

Description of Additional Supplementary Files

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 tauR406W transgenic flies.

Supplementary Data 6, related to Fig. 3. Phosphoproteomics from control flies, A β 1-42 transgenic flies, and tauR406W transgenic flies.

Supplementary Data 7, related to Fig. 3. Metabolomics from control flies, A β 1-42 transgenic flies, and tauR406W 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.