

A Multi-Protein Plasma Signature Enhances Tau-Pet Prediction Beyond Ptau217 Alone

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OLINK biomarkers, including glial fibrillary acidic protein (GFAP), serine/threonine-protein kinase PAK4 (PAK4), hepatitis A virus cellular receptor 1 (HAVCR1), and pentraxin 3 (PTX3), remain significantly associated with elevated Tau-PET SUVR after adjusting for pTau217 levels and demonstrate strong predictive value.

INTRODUCTION

RESULTS

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CONCLUSIONS

The blood-based biomarker with the highest accuracy for detecting Alzheimer’s disease (AD) is phosphorylated tau 217 (pTau217), but its ability to reflect Tau deposition as measured by Tau-PET is limited.

In the present study, we investigate whether a comprehensive plasma proteomic panel can improve the prediction of tau-PET positivity compared with pTau217 alone.

METHODS

Proteomic profiles were obtained using Olink proximity extension assays (PEA, 1,383 proteins) in 161 participants from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study (53 CU, 71 with MCI, 37 with AD). Tau-PET positivity was defined using a SUVR, (mesial) cut-off of >1.48 (tau-PET-: N=81; tau-PET+: N=80).

Plasma pTau217 (Lumipulse), available for 107 participants, was evaluated both as a stand-alone predictor of tau-PET status and included in the final multivariable model to determine whether Olink proteins would remain after model selection. Bootstrapped multivariate modelling and receiver operating characteristic analyses were applied to identify the optimal subset of proteins to predict tau-PET positivity.

Univariate modelling via LIMMA only saw GFAP to significantly associated with tau-PET status after adjustment for multiple comparisons.

Discovery assessment saw larger numbers of biomarkers both up and down regulated in participants with high levels of mesial tau SUVR (Figure 1).

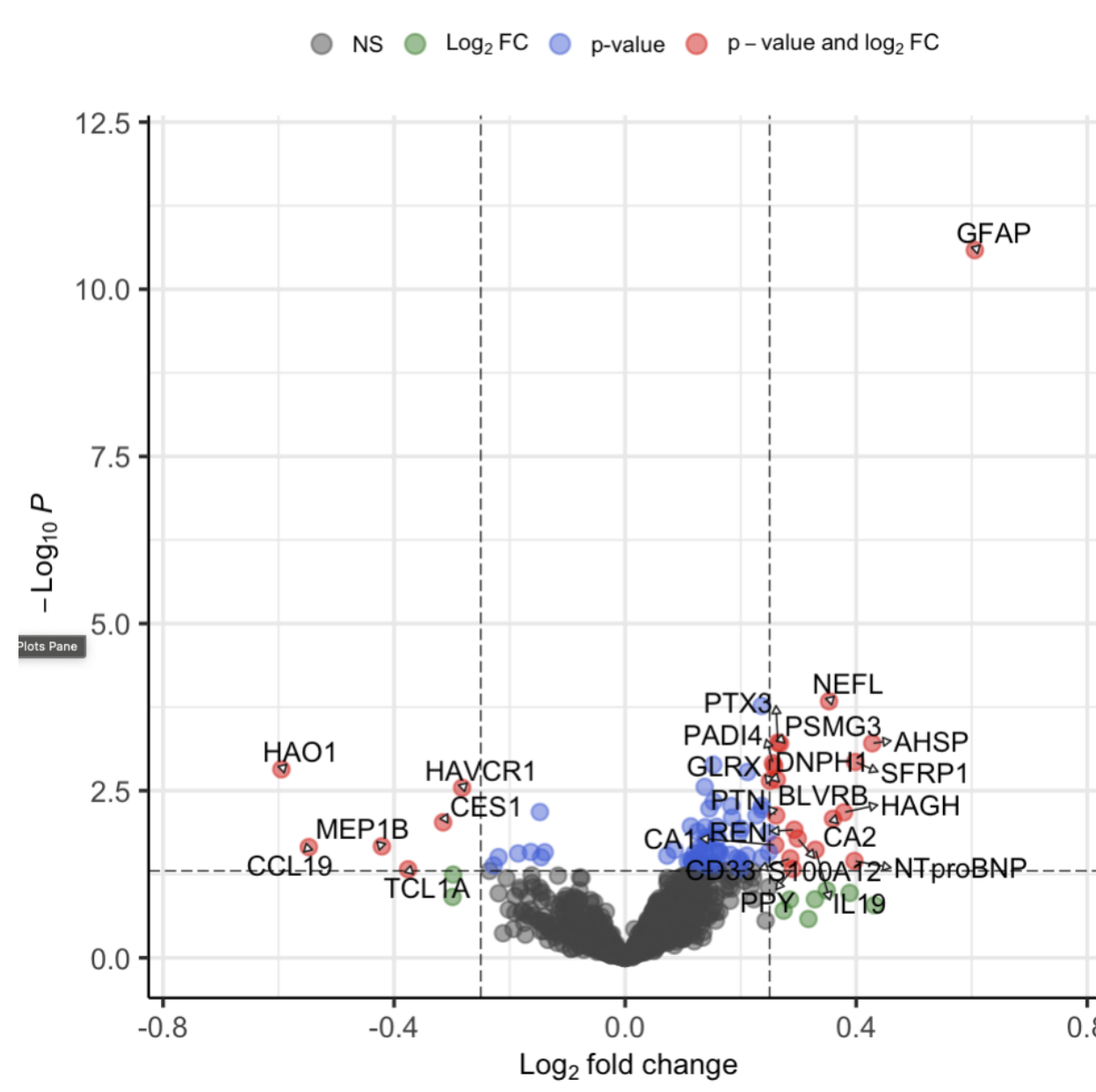


Figure 1: Volcano plot of OLINK biomarkers to differentiate tau status.

Using Olink proteomics combined with age, sex and APOE ε4 status, saw a large number of proteins selected to separate Tau-PET status (Figure 2).

The optimal multivariate model to predict tau-PET positivity included GFAP, NPTXR, PAK4, HAVCR1 & PTX3 and APOE ε4 allele status. This model achieved an AUC of 0.91 (95%CI:0.87-0.96, Figure 3).

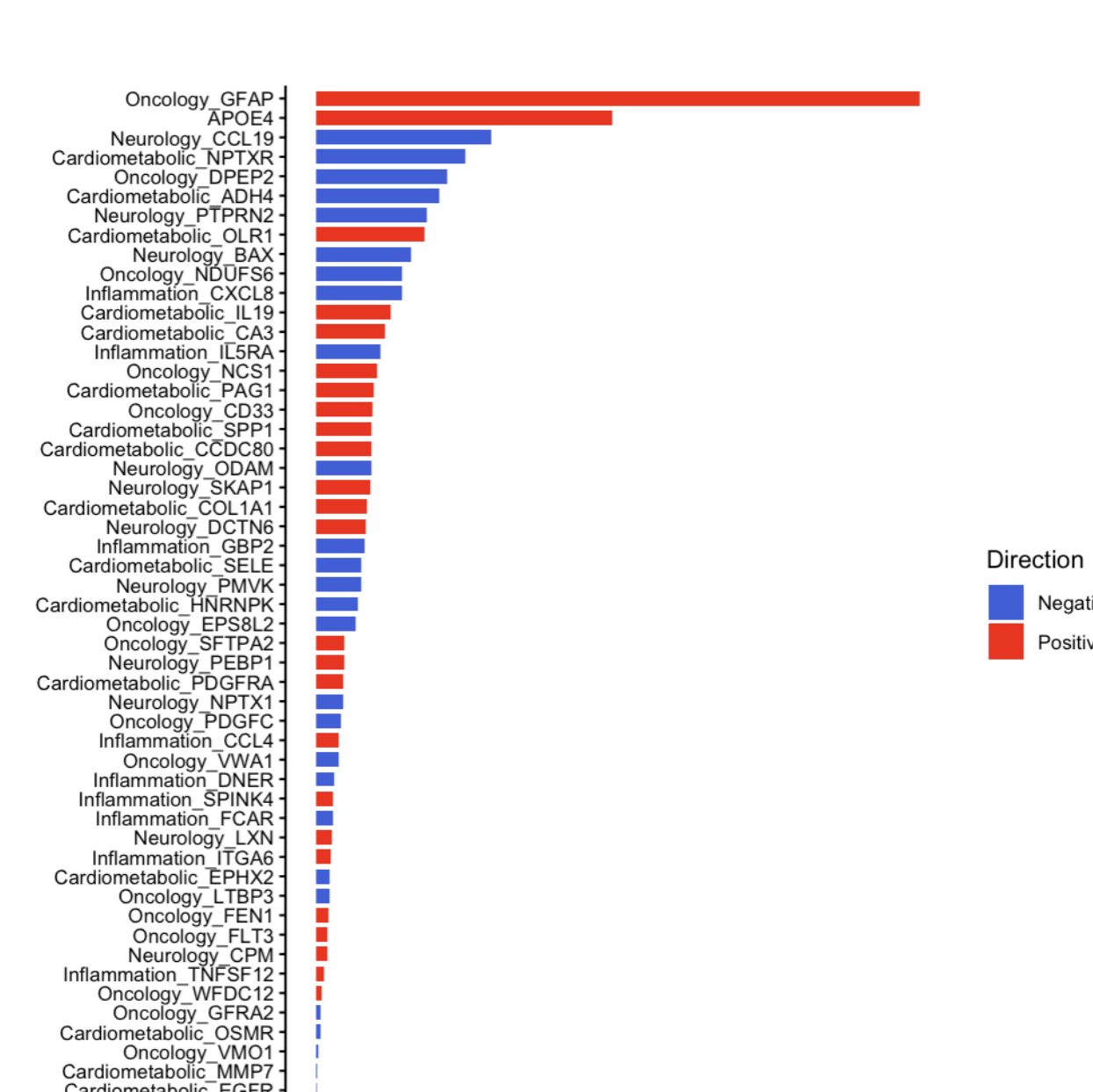


Figure 2: SHAP importance plot of OLINK biomarkers to differentiate tau status.

Plasma pTau217 alone showed significantly higher discriminative ability for tau-PET positivity, with an AUC of 0.96, (95%CI: 0.92-0.99, Figure 3).

When pTau217 was incorporated into the multivariate panel, four proteins (GFAP, PAK4, HAVCR1 & PTX3) remained alongside pTau217. This combined model improved performance, yielding an AUC of 0.98 (0.96 – 1.0, Figure 3).

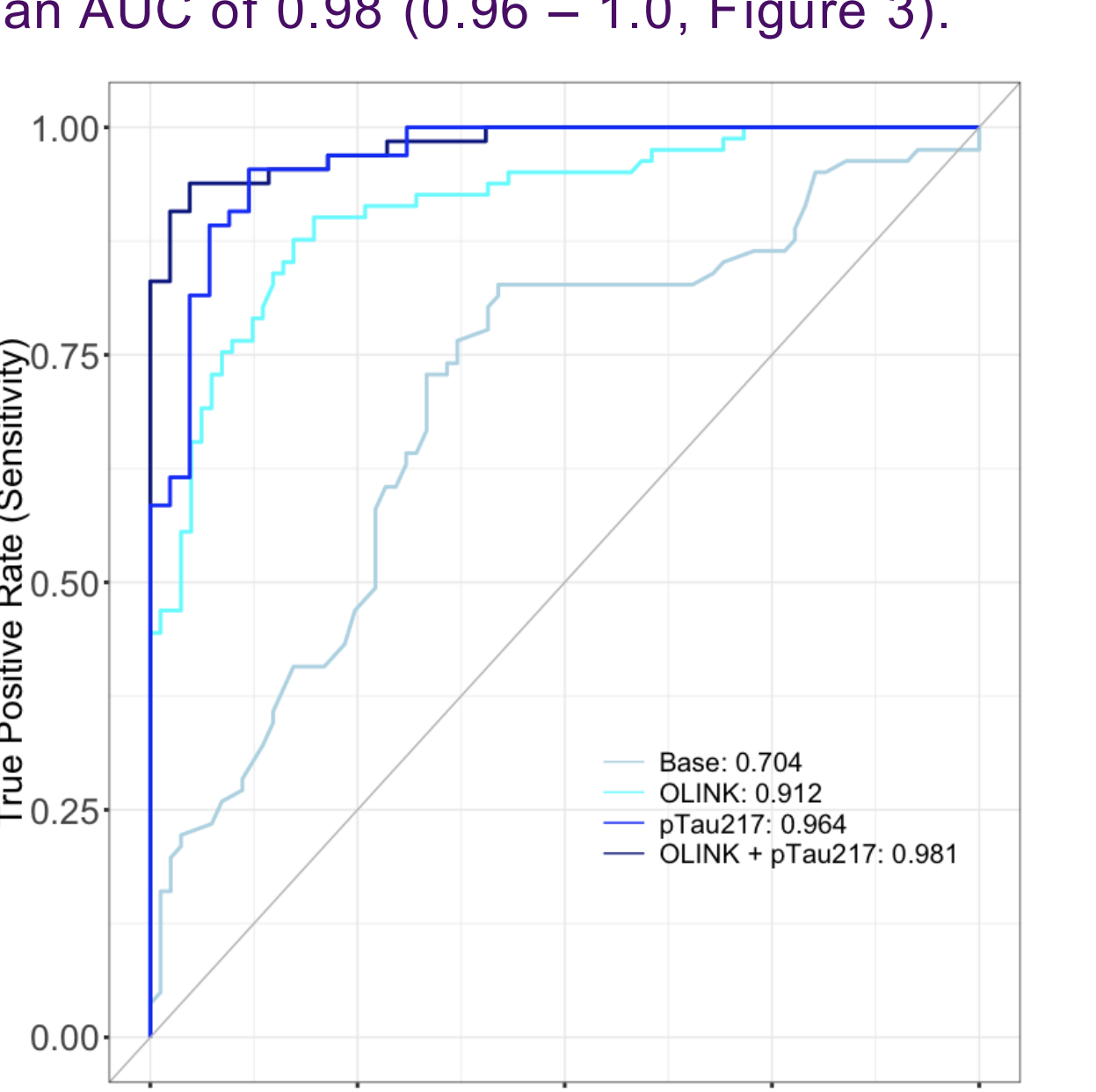


Figure 3: Multiple ROC curves for biomarker combinations to predict tau status.

The findings demonstrate that several proteins from the comprehensive proteomic panel retain independent predictive value even after the inclusion of pTau217, indicating that they capture additional biological processes relevant to AD pathology.

This work provides the promising evidence that a multi-protein plasma signature reflecting diverse pathological pathways can substantially enhance the detection of brain tau deposition beyond pTau217 alone.

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