

Introduction

Genetic polymorphisms are associated with altered risks of AD onset, pointing to biological processes and potential targets for interventions. Consistent with the important roles of microglia in AD development, genetic mutations of several genes expressed on microglia have been identified as risks for AD. Emerging evidences indicate that the expression of a microglia-specific gene *MS4A6A* is thought to be associated with AD, since AD patients show upregulation of *MS4A6A*, and its levels correlate with the severity of clinical neuropathology. However, the mechanism linking *MS4A6A* and AD has not been experimentally studied.

Results

Fig.1 Human *MS4A6A* SNPs are correlated with AD risks and amyloid biomarkers in the CSF

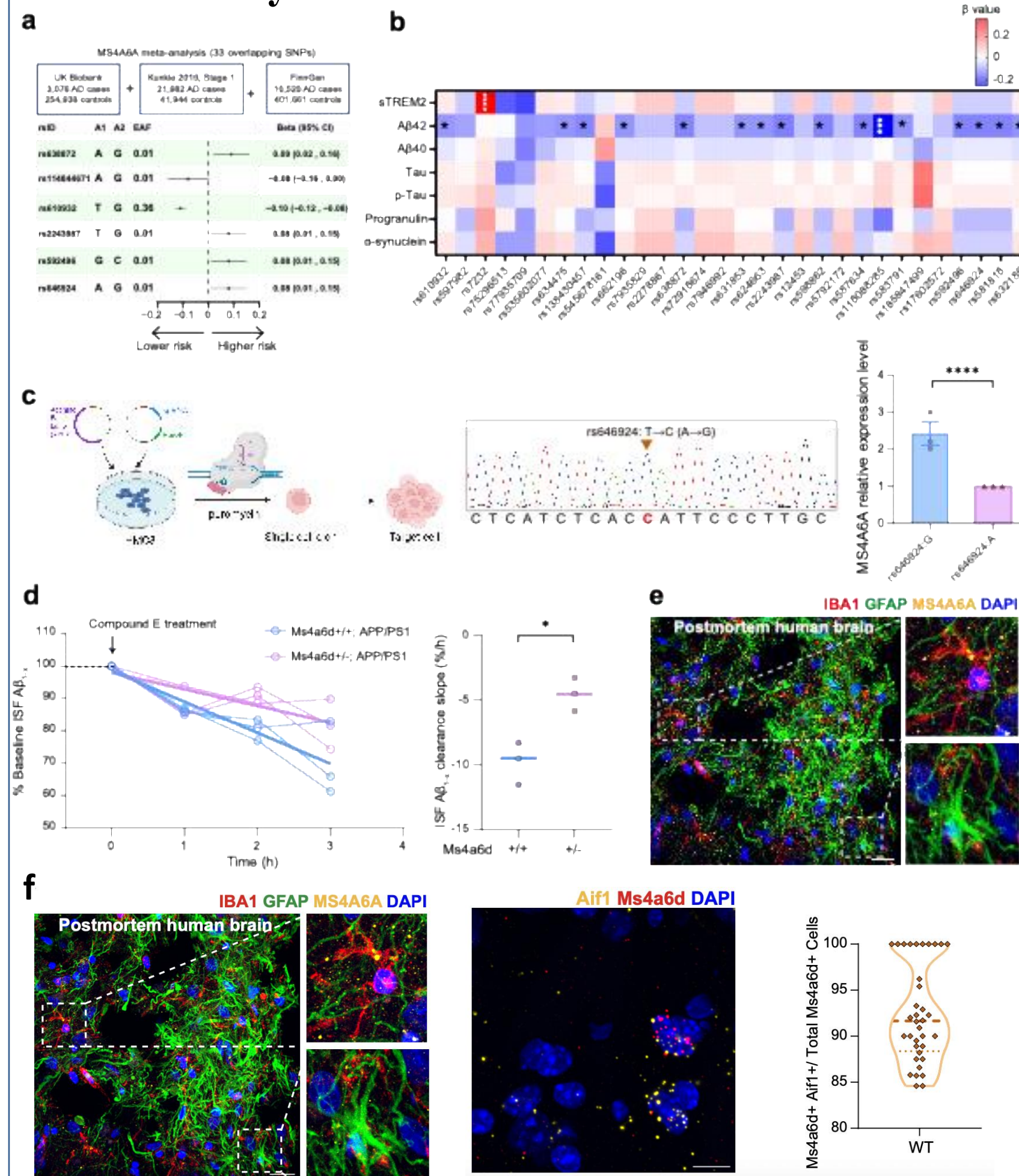


Fig.2 Ms4a6d deletion diminishes microglial responses to Aβ pathology in APP/PS1 mice

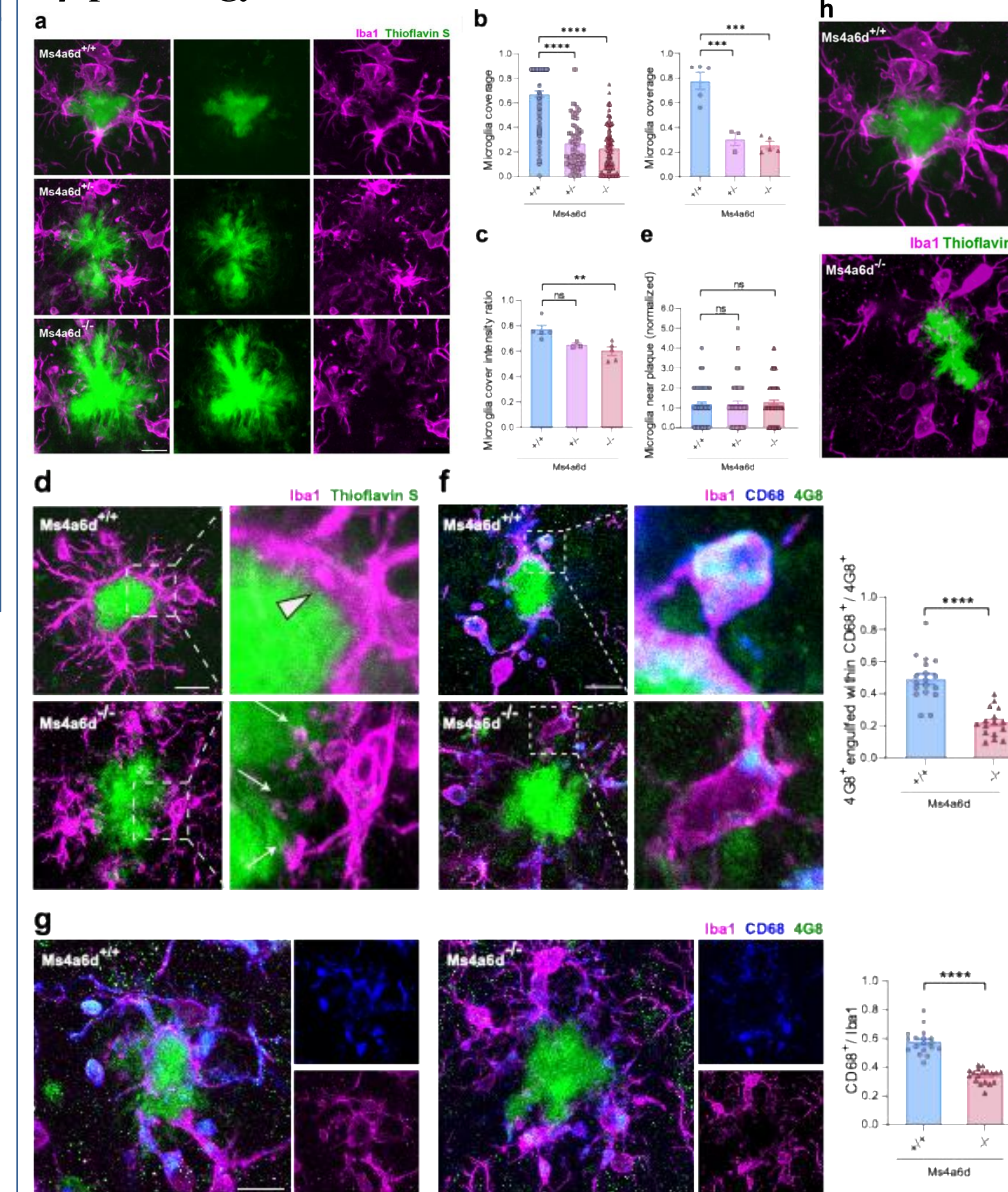


Fig.3 Ms4a6d-deficiency in APP/PS1 mice increases Aβ burden and markedly reduces plaque compaction

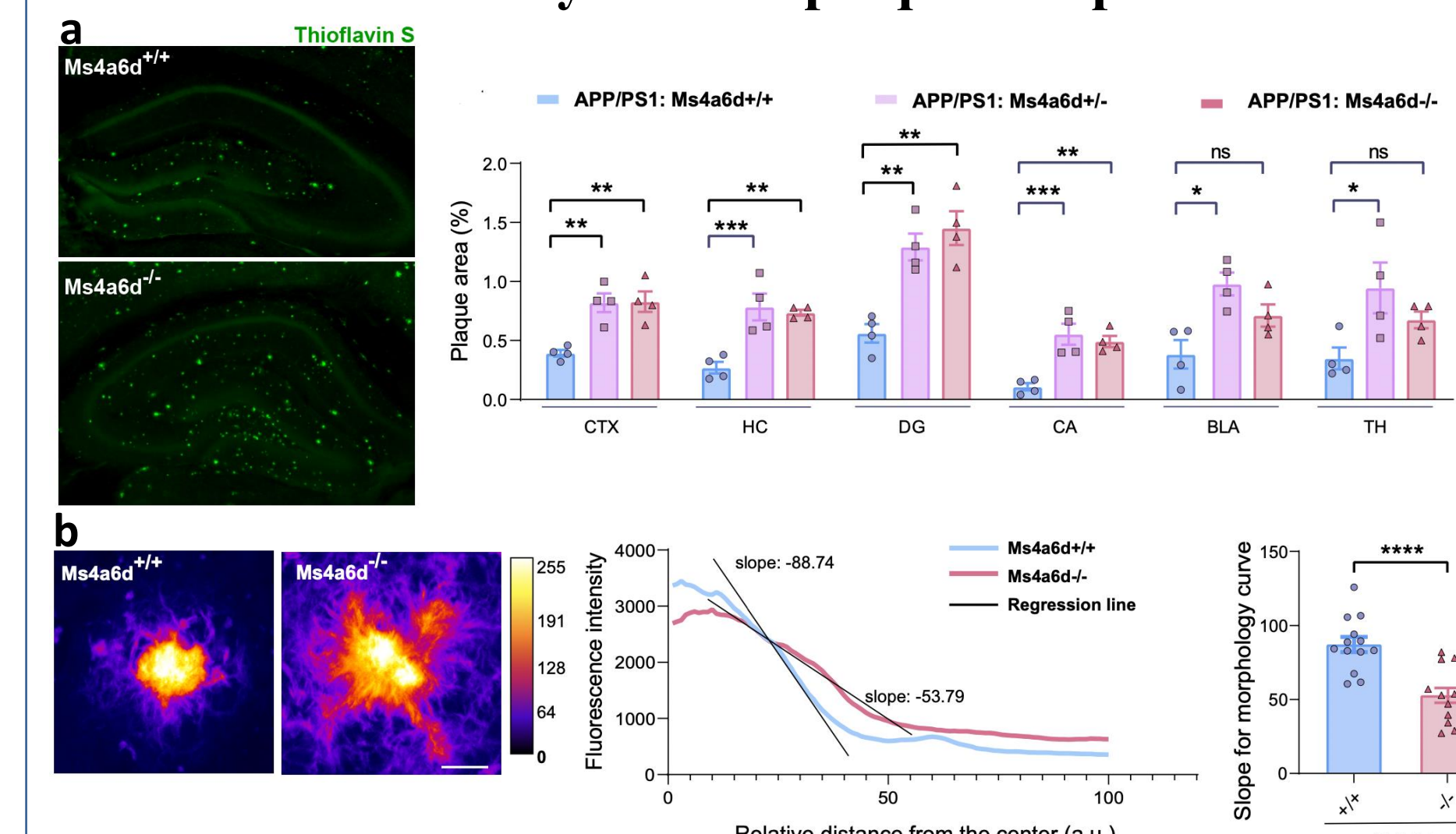


Fig.4 Ms4a6d deficiency dampens JAK2 signaling and promotes neuroinflammation

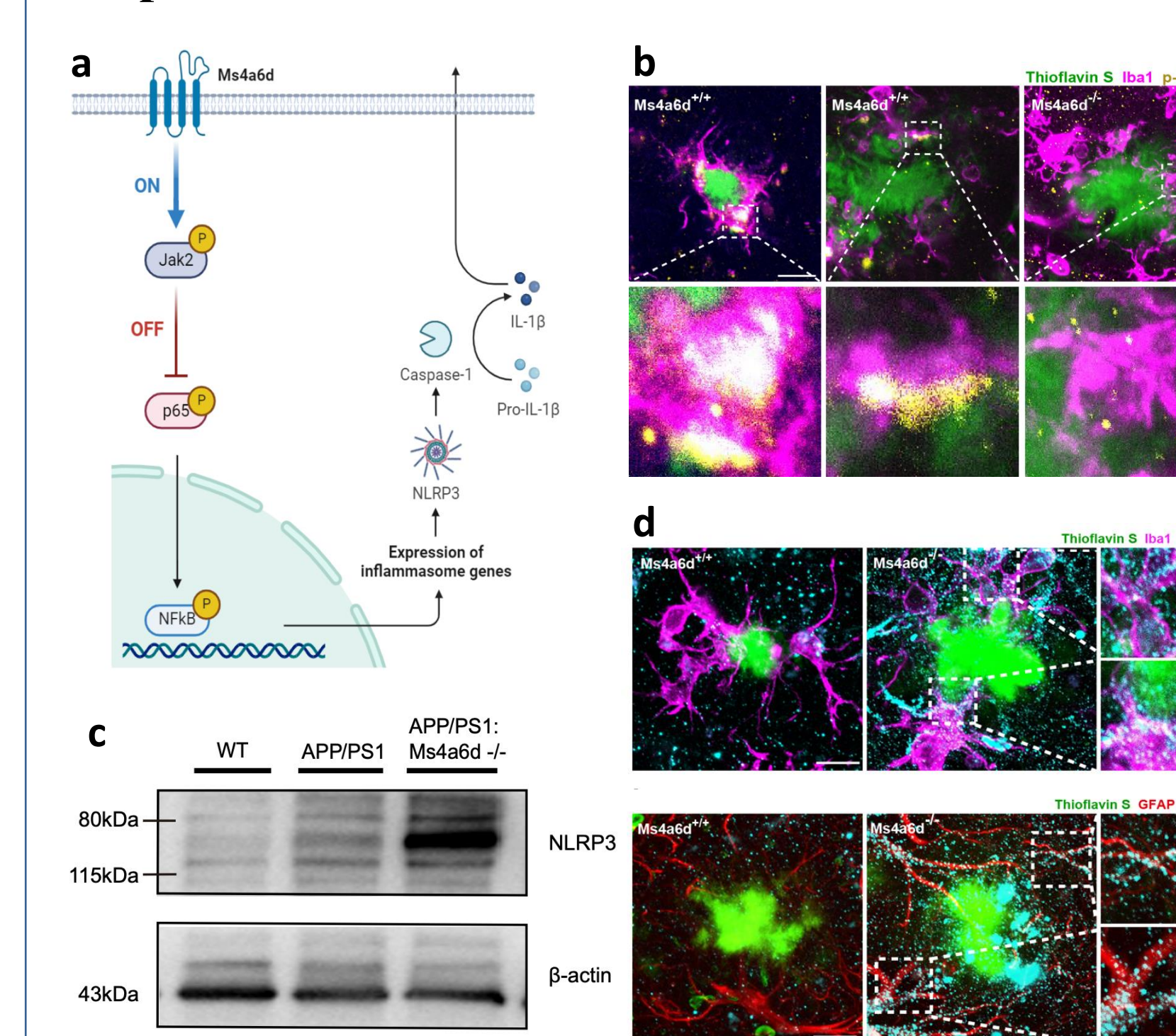


Fig.5 Ms4a6d deficiency exacerbates plaque-associated axonal spheroids, synapse loss and cognitive deficit

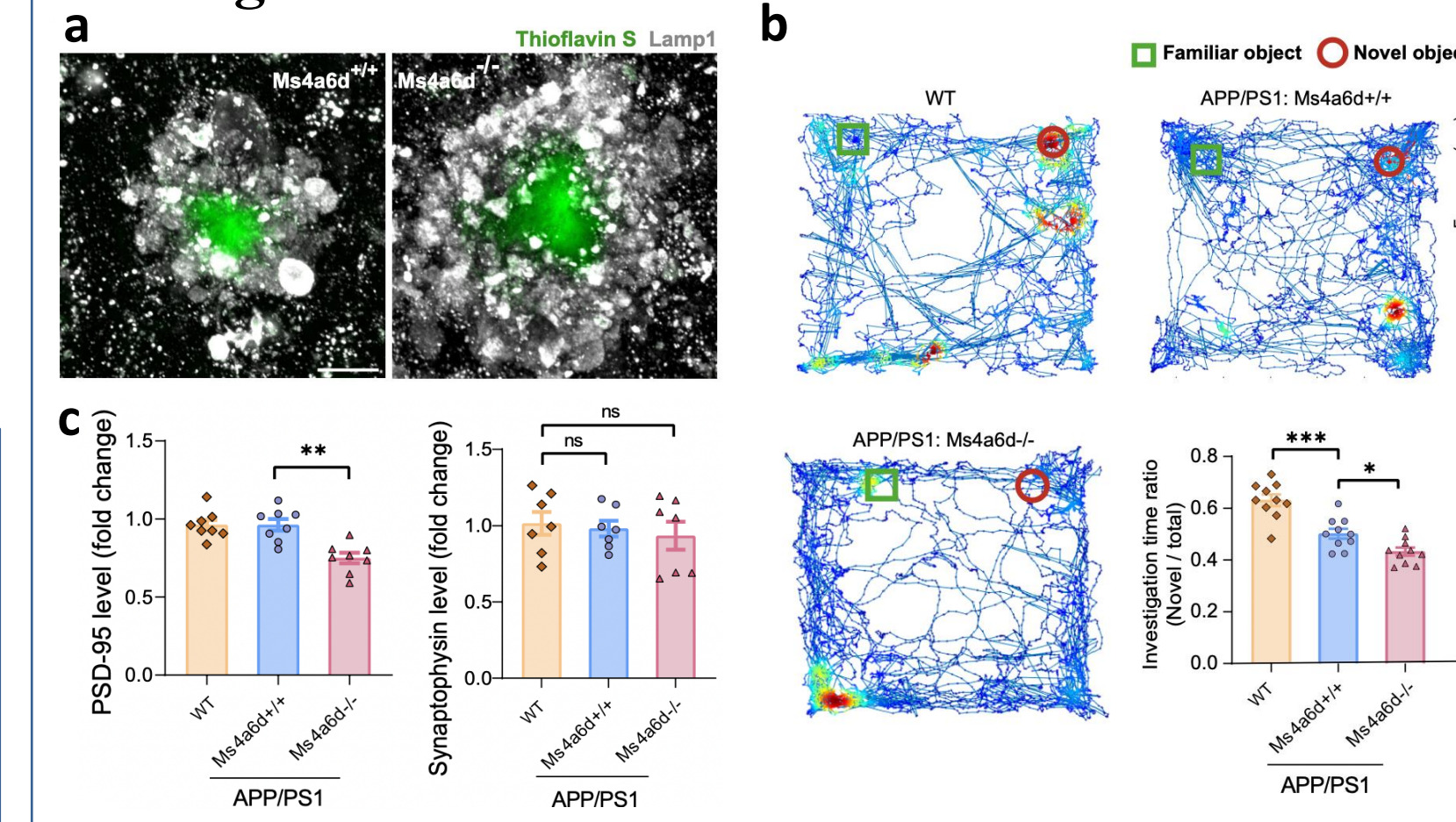
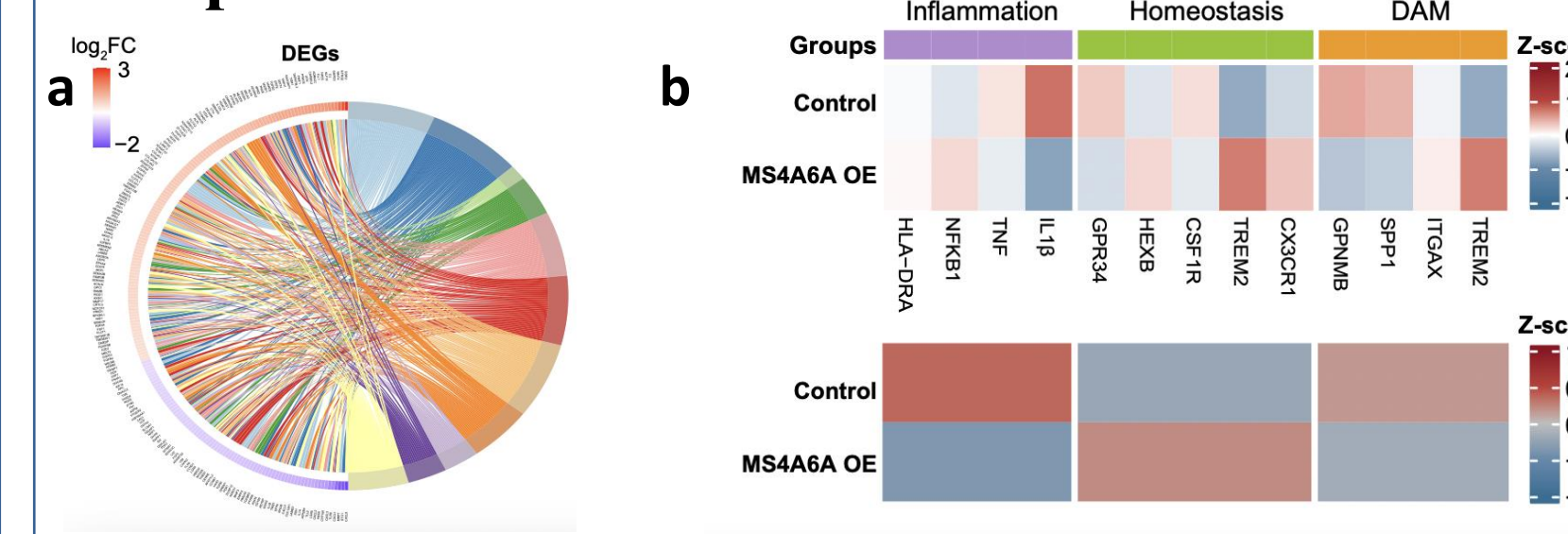


Fig.6 Enhancing MS4A6A expression is associated with protective effect



Conclusions

Our findings reveal that Ms4a6d deficiency suppresses neuroprotection and worsens neuroinflammation. Sufficient Ms4a6d maybe beneficial for boosting amyloid-related responses and suppressing inflammation in microglia, making it superior than previously reported candidates for microglia modulation. Thus, the elevated MS4A6A levels in AD are likely compensatory and boosting MS4A6A could be an effective treatment.

