

A diagnostic and prognostic plasma omics-biomarkers panel for Alzheimer’s Disease based on microglial single-cell transcriptomics

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Gene panels identified from single-nucleus RNA seq analysis of brain microglia transferred to monocytes showed accuracies to predict Alzheimer’s disease of 0.70. APOE and sex specific gene panels increased accuracy to 0.75. Integrating multiomics datasets into the AD biomarker discovery pipeline offers a powerful modality to increase precision and comprehensiveness in AD research and clinical applications.

INTRODUCTION

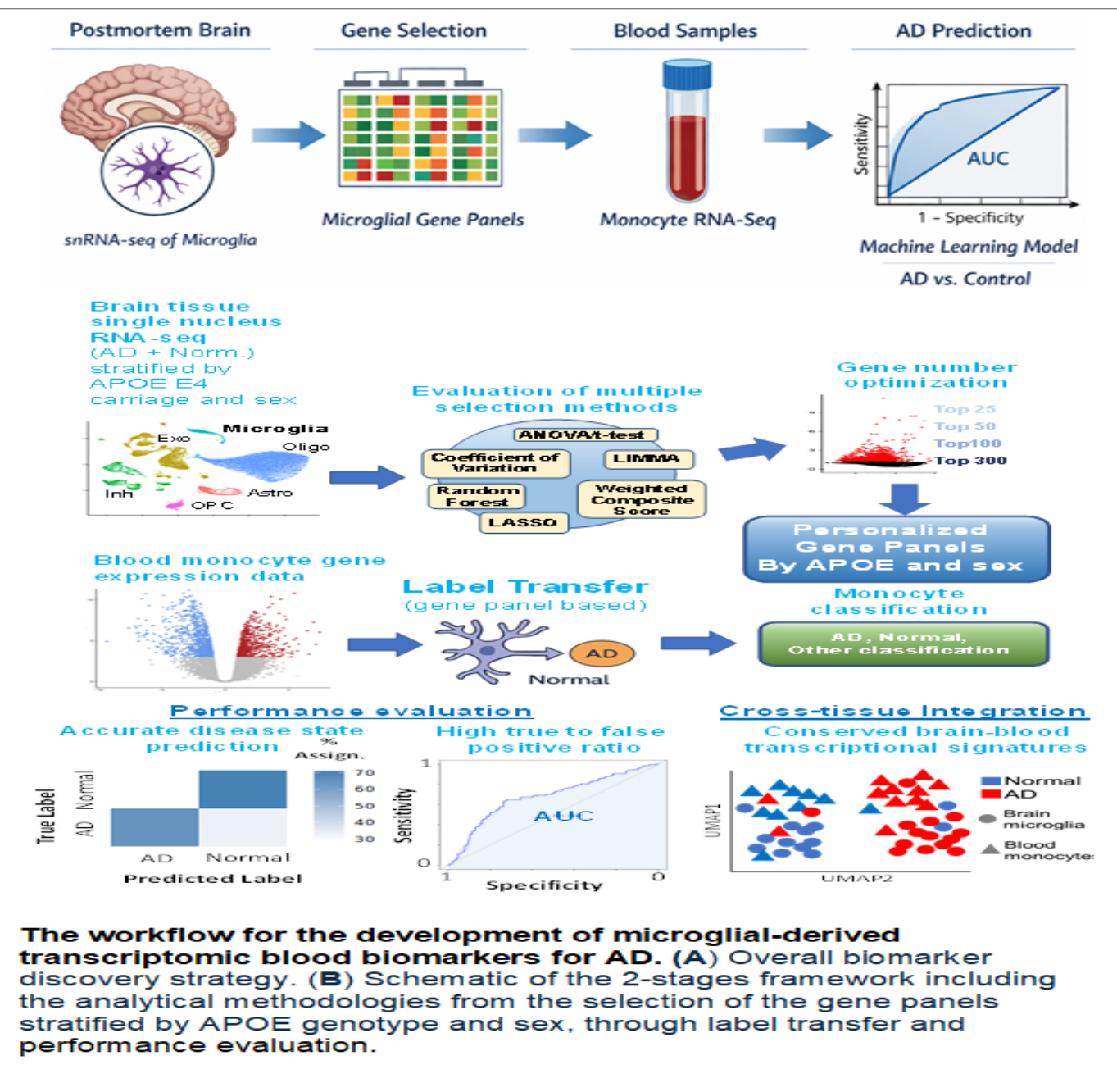
•The current biomarker framework for diagnosis and staging of Alzheimer’s disease (AD) relies mainly on amyloid beta (Aβ) and tau (primarily p-tau fragments) pathologies as core markers.

•AD initiates decades before clinical symptoms and neuropathological hallmarks appear.

→ There is an unmet clinical need for new diagnostic-biomarkers enabling precise and accurate early diagnosis at presymptomatic stages.

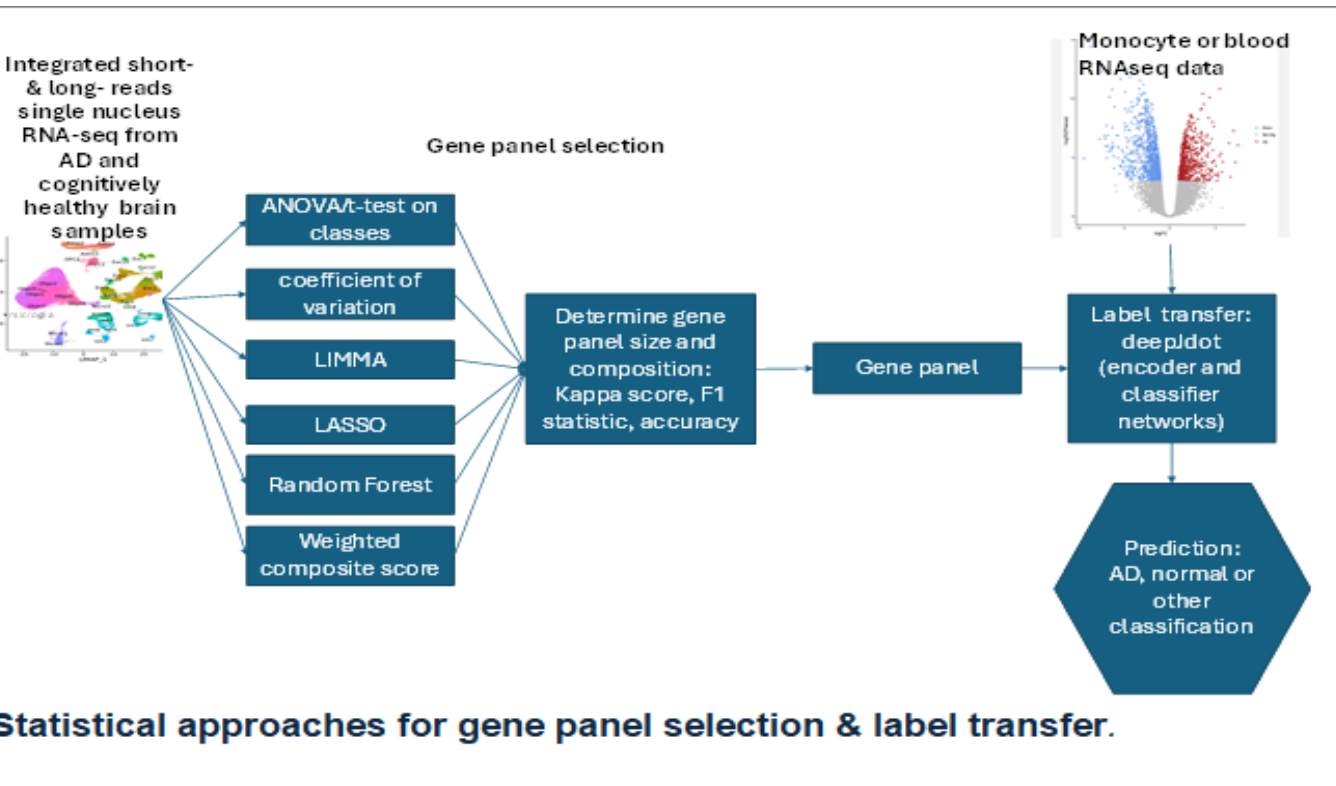
• The role of neuroinflammation and the involvement of microglia in the early pathogenesis of AD and related dementias (AD/ADRD) have been well-established¹⁻⁴.

→ we leveraged microglial and monocytes RNA-seq datasets to identify and evaluate the performance of gene panels as AD diagnostic biomarkers⁵.



METHODS

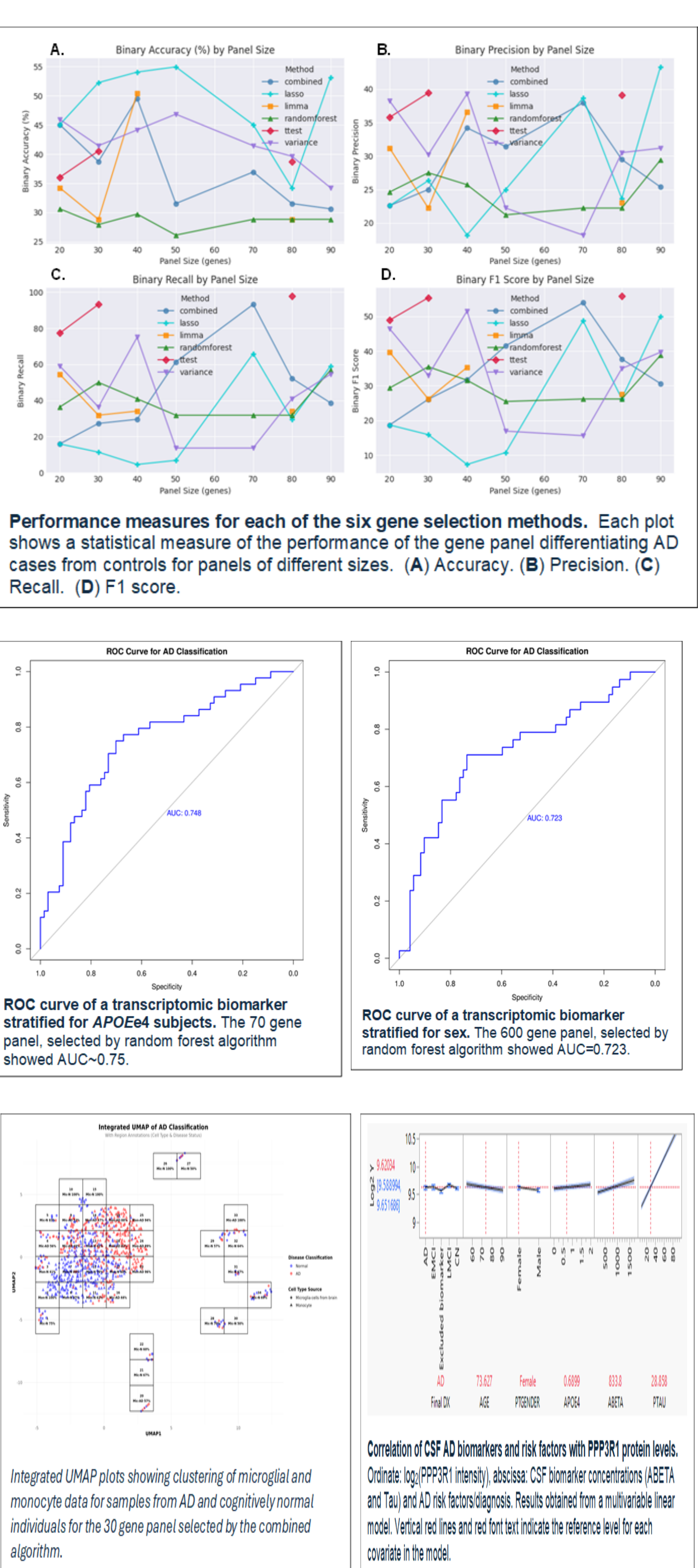
Data from ROSMAP⁶ was utilized: (1) single-nucleus (sn)RNA-seq data for microglia (N=465, DLPFC) and (2) bulk RNA-seq data for monocytes (N=558). To identify genes for distinguishing between individuals with and without AD, we applied five different statistical gene selection methods to the microglia data: ANOVA, coefficient of variation, random forest, limma, and weighted composite score. Label transfer process from the microglia to the blood monocytes data was performed using a Deep Joint Distribution Optimal Transport approach⁷. Performance of the corresponding proteins for the panels were assessed in the ADNI SOMAScan7k data⁸.



Demographics for the ROSMAP microglia and monocyte samples.

	Microglia (I)			Monocytes (II)		
Parameter	AD	MCI	NCI	AD	MCI	NCI
N	127	92	125	131	129	322
age at death (microglia) or sample (monocyte)	88.4 (3.2)	87.8 (3.4)	85.8 (5.1)	85.9 (5.2)	84.8 (5.2)	79.6 (7.9)
N, % female	97, 76%	59, 64%	80, 64%	93, 71%	92, 71%	250, 78%
APOE alleles						
0	75, 60%	72, 78%	100, 80%	85, 66%	100, 79%	252, 79%
1	48, 38%	20, 22%	25, 20%	40, 31%	27, 21%	64, 20%
2	3, 2%	0, 0%	0, 0%	4, 3%	0, 0%	3, 1%
Braak score	4.2 (1.0)	3.6 (1.1)	3.1 (1.2)			
Cerad score	1.6 (0.8)	2.3 (1.1)	2.7 (1.2)			
PMI	7.3 (4.4)	8.2 (5.8)	7.3 (4.3)			

RESULTS



CONCLUSIONS

- We developed and evaluated omics-biomarkers composed of panels of neuroinflammatory and immune response genes dysregulated in brain microglia at the earliest phases of AD.
- Panels of 30 and 50 genes provide optimal performance to classify AD vs. normal subjects based on monocyte transcriptomic data.
- Both panels show moderate prediction accuracy with AUCs of 0.70 and good balance between prediction of normal and AD classes.
- Personalized gene panels, developed for APOE genotype (APOE E4 carriage) and sex improve accuracy to AUCs ~ 0.75
- The selected 30 and 50 gene panels have a strong *translational* potential into accurate and sensitive diagnostic and prognostic transcriptomics-biomarkers for early presymptomatic stages of AD.
- The strongest association between the protein intensities corresponding to the gene panels was with p-tau: 73 proteins were FDR significant for the p-tau association with a range from 6·10⁻¹⁴⁸ to 0.05 including PPP3R, STX7 and PTPRJ. 50/94 genes were FDR significant (p<0.05) for the association with Ab with a range from 2·10⁻²² to 0.05 including STX7, VTI1A, PTPRJ and RAB1A. 43/94 proteins were FDR significant for an association with age with a range from 8·10⁻¹² to 0.05 including STX7, USP15 and UBE2K. An illustrative example is the strong association between PPP3R1 intensity and p-Tau (FDR p=9·10⁻¹⁴⁸), FDR significant associations are also observed between PPP3R1 intensity and sex (FDR p=2·10⁻⁵) and APOEe4 carriage (FDR p=2·10⁻⁴), supporting the premise to develop specific predictive panels for APOE genotype and sex.
- The technology will be administrated as a plasma test, thus, noninvasive and accusable.

→ Integrating omics-based biomarkers into biomarker discovery frameworks offers a powerful modality to enhance precision and comprehensiveness in AD research and clinical applications.

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