

Inflammation-Associated Transcriptional Changes in the Hippocampus of Alzheimer's Disease Mice

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SUMMARY

Amyloid- β (A β) and tau pathologies are associated with inflammatory responses in the Alzheimer's disease (AD) brain, whereas genome-wide association studies (GWAS) identified inflammation and immune response genes as key genetic risk factors in AD. How A β and tau pathologies affect the levels of these inflammatory genes leading to microglial and astrocyte activation in AD is still unclear. This study was aimed to investigate the effect of A β , tau and A β /tau pathologies in inflammatory responses and their link with inflammation-related AD risk genes in the brain of APP, Tau and double APP/Tau transgenic mice.

Experimental design and generation of AD mice

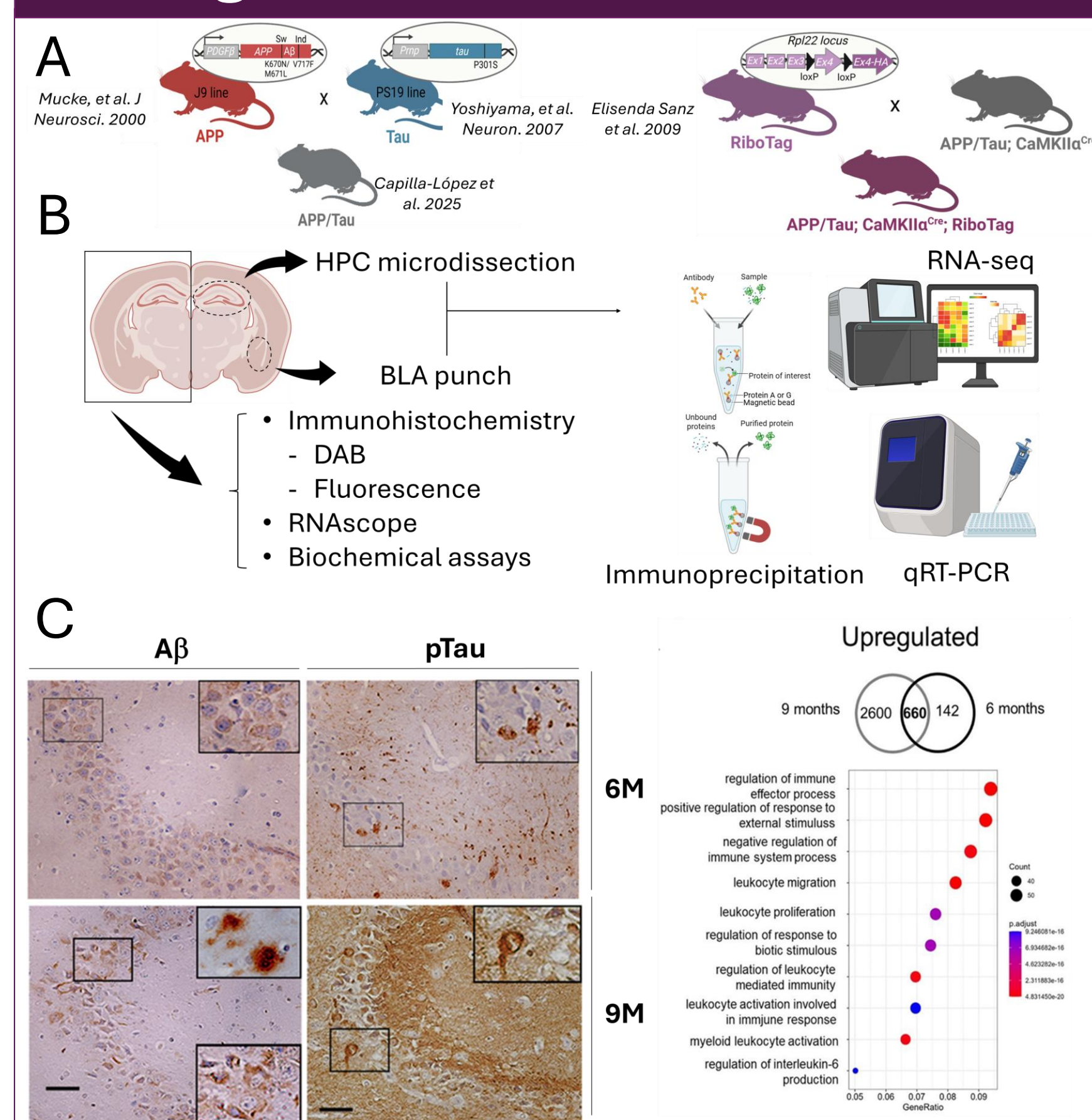


Figure 1. Experimental design in AD transgenic mice. **A**, Generation of double APP/Tau and APP/Tau;CaMKII α Cre;RiboTag transgenic mice. **B**, Protein and RNA analyses workflow in AD mice samples. **C**, Presence of A β and pTau pathologies (left) and increased inflammatory genes/pathways in the hippocampus of female APP/Tau mice (right).

Astrocytosis and microgliosis in 9 month-old Tau and APP/Tau mice

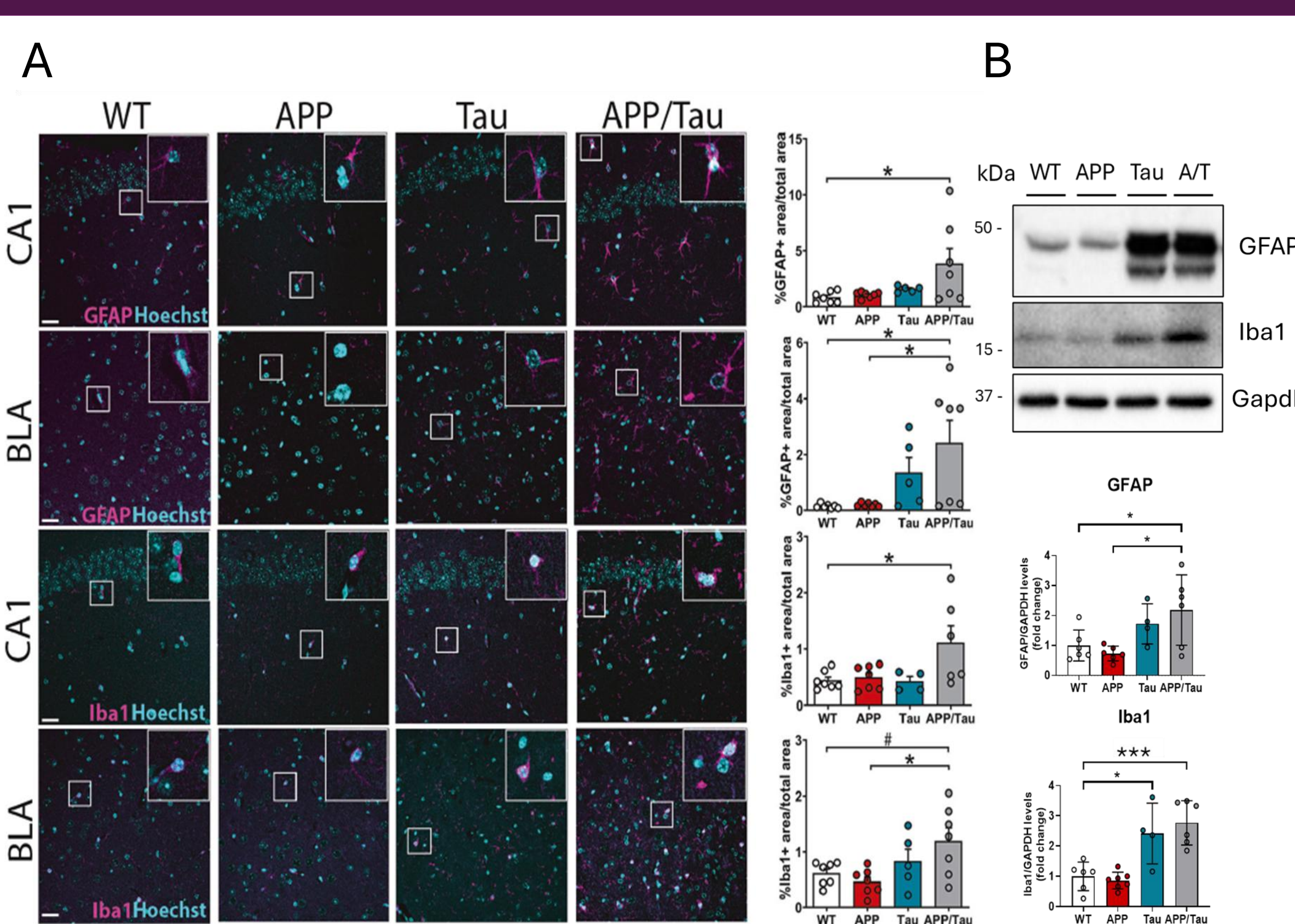


Figure 2. Enhanced inflammatory responses in 9 month-old APP/Tau transgenic mice. **A**, Confocal microscopy images and quantification of GFAP and Iba1 staining in CA1 hippocampus and basolateral amygdala (BLA) of AD mice. **B**, Biochemical analysis of GFAP and Iba1 proteins normalized to GAPDH in hippocampal lysates of 9 month-old female WT, APP, Tau, and APP/Tau mice (mean $\pm$ SEM). Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test. * P < 0.05, # P = 0.06, ** P < 0.01, *** P < 0.001 vs non-transgenic control mice.

Increased AD-risk inflammatory genes in Tau and APP/Tau mice at 9 months

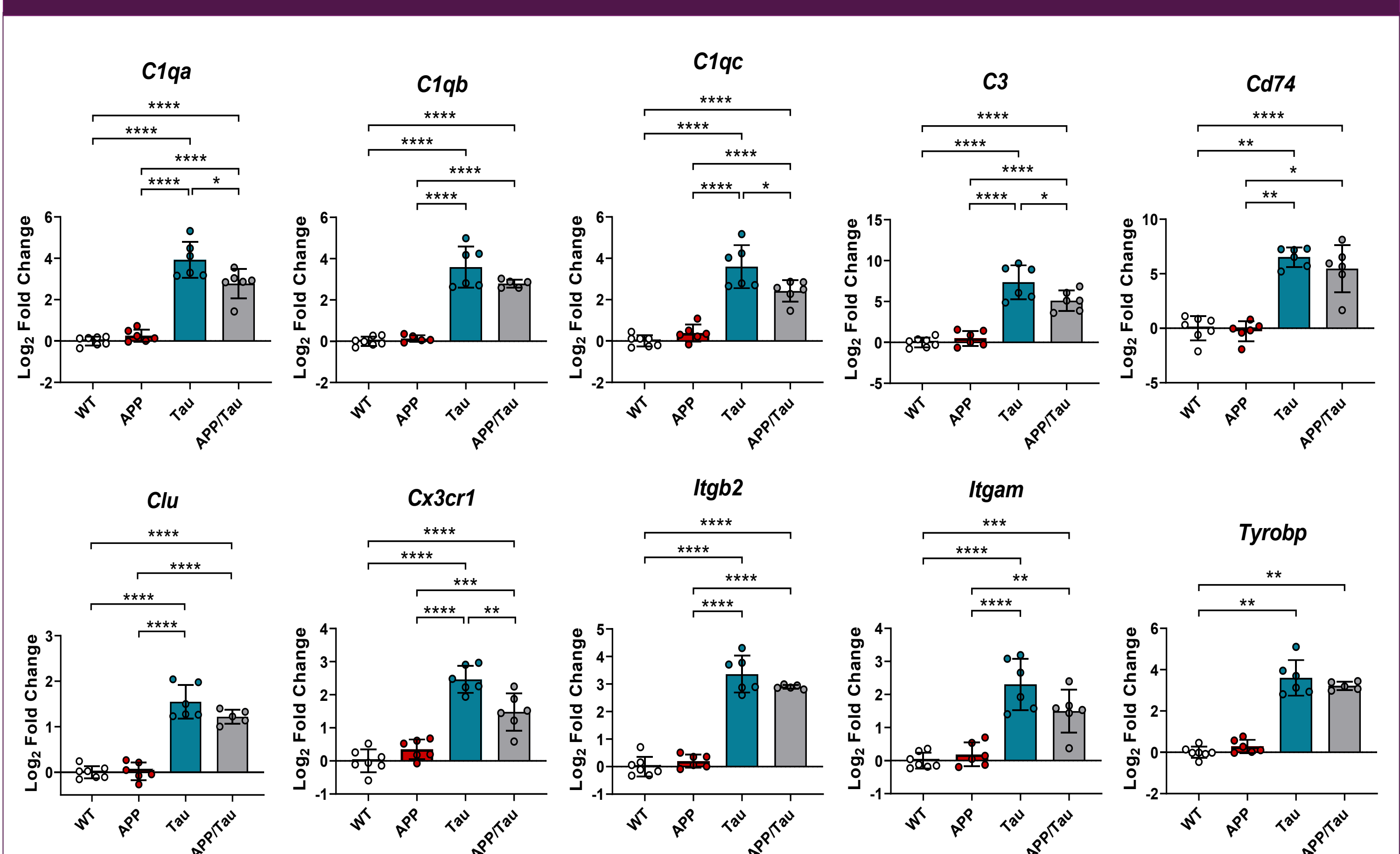


Figure 3. Levels of inflammation-related genes in the hippocampus of AD mice. qPCR analysis shows upregulation of inflammation-associated genes in hippocampus of Tau and APP/Tau mice at 9 months. Statistics were determined by one-way ANOVA or Kruskal-Wallis tests followed by Tukey's or Dunn's multiple comparisons tests according to the normality test, respectively. * P < 0.05, ** P < 0.01, *** P < 0.001 vs non-transgenic control group.

Increased C1qa and C1qb in hippocampal glutamatergic neurons of APP/Tau mice

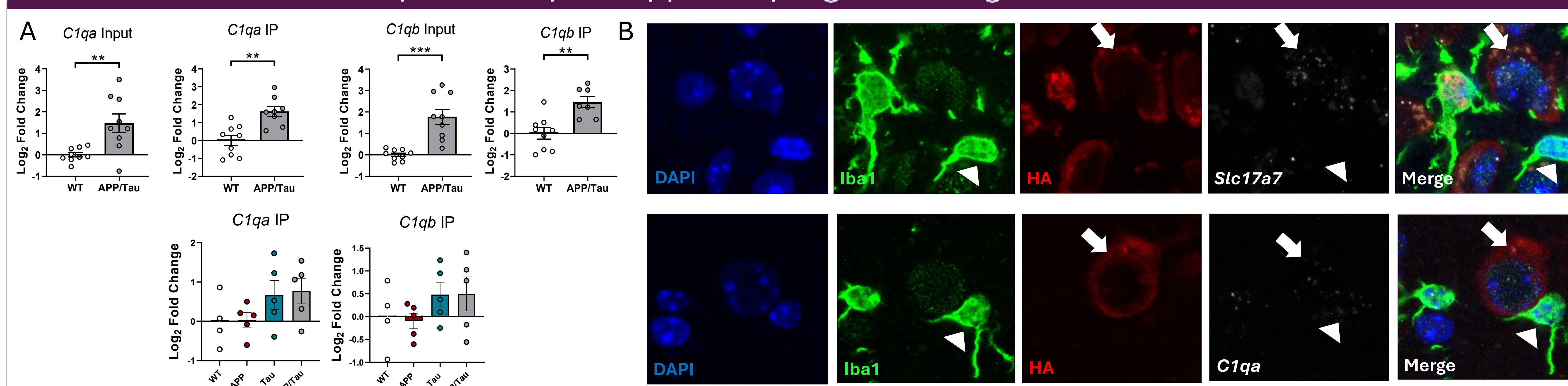


Figure 4. Increased C1qa and C1qb levels in hippocampal glutamatergic neurons of APP/Tau mice. **A**, qRT-PCR analysis shows upregulation of C1qa and C1qb genes in total hippocampus (input) and glutamatergic neurons (IP) of 9 month-old APP/Tau mice. Statistics were determined by one-way ANOVA or Kruskal-Wallis tests followed by Tukey's or Dunn's multiple comparisons tests according to the normality test, respectively or by unpaired Student's t-test. * P < 0.05, ** P < 0.01, *** P < 0.001 vs non-transgenic control group. **B**, RNAscope combined with immunohistochemistry showing: **Top**: Slc17a7 transcripts (white dots) in glutamatergic neurons (red; HA; arrow), but not in microglia (green; Iba1; arrowhead). **Bottom**: In contrast, C1qa (white dots) is present in both microglia (green; Iba1; arrowhead) and glutamatergic neurons (red; HA; arrow).

CONCLUSIONS

- Increased activated microglia and astrocytes in the hippocampus and BLA of APP/Tau mice.
- Increased AD-risk inflammatory genes are associated with tau pathology.
- C1qa and C1qb genes are elevated in the hippocampus of APP/Tau mice.
- C1qa gene is expressed in microglia and glutamatergic neurons of the mouse hippocampus.