

Gene expression alterations of synaptic genes in hippocampal excitatory neurons of Alzheimer's disease transgenic mice



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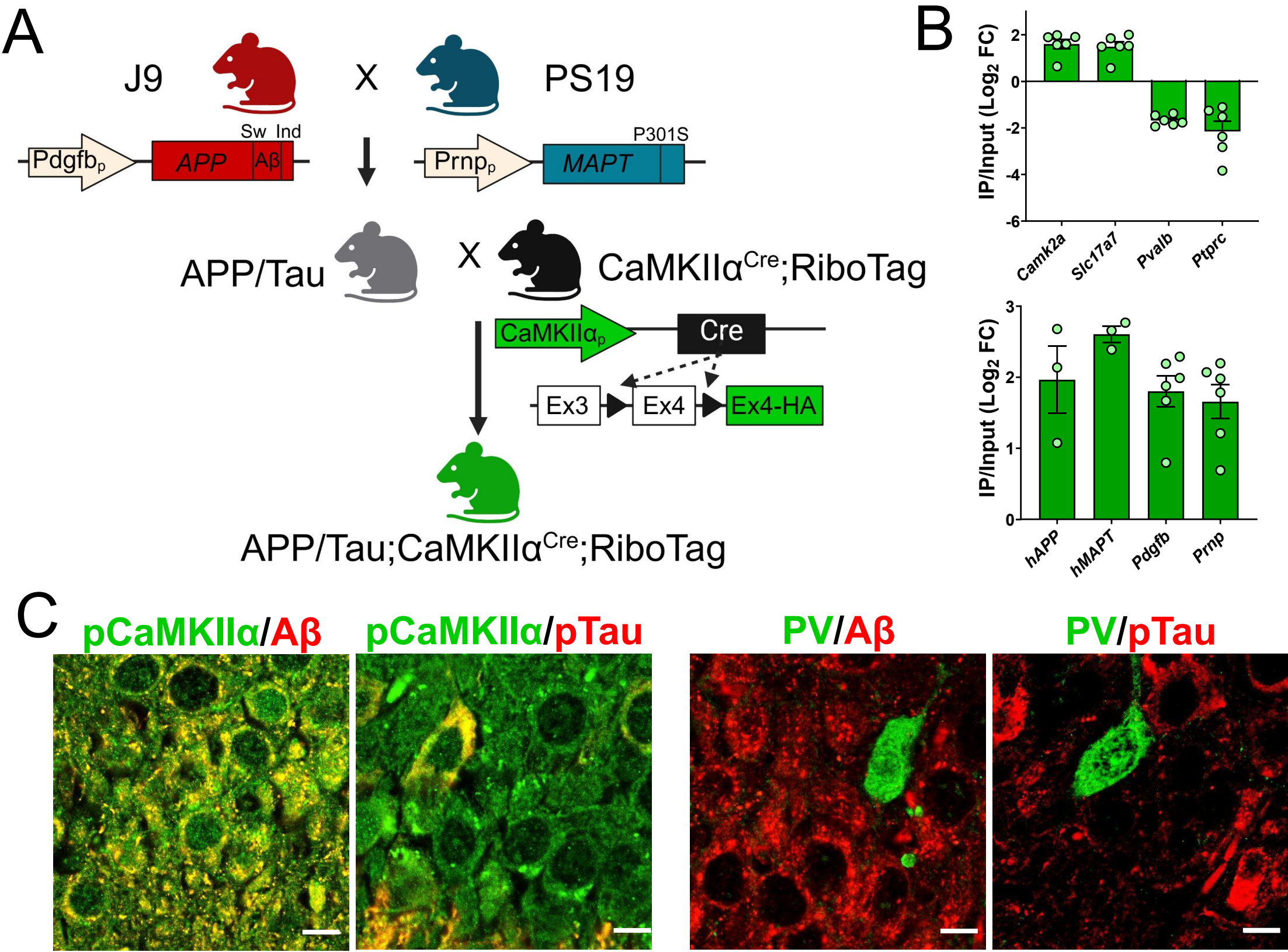
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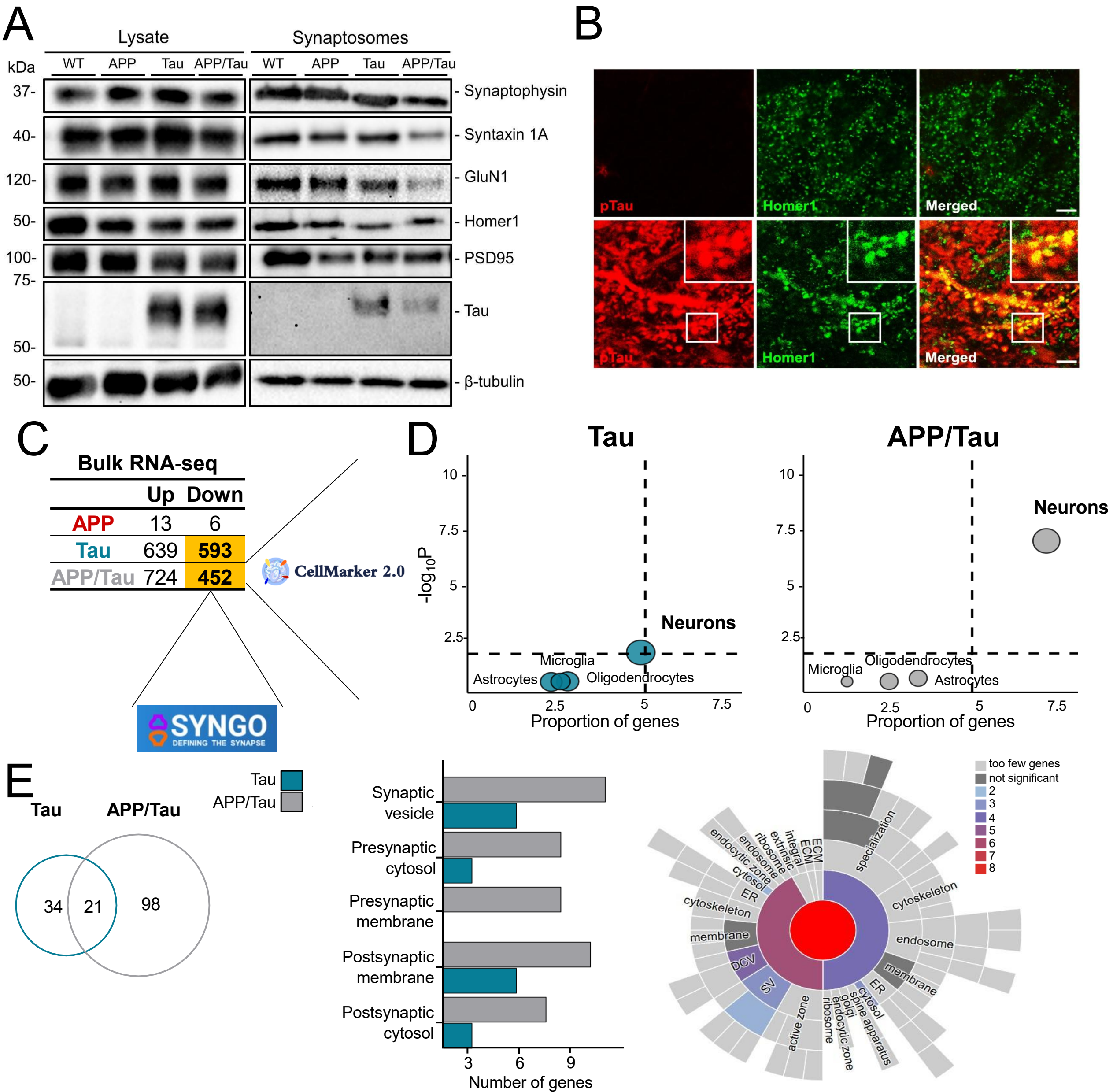


Altered excitatory neurotransmission in the hippocampus has been proposed to underlie memory deficits in Alzheimer's disease, but the mechanisms linking amyloid- β (A β) and tau pathologies to disruption of hippocampal excitatory neurons remain largely unknown. Here, we conducted behavioral, biochemical, molecular, cell-type specific transcriptomics and advanced microscopy techniques to study the effects of early neuronal A β and tau accumulation on hippocampal excitatory glutamatergic (CaMKII α) neurons in transgenic mice expressing the human mutant amyloid precursor protein (APP), microtubule-associated protein Tau (MAPT) or both APP/Tau genes.

1. Early A β and pTau pathologies in the hippocampus of APP/Tau mice



2. Excitatory synaptic pathology in the hippocampus of APP/Tau mice



3. Transcriptome alterations in hippocampal glutamatergic neurons of APP/Tau mice

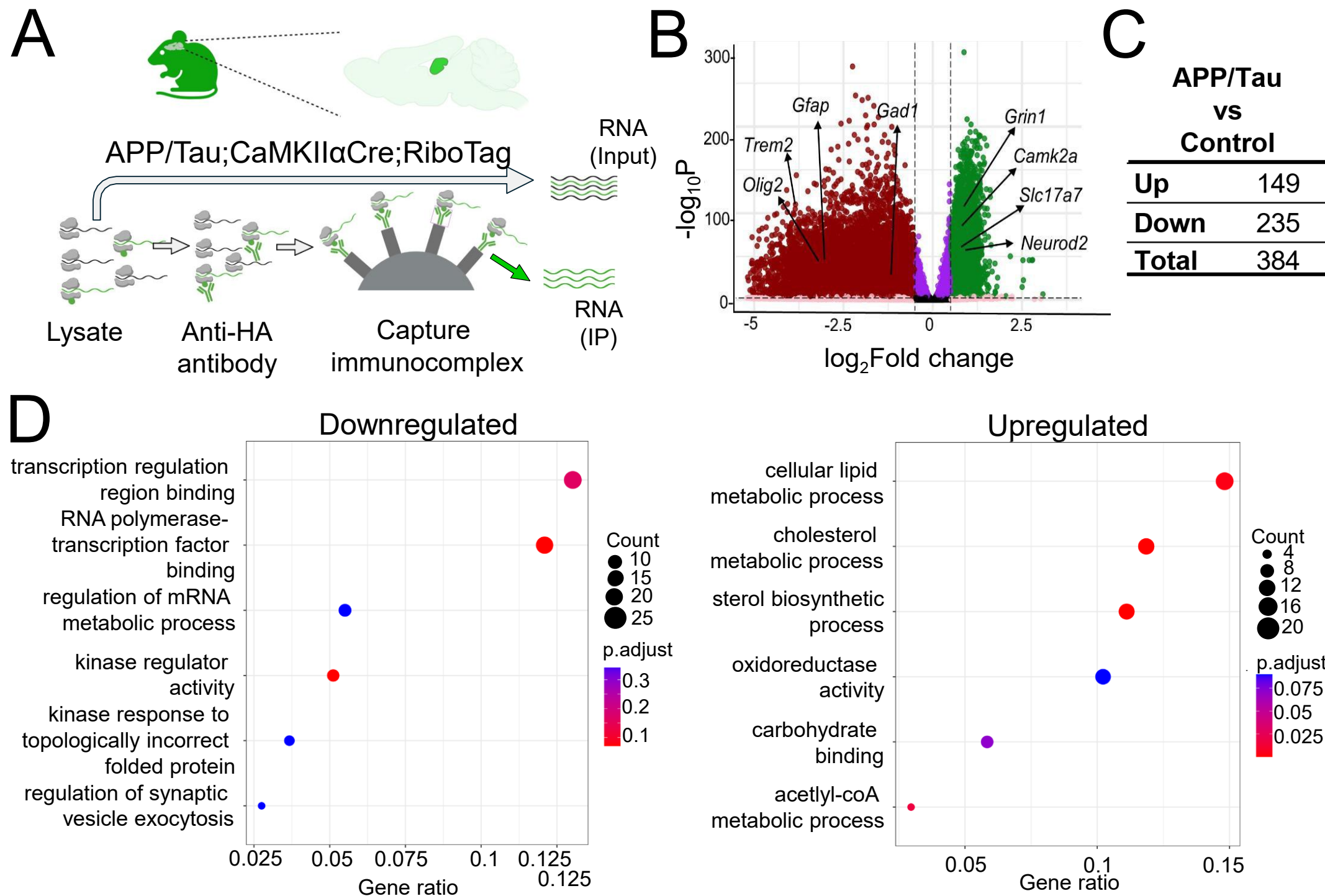


Figure 4. A) CaMKII α -specific transcriptomic profiling in the hippocampus of female APP/Tau-RiboTag mice. B) Volcano plot of IP vs Input (Bulk) fractions of 6 months-old control (WT;RiboTag) female mice show enrichment of excitatory genes as well as depletion of inhibitory and glial genes. C) Differentially expressed genes in glutamatergic neurons of the hippocampus of APP/Tau mice. D) Up and downregulated biological pathways in CaMKII α -positive neurons of APP/Tau mice.

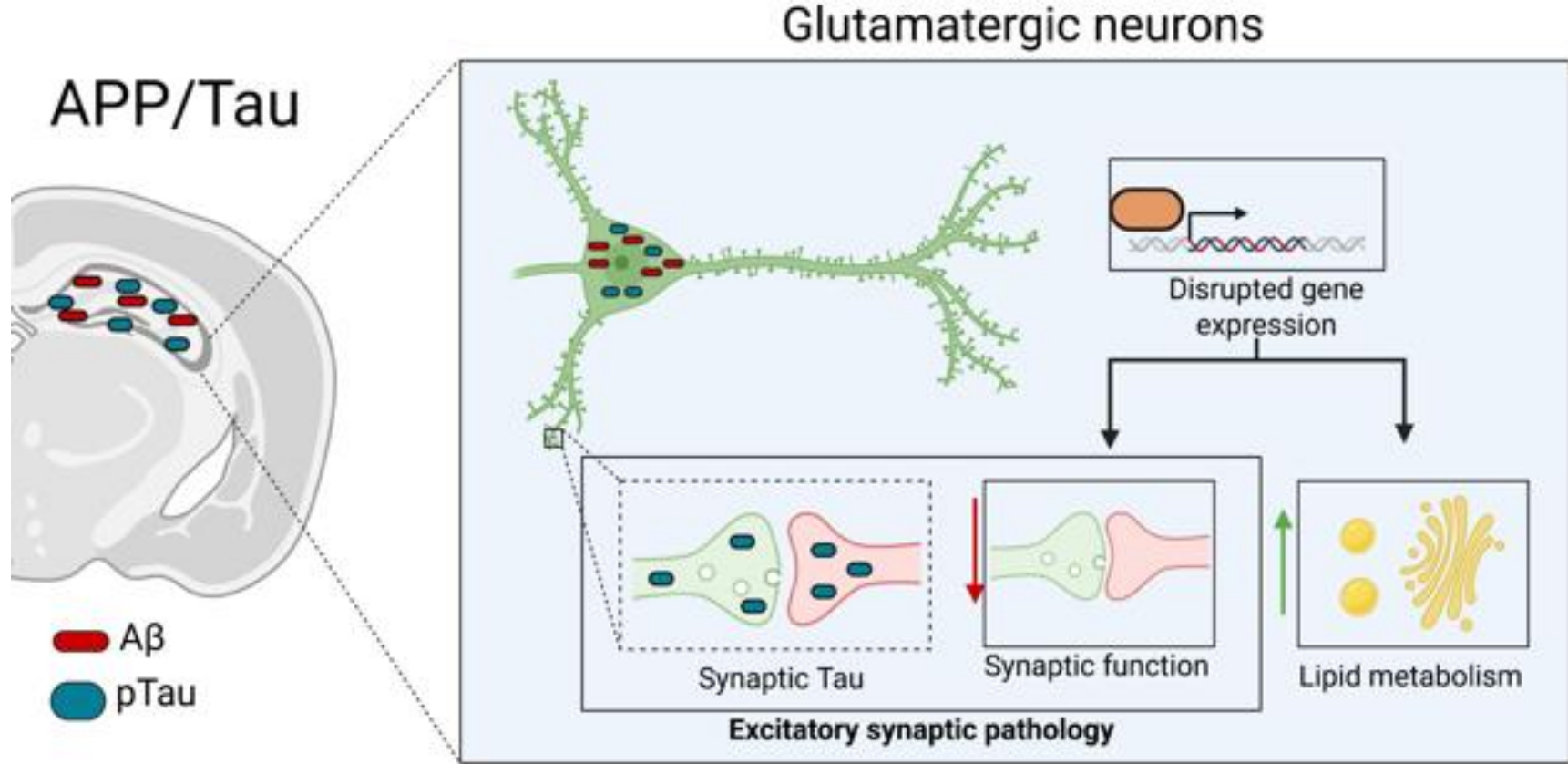


Figure 1. A) Generation of CaMKII α Cre;RiboTag;APP/Tau mice. B) Expression of control genes (*Pvalb*, *Camk2a* and *Ptpcr*), human transgenes and *Pdgfrb* and *Prnp* genes in APP/Tau hippocampus. C) Confocal images of excitatory and inhibitory neurons and A β or pTau in the hippocampus of APP/Tau mice. Scale bar: 10 μ m. D) Latencies to find the hidden platform (left) and % of time in quadrant (right) of 6-months-old WT, APP, Tau and APP/Tau mice in the Morris Water Maze task. * P < 0.05; ** P < 0.01; *** P < 0.001

Figure 3. A) Western blot analysis of synaptic proteins and Tau in total lysates and synaptosome fractions of WT, APP, Tau and APP/Tau mice at 6 months of age. B) Expansion microscopy assays showing colocalization of postsynaptic Homer1 (green) and pTau (CP13; red) in the CA1 hippocampus of APP/Tau mice. Scale bar: 10 μ m. C) Differentially expressed genes in the hippocampus of female APP, Tau and APP/Tau versus WT mice. D) Overrepresentation analysis of cell-type specific marker genes among downregulated genes in Tau (left) and APP/Tau (right) mice using CellMarker 2.0 database. E) Downregulation of synaptic-related genes in Tau and APP/Tau mice identified by SynGO database. SynGO sunburst plot (right) illustrates the hierarchical organization and significant enrichment of SynGO annotations in APP/Tau mice.

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