

Oligomeric Amyloid β : Association With Dysfunctional Presynaptic Organelles And Visualization During Life With A Novel P.E.T Ligand

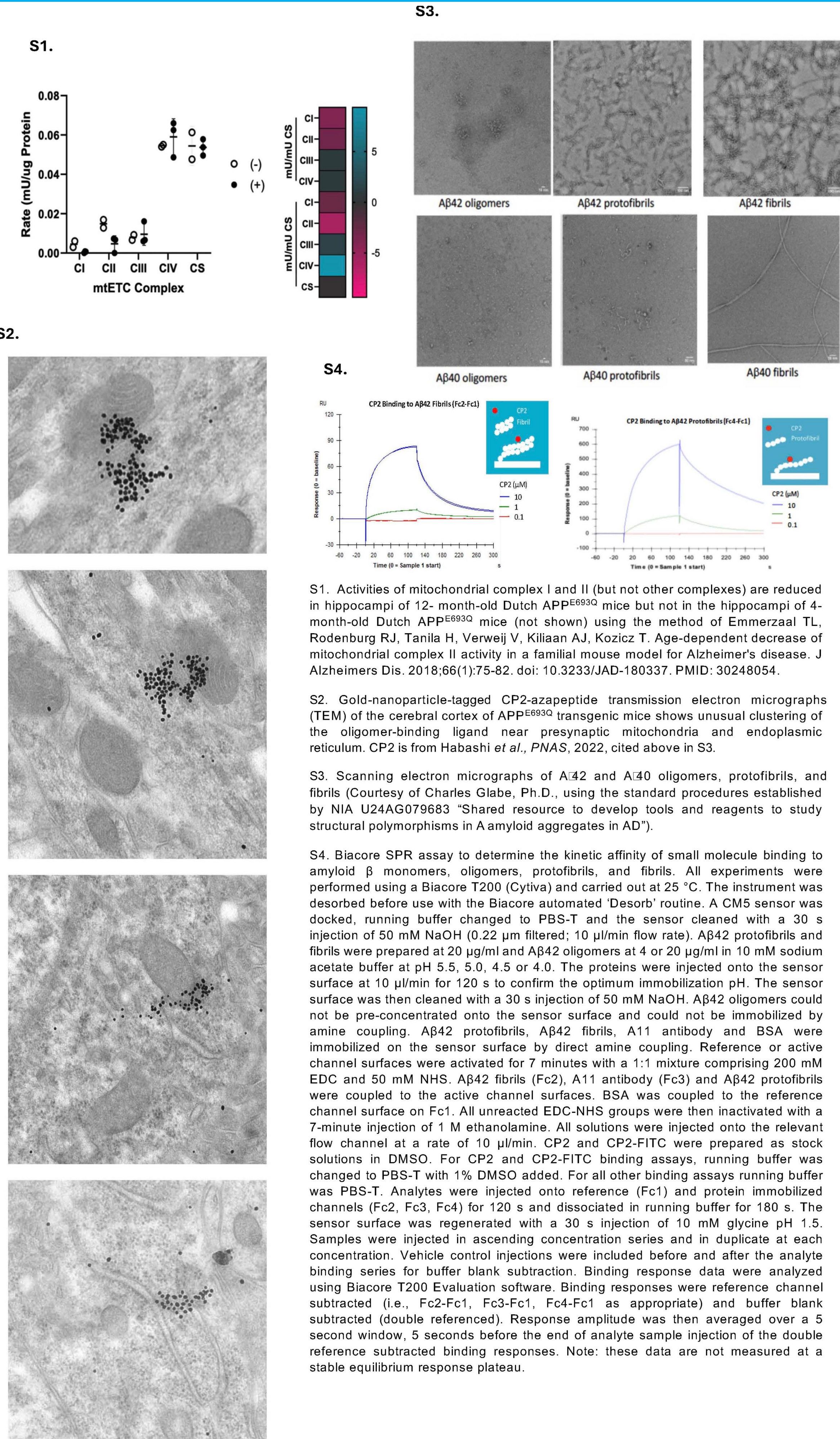
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BACKGROUND

Clinicopathological studies of Alzheimer's disease (AD) have demonstrated that synaptic loss and clinical cognitive decline do not reliably correlate with the burden of fibrillar amyloid. We created a transgenic mouse overexpressing Dutch mutant human amyloid precursor protein (*APPE693Q*) driven by the pan-neuronal Thy1 promoter¹. The Dutch mutation disrupts the formation of antiparallel β -sheets, thereby preventing fibril assembly and favoring the accumulation of nonfibrillar oligomeric A β (oA β). Levels of non-amyloidogenic APP α -CTFs are also elevated. The mice develop an impaired learning phenotype directly related to the brain levels of oA β ¹. The current multidisciplinary study argues against a major role for inflammation and implicates pathways of “protein translation”, “electron transport chain”, and “oxidative phosphorylation”, possibly pointing to dysfunction of endoplasmic reticulum-mitochondria crosstalk².

SUPPLEMENTAL PILOT DATA



CONCLUSIONS

1. Visible accumulation of endogenously generated nonfibrillar Dutch mutant A β oligomers is associated with presynaptic deficits and morphological and transcriptomic changes in mitochondria and the endoplasmic reticulum.
2. Pilot data suggest mitochondrial dysfunction in Dutch *APPE693Q* mice and localization of CP2 NFA ligand to endoplasmic reticulum, mitochondria, and to juxta-mitochondrial structures.
3. CP2 ligand binds differentially to various aggregation states of A β 42 (fibrils vs. protofibrils).

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2. Hedskog L, *et al.* Modulation of the ER-mitochondria interface in Alzheimer's disease models. *PNAS* 110, 7916-21 (2013).
3. Habashi M, *et al.* Early diagnosis and treatment of Alzheimer's by targeting toxic soluble A β oligomers. *PNAS* 119, e2210766119 (2022).
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RESULTS

Figure 1. Anti-prefibrillar oligomer antibody A11 and cyclic azapeptide probe CP2-FITC co-stain similar intracellular structures in CA1 of 24 mo Dutch APP mice that never form fibrils or plaques.

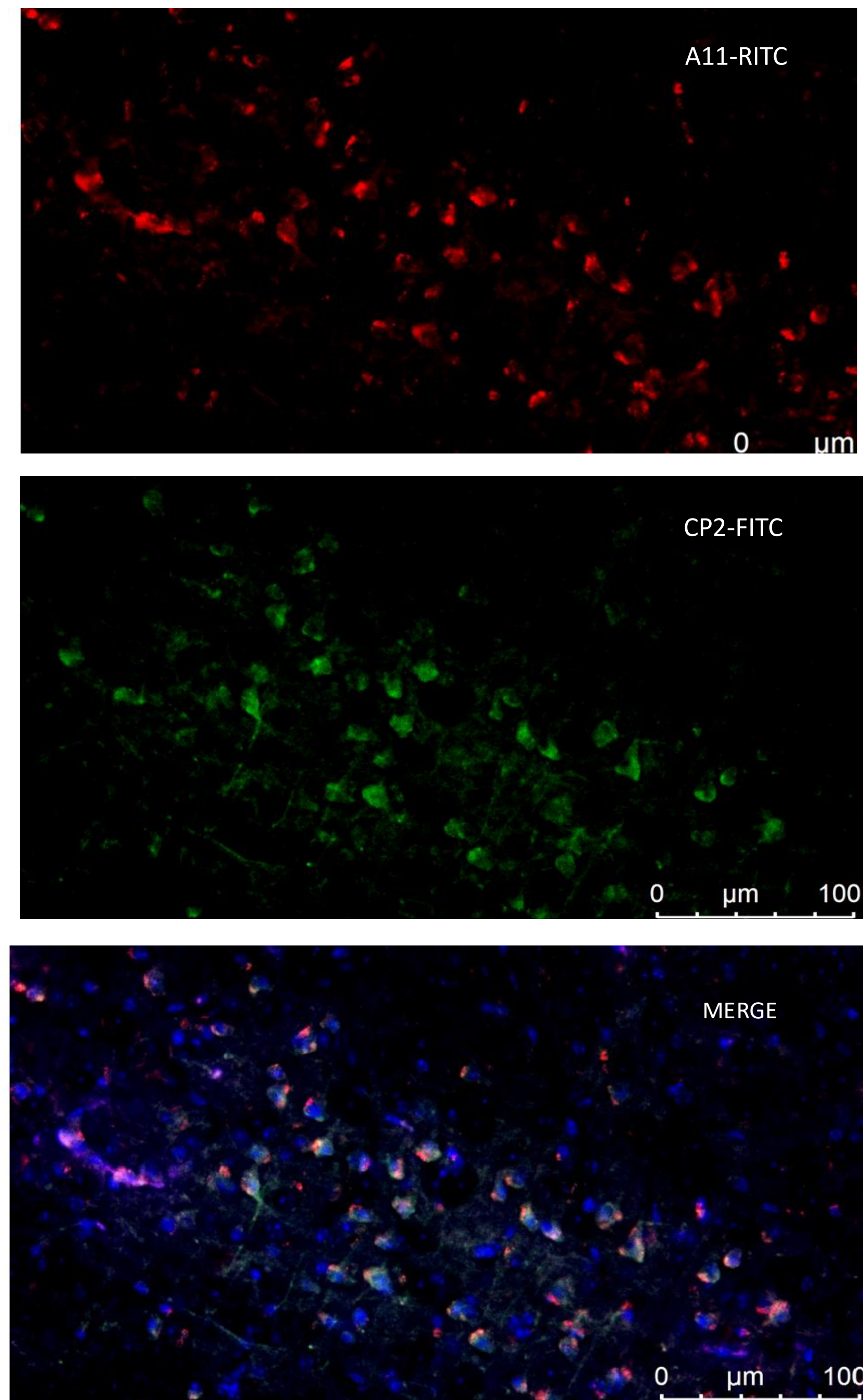


Figure 2. Dutch APP mice do not exhibit impairment in basal synaptic transmission or LTP, but do show impairment in certain measurements of short-term synaptic plasticity.

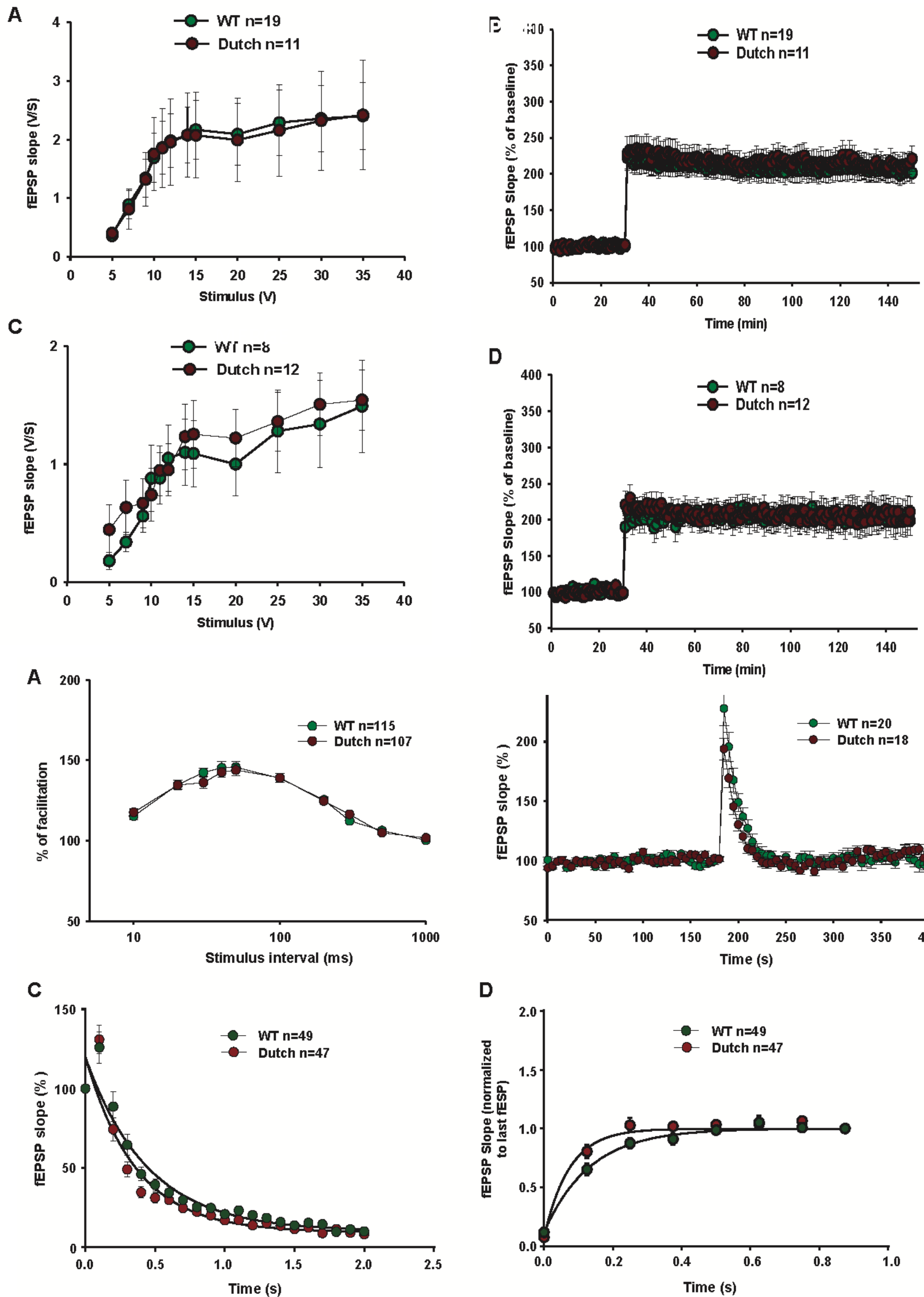


Figure 3. Single cell RNAseq identifies 14 cell clusters in Dutch and wildtype mice

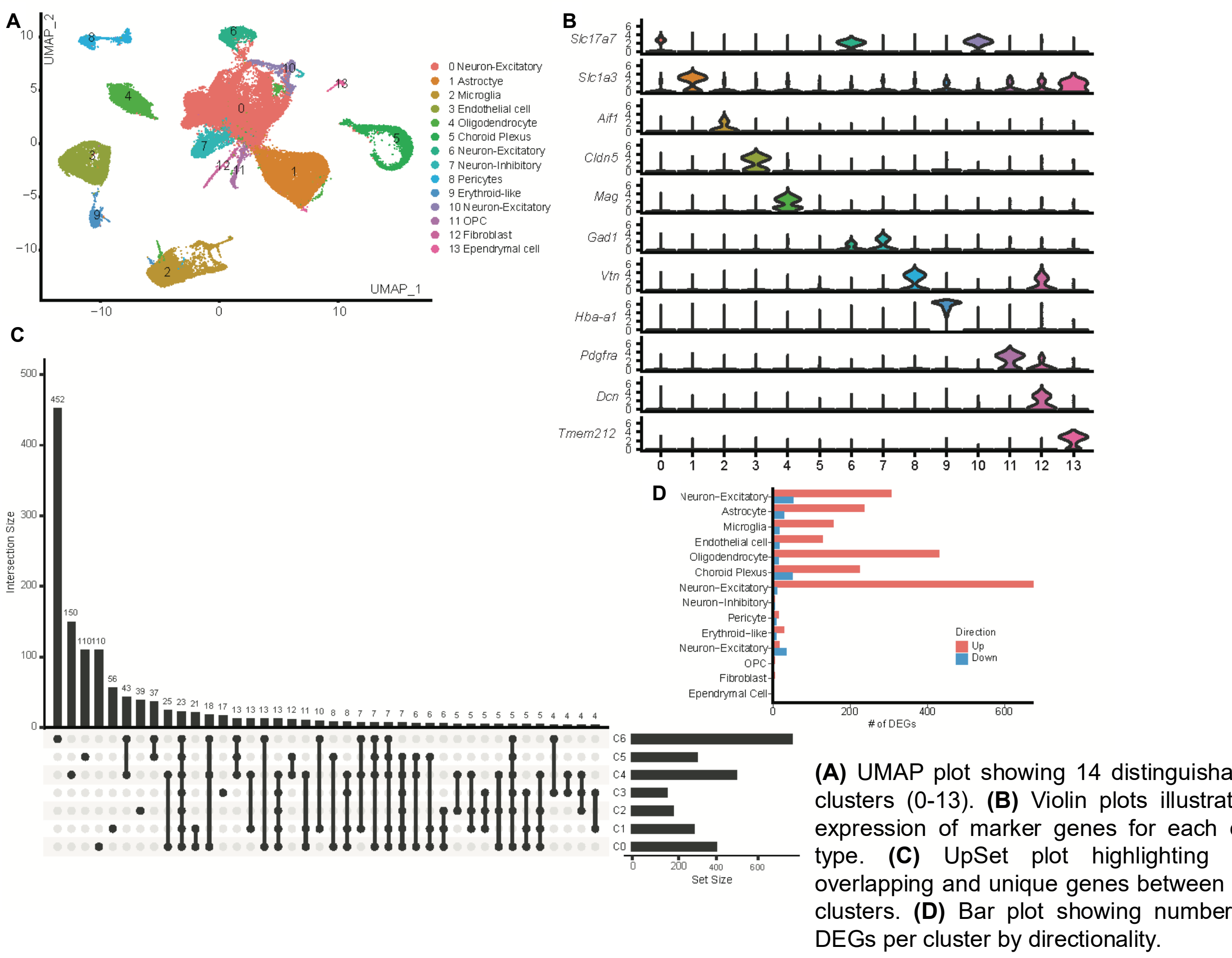


Figure 4. Overlapping transcriptomic profiles highlight multiple processes impacted in various cell types (e.g., protein translation, mitochondria).

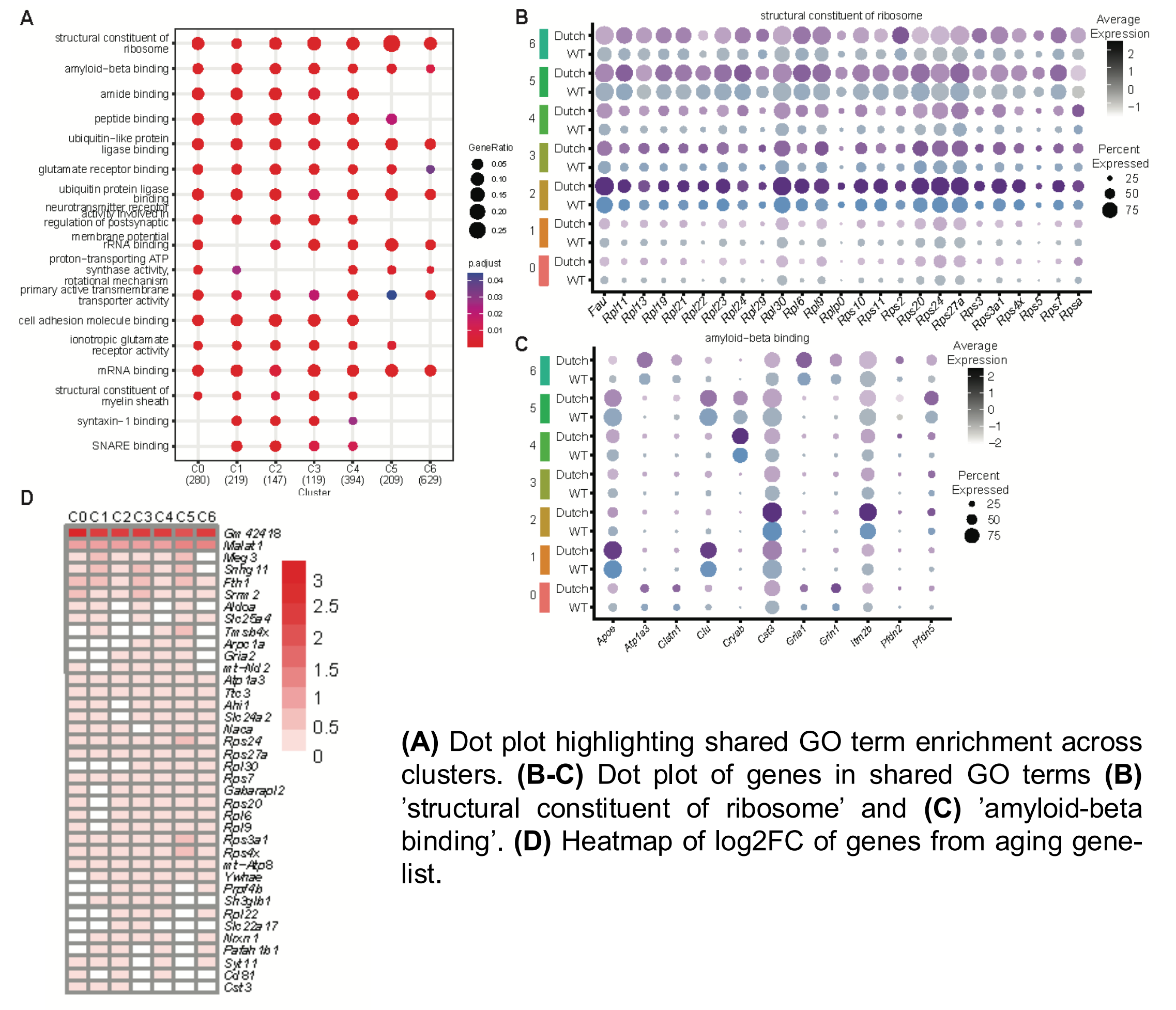


Figure 5. Microglia transcriptomic profiles are similar between Dutch and wildtype mice.

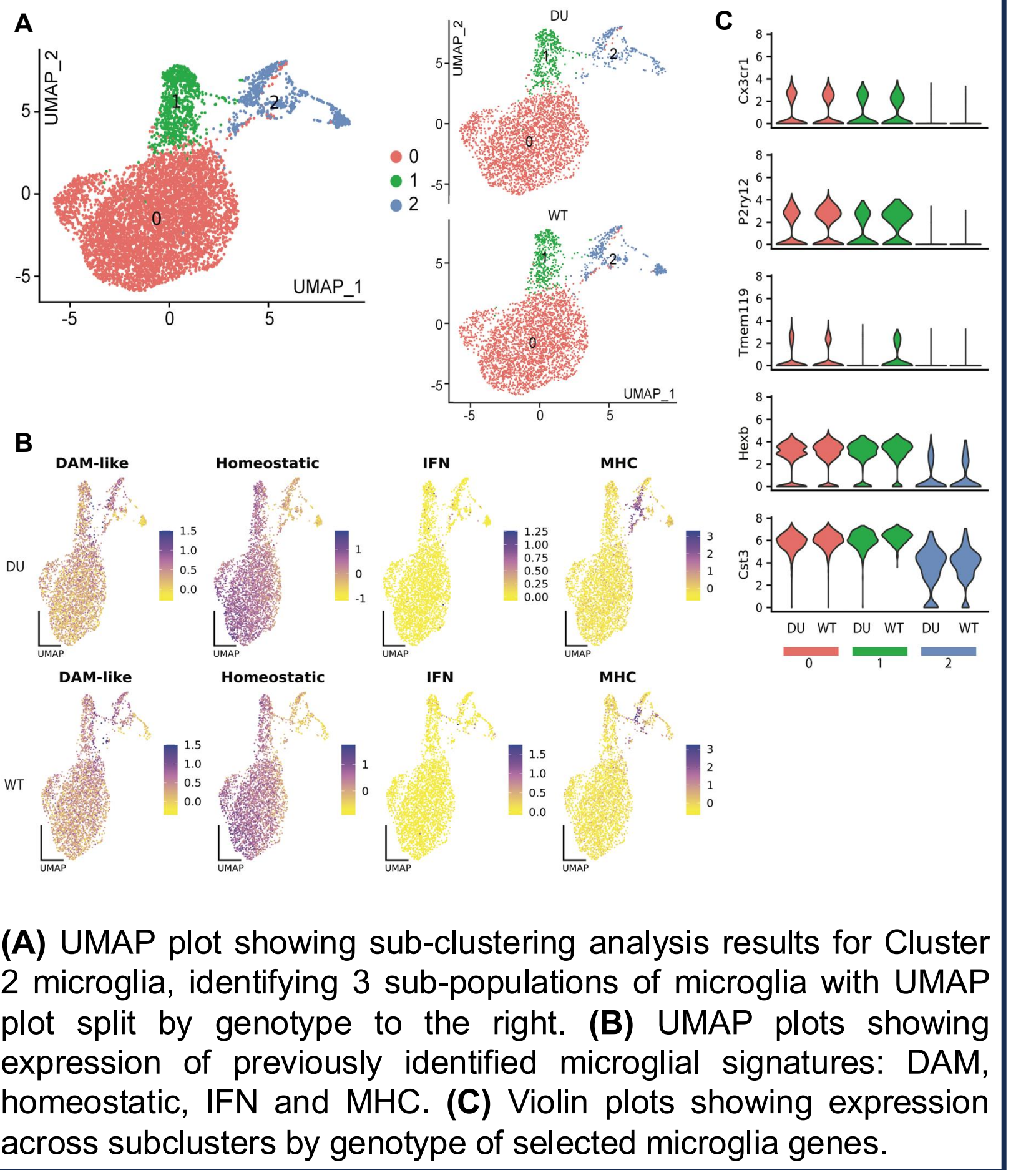


Figure 6. [⁶⁴Cu]-NOTA conjugated CP-X reveals A β O in the thalamus and cortex of 5XFAD mice (Habashi *et al.*, 2022)

