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STRUCTURAL INSIGHTS INTO HUMAN APOLIPOPROTEIN A1 VARIANTS AND THEIR CORRELATION WITH AMYLOIDOGENIC PROPENSITIES : AN *IN SILICO* APPROACH

Farah Ma'arfi[1], Mohd Yasir Khan[1], Jamal e Fatima[1], Uzma Fatima[2], Snober S. Mir[1] and Mohd Aslam Yusuf[1*]

[1]Department of Bioengineering, Integral University, Kursi Road, Dasauli, Lucknow - 226 026, India.

[2]RecsDesProt, 2 Burail, Sector 45, Chandigarh - 160 045, India.

*e-mail: aslamadhami@gmail.com

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ABSTRACT : Apolipoprotein A1 (ApoA1) is a prominent component of the "good cholesterol" and facilitates its functioning. Its misfolding is a critical risk factor for several diseases, such as cardiovascular diseases, Alzheimer's, diabetes and hereditary amyloidoses. Several naturally occuring mutants of ApoA1 are also associated with amyloidoses. The structural correlations between amyloidosis and protein stability are largely unknown for ApoA1. In this study, a sequence-based bioinformatics and molecular modeling approach was adopted to investigate the structural manifestations of selected ApoA1 mutations and their association with the amyloid-forming potential of the protein. Based on *in silico* analyses, we predicted the structure and aggregation propensities of the fibrilogenic ApoA1 polypeptides. Physico-chemical characterization using several parameters revealed the polypeptidesto be unstable and having anacidic nature. Secondary structure was also predicted along with different motifs. Because the three-dimensional structures for the mature wild type (WT) ApoA1 and its selected mutants were not available in the Protein Data Bank, we developed homology models using Modeller 9.10. The model was validated using RAMPAGE. The order of WT and the selected mutants in the formation of amyloid fibrils (L170P>WT = P143R) correlates with the involvement of protein in amyloidosis and directly with the strength of the protein–lipid association, which increases with the increasing protein hydrophobicity. However, this pattern was not observed in *in silico* prediction of proteolytically susceptible residues. We conclude that the amyloid-forming propensity and its stability is rooted in the hydrophobicity of Apo A1. The generated model would pavethe way for detailed *in vitro* and *in vivo* studies.

Key words : Apolipoprotein A1, amyloidosis, sequence-based prediction algorithm, tertiary structure.

INTRODUCTION

Apolipoprotein A1 (ApoA1) is synthesized mainly in the intestine and liver as a pre- and pro-protein of 267 amino acids. The cleavage of pre- and pro-proteins forms the mature 243 amino ApoA1, which gets into the plasma as a lipid-free protein. ApoA1 has a main role in the removal of cholesterol from the peripheral organs and its transport to the steroidogenic tissues and then to the liver, by a process referred to as "reverse cholesterol transport" (RCT), which is crucial in preventing atherosclerosis. ApoA1 is the main component of high density lipoprotein (Arciello *et al*, 2016). As light structural or functional perturbation leads to a potential risk of self-aggregation or dysfunction of this protein. The aggregation or deposition of insoluble protein fibrils is the main cause of amyloidosis and induction of fibrillogenesis, as in the case of the prion protein, APrP. Several mechanisms are thought to be responsible for the conversion of a solube native protein into its aggregated and misfolded form (Ramella *et al*, 2012). In native folded amyloidogenic proteins, destabilization by mutations or buffer conditions are the responsible key factors.

ApoA1 derived amyloidosis occurs either due to wild-type (WT) protein deposits in atherosclerotic plaques or sometimes because of hereditary amyloidosis in which variants of ApoA1 deposits cause complications leading to multiple organ failure. About 50 natural ApoA1 mutants have been reported till date, among which one-third are associated with familial amyloidosis. Molecular mechanisms underlying amyloid-associated pathology still needto be uncovered (Monti *et al*, 2011). The reasons behind each particular mutation mediated ApoA1 aggregation and deposition in plaques are still unclear. Mutants, such as Trp50, Gly26, Leu60 and Leu178 (pro-amyloidogenic mutations), involve substitution of neutral residues with cationic amino acids, inducing a change in the protein'snet charge (Van *et al*, 1969; Soutar *et al*, 1992; Petrlova *et al*, 2012). However, similar mutations in other domains of the protein do not favor the formation of insoluble aggregates. Several primary, secondary and