Computational Analysis of Alpha-Synuclein Protein Misfolding in Parkinson's Disease and Lewy Body Dementia Using AlphaFold-Predicted Structures and RMSD-Based Metrics

Cohen, Ruby (School: iPrep Academy North)

Parkinson's disease (PD) and Lewy Body Dementia (LBD) are two neurodegenerative disorders that are caused by the abnormal misfolding and aggregation of the same protein, a-synuclein. Despite these disorders sharing molecular origin, PD and LBD present different clinical symptoms and disease progressions. The structural mechanisms underlying these differences remain unclear, largely because experimental three-dimensional structures of individual a-synuclein mutants do not exist. Additionally, a-synuclein is intrinsically disordered, making traditional structural techniques such as cryo-electron microscopy and NMR difficult to apply. The goal of this study was to determine whether disease-associated a-synuclein mutation linked to PD and LBD misfolds in similar or distinct structural patterns. Five well-characterized mutations were analyzed: A30P and A53T (PD-associated), and E46K, H50Q, and G51D (LBD-associated). AlphaFold was used to generate consistent three-dimensional structural predictions for each mutant. An original Python-based computational pipeline was developed to perform sequence alignment, extract corresponding Ca atoms, apply the Kabsch alignment algorithm, and compute pairwise Root Mean Square Deviation (RMSD) values as a quantitative measure of structural similarity. RMSD calculation results revealed both strong similarities and significant differences among mutations. These findings suggest that a-synuclein misfolding depends more on specific genetic mutations than on disease classification, highlighting the potential for mutation-based structural grouping to inform future research and therapeutic strategies.

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