

Multitome single-nucleus atlas of the hippocampus in Alzheimer's disease and related dementias

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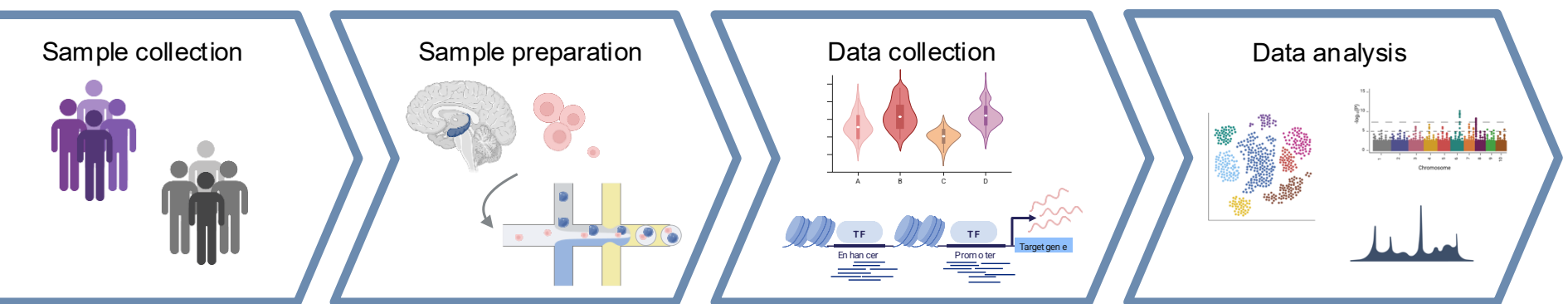
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INTRODUCTION

The hippocampus plays a significant role in learning and memory and is one of the affected brain regions in Alzheimer's disease (AD). This can take the form of rapid degeneration and loss of hippocampal cells in AD, or the formation of amyloid plaques and tau tangles affecting molecular pathways. Symptoms such as cognitive impairment or memory loss may occur due to these pathological changes.

This project aims to create a multitome atlas of the human hippocampus across AD and related dementias (ADRD) patients. We use these single-cell profiles to characterize the molecular changes associated with ADRDs and have intersected them with results from genome-wide association studies (GWAS) to nominate genomic regions that may be associated with disease.

METHODS



We collected post-mortem hippocampal tissue from 237 donors and isolated nuclei for single-nucleus multitome analysis (ATAC + gene expression). Libraries were prepared with the standard procedures and sequenced across multiple lanes of a NovaSeq 6000. Using the CellRanger ARC pipeline, sequencing reads were converted to gene expression and chromatin accessibility matrices.

Data processing and analysis were done in Python using the scMAVERICS workflow, including automated QC filtering, RNA and ATAC modeling, cell typing, ATAC peak calling, and chromatin co-accessibility.

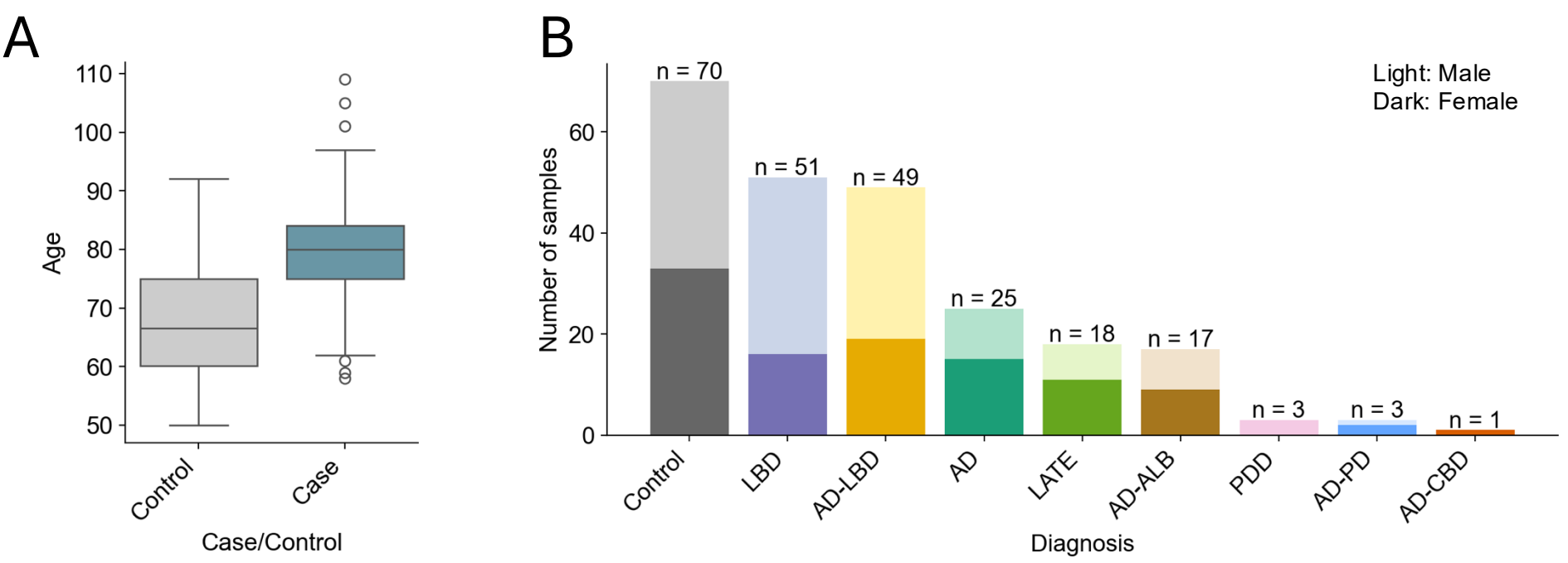


Figure 1. Sample metadata. A) Age distribution for case and control populations. B) Count of donors by post-mortem pathological diagnosis, divided by sex. LBD = Lewy Body Dementia, AD-LBD = AD with synuclein pathology, AD = Alzheimer's disease, LATE = Limbic-predominant Age-related TDP-43 Encephalopathy, AD-ALB= AD with Amygdala Lewy Bodies, PDD= Parkinson's Disease with Dementia, AD-PD = AD with Parkinson's symptoms, AD-CBD = AD with Corticobasal degeneration.

RESULTS

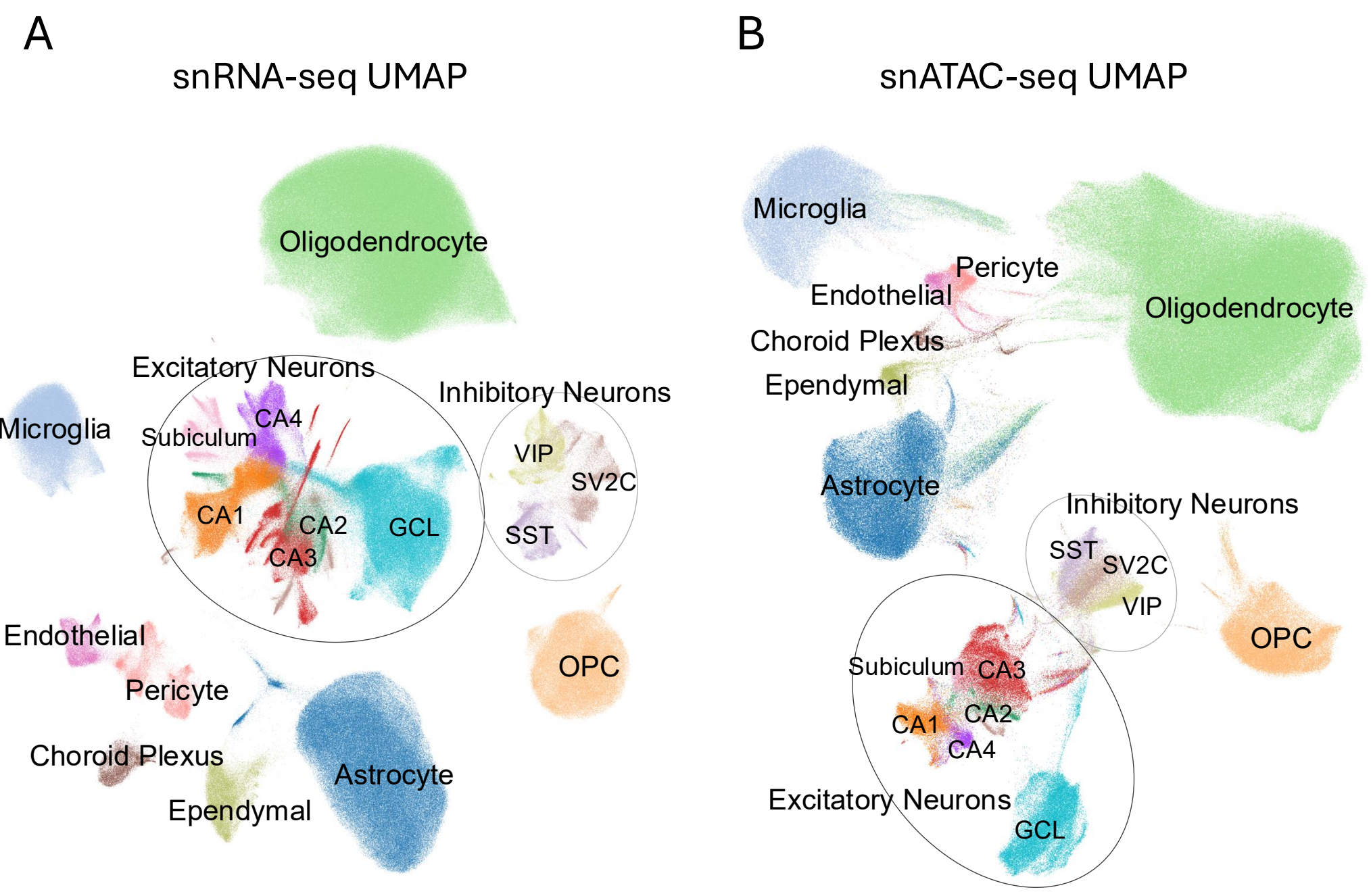


Figure 2. Annotated UMAPs by cell type. A) UMAP of cell types by clustered gene expression. B) UMAP of cell types clustered by chromatin accessibility. Cell types were annotated based on gene expression and labels transferred to the chromatin accessibility UMAP by shared barcode. OPC: Oligodendrocyte precursor cells. GCL: Dentate gyrus granule cell layer. CA1-4: Neurons of the cornu ammonis.

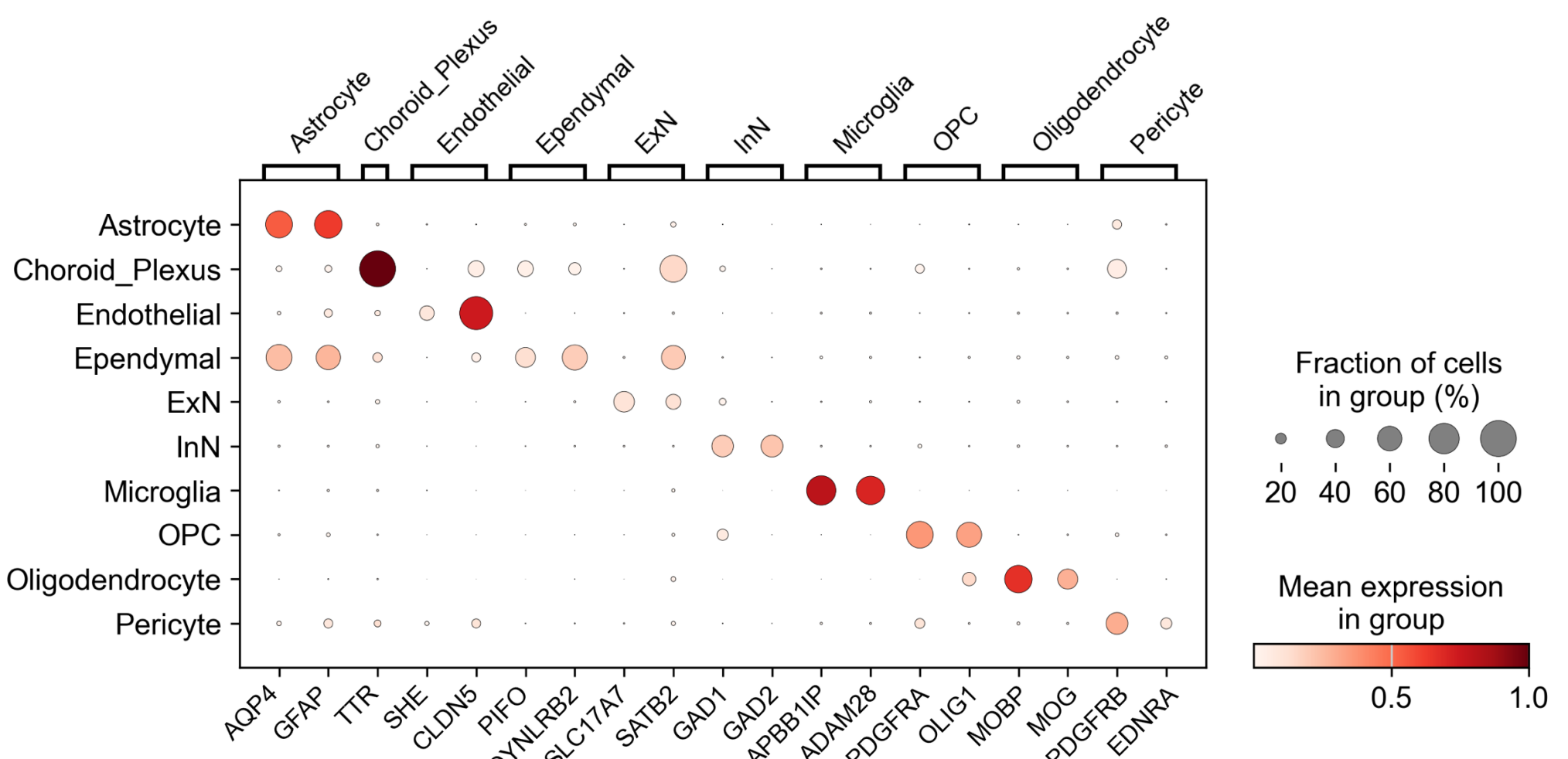


Figure 3. Dot plot showing gene expression of marker genes for each cell type.

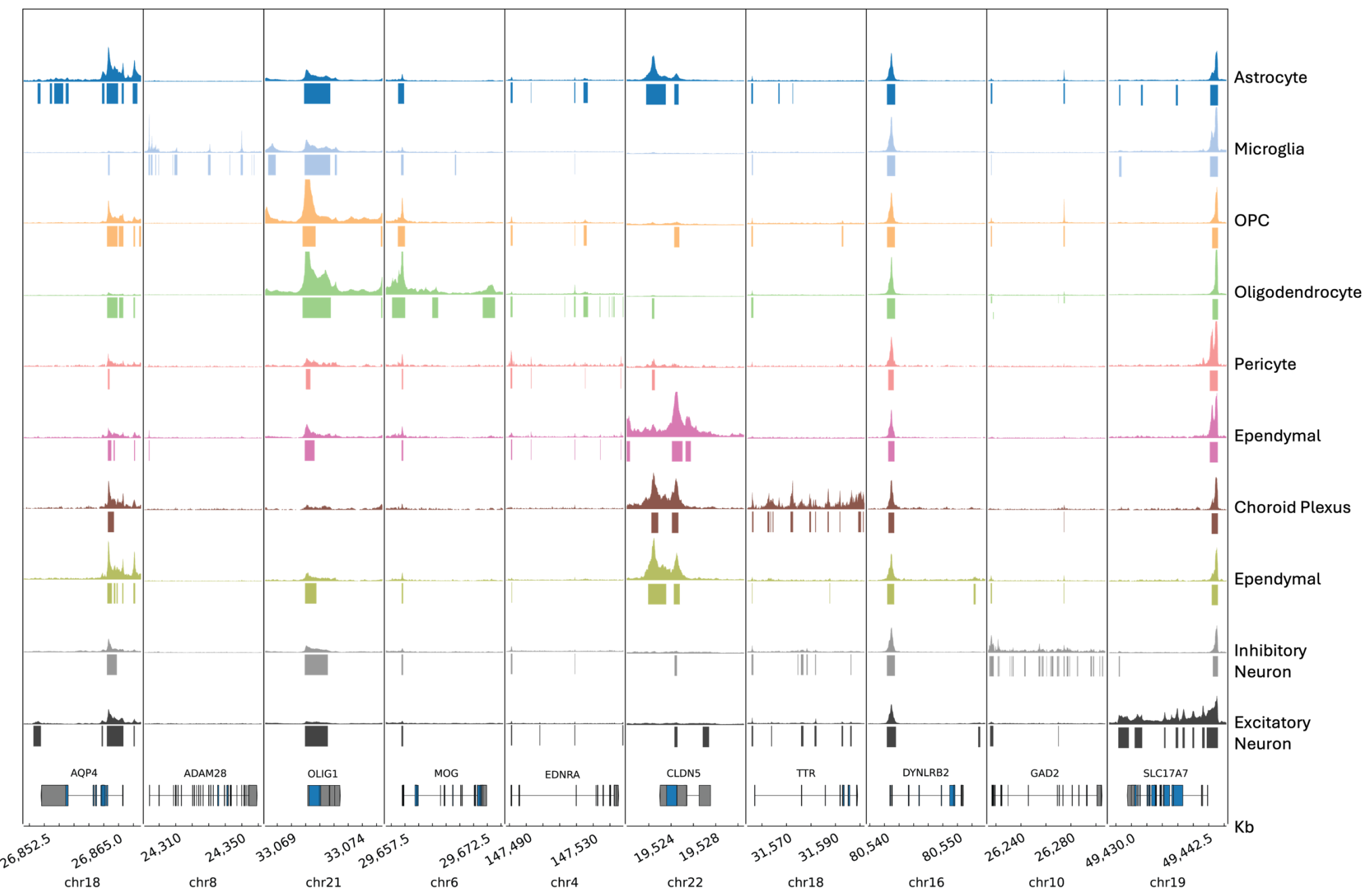


Figure 4. Locus plots of chromatin accessibility around selected marker genes for each cell type. Top shows read pileups from ATAC sequencing and colored bars below show peaks called by MACS.

RESULTS

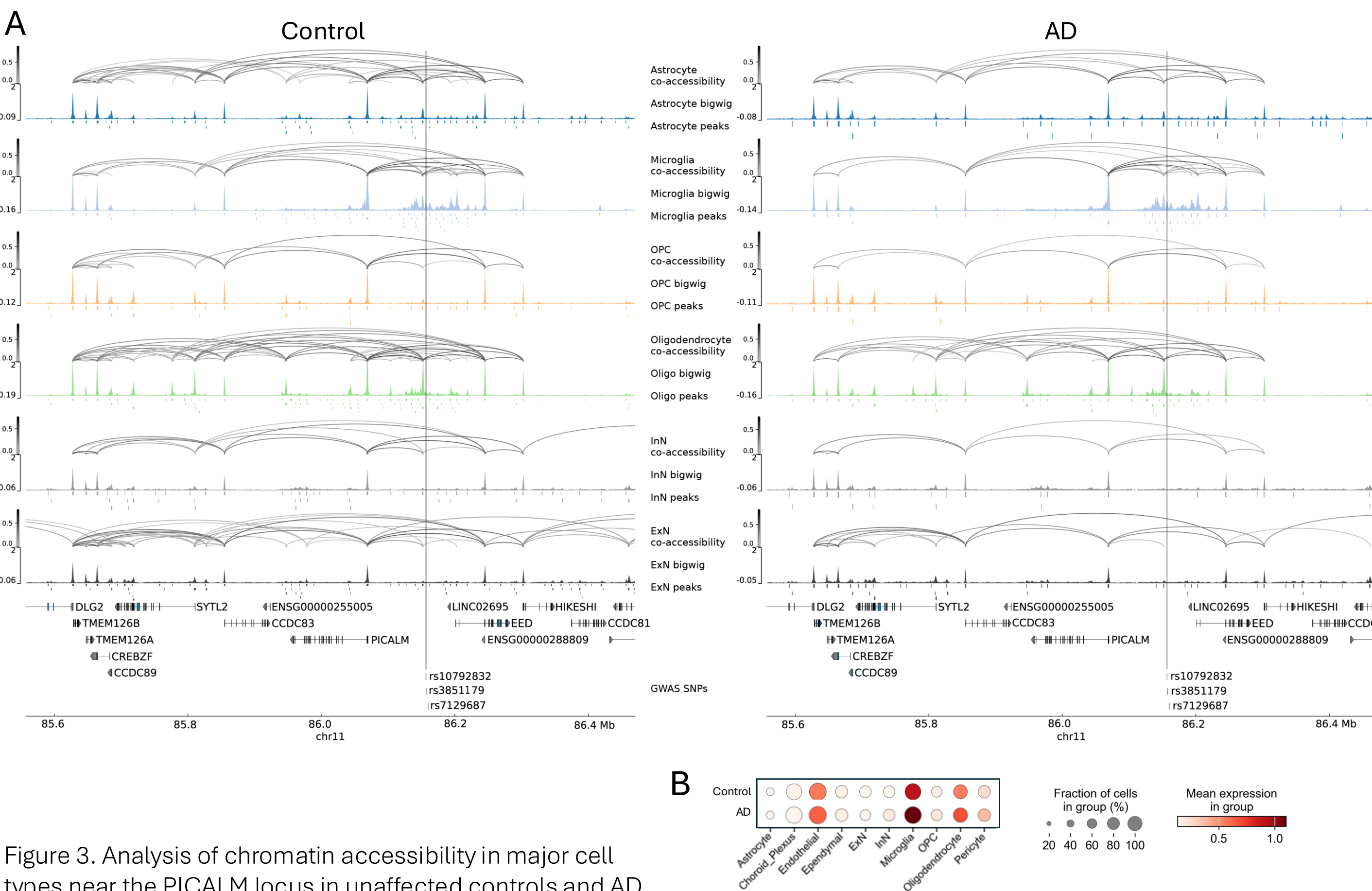


Figure 3. Analysis of chromatin accessibility in major cell types near the PICALM locus in unaffected controls and AD. A) Locus plot of PICALM across cell types for control and AD samples. Grey arcs show regions that are co-accessible within each cell type: connected regions correlate in levels of open chromatin. Bigwigs show read pileups from ATAC-seq data indicating the level of chromatin accessibility, and colored bars below show chromatin accessibility peaks in each cell type. Gene ideograms are below. Top GWAS hits for AD at the locus are labeled by rsID. The vertical line on both graphs shows the location of one of the top SNPs relative to the chromatin accessibility peaks. B) Gene expression of PICALM across cell types in control and AD samples.

CONCLUSION

We have created a large multitome single-cell atlas comparing snRNA and snATAC sequencing profiles in ADRD and control hippocampus tissue. Cell types were annotated based on gene expression and generated chromatin accessibility peaks for each cell type. This data can be used as a resource to examine the relationship between gene expression and chromatin accessibility in different forms of ADRD and nominate regions associated with disease for further functional analysis.

As an example of its utility, we examined the PICALM locus in AD and controls. Previous genome-wide association studies (GWAS) have identified PICALM, a gene involved in endocytosis and autophagy, as a genetic susceptibility locus in AD. PICALM has been reported to modulate APP processing, Amyloid beta transcytosis, and tau pathology progression. At this locus, our data show a decrease in chromatin accessibility and co-accessibility across cell types in AD samples when compared to controls.

Some of the most significant GWAS single-nucleotide polymorphisms (SNPs) at this locus are near a chromatin accessibility peak that is co-accessible with the transcription start site (TSS) of PICALM, suggesting a role for cis-regulatory elements in the increased expression of PICALM in AD.

REFERENCES/CONTACT

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