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Characterization of Alzheimer's Protective and Causative Amyloid-beta Variants Using a Combination of Simulations and Experiments PAYEL DAS, SRIRUPA CHAKRABORTY, ANITA CHACKO, IBM, BRIAN MURRAY, GEORGES BELFORT, RPI — The aggregation of amyloid-beta (Aβ) peptides plays a crucial role in the etiology of Alzheimer's disease (AD). Recently, it has been reported that an A2T mutation in Aβ can protect from AD. Interestingly, an A2V mutation has been also found to offer protection against AD in the heterozygous state. Structural characterization of these natural Aβ variants thus offers an intriguing approach to understand the molecular mechanism of AD. Toward this goal, we have characterized the conformational landscapes of the intrinsically disordered WT, A2V, and A2T Aβ1-42 variant monomers and dimers by using extensive atomistic molecular dynamics (MD) simulations. Simulations reveal markedly different secondary and tertiary structure at the central and C-terminal hydrophobic regions of the peptide, which play a crucial role in Aβ aggregation and related toxicity. For example, an enhanced double β-hairpin formation was observed in A2V monomer. In contrast, the A2T mutation enhances disorder of the conformational ensemble due to formation of atypical long-range interactions. These structural insights obtained from simulations allow understanding of the differential aggregation, oligomer morphology, and LTP inhibition of the variants observed in the experiments and offer a path toward designing and testing aggregation inhibitors.

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