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The Native-state Dynamics of A-synuclein Play a Crucial Role in Determining Its Aggregation Kinetics

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α-Synuclein (Syn) assembly into fibrils plays a central role in the pathogenesis of Parkinson disease. Recent studies have highlighted the impact of genetic mutations (H50Q and A53T) on Syn structure and its aggregation propensity. Syn populates an ensemble of conformations ensuing from its rugged folding energy landscape. Protein intramolecular interactions continuously open and close leading to forms that trigger aggregation. However, the influence of the native conformer distribution of mutants on Syn aggregation rate remains unclear. This study aims to investigate the correlation between dynamics properties in the native state of Syn and its familiar variants and their aggregation propensity. The analyses were performed using Native Mass Spectrometry (Native-MS), Size Exclusion Chromatography (SEC), Thioflavin-T assay (ThT) and Circular Dichroism (CD). Our results showed that in the native state the A53T mutation, which induces a destabilized and relaxed monomeric state, leads to a significantly faster aggregation rate. Differently, the H50Q mutant, which retains a compact conformation, exhibits a slower aggregation process. These findings provide important insights into the role of protein native conformation on its aggregation propensity. This understanding is crucial for developing targeted therapies that specifically address the structural factors driving aggregation.