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MOLECULAR AND CELL BIOLOGY

Single-nucleus transcriptomics and deep learning uncover alternative polyadenylation dysregulation in frontotemporal lobar degeneration and amyotrophic lateral sclerosis

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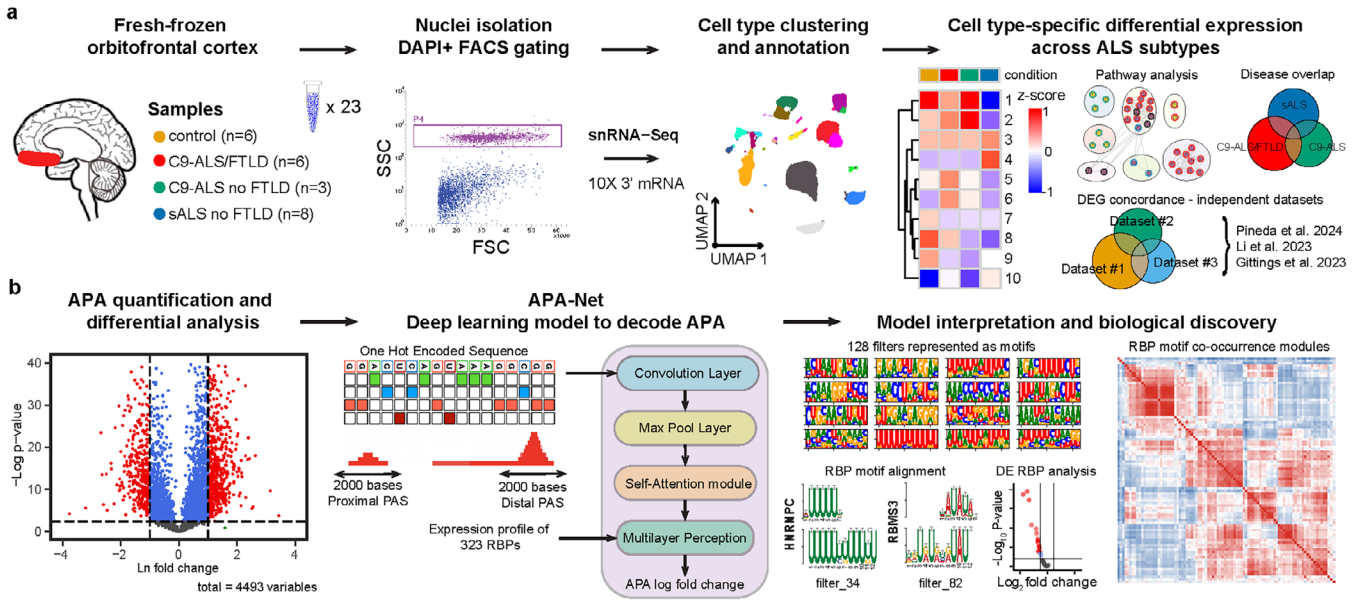
Abstract

Background: Frontotemporal lobar degeneration (FTLD) is a leading cause of dementia, often co-occurring with amyotrophic lateral sclerosis (ALS). Despite shared genetic and pathological features, the cell type-specific molecular mechanisms underlying FTLD in ALS remain poorly understood.

Method: Excitatory neurons exhibited synaptic dysfunction in ALS with and without FTLD, while inhibitory neurons were more affected in ALS without FTLD. Microglia displayed a disease-associated state in both groups, with ALS with FTLD showing elevated JAK-STAT signaling, indicative of a proinflammatory phenotype. We identified widespread shifts toward distal 3'UTR usage in ALS with and without FTLD, implicating APA dysregulation. APA-Net revealed coordinated RBP interactions, including TDP-43, HNRNPA1, and MBNL1, as key regulators of APA in ALS with and without FTLD. These findings highlight distinct and overlapping molecular signatures between the two disease subtypes.

Result: We identified cell type-specific transcriptional dysregulation, with excitatory neurons showing synaptic dysfunction in both C9-ALS and sALS, while inhibitory neurons were more affected in sALS. Microglia exhibited a disease-associated state, with C9-ALS microglia showing elevated JAK-STAT signaling, indicative of a proinflammatory phenotype. We detected widespread shifts toward distal 3'UTR usage in ALS/FTLD, implicating APA dysregulation. APA-Net revealed coordinated RBP interactions, including TDP-43, HNRNPA1, and MBNL1, as key regulators of APA in ALS/FTLD. These findings highlight distinct and overlapping molecular signatures in C9-ALS and sALS, with implications for FTLD pathogenesis.

Conclusion: This study provides a comprehensive single-nucleus transcriptomic atlas of the frontal cortex in ALS with and without FTLD, uncovering cell type-specific dysregulation of APA and RBP interactions. Our findings offer new insights into the molecular mechanisms driving FTLD and provide a resource for future therapeutic development.


a
Fresh-frozen orbitofrontal cortex
Nuclei isolation DAPI+ FACS gating
Cell type clustering and annotation
Cell type-specific differential expression across ALS subtypes
Samples
control (n=6)
C9-ALS/FTLD (n=6)
C9-ALS no FTLD (n=3)
sALS no FTLD (n=8)
x 23
SSC
FSC
snRNA−Seq
10X 3' mRNA
UMAP 2
UMAP 1
condition
z-score
Pathway analysis
Disease overlap
sALS
C9-ALS/FTLD
C9-ALS
DEG concordance - independent datasets
Dataset #1
Dataset #2
Dataset #3
Pineda et al. 2024
Li et al. 2023
Gittings et al. 2023
b
APA quantification and differential analysis
APA-Net
Deep learning model to decode APA
Model interpretation and biological discovery
−Log p−value
Ln fold change
total = 4493 variables
One Hot Encoded Sequence
2000 bases Proximal PAS
2000 bases Distal PAS
Expression profile of 323 RBPs
Convolution Layer
Max Pool Layer
Self-Attention module
Multilayer Perception
APA log fold change
128 filters represented as motifs
RBP motif alignment
DE RBP analysis
HNRNPC
RBM53
filter_34
filter_82
−Log10 P-value
Log2 fold change
RBP motif co-occurrence modules