# Supporting Information

## ALS-associated A315E and A315pT variants exhibit distinct mechanisms in inducing irreversible aggregation of TDP-43$_{312-317}$ peptide

Xianshi Liu[a], Zenghui Lao[a], Xuhua Li[b], Xuewei Dong[a]* and Guanghong Wei[a]*

[a] Department of physics, State Key Laboratory of Surface Physics, and Key Laboratory for Computational Physical Sciences (Ministry of Education), Fudan University, Shanghai 200438, People's Republic of China

[b] MOE Key Laboratory for Nonequilibrium Synthesis and Modulation of Condensed Matter, School of Physics, Xi'an Jiaotong University, Xi'an 710049, People's Republic of China

**Details of NVT/NPT equilibrium**

The purpose of the 0.1 ns simulations in the NVT (310 K) and NPT (310K, 1 bar) ensemble is to equilibrate the solvent and ions around the protein at 310 K and 1 bar before the production runs. In order to make the systems gradually reach the target temperature and pressure/density, we separated the equilibrium process into two stages (NVT and NPT). Firstly, we conducted 0.1 ns simulations in the NVT ensemble to make the systems equilibrated at 310 K. Since the solvent is not optimized with solute after energy minimization probably, it is necessary to heat the systems to the simulated temperature. After the systems reached the right temperature, we then performed 0.1 ns simulations in the NPT ensemble to apply pressure to the systems with keeping the temperature steady, making the systems dwell in the proper pressure/density stably. The heavy atoms on proteins were not restrained during our NVT and NPT simulations.

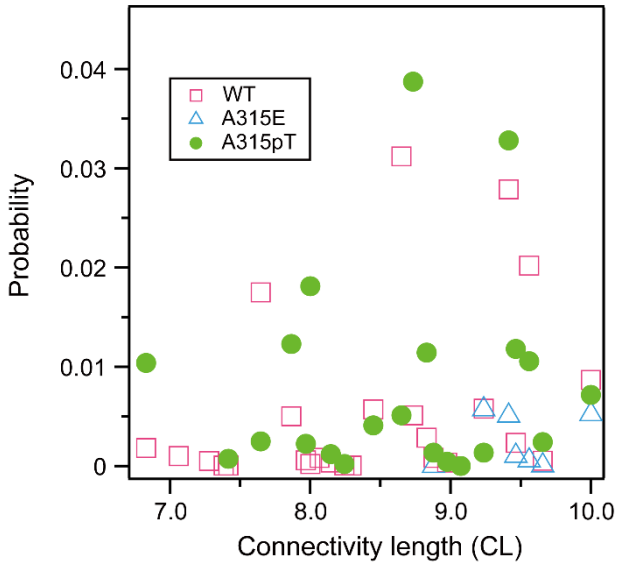


Fig. S1 Probability distribution of connectivity length (CL) of TDP-43$_{312\text{-}317}$ oligomers.

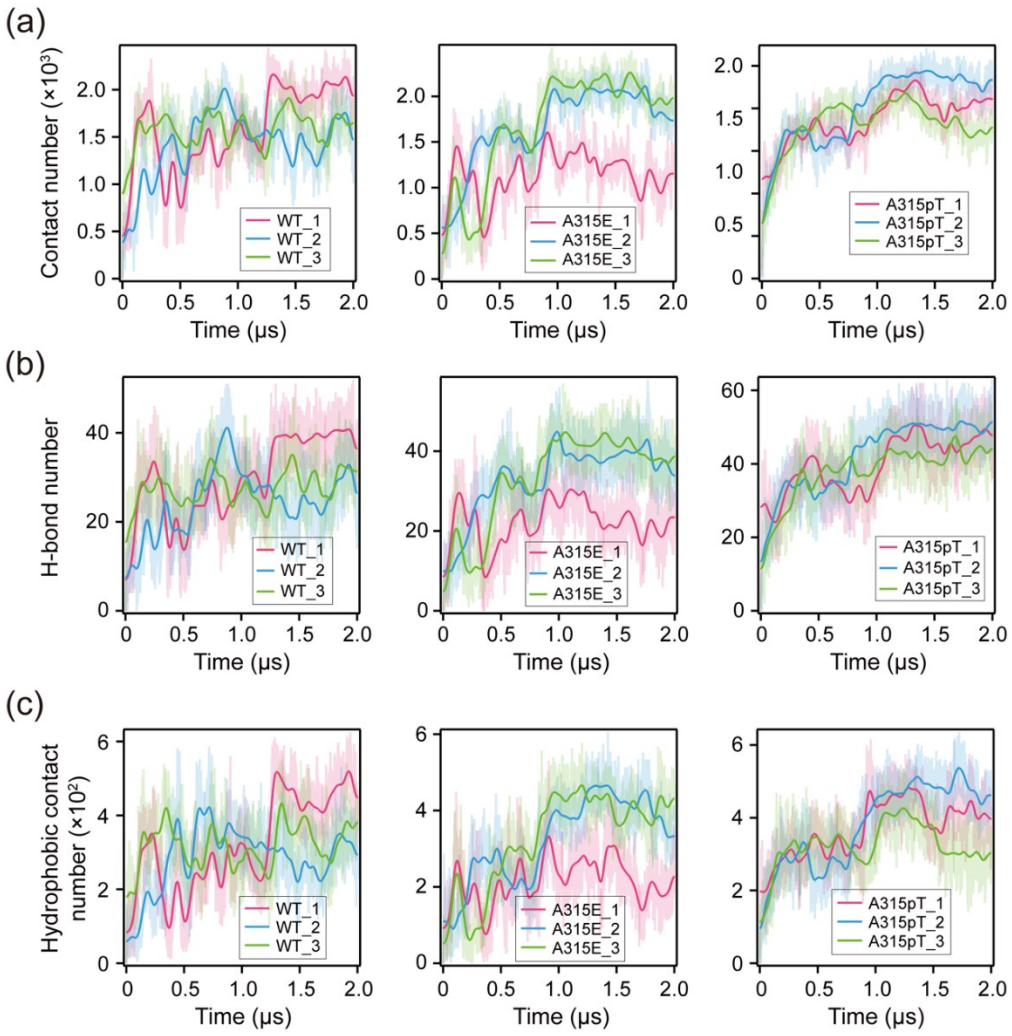


Fig. S2 The contact numbers, H-bond numbers and the hydrophobic contact numbers

of the three separate simulations in each system as a function of simulation time are shown in (a), (b) and (c) respectively.

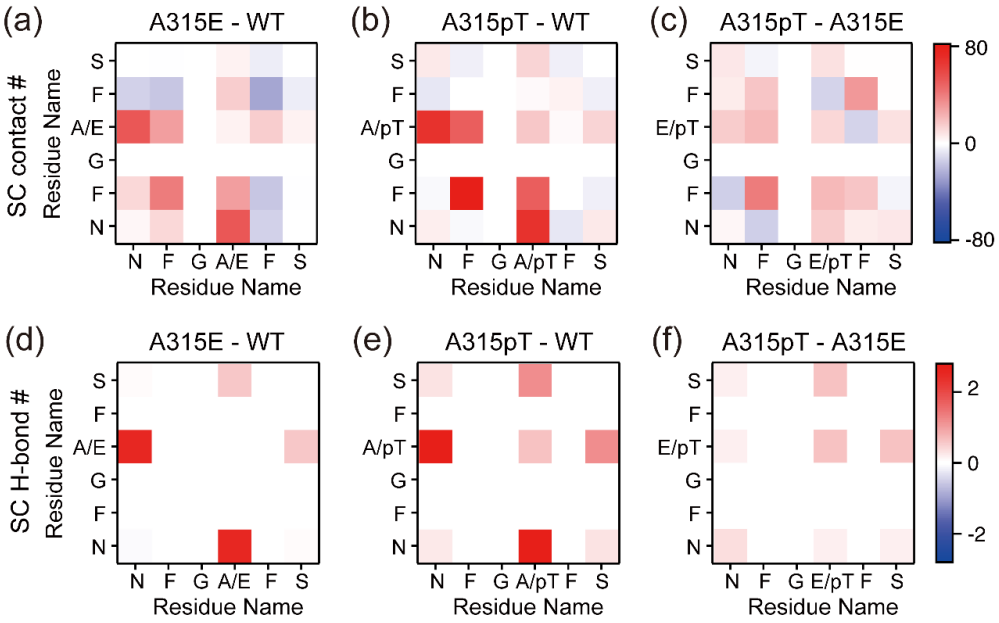


Fig. S3 Differences of residue-residue contact number maps and differences of residue-residue H-bond number maps between (a, d) A315E and WT, (b, e) A315pT and WT, (c, f) A315pT and A315E systems. In the calculation, interchain side chain atoms are considered only.