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ORIGINAL ARTICLE

Deciphering Role of Chameleon Fragments in Folding of Amyloidogenesis

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ABSTRACT
The present research focuses on the statistical relationship between chameleon sequences and amyloids. We have performed an exhaustive study for sequences capable of being found in secondary structure types viz., chameleons. Conformational plasticity of these peptides makes them prime candidates for amyloidogenic candidates which are characterized by a conformational change from an alpha helix to beta sheet conformation. Further, we have observed that discordant protein domains are enriched for specific protein fold types and functional categories. Our results substantiate the prediction potential of the given peptide for its amyloidogenic potential.
Keywords: Alzheimer's disease; Chameleon sequence; β-amyloid; Conformational transition; Unfolding simulations

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INTRODUCTION

Proteins are dynamic macromolecules and it is believed for most proteins, amino acid sequence determines the tertiary structure which eventually responsible for its function [1, 2]. Secondary structural elements like helices and beta sheets are building blocks for protein tertiary structure [3, 4] and the formation of these secondary structural elements is the result of a combination of local and non-local interactions [5, 6]. Proteins are stabilized by different biophysical forces and they can alter formation of their secondary structures upon different factors [7]. Number of methods and analysis has been reported in literature to identify and synthesize flexible sequence fragments [8-15]. These conformation changes are shown to be responsible for more than 30 human diseases associated with fibril formation and most common conformational diseases are amyloidoses like Alzheimers, Parkinson disease etc., [16].

Amyloid is an extra cellular protein and its characteristic is a conformational transition of the constituent proteins into a β-sheet rich filament [17]. The protein fragments with alpha helix forming propensity could lead to transition into a beta conformation and followed by the formation of amyloid fibrils [18]. It has been shown that some ionic self-complementary motifs with oppositely charged residues periodically arranged within the protein sequence could be capable of conformational transitions [19]. Peptides undergo conformational change to form typical structure dubbed as cross-β-sheets to break globular symmetry of the molecule and gives rise to linear assemblies of ordered fibres, during the process of amyloid aggregation [20]. Parallel studies too have confirmed that the conformational changes in proteins/peptides followed by amyloid aggregation also plays a pivotal role in the functions like cell signaling and many physiological processes in the cell [21-22].

In the context of current literature, it is necessary to understand the conformational switching phenomenon of the amyloid peptides by investigating the role of amino acid residues in terms of individual and segmental properties. In the present study, we explicitly account for a key feature in amyloid aggregation (conformational switch phenomenon) by computing secondary structure forming propensities of amino acid residues in amyloid beta peptides. In order to explore the secondary structure

of identical fragments of amyloid beta peptide with different proteins, heuristic sequence search has been performed in the whole Protein Data Bank [23]. Our further corroborates about the unfolding simulation of shark protein to understand the conformational switching.

MATERIAL AND METHODS

We have considered the crystal structure of amyloid beta (18-41) peptide fusion with antigen receptor variable domain from sharks. The four letter identifier of the structure is 3moq solved at a resolution of 2.05Å and exists in a tetrameric state. The sequence and three dimensional coordinates of the above entry are downloaded from Protein Data Bank (PDB). Overlapping five residue fragments (pentapeptides) in amyloid beta peptide is considered and subjected to heuristic sub-sequence search against the non redundant sequences in the PDB. Since, a stretch of five residues is enough to form a complete helix or β-strand, we considered five residue fragments to perform heuristic sub-sequence search. The propensity of residues to adopt a helix or strand is computed by using chou-fasman method. Dihedral angles of amino acid residues in amyloid beta peptide are also computed. Further, the protein is subjected to thermal unfolding simulation experiments by using Constraint Network Analysis (CNA) web server and fold amyloid program is used to predict the aggregation prone regions in the protein.

RESULTS AND DISCUSSION

Considering the beta amyloid peptide, we have generated twenty overlapping pentapeptides to perform heuristic sub sequence search in PDB sequences. The sequence search results have been shown in Table 1. First column of the table 1 represents the pentapeptide fragment of beta amyloid along with DSSP assigned secondary structure. Other columns of the same table indicate identical pentapeptides in other unrelated proteins along with DSSP assigned secondary structure. Base on our heuristic sub-sequence search, we found a novel pentapeptide (highlighted pentapeptide in Table 1: VLRDA) shows completely different secondary structure in an unrelated protein dubbed as annexin (PDB ID: 1DK5_A) with nil segment overlap measure. Segment overlap measure is a parameter used to compare the secondary structure of two protein segments. In beta amyloid peptide, the secondary structure of VLRDA is EEECC whereas in other unrelated protein it possesses a helical conformation (HHHHH). Similarly, 18^{th} and 19^{th} pentapeptides also have a completely different secondary structure in unrelated proteins which is clearly revealed from table 1. Since pentapeptide 'VLRDA' is composed of three hydrophobic (V, L and A) and two hydrophillic amino acid residues (R and D) paves the way to form a beta strand. Identical amino acid sequence fragments which adopt different secondary structures in proteins are termed as chameleon sequences, recent studies have revealed that chameleon sequences are significantly enriched in proteins possessing amyloidogenic sequences.

These chameleon regions have structural plasticity and involve in various biological functions. In order to distinguish the intrinsic propensity of forming alpha helices and beta strands in beta amyloid peptide, an algorithm by Chou and Fasman has been utilized. Chou and Fasman algorithm employs the grouping of twenty amino acid residues as strong helix formers, weak helix formers, strong beta former and weak beta former respectively. Beta amyloid peptide is subjected to computation of helix and beta forming propensity as proposed by Chou and Fasman. The amino acid residues positioned at 8-19 explicit strong alpha helix forming propensity. The crystal structure of beta amyloid peptide (3MOQ) assigned the above position as beta strands, clearly implies that the core amino acid residues in the beta amyloid peptide have structural ambiguity. To support the results of Chou-Fasman propensities, we have also performed neural network secondary structure prediction analysis as depicted in figure 1. The results of neural network secondary structure prediction are in agreement with that of Chou Fasman predictions.

THERMAL UNFOLDING SIMULATIONS OF β-AMYLOID PEPTIDE

To further dig in whether heuristically found chameleon pentapeptide is amyloidogenic or non amyloidogenic, thermal unfolding simulations were carried out by using CNA (Constraint Network Analysis) server, which profiles that percolation and rigidity indices. CNA not only uses thermodynamics simulations considering temperature dependence of hydrophobic tethers, but also computes a set of global and local indices to predict structural weak spots/ transition points. A cluster of amino acid residues with lower the percolation index can undergo conformational dynamics. In our thermal unfolding studies, percolation index and rigidity index for the chameleon pentapeptide is lower signifying its potential to undergo transition as depicted in figure 3.

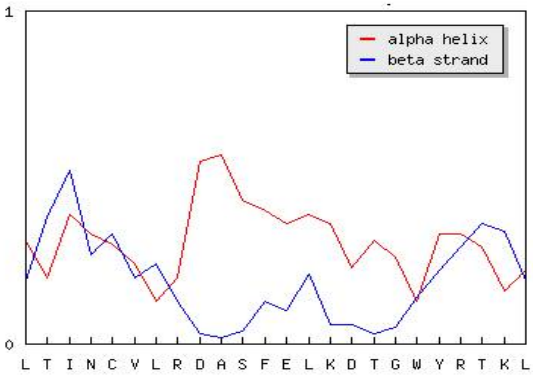
In order to identify the aggregation prone regions (APR) in proteins and peptides, several computational tools have been developed using various descriptors. *viz* beta strand propensity, hydrophobicity, charges etc., We aimed at utilizing a profound descriptor called foldamyloid, which predicts amyloidogenic cum non amyloidogenic amino acid residues in a protein. Foldamyloid program output the profile value of

amino acid residues which are amyloidogenic in nature and the same results have been shown in figure 3 depicting the value of chameleon pentapeptide above the threshold value. A trend line having a threshold value >21.4 signifies the value of the amino acid residues prone to aggregation and vice versa. Our thermal unfolding simulations and prediction of APRs ameliorate its potential amyloidogenic nature.

Table 1. Results of sub-sequence search of overlapping pentapeptides of β-amyloid in PDB sequences

S.No	Pattern/Sec Str	Identical patterns in PDB and its Sec Str								
1	LTINC	2V5I_A	2COQ_A	1SQ2_N	1VES_A	2YWY_A				
	EEEEE	CEEEE	EEEEE	EEEEE	EEEEE	EEEEE				
2	TINCV	1Y37_A	2COQ_A	1SQ2_N	1VES_A					
	EEEEE	EEEEE	EEEEE	EEEEE	EEEEE					
3	INCVL	2COQ_A	1SQ2_N	1VES_A						
	EEEEE	EEEEE	EEEEE	EEEEE						
4	NCVLR	2COQ_A	1SQ2_N	1VES_A						
	EEEEE	EEEEC	EEEEC	EEEEE						
5	CVLRD	2COQ_A	1SQ2_N	1VES_A						
	EEEEC	EEECC	EEECC	EEEEC						
6	VLRDA	1DK5_A	1TQY_A	3BE6_A	2NX9_A	1SQ2_N	2HYT_A	1VES_A	3DQQ_A	1YQ2_A
	EEECC	HHHHH	EEECH	HHHHC	CCCHH	EECCC	CCCHH	EEECC	HHCCC	EECCC
7	LRDAS	2ET6_A	2ICH_A	1M45_A	1SQ2_N	3EPC_R	1VES_A	1NEK_A		
	EECCC	CCCCC	EECCC	CCCCC	ECCCC	CCCCE	EECCC	CCCCC		
8	RDASF	2PET_A	1VES_A							
	ECCCC	CCCEE	ECCCC							
9	DASFE	1AK6_A	1VES_A							
	CCCCC	CCCCC	CCCCC							
10	ASFEL	1F08_A	1VES_A							
	CCCCC	HHHHH	CCCCC							
11	SFELK	1VES_A								
	CCCCC	CCCCC								
12	FELKD	2PA8_D	1VES_A	3F0Z_A	3F10_A	2ZY4_A				
	CCCCE	EEEEC	CCCCE	CCHHH	CCHHH	HHHHH				
13	ELKDT	1FXK_C	2PLS_A	2JPN_A	1VES_A					
	CCCEE	ECCCC	HHHHH	CCCCH	CCCEE					
14	LKDTG	1MIO_B	2JQZ_A	1VES_A						
	CCEEE	HHCCC	HHHHC	CCEEE						
15	KDTGW	1VES_A	3FTD_A							
	CEEEE	CEEEE	CCCCH							
16	DTGWY	1VES_A								
	EEEEE	EEEEE								
17	TGWYR	1VES_A								
	EEEEE	EEEEE								
18	GWYRT	1ESW_A	3CW9_A	1VES_A						
	EEEEE	HHHHH	CEEEE	EEEEE						
19	WYRTK	2COQ_A	1VES_A							
	EEEEE	EEEEE	EEEEE							
20	YRTKL	2HH6_A	2COQ_A	1VES_A						
	EEEEC	HHHHH	EEEEC	EEEEC						

Figure 1. Results of Chou-Fasman and Neural network based secondary structure prediction




```
AAseq  LTINCVLRDASFELKDTGWYRTKL
CF     EEEEEEHHHHHHHHCEEEEECCCC
NN     CEEEHHCCCCCHHHCCCCCCHECC
Joint  CEEECCCCCCCCCCCCCCCCCC
```

Figure 3. Thermal unfolding simulations correlating percolation and rigidity index

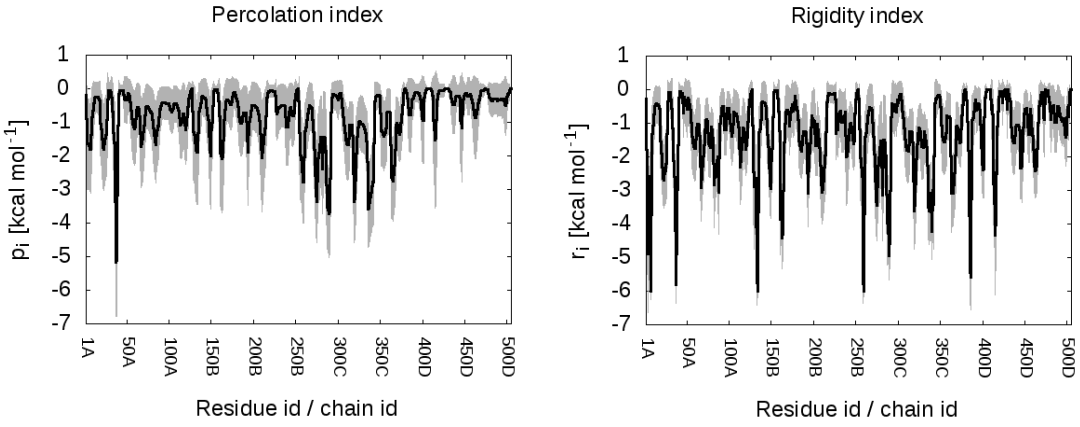
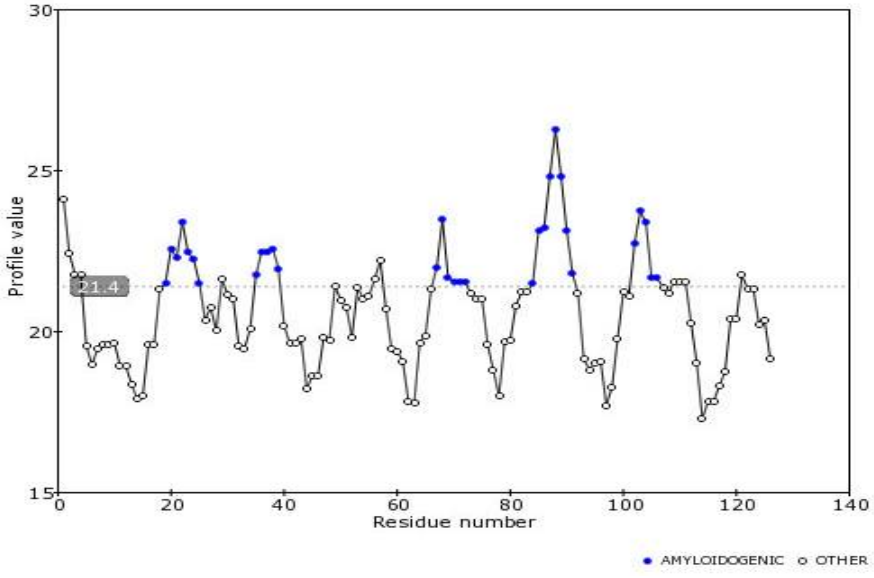


Figure 3. Prediction of amyloidogenic sequences in β-amyloid peptide



CONCLUSION

The information to code a fold of a protein is present in amino acid sequences. The conformational transitions lead to several neurodegenerative disorders in human and these transitions in a protein can be examined by looking the propensity of amino acid residues to adopt helix or a β-strand. Our detailed structural/heuristic characterization of the β-amyloid peptide from shark has made us to come up with a novel chameleon pentapeptide having a potential to undergo structural transition. To check the propensity of the pentapeptide, we carried out thermal unfolding simulations and prediction of APRs. Based on the simulations, percolation index, rigidity index and APR predictions has led to the interesting findings of a pentapeptide (VLRDA) having an amyloidogenic potential. This study is first of the kind to identify chameleon pentapeptide derived from crytallizable fragment of shark protein have ameliorating potential for amyloidogenesis.

CONFLICTS OF INTEREST

No conflicts of interest is declared

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