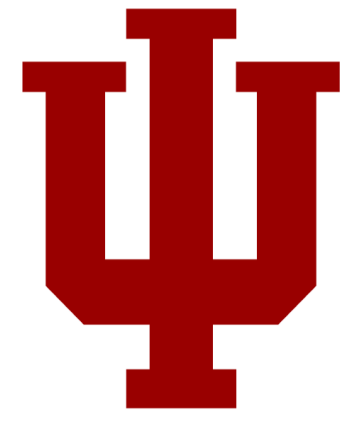


Genome-wide transcriptome analysis in Alzheimer's disease continuum in a Korean population: relation to A β deposition on PET



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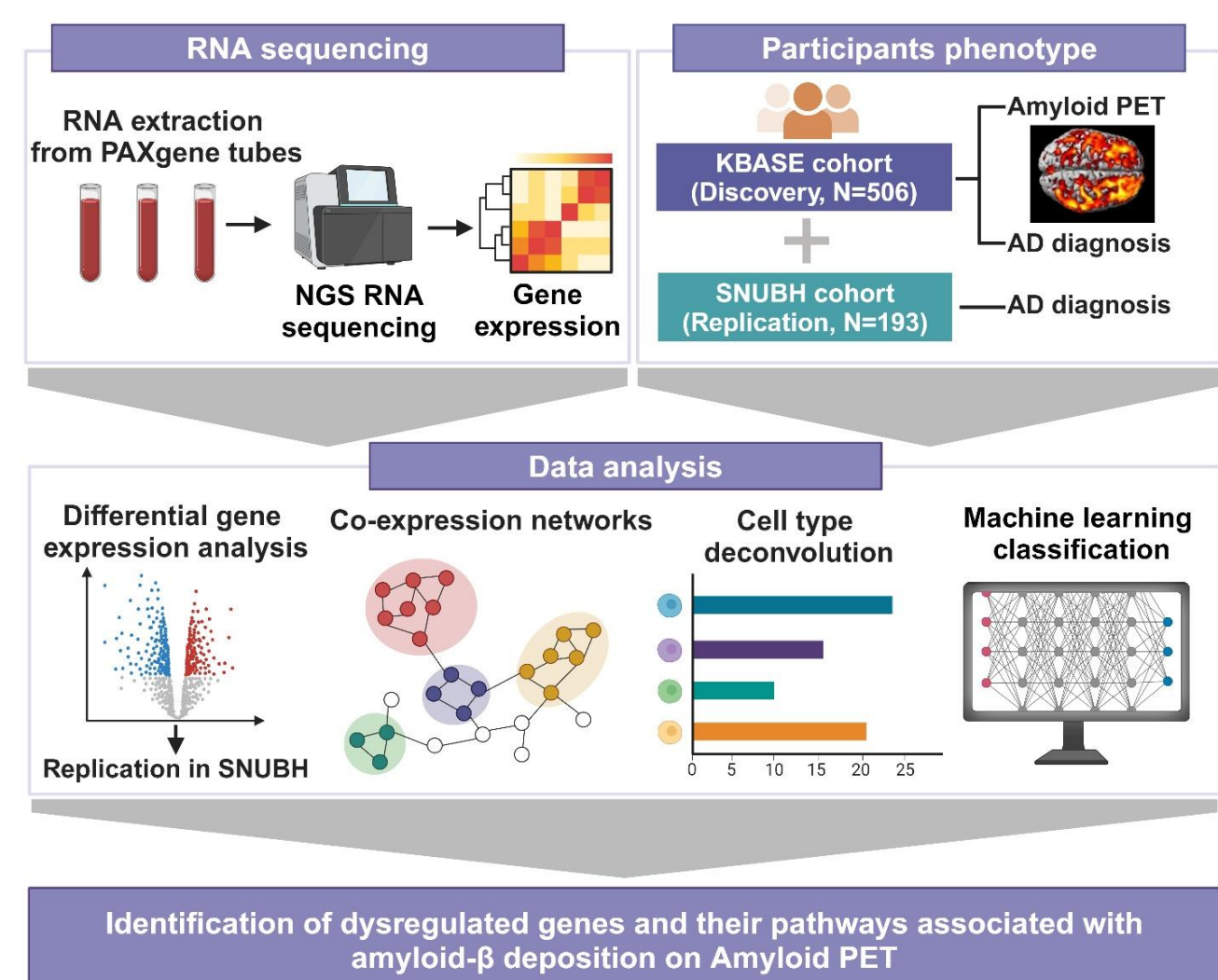
BACKGROUND

Alzheimer's disease (AD), the most common cause of dementia, is characterized by progressive cognitive decline, with amyloid- β (A β) accumulation representing one of the earliest pathological events. Despite increasing attention on ethnic diversity in AD research, most large-scale neuroimaging genomics studies have focused on populations of European ancestry, leaving the molecular mechanisms underlying AD in Asian populations insufficiently characterized.

METHODS

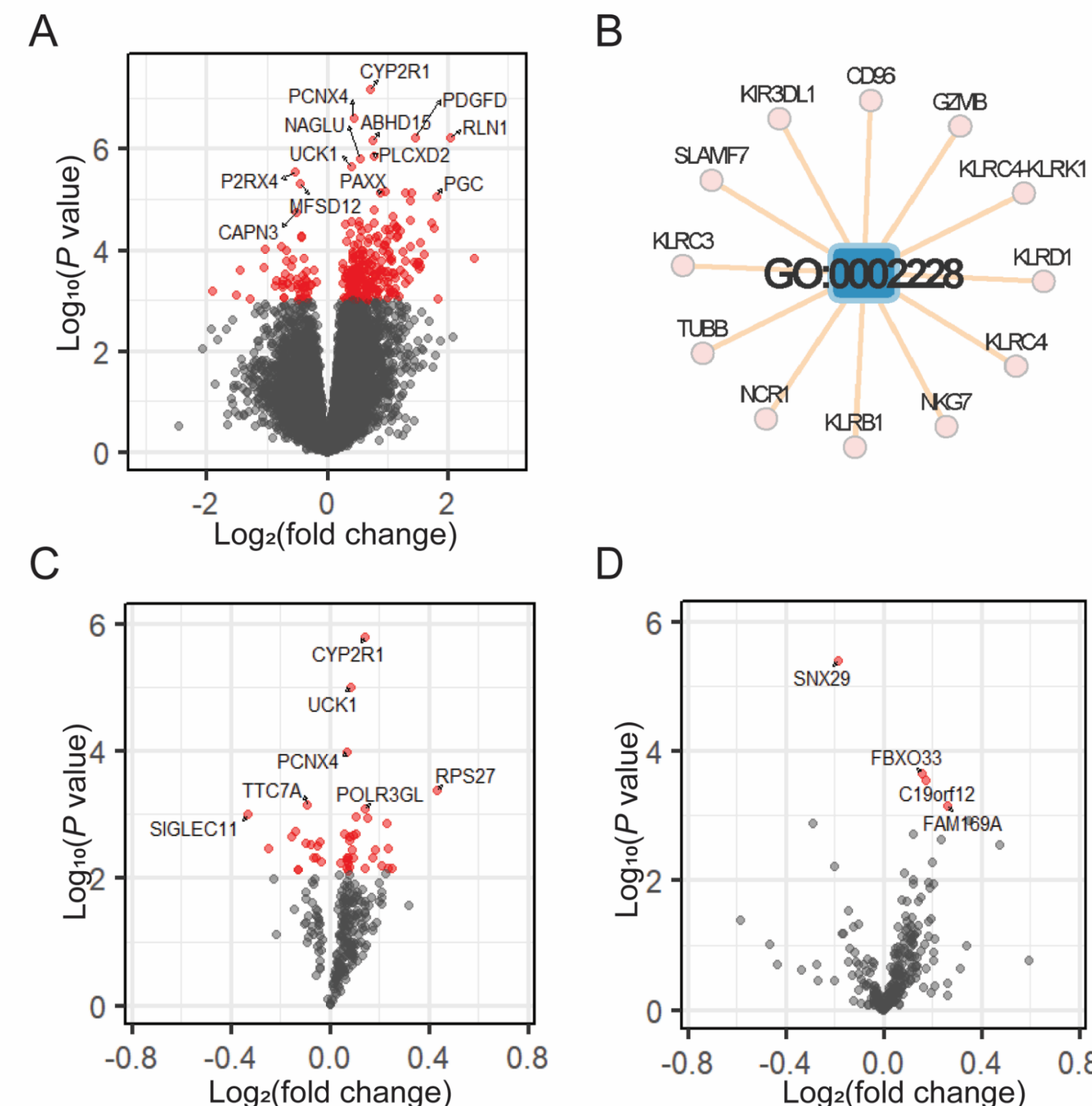
We performed genome-wide transcriptomic association analysis across the Alzheimer's disease continuum to identify blood-based dysregulated gene expression levels associated with global cortical A β deposition in participants from the Korean Brain Aging Study for Early Diagnosis and Prediction of AD (KBASE), followed by replication in an independent Korean cohort from Seoul National University Bundang Hospital (SNUBH).

RNA-Sequencing data from well-characterized KBASE participants (N=506) and A β PET imaging were analyzed using an integrative systems biology framework, including differential gene expression, weighted gene co-expression network analysis, functional enrichment, immune cell deconvolution, and machine learning-based classification.



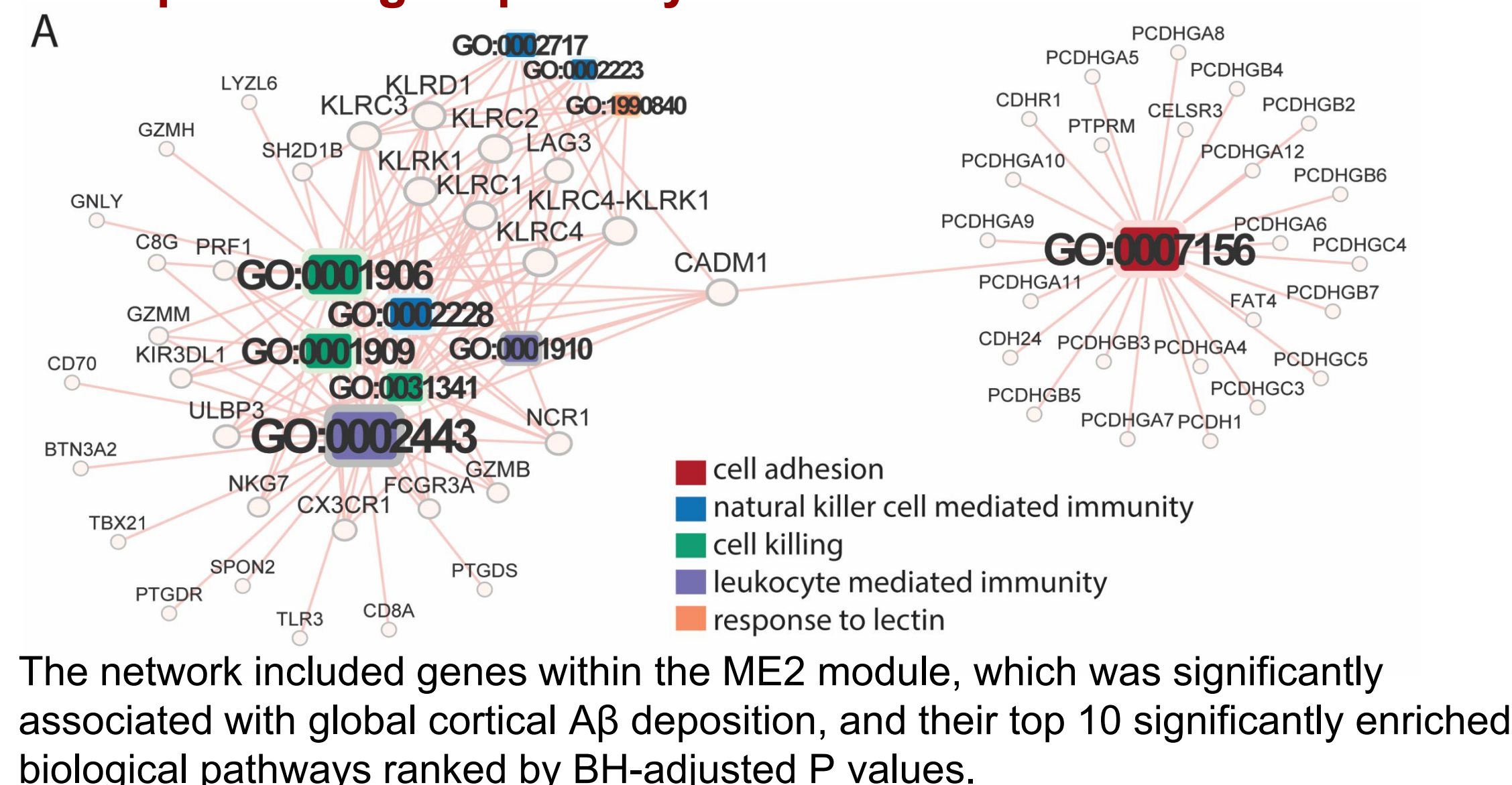
RESULTS

1. Differentially expressed genes (DEGs) associated with global cortical A β deposition and AD

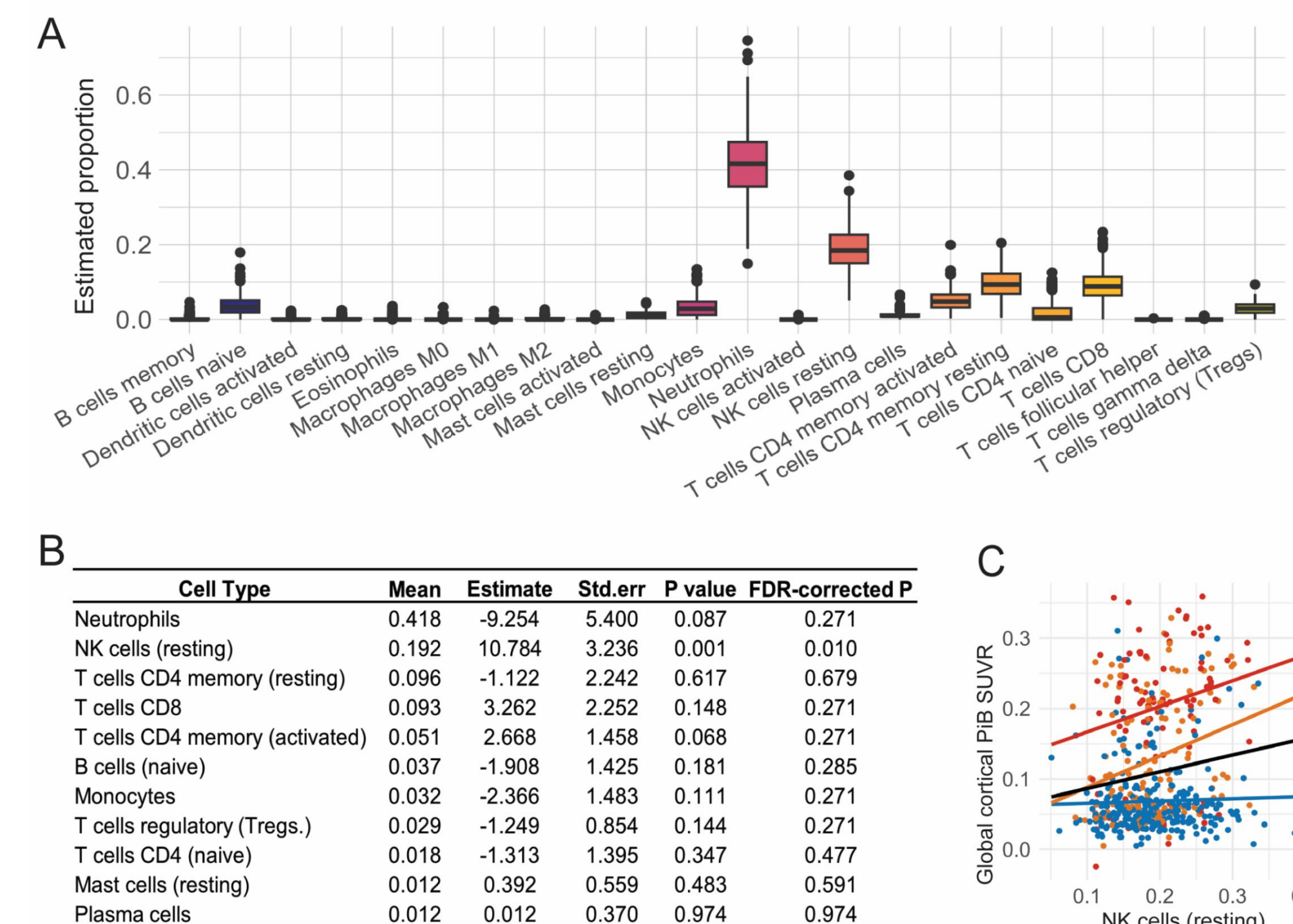


(A) The volcano plot showed 265 genes significantly associated with global cortical A β deposition measured by PET in the KBASE cohort (discovery dataset). (B) The network represented an NK cell-mediated immunity pathway (GO:0002228) and included 12 upregulated DEGs associated with global cortical A β deposition. (C) The volcano plot showed 44 significantly dysregulated genes in AD compared to CN in the KBASE cohort. (D) The volcano plot showed three replicated AD-associated genes (*SNX29*, *FBXO33*, and *C19orf12*) and one suggestively associated gene (*FAM169A*) in an independent Korean cohort, SNUBH.

2. Pathway enrichment analysis of network module genes and their top 10 biological pathways

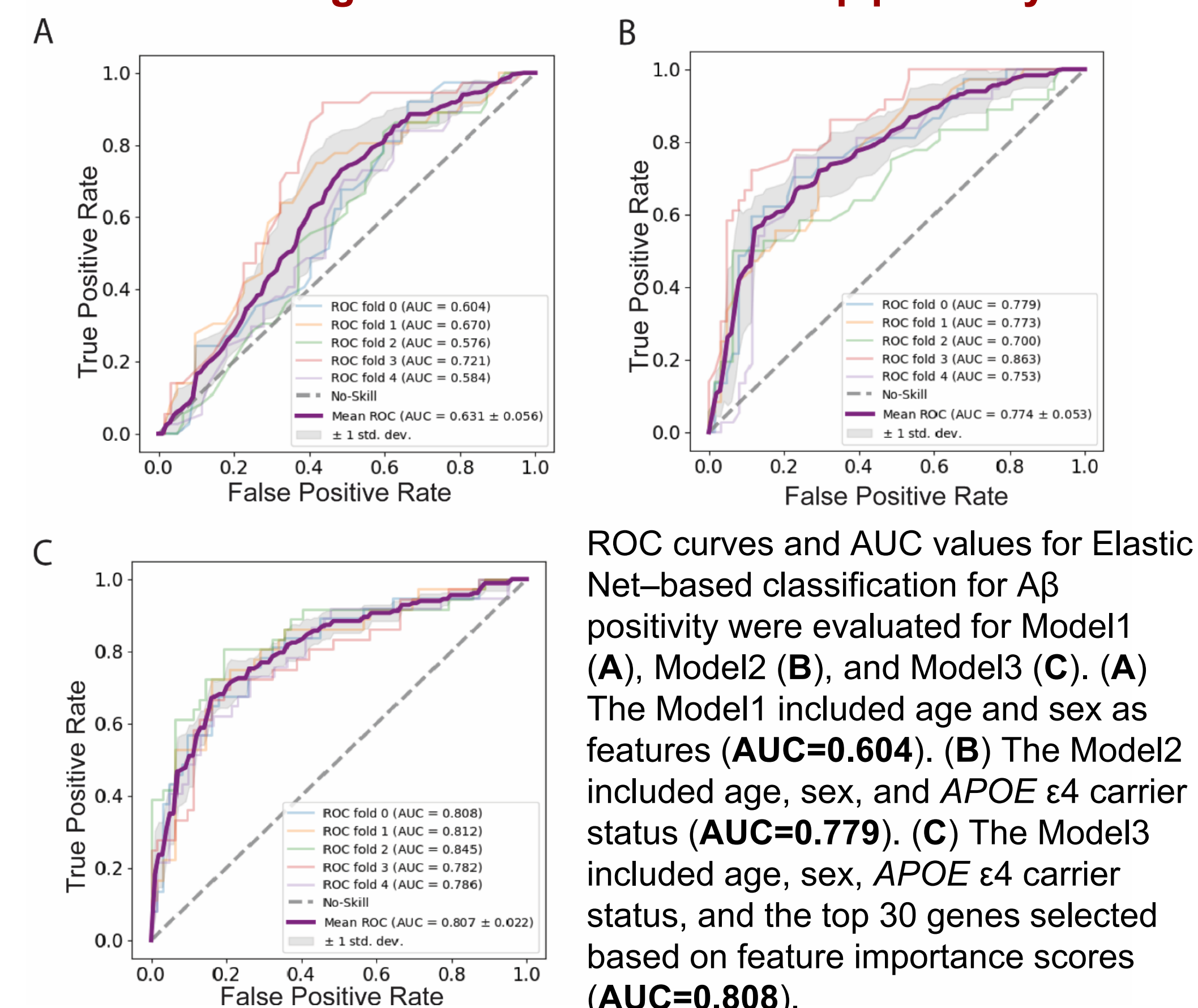


3. Immune cell type proportions estimated from blood RNA-Seq data using CIBERSORTx



(A) Boxplots showed estimated cell type proportions for 506 individuals in each of the 22 immune cell types. (B) The table represented the mean value of proportions and the results of association analysis between immune cell type proportions and global cortical A β deposition. (C) Resting NK cells were significantly associated with global cortical A β deposition.

4. Machine learning-based classification of A β positivity.



SUMMARY

- Dysregulated genes were associated with cerebral A β deposition measured by PET in a Korean cohort.
- AD-associated dysregulated genes were replicated in an independent Korean cohort.
- Gene network modules were associated with A β deposition.
- Dysregulated genes were related to natural killer (NK) cell-mediated immunity pathways.
- Blood NK cell proportions were associated with amyloid- β deposition.
- Integration of blood transcriptomic signatures with demographic and *APOE* ϵ 4 information enhanced the classification of A β positivity.

CONCLUSION

Our blood-based transcriptomics analysis in a Korean population demonstrates that genes associated with cerebral A β deposition are enriched in NK cell-mediated immune pathways, highlighting a potential role for peripheral innate immune responses in AD pathology.

Our findings provide important insights into AD molecular mechanisms in an East Asian population and establish a foundation for future longitudinal studies aimed at characterizing the temporal dynamics of immune activation throughout AD progression.

ACKNOWLEDGEMENTS

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