The structural basis of reversible fibrils involved in protein phase separation and neurodegenerative diseases

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Pathological amyloid fibrils are characteristic of highly thermostable cross-β structure¹,². However, the stable cross-β architecture cannot explain the reversible amyloid fibrils formed by hnRNPA1 involved in the dynamic assembly of stress granules. Here we found that the reversible amyloid cores (RACs) of hnRNPA1 that can form reversible amyloid fibrils in the liquid-like droplet under the regulation of temperature and phosphorylation. We further determined the atomic structures of the RACs in fibrillar forms by crystallography and cryo-EM. Combined with biochemical and cellular experiments, we reveal the structural basis of reversible amyloid formation and its role in liquid-liquid phase separation and explains how Amyotrophic Lateral Sclerosis (ALS) disease-associated mutation abolishes reversibility of RACs which results in abnormal aggregation observed in the brain of ALS patients.