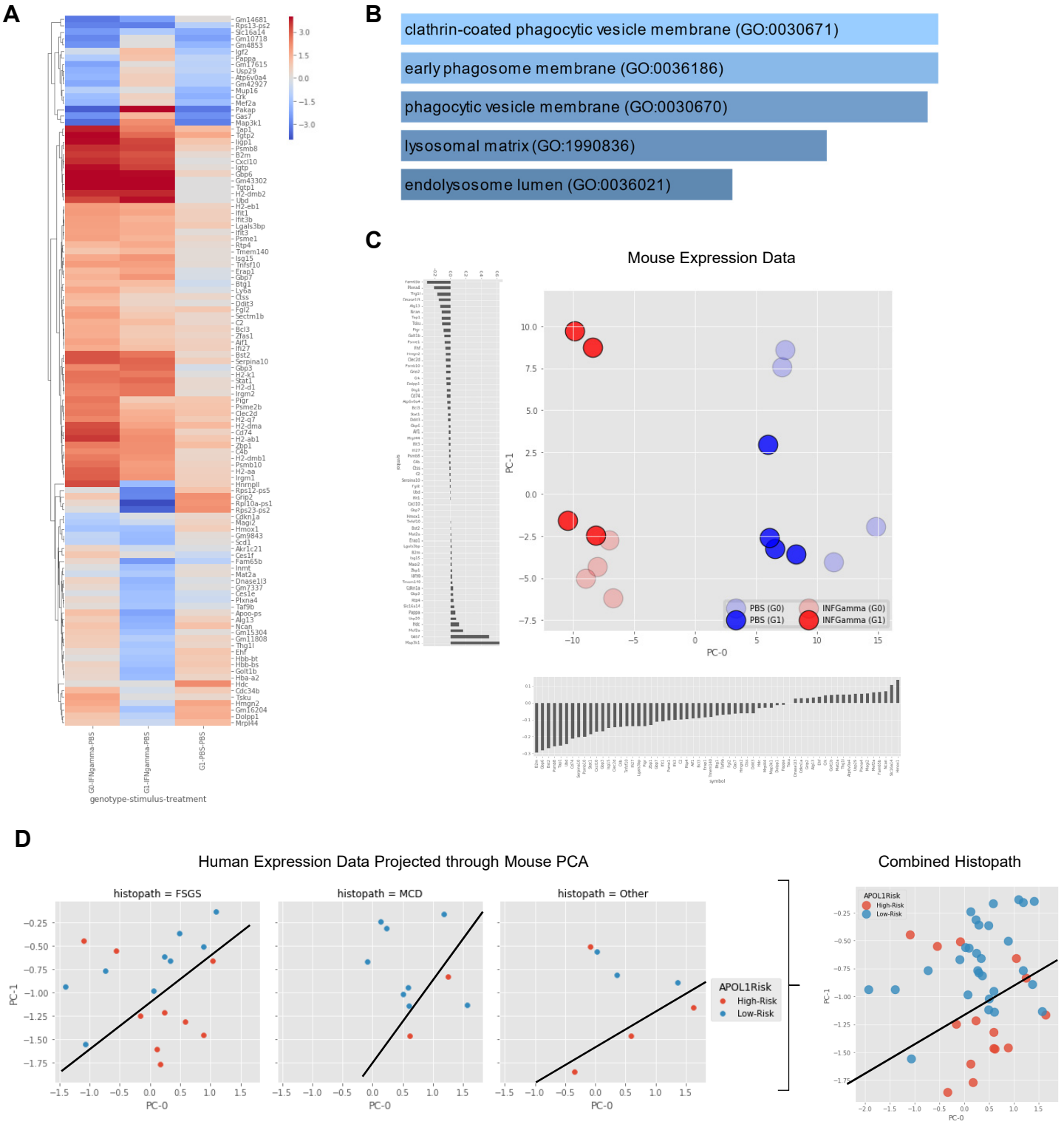
Supplemental Figure 3 IFNγ has no effects on kidney morphology or kidney functional markers but has transient effects on podocyte marker gene expression in *APOL1* G1 transgenic mice. Female *APOL1* G0 and G1 transgenic and WT littermate mice (n=3-4) were challenged with a single dose of IFNγ (1.125×10^7 U/kg) or vehicle (PBS). (**A**) Representative H&E-stained kidney images from *APOL1* transgenic mice 24 hours and 72 hours post-IFNγ challenge (scale bar, 50 μm). Plasma (**B**) BUN and (**C**) creatinine were measured 24 and 72 hours post-IFNγ challenge using a clinical chemistry analyzer. Kidney (**D**) *Wt1* and (**E**) *Nphs1* expression were measured by qRT-PCR 24 and 72 hours post-IFNγ challenge and normalized to *CYP* expression. Gene expression is shown relative to the PBS-challenged group for all genotypes. All data are presented as means ± SD. Two-way ANOVA with Tukey's multiple comparisons test, p= *<0.05; **<0.01.



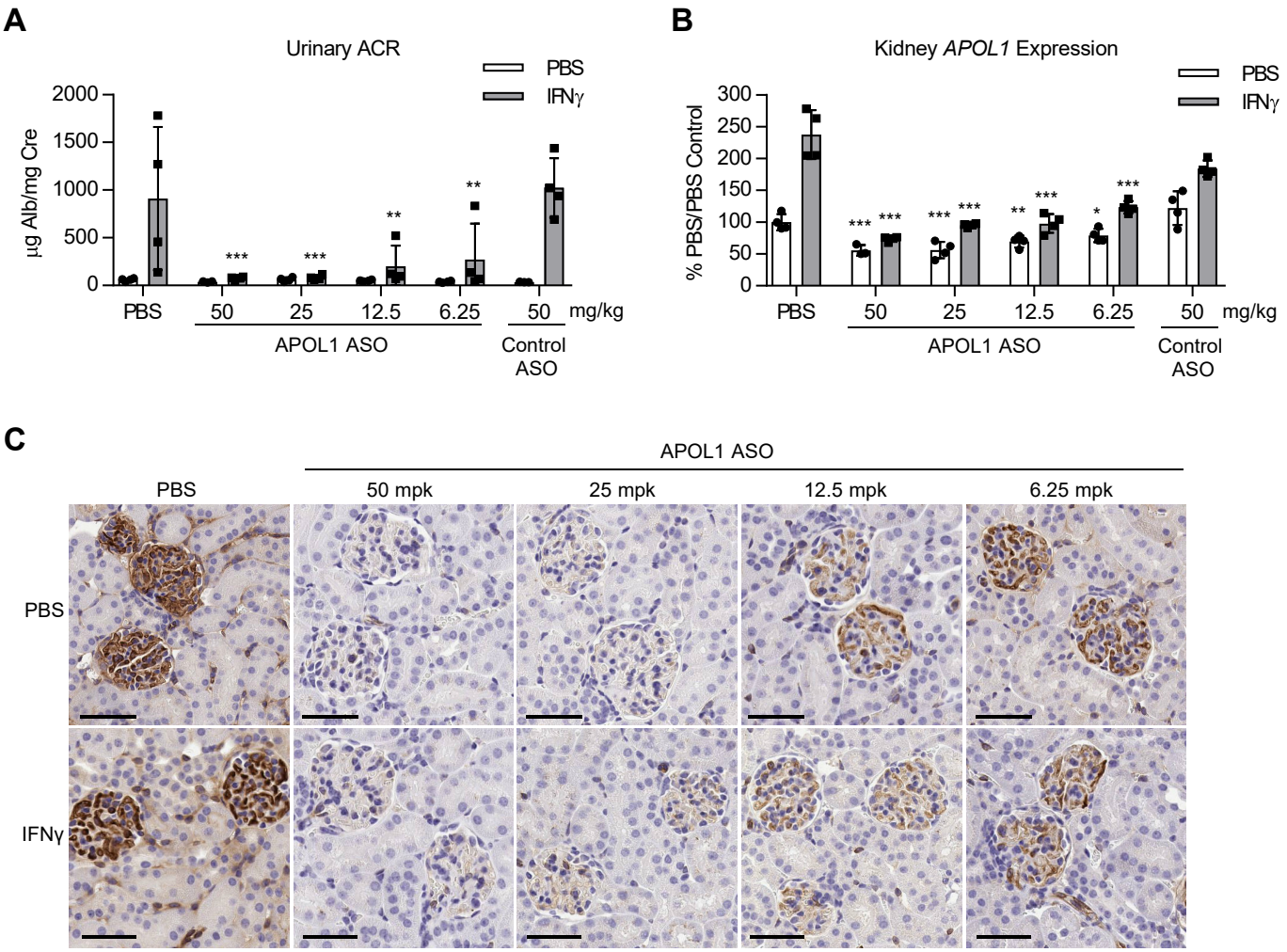
Supplemental Figure 4 IFNγ increases kidney APOL1 protein but has no effect on plasma APOL1 levels in *APOL1* transgenic mice. Female *APOL1* G0 and G1 transgenic and WT littermate mice (*n*=3-4) were challenged with a single dose of IFNγ ($1.125x10^7$ U/kg) or vehicle (PBS). (**A**) Western blot analysis of APOL1 expression in kidney 24 hours post-IFNγ challenge. Each lane represents an individual animal (only 2 of 3-4 WT animals shown per group). (**B**) Quantification of APOL1 Western blot was performed by normalizing APOL1 band intensity to that of α-tubulin and shown as relative to *APOL1* G0 TG PBS. (**C**) Plasma APOL1 was measured by ELISA 24 hours post-IFNγ challenge. All data are presented as means ± SD.



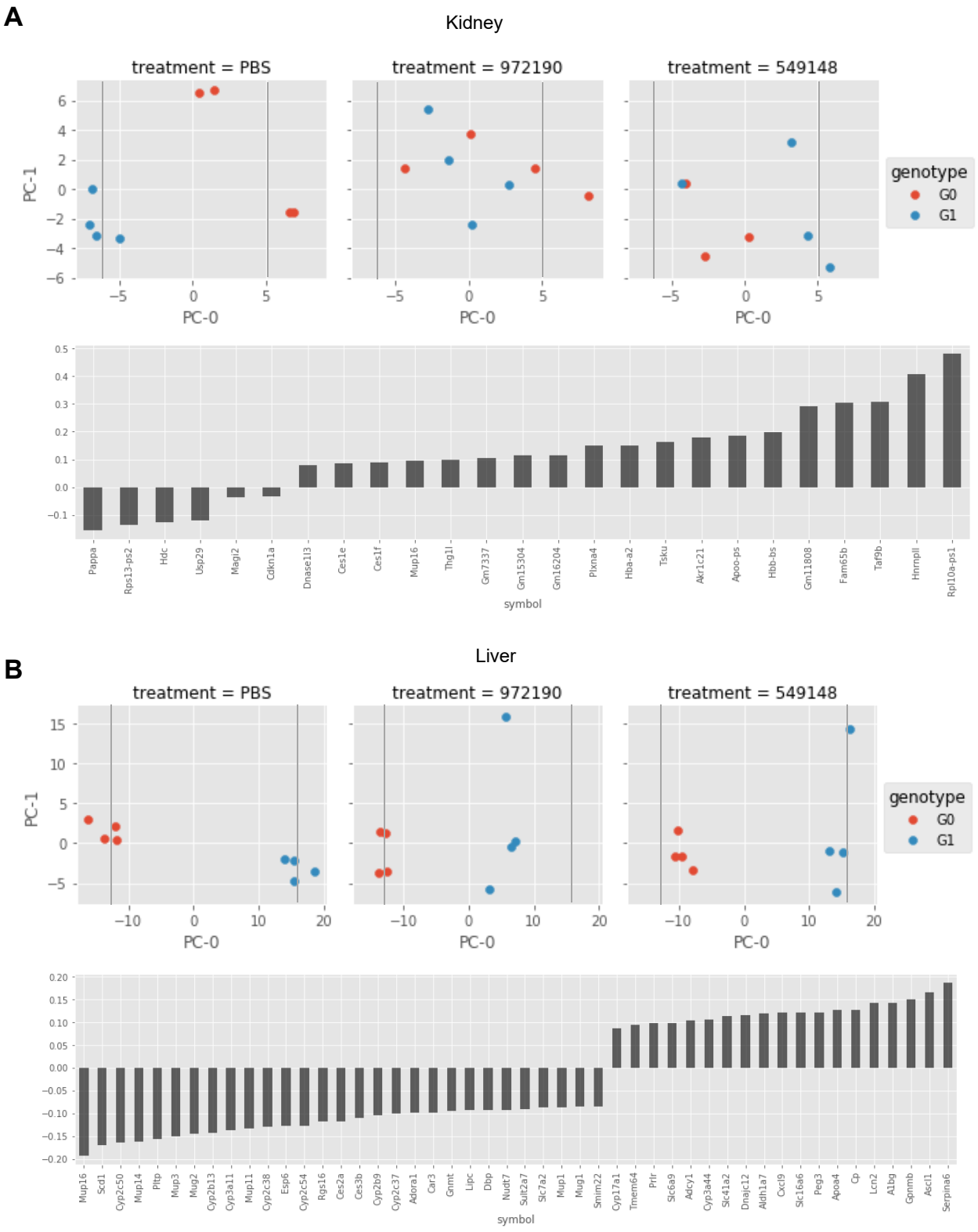
Supplemental Figure 5 Induction of proteinuria by IFNγ is specific to *APOL1* G1 transgenic mice. Female *APOL1* G0 and G1 transgenic and WT littermate mice (n=4) were challenged with a single dose of IFNγ ($1.125x10^7$ U/kg) or vehicle (PBS). (**A**) Kidney *APOL1* expression was measured by qRT-PCR 72 hours post-IFNγ challenge and normalized to *CYP* expression. (**B**) Urine was collected 24, 48, and 72 hours post-IFNγ challenge and urinary albumin was measured by ELISA and normalized to urine creatinine. (**C**) Kidney *Irf1* expression was measured by qRT-PCR 72 hours post-IFNγ challenge and normalized to *CYP* expression. All data are presented as means ± SD. Two-way ANOVA w/ Bonferroni's multiple comparisons test for (**A**) and two-way ANOVA w/ Tukey's multiple comparisons test for (**B**), p= ***<0.001.



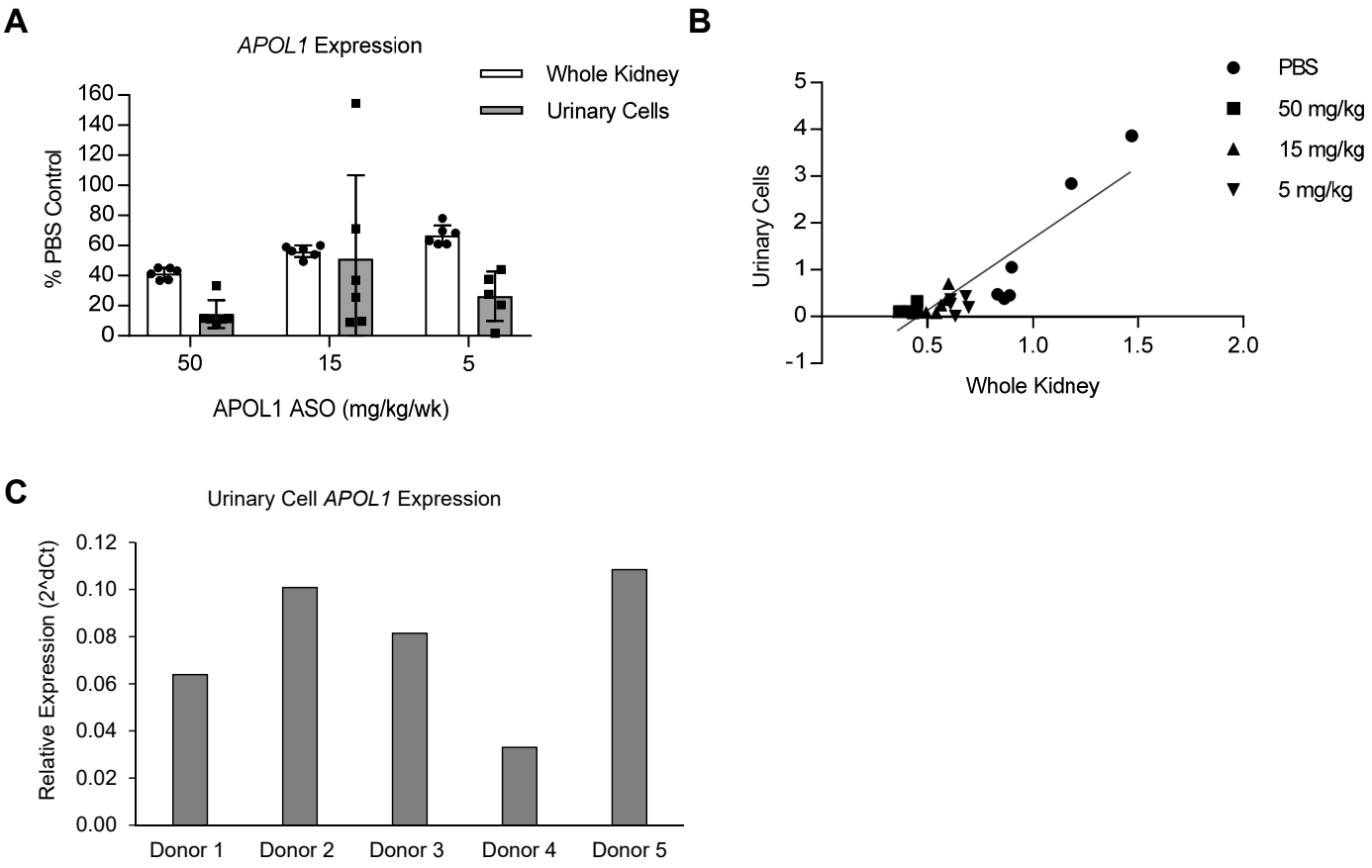
Supplemental Figure 6 Transcriptome signature from IFNγ-challenged *APOL1* G0 and G1 mice is sufficient to stratify CKD patients by histopathology and *APOL1* Risk status. Female *APOL1* G0 and G1 transgenic mice (*n*=4) were challenged with a single dose of IFNγ ($1.125x10^7$ U/kg) or vehicle (PBS) and sacrificed 48 hours later. Total RNA was isolated from whole kidney lysates and used for transcriptome profiling. (**A**) A heatmap displaying the average log2 expression ratios for all genes identified to be differentially expressed in contrasts comparing *APOL1* G0 to G1 mice or PBS to IFNγ-challenged mice (Supplemental Table 1). (**B**) Enrichr was used to interrogate the lists of differentially expressed genes, revealing significant enrichment of genes involved in various cellular components. (**C**) PCA was used to define a projection using the mouse gene expression levels (including only differentially expressed genes with measured human orthologues) that well-separated IFNγ-challenged animals from unchallenged animals (PC-0). *APOL1* G0 and G1 mice were also separable within this projection along PC-1. Gene weights for both PC-0 and PC-1 are shown along the respective axes. The projection including non-obvious human orthologous genes was similar (not shown). Excluding non-human orthologous genes is required for subsequent transfer of the projection to the human dataset. (**D**) Using this same projection, publicly available expression data from the NEPTUNE study (GSE68127) was rotated, and rotation matrix generated from mouse transcriptional profiles was found to provide a separation plane that can discriminate high risk (2 *APOL1* risk alleles) and low risk (0/1 *APOL1* risk alleles) *APOL1* individuals regardless of the reported histopathology. Solid black lines drawn to help visualize the separation.



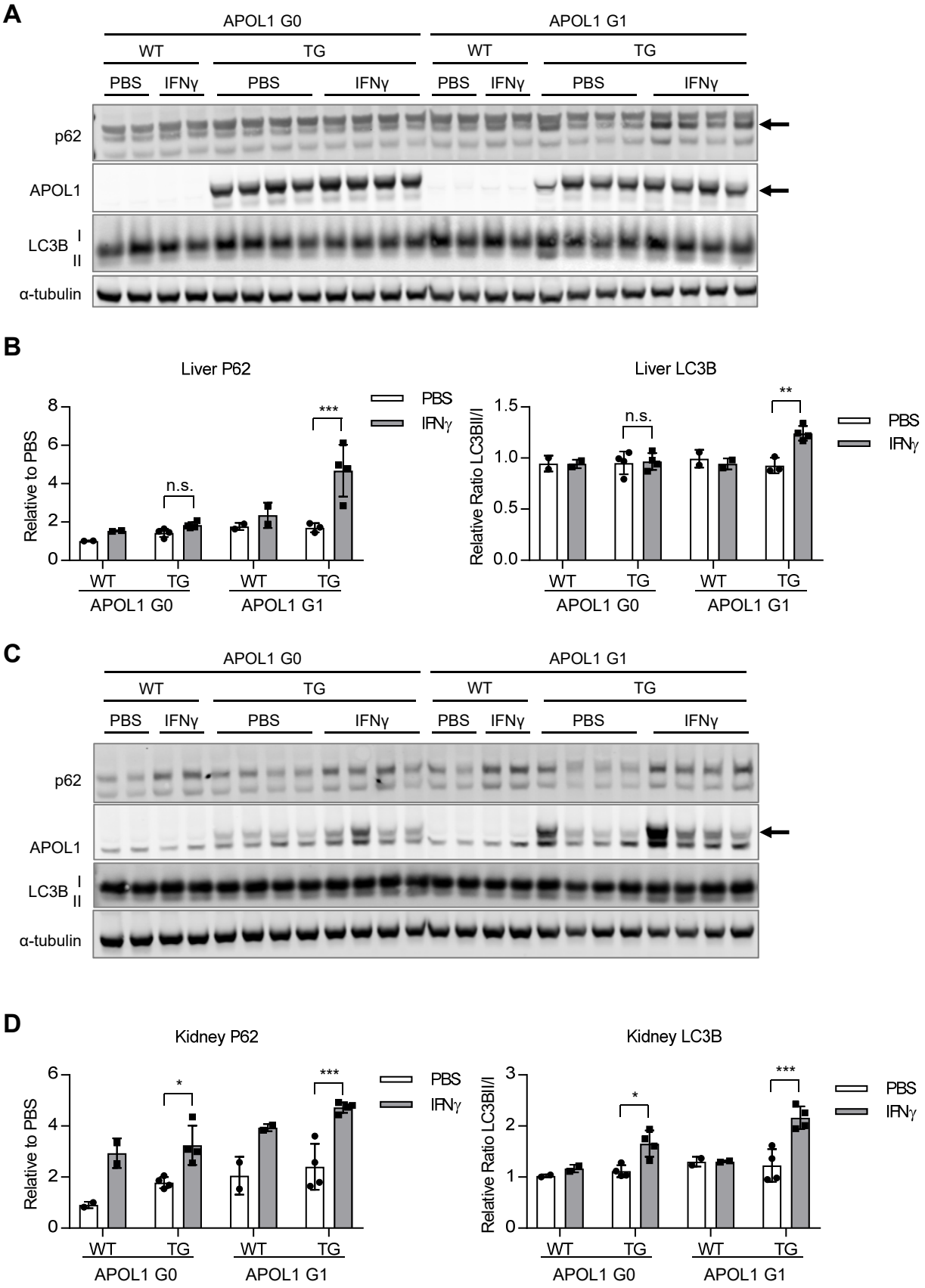
Supplemental Figure 7 Protective effect of IONIS-APOL1$_{Rx}$ on IFNγ-induced proteinuria is dose-dependent. Female *APOL1* G1 transgenic mice (*n*=3-4) were treated with IONIS-APOL1$_{Rx}$ or Control ASO 1x/week for 4 weeks and challenged with a single dose of IFNγ (1.125x10^7 U/kg) or vehicle (PBS). Study endpoints were evaluated 48 hours post-IFNγ challenge. (**A**) Urine was collected prior to sacrifice 48 hours post-IFNγ challenge and urinary albumin was measured by ELISA and normalized to urine creatinine. (**B**) Kidney *APOL1* expression was measured by qRT-PCR and normalized to *CYP* expression. (**C**) IHC analysis of APOL1 protein in kidney tissues from IONIS-APOL1$_{Rx}$-treated *APOL1* G1 transgenic mice 48 hours post-IFNγ or PBS challenge. Representative images shown (scale bar, 50 µm). All data are presented as means ± SD. Statistics performed by comparing each APOL1 ASO-treated PBS- or IFNγ-challenged group to the respective Control ASO group. Two-way ANOVA w/ Tukey's multiple comparisons test, *p*= *<0.05; **<0.01; ***<0.001.



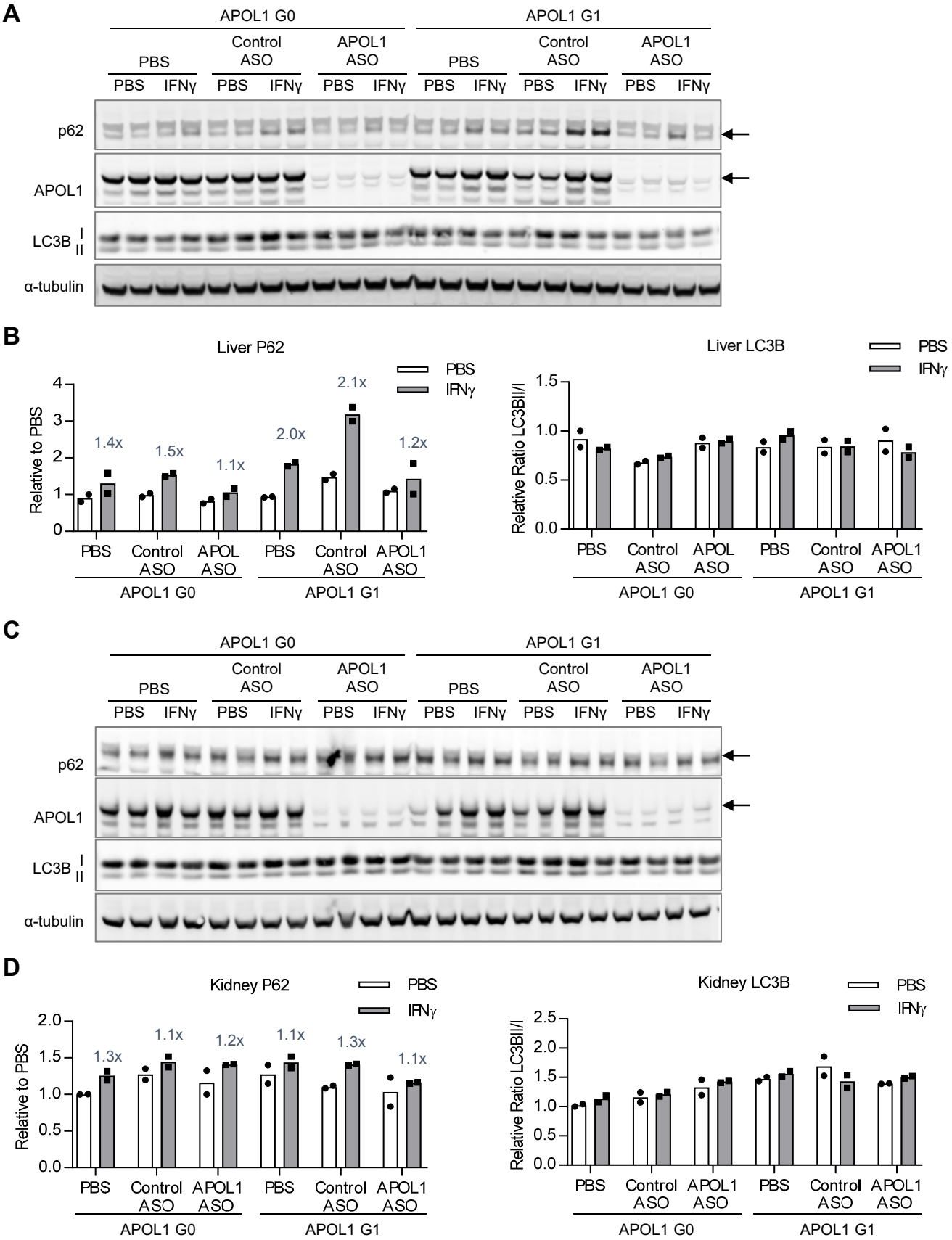
Supplemental Figure 8 IONIS-APOL1$_{Rx}$ treatment shifts the kidney and liver transcriptome profiles of G1 mice closer to that of G0 mice. Female *APOL1* G0 and G1 transgenic mice (*n*=4) were treated with PBS, 50 mg/kg IONIS-APOL1$_{Rx}$ or Control ASO 1x/week for 4 weeks. One day after the last ASO dose, mice were challenged with a single dose of IFNγ ($1.125x10^7$ U/kg) and sacrificed 48 hours later. Total RNA was isolated from whole kidney and liver tissue lysates and used for transcriptome profiling. PCA projections derived from all genes identified as being differentially expressed between the PBS-treated IFNγ-G0 mice and each of the indicated treatment groups for the **(A)** kidney and **(B)** liver transcriptome profiles of individual animals is shown. The sample-wise PCA rotation was defined using the 25 genes in kidney and 136 genes in liver identified to be differentially expressed in IFNγ-challenged G0-PBS mice (Supplemental Tables 2 and 3) variance stabilized gene expression levels. The transcriptional profiles of G0 and G1 mice are well-separated along PC-0 for both kidney and liver. IONIS-APOL1$_{Rx}$-mediated *APOL1* knockdown drives the transcriptional profile of these genes within this PCA projection to be more similar to mice expressing the *APOL1* G0 allele. Gene-weights for all genes (kidney) or genes whose weight was >1 standard deviation from the mean (liver) PC-0 weight are shown below.



Supplemental Figure 9 *APOL1* mRNA correlates to whole kidney *APOL1* expression in *APOL1* transgenic mice and can be detected in human urinary shed cell samples. (**A**-**B**) Male *APOL1* G1 transgenic mice (*n*=5-6) were treated with IONIS-APOL1$_{Rx}$ 1x/week for 4 weeks and urine was collected prior to sacrifice 48 hours after the last dose. (**A**) Urinary shed cell *APOL1* expression was measured by qRT-PCR and normalized to *36B4/Rplp0* expression. (**B**) Correlation graph showing the linear relationship (R^2=0.78) between *APOL1* mRNA levels in whole kidney and that in urinary shed cells. Fraction of average PBS control plotted for each animal. (**C**) Human urine was collected from healthy donors (*n*=5) and urinary shed cell *APOL1* expression was measured by qRT-PCR and normalized to *36B4/RPLP0* expression.



Supplemental Figure 10 IFNγ-induced suppression of autophagy is enhanced in G1 mice. Female *APOL1* G0 and G1 transgenic and WT littermate mice (*n*=3-4) were challenged with a single dose of IFNγ ($1.125x10^7$ U/kg) or vehicle (PBS). Western blot analysis of APOL1, p62 and LC3B expression in (**A**) liver and (**C**) kidney 24 hours post-IFNγ challenge. Each lane represents an individual animal (only 2 of 3-4 WT animals shown per group). Quantification of (**B**) liver and (**D**) kidney p62 Western blots were performed by normalizing the intensity of p62 to that of α-tubulin and shown as relative to *APOL1* G0 WT PBS. Quantification of LC3B Western blots was performed by calculating the ratio between intensities of LC3B-II to LC3B-I and normalizing the ratio to the intensity of α-tubulin. Data are presented as means ± SD. Two-way ANOVA w/ Tukey's multiple comparisons test, *p*= *<0.05; **<0.01; ***<0.001.



Supplemental Figure 11 IFNγ-induced suppression of autophagy is reduced by IONIS-APOL1$_{Rx}$ treatment. Female *APOL1* G0 and G1 transgenic mice (*n*=3-4) were treated with 50 mg/kg IONIS-APOL1$_{Rx}$ or Control ASO 1x/week for 4 weeks and challenged with a single dose of IFNγ ($1.125x10^7$ U/kg) or vehicle (PBS). Western blot analysis of APOL1, p62 and LC3B expression in (**A**) liver and (**C**) kidney 48 hours post-IFNγ challenge. Each lane represents an individual animal (2 representative animals shown per group). Quantification of (**B**) liver and (**D**) kidney p62 and LC3B Western blots were performed as in Supplemental Figure 9. Fold-change in p62 levels shown are in comparison to PBS-challenged controls in each group. Data are presented as means.