



Insights from DNA methylomics and transcriptomics into early oligodendrocyte dysfunction in Alzheimer's disease



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Our findings implicate oligodendrocyte-specific DNA methylation and downstream gene expression changes as potential early features in Alzheimer's disease.

INTRODUCTION

Much research into the aetiology of Alzheimer's disease (AD) has focused on neuronal dysfunction, while studies on the contribution of glial cells, particularly oligodendrocytes, which produce the myelin sheath insulating neuronal axons, are only starting to emerge. Altered DNA methylation, an epigenetic modification that regulates gene expression, is well documented in AD. Yet, cell-type-specific investigations remain limited. Here, we examine the role of oligodendrocyte (OLG)-related DNA methylation signatures in AD, and how their changes impact gene expression.

METHODS

We performed weighted-gene correlation network analysis (WGCNA) on multiple brain omics AD datasets across species, including human DNA methylation data from 4 brain regions, human brain single-nuclei RNA sequencing data and mouse brain RNA sequencing data. We then compared dysregulated AD-associated network modules enriched for OLG genes across AD datasets and disease stages, and with other neurodegenerative disease DNA methylation datasets.

1. Human brain co-methylation network analyses reveal DNA methylation signatures associated with AD and enriched for OLG genes, which are preserved across brain regions and neurodegenerative diseases, and relate to AD pathology

- We generated co-methylation networks for four brain regions affected by different degrees of AD pathology - the Dorsolateral Prefrontal Cortex (DLPFC)-greenyellow, Entorhinal Cortex (ERC)-tan and Hippocampus (HIPPO)-grey60 co-methylation modules/signatures were all significantly associated with AD and enriched for OLG genes (Fig. 1)
- These signatures were replicated in an additional AD dataset and preserved in other neurodegenerative diseases, including tauopathies and alpha-synucleinopathies
- Hub gene analysis, which identifies the most strongly connected CpGs and related genes for each OLG-enriched module, reinforced the relevance for OLG lineage cells in AD-associated modules:
→ *MOG*, *MYRF* and *FAM222A* are the hub genes for the DLPFC-greenyellow, ERC-tan and HIPPO-grey60 modules, respectively.

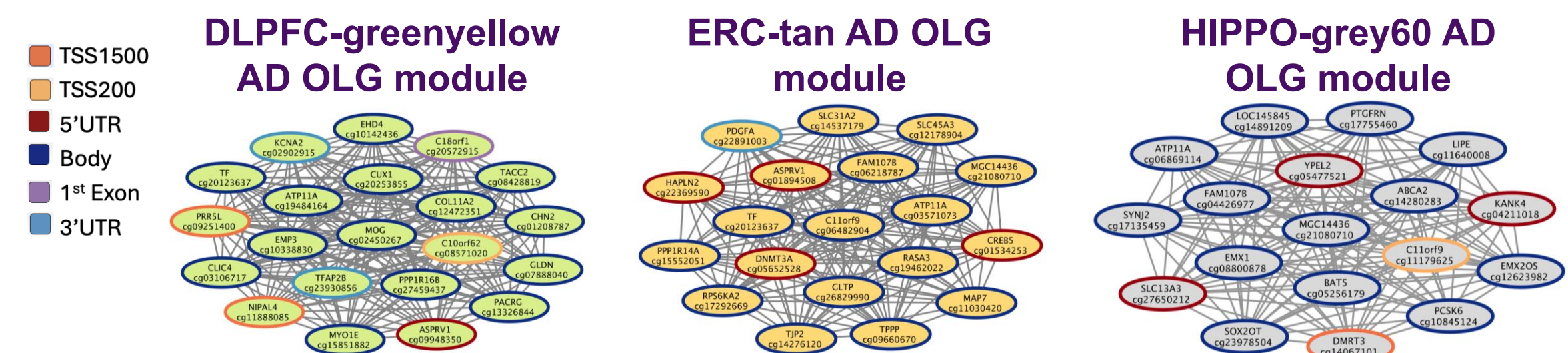


Figure 1 | Co-methylation network analyses across brain regions reveal dysregulated AD-associated signatures that are enriched for oligodendrocyte-related genes. Top 25 CpGs across the Dorsolateral Prefrontal Cortex (DLPFC)-greenyellow, Entorhinal Cortex (ERC)-tan and Hippocampus (HIPPO)-grey60 modules. Edge surrounding the genes indicates the feature of the CpG mapping to each gene as given by the legend.

- The identified coordinated methylation variation within these signatures is linked to increasing AD pathology (Braak stage) and is positively associated with the expression of key OLG genes (e.g. hub genes) (Fig. 2)

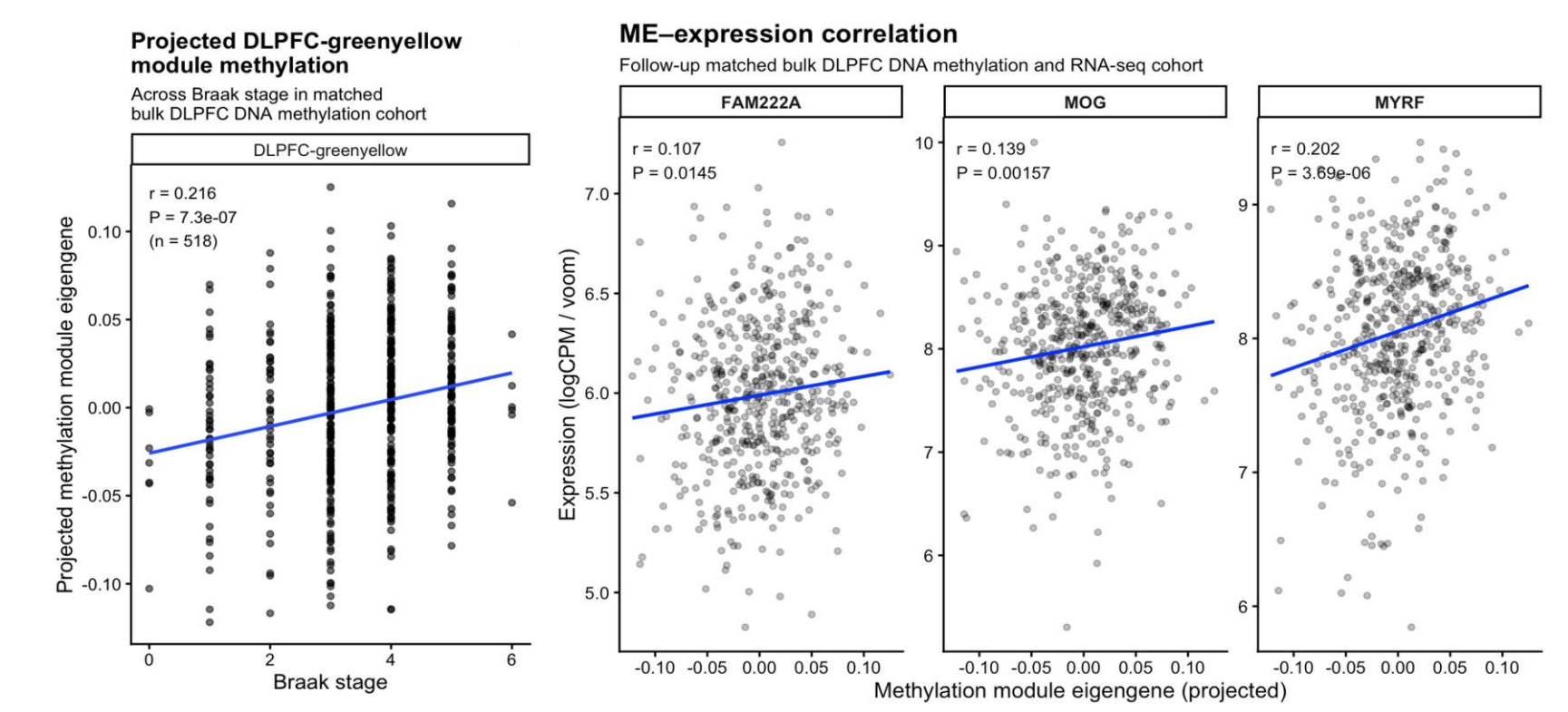


Figure 2 | AD-associated OLG DNA co-methylation signature is positively linked to Braak stage pathology and expression levels of OLG genes.

2. Dysregulated OLG co-methylation module genes show mostly upregulation in human AD OLGs

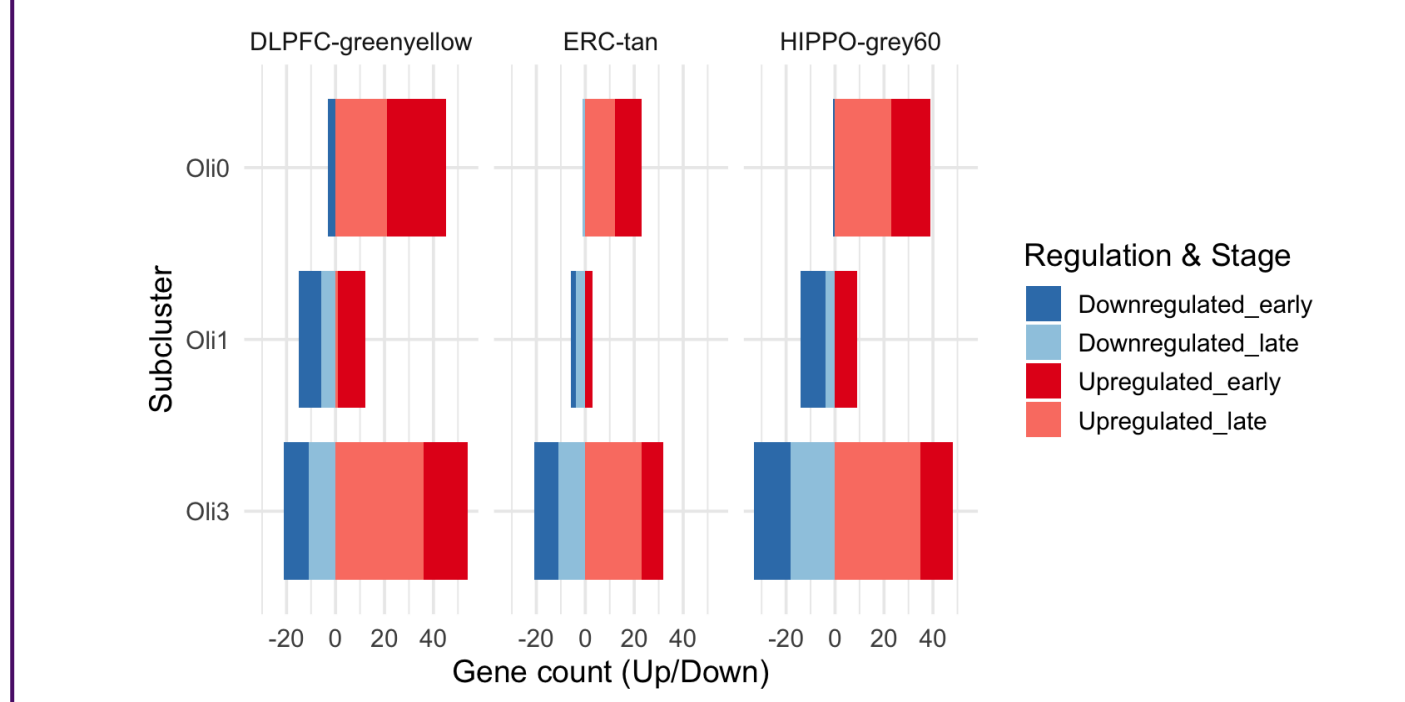


Figure 3| Differential expression patterns of genes present in AD-associated co-methylation modules in oligodendrocyte snRNA-sequencing clusters. Bar plots show the number of genes from each co-methylation module that are upregulated or downregulated (blue) in each OLG subcluster (Oli0–Oli3) and stratified by early (light shades) and late (dark shades) AD pathology stages.

4. AD-associated OLG co-methylation networks show dysregulation of gene expression in early-stage AD mouse models

- We identified one mouse co-expression module (pink, Fig. 5) as significantly associated with AD-related pathology and enriched for OLGs
- There was a significant overlap between the mouse pink module genes with all three human OLG-relevant AD co-methylation modules
- Hub genes of the human DLPFC-greenyellow, ERC-tan, and HIPPO-grey60 modules, *Mog*, *Myrf* and *Fam222A* were also present within the pink mouse module

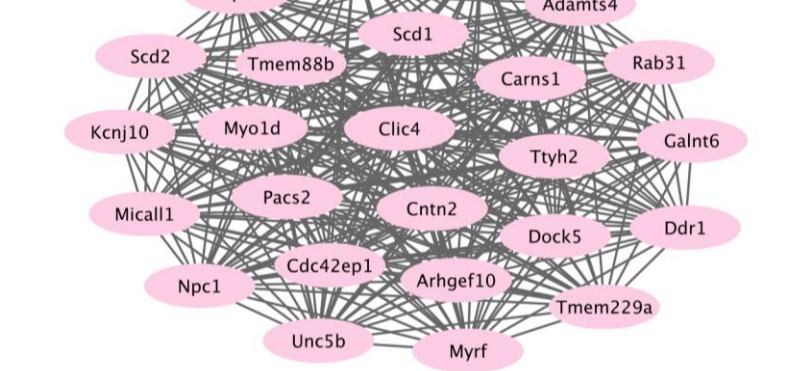


Figure 5 | Brain co-expression network analysis of early-stage AD mouse models. WGCNA 'pink' OLG enriched co-expression module. Top 25 most connected genes are shown.

3. Human snRNA-seq co-expression modules show overlapping dysregulation of genes in AD

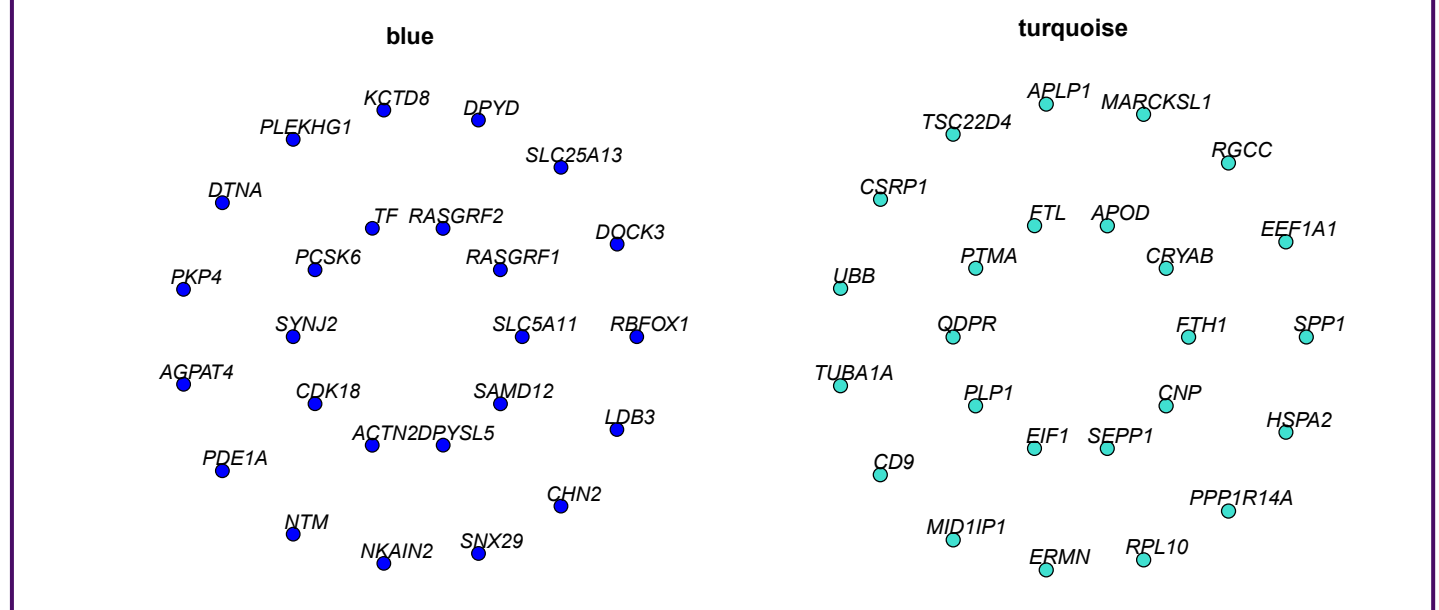


Figure 4 | Co-expression network analysis of human oligodendrocyte snRNAseq clusters.

- Using human brain snRNA-sequencing data from OLG clusters, we identified 2 co-expression modules that showed high correlation with at least one of the co-methylation modules: hd-turquoise and hd-blue.
- Both modules showed significant associations with pathological traits (e.g. amyloid, Braak stage and/or cognitive decline)
- This analysis also confirms cell-type specificity of AD DNA co-methylation signatures

CONCLUSIONS

- We identified an AD-associated DNA methylation signature enriched for OLGs, which was preserved across brain regions, and linked to altered OLG gene expression.
- Dysregulated signatures spanned multiple disease stages, suggesting early OLG alterations are consistent features of AD.
- Our findings implicate early OLG-specific DNA methylation changes as a potential initiating factor of AD pathogenesis.