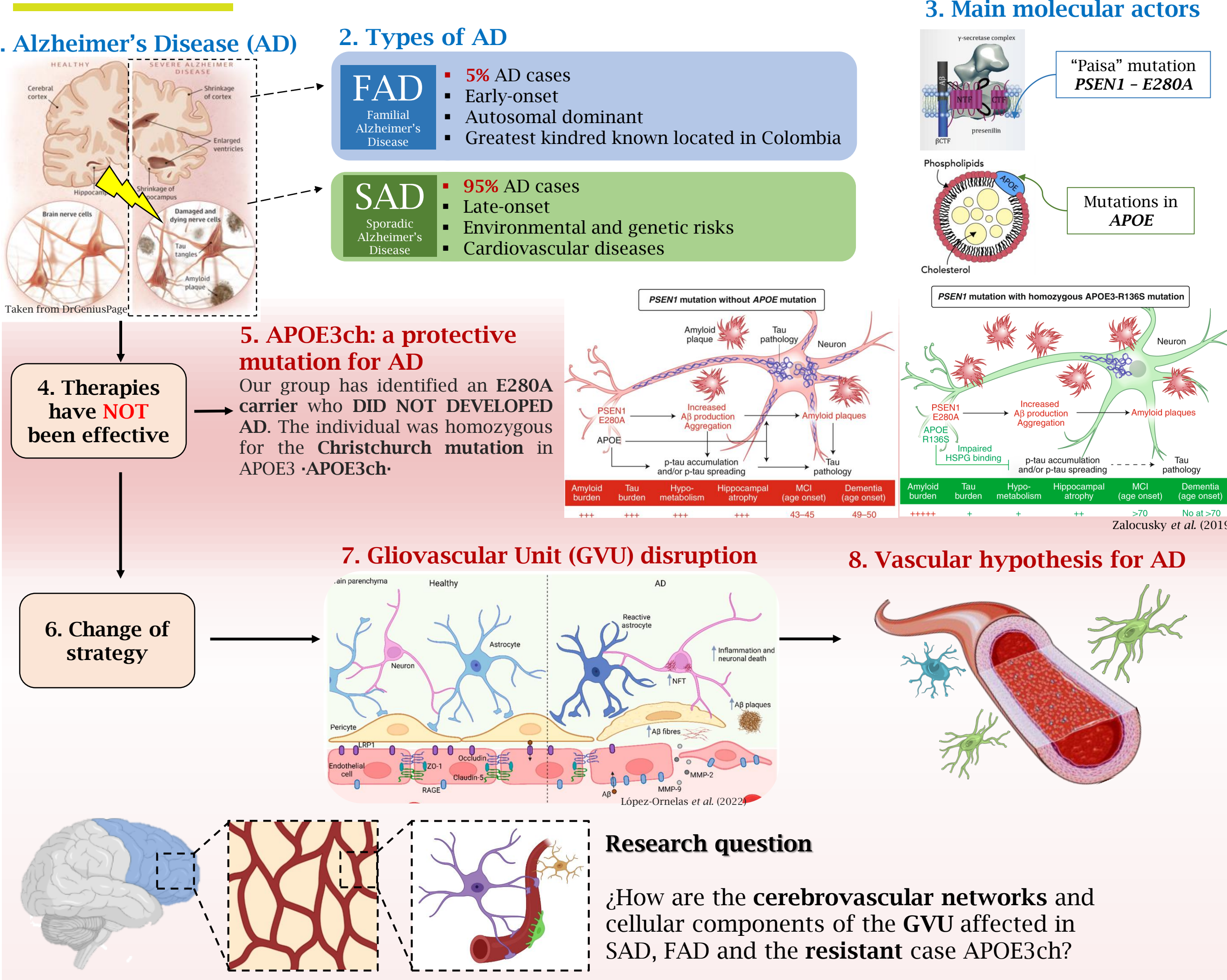# Differential cerebrovascular network alterations in Alzheimer's Disease: APOE3CH vascular protection
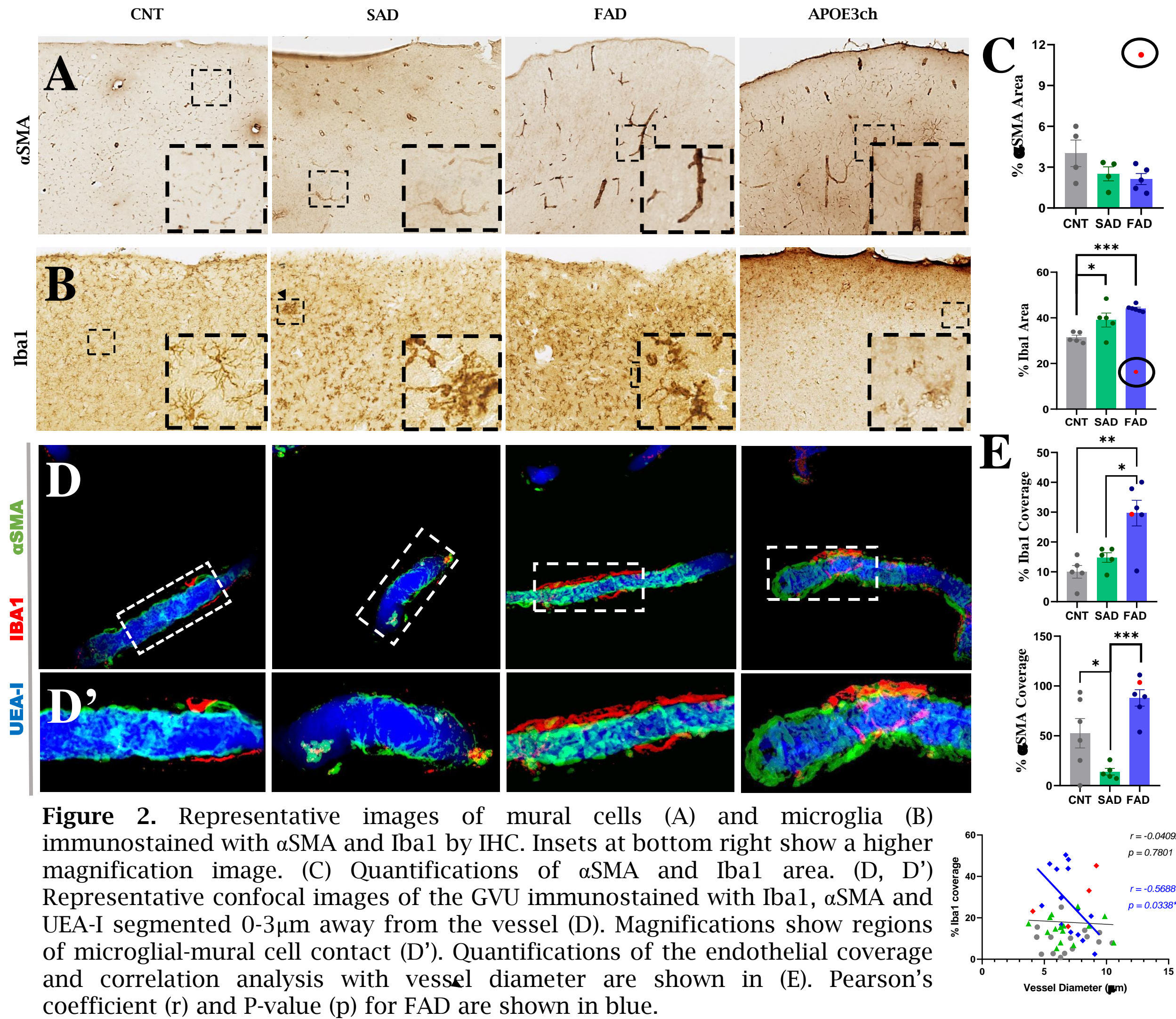
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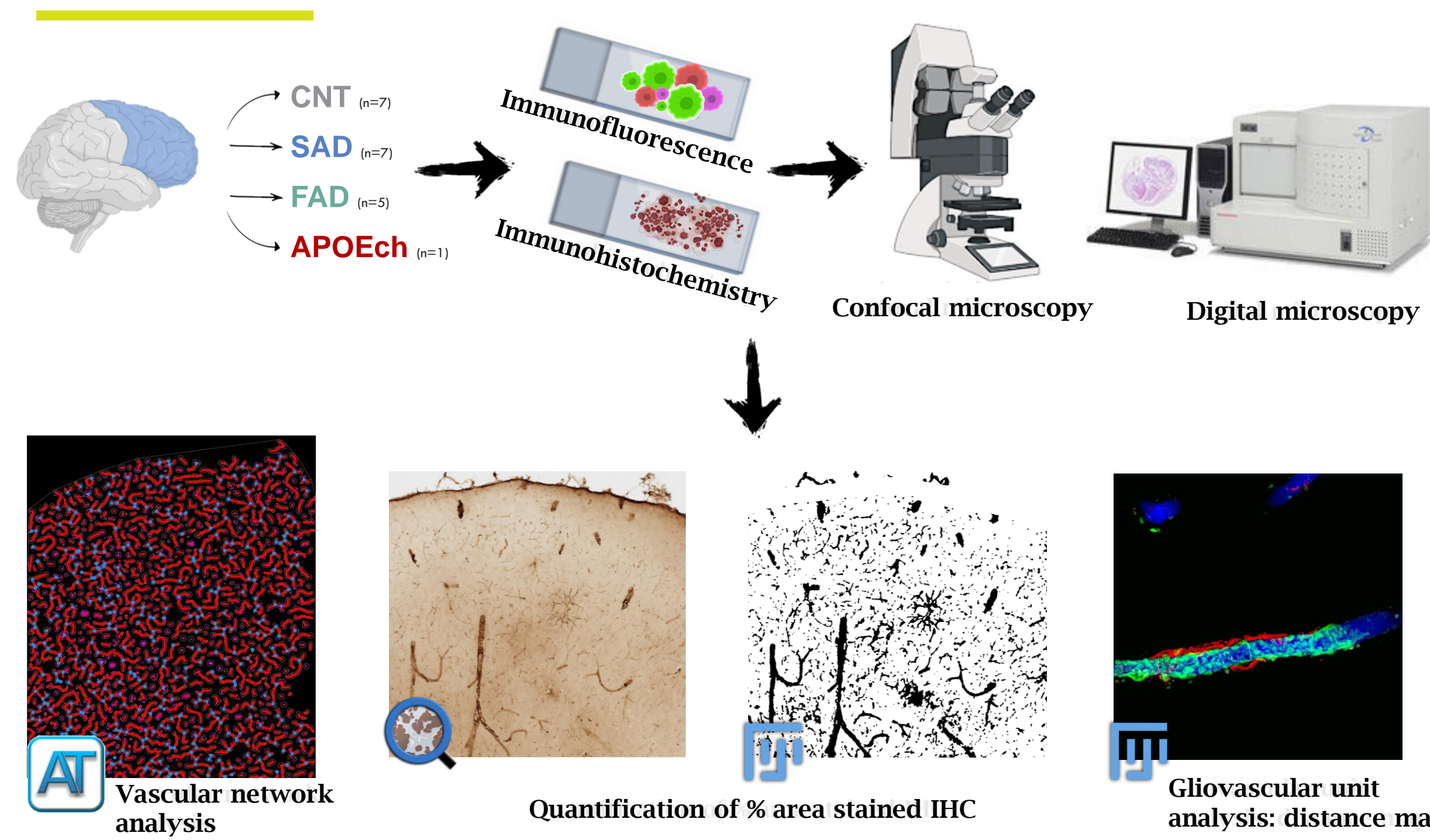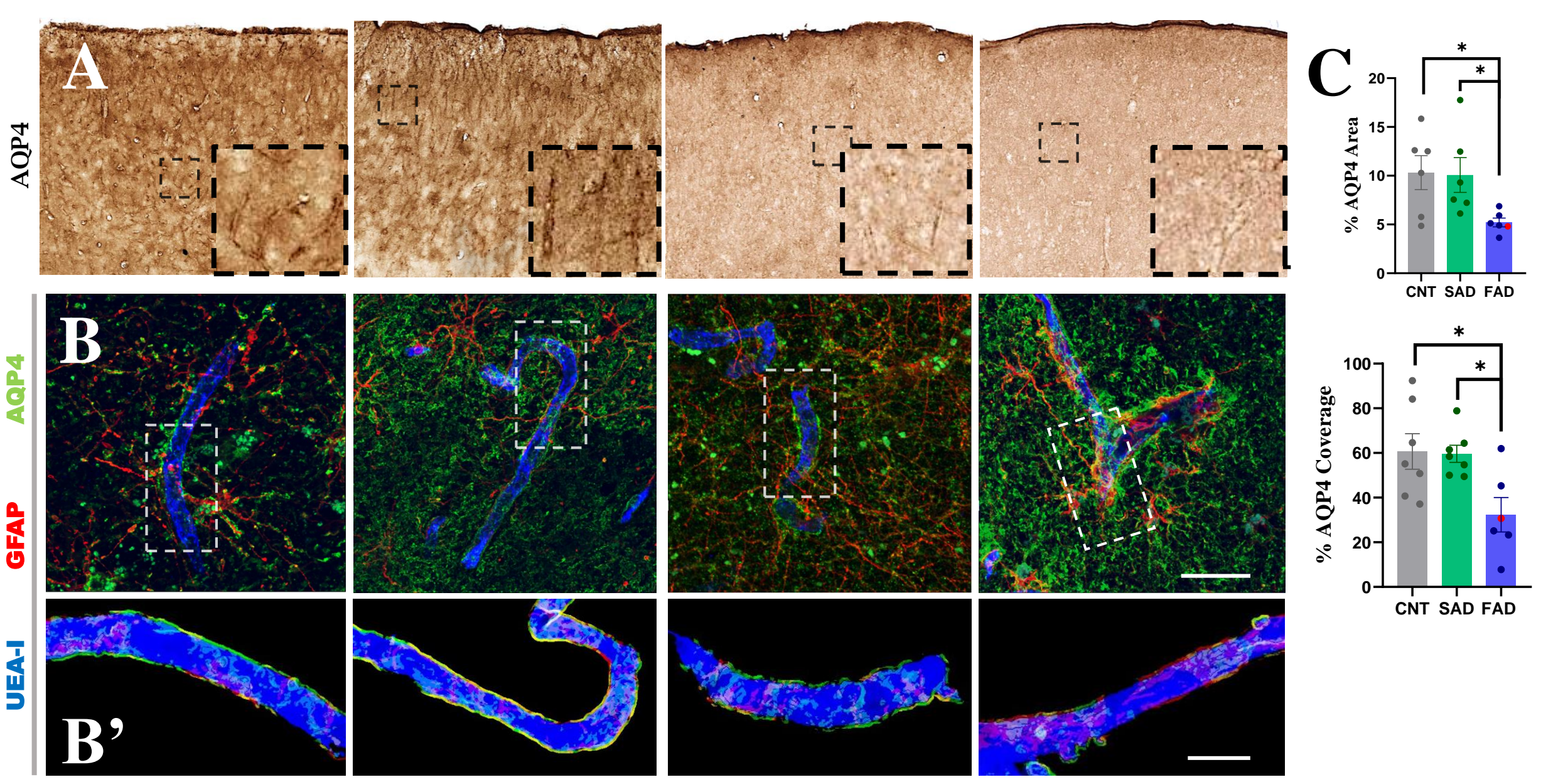
INTRODUCTION

1. Alzheimer's Disease (AD)

2. Types of AD

FAD Familial Alzheimer's Disease
- 5% AD cases
- Early-onset
- Autosomal dominant
- Greatest kindred known located in Colombia

SAD Sporadic Alzheimer's Disease
- 95% AD cases
- Late-onset
- Environmental and genetic risks
- Cardiovascular diseases

3. Main molecular actors

"Paisa" mutation *PSEN1 – E280A*

Mutations in *APOE*

4. Therapies have NOT been effective

5. APOE3ch: a protective mutation for AD
Our group has identified an E280A carrier who DID NOT DEVELOPED AD. The individual was homozygous for the Christchurch mutation in APOE ·APOE3ch·

6. Change of strategy

7. Gliovascular Unit (GVU) disruption

8. Vascular hypothesis for AD

Research question
¿How are the cerebrovascular networks and cellular components of the GVU affected in SAD, FAD and the resistant case APOE3ch?

METHODS

CNT (n=7)
SAD (n=7)
FAD (n=5)
APOEch (n=1)

Immunofluorescence
Immunohistochemistry

Confocal microscopy
Digital microscopy

Vascular network analysis

Quantification of % area stained IHC

Gliovascular unit analysis: distance map

RESULTS

1. FAD shows alterations in the topology of cerebrovascular networks, while APOE3ch is protected

Figure 1. Representative confocal tiling images of Lectin UEA-I (endothelial cells), showing the cerebrovascular network in the frontal cortex (A). Dashed lines indicate the limit between grey matter and white matter. Quantifications of topological parameters of the vascular network using the software Angiotool are shown in (B). Red dots in all graphs indicate the mean value of APOE3ch. *p < 0.05, **p < 0.01, ***p < 0.001.

2. FAD exhibits small vessel vascular inflammation, while APOE3ch is protected from neuroinflammation and mural cell loss
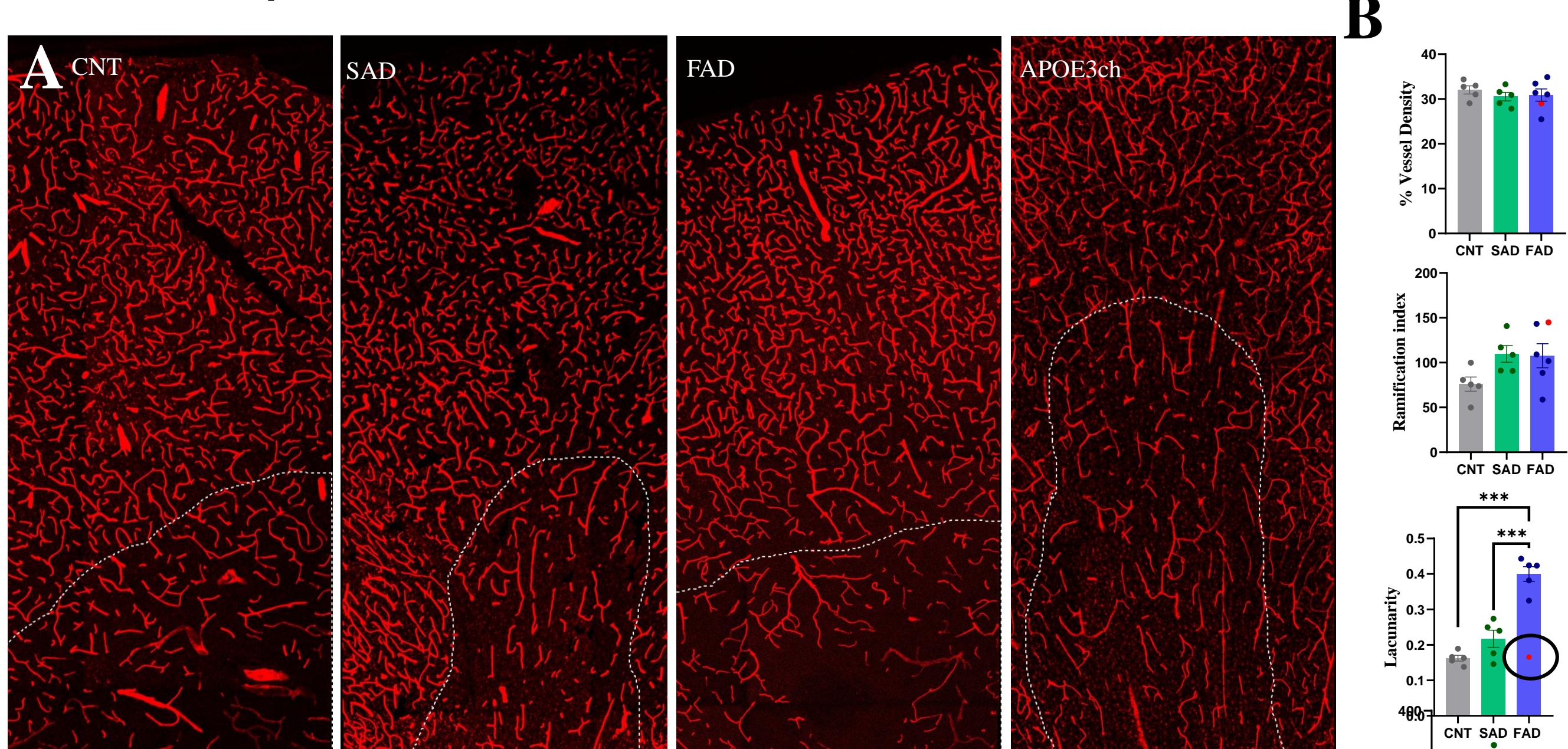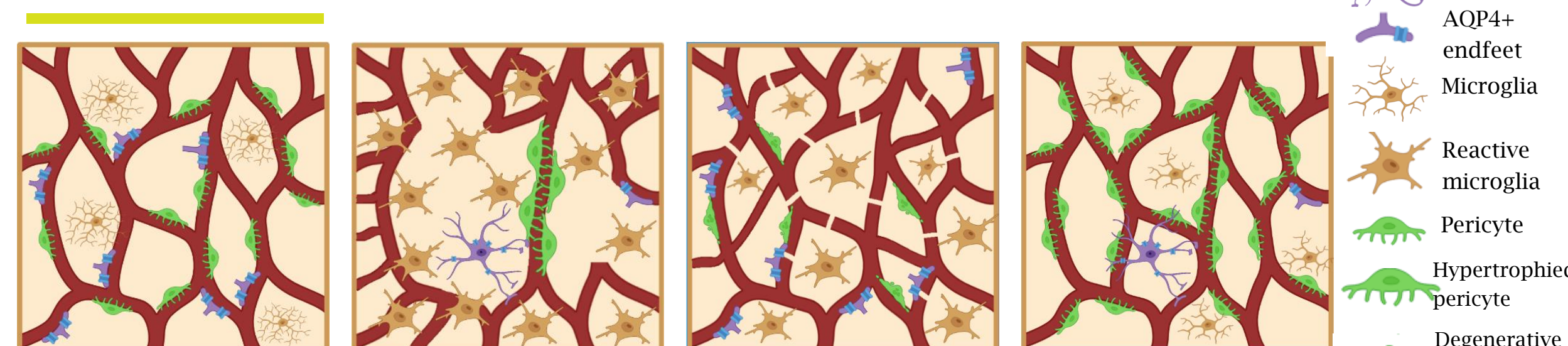

Figure 2. Representative images of mural cells (A) and microglia (B) immunostained with αSMA and Iba1 by IHC. Insets at bottom right show a higher magnification image. (C) Quantifications of αSMA and Iba1 area. (D, D') Representative confocal images of the GVU immunostained with Iba1, αSMA and UEA-I segmented 0-3μm away from the vessel (D). Magnifications show regions of microglial-mural cell contact (D'). Quantifications of the endothelial coverage and correlation analysis with vessel diameter are shown in (E). Pearson's coefficient (r) and P-value (p) for FAD are shown in blue.

3. AQP4 is mislocalized and its vascular coverage is decreased in FAD and APOE3ch, but not in SAD

Figure 3. Representative images of AQP4 by IHC (A). Insets show a 5X magnification. Representative confocal images immunostained with AQP4, GFAP and UEA-I (B). Insets show vascular coverage by astrocytic endfeet (B'). Quantification of AQP4 area by IHC and endothelial coverage by IF are shown in (C).

CONCLUSIONS

Astrocyte
AQP4+ endfeet
Microglia
Reactive microglia
Pericyte
Hypertrophied pericyte
Degenerative pericyte

The integrity of cerebrovascular networks, neuroinflammation and small-vessel vascular inflammation play a role in the development and protection from FAD, which suggests them as alternative therapeutic targets with potential for protection or onset-delay of the disease, as nature taught us with the APOE3ch resistant case

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