

A Computational Method for the Prediction of Amyloid Fibril Formation

Background

Amyloid fibril formation, or amyloidosis is widely observed in many unrelated human diseases including common neurodegenerative and neuromuscular pathologies such as, for example, Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease. It also figures prominently in Type II (or Late-Onset) diabetes mellitus, a metabolic disorder that accounts for 90-95% of all cases of diabetes. Amyloid fibril formation is also associated with the so-called prion diseases, also known as spongiform encephalopathies. Among the numerous prion diseases, familiar examples include Scrapie in sheep, Bovine Spongiform Encephalopathy (BSE) in cows more commonly known as "Mad Cow Disease", and Creutzfeld-Jacob Disease (CJD) in humans.

In these diseases, proteins with unrelated sequences aggregate to form highly characteristic amyloid fibrils. Amyloid fibril formation occurs as a consequence of increase in β strands in amyloidogenic proteins. However, sequence analyses have failed to reveal consensus sequences predictive of the β strand propensity in amyloidogenic proteins.

Recent studies have shown that diverse proteins not related to amyloid diseases can also aggregate into fibrils under laboratory-controlled conditions, suggesting that amyloid fibril formation appears to be a generic feature of many if not all proteins. Thus, understanding the fundamental driving forces that control amyloid fibril formation would provide guidance in the rational design of therapeutic agents that interfere with the process of amyloidosis.

There are many secondary structure prediction algorithms, such as the PHD algorithm, that predict native secondary structure based on sequence information. However, these algorithms fail to predict consistently the tendency of α -helical or random coil sequences to transform into nonnative β strands under physiological conditions. For example, although the islet amyloid polypeptide (hIAPP) has been shown to accumulate as amyloid fibrils in the pancreas of individuals with type II diabetes the PHD algorithm fails to predict β strand propensity for this protein. **Thus, there exists an unmet medical need for a method that can consistently and accurately detect hidden β strand propensity in proteins. Such a method would have utility in the identification of therapeutic agents capable of breaking β strands.**

Description of the Technology

UMDNJ researchers have developed a computational method for predicting sequences in proteins with hidden propensities for amyloid fibril formation. Using this method, local sequences with hidden β strand propensity were identified in a wide variety of proteins and polypeptides. Further, the computational method of the present invention has, without exception, correctly identified sequences that have been shown to initiate amyloid fibril formation under both *in vitro* and *in vivo* conditions. Thus, the present invention provides methods for detecting hidden sequence propensity for amyloid fibril formation in any protein. This invention has applications for the discovery of agents that specifically target these sequences for the prevention, treatment, and diagnosis of amyloid diseases. The peptides provided by this invention are useful as potential therapeutic agents called " β -sheet breakers" capable of blocking and/or inhibiting amyloid fibril formation. These same peptides can be also used as diagnostic agents (or templates thereof) of amyloid plaque. This invention also has applications in protein engineering for the detection, and selective removal or replacement, of these offending sequences associated with strong β -strand propensity.

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Additionally, this invention is embodied in a computational tool known as an artificial neural network (ANN) for fast and accurate prediction of hidden β -strand propensity in any protein or polypeptide based solely on knowledge of its amino-acid sequence. Peptide sequences in known amyloidogenic proteins identified by the artificial neural network program to have strong β strand propensity have been compiled into a database. This wealth of knowledge could be utilized to identify agents that disrupt or inhibit β strand formation of proteins implicated in neurodegenerative diseases and other human diseases caused by protein misfolding.

Advantages

- This invention is unprecedented in its ability to predict the hidden β -strand propensity in any protein or polypeptide. It is this hidden β -strand propensity that appears to be the hallmark of amyloid fibril formation.

Applications

- Therapeutics: to design peptides or agents that can be used to break β strands
- Diagnostics: to predict tendency of proteins to form amyloid fibrils
- The neural network program can be used for the rapid prediction of β strand propensity for any protein or peptide
- Protein Engineering: for the detection and removal of sequences with β strand propensity

Patent Status

- PCT patent application filed.
- Application No.: PCT/US2004/004122

Licensing Opportunity

- This technology is available for non-exclusive license.

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