Computational Analysis of Cerebral Amyloid Protein using Homology Protein Modeling Technique and its role in Pathogenesis of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) isa disorder of brain that results in degeneration of brain cells that ultimately leads to dementia. It affects more than 35 million people worldwide with increasing tendency. It is a neurodegenerative disease characterized by neuritic plaques and neurofibrillary tangles from amyloid apeptide build up in the medial temporal lobe and neocortical areas of the brain.Clinically AD, is linked with a slow progression of cognitive and behavioral impariment. In this research article we will discuss about the bioinformatics of Alzheimer's disease and work has been done on the computational structure of cerebral amyloid protein using homology Protein Modeling Technique and defining the structural role in pathophysiology of Alzheimer's disease. Characterizing different domains of this protein and predicting the subjective role of particular domains of this protein involved in AD prognosis. This will provide a detailed insight about working mechanism of cerebral amyloids protein and new doors to therapeutic targets in AD treatment and management.

Keywords:

Alzheimer, neurodegenerative, neuritic plaques, amyloid-a peptide, bioinformatics.

1. INTRODUCTION

The latest clinical data indicate that the prevalence of dementia will double in Europe and triple worldwide, by 2050, and that estimate is three times higher when based on a biological (rather than clinical) definition of Alzheimer's disease. The German psychiatrist and neuropathologist Dr. Alois Alzheimer is credited with describing for the first time a dementing condition which later became known as AD. Dementia is a clinical syndrome (a group of co-occurring signs and symptoms) that involves progressive deterioration of intellectual function. Various cognitive abilities can be impaired with dementia, inc-

luding memory, language, reasoning, decision making, visuospatial function, attention, and orientation. There are several reversible and deterioration of intellectual function. Various cognitive abilities can be impaired with dementia, including memory, language, reasoning, decision making, visuospatial function, attention, and orientation. There are several reversible and irreversible causes of dementia. Six reversible dementias are relatively rare but potentially treatable and occur secondary to another medical condition, including depression, nutritional deficiencies (e.g., vitamin B12), metabolic and endocrine disorders (e.g., hypothyroidism), space occupying lesions (e.g., brain tumor), normal pressure hydrocephalus, or substances abuse. The vast majority of individuals suffering from AD are aged 65 or older and have 'late-onset' or 'sporadic' AD (95% of all cases).

Alzheimer's disease (AD) is a neurodegenerative disease characterized by neuritic plaques and neurofibrillary tangles from amyloid-a peptide A build-up in the medial temporal lobe and neocortical areas of the brain (De-Paula et al., 2012). The disease clinically presents with a slow progression of cognitive and behavioral impairment. Approximately 50 million people across the globe suffer from the most common manifestation of the disease—dementia—and this figure is expected to double every 5 years, with an estimated 152 million cases by the year 2050 (Livingston et al., 2020; Yiannopoulou &Papageorgiou, 2020).

Although the pathogenesis of the disease is still not completely understood, it has been shown that at post mortem there are two histopathological changes that occur within the brain. These changes involve the abnormal clustering of proteins, which characterize individuals with AD. This abnormal clustering occurs in two forms: (i) those that occur within the neurons, i.e. the neurofibrillary tangles and (ii) those that cluster extracellularly outside of the neuronal body, i.e. the amyloid based neuritic plaques. Amyloid beta-protein (A beta), the 40-43-amino acid polypeptide that is the principal constituent of senile plaques found in Alzheimer's disease, is constitutively produced and released into medium of cultured cells by an unclear mechanism. AD results from the intracranial build-up of two proteins, Aâ and tau, forming extracellular neuritic plaques and intracellular neurofibrillary tangles, respectively. This results in neuronal dysfunction and death, and inflammatory responses. When amyloid precursor protein (APP) is cleaved by â-amyloid-converting enzyme and ã-secretase instead of á-secretase and a-secretase, it releases Aa peptides, which culminate in the accumulation of plaques and tangles (De-Paula *et al*., 2012).

Many different genes are possibly involved in Alzheimer's disease. Three genes were found to carry these mutations: APP, PSEN1 and PSEN2 (Amyloid beta (A4) precursor protein, Presenilin 1, and Presenilin 2). The APP gene is located on chromosome 21. Triplication of chromosome 21 results in the triplication of the APP gene, which might enhance APP expression and Abeta accumulation. Down syndrome patients have been reported to develop AD pathology (deposition of senile plaques and neurofibrillary tangles) earlier than those without Down Syndrome. These findings suggest that overexpression of APP might be related to AD pathology. The APP gene contains 19 exons for encoding the APP protein. The Abeta peptide is encoded by exons 16 and 17. The structures of PSEN1 and PSEN2 are similar, with a homology of 67%. Both of them contain 12 exons with ten coding exons (exons 3–12) for a

protein of <"450 amino acids. Presenilin 1 (PS1) and presenilin 2 (PS2) proteins are transmembrane (TM) proteins with at least seven TM domains.

Most AD risk-factor mutations have been detected in PSEN1 (approximately 30%–70% of early onset FAD), which is located on chromosome 14. More than 180 mutations were found in PSEN1 in association with FAD, but they might be involved in sporadic AD or LOAD. Patients with PSEN1 mutations might develop AD symptoms in their 40s or early 50s, with a few cases occurring in persons in their late 30s and early 60s. Several missense mutations in PSEN1 can increase the production of Abeta 42 and 40. In an alternative mechanism, the levels of Abeta 42 and Abeta 40 might be increased and decreased, respectively. Two PSEN2 mutations, Arg62His and Arg71Trp, may be involved in breast cancer, although the pathomechanism is not clear. Mutations in these genes might result in alteration of amyloid beta (A beta) production (both A beta 40 and A beta 42), leading to apoptosis of the neurons and dementia presents a timeline of AD onset according to age. A major aim both for clinician and researchers would be the identification of the genes involved in AD, to better understand the biological mechanism of this disease and consequently to develop appropriate treatment.

2.MATERIALS AND METHODS

The protein structure prediction modelling for comparative modelling consisted of the following steps. Target identification came first, followed by alignments of the target and prototype sequences. The model was built when the alignment template procedure was completed. Finally, the model's strength, stearic collisions, and stability were evaluated.

2.1. Protein Sequence Retrieval

The Cerebral or plaque core protein sequence was saved from the UniProt database.

Protein Secondary Structure Prediction

The Cerebral or plaque core protein sequence further subjected to secondary structure prediction on the Expasy server using QMEAN.

2.2. Protein Tertiary Structure Prediction through Template Identification

A thorough search of the PDB (Protein Data Bank) (http://www.rcsb.org/ (accessed on 16 February 2021) was conducted to search the most similar sequences already known for experimentally designed structures.

2.3. Modelling

The Cerebral or plaque core protein three-dimensional structure was calculated using automated server https://swissmodel.expasy.org/interactive/XB35VY/models.

2.4. Validation of the Structure

The Expasy server was used to create Ramachandran plots in order to validate the predicted protein structures by looking at criteria such as preferred, allowed, and outside amino acid residue areas.

3. RESULTS AND DISCUSSION

3.1. Basic Principles of Cerebral or Plague Core Protein Structure

Protein structure is the three-dimensional setting of atoms in an amino acid. When all atoms of a protein structure is identified for the first time (be it a figure, a three-dimensional model or a computer graphics representation) it may appear a difficult task to analyze any elementary pattern within it. Eventually, such structures often have thousands of atoms. As a result, it is often believed convenient to clarify the problem by applying a hierarchical explanation of protein str-

ucture in which sequential layers of the hierarchy describe increasingly more complicated levels of organization. Generally four levels are used and assign to as the primary, secondary, tertiary and quaternary structure of a protein. It is made by condensation of amino acids making peptide bonds. The sequence of amino acids in a protein makes primary structure. The secondary structure is determined by dihedral angles of the peptide bonds, the tertiary structure is made by the folding of protein chains in space.It is often helpful to include two additional interceding levels between the secondary and tertiary structures, which are mention to as super secondary structures and domains.

3.2. Primary Structure of Celebral or Plaque Core Protein

The primary structure of a protein initially mention to its complete covalent composition but is more often explain as being the pattern of amino acids of each polypeptide series of which the protein is composed. These are usually one and the same thing but di-sulphide bonds and other rarer kind of covalent bond formed between amino acid side chains are not exactly encoded by the order itself.

A polypeptide chain is a uni dimensional heteropolymer arranged of amino acid residues. There are fundamentally only twenty naturally exist amino acids which are precisely encrypted by the corresponding gene, while in abnormal cases stop codons can be apply for the incorporation of two additional amino acids (selenocysteine and pyrrolysine (32). All of these amino acids are a-amino acids which hold the generic structure. usually to all such amino acids is the amino group, carboxylic acid group and hydrogen bound to the central carbon atom (the a carbon). Only the R group (also known as the side chain) differs from one amino acid to other and it differ in terms of size, polarity, hydrophobicity, charge, shape, volume etc. With the twenty unlike amino acids accessible, nature is able to make the broad diversity of functions which proteins do in living organisms. In (a) the generic structure of an á-amino acid is given, in which only the R group (side chain) differ from one type to other. In (b) and (c) the variation between L- and D- amino acids apart is shown (one being the mirror image of the other).

It should be notable that the á-carbon is tetrahedral and in common is bound to four distinct chemical moieties. As such it is asymmetric (a chiral center) and two different enantiomers (D and L) for each amino acid exist. Amongst the naturally occurring amino acids, the only exception is the amino acid glycine, whose R-group is a hydrogen atom, making the á-carbon symmetric. This confers a series of important conformational properties on this amino acid which are often essential for the maintenance of a given structure. For this reason, critical glycines are often conserved amongst members of a given protein family. The remaining amino acids are (with very few exceptions) always found to be L-amino acids. This has important consequences for the chiral structures observed in proteins at all levels of the hierarchy. Only two other chiral centers exist within the twenty amino acids, these are the â-carbons within the side-chains of the amino acids threonine and isoleucine, which also exist as only one of the two possible enantiomers.

3.3.Secondary Structure Cerebral or Plaque Core Protein

Complete consolidation of Õ and ø are not stereo chemical desirable therefore countless

supremacy toward steric interference. Indeed, exhibited formerly through Ramachandran exclusive around one third of Õ ø slot is stereo chemically attainable to amino acid residues in original polypeptide. Assuming that the Õ and ø are reciprocated consistently considering all residues including stretch of polypeptide, the product determination necessarily be a helix. Absolute statistic of kind of helix apparently supremacy, relative on the consolidation of Õ and ø, they both may be confidently illustrated by two amplitudes n and d interrelated subsequently towards the sum of residues per helical departure and deviation coordinate along the helical axis per residue. Helices determine endure although they are adequate spare ordinarily recognized As the first or last departure. ð-helices be permitted a limited frequent than real core. Candidacy among water and the amide groups of protein firmness influence along with prolong hydrogen bonds adjacent to the hydrophilic aspect dominant to helix deflection. Decomposition of amyloid âA4 in the brain is chief therapeutic indication pertaining to Alzheimer's disease. Amyloid âA4 is a peptide made up of forty two or forty three amino acid silts.

Now brain, it emerges in the pattern of deeply emulsifiable filamentous accumulation. Adopting manufactured peptides analogous toward the essential aA4 sequence in addition to correlate peptides, we indicate exigency considering filament arrangement in vitro. We also regulate accumulational characteristics and secondary structure of âA4.

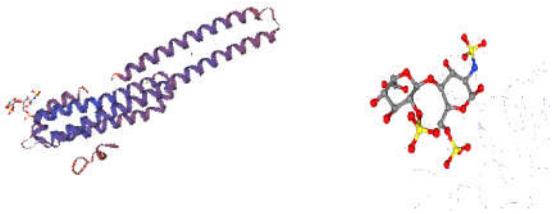

Fig-1. Cerebral or Plaque core proteins model

3.4. Tertiary structure

In order via structure of plaque core protein the particular aspects about secondary structure appropriate to polypeptide prerequisite bundle in opposition to one other in order to design reliable bunched and biologically effective tertiary structure. The approach for secondary structure is better as a rule equipment has been extensively studied. The complementary access can be recycled for the stuffing of beta sheets in opposition to one other or of helices in opposition to sheets. The concluding consequence attributed to the developing mechanism is the full of three dimensional framework of polypeptide.

Apparently this build upon the amino acid sequence and accordingly on the fragmentary element of the structure. There is a generic assumption that the absolute statistics of folds is approximately defined and it is familiar that as a consequences of structural genomics leadership with in the adjacent less senescence our familiarity of the nature of achievable folds recycled by soluble protein at bottom will be judiciously outright. Earlier some authors mention that some folds are also accepted that alternative and they

have been labeled super folds.

4. CONCLUSION

Cerebral amyloid angiopathy CAA obtain the consequence about the degradation of an Amyloidogenic protein in cortical and leptomeningeal vessels. The utmost frequent kind of CAA is acquired by amyloid beta protein (Aâ), that is Principally analogous by Alzheimer's disease (AD). Extreme â-CAA development can be acquired by considerable deviation in the Aâ precursor protein and presenilin genes. The influence of Aâ in CAA is feasible to be neuronal, admitting cerebrovascular cells or the circulation cannot be illegal as a authority. In the completion the short impact of CAA on AD or dementia persist unclear, however, its role may have been miscalculating in the previous, and more comprehensive studies of in vitro and in vivo models for CAA will be essential to explicate the emphasis of CAA-definitive access in scheming interference scenario for AD.cerebral amyloid angiopathy (CAA) has a direct role in the pathogenesis of Alzheimer's disease (AD). Firstly, there is a very close relationship between CAA and AD and they share genetic risk factors. Secondly, we propose a specific mechanism which puts age-related cerebrovascular degeneration at a crucial point in the pathogenesis of AD as follows. Amyloid â-protein (Aâ) is normally eliminated from the brain along with extracellular fluid by bulk flow along the perivascular pathway. Age-related fibrosis of cerebral cortical and meningeal arteries leads to impaired drainage of Aâ along the perivascular pathway and, together with the production of Aâ by smooth muscle cells and perivascular cells, is responsible for accumulation of Aâ as CAA. Reduced elimination leads to increased concentration of soluble Aâ in the extracellular fluid of the brain parenchyma. Increased concentration of soluble Aâ leads to the formation of insoluble Aâ plaques.

The mutual appearance of amyloid beta displacement in Alzheimer's disease is feasible the luminous illustration of crosstalk among neurodegenerative and cerebral vascular processes. The pathogenic pathways of CAA and AD converge at the equivalent of amyloid beta generation, its dissemination with in the intestitial fluid and perivascular drainge pathways and its brain clearance, but radiate in their mechanisms of brain injury and disease presentation.

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