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Structures of pathological TDP-43 filaments in human neurodegenerative disease

The abnormal aggregation of transactive response DNA-binding protein of 43 kDa (TDP-43) in neurons and glia is the defining pathological hallmark of amyotrophic lateral sclerosis (ALS) and multiple forms of frontotemporal lobar degeneration (FTLD). It is also common in other diseases, including Alzheimer's and Parkinson's. We used electron cryo-microscopy (cryo-EM) to determine the structures of pathological TDP-43 extracted from the frontal and motor cortices of individuals who had ALS with FTLD. We found a conserved amyloid-like filament structure comprising a single protofilament. The ordered filament core is formed by residues 282 to 360 in the TDP-43 low-complexity domain, which adopt a novel double-spiral-shaped fold. The fold shows no similarity to those of TDP-43 filaments formed in vitro. Abundant glycine and neutral polar residues facilitate numerous turns that restrict beta-strand length, resulting in the absence of beta-sheet stacking associated with cross-beta amyloid structure. An uneven distribution of these residues gives rise to structurally and chemically distinct filament surfaces. External densities adjacent to these surfaces suggest possible ligand binding sites. This work enhances our understanding of the molecular pathogenesis of ALS and FTLD, revealing the formation of filaments that are structurally distinct from amyloid filaments in other neurodegenerative diseases. The structure of pathological TDP-43 filaments in ALS-FTLD informs the development of accurate disease models, as well as diagnostic and therapeutic agents.