Probing the role of V30M mutation in human transthyretin aggregation using molecular simulations

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Transthyretin (TTR), also known as prealbumin, is a highly conserved protein found in several vertebrate species. Dissociation of TTR tetramer followed by aggregation and misfolding of the monomers causes genesis of insoluble amyloid fibrils, which might systematically lead to peripheral and/or autonomic neuropathy and other systemic manifestations. Structural insights into the conformational landscape of TTR monomers upon mutation are useful for understanding amyloid aggregation. In this study, we used all-atom molecular dynamics (MD) simulations to investigate the role of V30M mutation on the structure of TTR monomer. The MD simulations of the wild-type and V30M TTR monomeric showed that the V30M mutation leads to dissociation of one of the edge strands, strand C, from the core of the monomer and forms an ensemble of partially unfolded conformations. These changes can be linked to disruption in the inter-strand hydrogen bonding and the secondary structure of the monomeric state. Moreover, non-covalent interactions in the E–F loop region, which is important for aggregation propensity of TTR, are also perturbed. Overall, the MD simulations provide comparative structural insights into the dynamics of wild-type and V30M TTR monomers.

Keywords: Amyloid fibrils, molecular dynamics simulation, monomers, mutation, transthyretin.

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deposition in multiple tissues and organs can cause fatal transthyretin-mediated (ATTR) amyloidosis[11,12].

Over 140 single-point mutated variants of TTR have been identified, comprising of both amyloidogenic and non-amyloidogenic nature. Of these, V30M is one of the most prevalent mutations and is associated with familial amyloid polyneuropathy[13]. Prior experimental studies indicate that the replacement of valine side-chain with the longer unbranched side-chain of methionine modifies its local interactions, in particular its hydrophobic interactions, leading to substantial structural changes as compared to its wild-type (WT) state[14,15].

Molecular dynamics (MD) simulations are extensively used to investigate the conformational landscape of disease-associated biomolecular systems as they show how the atomic-level structural details and their dynamic behaviour are. While advanced methods, such as replica-exchange MD[16], are required to delineate the conformational energy landscape of intrinsically disordered proteins[17–21], all-atom MD simulations with explicit solvent models provide adequate sampling of ordered proteins within nano-second timescales[22–25]. A wide range of studies have utilized MD simulations for the atomic level characterization of TTR misfolding mechanism[26–34]. The partial unfolding of the monomeric state is considered an important step in the onset of aggregation[6,35]. Accordingly, the misfolding mechanism