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BIOMARKERS (NON-NEUROIMAGING)

Multiomics Blood Biomarkers Predict Alzheimer from predementia with High Specificity

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Abstract

Background: The core criteria for mild cognitive impairment (MCI) or dementia due to Alzheimer's disease (AD) is based in part on cognitive criteria and biological evidence of at least moderately frequent amyloid plaques (Albert et al., 2011; McKhann et al., 2011). They predict AD among cognitively impaired patients with high sensitivity but low specificity (Kokkinou et al. 2021; Martinez et al. 2017; Ritchie et al. 2014): up to 25% of amyloid-positive patients would be misdiagnosed as AD while suffering from another brain disorder. Therefore, there is a need to develop new biomarkers with high specificity to facilitate earlier diagnosis, rapid therapeutic intervention and monitoring of clinical trials.

Method: Targeted mass spectrometry assays were developed for 81 blood biomarkers (45 proteins and 36 metabolites) pre-identified in AAV-AD rats (Audrain et al. 2018). 345 cognitively impaired participants (193 MCI and 152 demented) were collected in plasma at baseline and followed clinically from 1 to 13 years. Participants' diagnosis (AD, or non-AD) was established at the last clinical visit based on cognitive diagnosis standard for each brain disorder subtype. 82.9% of participants had available amyloid status at baseline, 61.9% were determined as amyloid positive. Each clinical group contained amyloid positive and negative participants. Predictive machine learning models for AD participants (n = 123 Prodromal AD, n = 126 AD dementia) among individuals with Non-AD brain disorder (Non-AD, n = 96) was developed. The training dataset (70%) aimed to select the biomarkers subset, train the algorithm, and define the cut-off. External test dataset (30%) aimed to validate in blind the locked predictive model.

Result: With 19 blood biomarkers and age, the model predicted AD participants (n = 41 Prodromal AD, n = 43 AD dementia) from non-AD participants (n = 25) with 92.0% specificity and 52.4% sensitivity during external validation (AUROC = 71.8%, p = 0.001). When amyloid status (CSF or PET) and this predictive ML model were applied

in series, and participants positive for both were predicted as AD, 100% specificity and 39.7% sensitivity were achieved.

Conclusion: Multiomics blood peripheral biomarkers predicted AD patients among cognitively impaired population with low FPR. In combination with amyloid screening, these biomarkers could identify a nearly pure AD population.