

Alzheimer's risk factors *Trem2*^{R47H} and high-fat diet influence an overlapping pathway in the response to cored plaques

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1. Introduction

Lipid homeostasis is strongly linked to Alzheimer's disease (AD) with obesity as a risk factor¹. Our spatial transcriptomics reveals increased lipid-associated genes (ApoE, Npc2) in microglia contacting plaques² and we found that more aggregated plaques are more neurotoxic³. This study explores the effect of plaque-type on microglial and astrocytic clustering and lipid droplet accumulation, and how the AD risk factors of a high-fat diet and the *Trem2*^{R47H} mutation affect these processes.

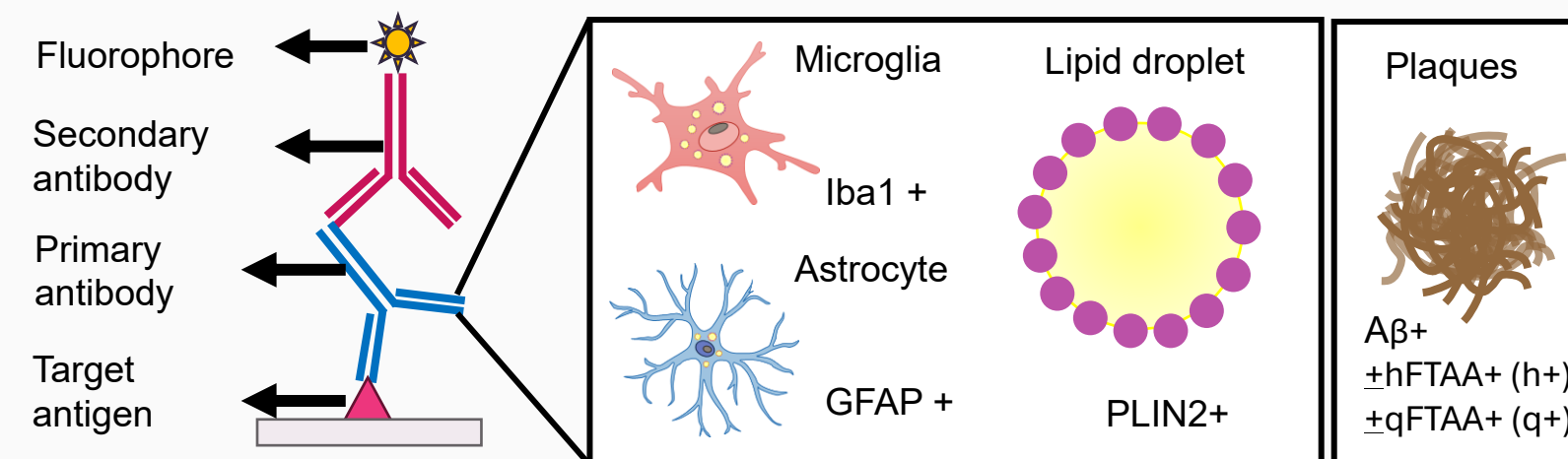
2. Method

Mice



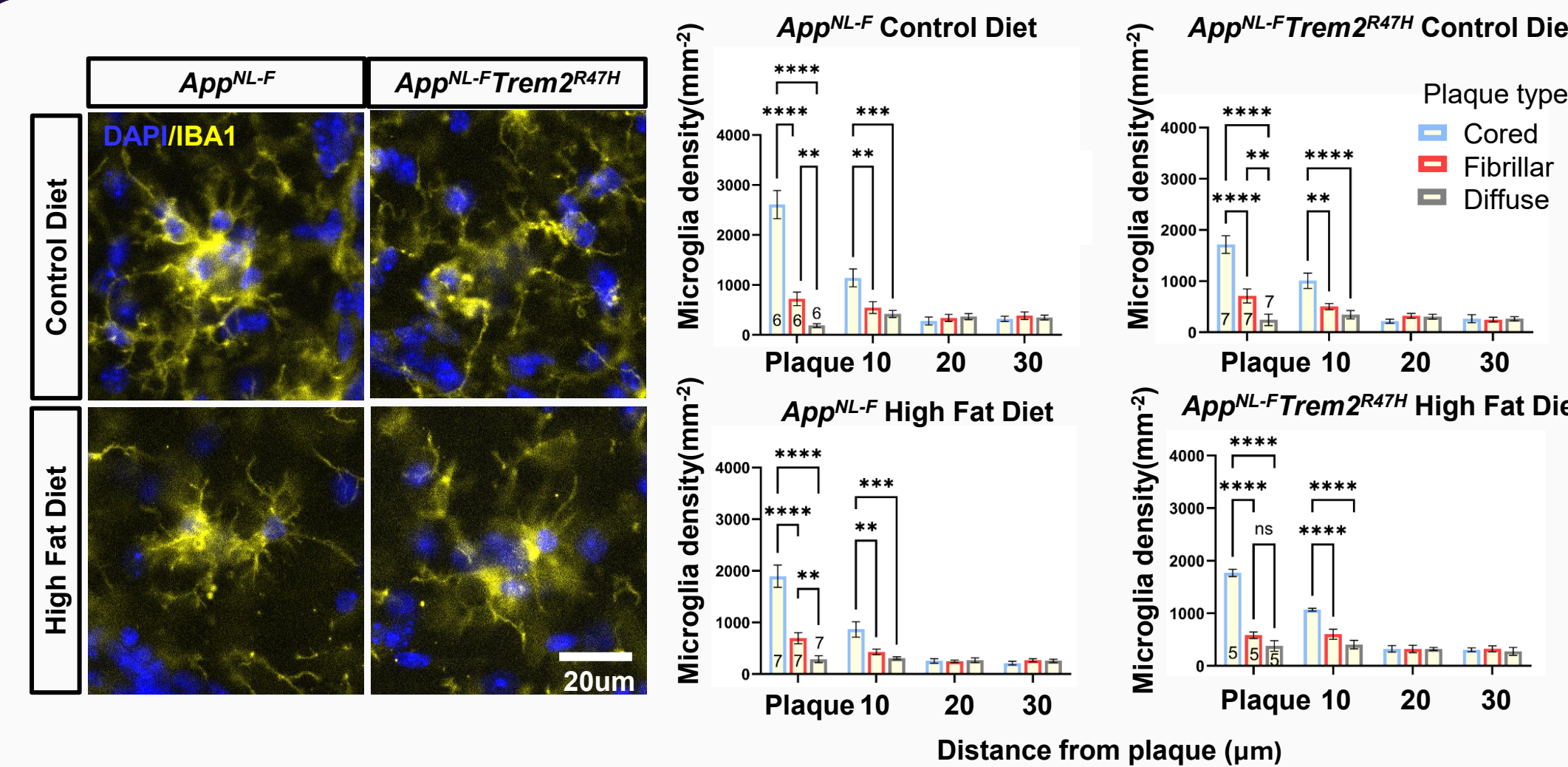
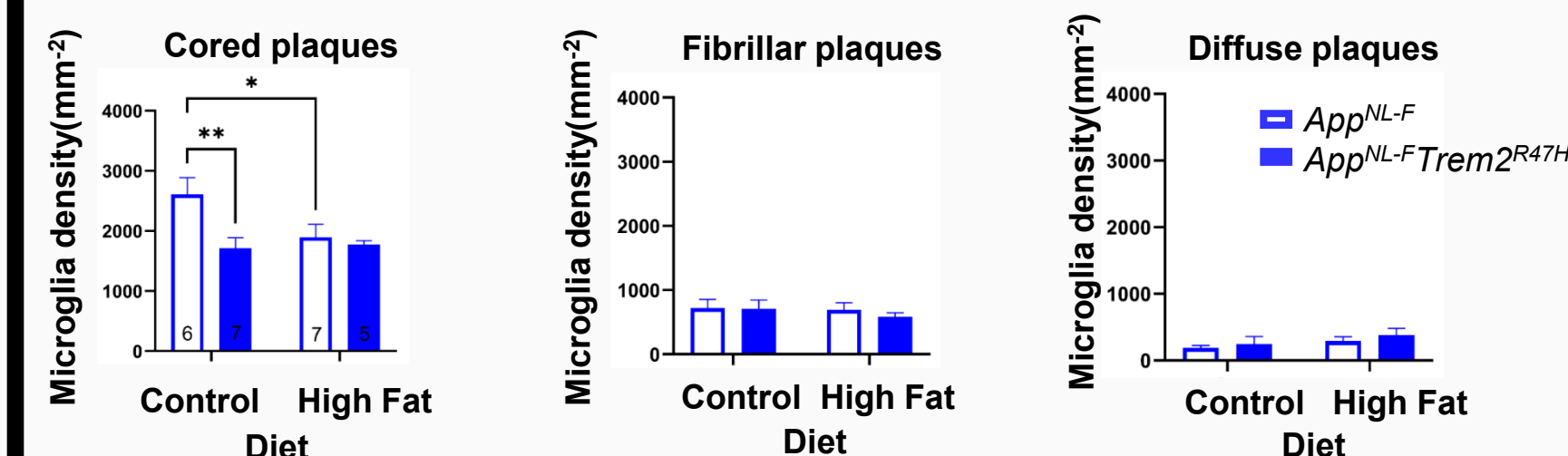
App^{NL-F} Control Diet (N=6)
App^{NL-F} High Fat Diet (N=7)
App^{NL-F}*Trem2*^{R47H} Control Diet (N=7)
App^{NL-F}*Trem2*^{R47H} High Fat Diet (N=5)

Immunofluorescence staining

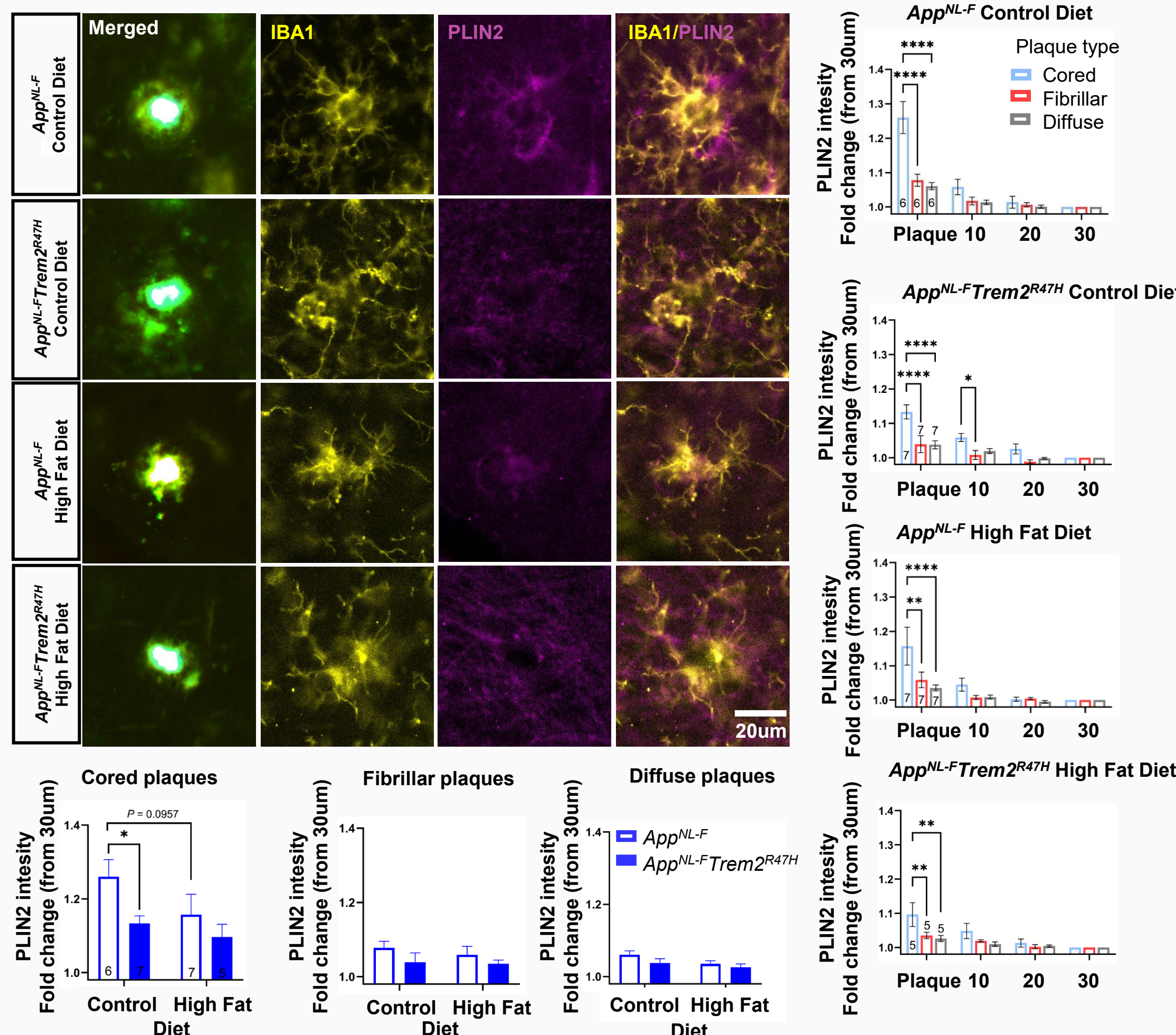


3. Results

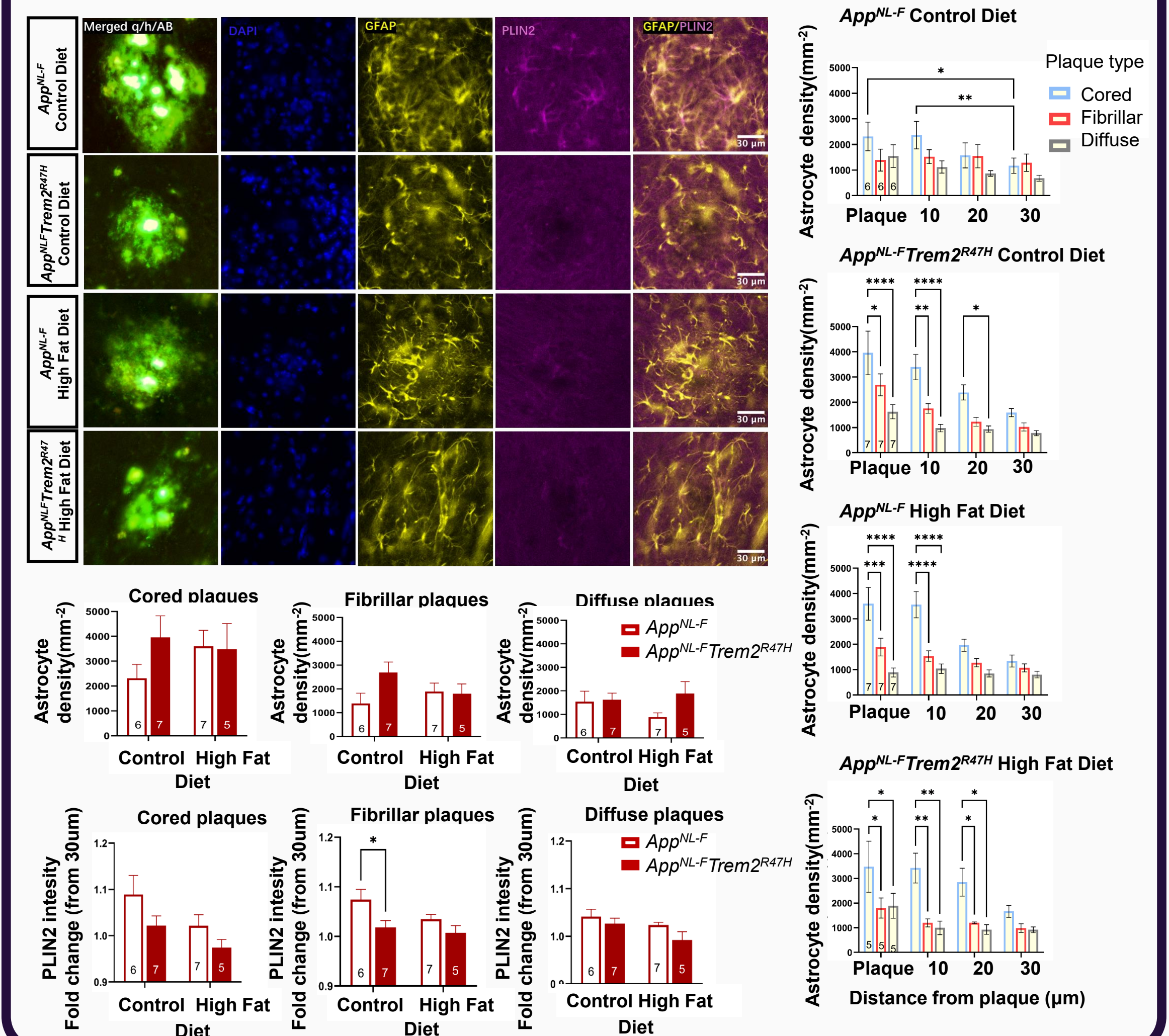
(1) The *Trem2*^{R47H} mutation and HFD suppress the microglial response to cored plaques.



(2) The *Trem2*^{R47H} mutation and HFD tend to reduce microglial lipid droplet levels at cored plaques and are not additive.



(3) The *Trem2*^{R47H} mutation and HFD tend to increase astrocytic density around cored plaques, while decreasing lipid droplet levels, similar to the reduction seen in microglia.



4. Conclusion and hypothesis

- (1) The microglial response is greater at cored plaques. The lack of an additive effect of a high-fat diet on *Trem2*^{R47H}-induced reductions in microglial density and lipid droplets suggests a convergence on a shared pathway, potentially triggered by a cored plaque-specific TREM2 ligand or another molecule associated with this pathway.
- (2) Astrocytes may become compensatory when microglial responses are damaged.

References

1. Maioli S et al. Bioenergetics and lipid metabolism in Alzheimer's disease: From cell biology to systemic health. J Intern Med. 2026 Jan;299(1):20-43.
2. Wood et al. (2022) Plaque contact and unimpaired Trem2 is required for the microglial response to amyloid pathology. Cell Rep, 41, 111686
3. Wood JI, Dulewicz M et al. Isotope-encoded spatial biology identifies plaque-age-dependent maturation and synaptic loss in an Alzheimer's disease mouse model. Nat Commun. 2025 Sep 1;16(1):8170.