

Cell-type-specific differences in chromatin accessibility associated with Alzheimer's disease pathology

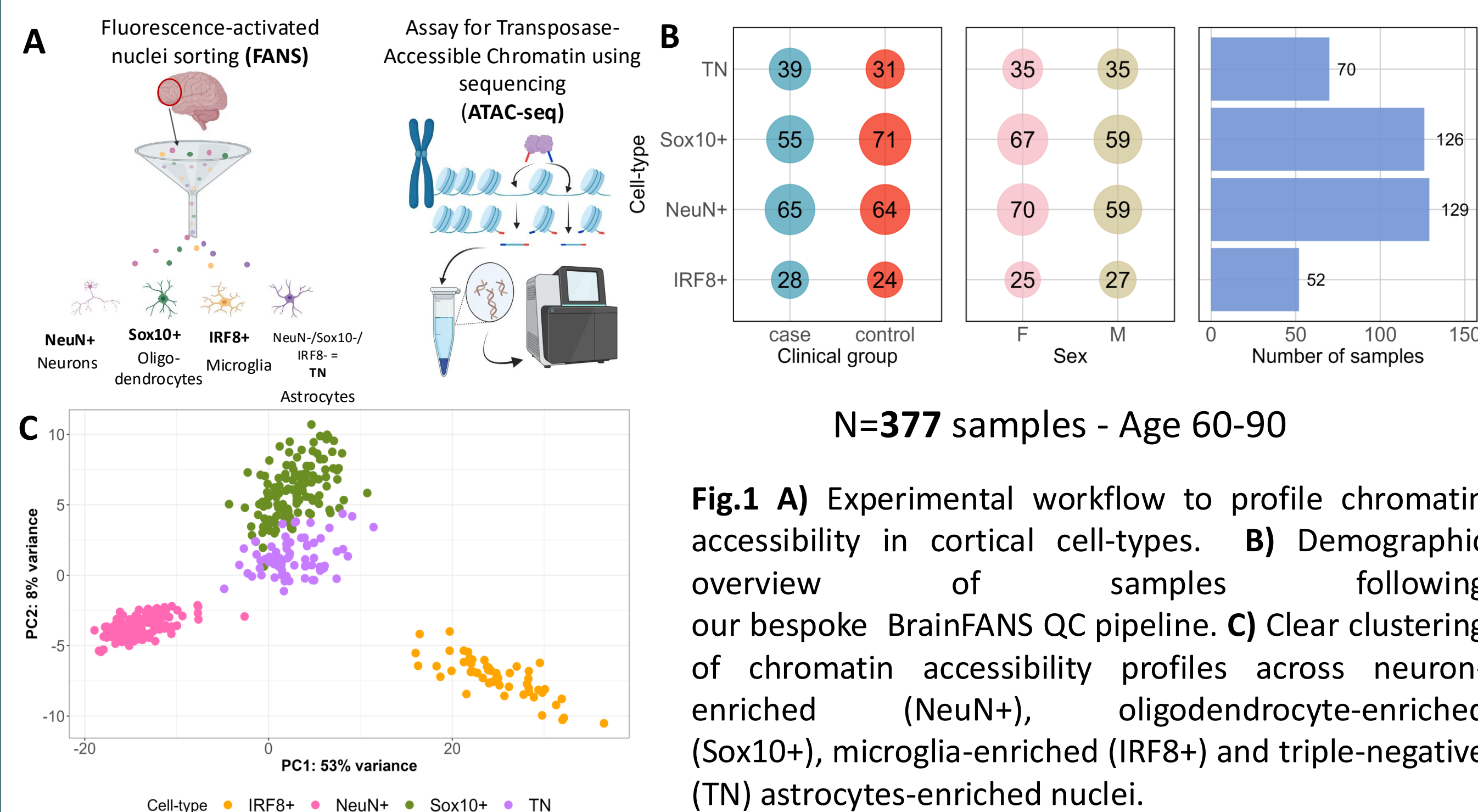
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Background

Alzheimer's disease (AD) is a chronic neurodegenerative disorder affecting over 26 million people worldwide. There is evidence for a role of epigenetic dysregulation in AD, with widespread changes in DNA methylation associated with neuropathology. Little is known about the role of variation in other regulatory mechanisms including chromatin accessibility in AD, and the specific cell types in which these changes occur. **AIM:** Identify AD associated differences in chromatin accessibility in different human cortical cell types and identify AD-associated regulatory variation.

Methods



N=377 samples - Age 60-90

Fig.1 **A)** Experimental workflow to profile chromatin accessibility in cortical cell-types. **B)** Demographic overview of samples following our bespoke BrainFANS QC pipeline. **C)** Clear clustering of chromatin accessibility profiles across neuron-enriched (NeuN+), oligodendrocyte-enriched (Sox10+), microglia-enriched (IRF8+) and triple-negative (TN) astrocytes-enriched nuclei.

Differential accessible regions (DARs)

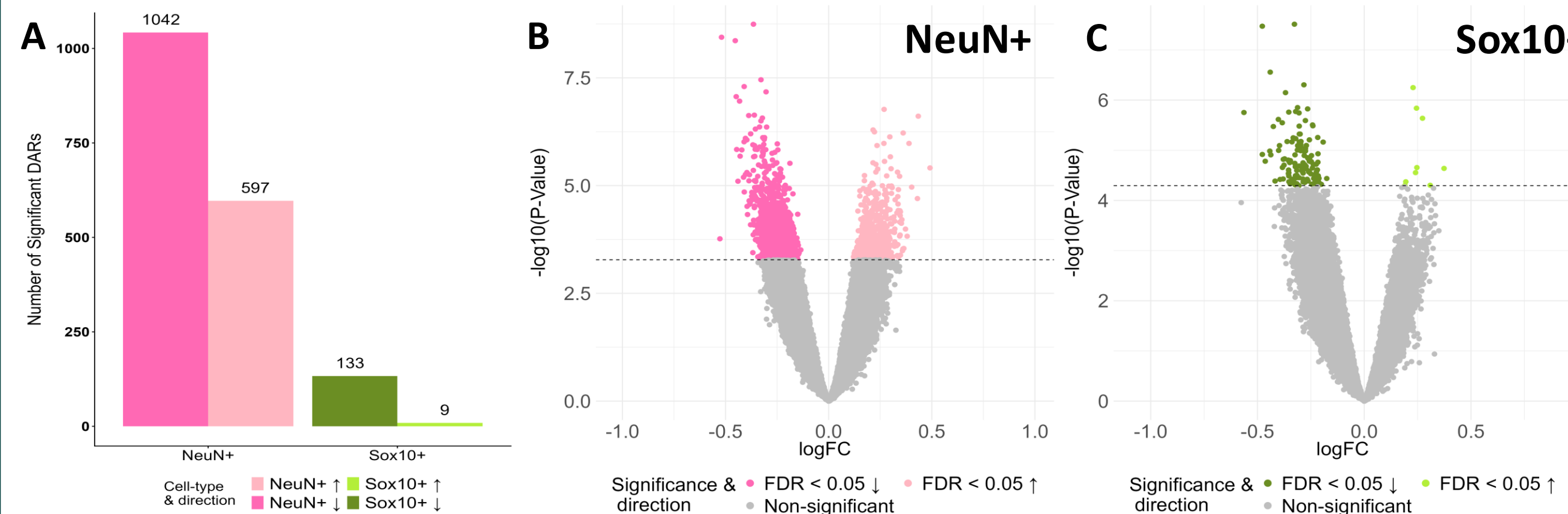


Fig.2 Cell-type-specific patterns of chromatin accessibility associated with AD pathology. We used *edgeR* with surrogate variable analysis to find DARs associated with AD neuropathology (**A**); adjusted P < 0.05). Volcano plots highlighting significant DARs in NeuN+ (n = 1639 DARs) (**B**) and Sox10+ (n = 142) (**C**) show a bias towards lower accessibility in AD cases compared to controls. 2 DARs in TN were also identified and none in IRF8+.

Differential accessibility at AD-risk genes

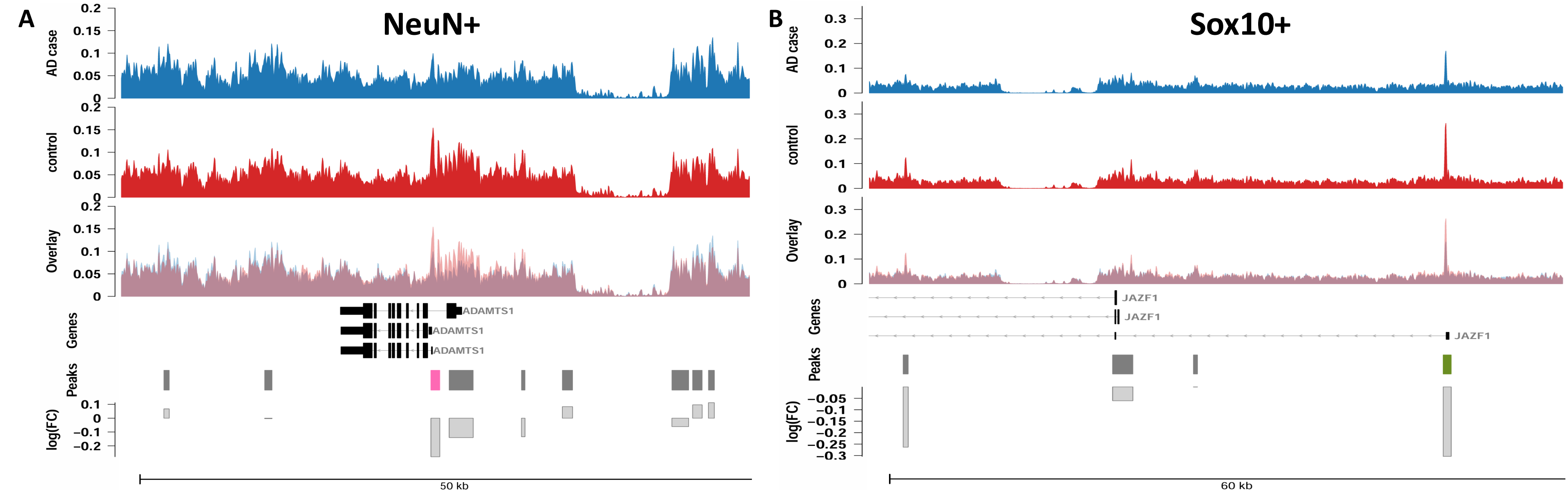


Fig.3 Examples of significant DARs mapped to promoters of AD risk genes (Bonn *et al.* 2026), both showing lower accessibility in AD cases compared to controls. **A)** ADAMTS1 plays a significant role in amyloid-beta metabolism. **B)** JAZF1 is involved in lipid metabolism.

Biological pathways

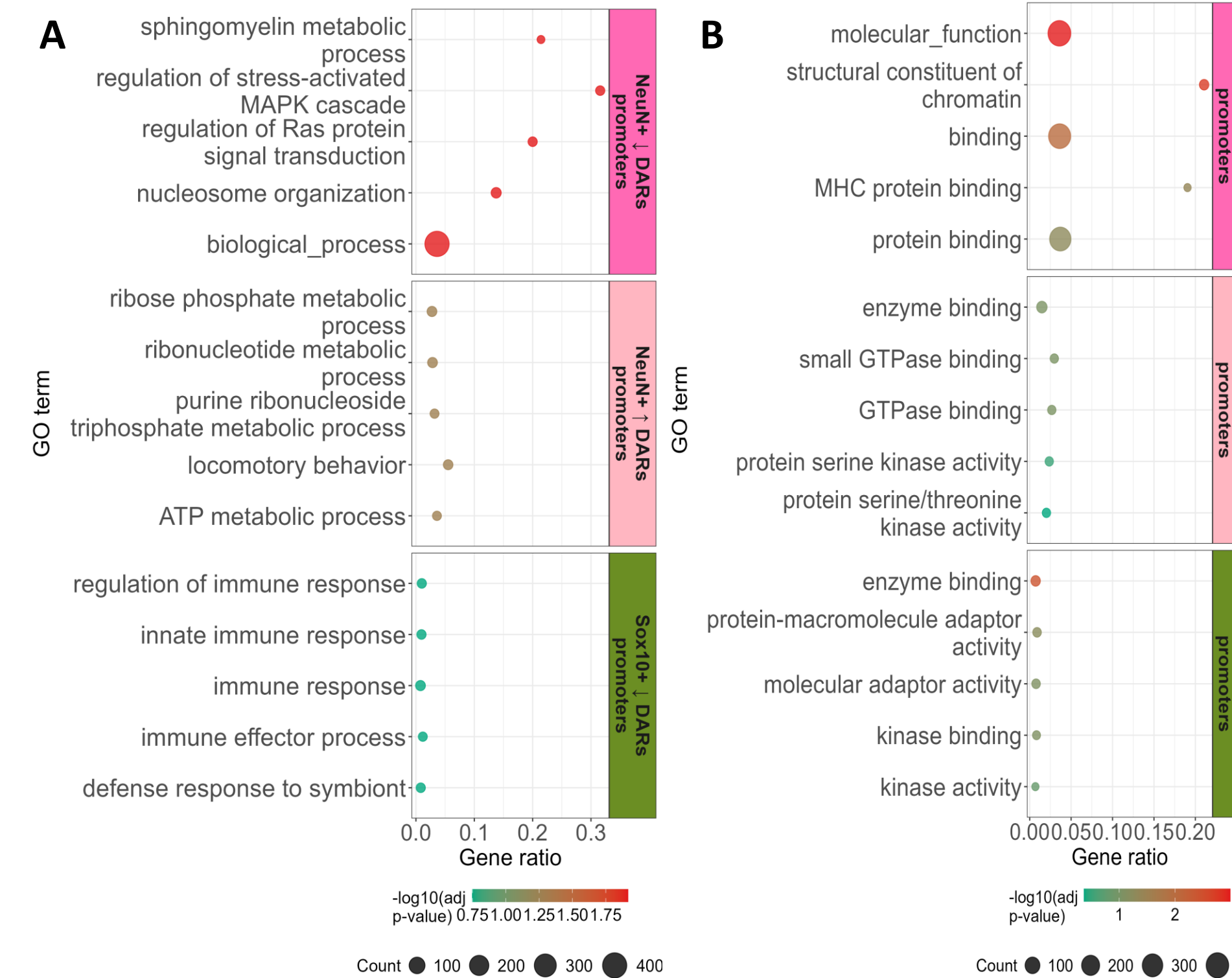


Fig.4 Pathway analysis of DARs revealed that specific enrichment of terms dependent on cell-type and direction of effect for both **A)** biological processes and **B)** molecular function.

1. EADB., EADI., Bonn. *et al.* Consensus meta-analysis of genome-wide association studies for Alzheimer's disease and related dementias. *Nat Genet* 58, 1214–1225 (2026). <https://doi.org/10.1038/s41588-026-02583-1>

Motif analysis

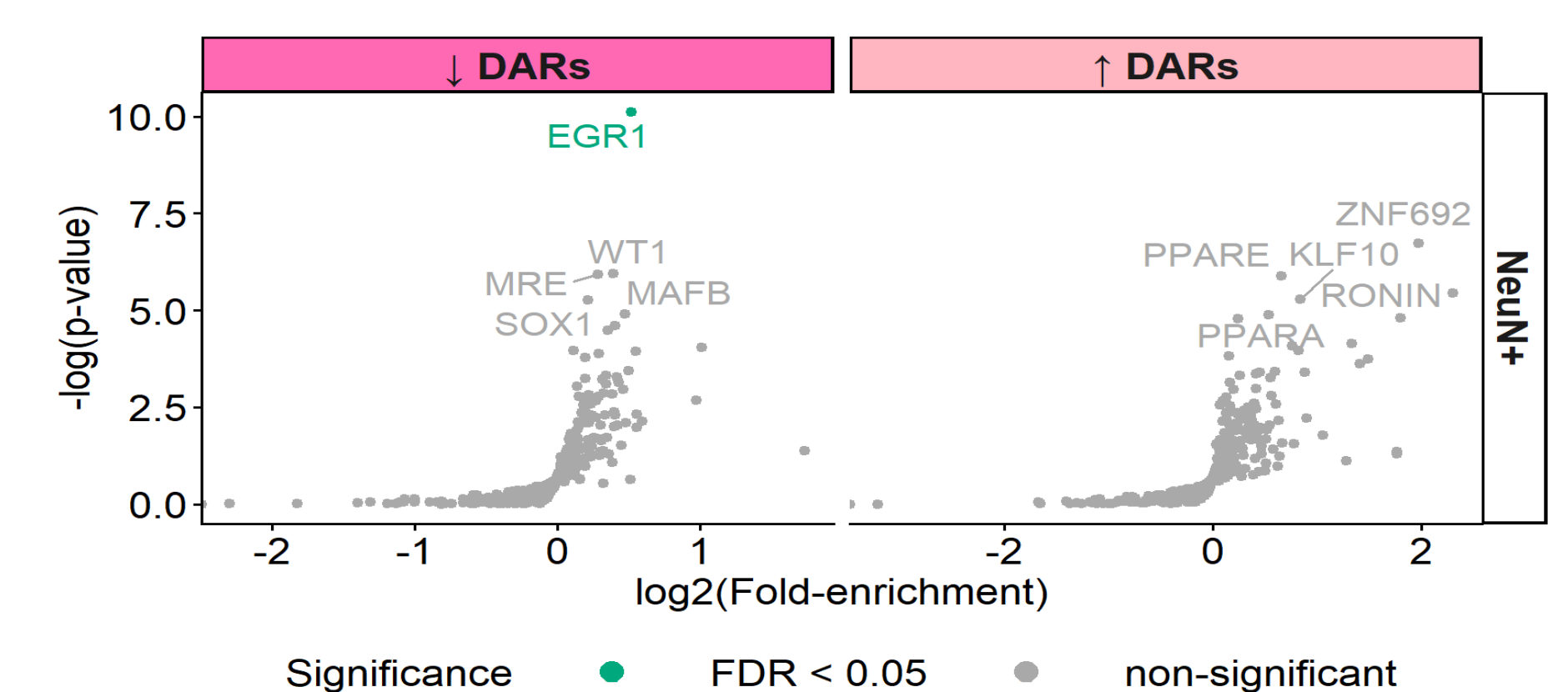


Fig.5 HOMER motif enrichment analysis showed a significant enrichment of EGR1 motif in significantly less accessible regions in NeuN+ (FDR < 0.05). Transcription factor EGR1 plays a role in cholinergic functions in the brain (memory, cognitive functions, attention.)

Conclusions

1. Widespread cell-type-specific differences in chromatin accessibility associated with AD neuropathology, including at known AD genes.
2. Cell-type-specific chromatin accessibility profiles can contribute to a better understanding of the functional impact of epigenetic alterations in AD.