

APOE ε4 Status Modulates the Association Between Alzheimer’s Disease Blood Biomarkers and White Matter Hyperintensity Volume

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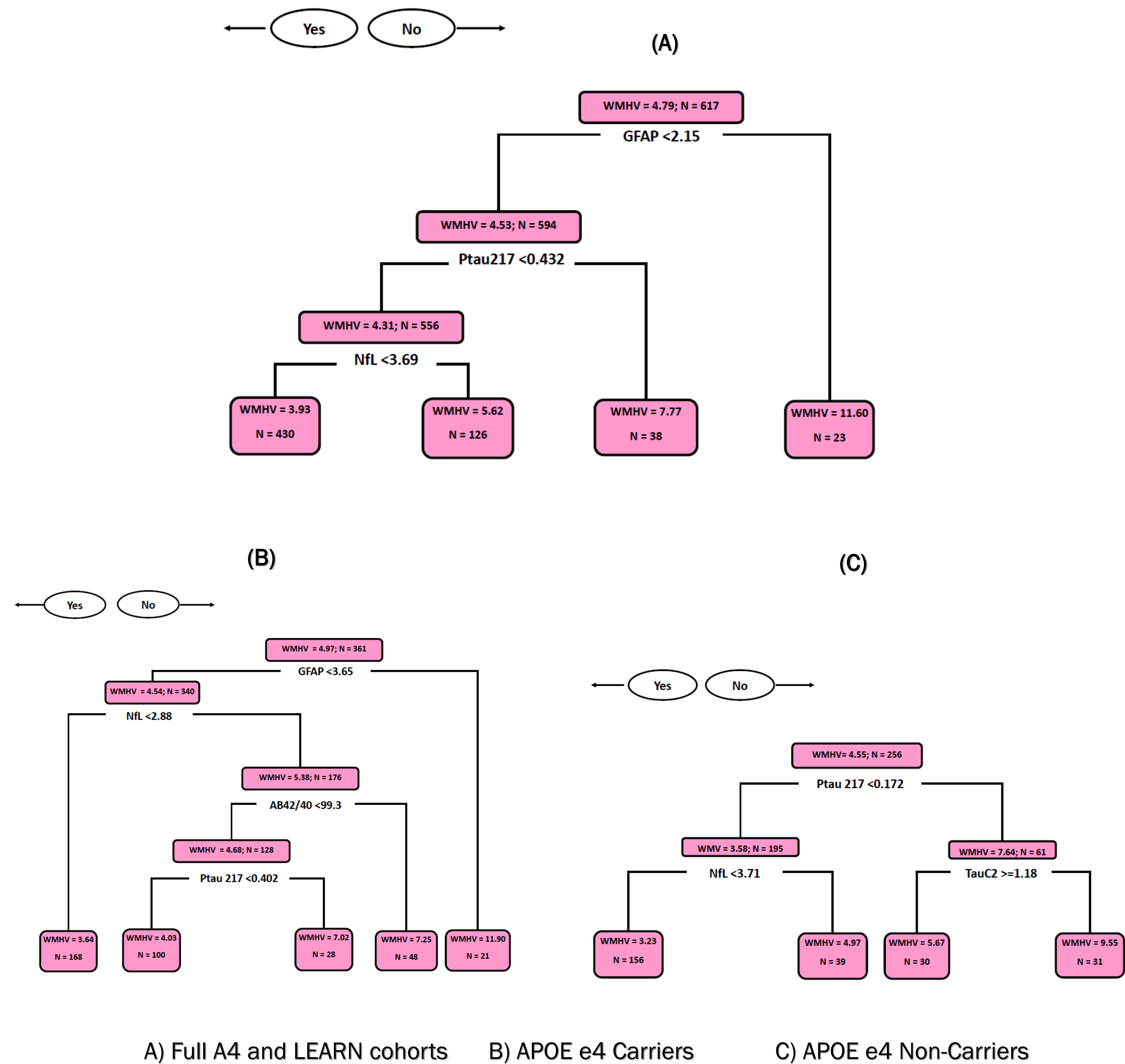
Background

- White matter hyperintensities (WMH) are MRI markers of small-vessel and white-matter disease frequently observed in aging and Alzheimer’s disease (AD) and correlate well with cerebral amyloid angiopathy.
- The APOE ε4 allele is a major genetic risk factor for AD which may influence the pathways underlying WMH accumulation.
- This study sought to determine whether AD-related BBMs are associated with WMH volume (WMHV) and whether these associations differ by APOE ε4 carrier status..

Methods

- Baseline data from 617 participants from the A4 (n=361) and LEARN (n=256) studies were used for this analysis.
- BBMs included p-tau217, GFAP, NfL, TauC2, and Abeta 42/40 which analyzed on the Roche Elecsys platform. WMHV values were quantified using the HyperMapp3r algorithm and adjusted for intracranial volume.
- Regression tree analysis was used to determine which BBMs had the highest predictive value for WMHV for the entire sample and separately for APOE ε4 carriers and non-carriers.

Regression Trees for the Association Between Plasma Biomarkers and White Matter Hyperintensity Volume.



Results

- For the entire sample, subjects with the highest GFAP levels (≥ 0.23) had the highest WMHV (11.60). The lowest WMHV (3.93) was associated with lower GFAP (< 0.23), lower ptau-217 (< 0.43), and lower NfL (< 3.69).
- For APOE ε4 carriers, the highest WMHV (11.90) was also associated with higher GFAP (≥ 0.23) while the lowest WMHV (3.64) was associated with lower GFAP (< 0.23), and lower NfL (< 2.88).
- In APOE ε4 non-carriers the lowest WMHV (3.23) was associated with lower ptau-217 (< 0.17) and lower NfL (< 3.71) while the highest WMHV (9.55) was associated with higher ptau-217 (≥ 0.17) and lower TauC2 levels (< 1.18).

Discussion

These APOE-stratified differences in WMH predictors highlight potentially distinct mechanisms of white matter injury and suggest that WMH etiology may differ between APOE ε4 carriers and non-carriers. In ε4 carriers there is a strong inflammatory component through GFAP which then involves Abeta42/40 ratio and ptau-217 in those with greater levels of neurodegeneration. In ε4 non-carriers the WMHV pathway was driven primarily by ptau-217. These findings may be useful in helping to determine the risk of amyloid-related imaging abnormalities associated with amyloid clearing therapies.