# Characterization of Vascular Alterations in Human Alzheimer's Disease Patients in Comparison to the $APP_{SL}$ and 5xFAD Mouse Models

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## ABSTRACT

Converging evidence suggests a link between vascular dysfunction and Alzheimer's disease (AD). This study aimed at investigating vascular changes in AD patients as well as in two transgenic AD mouse models showing amyloid beta (Aβ) pathology - $APP_{SL}$ and 5xFAD. To this end, we quantified immunofluorescently labeled sections from human AD patients at different Braak stages and brain sections from the two transgenic mouse lines across different time points. Most of the parameters analyzed in the cortex and the hippocampus showed a parallel progression in both species. Our data highlight the validity of the quantitative histological approach used here. Furthermore, they demonstrate that the $APP_{SL}$ and the 5xFAD mouse models are valuable tools to study Aβ as well as vascular-related alterations in AD.

## MATERIALS AND METHODS

### Tissue processing and imaging

Systematic random sets of 6-10 µm thick brain sections were immunofluorescently labeled for Aβ (6E10, Convance) and collagen IV (Abcam), imaged and quantitatively evaluated using image analysis software (Axio.Imager Z1 microscope, ImageProPlus).

| Human brain tissue | Mouse brain tissue | |
|---|---|---|
| AD patients (Braak I/II, II/IV, V/VI) | • $APP_{SL}$<br>• 5xFAD | 6, 9, 12 months |
| Non-AD subjects | Non-transgenic (nTg) | |

### Measurement of cerebral amyloid angiopathy (CAA)

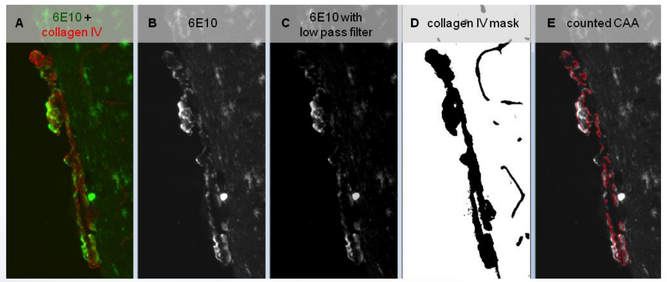


**Fig. 1: Exemplary measurement process of CAA in the cortex of a 12 month old $APP_{SL}$ mouse. (A)** Composite image of 6E10 + collagen IV channels. **(B)** Single Aβ (6E10) labeling. **(C)** Modified human amyloid labeling with the low pass filter correction. **(D)** Inverted collagen IV mask. **(E)** Ultimate count of CAA (red outline).

## RESULTS

### Aβ accumulates in brain tissue of humans and both AD mouse models – $APP_{SL}$ and 5xFAD

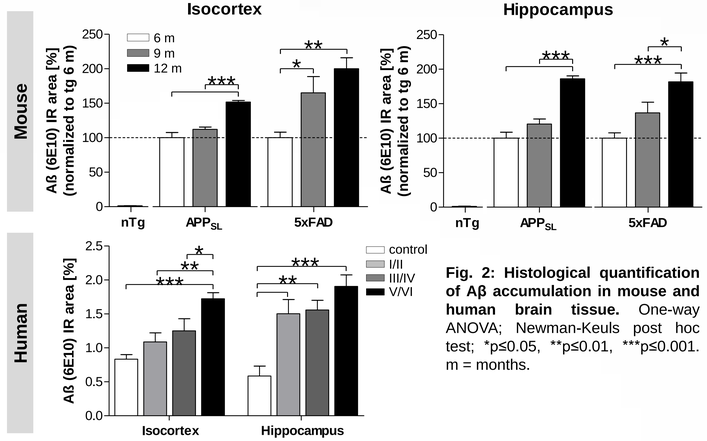


**Fig. 2: Histological quantification of Aβ accumulation in mouse and human brain tissue.** One-way ANOVA; Newman-Keuls post hoc test; *p≤0.05, **p≤0.01, ***p≤0.001. m = months.

### CAA builds up with age in $APP_{SL}$ and 5xFAD mice

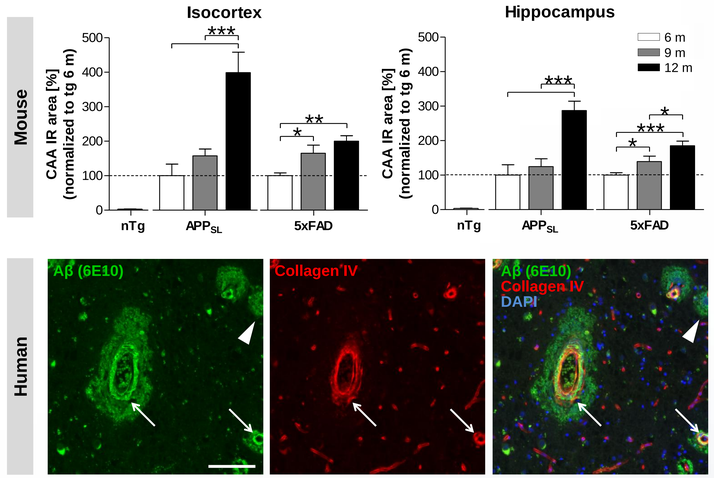


**Fig. 3: Quantification of CAA progression in $APP_{SL}$ and 5xFAD mice over age.** Images show an example of CAA in the cortex of a human AD patient (Braak V/VI).
Scale bar: 100 µm; arrows: Aβ in blood vessels (CAA); arrowhead : parenchymal Aβ.
One-way ANOVA; Newman-Keuls post hoc test; *p≤0.05, **p≤0.01, ***p≤0.001,

### CAA load per blood vessel increases over age in both AD mouse models

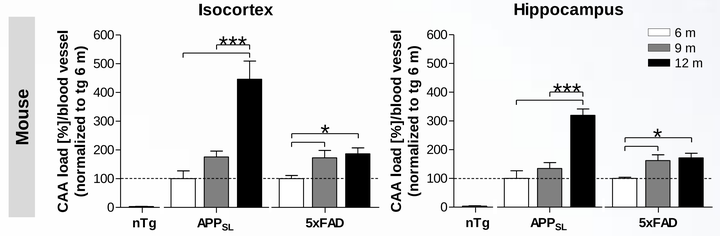


**Fig. 4: Quantification of CAA per blood vessel.** One-way ANOVA; Newman-Keuls post hoc test; *p≤0.05, ***p≤0.001.

### Collagen IV labeling intensity is associated with disease progression

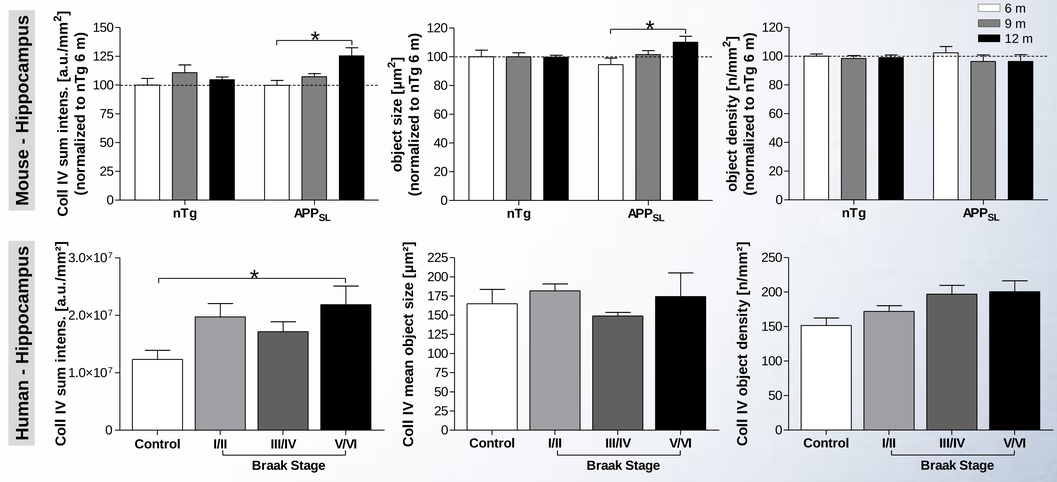


**Fig. 5: Quantification of collagen IV in mouse (top row) and human (bottom row) hippocampi.**
Mouse: Two-way ANOVA; Bonferroni post hoc test. Human: One-way ANOVA ; Newman-Keuls post hoc test. *p≤0.05, **p≤0.01, ***p≤0.001.

## CONCLUSION

- **Aβ accumulation can be detected in mouse and human using the same approach.**
- **CAA increases significantly in $APP_{SL}$ as well as in 5xFAD mice with age.**
- **Collagen IV levels are associated with disease progression in human and analyzed mouse models.**

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