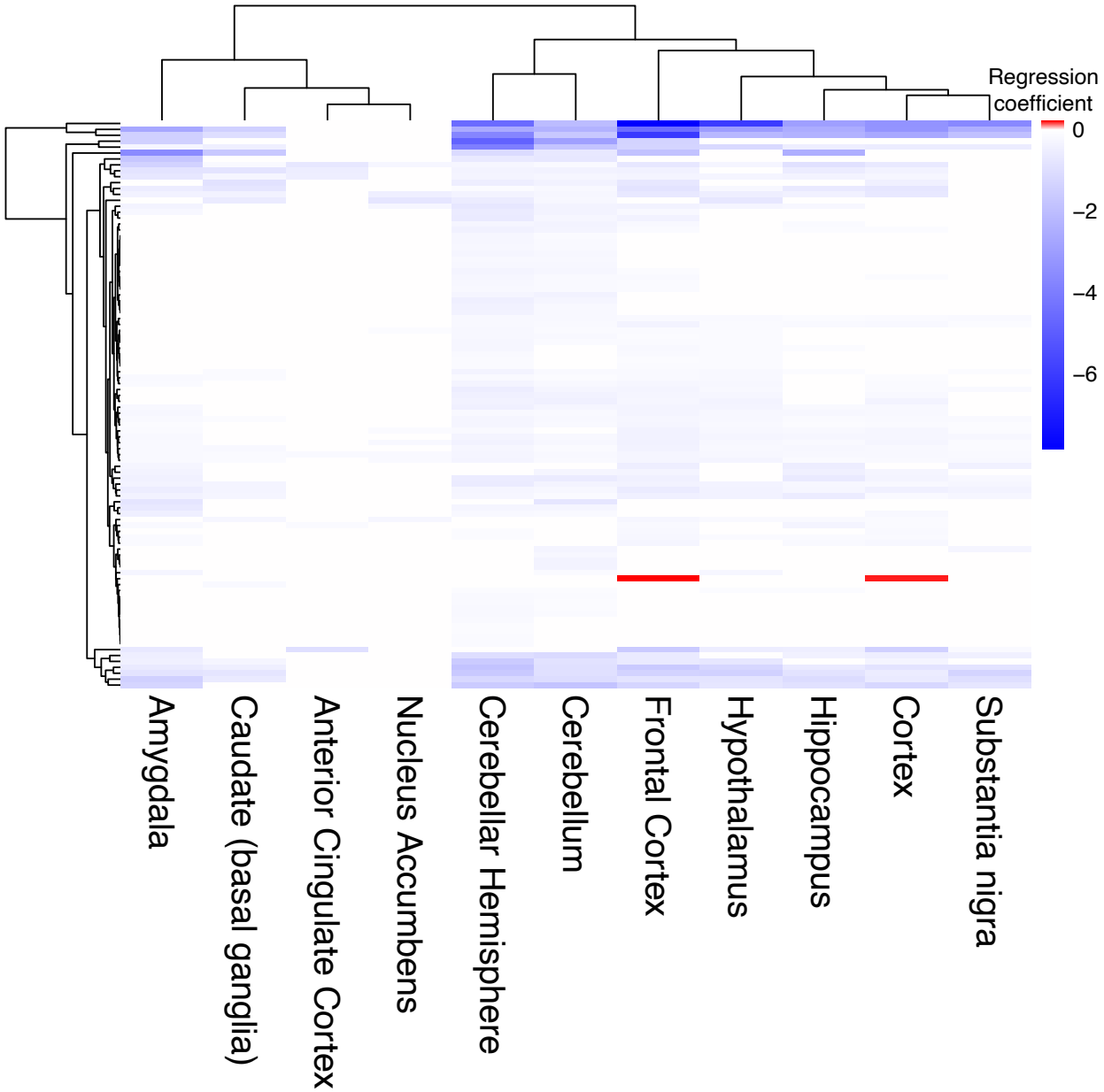
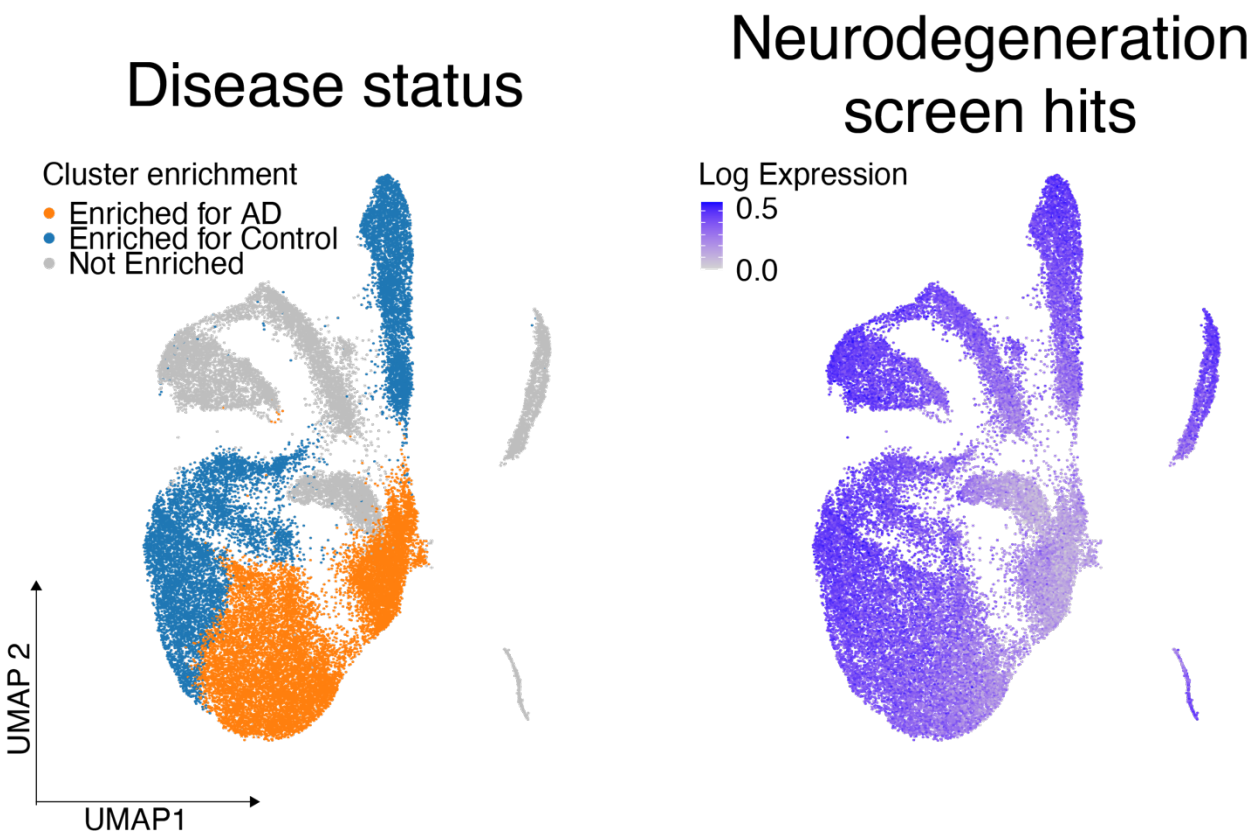
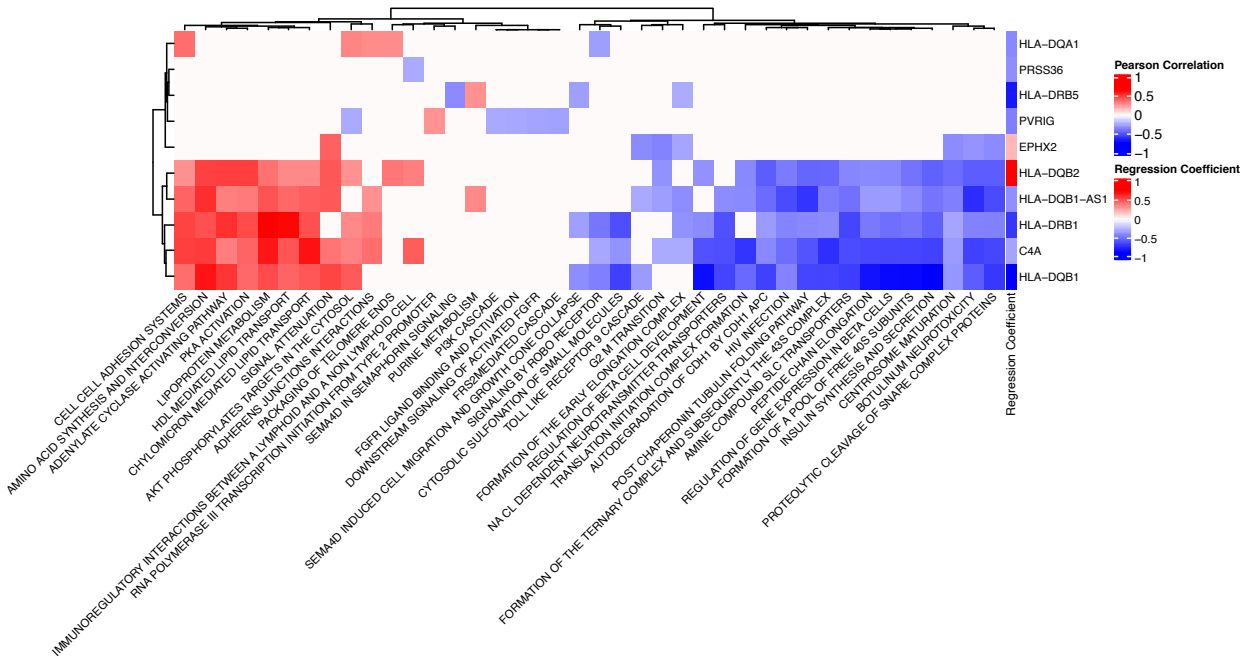


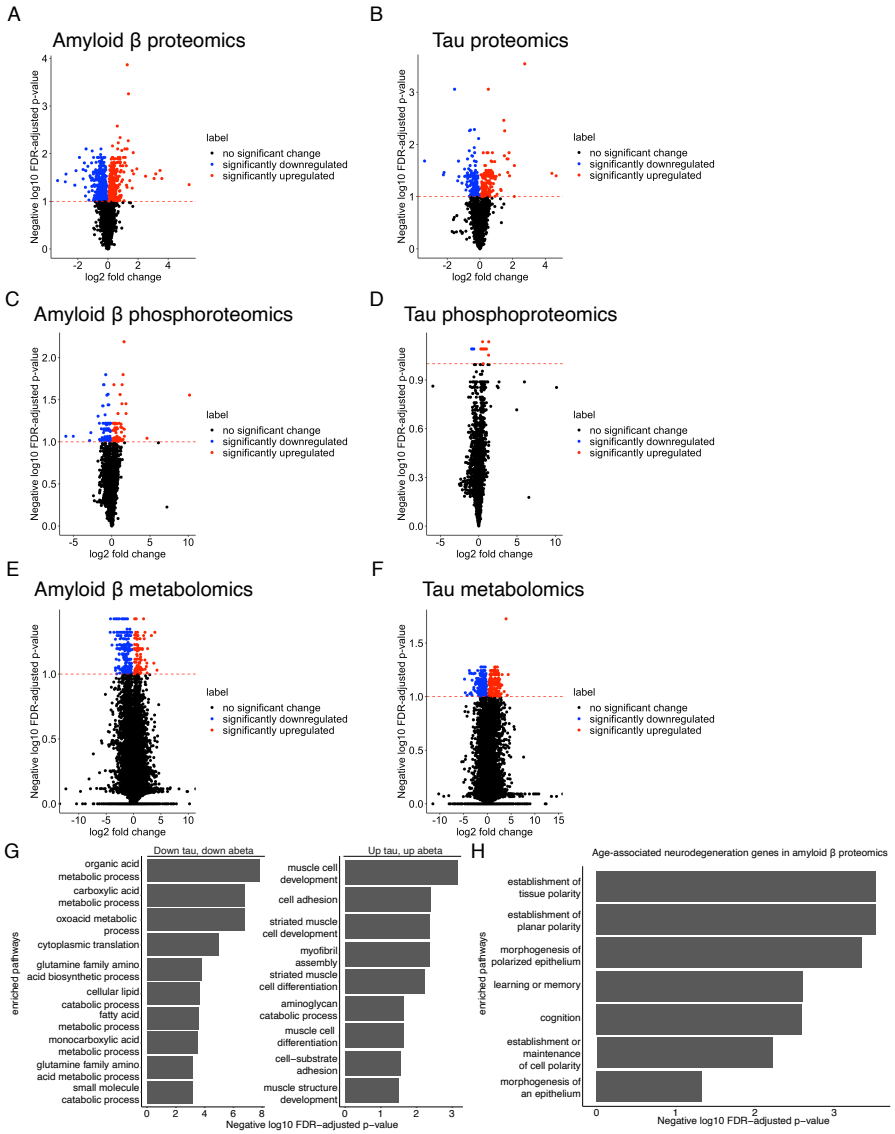
Supplementary figure 1, related to figure 2: Neurodegeneration screen hits have significant changes in gene expression with respect to age across multiple brain tissues. Heatmap depicts significant linear mixed model regression coefficients between the expression of neurodegeneration screen hits and 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*.



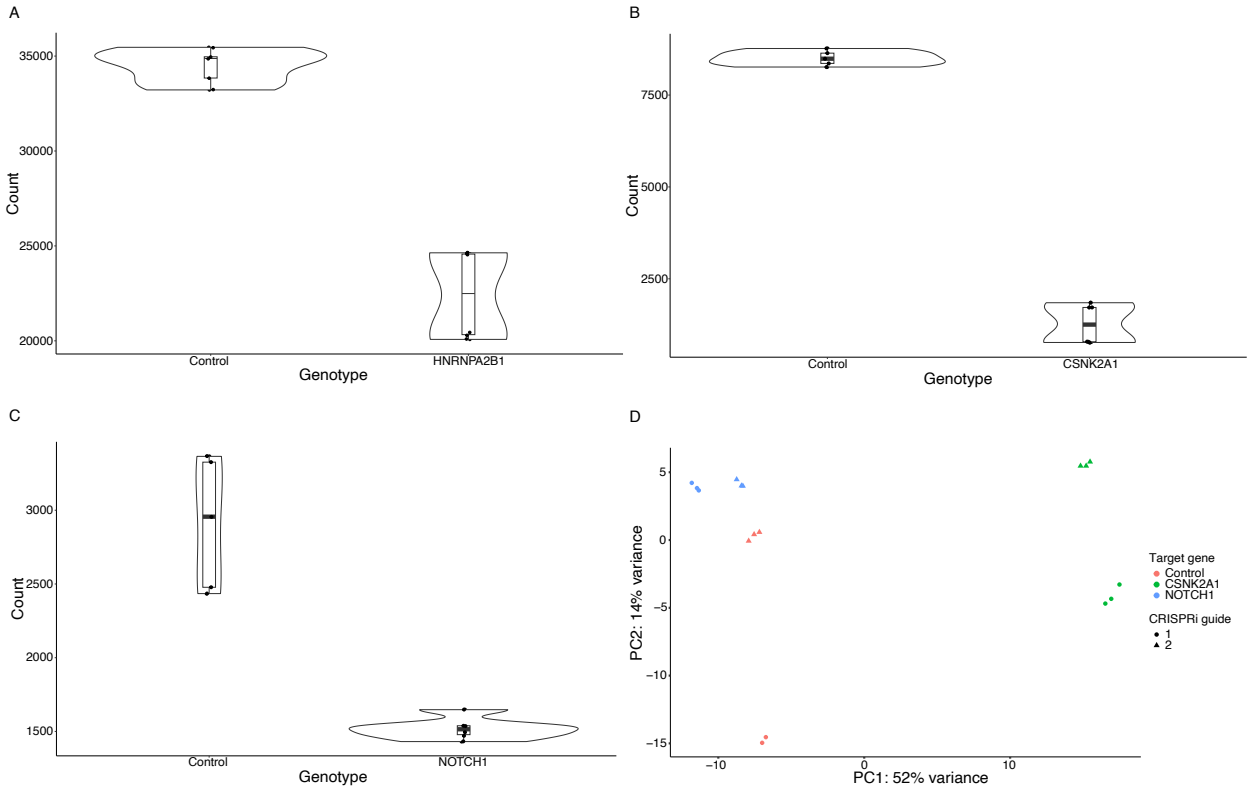
Supplementary figure 2, related to figure 2: The average expression of screen hits declines in Alzheimer's disease-associated excitatory neurons. UMAP projections depict excitatory neurons from Mathys et al. 2019. In the left plot, cells are shaded by whether they belong to clusters overrepresented by 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.



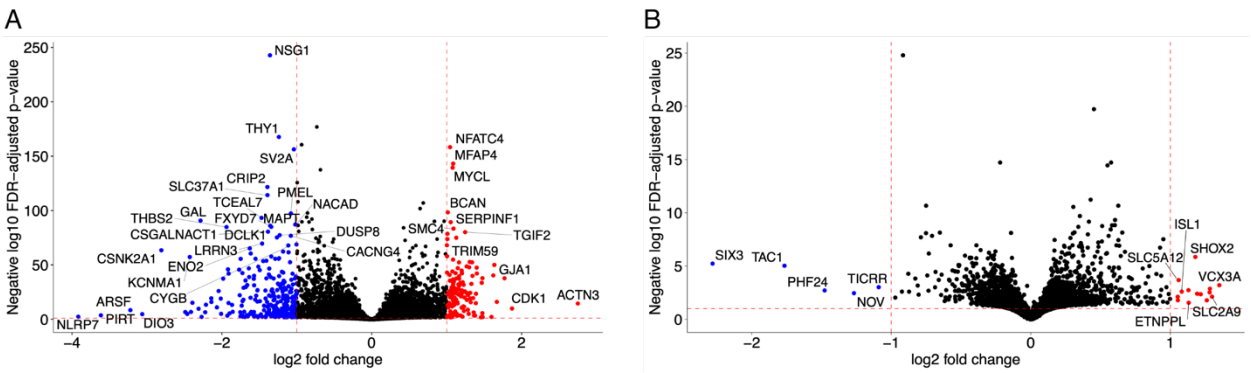
Supplementary figure 3, related to figure 3. Heatmap showing significant Pearson correlations between the RNA-seq expression of temporal cortex pyramidal neuron eGenes and Gene Set Variation Analysis signatures for REACTOME pathways. The gene names on the rows are annotated for the regression coefficient representing the association between gene expression and the presence of the associated Alzheimer's disease eQTL. The legend for these regression coefficients is labeled as "Regression Coefficient". Columns are clustered with hierarchical clustering.



Supplementary figure 4, related to figure 3. Volcano plots depicting negative $\log_{10}$ FDR-adjusted p-values and $\log_2$ fold changes between case and control in A) proteomics from $A\beta_{1\text{-}42}$ transgenic flies (amyloid β), B) proteomics from tau^{R406W} transgenic flies, C) phosphoproteomics from $A\beta_{1\text{-}42}$ transgenic flies, D) phosphoproteomics from tau^{R406W} transgenic flies, E) metabolomics from $A\beta_{1\text{-}42}$ 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) Barplots showing the negative $\log_{10}$ FDR-adjusted p-values for enriched GO terms in proteins that are significantly upregulated or significantly downregulated in both *Drosophila* models of tau and amyloid β. H) Barplot indicating GO terms overrepresented in neurodegeneration screen hits that are differentially abundant in proteomics from $A\beta_{1\text{-}42}$ transgenic flies.



Supplementary figure 5, related to figures 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 figure 6, related to figure 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 $\log_{10}$ Benjamini-Hochberg FDR-adjusted p-value cut-off of 0.1 and the vertical dashed lines indicate the $\log_2$ fold change cut-offs of 1 and -1. Red dots indicate significantly upregulated genes ($\log_2$ fold change greater than 1) and blue dots indicate significantly downregulated genes ($\log_2$ fold change less than -1).

Supplementary table 1, related to figure 2. GO biological process pathway enrichment analysis results for *Drosophila* modifiers of age-associated neurodegeneration.

No.	Stage	Gene expression	Genotype	N	Source	Age at death mean (sd)	RIN mean (sd)	PMI mean (sd)	Male %
1	D	RNA-seq	WGS	334	Frontal cortex	85.8 (4.9)	7.2 (1.0)	7.5 (4.9)	37.7
2	D	RNA-seq	WGS	65	Frontal cortex	80.9 (8.8)	6.7 (1.1)	10.5 (7.2)	44.6
3	D	RNA-seq	Array	200	Frontal cortex	64.9 (19.5)	7.9 (0.8)	14.8 (7.8)	57.5
4	D	Microarray	Array	144	Frontal cortex	63.7 (8.8)	6.8 (0.8)	17.8 (8.3)	77.8
5	R	RNA-seq	WGS	118	Frontal cortex	57.9 (9.8)	7.4 (0.9)	NA	70.3
6	R	RNA-seq	WGS	103	Temporal cortex	83.6 (7.3)	7.6 (1.0)	5.5 (6.2)	48.5
7	R	Microarray	Array	123	Frontal cortex	59.0 (NA)	3.85 (NA)	43.7 (NA)	75.6
8	TCPY	RNA-seq	Array	75	Pyramidal neurons	90.9 (8.5)	7.4 (0.9)	2.9 (0.7)	40
Total				1162					

Supplementary Table 2, related to figure 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 table 3, related to Table 1: Results from the discovery phase of the eQTL analysis.

Supplementary table 4, related to figure 3: Proteomics from control flies, $A\beta_{1-42}$ transgenic flies, and tau^{R406W} transgenic flies.

Supplementary table 5, related to figure 3: Phosphoproteomics from control flies, $A\beta_{1-42}$ transgenic flies, and tau^{R406W} transgenic flies.

Supplementary table 6, related to figure 3: Metabolomics from control flies, $A\beta_{1-42}$ transgenic flies, and tau^{R406W} transgenic flies.

Supplementary table 7, related to figure 4: Input prize 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.

Supplementary table 8, related to figures 5 and 6: Results from the differential expression analyses for *NOTCH1*, *CSNK2A1* and *HNRNPA2B1* knockdown in NGN2 neural progenitor cells.

Supplementary table 9, related to figures 5 and 6: Gene Set Enrichment analysis results for NGN2 neural progenitor cells after *NOTCH1*, *CSNK2A1* and *HNRNPA2B1* knockdown.