

News Release

New Molecular Mechanisms of Dopaminergic Dysfunction and RNA Dysregulation Identified in Progressive Supranuclear Palsy

— Multi-omics and Long-read Sequencing Reveal New Insights into Disease Pathogenesis —

Key Points

- Multi-omics and behavioral analyses of filamin-A-transgenic (FLNA-Tg) mice revealed AP-1-associated transcriptional dysregulation, altered dopamine metabolism, and age-dependent motor and cognitive impairments.
- Dopaminergic alterations included reduced cortical dopamine levels and an age-dependent shift in striatal dopamine D2 receptor (D2DR) expression, from early elevation to later decline.
- Human progressive supranuclear palsy (PSP) brain analyses, using long-read RNA sequencing and single-nucleus ATAC-seq data reanalysis, revealed AP-1-associated chromatin alterations and increased non-canonical RNA isoforms, alongside reduced D2DR expression.

Summary

A research team led by Associate Professor Koyo Tsujikawa (first author and co-corresponding author) of the Center for Human Disease Genomics and Medical Science, Research Institute of Environmental Medicine, Nagoya University; Associate Professor Kentaro Sahashi (co-corresponding author) and Professor Masahisa Katsuno of the Department of Neurology, Nagoya University Graduate School of Medicine; and Professor Tomoo Ogi of the Department of Genetics, Research Institute of Environmental Medicine, Nagoya University, in collaboration with Professor Yasushi Iwasaki and Assistant Professor Yuichi Riku of Institute for Medical Science of Aging, Aichi Medical University, has identified novel molecular alterations associated with PSP.

PSP is a rare neurodegenerative disorder characterized by abnormal tau accumulation, causing motor and cognitive impairments. No disease-modifying treatment is currently available. In 2022, the research team demonstrated that filamin-A promotes tau aggregation (Tsujikawa et al., *Science Advances*, 2022).

In this study, multi-omics and behavioral analyses of FLNA-Tg mice revealed AP-1-associated transcriptional dysregulation, reduced cortical dopamine levels, and age-dependent changes in striatal D2DR expression accompanied by motor and cognitive impairments. Analyses of postmortem PSP brains revealed reduced D2DR expression and AP-1-associated chromatin alterations.

Long-read RNA sequencing (Iso-Seq) further identified increased non-canonical RNA isoforms, including transcripts with intron retention.

These findings link filamin-A-associated cytoskeletal alterations to transcriptional and dopaminergic dysfunction and identify additional RNA-processing abnormalities in human PSP, providing new insights into disease mechanisms beyond tau aggregation.

The findings were published in *Brain* at 10:00 a.m. JST on October 19, 2026.

Research Background

PSP is a neurodegenerative disorder characterized by abnormal accumulation of tau protein in the brain, resulting in gait instability, frequent falls, cognitive impairment, and other neurological symptoms. Although PSP shares several clinical features with Parkinson's disease, its response to dopamine replacement therapy is generally limited, and no disease-modifying treatment has been established.

In 2022, the research team demonstrated that filamin-A (FLNA), an actin-binding cytoskeletal protein, promotes abnormal tau aggregation and contributes to PSP pathology (Tsujikawa et al., *Science Advances*, 2022). However, how FLNA-associated abnormalities contribute to neuronal dysfunction beyond tau aggregation remained unclear.

To address this question, the researchers performed integrated multi-omics analyses, including RNA-seq, ATAC-seq, and metabolomic profiling, together with automated behavioral analyses in FLNA-Tg mice. They further investigated postmortem brain tissues from patients with PSP using biochemical analyses, long-read RNA sequencing, and reanalysis of publicly available single-nucleus ATAC-seq datasets to characterize dopaminergic, transcriptional, and RNA-processing abnormalities in human disease.

Research Results

1. FLNA overexpression is associated with transcriptional dysregulation

RNA-seq and ATAC-seq analyses of young FLNA-Tg mice revealed increased expression of immediate early genes, including c-Fos and Junb, and dysregulation of transcriptional networks associated with AP-1. Alterations in chromatin accessibility were also observed, particularly in genomic regions enriched for AP-1-related transcription factor binding motifs.

In cultured cells expressing FLNA, pharmacological inhibition of Rho-associated protein kinase (ROCK), a regulator of cytoskeletal tension, reduced nuclear c-Fos expression. These findings support a functional association between FLNA-dependent cytoskeletal alterations and

transcriptional regulation.

2. FLNA overexpression is associated with abnormalities in dopamine metabolism and signaling

Metabolomic profiling revealed reduced dopamine levels and decreased abundance of its metabolite 3-methoxytyramine in the cerebral cortex of FLNA-Tg mice. In contrast, no significant differences were detected in the dopamine precursors tyrosine and L-DOPA, suggesting altered dopamine metabolism.

In young FLNA-Tg mice, striatal D2DR protein levels were increased, whereas the midbrain showed reductions in tyrosine hydroxylase (TH) and aromatic L-amino acid decarboxylase (AADC), two enzymes involved in dopamine synthesis.

These findings indicate that FLNA overexpression is associated with region-specific alterations in dopamine metabolism and receptor-related signaling across the cortex, striatum, and midbrain.

3. Age-dependent changes in D2DR expression are accompanied by behavioral impairments

Striatal D2DR expression, which was elevated in young FLNA-Tg mice, declined markedly in aged FLNA-Tg mice. The positive correlation between D2DR and c-Fos expression observed in young mice was also lost with aging. RNA-seq further identified age-associated alterations in gene networks related to learning, memory, and cognition.

Automated behavioral analyses demonstrated reduced locomotor activity and movement velocity, impaired novel object recognition, and decreased social interaction in aged FLNA-Tg mice.

Together, these findings suggest that FLNA-associated molecular alterations are linked to age-dependent changes in dopaminergic regulation and impairments in motor and cognitive functions.

4. Human PSP brains reveal dopaminergic, transcriptional, and RNA-processing abnormalities

To investigate whether the molecular abnormalities identified in FLNA-Tg mice were relevant to human PSP, the researchers analyzed postmortem brain tissues from patients with PSP.

D2DR expression was reduced in both the cerebral cortex and striatum of PSP patients. In contrast, c-Fos showed region-dependent changes, with relatively increased expression in the cortex and reduced expression in the striatum.

Reanalysis of publicly available single-nucleus ATAC-seq datasets from human frontal cortex revealed marked changes in chromatin accessibility in excitatory neurons, particularly layer 2/3 intratelencephalic (IT) neurons. Genomic regions with reduced accessibility were enriched for AP-1-related transcription factor binding motifs. These findings suggest that AP-1-associated transcriptional dysregulation is a shared molecular feature of FLNA-Tg mice and human PSP brains, although its manifestations differ across brain regions.

To further characterize RNA abnormalities, Iso-Seq was performed on postmortem frontal cortex samples from patients with PSP. Among genes associated with neuronal populations showing chromatin accessibility alterations, increased proportions of non-canonical RNA isoforms were identified, including transcripts with novel splicing patterns and intron retention.

Together, these findings indicate that AP-1-associated transcriptional dysregulation and dopaminergic abnormalities observed in FLNA-Tg mice have partial, region-dependent counterparts in human PSP brains. Furthermore, long-read transcriptomic analysis revealed RNA-processing abnormalities, extending the molecular characterization of PSP beyond gene expression changes.

Research Summary and Future Perspective

This study identified FLNA-associated abnormalities in transcriptional regulation and dopaminergic function, together with alterations in RNA processing in postmortem brains from patients with PSP. These findings extend the current understanding of PSP pathogenesis beyond the abnormal aggregation of tau protein.

The research team will continue to investigate the molecular mechanisms underlying PSP using advanced multi-omics approaches, long-read sequencing, and integrated genomic and transcriptomic analyses to further elucidate the molecular basis of this neurodegenerative disorder.

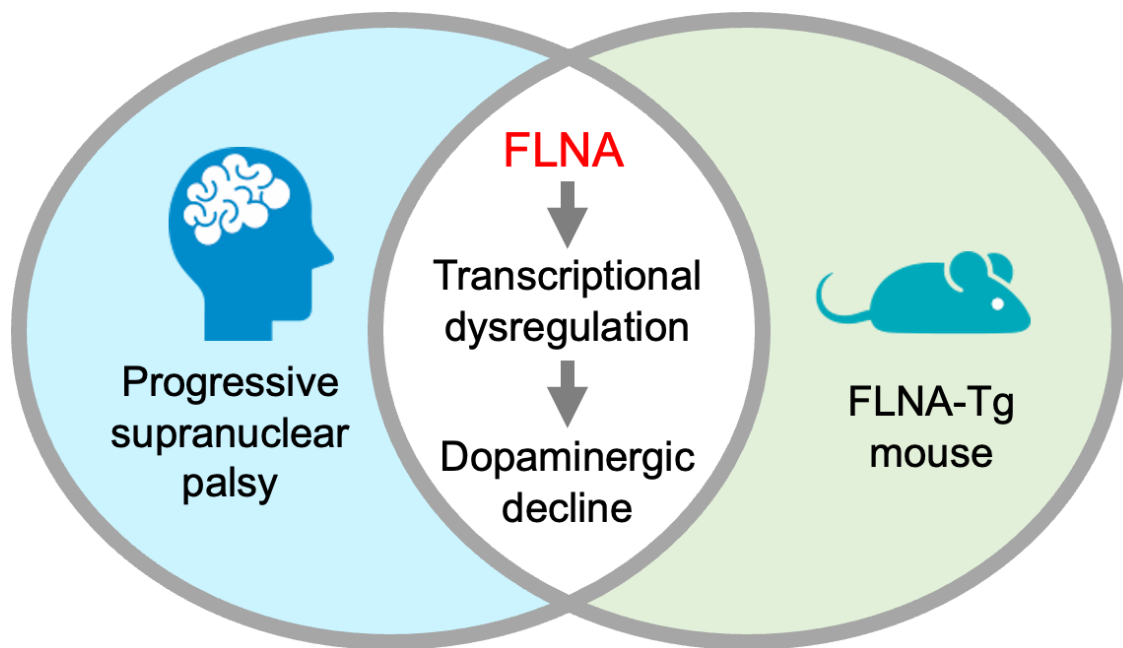


Figure 1. Shared molecular alterations in patients with progressive supranuclear palsy and FLNA-transgenic (FLNA-Tg) mice

Analyses of postmortem brains from patients with progressive supranuclear palsy (PSP) and FLNA-Tg mice revealed common features of AP-1-associated transcriptional dysregulation and dopaminergic dysfunction. These findings suggest that filamin-A-associated cytoskeletal alterations may contribute to neuronal dysfunction beyond their previously identified role in tau aggregation.

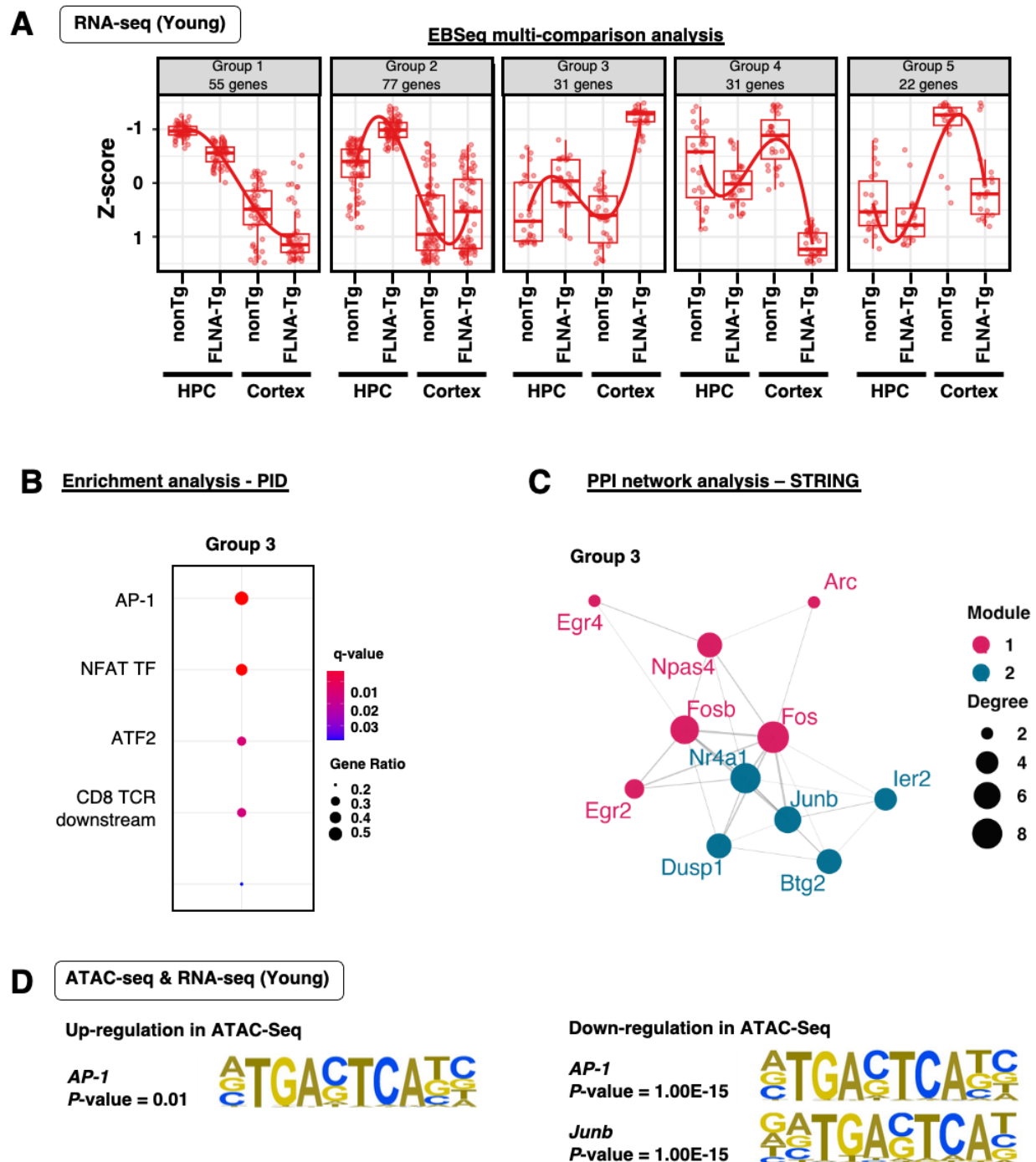


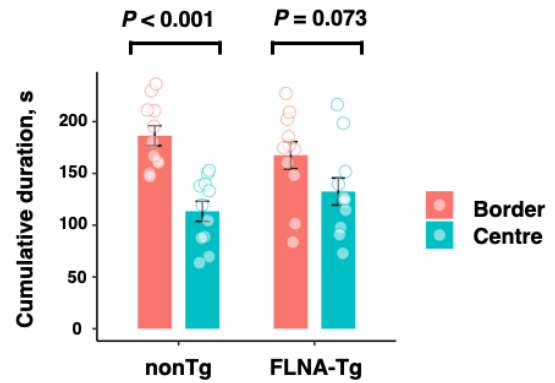
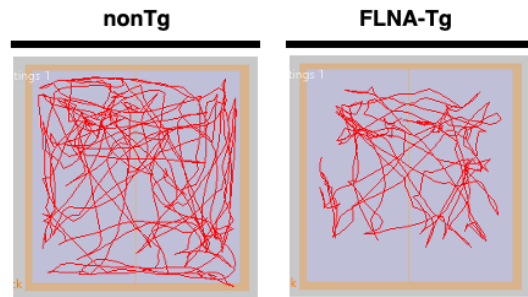
Figure 2. Transcriptional dysregulation in the brains of FLNA-Tg mice

(A) Differentially expressed genes identified by RNA-seq were classified into five groups based on their expression patterns in the cerebral cortex and hippocampus of FLNA-Tg and control mice. (B) Group 3 genes showed significant enrichment of AP-1 signaling pathways associated with neuronal activity and transcriptional regulation. (C) Protein-protein interaction network analysis identified a network centered on immediate early genes, including *c-Fos* and *Junb*. (D) ATAC-seq analysis revealed enrichment of AP-1-related

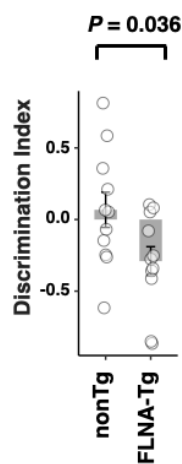
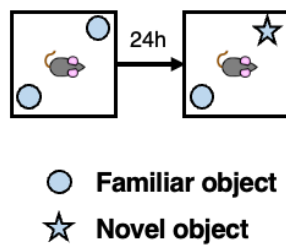
transcription factor binding motifs in regions with altered chromatin accessibility. Together, these findings indicate that FLNA overexpression is associated with AP-1-related transcriptional dysregulation.

A Behaviour (Aged)

Open field test



B Novel object recognition test



C Social interaction test

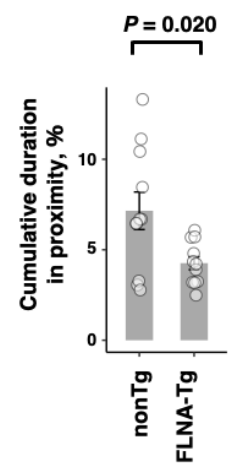
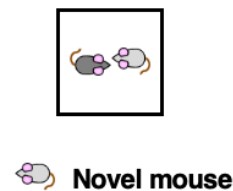


Figure 3. Age-associated behavioral abnormalities in FLNA-Tg mice

(A) Open-field testing revealed reduced locomotor activity and a diminished preference for peripheral areas in FLNA-Tg mice compared with control mice. (B) In the novel object recognition test, FLNA-Tg mice showed a reduced discrimination index for novel objects, indicating impaired recognition memory. (C) Social interaction testing revealed that FLNA-Tg mice spent less time in close proximity to other mice, indicating altered social behavior. Together, these findings suggest that FLNA overexpression is associated with age-dependent impairments in locomotor activity, object recognition, and social interaction.

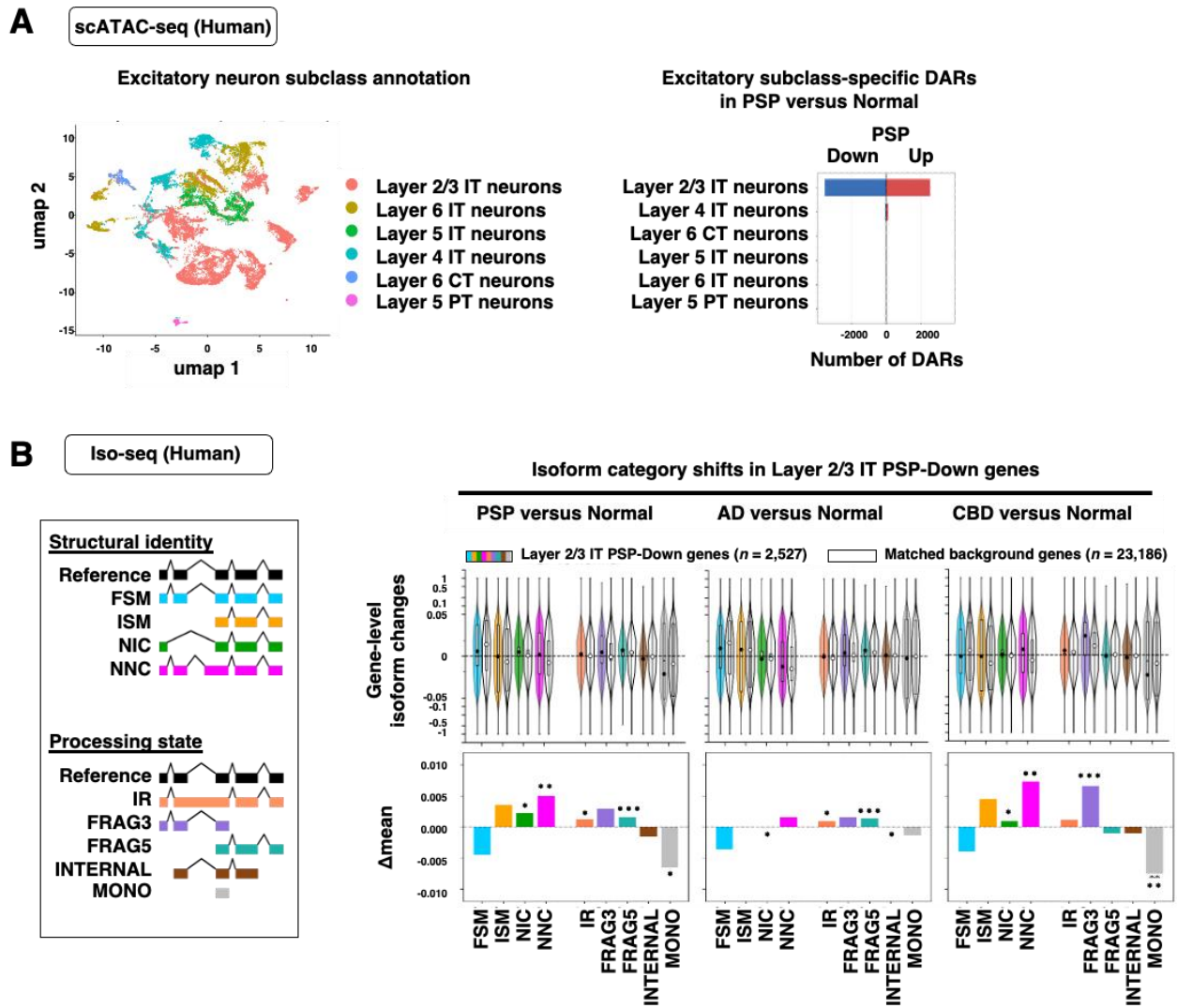


Figure 4. Transcriptional and RNA-processing abnormalities in postmortem PSP brains

(A) Reanalysis of publicly available single-nucleus ATAC-seq data visualized brain cell populations using uniform manifold approximation and projection (UMAP). In PSP, marked chromatin accessibility alterations were observed in cortical excitatory neurons, particularly layer 2/3 neurons. Regions with reduced accessibility were enriched for AP-1-related transcription factor binding motifs. (B) Long-read RNA sequencing (Iso-Seq) of postmortem PSP brains revealed increased proportions of RNA transcripts with non-canonical splicing patterns and intron retention. These alterations showed partial similarities to those observed in corticobasal degeneration (CBD), a related tauopathy, but differed from those in Alzheimer's disease (AD). Together, these findings demonstrate abnormalities in both transcriptional regulation and RNA processing in PSP brains.

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