

Spatial transcriptomic profiling reveals cluster-specific synaptic, lysosomal, and mitochondrial dysregulation in the Tg2576 mouse model of Alzheimer's disease

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Introduction

Alzheimer's disease (AD) remains the most common cause of dementia, with an estimated 7.2 million Americans aged 65 and older currently affected and prevalence projected to nearly double by 2060¹. The Tg2576 mouse, which overexpresses the Swedish-mutant (KM670/671NL) human APP695 transgene, develops elevated A β 40/A β 42, Congo red-positive amyloid plaques, and correlative memory impairment that emerge over the course of aging, making it one of the most widely used and well-characterized models for studying AD-relevant molecular and behavioral pathology². Despite decades of characterization at the histopathological and behavioral level, the region- and cell population-specific transcriptional programs that accompany amyloid pathology in this model remain incompletely mapped, limiting insight into which gene networks are most proximal to disease-relevant circuits such as the hippocampus and its cortical, thalamic, and hypothalamic connections.

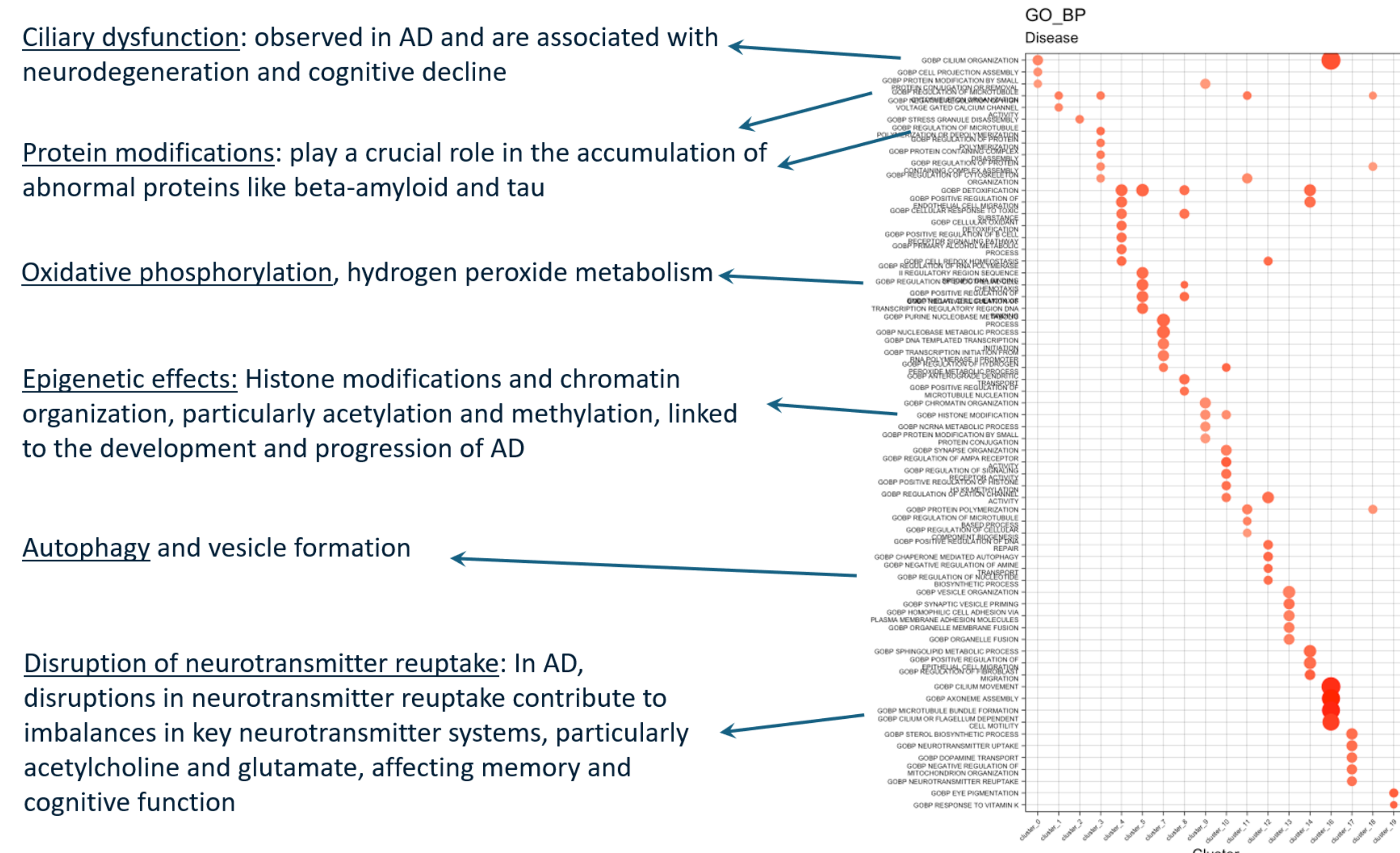
Spatial transcriptomics has recently emerged as a tool for resolving this gap, enabling transcriptome-wide profiling that preserves anatomical context and can reveal regionally restricted gene expression changes in neurodegenerative disease models that would be obscured by bulk or dissociated-tissue approaches³. Combining sequencing-based spatial platforms with complementary in situ imaging further allows disease-associated transcriptional signatures to be localized to specific cell populations and anatomical niches relevant to AD pathophysiology, including microglial, astrocytic, and neuronal compartments⁴.

Here, we applied spatial transcriptomics with cluster-stratified differential expression analysis to Tg2576 and wild-type mouse brain to localize disease-associated transcriptional changes across the dorsal hippocampus and surrounding cortical, thalamic, and hypothalamic regions, with the goal of identifying both established and novel candidate genes and pathways relevant to AD etiology and translational biomarker or target discovery.

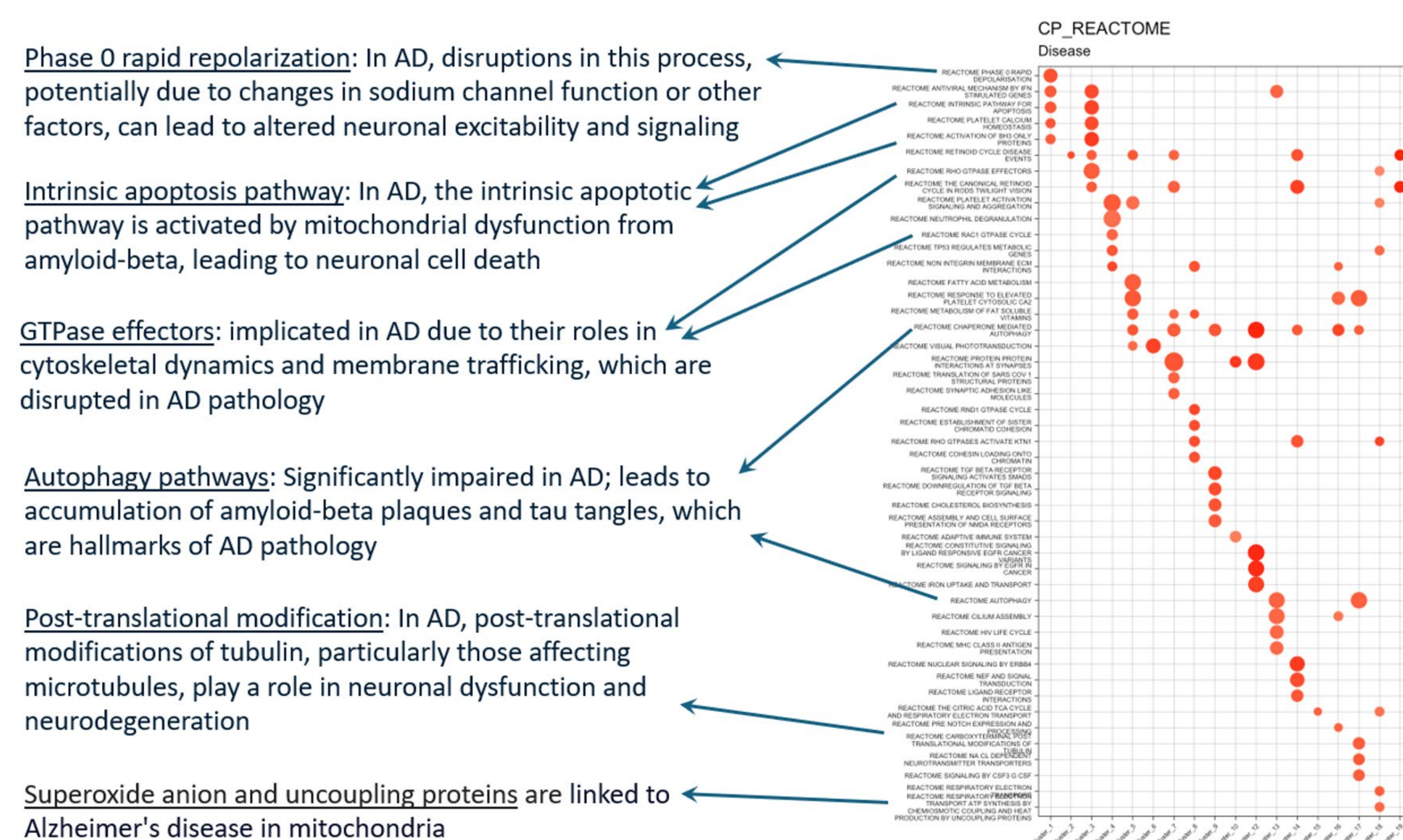
Methods

- Coronal brain sections were collected from 10-month-old wild type and Tg2576 mice (n = 1 each) at approximately bregma -2.2 mm, containing dorsal hippocampus, as well as cortical, thalamic, and hypothalamic brain regions.
- These brain sections were profiled on the 10X Genomics Visium VR platform with complementary Xenium in situ profiling and visualized on the Loupe Browser. Twenty transcriptional clusters were resolved across the integrated data set. Disease vs. control differential expression was computed within each cluster and ranked gene lists were analyzed by gene set enrichment analysis.

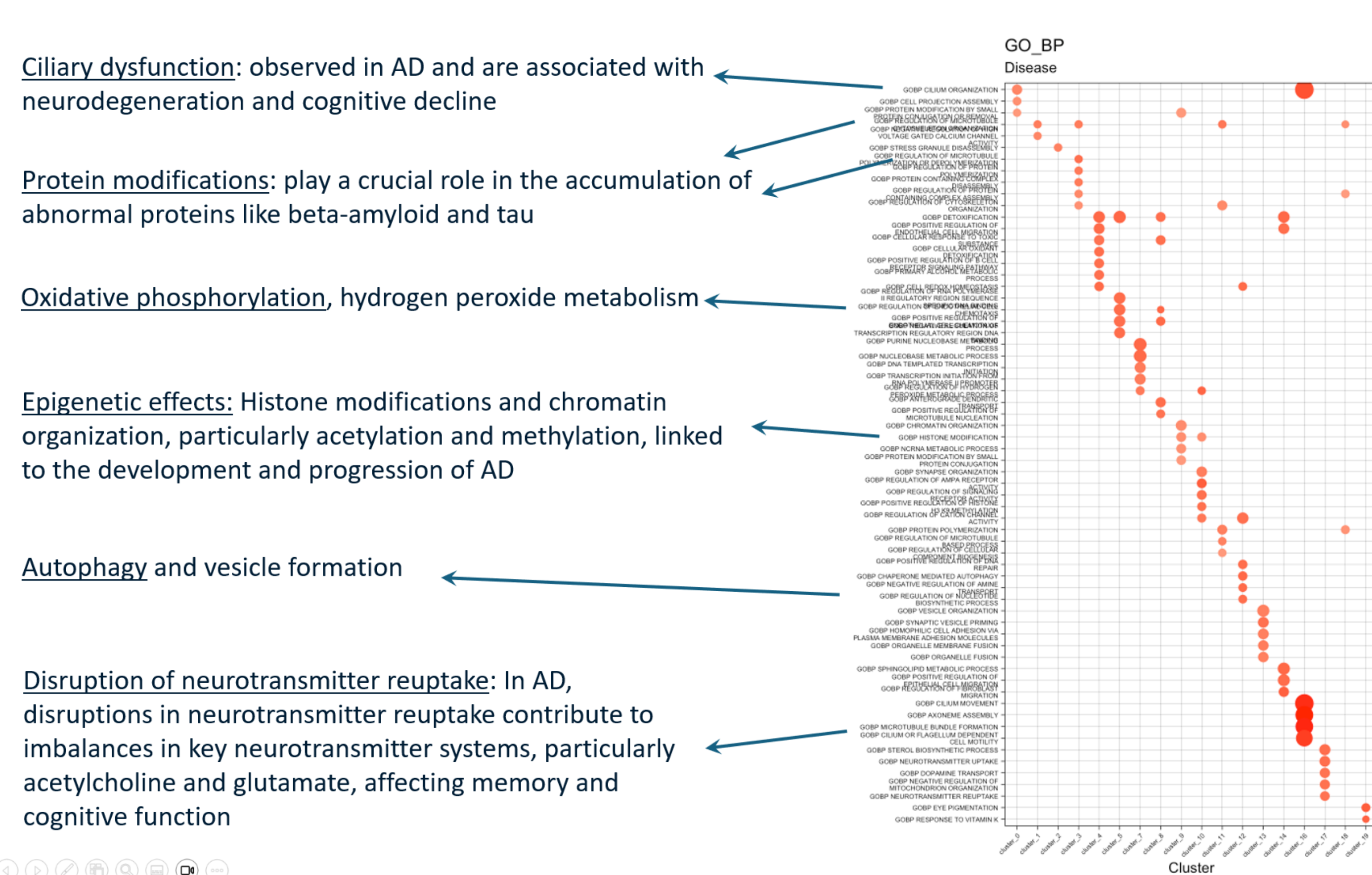
Genes enriched in AD mice: KEGG



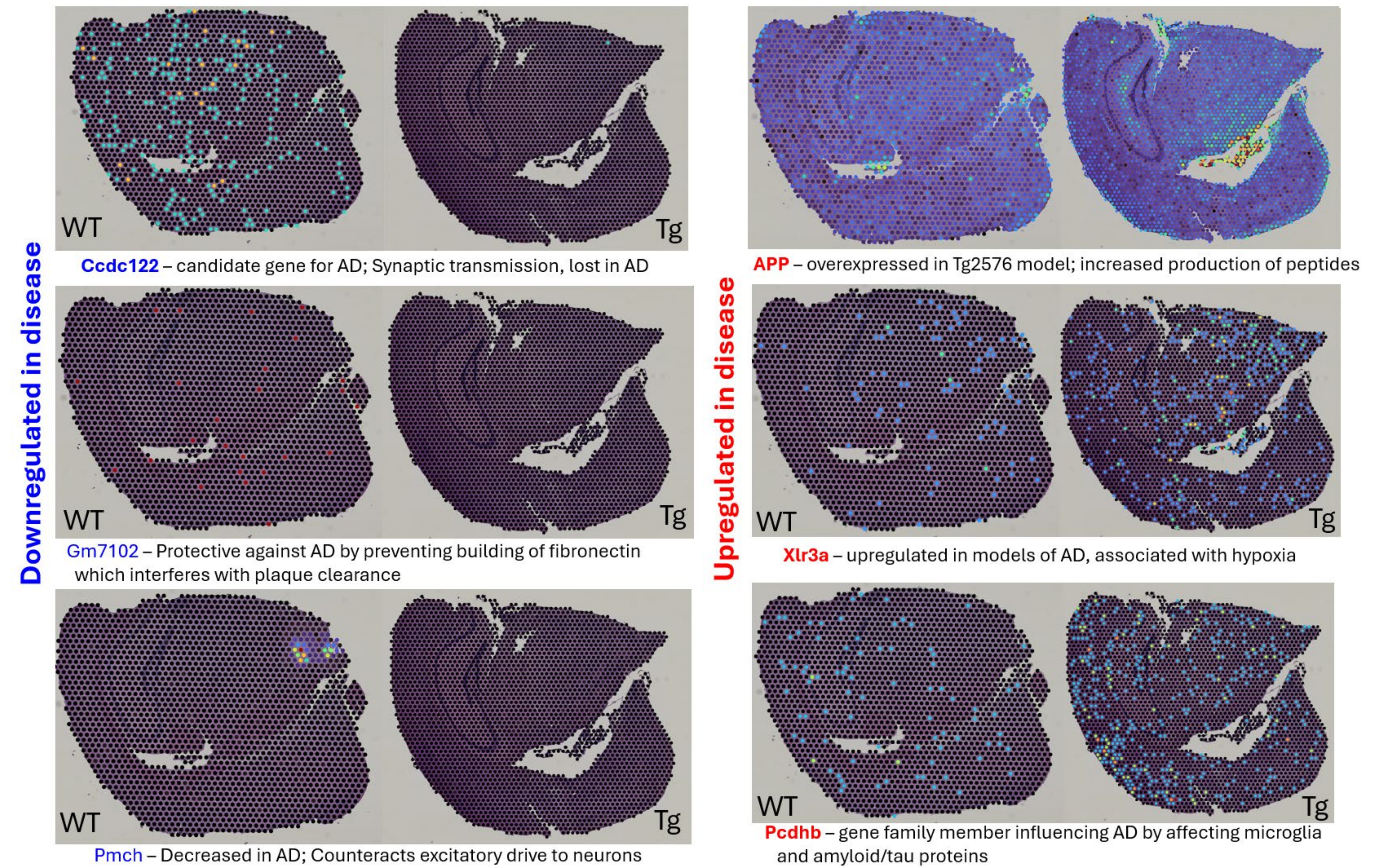
Genes enriched in AD mice: Reactome



Genes enriched in AD mice: GO BP



Examples of genes up/downregulated in AD



Summary

Cluster-stratified spatial transcriptomics revealed widespread, region-specific gene expression dysregulation in the hippocampus, cortex, thalamus, and hypothalamus of Tg2576 mice, encompassing 2,293 DEGs and pathways central to AD pathophysiology, including synaptic plasticity, lysosomal-autophagic and mitochondrial function, apoptosis, chromatin regulation, and neurotransmitter reuptake. Beyond confirming expected App upregulation, this approach identified Xlr3a, Pcdhb, Ccdc122, and Gm7102 as novel, spatially resolved candidates not previously linked to AD. These findings demonstrate the value of spatial transcriptomics for localizing disease-relevant transcriptional programs within anatomically and functionally distinct brain regions, and nominate new candidates with potential utility as early biomarkers or therapeutic targets warranting further validation in larger cohorts.

References

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- Zhou and Glass, 2025. Mol Neurodegener. 20:102.