

Altered Polyubiquitin Positioning Modifies Tau Filament Architecture

Translational
Neuropathology
Research Laboratory



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Key Takeaways:

- 1. AD and VT polyubiquitinated tau filaments show distinct *in vivo* seeding patterns in WT mice and cryo-EM core structures.
- 2. Chemical modulation with ubistatin B repositions poorly structured, polyubiquitin-associated densities adjacent to the tau core.
- 3. Ubistatin B treatment leads to protofilament interface shifting and additional VT tau filament conformers.

INTRODUCTION

RESULTS

CONCLUSIONS

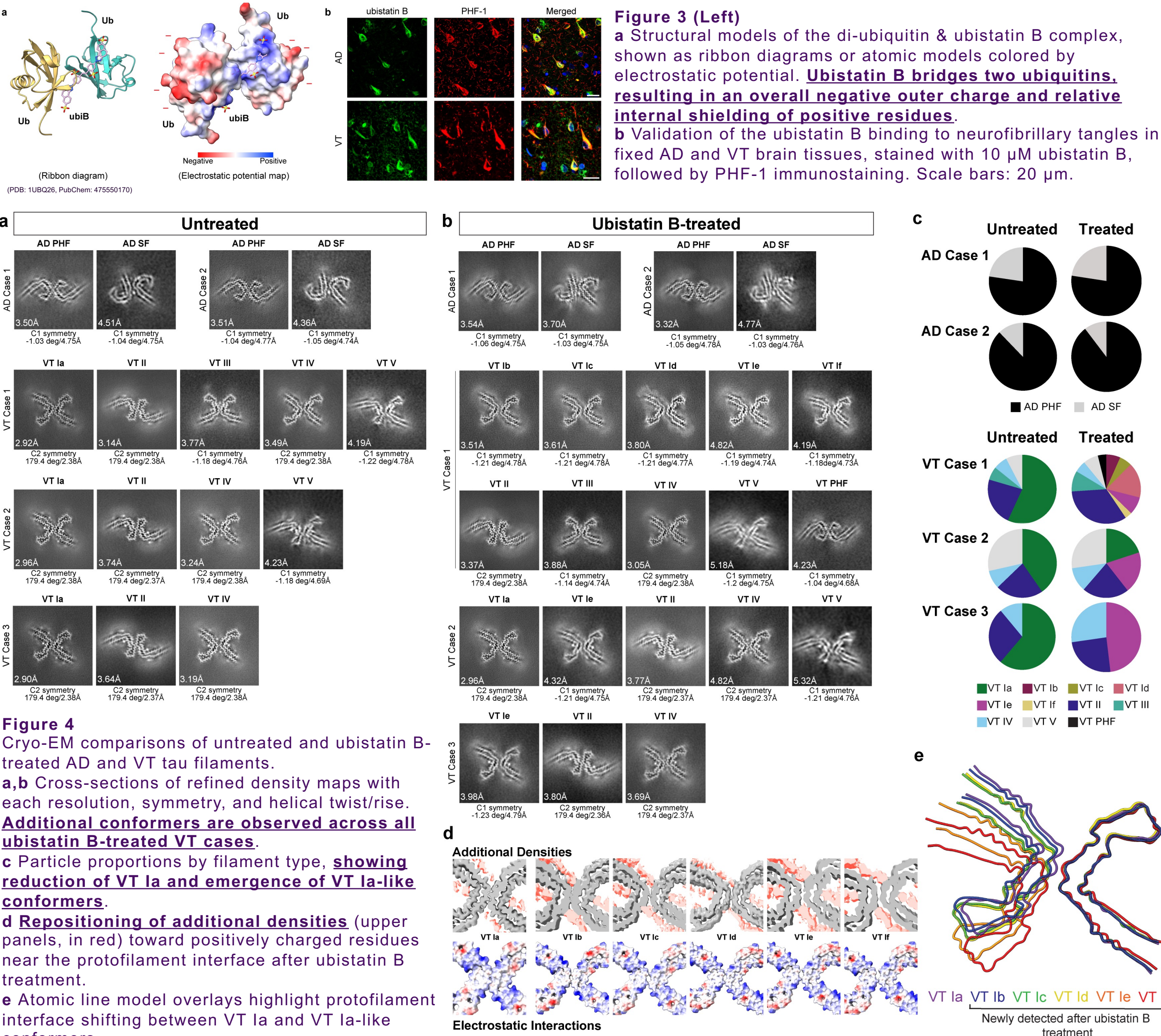
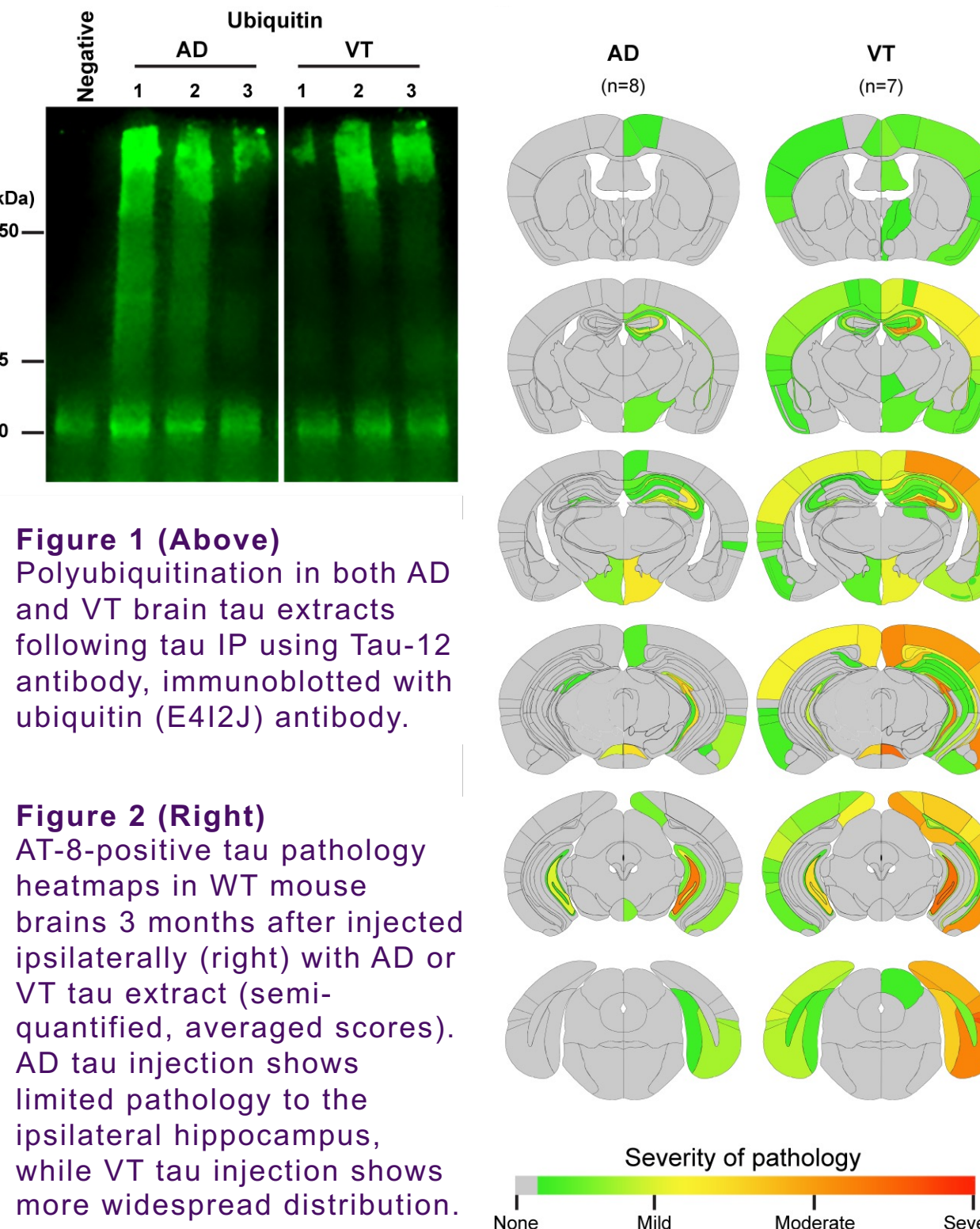
- Tauopathies are characterized by structurally heterogeneous tau filaments. **Factors outside the ordered core may influence filament stability.**
- We compared the *in vivo* activity and ultrastructures of polyubiquitinated tau filaments from Alzheimer’s disease (AD) and vacuolar tauopathy (VT) cases.
- We tested whether **chemical modulation of polyubiquitin** near the tau core alters filament architecture.

METHODS

- Pathologic tau filaments were extracted from AD (n=2) and VT (n=3) neocortex.
- AD and VT tau extracts were injected into WT mouse brains (AD, n=8; VT, n=7).
- Tau filament ultrastructure was determined by cryo-EM.
- **Tau filaments were treated with ubistatin B** to modulate polyubiquitin near the core and treated vs. untreated filament structures were compared.

Table 1. Demographic information of AD and VT cases

	AD Case 1	AD Case 2	VT Case 1	VT Case 2	VT Case 3
Age at Death	60s	50s	60s	50s	50s
Brain weight (g)	1,005	1,146	938	1,215	1,090
PMI (hrs)	4	14	17.5	24	9
Braak stage (Tau)	6	6	N/A	N/A	N/A
ADNC A score (Aβ)	3	3	0	1	0



- The ultrastructure of tau filaments associated with different seeding activities *in vivo* can be influenced by post-translational modifications.
- Polyubiquitin positioning around the tau core may contribute to stabilization of specific filament types through protofilament interfaces.

[References]
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