



Peripheral cellular transcriptional changes are associated with Alzheimer’s disease related phenotypes

Xuan Chen, B.S.¹, Xue Wang, Ph.D.², Wei Tsai, B.S.¹, Thuy Nguyen, B.S.¹, Denise A. Reyes, B.S.³, Val J. Lowe, M.D.³, Ronald C. Petersen, M.D., Ph.D.⁵, Kejal Kantarci, M.D., M.S.³, Minerva M. Carrasquillo, Ph.D.¹, Kwangsik Nho⁶, Andrew J. Saykin, M.S., Psy.D.⁶; Joseph S. Reddy, Ph.D.², Mariet Allen, Ph.D.¹, Nilüfer Ertekin-Taner, M.D., Ph.D.^{1,7}

¹ Mayo Clinic, Department of Neuroscience, Jacksonville, FL, ² Mayo Clinic, Department of Quantitative Health Sciences, Jacksonville, FL, ³ Mayo Clinic, Department of Radiology, Rochester, MN, ⁴ Mayo Clinic, Department of Health Sciences Research, Rochester, MN, ⁵ Mayo Clinic, Department of Neurology, Rochester, MN, ⁶ Indiana University School of Medicine, Center for Neuroimaging, Department of Radiology and Imaging Sciences, Indianapolis, IN, ⁷ Mayo Clinic, Department of Neurology, Jacksonville, FL

ABSTRACT

BACKGROUND
Alzheimer’s disease (AD) is characterized by changes in core neuropathologies including amyloid, tau, neurodegeneration (ATN) that are reflected in established blood biomarkers and track with clinical changes. Mild cognitive impairment (MCI) is a transitional stage to dementia, oftentimes AD. However, peripheral cell-specific molecular signatures and their association with AD/MCI-related phenotypes remain poorly characterized. In this study, we used computational deconvolution methods to assess the association of cell-type specific gene expression levels with AD/MCI-related phenotypes.

METHODS
We analyzed bulk blood transcriptome data from the Mayo Clinic Study of Aging (MCSA) and Alzheimer’s Disease Neuroimaging Initiative (ADNI).
• Deconvoluted cell proportion and cell type specific gene expression¹
• Tested association between cell proportion or cell type specific gene expression and AD/MCI-related phenotypes including clinical diagnosis, cognitive, and neuroimaging measures
• Performed meta-analysis of associations across two cohorts
• Conducted gene ontology analysis to assess the enriched biological pathways for significantly associated genes.

RESULTS

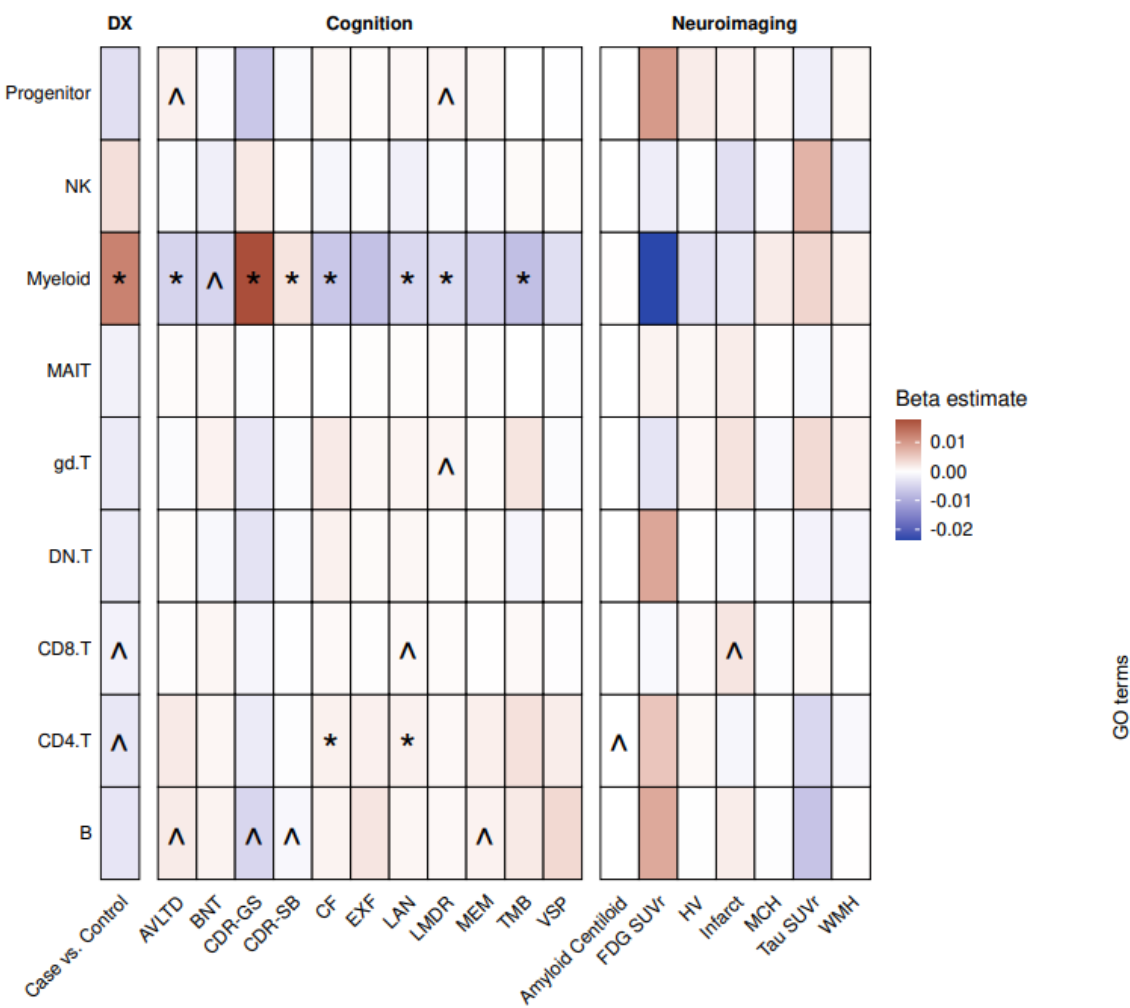


Figure 1. Blood cell proportions associate with AD/MCI diagnosis, cognitive and neuroimaging phenotypes. Proportion of myeloid cells is significantly associated with worse phenotypes while that of CD4+ T cells with better phenotypes. ^ p value < 0.05 and * FDR < 0.05

RESULTS (CONT.)

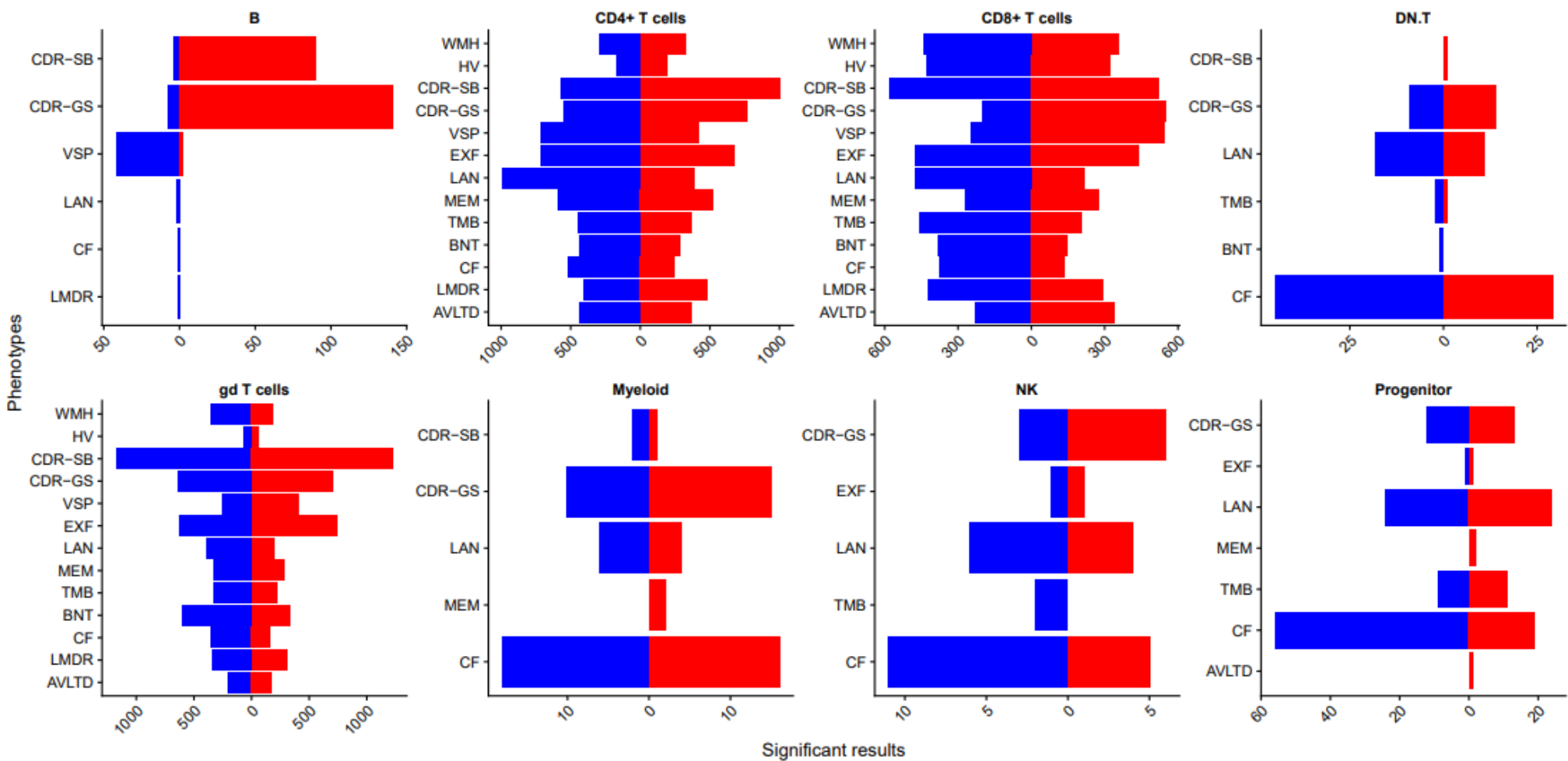
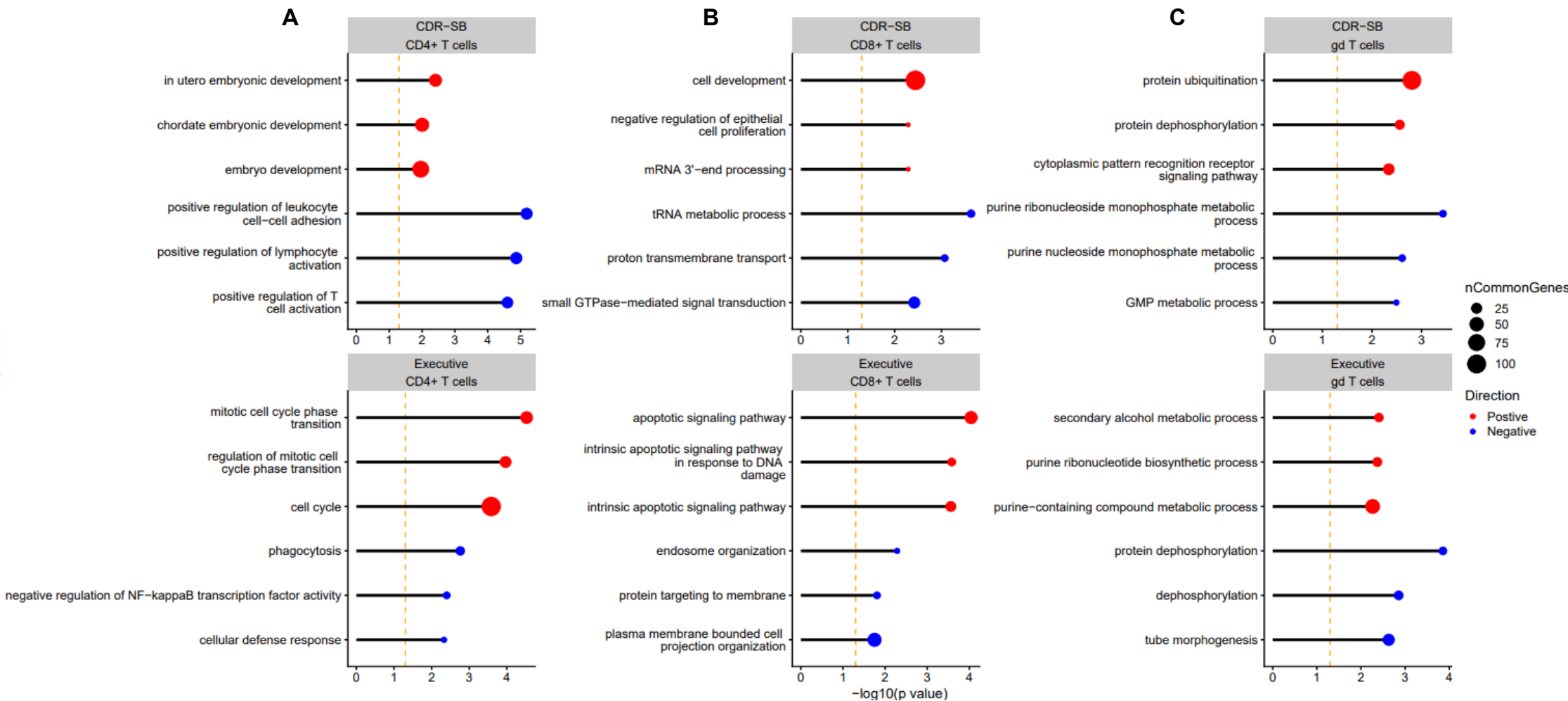


Figure 2. Transcript levels in specific blood cell types are significantly associated with AD/MCI diagnosis, cognitive and neuroimaging phenotypes. There are statistically significant associations (FDR < 0.05) between gene expression levels and phenotypes in each cell type. T cells, including CD4+ T, CD8+ T, and gd T cells, have the greatest number of significant associations. AVLTD, Rey Auditory Verbal Learning Test 30 min delay; LMDR, Logical Memory Delayed Recall; CF, Category Fluency; BNT, Boston Naming Test; TMB, Trail Making Test B; MEM, memory; LAN, language; EXF, executive function; VSP, visuospatial function; CDR-SB, Clinical Dementia Rating – Sum of Boxes; CDR-GS, Clinical Dementia Rating – Global Scores; HV, hippocampal volume; MCH, microhemorrhages; WMH, White matter hyperintensities; neg, negative; pos, positive.



RESULTS (CONT.)

Figure 3. Gene Ontology analysis provides biological insights from T cell gene expression levels that are significantly associated with AD/MCI phenotypes. (A) In CD4+T cells, genes associated with better cognition are enriched in mitotic cell cycle and leukocyte regulation while those with worse cognition were enriched in phagocytosis and embryo development (p value < 0.05). (B) In CD8+T cells, genes associated with better cognition are enriched in apoptotic signaling and tRNA metabolic process while those associated with worse cognition are enriched in cell development and endosome organization. (C) In gd T cells, genes associated with better cognition are enriched in purine metabolism while those associated with worse cognition are enriched in protein dephosphorylation/ubiquitination.

CONCLUSIONS

We identified peripheral cellular transcriptional levels of genes associated with AD/MCI phenotypes. These blood cell type specific genes are enriched in important biological pathways, revealing potential disease mechanisms in AD especially involving subsets of T cells. These cell-specific transcriptional perturbations may serve as potential therapeutic targets and biomarkers for AD/MCI and cognitive decline.

REFERENCE

1. Chu, T., Wang, Z., Pe'er, D. *et al.* Cell type and gene expression deconvolution with BayesPrism enables Bayesian integrative analysis across bulk and single-cell RNA sequencing in oncology. *Nat Cancer* 3, 505–517 (2022). <https://doi.org/10.1038/s43018-022-00356-3>

ACKNOWLEDGEMENT

This work was supported in part by National Institutes of Health, National Institute on Aging RF1 AG051504, U01 AG046139, R01 AG061796, P30 AG062677 and U19 AG074879 and the Alzheimer’s Association Zenith Fellows Award (ZEN-22-969810) to NET. Data collection and sharing for this project was in part funded by the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904).



Email: Chen.Xuan@mayo.edu