



Intracerebral Viral Expression of APOE4-Ch Variant Modulates Amyloid and Tau Pathology and Associated Glial Response in Transgenic AD Mice

Minwoo Kim¹, Josslen Thieschafer¹, Kristina Fredriksen^{1,2}, Holly Korthas¹, and Ling Li^{1,2}

¹Department of Experimental and Clinical Pharmacology, ²Graduate Program in Neuroscience, University of Minnesota, Minneapolis, MN 55455, USA

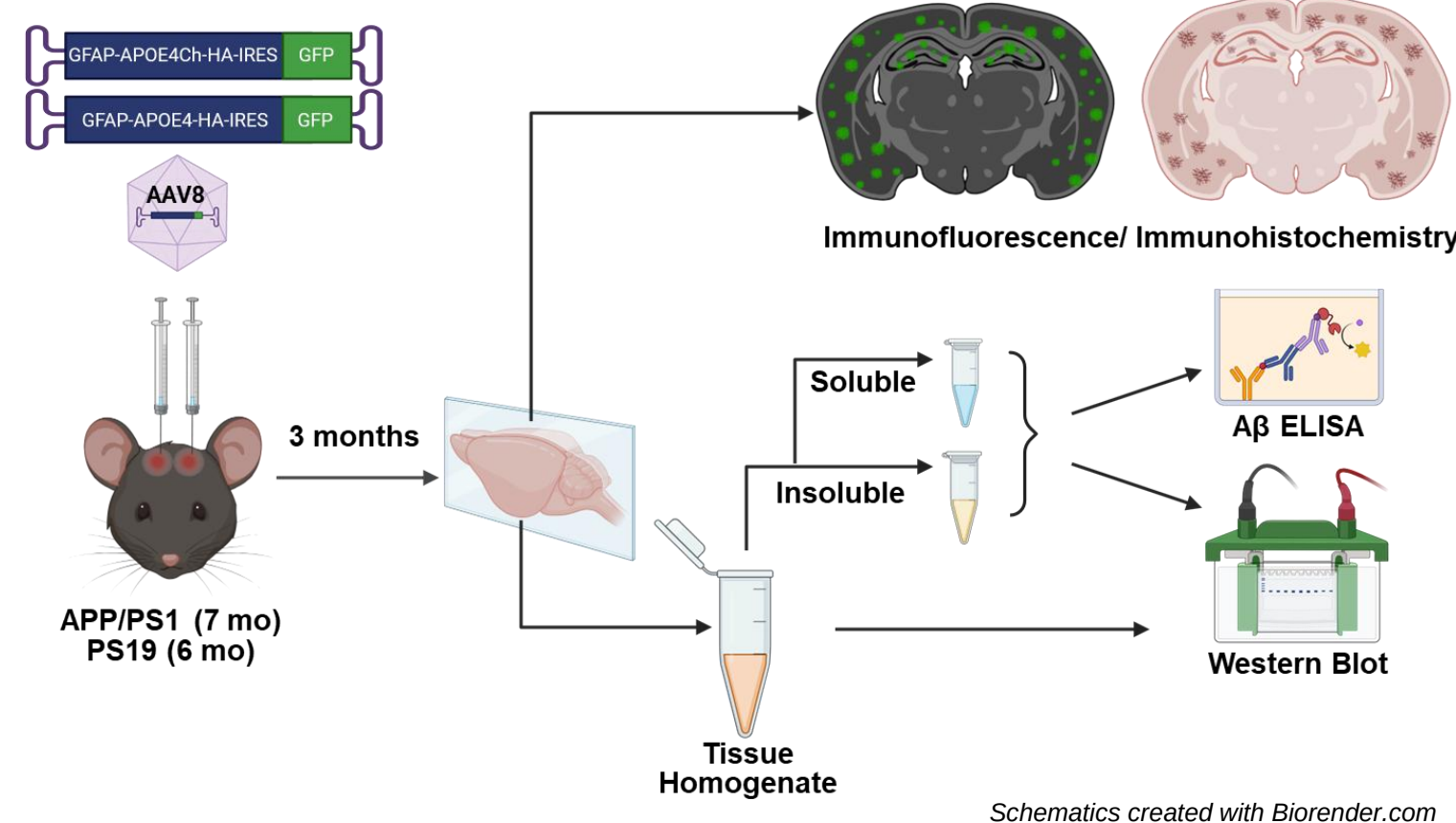
INTRODUCTION

- Mutations in presenilins (PSEN1, PSEN2) and amyloid- β precursor protein (APP) cause familial early-onset Alzheimer's disease (AD).
- The APOE4 allele is the greatest genetic risk factor for sporadic late-onset AD, while APOE2 decreases the risk and the most common APOE3 is neutral.
- A special case was reported in 2019 about an individual carrying the PSEN1 mutation (E280A) and the rare APOE3 Christchurch (Ch) variant who did not develop mild cognitive impairment until her 70s, three decades after the expected age of clinical onset.
- This individual had very high brain amyloid levels but limited tau and neurodegeneration.
- Germ-line expression of the APOE Ch variant has been shown to reduce amyloid and tau pathology in mouse models of AD.
- However, the impact of the Ch variant on AD-related pathology in the context of APOE4 and its therapeutic potential have not been fully explored.

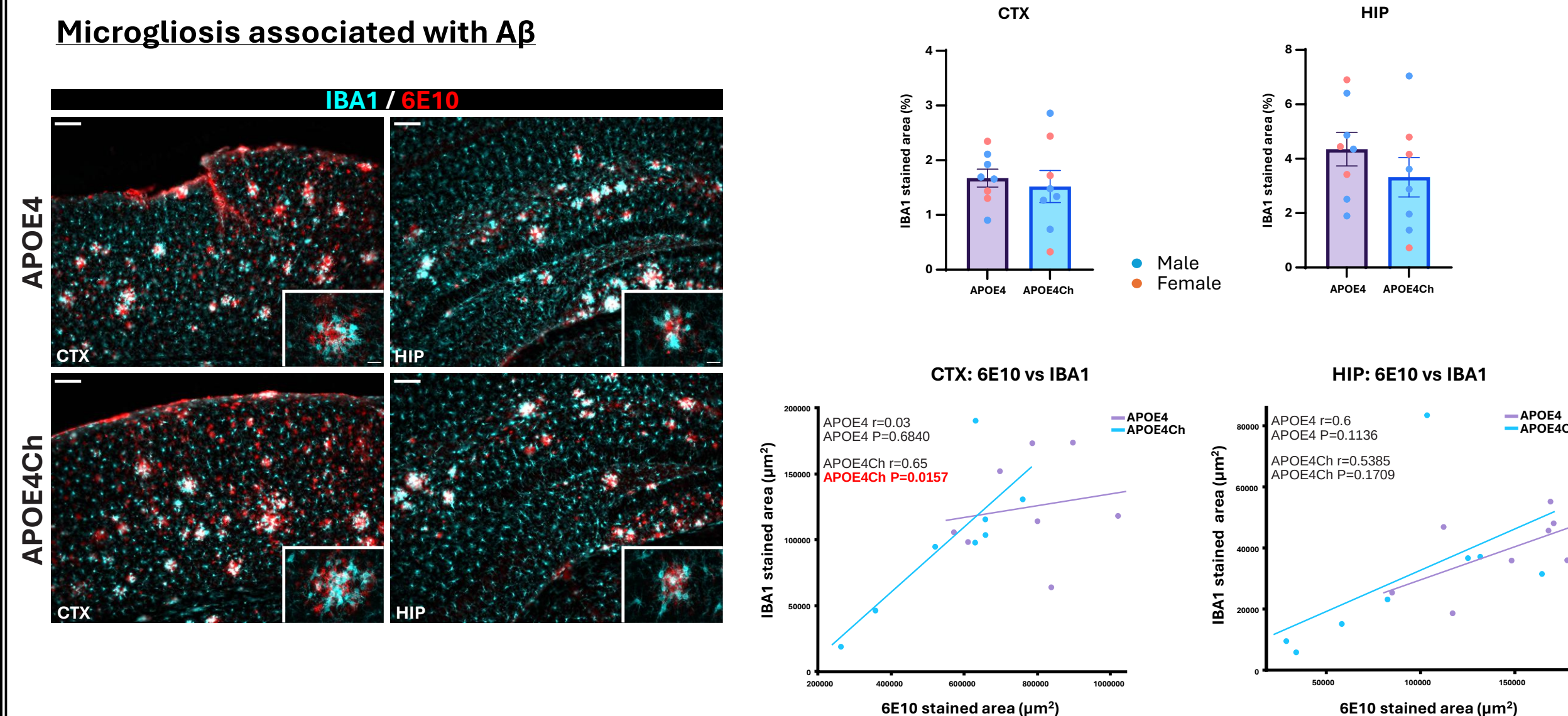
OBJECTIVE

This study aims to investigate the impact of expressing the Ch variant of APOE4 in adults on the progression of amyloid and tau pathology in transgenic AD mice.

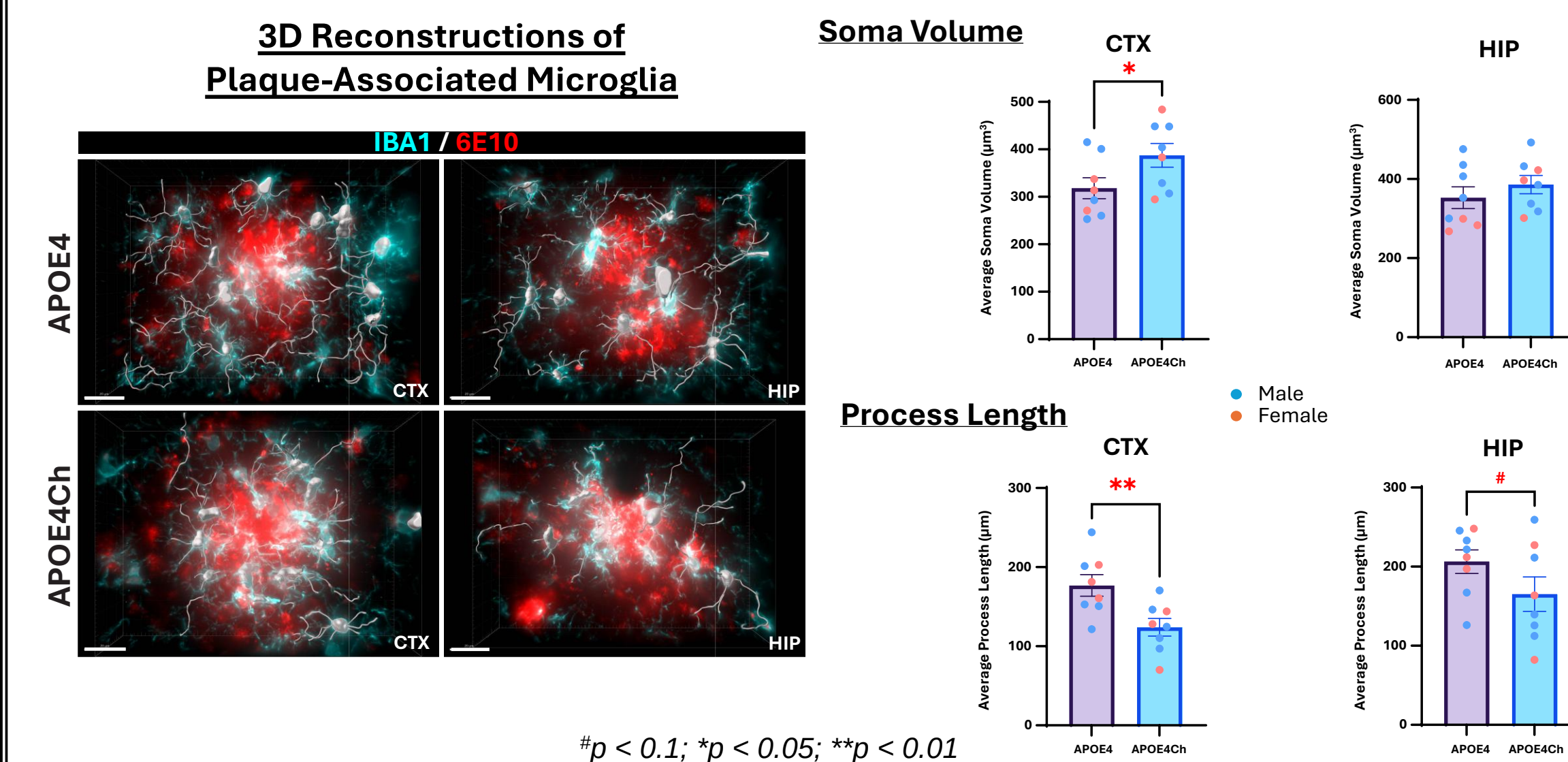
EXPERIMENTAL DESIGN



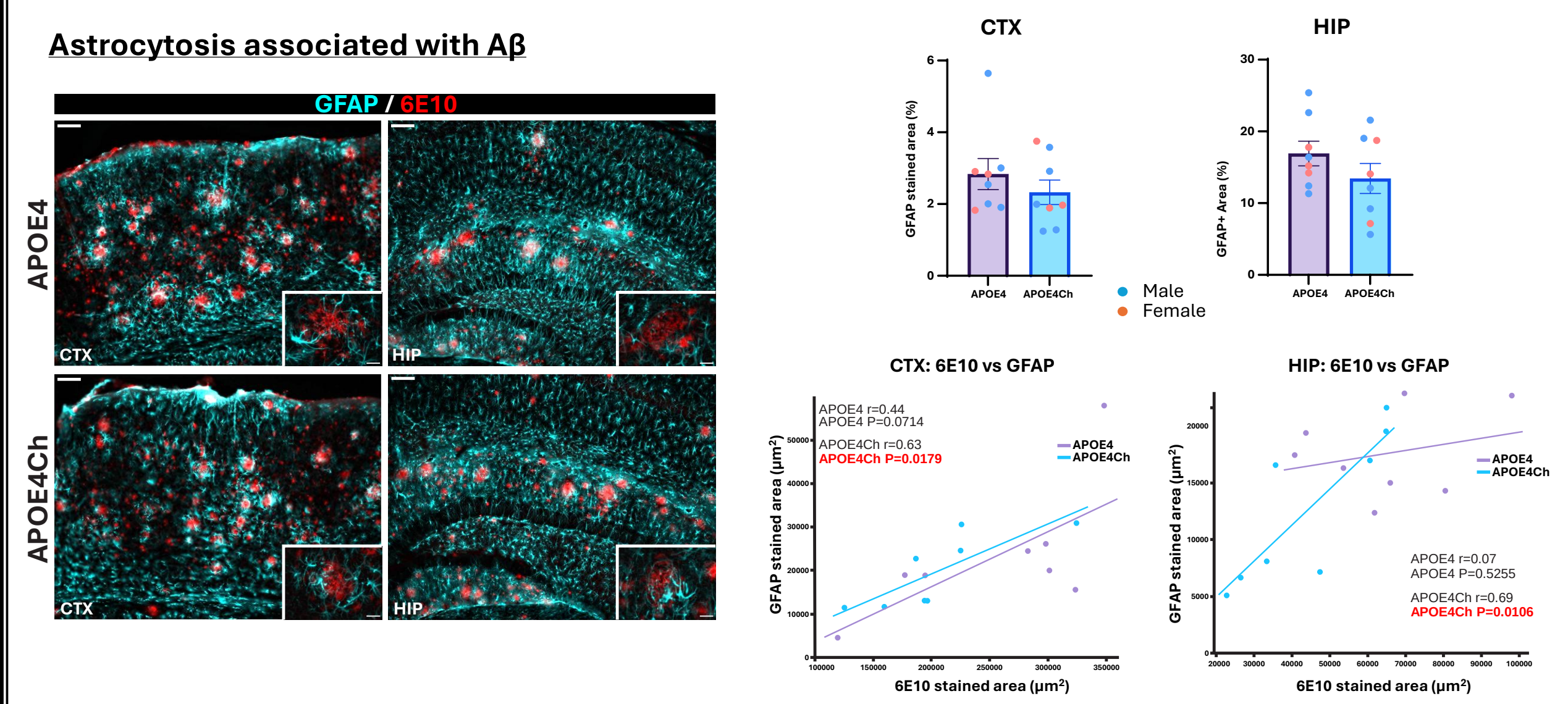
APOE4Ch enhances microglial response to amyloid plaques in APP/PS1 mice



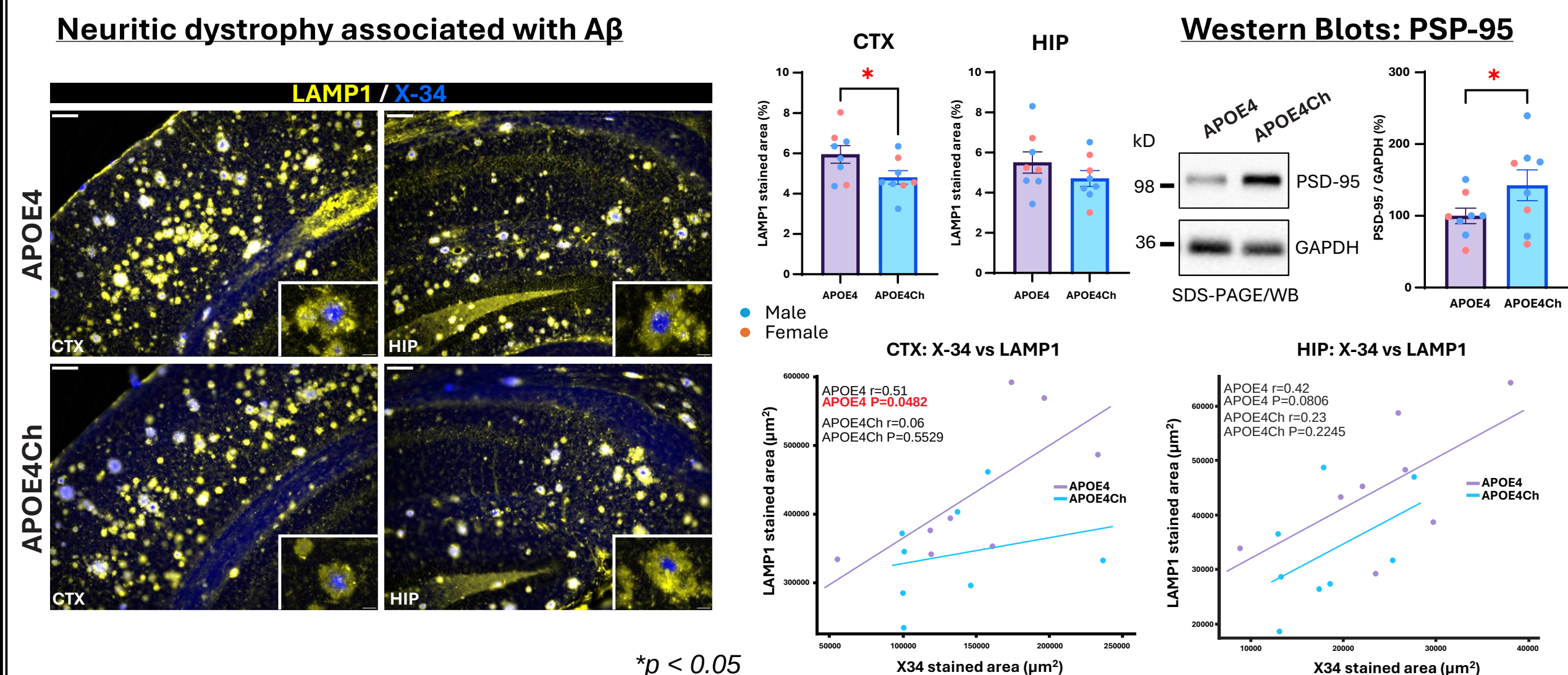
APOE4Ch modulates morphology of microglia associated with amyloid plaques in APP/PS1 mice



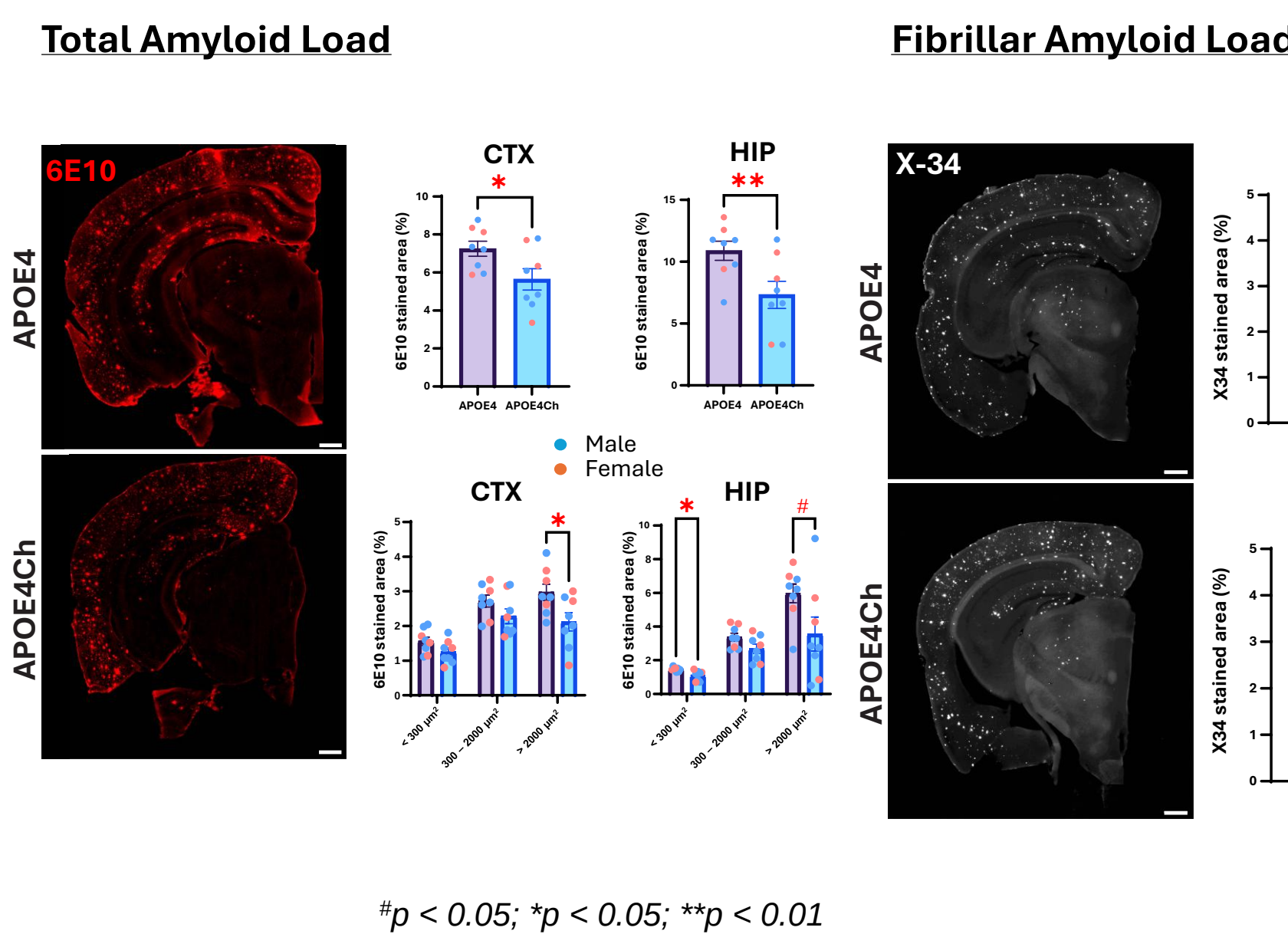
APOE4Ch enhances astrocytic response to amyloid plaques in APP/PS1 mice



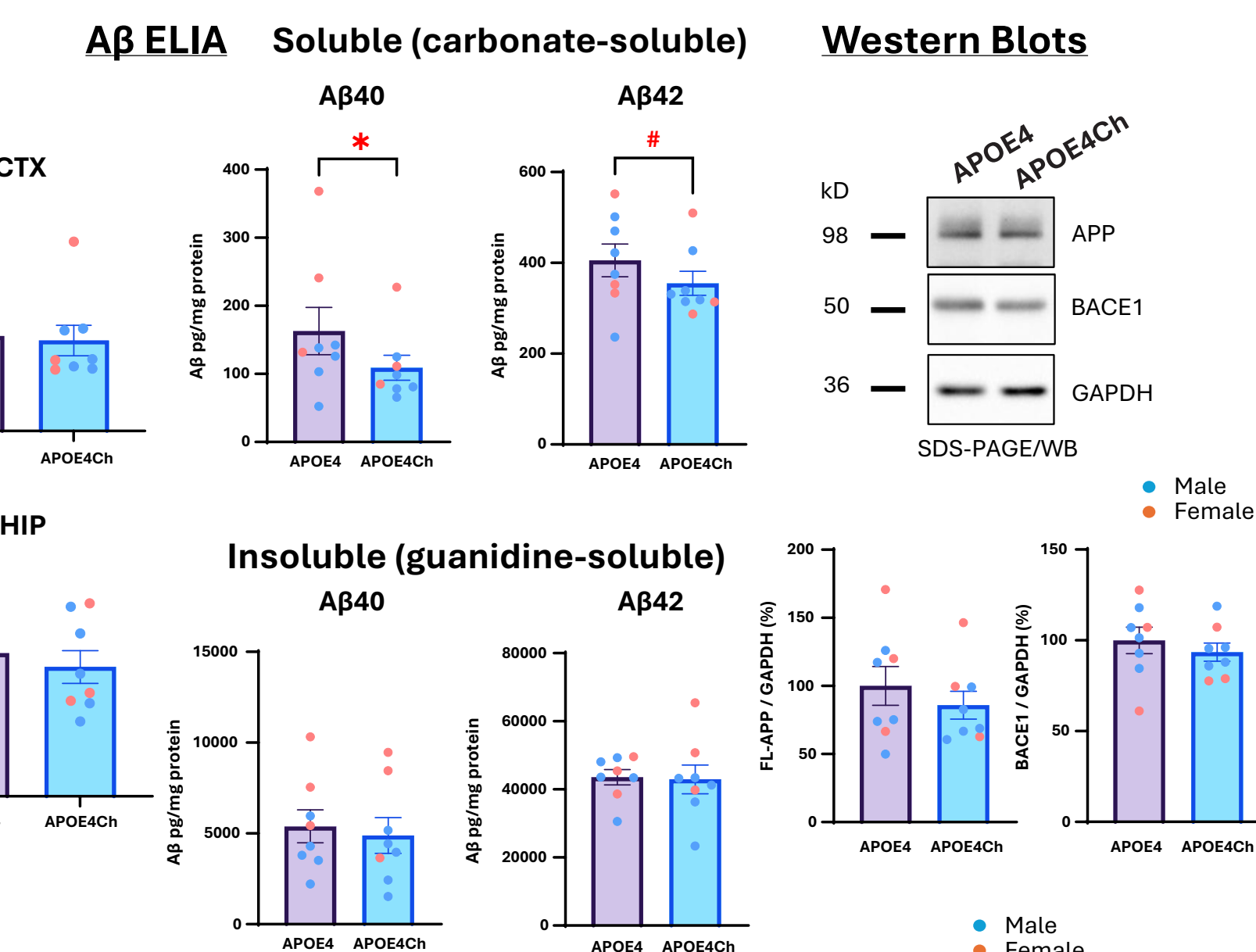
APOE4Ch reduces cortical amyloid plaque-associated neuritic dystrophy and improves synaptic marker in APP/PS1 mice



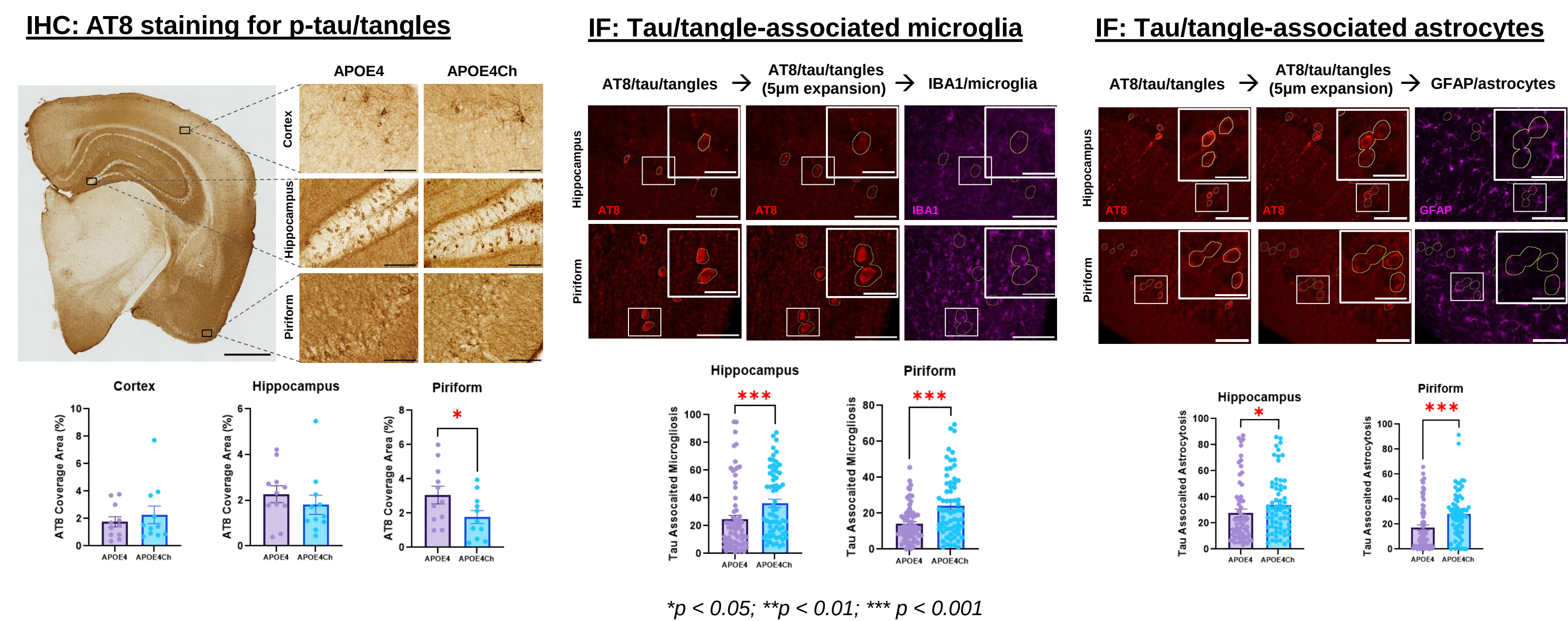
APOE4Ch reduces total amyloid deposition but not fibrillar plaques in the brain of APP/PS1 mice



APOE4Ch reduces soluble but not insoluble Aβ independent of APP expression or processing



APOE4Ch reduces tau pathology in selected brain regions and enhances microglial and astrocytic response to tau pathology in PS19 mice



SUMMARY & CONCLUSIONS

- AAV-mediated expression of APOE4Ch post-onset of pathology significantly reduces the progression of amyloid deposition in APP/PS1 mice, compared to control mice expressing APOE4.
- APOE4Ch expression enhances glial response to amyloid plaques, which most likely contributes to the reduction of overall amyloid pathology in APP/PS1 mice.
- APOE4Ch expression confers resilience against amyloid plaque-associated neuritic dystrophy and improves synaptic marker in APP/PS1 mice.
- APOE4Ch expression post-onset of pathology also leads to modest but significant regional reduction of tau/tangle load in PS19 mice, along with enhanced glial response to tau pathology.
- These findings support the gene therapy potential of APOE Christchurch for Alzheimer's disease, particularly in the context of APOE4.

ACKNOWLEDGEMENTS

This work was supported by grants from the National Institutes of Health/National Institute on Aging (NIH/NIA; RF1/R01AG077772, R01AG081426) and the College of Pharmacy at the University of Minnesota (UMN). The AAVs were generated at the UMN Viral Vector and Cloning Core.