

ALZHEIMER’S DISEASE RELATED CELL TYPES

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INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Different brain cell types have been suggested to be related to Alzheimer’s disease (AD) ¹⁻³ . However, there has not been a systematic study to explore which cell type is specific to AD.	We have collected postmortem brain samples from 584 non-Hispanic Whites and 195 Caribbean Hispanics from the Washington Heights-Inwood Columbia Aging Project (WHICAP), The Alzheimer’s Disease Family Based Study (AD FBS), and New York Brain Bank (NYBB). In addition, blood samples were obtained from 751 unrelated Caribbean Hispanics cases and controls from the Estudio Familiar de la Influenza Genetica en Alzheimer (EFIGA) cohort. The brain DNA methylation profiles were measured by Illumina Infinium MethylationEPIC and the blood DNA methylation profiles were measured by the NEBNext Enzymatic Methyl-seq (EM-seq) platform. We applied CellDMC to drive the information of the cell type proportion. We have conducted the random effect meta-analysis to combine the results from non-Hispanic Whites and Caribbean Hispanics.	For the pathological diagnosis of AD based on the neuropathological traits measured in the postmortem human brains, the significantly associated CpG sites and cell types include <i>PLCL2</i> in both oligodendrocytes and inhibitory neurons, <i>MYOC1</i> in the astrocytes, and <i>NT5DC1</i> in the microglia. There are genome-wide significant CpG sites from different cell types associated with all the analyzed blood AD biomarkers, including phosphorylated Tau-217 (P-tau217), phosphorylated Tau-181 (P-tau181), Aβ42/Aβ40 ratio, P-tau181 to Aβ42 ratio, glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL). Compared to all the other blood AD biomarkers, phosphorylated Tau-217 (P-tau217) has the greatest number (N=815) of significant CpG sites in almost all cell types including B cells (N=143 sites), monocytes (N=133 sites), neutrophils (N=175 sites), NK cells (N=117 sites), CD4+ T cells (N=102 sites), and CD8+ T cells (N=145 sites). On the other hand, GFAP has the least genome-wide significant CpG sites (N=140) across B cells (N=34 sites), monocytes (N=48 sites), neutrophils (N=32 sites), CD4+ T cells (N=8 sites), and CD8+ T cells (N=18 sites).	We have identified cell type signature DNA methylation CpG sites relevant to pathological AD diagnosis in human brains and peripheral AD biomarkers in human blood.	1. Mathys, H. <i>et al.</i> Single-cell multiregion dissection of Alzheimer's disease. <i>Nature</i> 632, 858–868 (2024). 2. Mathys, H. <i>et al.</i> Single-cell atlas reveals correlates of high cognitive function, dementia, and resilience to Alzheimer's disease pathology. <i>Cell</i> 186, 4365–4385 e27 (2023). 3. Merighi, S., Nigro, M., Travagli, A. & Gessi, S. Microglia and Alzheimer's Disease. <i>Int J Mol Sci</i> 23(2022).
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