

Plasma Neurodegenerative Markers as Predictors of Braak Stage in an Autopsy Cohort

Sophia Dustrud¹, Michael Malek-Ahmadi², Ileana Lorenzini³, Thomas G. Beach³, Alpana Singh³, Marisa Denkinge³, Geidy E. Serrano³, Nicholas J. Ashton³
¹University of Arizona Department of Neuroscience, ²Banner Alzheimer’s Institute, ³Banner Sun Health Research Institute

Background

Alzheimer’s Disease (AD) pathology leads to neurodegeneration in cortical areas of the brain, which results in cognitive impairment. The underlying processes and known markers of neurodegeneration are not fully understood. However, it is possible that these markers could be treatment targets for disease modifying therapies for AD. While neurodegenerative biomarkers are not specific to AD, they have shown to be helpful in identifying those highest-risk for disease progression. Using a large panel of plasma biomarkers known to be associated with neurodegeneration we determined the neurodegenerative biomarkers most associated with Braak Stage, a standard neuropathological measure of neurofibrillary tangle burden.

Methods

Subject Data

- Data for 253 autopsy cases from the Banner Sun Health Brain and Body Donation program were used for this analysis. All participants underwent clinical and neuropsychological evaluation annually.

Measurements

- Data was measured using the NUcleic acid Linked Immuno-Sandwich Assay (NULISA) disease panel, which measures ~120 protein targets. NULISA is a proteomic liquid biopsy technology that allows for sensitive and multiplexed detection of proteins.
- Our study focused on 10 known neurodegenerative markers: microtubule-associated protein tau (*MAPT*), neurogranin (*NRGN*), synaptosomal-associated protein 25 (*SNAP25*), 14-3-3 protein gamma (*YWHA*G), 14-3-3 protein zeta/delta (*YWHA*Z), neuronal pentraxin-1 (*NPTX1*), neuronal pentraxin-2 (*NPTX2*), neuronal pentraxin-receptor (*NPTXR*), neurofilament light chain (*NEFL*), and neurofilament heavy chain (*NEFH*).

Statistical Analysis

- Regression tree analysis identified biomarkers that best predicted subject’s Braak stage. Classification and regression trees are decision tree algorithms used for predicting categories or continuous variables.

Table 1. Subject Characteristics

Age	85.89±8.72
Sex (M/F)	141 / 112
Time between plasma draw and autopsy	2.68±2.67
Last MMSE test score	22.07±7.72
Pathological AD (Yes/No)	152/93

Results

- Biomarkers of significance included MAPT, NEFH, NPTX1, and NPTXR
- Individuals with MAPT levels above 12 and NEFH levels above 23 had the highest Braak stages
- NPTX1 and NPTXR identified subgroups where Braak stage was attenuated in the presence of high NEFH levels
- Mean Squared Error (MSE) values for final predicted Braak scores ranged from 0.68 to 1.56

Figure 1. Increased MAPT Levels Correlate With Braak Stage

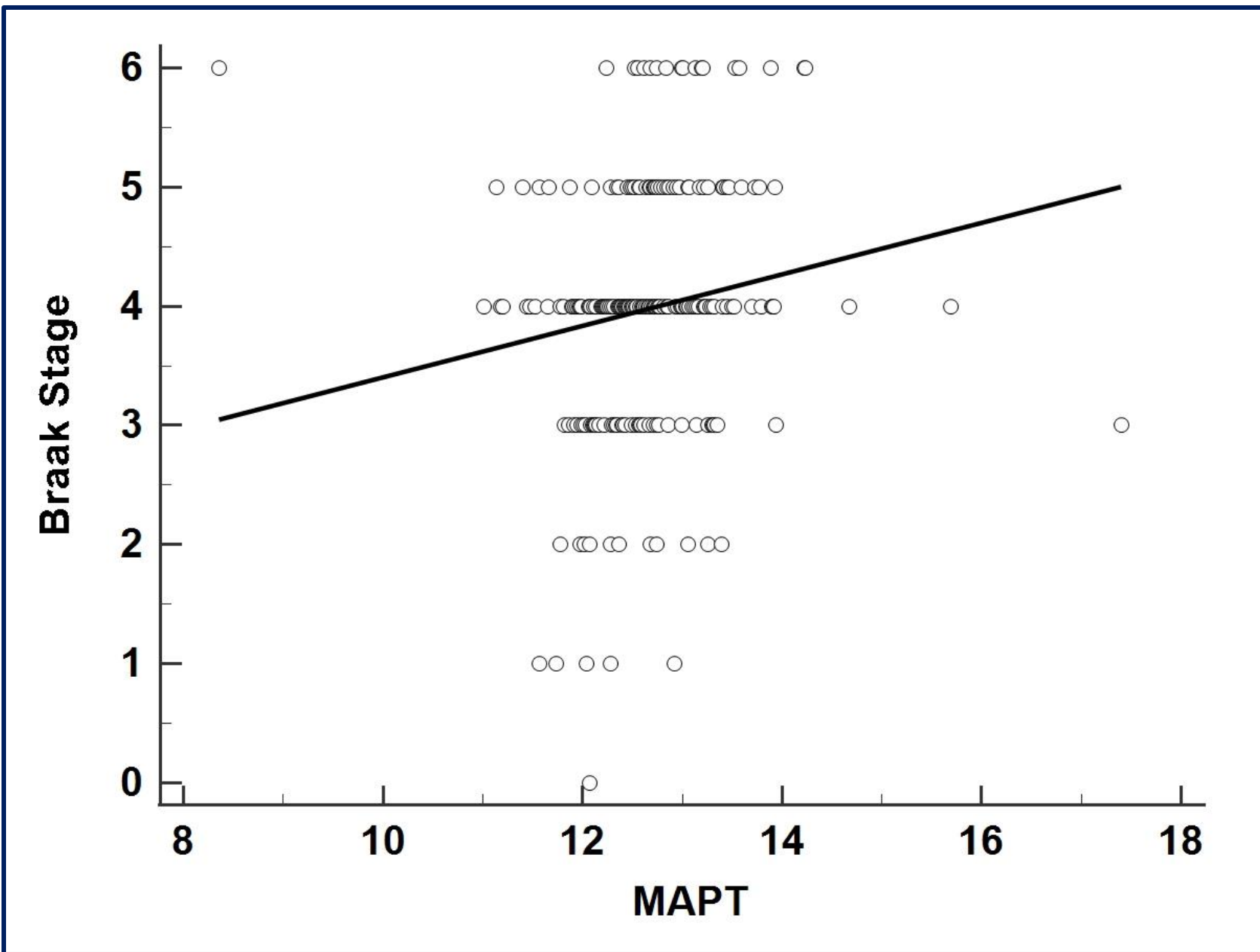


Figure 2. Braak Stage as Predicted by Neurodegenerative Markers

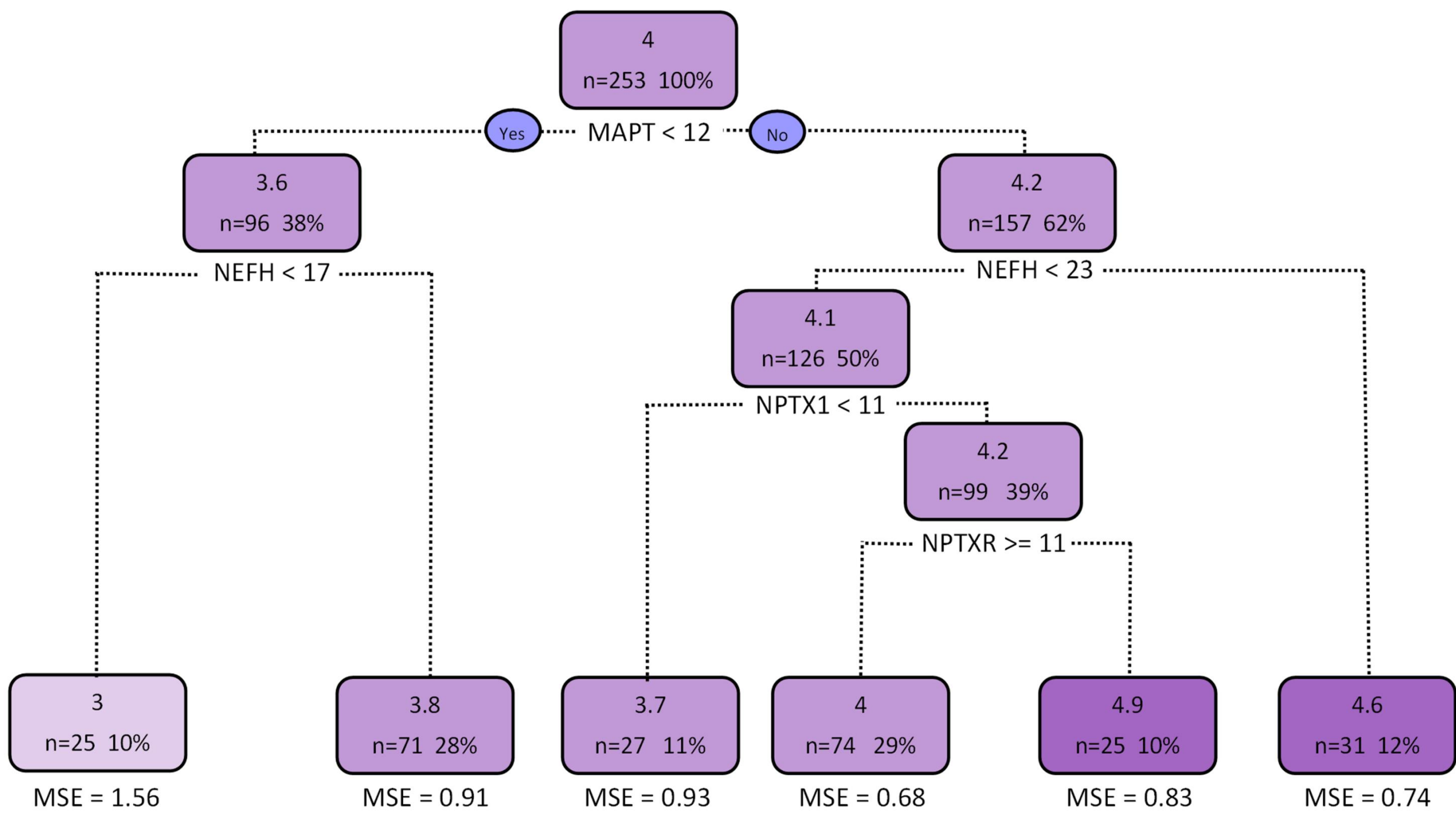


Table 2. Correlation of Neurodegenerative Markers

		MAPT	NEFH	NPTX1	NPTXR
MAPT	Correlation Coefficient Significance Level P	1	0.30 <0.0001	0.17 0.007	0.28 <0.0001
NEFH	Correlation Coefficient Significance Level P	0.30 <0.0001	1	0.08 0.17	0.23 0.0002
NPTX1	Correlation Coefficient Significance Level P	0.17 0.007	0.09 0.17	1	0.48 <0.0001
NPTXR	Correlation Coefficient Significance Level P	0.28 <0.0001	0.23 0.002	0.48 <0.0001	1

Discussion

- AD-associated neurodegeneration is driven by several different factors that function synergistically
- NPTX1 and NPTXR appear to identify subgroups with higher Braak stages despite lower NEFH levels
- NEFL levels in blood are typically associated with AD progression, with higher NEFL levels correlating with more extensive pathology. High NEFH levels are typically associated with the degeneration of motor neurons