

Supplementary Information

Supplementary Data 1, related to Fig. 2. The first sheet shows the list of *Drosophila* genes and human orthologs that were hits from the screen for age-associated neurodegeneration. Human orthologs of genetic screen hits in *Drosophila* were inferred using DIOPT. The second sheet shows GO biological process pathway enrichment analysis results for *Drosophila* modifiers of age-associated neurodegeneration. The third sheet shows the GO biological pathway enrichment analysis for all tested *Drosophila* genes. P-values are defined as hypergeometric p-values after g:SCS correction. The fourth sheet lists all *Drosophila* stocks tested.

Supplementary Data 2. Tables of previously published *Drosophila* proteomics and transcriptomics to show that neurodegeneration screen hits are enriched in proteins and genes whose abundance and expression significantly changes with age. Each table corresponds to a different study, as cited in the table names.

Supplementary Data 3, related to Fig. 3. eQTL analysis was performed in eight cohorts based on cortex and laser captured temporal cortex pyramidal neurons (TCPY). Abbreviations: D, Discovery phase; TCPY, temporal cortex pyramidal neurons; R, Replication phase; RIN, RNA Integrity Number; PMI, Post-mortem interval; sd, standard deviation; WGS, Whole Genome Sequencing.

Supplementary Data 4, related to Table 1: Results from the discovery phase of the eQTL analysis. P-value is derived from a chi-squared test. Significance is determined by Bonferroni FDR correction.

Supplementary Data 5, related to Fig. 3: Proteomics from control flies, A β ₁₋₄₂ transgenic flies, and tau^{R406W} transgenic flies.

Supplementary Data 6, related to Fig. 3: Phosphoproteomics from control flies, A β ₁₋₄₂ transgenic flies, and tau^{R406W} transgenic flies.

Supplementary Data 7, related to Fig. 3: Metabolomics from control flies, A β ₁₋₄₂ transgenic flies, and tau^{R406W} transgenic flies.

Supplementary Data 8, related to Fig. 4: Files regarding network inputs and outputs. The first sheet is the Input file for OmicsIntegrator2 analysis. "ID" indicates the gene or metabolite name, "prize_val" is the min-max normalized weight for the individual node, "source" is the data type of origin and "magnitude" is the effect size of change, where available. "Node prize overlap" shows the nodes in the network enriched in multiple data sources, the data sources from which they were derived and the normalized prize values per group. "Nodes in network" shows the nodes in the final network solution. "Edges contributed" shows the number of edges that include a particular data source. Pathways by subnetwork shows the enriched pathways in each subnetwork. "Contributed pathways" shows the pathways that were contributed by a

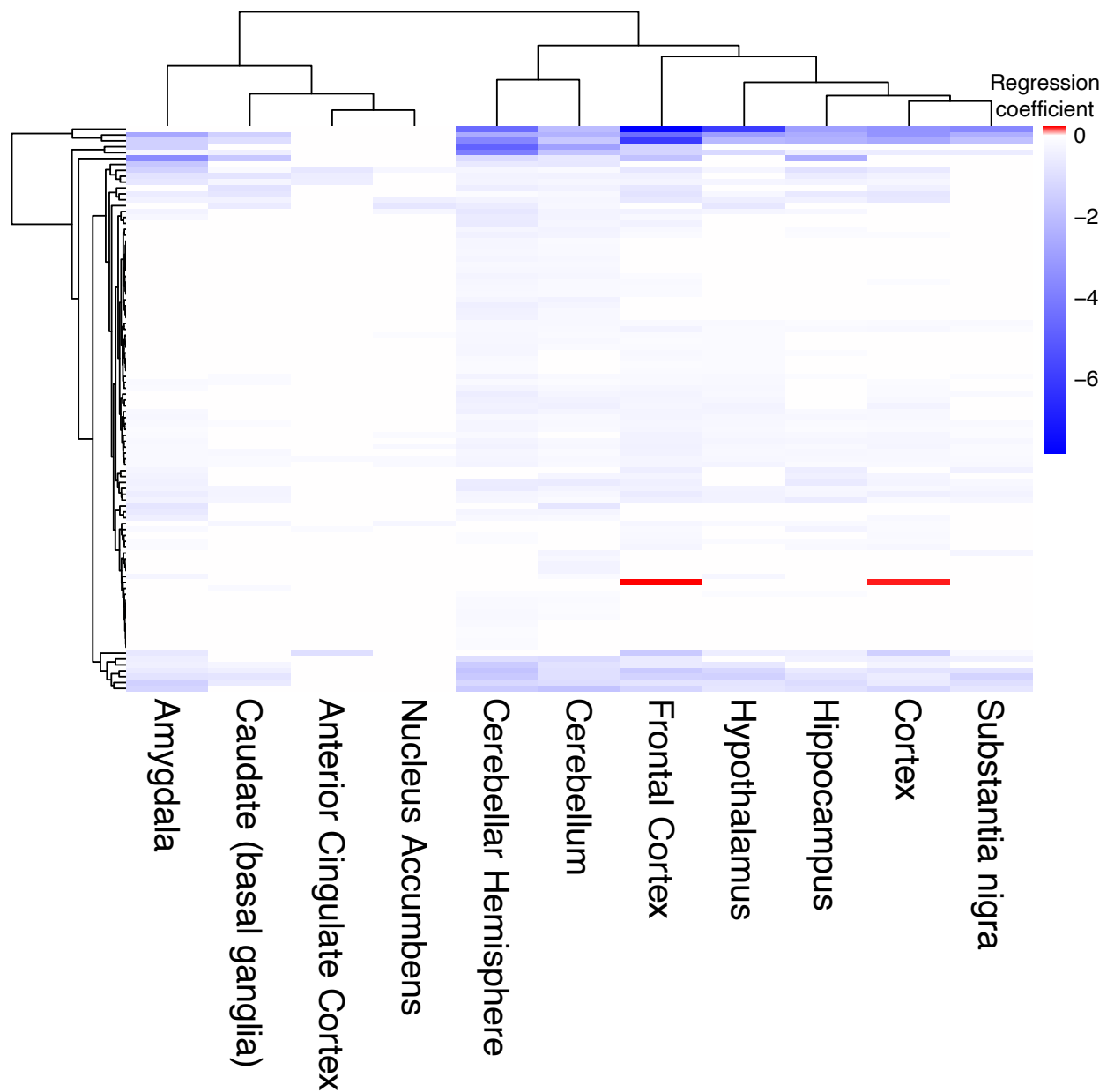
particular data type, while contributed nodes shows the pathways that were contributed by a particular data type. “Node count by parameter” shows the number of nodes in the final network solutions depending on the hyperparameter choices. “Pathway enrichments overlapping” shows the results of hypergeometric tests for pathway enrichment in nodes that are enriched in more than one data type. P-values are FDR corrected using the g:SCS correction. “Pathway enrichments by method” shows the pathway enrichments using different network optimization methods. P-values of pathway enrichments are derived from a g:SCS FDR-corrected binomial test.

Supplementary Data 9, related to Figs. 5 and 6: Results from the differential expression analyses using DeSeq2 for *NOTCH1*, *CSNK2A1* and *HNRNPA2B1* knockdown in NGN2 neural progenitor cells. P-value is derived from a Wald test and is displayed as an FDR-corrected p-value using the Benjamini-Hochberg procedure.

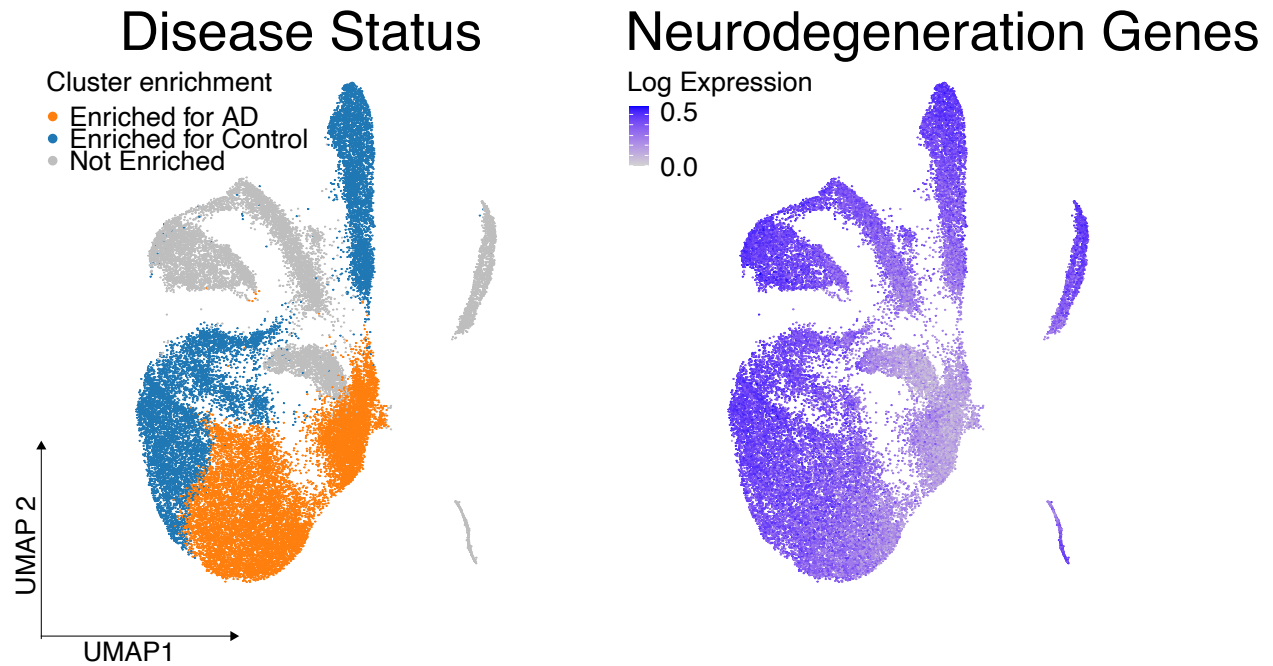
Supplementary Data 10, related to Figs. 5 and 6: Gene Set Enrichment analysis results for NGN2 neural progenitor cells after *NOTCH1*, *CSNK2A1* and *HNRNPA2B1* knockdown. P-value is presented as an empirical p-value after 1000 randomizations. The table reports the p-values after Benjamini-Hochberg FDR correction.

Supplementary Data 11, related to Fig. 6: Measurement of betweenness centrality among nodes that regulate DNA damage and neurodegeneration screen hits.

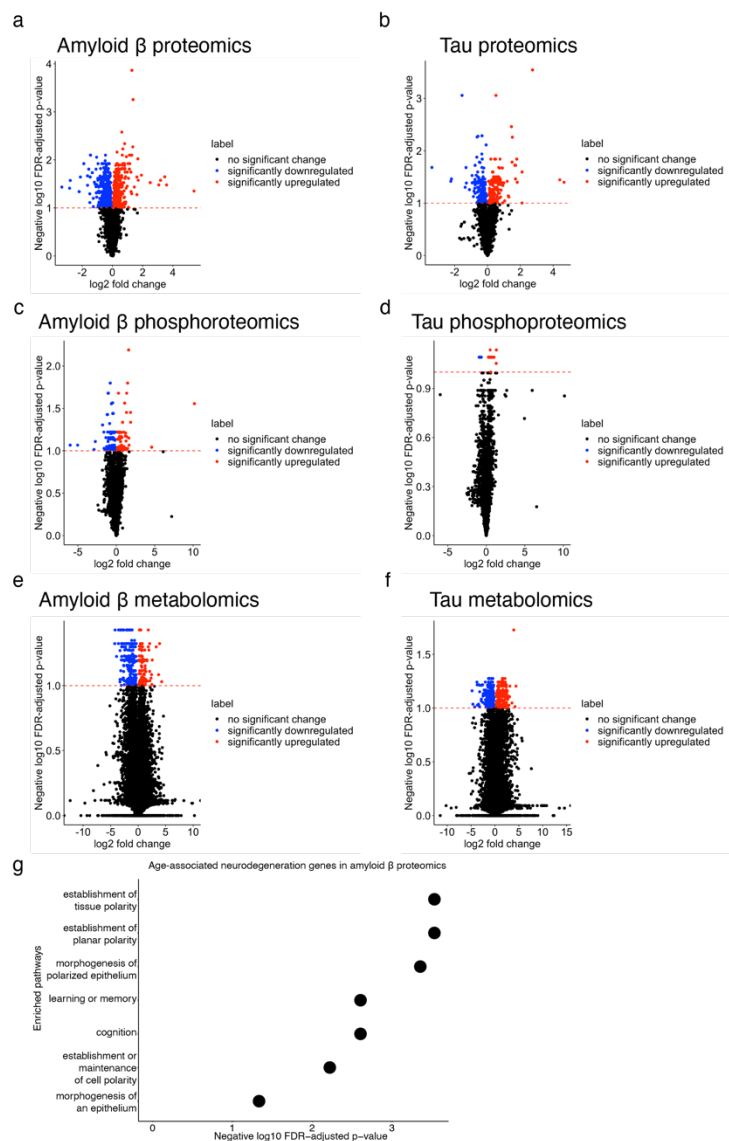
Supplementary Figures:



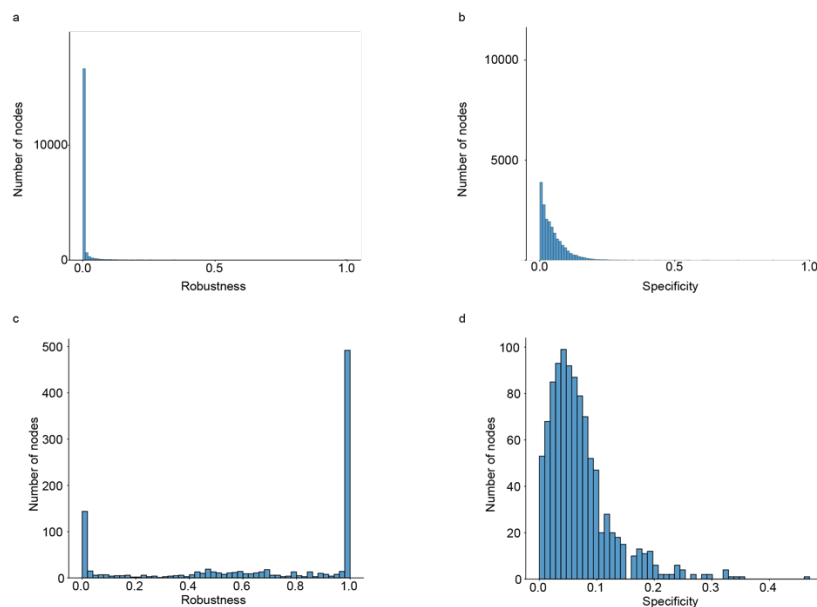
Supplementary Fig. 1, related to Fig. 2: Neurodegeneration screen hits have significant changes in gene expression with respect to age across multiple brain tissues. Heatmap depicts significant linear mixed model regression coefficients between the expression of neurodegeneration screen hits and patient age in human RNA-seq in the Genotype-Tissue Expression project (GTEx) for each brain tissue. Each row is an age-associated neurodegeneration gene while each column indicates the brain tissue in GTEx, grouped by hierarchical clustering. Blue indicates a negative association and red indicates a positive association between gene expression in age as measured by the model regression coefficient. The gene with a positive regression coefficient is *HES6*.



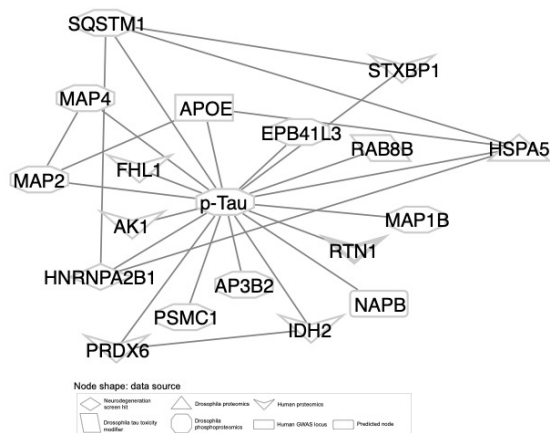
Supplementary Fig. 2, related to Fig. 2: The average expression of age-associated neurodegeneration genes declines in Alzheimer's disease-associated excitatory neurons. UMAP projections depict excitatory neurons from Mathys et al. 2019. In the left plot, cells are shaded by whether they belong to clusters overrepresented by cells from control or Alzheimer's disease patients. The right UMAP shows the average expression of age-associated neurodegeneration genes in this group of excitatory neurons.



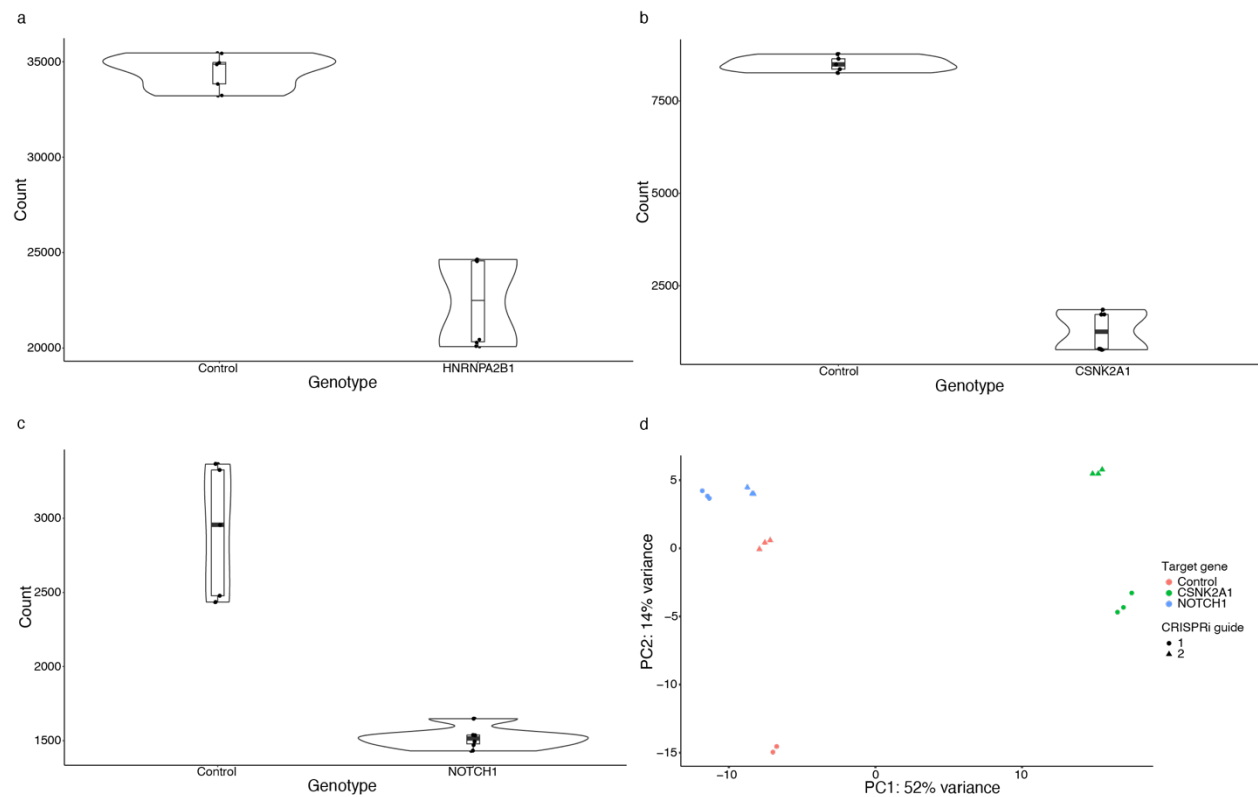
Supplementary Fig. 4, related to Fig. 3. Volcano plots depicting negative log₁₀ FDR-adjusted p-values and log₂ fold changes between case and control in a) proteomics from A β ₁₋₄₂ transgenic flies (amyloid β), b) proteomics from tau^{R406W} transgenic flies, c) phosphoproteomics from A β ₁₋₄₂ transgenic flies, d) phosphoproteomics from tau^{R406W} transgenic flies, e) metabolomics from A β ₁₋₄₂ transgenic flies, and f) metabolomics from tau^{R406W} transgenic flies. Blue dots indicate significantly downregulated omics and red dots indicate significantly upregulated omics. The horizontal red dashed line indicates the FDR cut-off at 0.1. g) Dot plot indicating GO terms overrepresented in neurodegeneration screen hits that are differentially abundant in proteomics from A β ₁₋₄₂ transgenic flies.



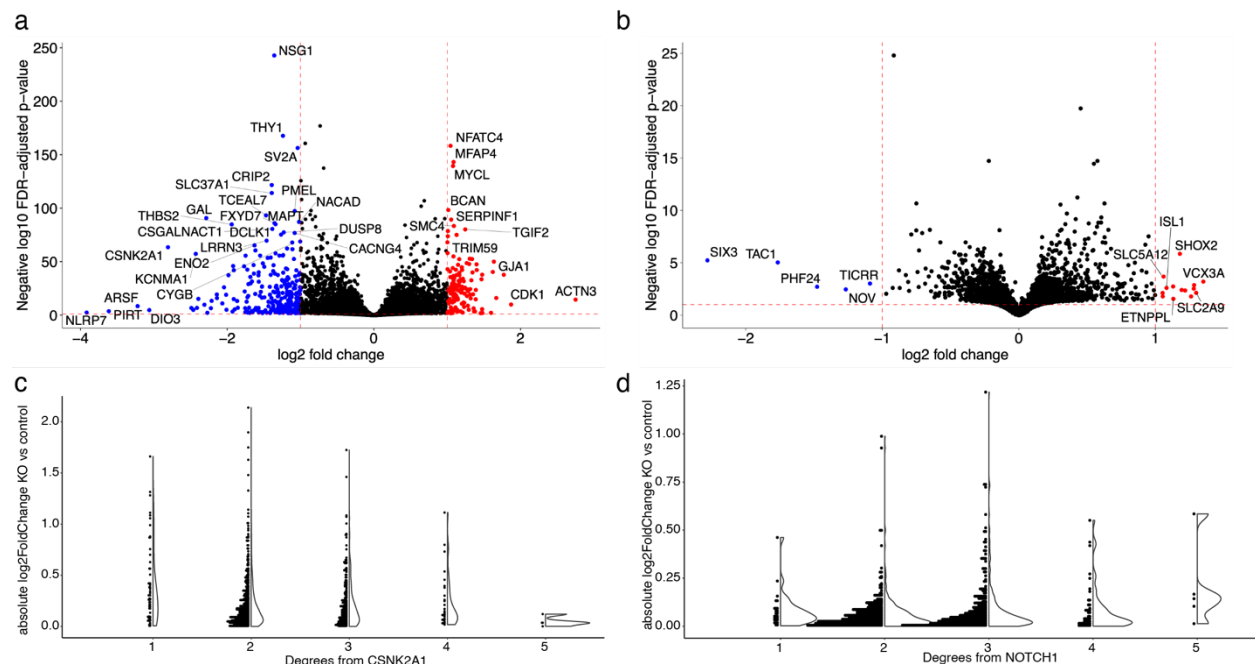
Supplementary Fig. 5: Histograms showing the distribution of a) node robustness and b) node specificity after randomizations. 0 indicates low robustness and 1 indicates high robustness, while 0 indicates high specificity and 1 indicates low specificity. After removing nodes for a robustness of at least 0.4 and a specificity of at most 0.4, we filtered out 19102 nodes. c) node robustness and d) node specificity distributions of nodes after filtering predicted nodes for insufficient robustness or specificity.



Supplementary Fig. 6, related to Fig. 5: pTau and its first neighbors in the network solution. Nodes are shaped by the data source from which they were contributed.



Supplementary Fig. 7, related to Figs. 5 and 6: Knockdown efficiency and principal component analysis of the NGN2 RNA-seq data. Violin plots depict library-corrected RNA-seq counts in NGN2 neuronal progenitor cells for controls and a) *HNRNPA2B1*, b) *CSNK2A1* or c) *NOTCH1* knockdown. d) Principal Component Analysis plot of individual control, *NOTCH1* and *CSNK2A1* RNA-seq replicates from expression data. Colors indicate the knockdown for each replicate and the shape indicates whether the knockdown was performed with the first or second guide RNA. For control, we used non-targeting guide RNAs.



Supplementary Fig. 8, related to Fig. 6: RNA-seq analysis after knockdown of *NOTCH1* and *CSNK2A1*. Volcano plot depicts differential expression analysis by DeSeq2 of bulk RNA-seq after a) *CSNK2A1* CRISPRi knockdown and b) *NOTCH1* CRISPRi knockdown in NGN2 iPSC-derived neural progenitor cells. Each dot represents a single gene. The horizontal dashed line indicates the negative log₁₀ Benjamini-Hochberg FDR-adjusted p-value cut-off of 0.1 and the vertical dashed lines indicate the log₂ fold change cut-offs of 1 and -1. Red dots indicate significantly upregulated genes (log₂ fold change greater than 1) and blue dots indicate significantly downregulated genes (log₂ fold change less than -1). c) Dot and volcano plots show the absolute value of the log₂ fold change of nodes in the network after *CSNK2A1* knockout compared to controls relative to the degree of separation from *CSNK2A1*. d) Dot and volcano plots show the absolute value of the log₂ fold change of nodes in the network after *NOTCH1* knockout compared to controls relative to the degree of separation from *NOTCH1*.