Supplemental Methods

Glomerular RNA-seq:

Total RNA from 269 biopsies were prepared using the Clontech SMARTSeq v4 kit. Samples underwent sequencing using Illumina HiSeq 2500, resulting in 150bp unstranded, paired-end reads. Fastq files underwent quality control filtering and trimming using fastQC, fastQScreen[1], and Picard Tools (http://broadinstitute.github.io/picard/). Trimmed reads were aligned to the human genome (GRCh37) with STAR 2.6.0a[2]. Gene expression counts were quantified using StringTie v2.1.4[3]. The genes were filtered to protein-coding genes with at least ten normalized counts in 14 samples. Variance stabilizing transformation was applied to counts in DESeq2[4]. The transformed reads were quantile normalized (https://github.com/bmbolstad/preprocessCore) and corrected for batch effects with Combat[5]. We used sampleNetwork[6] to identify samples with outlying expression profiles, standardized connectivity < -3. This process was repeated until no outliers remained.

Differential Coexpression:

Differential co-expression gene modules were built using methods outlined by DiffCoEx[16] (see Supplement for full details). We calculated the adjacency matrix of Spearman correlations for high-risk and low-risk separately. We then computed the matrix of adjacency differences, ranging from 0 to 1, where 1 indicates the strongest difference in correlations and 0 indicates no difference, followed by the topology overlap matrix (TOM) using the TOMdist function from WGCNA. The TOM was then clustered using flashClust with the "average" method. Modules were identified with the WGCNA function cutreeDynamic, with the "hybrid" method, cutHeight=0.996, deepSplit=T, pamRespectsDendro=F, and minClusterSize =20. Close modules were merged with mergeCloseModules using a cutHeight=0.2. Intra-modular connectivity for each gene was defined as the sum of adjacencies (from the matrix of adjacency differences) normalized by the largest connectivity value in the gene module; thus, the most connected gene would have normalized intra-modular connectivity of 1. Hub genes were defined as genes with intra-modular connectivity greater than 0.7. We used Cytoscape (v3.7.2) to visualize the correlation networks utilizing the ExpressionCorrelation (v1.1.0) app. Submodules were identified by comparing the genes' hierarchical clustering within a DiffCoEx module in high-risk and low-risk separately. Permutation methods described by Tesson BM et al. [16] were used to test significance of gene modules. Submodule eigengenes (1st principal component) were used to compare patterns between submodules.

1. Wingett SW, Andrews S. FastQ Screen: A tool for multi-genome mapping and quality control. *F1000Res* 2018; **7:** 1338.

2. Dobin A, Davis CA, Schlesinger F*, et al.* STAR: ultrafast universal RNA-seq aligner. *Bioinformatics* 2013; **29:** 15-21.

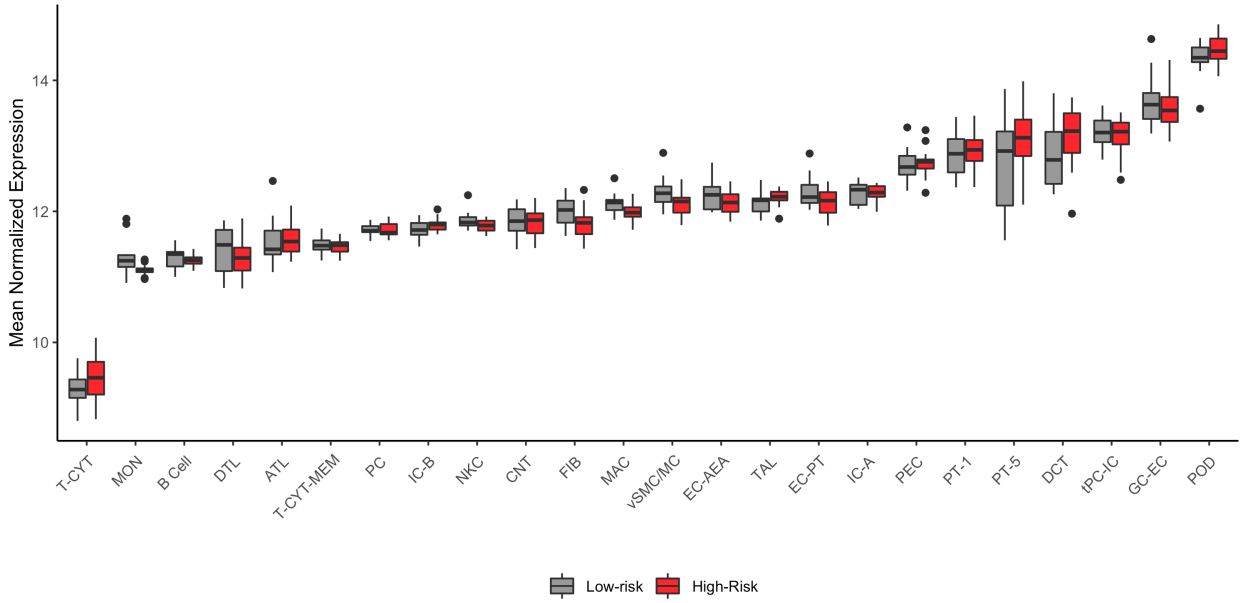
3. Pertea M, Pertea GM, Antonescu CM*, et al.* StringTie enables improved reconstruction of a transcriptome from RNA-seq reads. *Nat Biotechnol* 2015; **33:** 290-295.

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

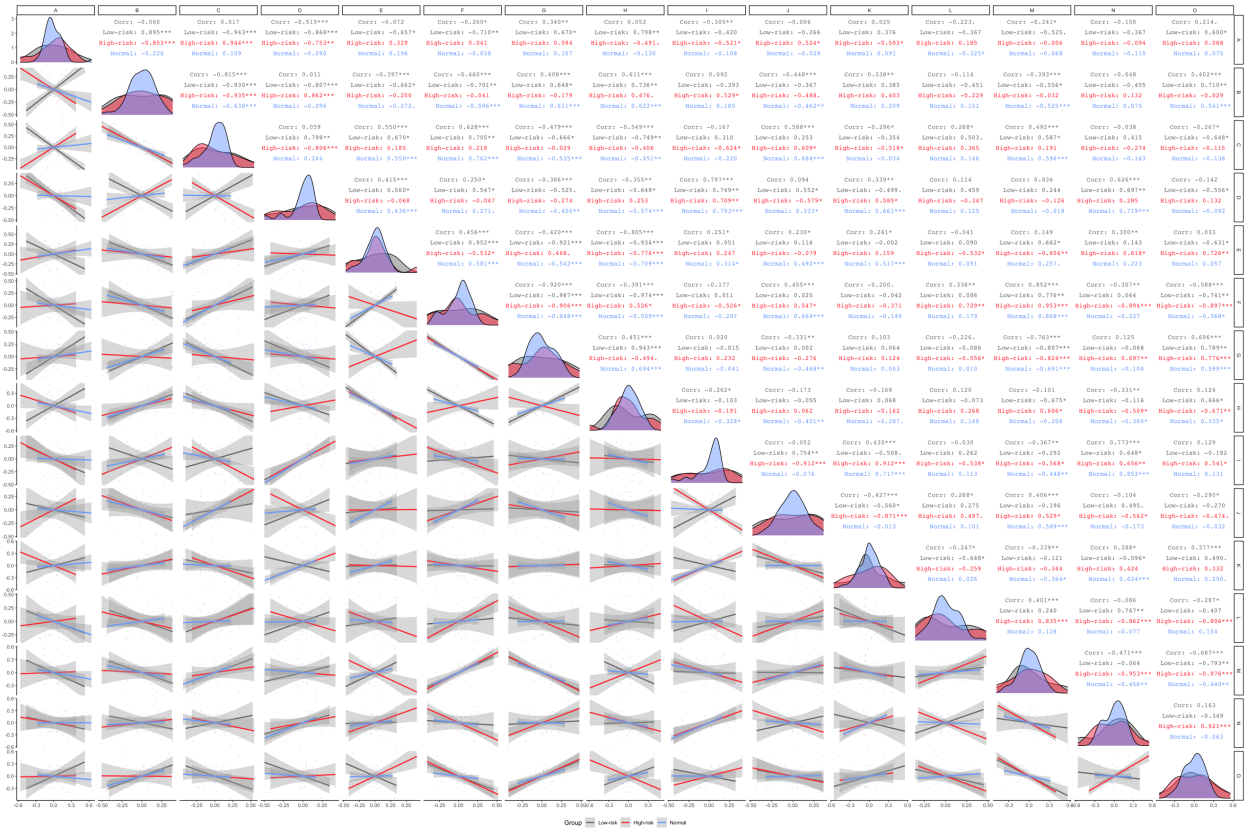
5. Zhang Y, Jenkins DF, Manimaran S*, et al.* Alternative empirical Bayes models for adjusting for batch effects in genomic studies. *BMC Bioinformatics* 2018; **19:** 262.

6. Oldham MC, Langfelder P, Horvath S. Network methods for describing sample relationships in genomic datasets: application to Huntington's disease. *BMC Syst Biol* 2012; **6:** 63.

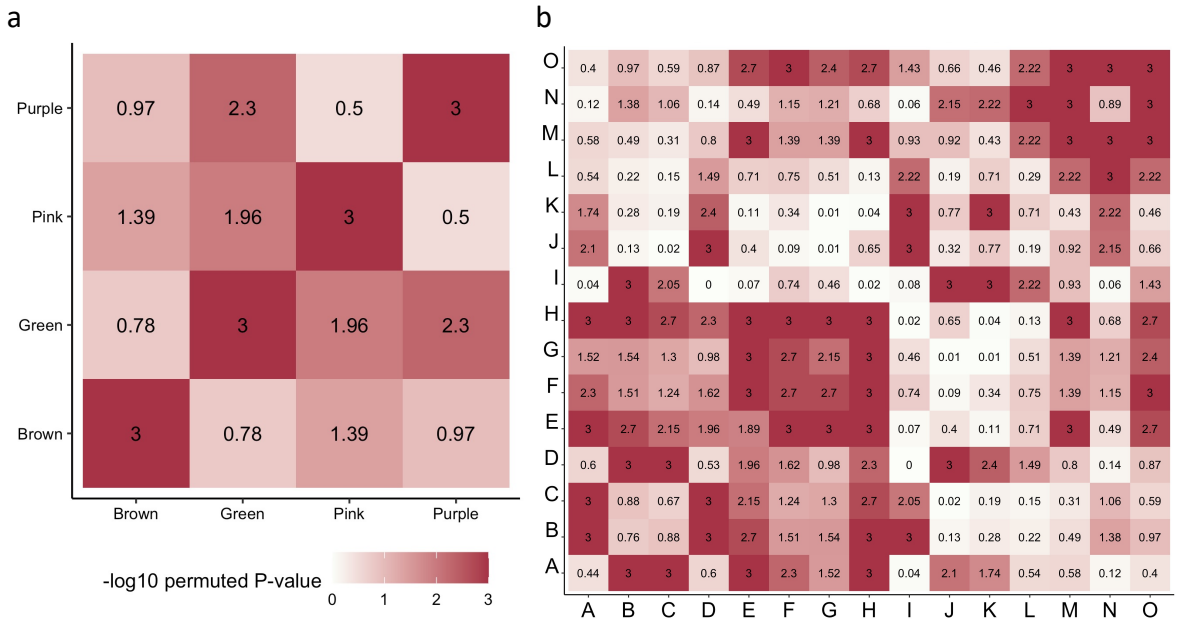
Supplemental Figures



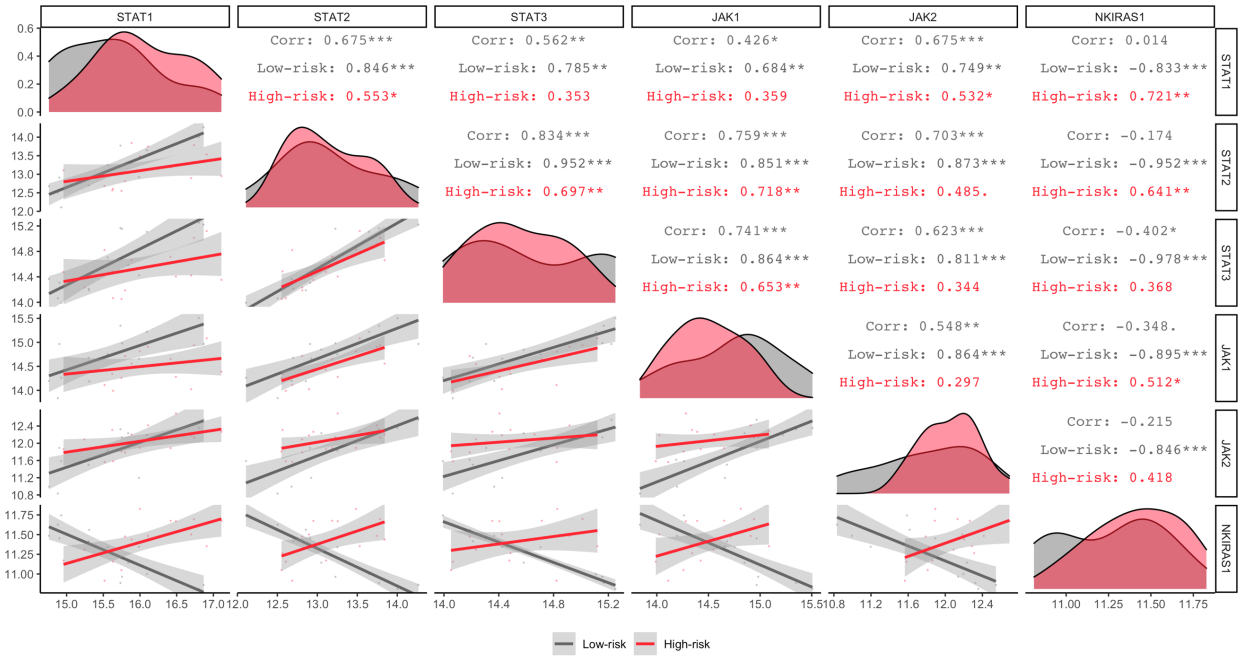
Supplemental Figure 1 - Mean expression of cell-type-specific genes per person stratified by high-risk and low-risk *APOL1* genotype: No significant differences were identified using a Bonferroni adjusted threshold = 0.004. T-CYT=cytotoxic T-cell, MON=monocyte, DTL=descending thin limb cell, ATL=ascending thin limb cell, T-CYT-MEM=memory T-cell, PC=principal cell, IC-B=intercalated beta cell, NKC=NK cells, CNT=connecting tubule, FIB=fibroblast, MAC=macrophage, vSMC/MC=vascular smooth muscle cell and mesangial, EC-AEA=endothelial cell, TAL=thin ascending limb cell, EC-PT=peritubular endothelial cell, IC-A=intercalated alpha cell, PEC=parietal epithelial cell/loop of Henle, PT-1=proximal tubule, PT-5=proximal tubule, DCT=distal convoluted tubule cell, tPC-IC=transitioning principal cell/intercalated cell, GC-EC=glomerular capillary endothelial cell, POD=podocyte.



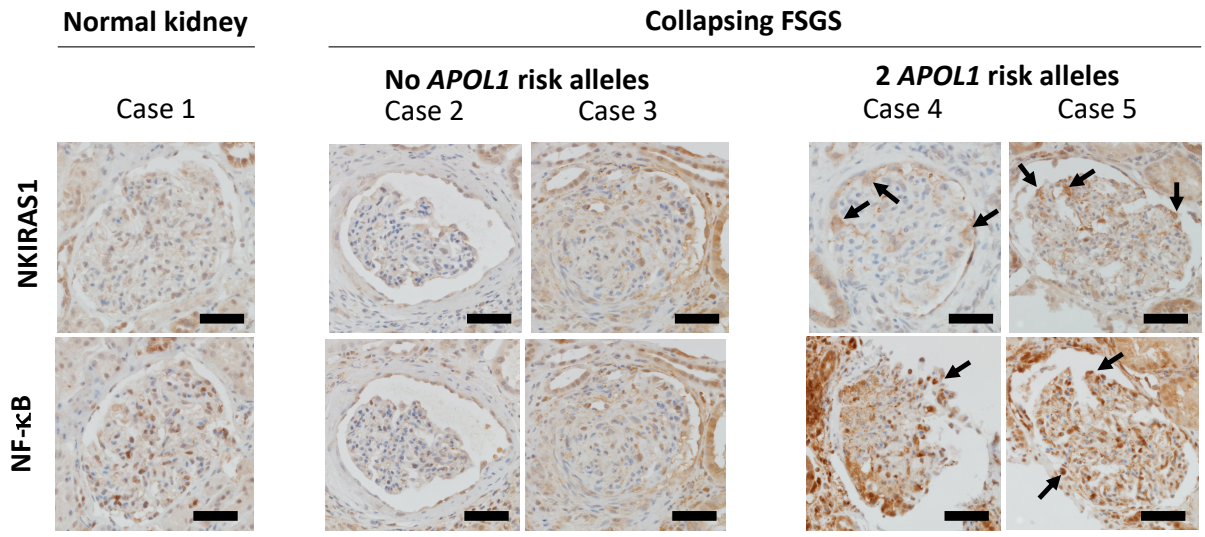
Supplemental Figure 2 - Eigengene Spearman correlations for all differentially co-expressed submodules in high-risk, low-risk, and healthy glomerular tissue: Eigengenes summarized gene expression behavior in each submodule and were defined as the first principal component of the group-specific gene expression matrices. Submodules are labeled along the x and y-axis. Diagonal – eigengene density plots. Below diagonal – scatter plot comparing submodule eigengenes (each point represents a sample). Above diagonal – Spearman correlations stratified by group ("Corr" is correlation in groups combined). Correlation significance - "***" $p < 0.01$, "**" $p<0.01$, "*" $p<0.05$, "." $p<0.1$



Supplemental Figure 3 - Significance of correlation changes within (diagonal) and between (off-diagonal) differentially co-expressed modules (A) and submodules (B)*:* Both heatmaps are symmetric. For each figure, 1,000 permutations of samples were performed, and dispersion (correlation changes between groups) was calculated. We recorded the number of times the permuted data set resulted in more dispersion than our HR vs. LR analysis. We then -log10 transformed the permuted p-value (number of permutations with higher dispersion / 1,000). A -log10 p-value of 3 indicates changes in correlation patterns between HR and LR were stronger than any 1,000 permutation sample sets.



Supplemental Figure 4 Spearman correlations between *JAK/STAT* genes from submodule E and hub-gene *NKIRAS1* stratified by high-risk and low-risk: Genes are labeled along the x and y-axis. Diagonal –gene expression density plots. Below diagonal – scatter plot comparing gene expression (each point represents a sample). Above diagonal – Spearman correlations stratified by group ("Corr" is correlation in groups combined). Correlation significance - "***" $p < 0.01$, "**" $p<0.01$, "*" $p<0.05$, "." $p<0.1$



Supplemental Figure 5. Differences in glomerular immunohistochemical staining for NF-κB and NKIRAS1 in the normal human kidney compared to biopsies of patients with Collapsing FSGS and 0 or 2 confirmed *APOL1* risk alleles. **Upper panel:** NKIRAS1 appears to be weakly expressed in the nucleus of podocytes in the normal kidney. This staining shows a partial shift to the podocyte cytoplasm in patients with collapsing FSGS and zero *APOL1* risk alleles; the shift and intensity of the cytoplasmic staining appears to be enhanced in patients with collapsing FSGS and 2 *APOL1* risk alleles (arrows). **Lower panel**: NFκB shows a nuclear staining pattern in the normal kidney, most prominently in glomerular podocytes. No significant difference in staining is noted in glomeruli of patients with a diagnosis of collapsing FSGS and confirmed 2 wildtype *APOL1* alleles. In contrast, glomeruli of patients with collapsing FSGS and 2 confirmed *APOL1* risk alleles show enhanced nuclear and weak cytoplasmic staining for NFκB (arrows). Scale bars: 50mm.