Identification of Interaction of Proteins LRP1 and NYGGF4 in Alzheimer's Disease using Computational Tools

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Abstract— Alzheimer's disease (AD) is characterized by a widespread functional disturbance of the human brain. It may be caused by the deposition of amyloid beta-peptide (Aβ) in plaques in brain tissue. In AD, there is the formation of neurofibrillary tangles containing tau protein, which is proposed to result from an imbalance between the production and clearance of amyloid beta-peptide (Aβ). The degradation and production of Aβ is significantly regulated by low-density lipoprotein receptor-related protein, LRP1, which is a large endocytic receptor. The LRP1 is known to regulate this function by interacting with a novel and specific interactor, NYGGF4 (phosphotyrosine interaction domain containing 1). NYGGF4 is known to be differentially expressed during AD progression. Here, we are trying to computational predict the interaction of LRP1 and NYGGF4 through protein structure prediction and protein-protein interaction.

Keywords: Alzheimer Disease, Protein-Protein Interaction, Structure

I. INTRODUCTION

Alzheimer's disease (AD) is a common neurodegenerative disorder characterized by the excessive deposition of amyloids in the brain [5]. Alzheimer's disease is mainly caused by the deposition of Fibrillar amyloid proteins inside neurons as neurofibrillary tangles and extracellularly as amyloid plaque cores and in blood vessels [4].

In AD, there is the formation of neurofibrillary tangles containing tau protein, which is proposed to result from an imbalance between the production and clearance of amyloid beta-peptide (Aβ) [1]. The degradation and production of Aβ is significantly regulated by low-density lipoprotein receptor-related protein, LRP1, which is a large endocytic receptor [2]. The LRP1 is known to regulate this function by interacting with a novel and specific interactor, NYGGF4 (phosphotyrosine interaction domain containing 1). NYGGF4 is known to be differentially expressed during AD progression [3]. Here in this study we are computationally predicting the interaction of LRP-1 and NYGGF4 in AD.

II. DATABASES AND TOOLS USED

A. NCBI:

National centre for Biotechnology Information is a database which includes GenBank for DNA sequences and PubMed, a bibliographic database for the biomedical literature. The protein sequence in fasta format is obtained from NCBI [6].

B. SOPMA:

Self-Optimized Prediction Method with Alignment is a secondary structure prediction method, which is used to predict the secondary structures of the proteins like helixes, strands, coils, turns and loops [7].

C. Motif Search:

Is a tool for the prediction of motifs and domains of a protein which determine the structural and functional characteristics of a protein [8].

D. Swiss Model:

It is a fully automated protein structure homology-modelling server, accessible via the ExPASy web server. It is used for the tertiary structure prediction[9.]

E. SPDBV:

The structure predicted through the Swiss-model is optimized through energy minimization using Swiss-PDB Viewer software[10].

F. ClusPro:

ClusPro represents the first fully automated, web-based program for the computational docking of protein structures. The protein-protein interactions are done using ClusPro[11].

III. RESULTS AND DISCUSSIONS

A. Sequence Retrieval

In Computational biology, sequence plays an important role for the prediction of a structure and function of a protein. The sequence in fasta format for the protein LRP1 and NYGGF4 having 296 and 250 amino acid residues in human were obtained from NCBI.

B. Secondary Structure Prediction

Stretches or strands of proteins or peptides have distinct characteristic local structural conformations or *secondary structure*, dependent on hydrogen bonding. Types of secondary structure are the α-helix, the ß-sheet/strand, loops, coils and turns. The secondary structure of LRP1 and NYGGF4 obtained are shown in Table 1.

Features	LRP1	NYGGF4
Alpha-helix	66(22.30%)	86(34.40%)
Coils	145(48.99%)	25(10%)
Beta turns	25(8.25%)	89(35.60%)

Table 1: Secondary Structure predicted for LRP1 and NYGGF4

C. Super Secondary Structure

Super secondary structures (also called motifs) involves the association of secondary structures in a particular geometric arrangement. "Motifs" are the structural characteristics of a protein. Using motif search tool, the super secondary structure of the NYGGF4 protein was obtained as:

1) Motif Name- PID

a) Description:

PS01179, Phosphotyrosine interaction domain (PID) profile.

Position	163..223
Alignment Query Database	VARIAYCTADHNVSPNIFAWVYreinddlsyqmDCHAVECES-KLEAKKLAHAMMEAFRKTF VRKISFIADggDRDsDARRFAY----------SCHVFECEKtgqlAEDIALAIGQAFSVRY
Score	414

And for LRP1:

2) Motif Name - LDLRA_2

a) Description - PS50068, LDL-receptor class A (LDLRA) domain profile.

Position	26..65
Alignment Query Database	TCSPKQFACRDqITCISKGWRCDGERDCPDGSDEapEICP TCSPNEFQCSN-GRCIPRSWVCDGDBDCGDGSDE--ENCS
Score	1183

D. Tertiary Structure and Validation-

The overall three-dimensional shape of an entire protein molecule is the tertiary structure. The protein molecule will bend and twist in such a way as to achieve maximum stability or lowest energy state. Although the three-dimensional shape of a protein may seem irregular and random, it is fashioned by many stabilizing forces due to bonding interactions between the side-chain groups of the amino acids**.**

Henceforth LRP1 and NYGGF4 structures are predicted using automated Swiss-model (Figure 1) from their sequences obtained from NCBI in fasta format. These structures are visualized using Swiss PDB viewer (SPDBV) and optimized through energy minimization. The predicted protein structures: LRP1 and NYGGF4 stability is checked using Ramachandran plot.

In a polypeptide the main chain N-Calpha and Calpha-C bonds relatively are free to rotate. These rotations are represented by the torsion angles phi and psi, respectively. Ramachandran plot uses computer models of small polypeptides to systematically vary phi and psi with the objective of finding stable conformations. For each conformation, the structure is examined for close contacts between atoms. Atoms are treated as hard spheres with dimensions corresponding to their van der Waals radii. Therefore, phi and psi angles which cause spheres to collide correspond to sterically disallowed conformations of the polypeptide backbone.

Using the same, it is predicted that 9 and 3 residues in LRP1 and NYGGF4 respectively were lying in the disallowed region. The structure is stabilized by energy optimization and mutation by subsitution. The list of amino acids substituted list and its position is given in Table 2.

Original	**Mutated**
LEU118	VAL118
LYS191	GLN191
ASP152	GLU152
HIS107	ASN107

Table 2(a): LRP1

Original	**Mutated**
LYS113	GLN113
LEU206	ILE206

Table 2(b): NYGGF4

Table 2: Amino acids in the disallowed region with its substituting amino acid along with its position in LRP1 and NYGGF4 are given below:

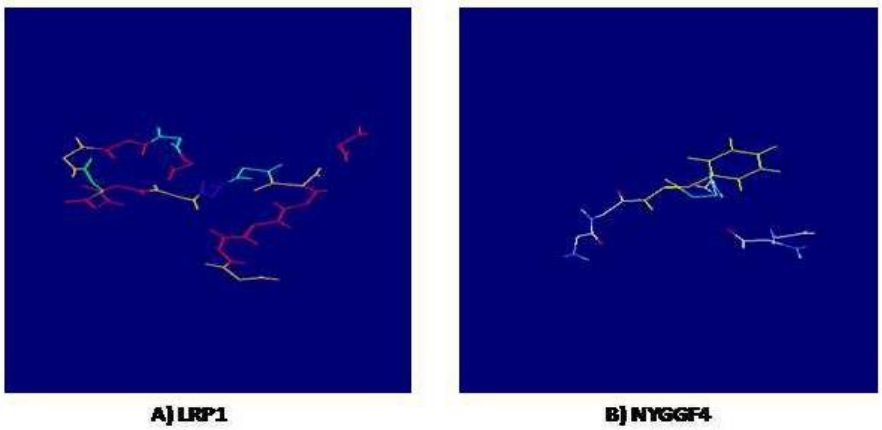

Fig. 1: Predicted protein structure of LRP1 and NYGGF4.

E. Protein- Protein Interaction

The protein-protein interaction for the predicted proteins, LRP1 and NYGGF4 is studied using ClusPro docking tool. In which, docking is based on the best fit between the interacting proteins. The best fit between the interacting proteins is given by clusters and the weighing scores (Figure 2). The top 10 best fit with the number of atoms and weightage score is given in Table 3.

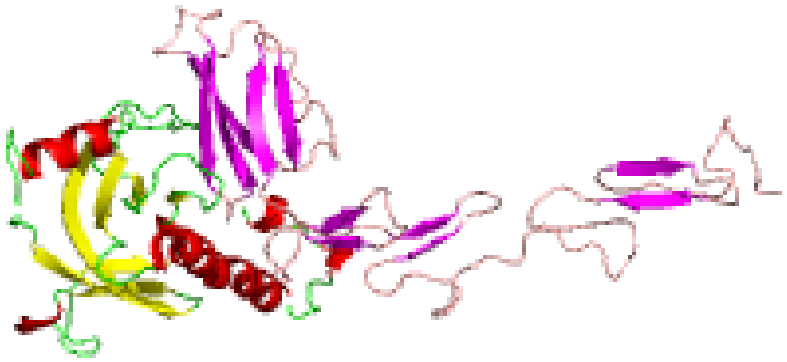

Fig. 2: Interaction between LRP1 and NYGGF4 using Cluspro involving 88 atoms with a weightage score of -1114.9.

Cluster	Members	Representative	Weighted Score
0	88	Center	-1114.9
		Lowest Energy	-1114.9
1	68	Center	-959.1
		Lowest Energy	-1094.3
2	53	Center	-847.5
		Lowest Energy	-1032.4
3	52	Center	-1030.9
		Lowest Energy	-1030.9
4	43	Center	-889.9
		Lowest Energy	-977.5
5	38	Center	-1007.0
		Lowest Energy	-1145.3
6	38	Center	-898.0
		Lowest Energy	-1007.0
7	37	Center	-864.6
		Lowest Energy	-1139.0
8	37	Center	-1132.5
		Lowest Energy	-1132.5
9	36	Center	-860.8
		Lowest Energy	-971.7

Table 3: shows the top 10 best fit with the number of atoms and weightage score

IV. CONCLUSION

The work has led to computational prediction, stabilization and optimization of the structure of the proteins and to study the interaction between low-density lipoprotein receptor-related protein, (LRP1) and (phosphotyrosine interaction domain containing 1) NYGGF4, which is involved in Alzheimer disease.

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