



Figure 1: Structural study of TDP-43 fibrils extracted from a type C FTLD case by cryo-EM.

- A) Immunogold negative stain electron microscopy using TDP-43 monoclonal antibody 6H6E12.
 B) Cryo-EM micrograph of fibrils extracted from a type C FTLD patient brain, in which thick twisters (blue arrow) and thin rods (orange arrow) can be distinguished. Scale bar, 100nm.
- C) Manual stitching of 2D classes reveals three distinct fibril polymorphs: thin rod, thick twister, and thin twister (top to bottom).

References

- 1. Colombrita, C. et al. TDP-43 is recruited to stress granules in conditions of oxidative insult. J. Neurochem. 111, 1051–1061 (2009).
- 2. Neumann, M. *et al.* Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* **314**, 130–133 (2006).
- 3. Hasegawa, M. *et al.* Phosphorylated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Ann. Neurol.* **64**, 60–70 (2008).
- 4. Amador-Ortiz, C. et al. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. Ann. Neurol. 61, 435–445 (2007).
- 5. Nelson, P. T. *et al.* Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. *Brain* **142**, 1503–1527 (2019).
- 6. Laferrière, F. *et al.* TDP-43 extracted from frontotemporal lobar degeneration subject brains displays distinct aggregate assemblies and neurotoxic effects reflecting disease progression rates. *Nat. Neurosci.* **22**, 65–77 (2019).
- 7. Cao, Q., Boyer, D. R., Sawaya, M. R., Ge, P. & Eisenberg, D. S. Cryo-EM structures of four polymorphic TDP-43 amyloid cores. *Nat. Struct. Mol. Biol.* 26, 619–627 (2019).
- 8. Li, Q., Babinchak, W. M. & Surewicz, W. K. Cryo-EM structure of amyloid fibrils formed by the entire low complexity domain of TDP-43. *Nat. Commun.* 12, 1620 (2021).
- 9. Lee, E. B. *et al.* Expansion of the classification of FTLD-TDP: distinct pathology associated with rapidly progressive frontotemporal degeneration. *Acta Neuropathol.* **134**, 65–78 (2017).
- 10. Fitzpatrick, A. W. P. et al. Cryo-EM structures of tau filaments from Alzheimer's disease. Nature 547, 185–190 (2017).
- 11. Falcon, B. et al. Structures of filaments from Pick's disease reveal a novel tau protein fold. Nature 561, 137-140 (2018).
- 12. Falcon, B. *et al.* Novel tau filament fold in chronic traumatic encephalopathy encloses hydrophobic molecules. *Nature* **568**, 420–423 (2019).