

Vascular-associated Fibroblast-expressed APOE4 Is A Driver For Cerebral Amyloid Angiopathy And Vascular Dysfunction

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Background

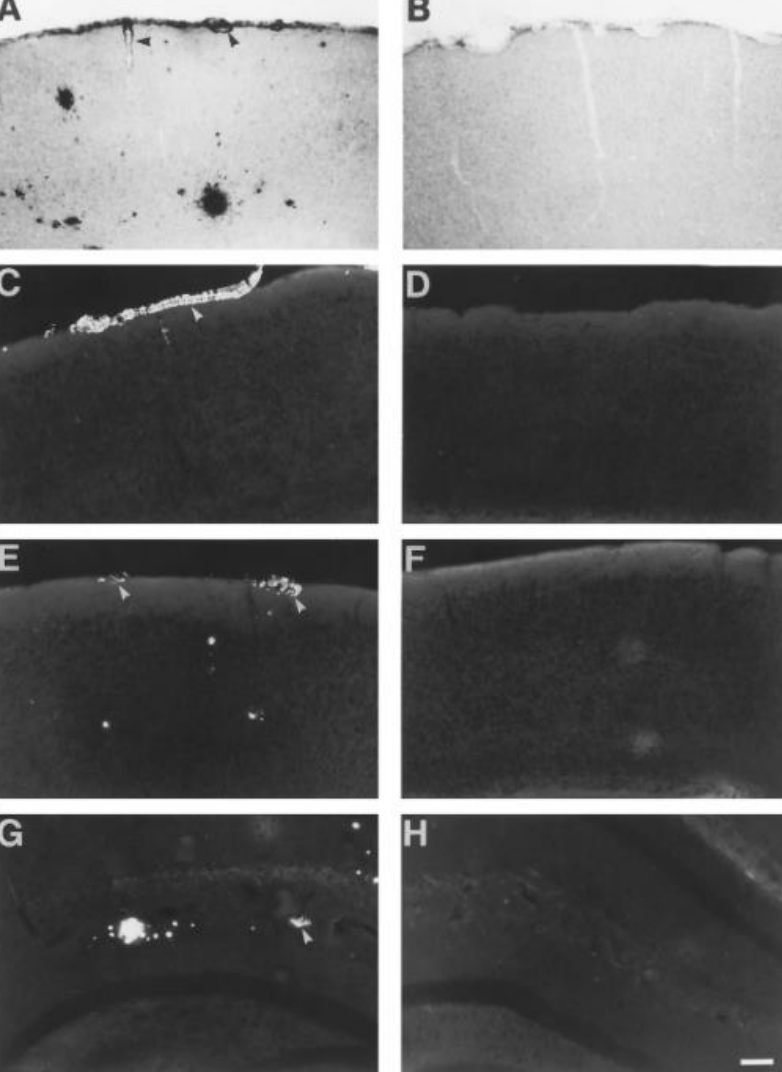
APOE genotype strongly modifies CAA

Table 1. Distribution of APOE Genotypes in the Study Population Relative to the Presence or Absence of Severe CAA*

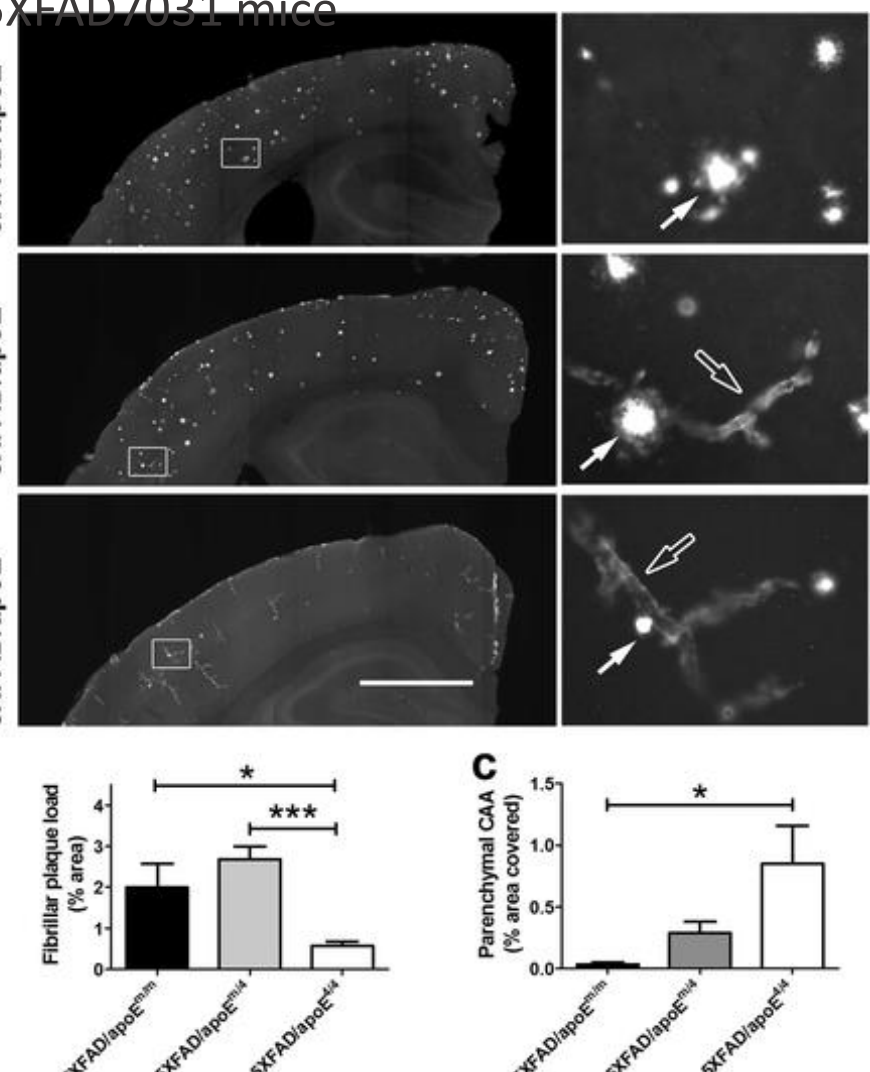
APOE Genotype	Severe CAA (n = 165)	No CAA (n = 194)
ε3/ε3	54 (34.2)	104 (55.8)
ε3/ε4	53 (45.7)	63 (54.3)
ε2/ε3	4 (36.4)	7 (63.6)
ε4/ε4	47 (73.4)	17 (26.6)
ε2/ε4	7 (70.0)	3 (30.0)

Abbreviation: CAA, cerebral amyloid angiopathy.
* $\chi^2 = 31.03$; $P < .001$.

ApoE KO APPsw mice lack CAA and fibrillar amyloid deposition

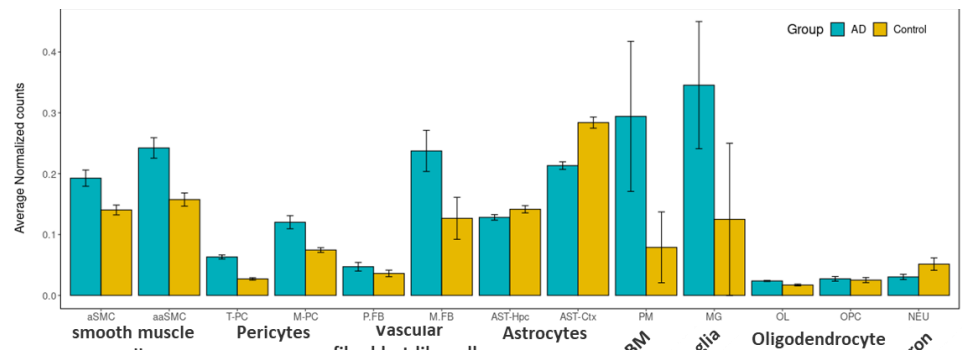


ApoE4 shifted parenchymal Aβ deposition from plaques to CAA in 5XFAD/2031 mice

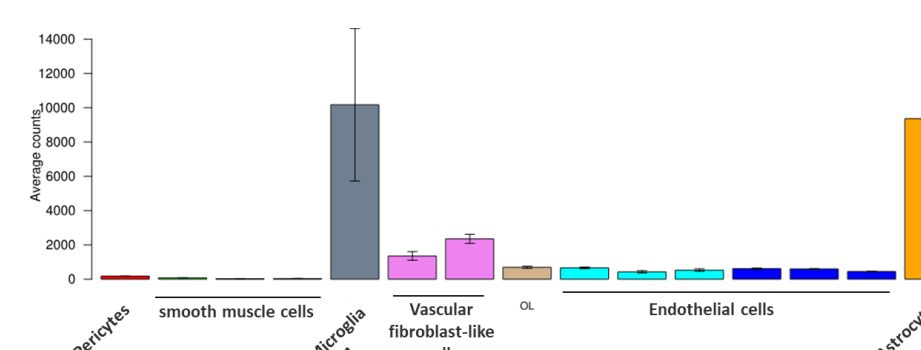


APOE is expressed by the cells of brain vasculature

Human brain vasculature

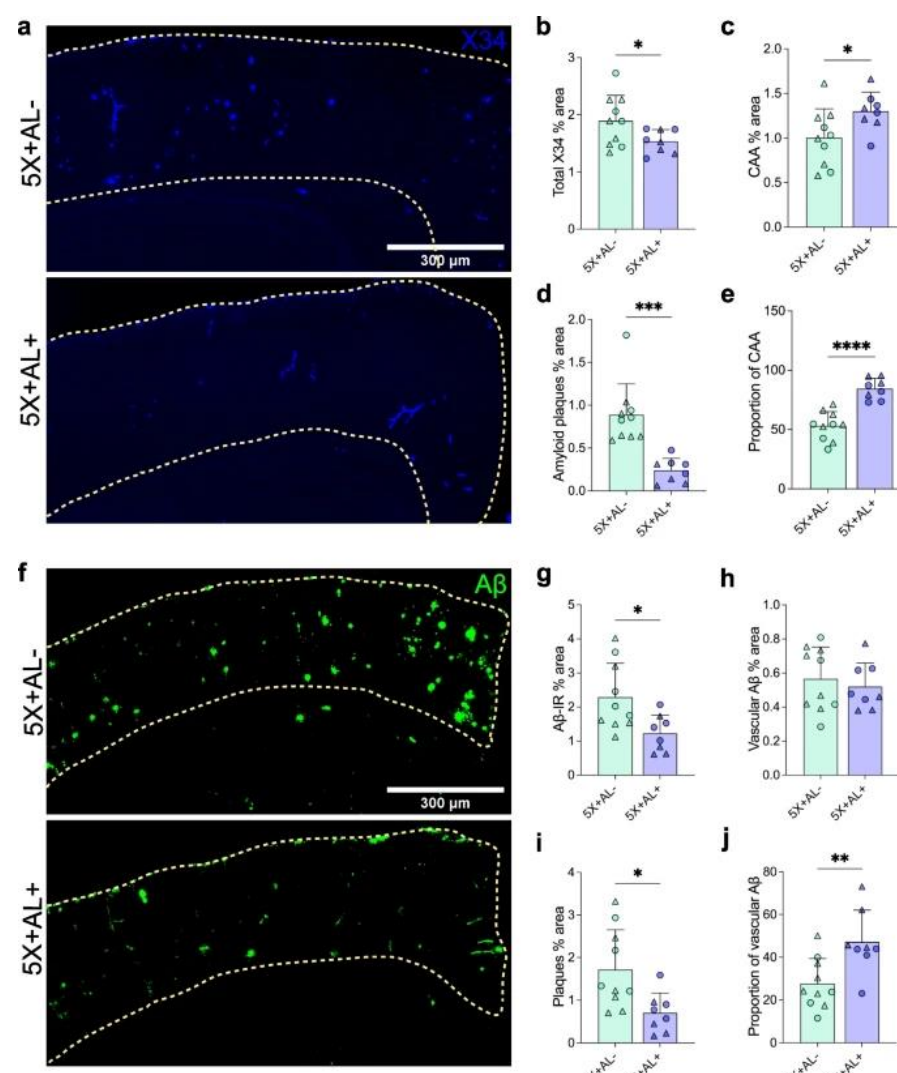


Adult mouse brain vasculature

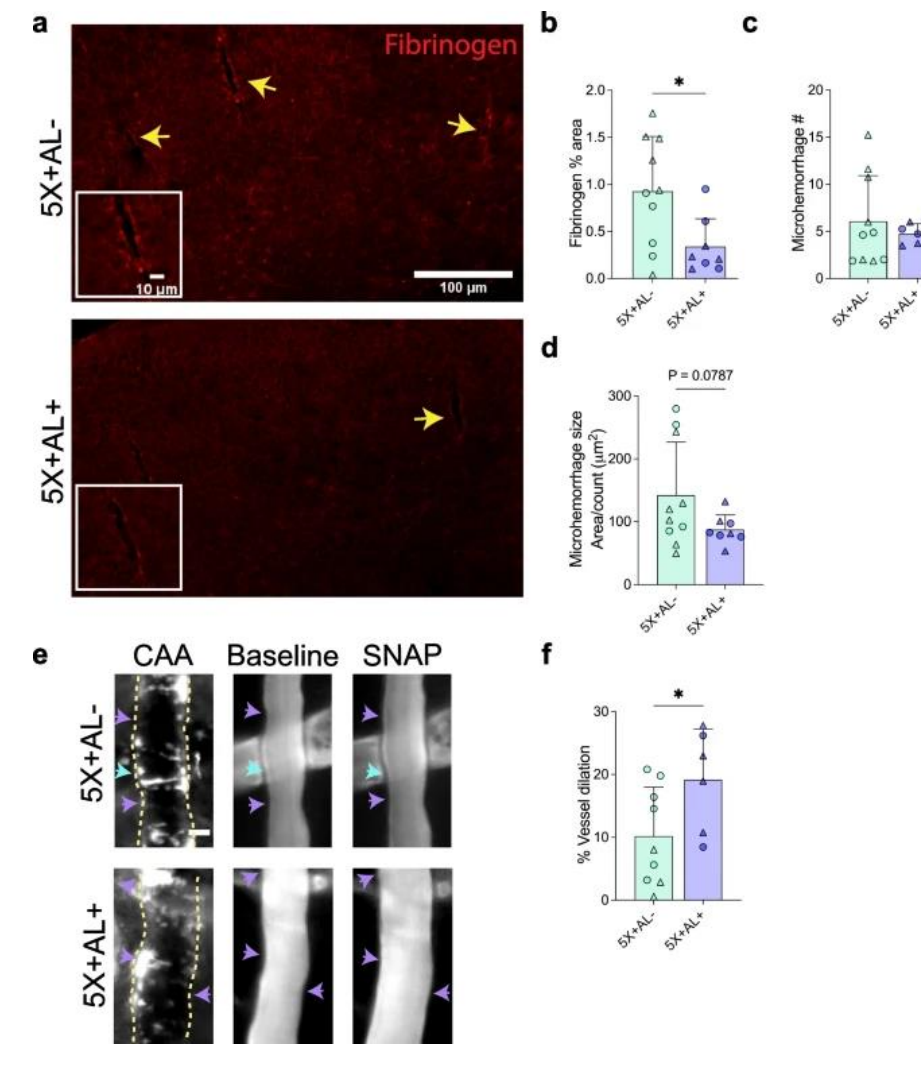


Effect of astrocyte-produced apoE4 on both parenchymal plaques and CAA

Removal of astrocyte ApoE4 decreases parenchymal Aβ but increases CAA



Removal of astrocyte ApoE4 results in decreased vascular degeneration

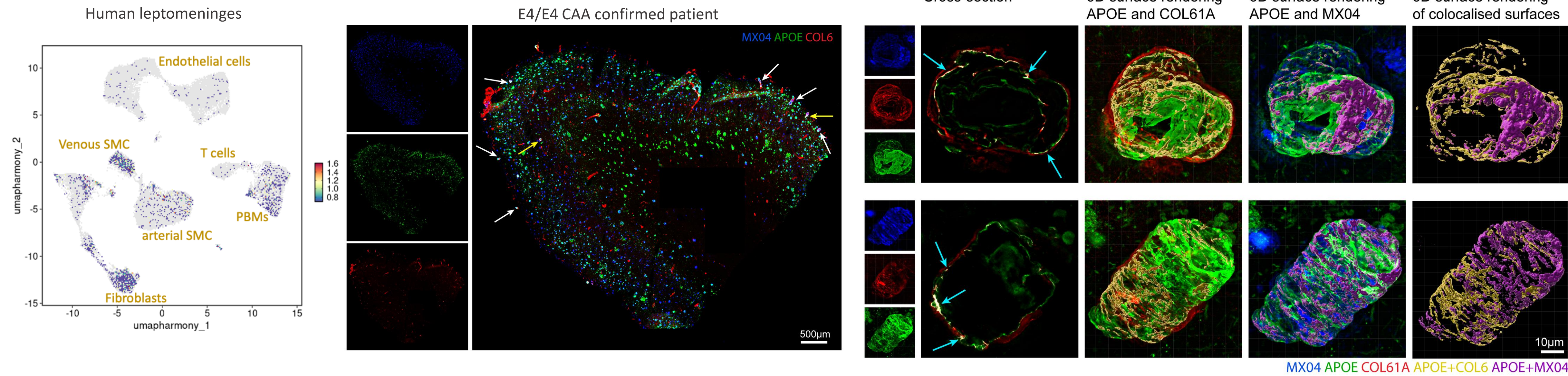


References

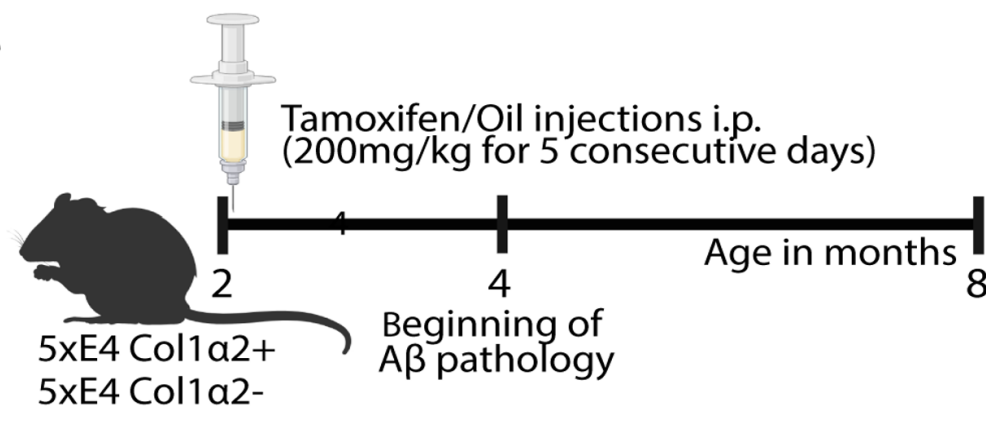
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Results

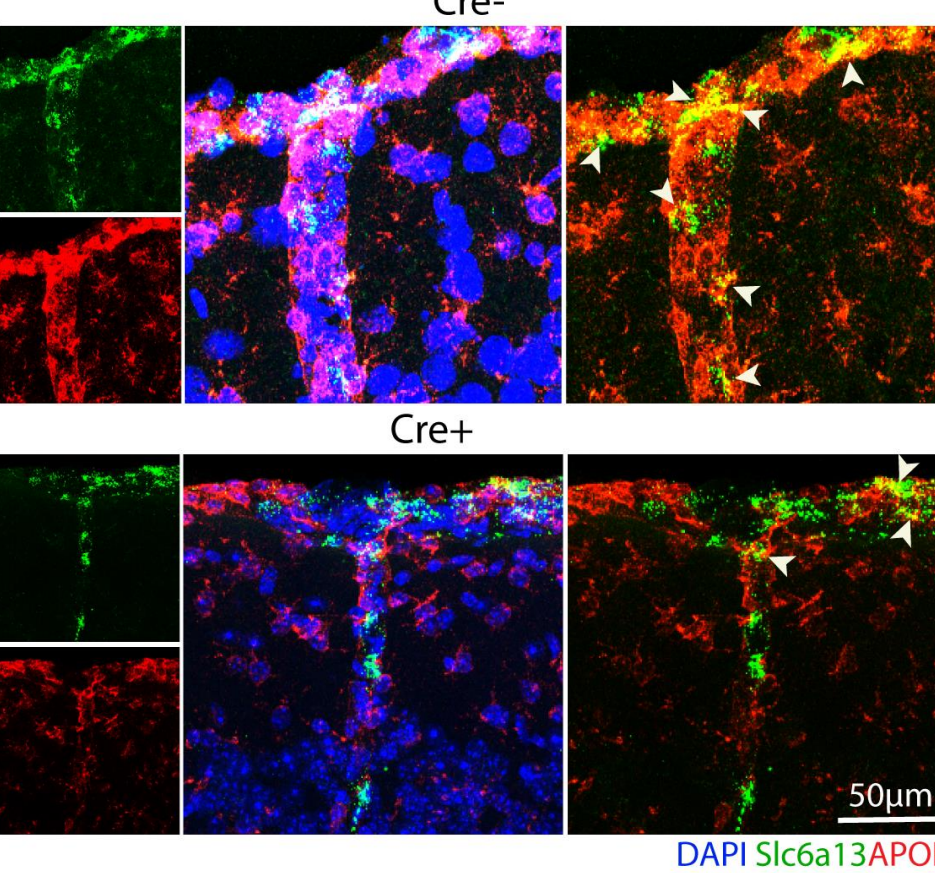
APOE is expressed by VAFs in human CAA



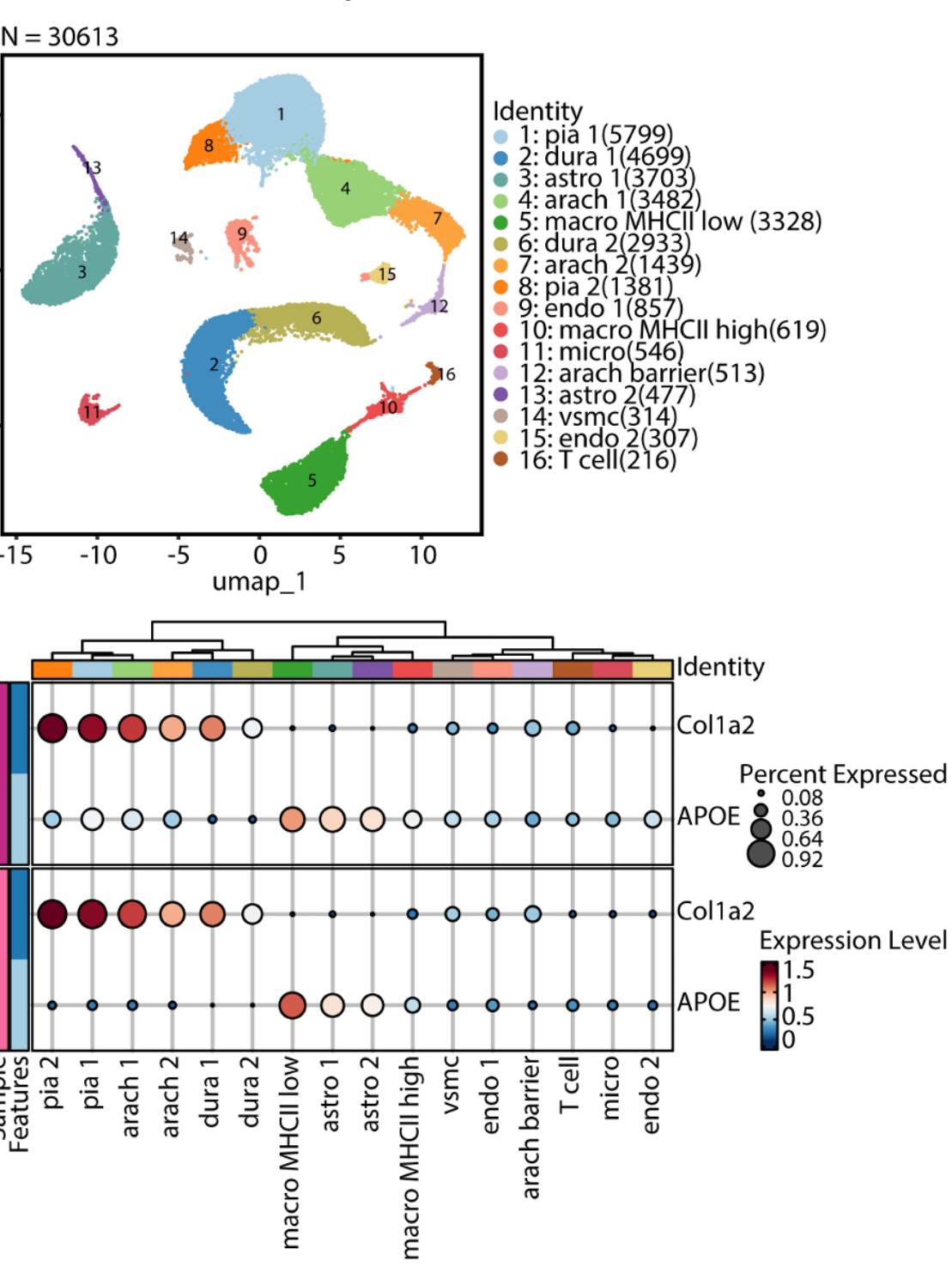
Experimental Design



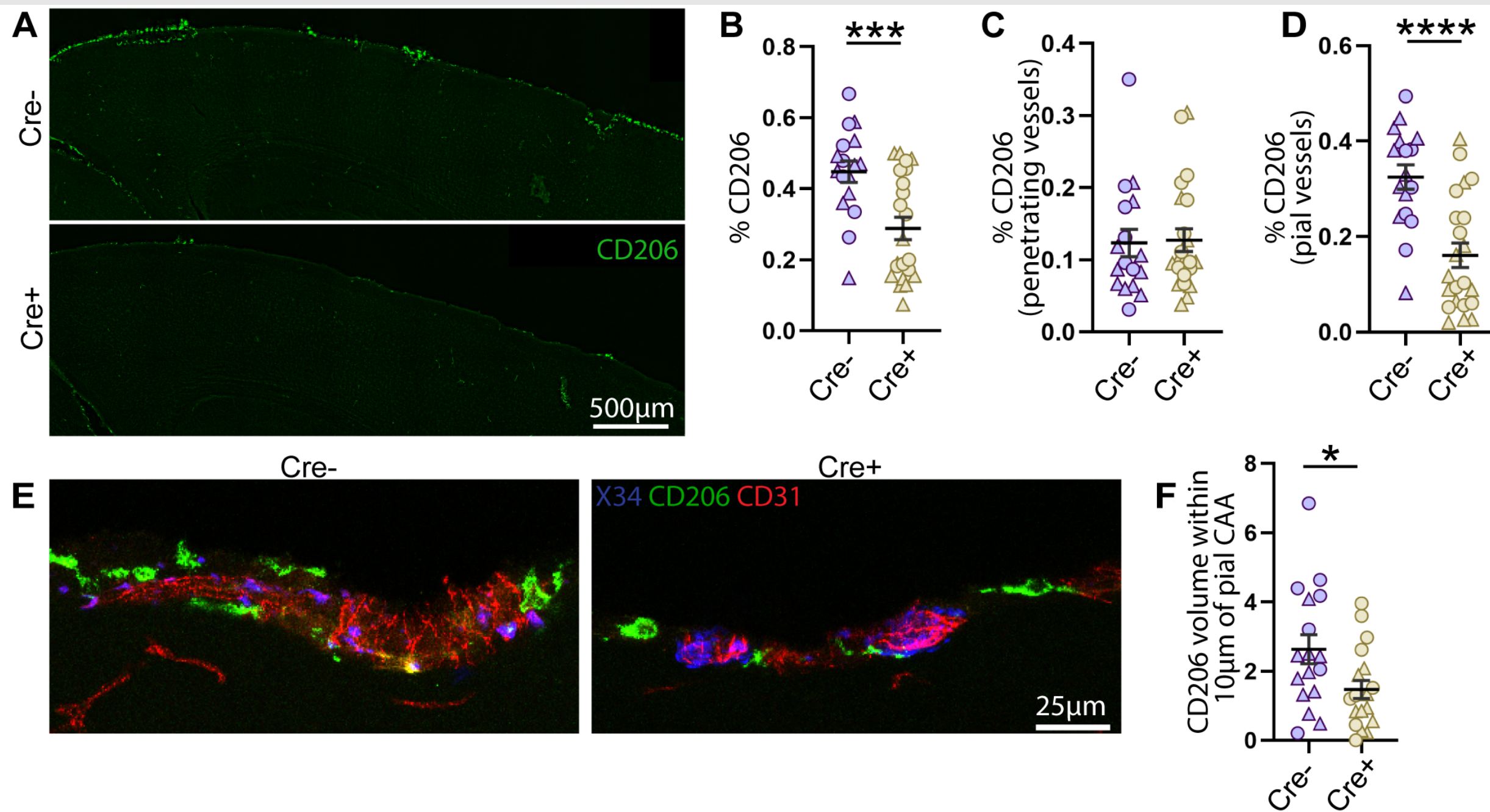
APOE4 is reduced in Slc6a13+ VAFs in the pial and penetrating vessels by in situ hybridization



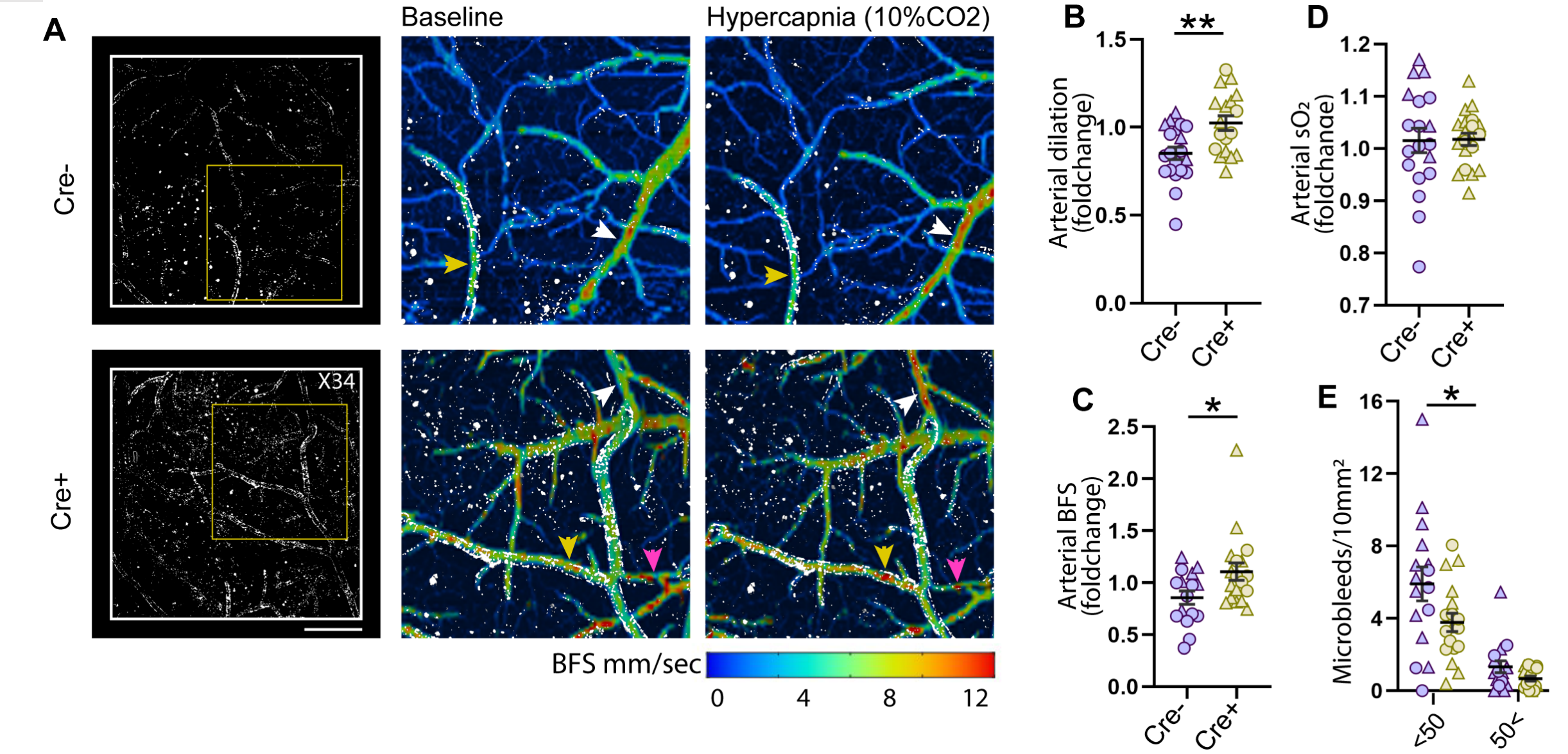
APOE4 is depleted in the pial and arachnoid fibroblasts upon TAM treatment



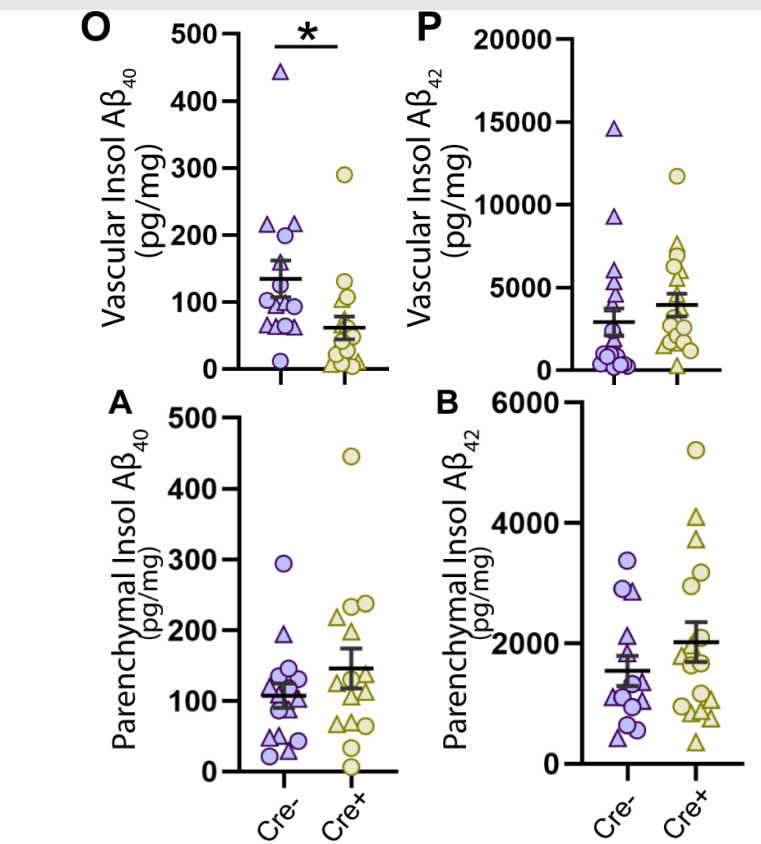
APOE4 depletion in the VAFs results in reduced PBM reactivity at the pia



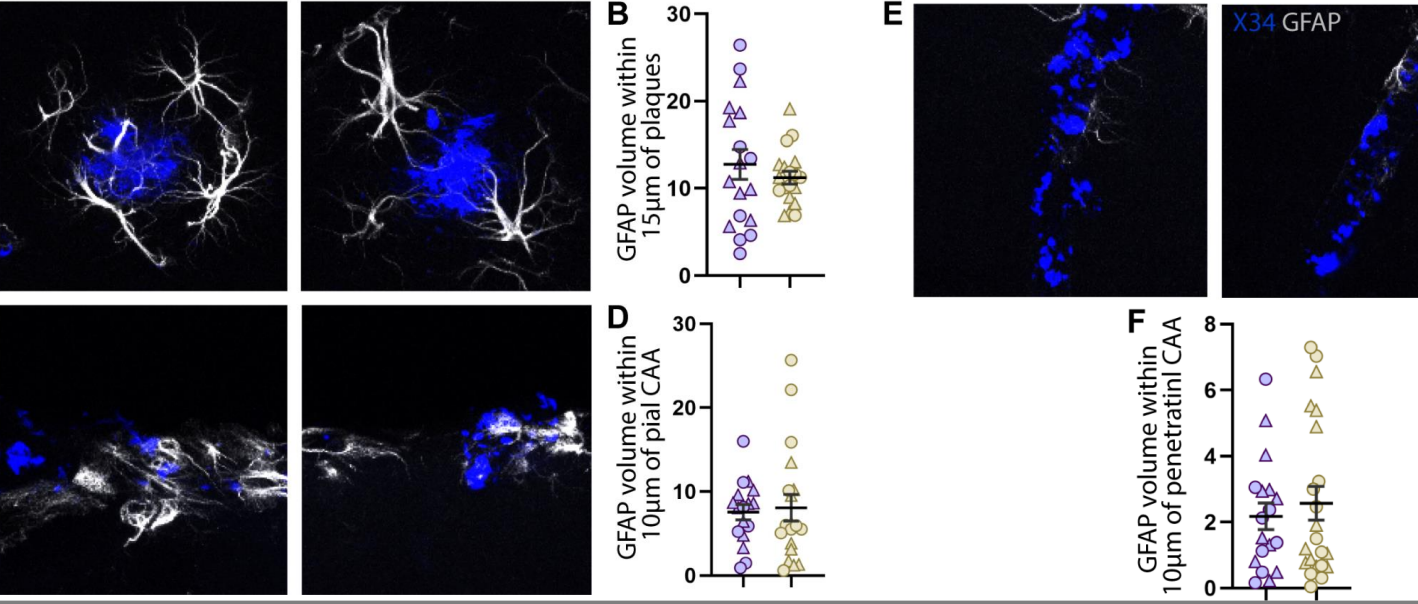
APOE4 depletion in the VAFs improves vascular function and reduces microbleeds



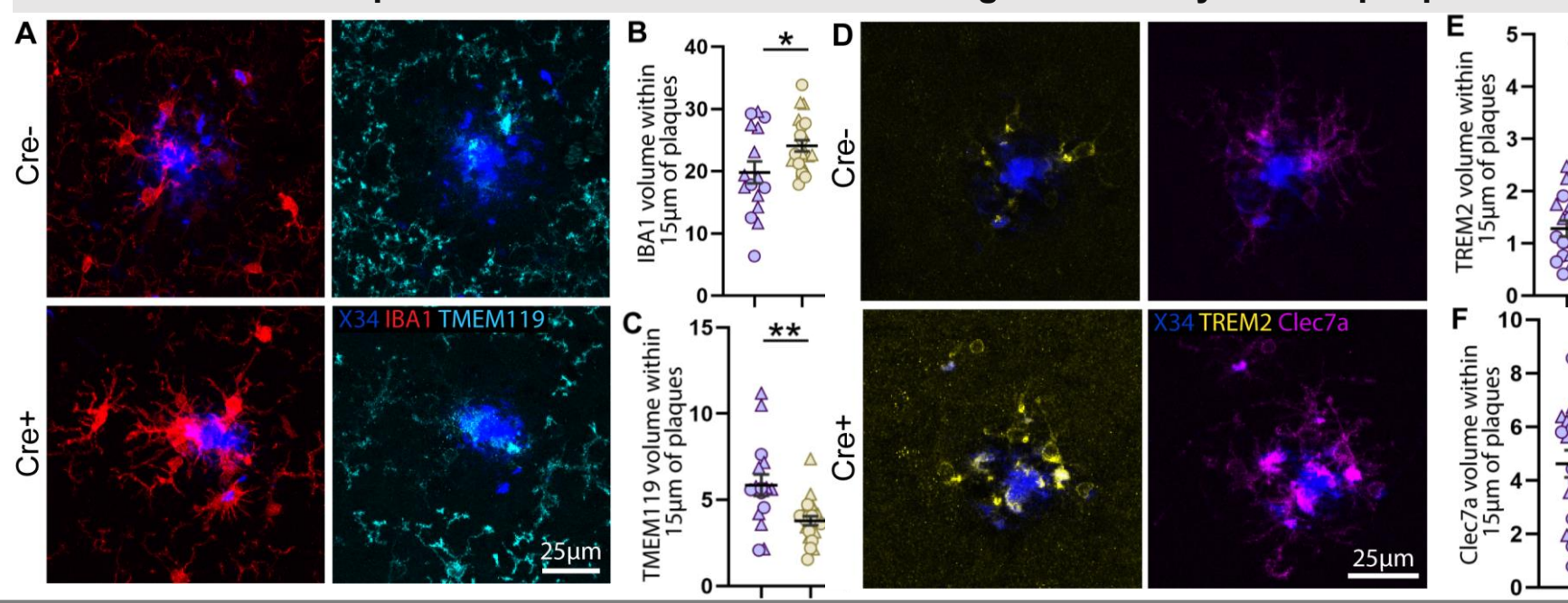
Significant reduction in Aβ40 in the FA-soluble vascular fraction



APOE4 depletion in the VAFs does not affect GFAP expression around CAA and parenchymal plaques



APOE4 depletion in the VAFs increases microglial reactivity around plaques



Conclusion

- VAFs are a critical source of pathogenic APOE4
- VAF-expressed APOE4 locally regulates leptomeningeal CAA, perivascular immune responses, and cerebrovascular function
- APOE4 targeting can be spatially constrained to control CAA while preserving essential APOE functions in other brain cell types without inducing global inflammation or altering parenchymal amyloid burden