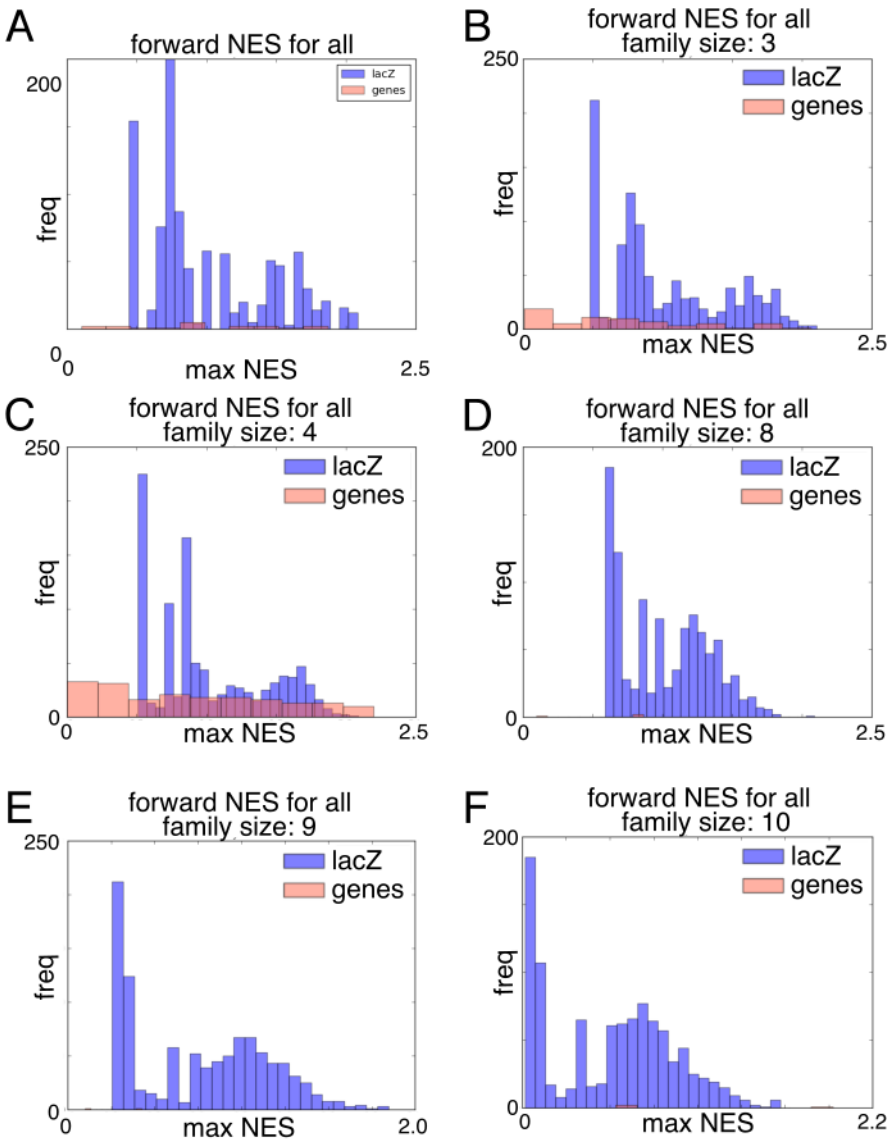
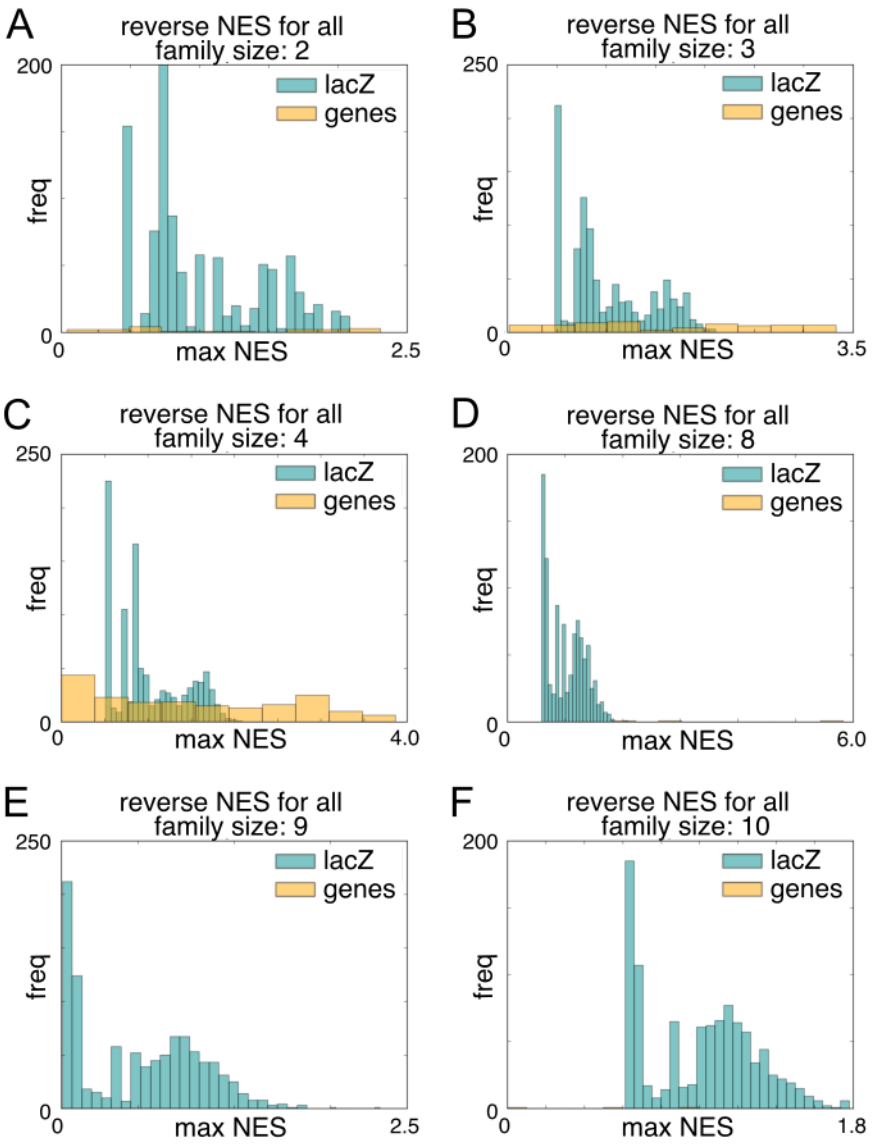
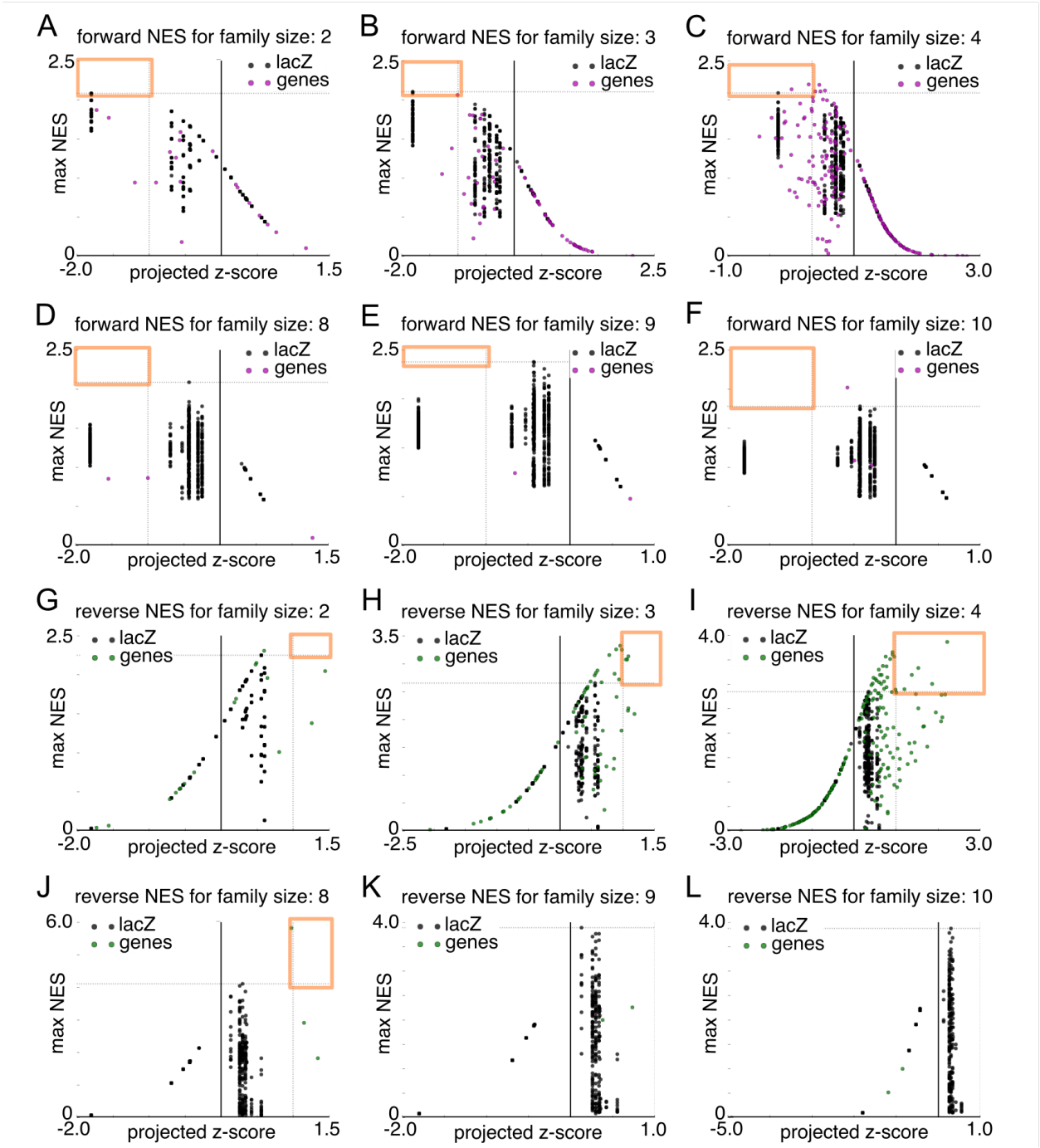


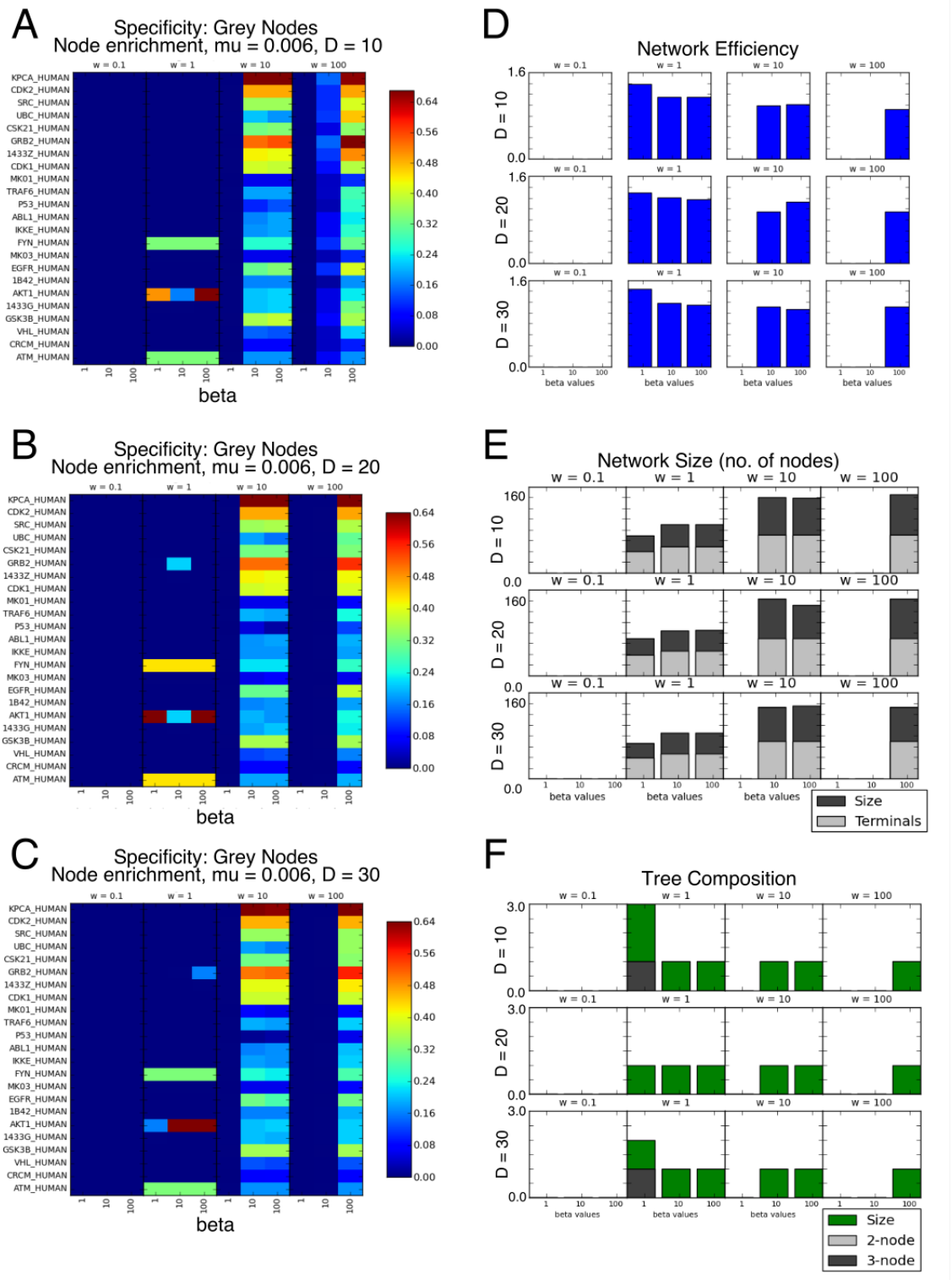
Supplemental Fig. 1. Forward normalized enrichment scores (NES) histograms for shRNA families with 2/3/4/8/9/10 shRNAs. **(A-F)** Histograms for 5-shRNA family shown in Figure 1. In all panels, the dark purple distributions represent a distribution of shRNA scores calculated from lacZ controls and the light pink distributions represent scores calculated using gene-targeting shRNAs.



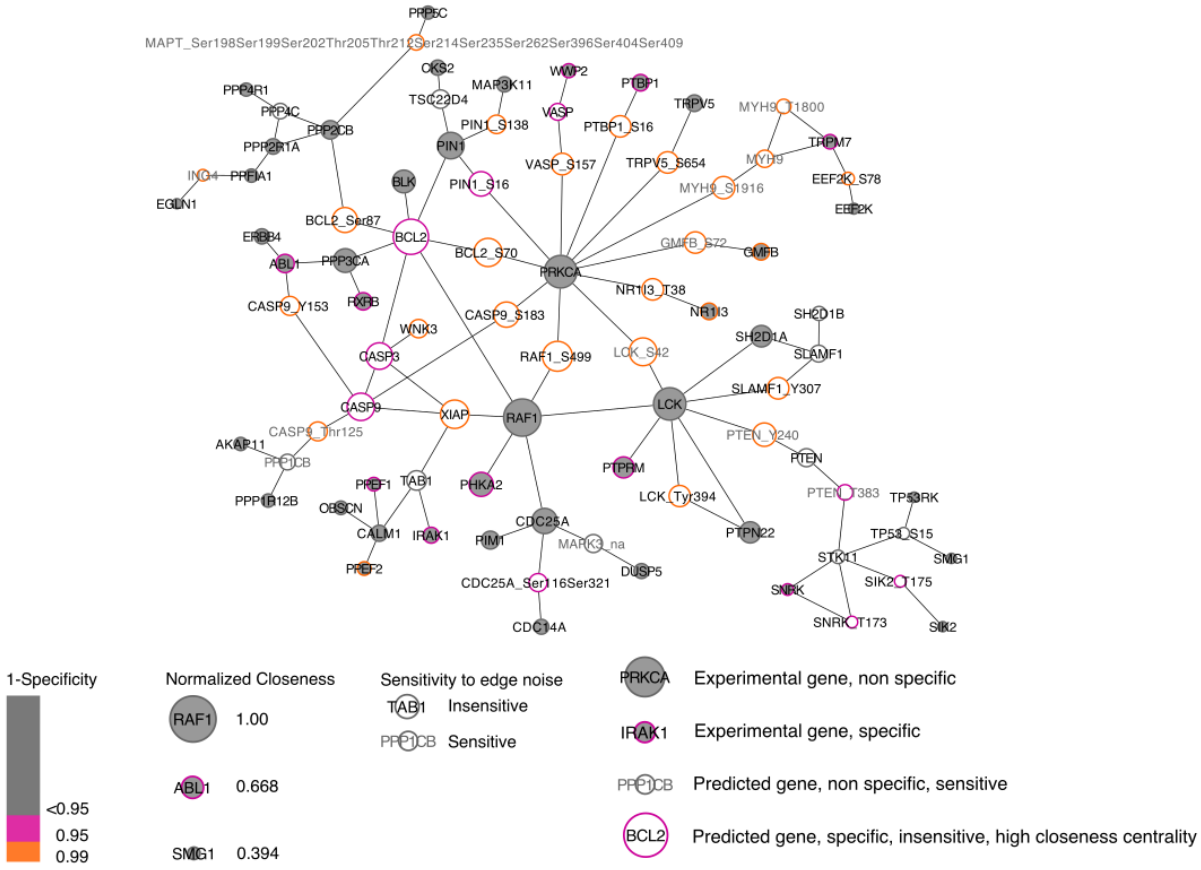
Supplemental Fig. 2. Reverse normalized enrichment scores (NES) histograms for all shRNA families with 2/3/4/8/9/10 shRNAs. (**A-F**) Histograms for 5-shRNA family shown in Figure 1. In all panels, the blue distributions represent a distribution of shRNA scores calculated from lacZ controls and the yellow distributions represent scores calculated using gene-targeting shRNAs.



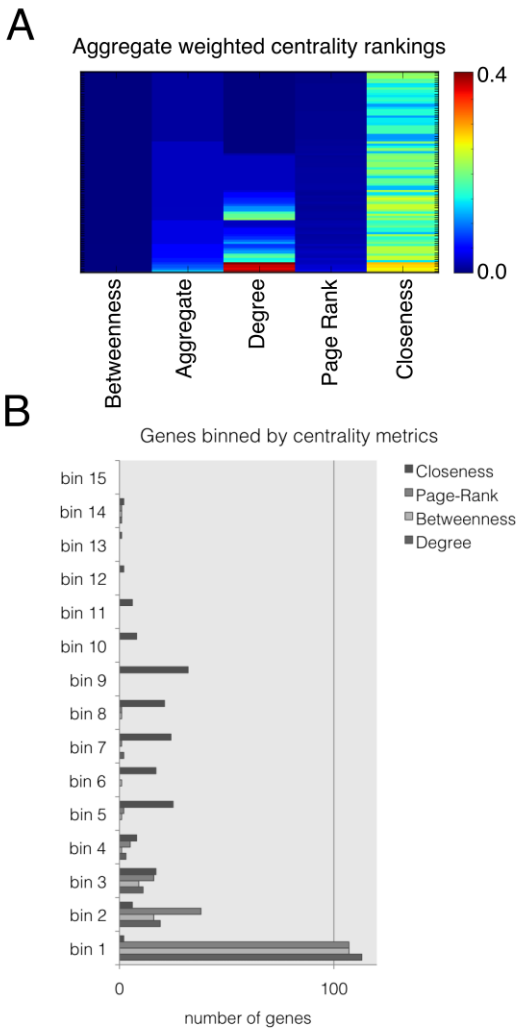
Supplemental Fig. 3. Scatter plots for all shRNA family sizes in the forward (**A-F**) and reverse directions (**G-L**). In all plots, each individual point represents an shEnrich score (y-axis) and max effect size (x-axis) for each gene (colored points) with a particular shRNA family size or a random sampling of lacZ controls (black points). Orange rectangles define a region for selecting gene targets for further modeling. This region is defined as having an shEnrich score above all lacZ controls and a max effect size < -1.0 z-scores (for forward calculations, **A-F**) or an shEnrich score above lacZ controls and a max effect size >1.0 z-scores (for reverse calculations, **G-L**). For most genes, they were no more consistent than the lacZ controls and did not make the threshold for further modeling.



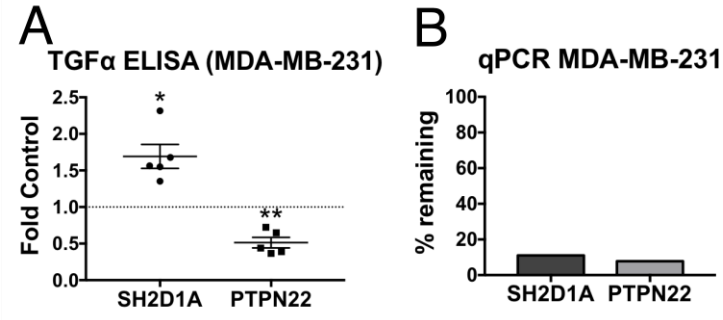
Supplemental Fig. 4. Optimization of network node selection. We optimized the PCSF parameters, beta, omega, and depth. (**A-C**) show fractional representation of 'grey nodes' (the nodes with the highest connectivity in our starting interactome) in 100 random networks created with depth=10 (**A**), depth=20 (**B**), and depth=30 (**C**). Each row represents an individual grey node, and the columns represent different combinations of omega (0.1,1,10, and 100) and beta (1,10,100). We additionally measured network efficiency (ratio of experimental: predicted nodes) (**D**), the relative network size (**E**), and the number of 1/2/3-node trees (**F**) at each of these parameter combinations.



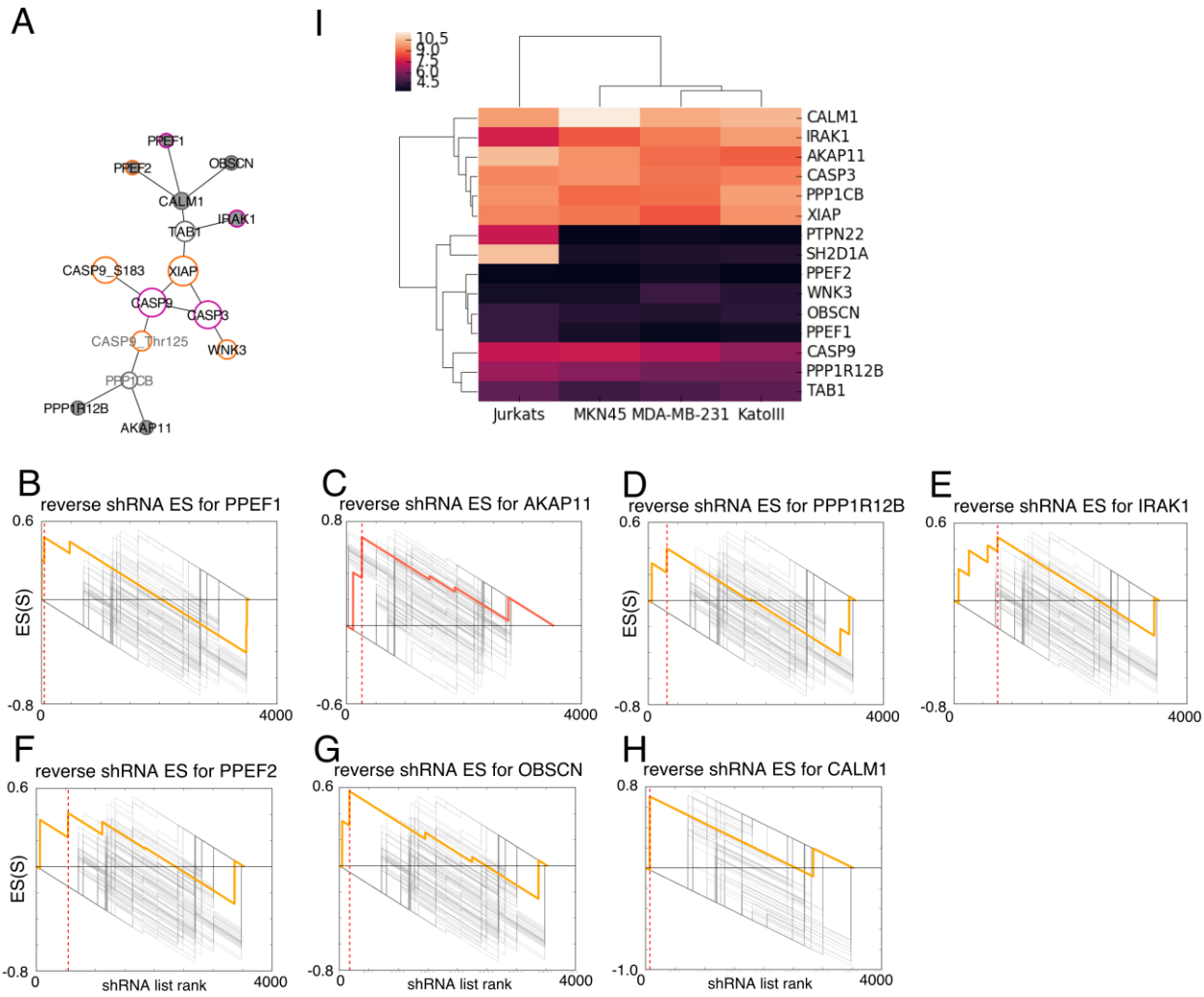
Supplemental Fig. 5. The full network selected by PCSF. Grey face coloring indicates genes selected from the original experimental data set; white face represents predicted genes (genes and phospho-sites) selected by the algorithm. Gene border represents specificity to randomization (pink<=0.1; orange<=0.05), and gene size represents closeness centrality (larger genes are more central and more robust). Grey gene labels indicate genes that are sensitive to edge noise. Genes on the far right are annotated examples to help interpret all their network properties. This network includes all edges contained in the augmented forest created by PCSF and shows interaction edges before cluster with the GLay plugin in Cytoscape.



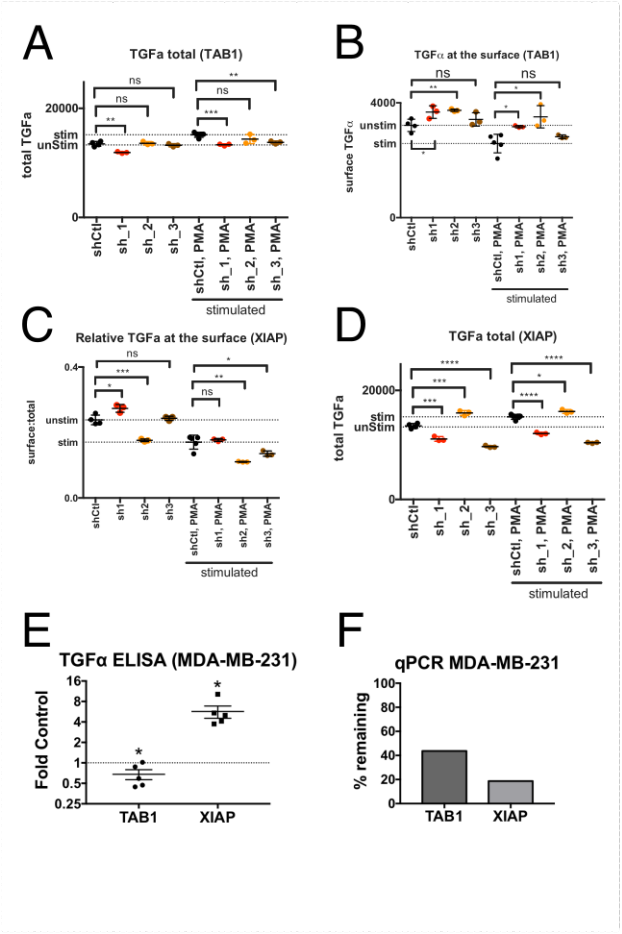
Supplemental Fig. 6. Centrality metrics test gene robustness. (**A**) Network genes ranked by Degree, Betweenness, Page-Rank, and Closeness centrality. The Aggregate represents the multiplicative sum of all ranks. (**B**) Gene membership in centrality metric bins. Bin 1 contains genes with low centrality scores and bin 15 contains genes with high centrality scores.



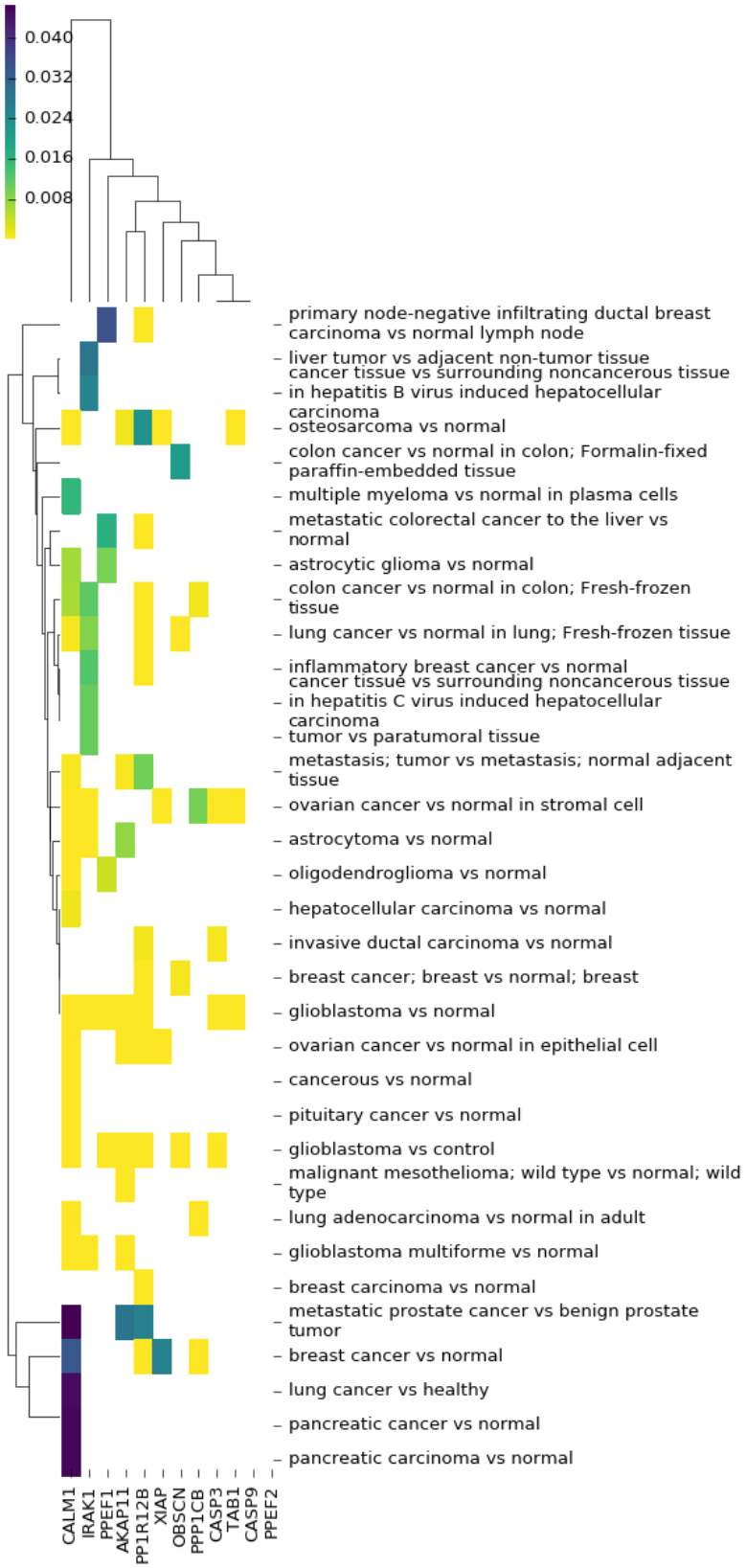
Supplemental Fig 7. Validation of effect of experimental genes on TGFα cleavage in MDA-MB-231 cells. **(A)** Knockdown of SH2D1A enhanced and knockdown of PTPN22 decreased TPA-stimulated TGFα cleavage from MDA-MB-231 cells as measured by ELISA. *p≤0.05; **p≤0.01. **(B)** Knockdown of SH2D1A and PTPN22 was monitored by qPCR.



Supplemental Fig. 8. Validated gene cluster with known associations to the NFκB pathway. The cluster of genes is shown in the upper left (**A**). Lightening plots for experimental genes within the validated cluster are plotted for PPEF1 (**B**), AKAP11(**C**), PPP1R12B (**D**), IRAK1 (**E**), PPEF2 (**F**), OBSCN (**G**), and CALM1 (**H**). The enrichment score (ES) is plotted against the ranked shRNAs. The ES increases each time that an shRNA at a ranking targets the gene of interest. Otherwise, the ES decreases linearly. The grey lines are 100 representative plots of subsets of the non-targeting shlacZ controls. Genes which are enriched in the forward/reverse direction correspond to genes whose shRNAs increase/decrease shedding. (**I**) RMA-normalized mRNA expression for NF-κB associated genes, SH2D1A, and PTPN22 in Jurkat, MKN-45, MDA-MB-231, and Kato-III cells. Color bar indicates RMA-normalized mRNA expression values as reported by CCLE.



Supplemental Fig. 9. Validation of predicted genes on TGFα cleavage in Jurkat and MDA-MB-231 cells. (**A**) Knockdown of TAB1 has no effect on total TGFα with three individual shRNAs (**B**) Knockdown of TAB1 increases TGFα at the surface with three individual shRNAs (**C**) Knockdown of XIAP with three individual shRNAs had mixed effects on relative amount of TGFα at the surface (**D**) Knockdown of XIAP with three individual shRNAs had mixed effects on total TGFα in both stimulated and unstimulated conditions. Error bars are standard error of the mean. We used an unpaired t-test to test significance. *p≤0.05; **p≤0.01;***p≤0.001; ****p<0.0001. (**E**) Knockdown of TAB1 decreased and knockdown of XIAP enhanced TPA-stimulated TGFα cleavage from MDA-MB-231 cells as measured by ELISA. *p≤0.05. (**F**) Knockdown of TAB1 and XIAP was monitored by qPCR.



Supplemental Fig. 10. Statistical significance of differential expression in cancer cell lines from Expression Atlas. P-values for differential expression comparisons from **Figure 6F** are plotted as reported from the Expression Atlas. Colorbar indicates p-value.