

# Association Between Postmortem Pathologic Burden and the Rate of Clinical Progression in Patients with Frontotemporal Lobar Degeneration

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### Background and Objectives

Histopathologic staging of Alzheimer's<sup>1</sup> has led to validation of imaging techniques that guide treatment.<sup>2</sup> Here, we expand on prior attempts to construct similar stages in frontotemporal dementia<sup>3-5</sup> to more comprehensively model the relationship between clinical progression and the distribution and severity of postmortem FTLT pathologic.

### Methods

We selected n=101 autopsy cases from the Penn Integrated Neurodegenerative Disease Database<sup>6</sup> with more than 1 clinical assessment and neuropathologic diagnosis of FTLT-Tau or FTLT-TDP (Table 2).<sup>7-8</sup> We quantified grey matter pathologic burden from up to six cortical regions across hemispheres using validated methods.<sup>9</sup> FTLT-TDP phase was assessed based on published criteria using diagnostic pathology data.<sup>10</sup> In linear mixed models (LME), we associated burden and (1) disease duration or (2) rate of clinic progression (measured per CDR-SB and MMSE separately). Models were adjusted for hemisphere sampled, sex, age at onset, pathogenic variant status, and pathologic subtype.

### Discussion and Conclusions

Disease duration correlated with mean TDP (rho = -0.3, p = 0.04) but not tau burden (Fig 1). However, this association did not persist in adjusted LME (FTLT-TDP β=0.01 [-0.06,0.09]; p=0.7; FTLT-Tau β=0.1 [-0.4,0.7]; p=0.7). In contrast, mean TDP-43 burden but not tau burden associated with decline in CDR-SB (β = 0.1, [0.06, 0.2]) and MMSE (β = -0.1, [-0.2, -0.04]) among all patients and in sensitivity analysis with behavioral variant FTD (Fig 2, Table 1). TDP phase (IV vs. III) also associated with worse relative decline in CDR-SB (β = 0.09 [0.04, 0.1]) and MMSE (β = -0.2 [-0.3, -0.2]) among all patients. Higher TDP-43 burden associated with antemortem clinical decline rather than disease duration. These human data suggest that the temporal dynamics of aggregation may differ among FTLT proteinopathies, with implications for the interpretation of FTLT-Tau and FTLT-TDP specific biomarkers as these are developed.

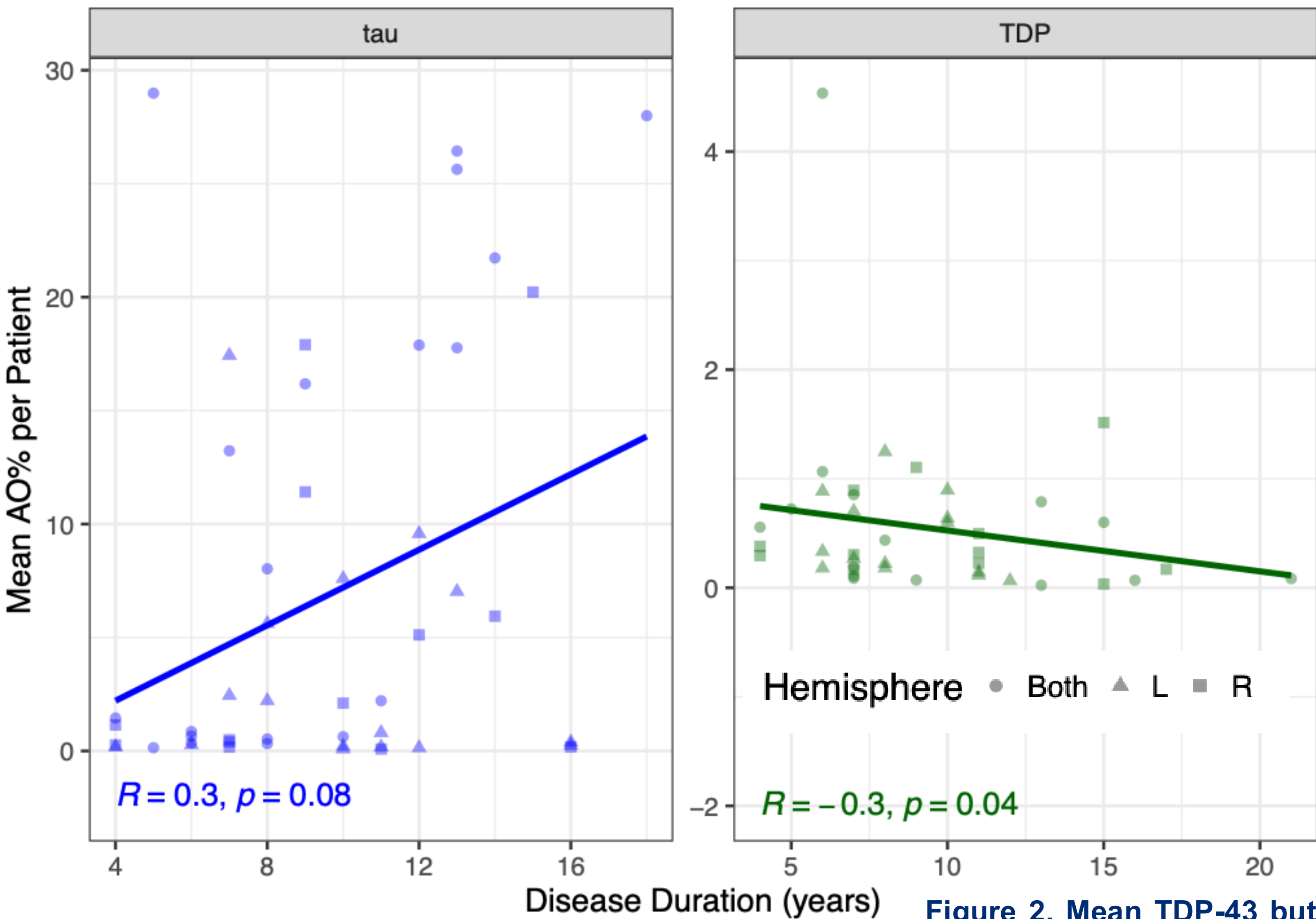


**Figure 1. Mean grey matter tau but not TDP-43 quantitative pathologic burden (%AO) at autopsy correlates with disease duration.** Scatterplots of the mean %AO for tau (blue) and TDP-43 (green) (y-axis) are shown as a function of duration from symptom onset until death in years (x-axis). Hemisphere sampled is represented by shape (L = triangle, R = square, both = circle). Spearman correlations and lines of best fit are plotted.

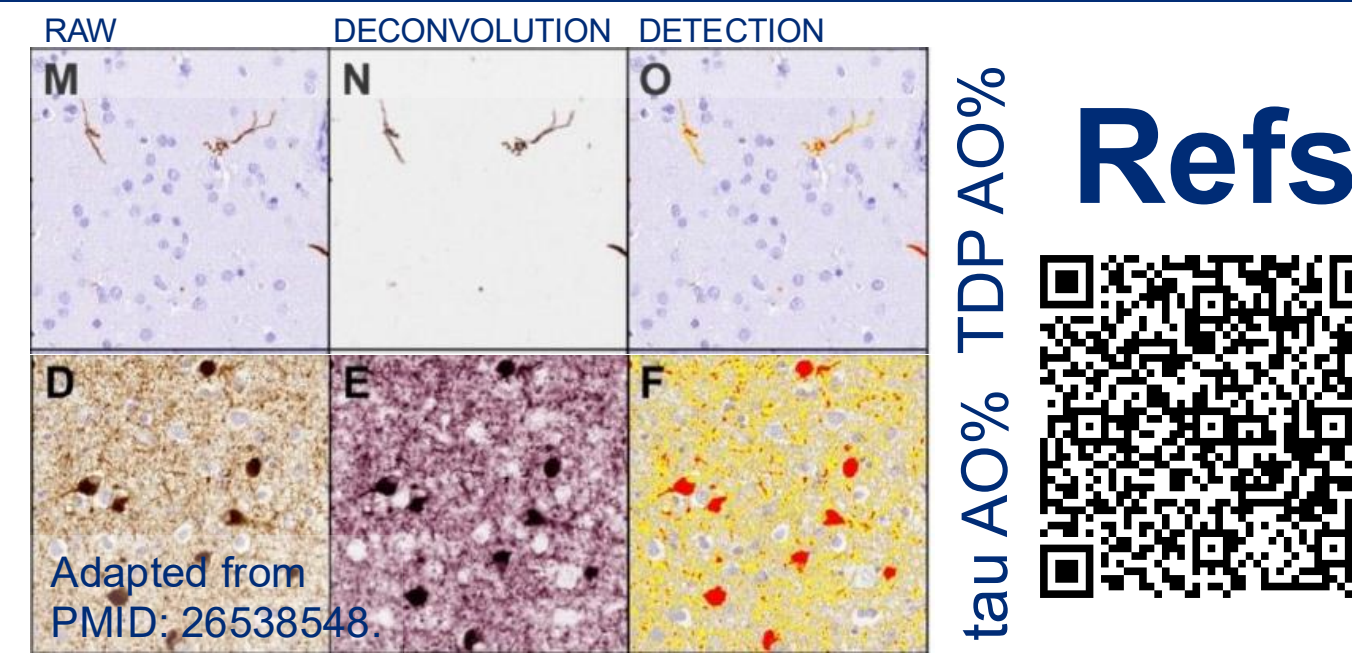


**Figure 2. Mean TDP-43 but not Tau %AO associates with clinical progression.** Individual dot plots relate cognitive test score and time since symptom onset, CDR-SB and MMSE separately. Datapoints are colored according to whether the individual patient had a mean TDP-43 grey matter (A,B,G) greater than the group median. Plots are similarly dichotomized for tau grey matter (C,D), TDP phase (E,F), and the sensitivity analysis of TDP-43 for bvFTD patients (G, H).

**Table 1. Linear mixed-effects models associated the change in cognitive testing and time since symptom onset, in a base model including sex, education level, mutation status, and pathologic diagnosis.** Results are listed as the outcome in the interaction term [outcome : time since symptom onset] and the beta coefficient (with 95% confidence intervals).

| All Patients                      |                        |
|-----------------------------------|------------------------|
| Model                             | β [95% CI]             |
| CDR_SB ~ TDP %AO                  | 0.1 [0.06, 0.2]        |
| CDR_SB ~ Tau %AO                  | 3e-04 [-0.001, 0.002]  |
| MMSE ~ TDP %AO                    | -0.1 [-0.2, -0.03]     |
| MMSE ~ Tau %AO                    | -5e-04 [-0.004, 0.003] |
| CDR_SB ~ TDP Phase III vs. IV     | 0.08 [0.04, 0.1]       |
| MMSE ~ TDP Phase III vs. IV       | -0.2 [-0.3, -0.1]      |
| CDR_SB ~ Pick Phase III vs. IV    | -0.006 [-0.05, 0.04]   |
| MMSE ~ Pick Phase III vs. IV      | 0.05 [-0.04, 0.1]      |
| Sensitivity Analysis - bvFTD Only |                        |
| Model                             | β [95% CI]             |
| CDR_SB ~ TDP %AO                  | 0.1 [0.03, 0.2]        |
| MMSE ~ TDP %AO                    | -0.2 [-0.4, -0.05]     |
| CDR_SB ~ TDP Phase III vs. IV     | 0.02 [-0.03, 0.08]     |
| MMSE ~ TDP Phase III vs. IV       | -0.04 [-0.1, 0.07]     |

| Characteristic                 | FTLD-tau N=55    | FTLD-TDP N=46   |
|--------------------------------|------------------|-----------------|
| Sex                            |                  |                 |
| Female                         | 22 (40%)         | 20 (43%)        |
| Male                           | 33 (60%)         | 26 (57%)        |
| Age at Onset                   | 65 (57, 70)      | 62 (56, 67)     |
| Disease Duration (years)       | 10.0 (7.0, 13.0) | 8.0 (7.0, 11.0) |
| # Clinical Score Timepoints    | 7 (5, 10)        | 6 (4, 9)        |
| Mutation in Gene               |                  |                 |
| C9orf72                        | 0 (0%)           | 11 (24%)        |
| GBE1                           | 0 (0%)           | 1 (2.2%)        |
| GRN                            | 0 (0%)           | 5 (11%)         |
| MAPT                           | 6 (11%)          | 0 (0%)          |
| None                           | 49 (89%)         | 28 (61%)        |
| VCP                            | 0 (0%)           | 1 (2.2%)        |
| Primary Clinical Diagnosis     |                  |                 |
| Corticobasal syndrome          | 6 (11%)          | 2 (4.3%)        |
| bvFTD                          | 28 (51%)         | 29 (63%)        |
| lvPPA                          | 0 (0%)           | 2 (4.3%)        |
| naPPA                          | 10 (18%)         | 0 (0%)          |
| svPPA*                         | 3 (5.5%)         | 8 (17%)         |
| Probable Alzheimer's Disease   | 3 (5.5%)         | 5 (11%)         |
| Progressive supranuclear palsy | 4 (7.3%)         | 0 (0%)          |
| Vascular dementia              | 1 (1.8%)         | 0 (0%)          |
| Pathologic Diagnosis           |                  |                 |
| Argyrophilic grain disease     | 3 (5.5%)         |                 |
| Corticobasal degeneration      | 6 (11%)          |                 |
| FTLD-TDP-A                     |                  | 21 (46%)        |
| FTLD-TDP-B                     |                  | 8 (17%)         |
| FTLD-TDP-C                     |                  | 14 (30%)        |
| FTLD-TDP-D                     |                  | 1 (2.2%)        |
| FTLD-TDP-E                     |                  | 2 (4.3%)        |
| Globular glial tauopathy       | 4 (7.3%)         |                 |
| Pick's disease                 | 16 (29%)         |                 |
| Progressive supranuclear palsy | 18 (33%)         |                 |
| Tauopathy unclassifiable**     | 8 (15%)          |                 |
| TDP Phase                      |                  |                 |
| II                             |                  | 6 (13%)         |
| III                            |                  | 12 (26%)        |
| IV                             |                  | 25 (54%)        |
| Unstageable                    |                  | 3 (7%)          |
| Pick Phase                     |                  |                 |
| I                              | 1 (6%)           |                 |
| II                             | 1 (6%)           |                 |
| III                            | 9 (56%)          |                 |
| IV                             | 5 (32%)          |                 |