Global Upregulation of the Neuronal Retinoblastoma Binding Protein 7 (Rbbp7) Reduces Tau Pathogenesis in the PS19 mouse Model of Tauopathies

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STEP-UP Short-Term Research Experience Program to Unlock Potential

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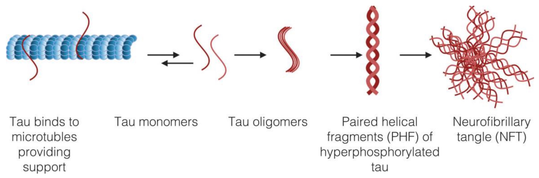
Introduction

Alzheimer's disease (AD), is the most prevalent neurodegenerative disorder worldwide, clinically characterized by impairments in cognition, memory, and intellectual disabilities. The accumulation of amyloid-β plaques and neurofibrillary tau tangles are the common pathologies in AD .



- Epigenetic dysregulation is a major contributor to AD development.
- The **Retinoblastoma Binding Protein 7 (Rbbp7)** is a histone-binding subunit of the Nucleosome Remodeling and Deacetylase (NuRD) complex, that chaperones chromatin remodeling proteins to their nuclear histone substrates, including histone acetylases and deacetylases.
- Rbbp7 shuttles histone acetyltransferases to the nucleus, such as p300.
- Tau, which exists only in the cytoplasm, can be acetylated by acetyltransferases such as p300 when present in cytoplasm.
- Notably, Rbbp7 protein levels are significantly reduced in human AD post-mortem brain tissue at early and late stages of AD, suggesting that p300 may remain in the cytoplasm, acetylating tau, contributing to pathogenesis.
- Previously, we found that Rbbp7 levels are reduced in CA1 of the hippocampus of PS19 mice.

Rbbp7 levels are reduced in human post-mortem brain tissue

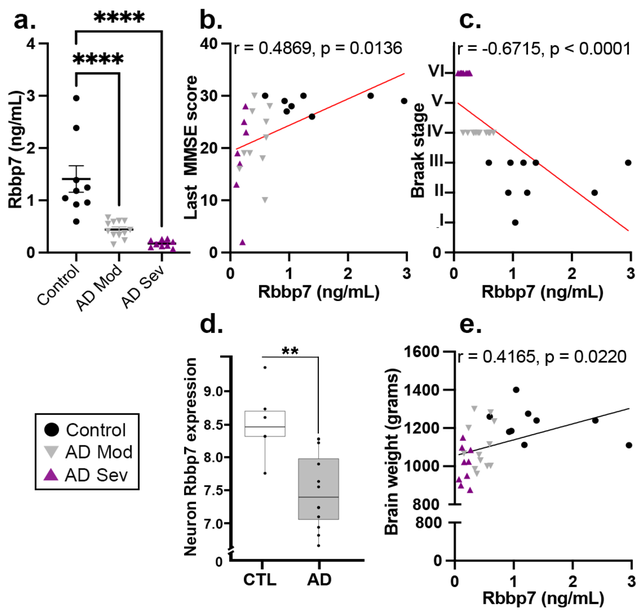
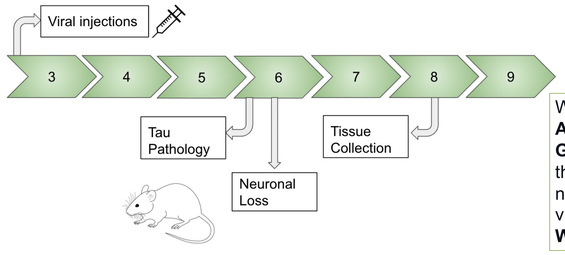


Figure 1. (a) Frontal cortical Rbbp7 protein levels are significantly reduced in AD moderate (AD Mod; moderate neuritic plaque density and Braak = IV; n=12) and severe (AD Sev; frequent neuritic plaque density and Braak = VI; n =10) cases compared to non-demented Controls (n=9). **(b-c)** Rbbp7 levels positively correlate with MMSE and negatively correlate with Braak stage. **(d)** AD cases show neuron specific down-regulation of Rbbp7 in the middle temporal gyrus. **(e)** Rbbp7 levels positively correlate with brain weight. ****p < 0.0001, **p < 0.1.

Methods

Hypothesis: Global upregulation of neuronal Rbbp7 will reduce tau hyperphosphorylation and protect against neuronal loss in PS19 mice.



Genotype	AAV-GFP	AAV-Rbbp7
NonTg	4	4
PS19	4	4
Animals were balanced for sex.		

We retro-orbitally injected either an **AAV/PHP.eB-CamKII(0.4)-mRbbp7-T2A-GFP-WPRE (AAV-Rbbp7)**, which crosses the blood-brain-barrier, to overexpress neuronal Rbbp7 or a control virus, **AAV/PHP.eB-CamKII(0.4)-GFP-WPRE (AAV-GFP).**

- Immunohistochemistry was performed using the NeuN antibody (dilution of 1:10,000).
- MBF unbiased stereological analysis was employed by a single investigator who was blinded to the groups to assess neuronal number in CA1 of the hippocampus. We sampled every sixth section from the mice brains for a total of about 6 slices per sample. The Gunderson score remained below 0.1.

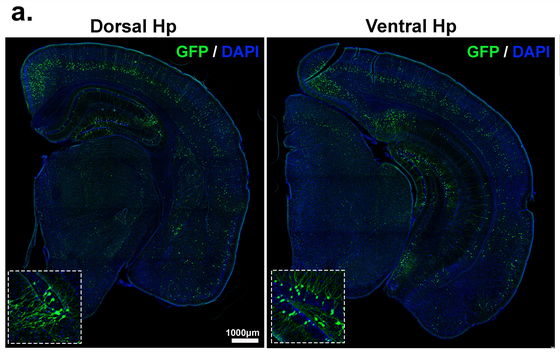


Figure 2. (a) Photomicrographs depicting the spread of AAV with the GFP reporter. **(b, c)** PS19 mice exhibit lower Rbbp7 levels than NonTg mice in the hippocampus and cortex. A main effect of virus, reveals that the **AAV-Rbbp7** significantly elevated hippocampal and cortical Rbbp7 in both the NonTg and PS19 mice. ****p < 0.0001.

Neuronal Rbbp7 overexpression reduces tau hyperphosphorylation

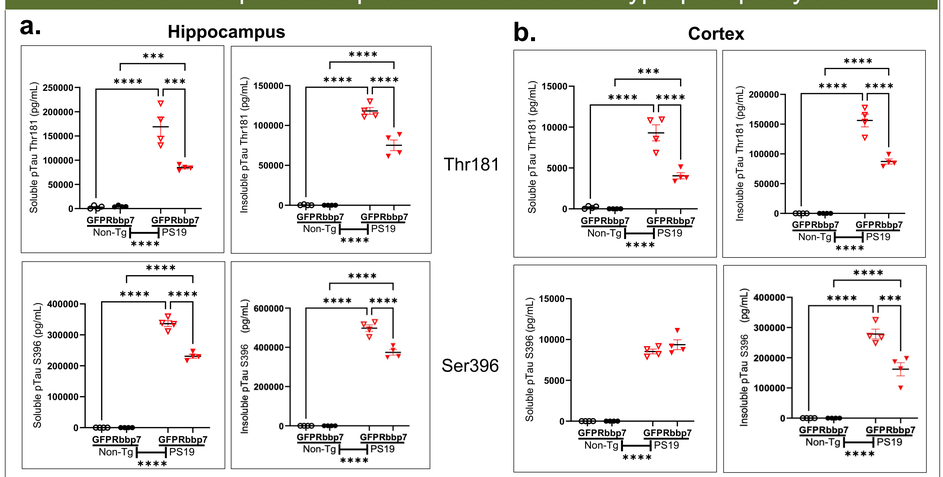


Figure 3. (a, b) Soluble and insoluble phosphorylated tau (ptau) at Threonine (Thr) 181 and Serine (S) 396 in the hippocampus and cortex were significantly higher in PS19 mice compared to NonTgs. Neuronal upregulation of Rbbp7 significantly reduced both fractions of pTau at Thr181 and S396 in the hippocampus. In the cortex, neuronal upregulation of Rbbp7 significantly reduced soluble and insoluble fractions of pTau epitopes except for soluble pTau at S396. ****p < 0.0001, ***p < 0.001.

Results continued

Neural Cell Counts

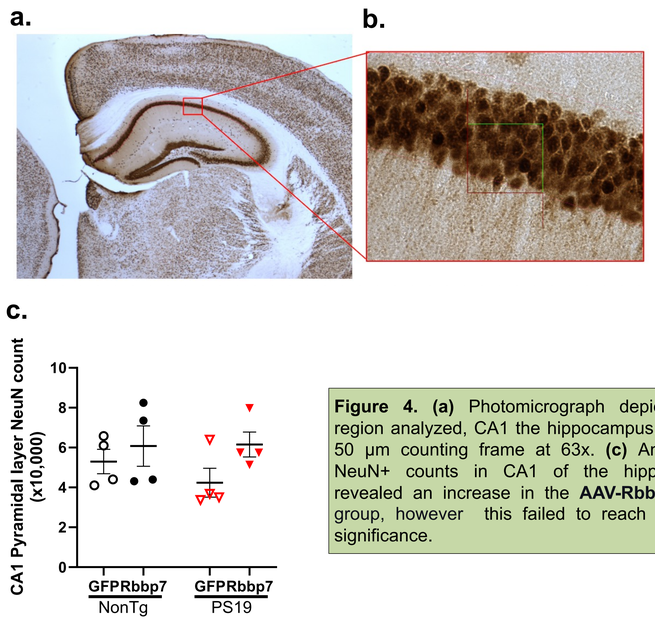


Figure 4. (a) Photomicrograph depicting the region analyzed, CA1 the hippocampus. **(b)** 50 x 50 μm counting frame at 63x. **(c)** Analysis of NeuN+ counts in CA1 of the hippocampus revealed an increase in the **AAV-Rbbp7** PS19 group, however this failed to reach statistical significance.

Conclusions

Rbbp7 protein levels were found to be significantly reduced in post-mortem brain tissue of AD Mod and AD Sev cases compared to healthy age-matched controls.

Global upregulation of neuronal Rbbp7 ameliorated tau pathology in multiple brain regions of PS19 mice.

Our data reveals a pattern of increased neuron number in PS19 mice with Rbbp7 upregulation, however this did not reach statistical significance.

Notably, there was much variability in our count data. We will further determine whether this was due to underpower.

Collectively, these data identify a role of Rbbp7 protecting against tau-related pathologies, highlighting its potential as a therapeutic target in AD and related tauopathies.

Acknowledgements

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