Translational Neuropathology in Neurodegenerative Disease Research

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Postmortem study for biomarker validation and discovery

Tissue-Guided Biomarker Validation and Discovery

Prospective Natural History Studies
Clinical, Genetics, Biofluid, Neuroimaging

Clinical Syndrome

Clinical DNA CSF IMAGING

Autopsy

Tau α-SYN LB TDP-43 Aβ Plaques
Novel quantitative assessments of pathology

Traditional Scoring

0 = “none”  
1 = “mild”  
2 = “moderate”  
3 = “severe”

♦ Reproducible between labs
♦ Subjective, Descriptive > Quantitative

Digital Measurement

♦ Objective
♦ Fine-grained data
♦ High-throughput
♦ Reproducible between labs

From: Montine et al, Acta Neuropathologica 2011
From Irwin et al. J Histochem Cytochem 2016
Improving antemortem diagnosis of molecular pathology in bvFTD

Clinical symptoms
- Behavioral disinhibition
- Apathy
- Ritualistic/Perseverative behavior
- Loss of Empathy
- Hyperorality
- Executive Impairments

FTLD- TAU

bvFTD

FTLD- TDP
Asymmetry of FTLD pathology in bvFTD

23 bvFTD bilateral sampling of Insula (INS), Orbitofrontal (OFC), Ventral Temporal (VLT) and Superior Parietal (SPL) Cortex

FTLD-TDP = 14
FTLD-Tau = 9

Irwin et al. Brain 2017
Asymmetry Index (AI) = \[ \frac{(R – L)}{(\text{Average } R+L)} \] *100

Absolute value of AI = asymmetry independent of direction

One sample t-test for Ho=0 p<0.001 all

Irwin et al. Brain 2017
Asymmetry of pathology in bvFTD

Asymmetry Index (AI) = \[\frac{(R - L)}{(\text{Average } R+L)}\]
Asymmetry of pathology in bvFTD

CLINICAL DATA

MRI DATA

OFC GM Lateralization Group
\[ \lambda^2 = 3.8, \ p < 0.05 \]
The goal of bvFTD diagnosis: FTLD-Tau vs FTLD-TDP

**bvFTD-Tau**

- Tau-directed therapies

**bvFTD**

**bvFTD-TDP**

- TDP-directed therapies

**Clinical symptoms**
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