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Homology modeling, molecular docking and elucidating of potent binding domain of Synapsin 1: A schizophrenia gene

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Abstract

Synapsin 1 is phosphoprotein consist onto the surface of synaptic vesicles. It is involved in development of neurons. SYN1 play an important role in axonogenesis and synaptogenesis neurotransmitter release and connection of vesicles to the cytoskeleton. Mutations in SYN1 can cause schizophrenia. The alterations in SYN1 lead to a neurodegenerative disorder known schizophrenia affects 1% of the population and is classified by lack of social behavior and various behavioral abnormalities. In silico approaches were employed to predict 3D structures and protein-protein docking of SYN1. Comparative modeling and threading computational approaches were applied to predict 3D structure of SYN1. STRING database calculated 1AUV as the interacting partner of SYN1. SYN1 protein-protein molecular docking study was done against 1AUV to identify the interacting residues. The observed interacting residues may have effective response against schizophrenia. The generated findings of this effort help to design the effective therapeutic targets against SYN1 by targeting schizophrenia.

Introduction

Synapsin 1 (SYN1) is a member of a phosphoprotein and also has other members Synapsin 2 and Synapsin 3 [1, 2]. The synapsins (SYNs) exist in the central and peripheral nervous system that consist onto the top of synaptic vesicles [2, 3]. The family members have been identified by regular domain of protein, interlaced in neuronal expansion, involved in synaptogenesis and the transition of neurotransmitter break [4]. SYNs manage synaptic vesicles and elaborate to the management of synaptic vesicles [5, 6].

The phosphoprotein SYN1 involves in axonogenesis and synaptogenesis regulation as well as in synaptic transmission and plasticity of mature neurons [5-7]. In vertebrate species, SYN1 plays an important role in the breakage of neural transmitter, axonogenesis and synaptogenesis demonstrated by mouse introducing with an epileptic constitution [5-8]. In nerve ending, SYN1 participate in connecting the cavity to the cytoskeleton and to one another [9, 10].

SYN1 involved in the development of neurons and also in the formation of synaptic junction between the neurons [11, 12]. SYN1 has two isoforms as isoform IA and IB with different lengths. The length of isoform IA is 705 and IB is 669 residues. During brain development, the expression of SYN1 moderately increased and reaches at the highest level in adult neural tissues [13]. SYN1 is phosphor-protein plays multiple roles in the synaptic transmission [14-16]. The SYN1 is phylogenetically conserved and has been mapped on chromosome X in human, mouse and other mammals [17, 18].

Non sense and missense mutations in human SYN1 cause epilepsy and autism. Autism disorder occurred in the presence and absence of epilepsy [19, 20]. The modifications in SYN1 are due to mutations, that causing imperfection in synaptic vesicles and nerve terminal functions [21]. According to its natural purpose, SYN1 is present in brain and neuron represented by the supporter domain of SYN1 [22]. The SYN1 act as a substance for various protein phosphokinases and phosphorylation and also perform key role in the management of SYN1 in nerve ending [23-26].

Garcia et al., explained that only variations causing a imperfection in SV trade and neural transmitter breakage in humans [27], announced a W356X modification in SYN1 in a family separating a jumble of neural expansion defects along with epilepsy. SYNs are a family member of neuron specific SV phosphoproteins interlaced in synaptic transmission and softness. SYNs manage SV trade in the middle of reserve pool (RP) and readily releasable pool (RRP). SYNs also involved in neuronal evolution, synaptogenesis and preservation of adult synapses [14, 28]. It has been recognized that variations (one non-sense and three mis-sense) within SYN1 connected with Epilepsy and Autism Spectrum Disorders. Three out of four variations were gathered in SYN1 D-domain that were related to effective flaws in nerve ending function [29].

Schizophrenia is a severe debilitating psychiatric mental disorder with heritability about 80% unorganized speeches, abnormal behave and illusion of imagination. Schizophrenia is characterized by abnormal behavior including obsession, dampening of emotions and self-deceptions. Approximately 1% of the population effected from schizophrenia in late teen to early twenty period of lifetime. Many analyses provided helping information to the plan that malfunction of SYN are associated to the schizophrenia onset. Over years some data analyses assembled characterized expression level of different SYNs on post-mortem brain sample of human. Display general decreasing of the size of SYNs protein and various expressions of SYNs modifications in brains obtain from schizophrenia.

Bioinformatics is an interdisciplinary field of science helps to solve numerous biological problems by utilizing molecular biology, computational science and statistics. Computer aided drug design has progressive success in computational research methodologies to solve biological problems [30-32] and computationally designed molecules against cancer [33, 34] and neurological disorders [35, 36]. The present study has structural modeling and identification of drug target sites of SYN1 against schizophrenia. The NMR and X-ray crystallographic structure of SYN1 has not been reported yet.

Material and Methods

Structural bioinformatics involved in the prediction of protein structure. In case of neurological diseases, it has constructive methods to sketch functional composite. SYNs involved in development of neurons. The expression of SYNs in brain development cause nervous disorders.

SYN1 protein sequence was retrieved from Uniprot KB having the accession number P17600. In this work, structure prediction and protein-protein docking analyses were executed.

The amino acid sequence of SYN1 was subjected to BLASTp for the selection of suitable templates

against Protein Data Bank (PDB) [37]. MODELLER 9.20 was utilized to predict the 3D structure of SYN1. 3D structures of SYN1 were predicted from MODELLER 9.20 [38]. For structure projection, SWISS MODEL [39], I-TASSER, MOD-WEB, Phyre2, HHpred, PSIPRED, CPHModel, M4t [40], Robetta [41], SPARKS-X, Raptor-X were utilized. UCSF Chimera 1.13 was used for the visualization of SYN1 3D structures. Anolea [42], ERRAT [43], Rampage and Verify 3D [44] were used structure evaluation. The graph and excel sheet described overall assessment of the protein structures. For the analyses of overall quality factor, Errat software was employed. Anolea evaluation tool was used for the calculation of Z-score of all predicted structures. Rampage tool was used to calculate the favored region, allowed region and outliers. The energy minimization was done by UCSF Chimera 1.13.1 [45].

The geometry expansion and energy minimization of the molecules were executed by Chem3D Ultra. PatchDock, FireDock, and PyRx were utilized for comparative molecular docking. Ligplot and UCSF Chimera 1.13.1 were used for visualization.

STITCH4 [46] (Search Tool for InTeracting CHemicals) and STRING [47] (Search Tool for the Retrieval of INteracting Genes/Proteins) were used to examine the interacting partner of SYN1. PatchDock was used for verifying as well as acceptance of the generated protein-protein results [48, 49].

Result and Discussion

Extensive literature review and biological databases showed interesting information about the sequence of SYN1. Ala, Pro and Ser were observed polar residues perform significant functions including stability, folding and function of SYN1 (**Fig. 1**).

Structure Prediction

Comparative modeling and threading were used to predict 3D structures of SYN1. The sequences of SYN1 were subjected to BLASTp against PDB database used to search suitable templates (**Table 1**). The five suitable templates with properties of query coverage, maximum identity, E values and total score were selected for homology modeling. The five selected templates were used to generate 50 structures in which each template generated 10 structures. The templates were used to predict 3D structures of SYN1. The highest query coverage of suitable templates was 59% and leftover templates have query coverage less than 42%. All the generated models were evaluated for favored region, allowed region, outliers, overall quality factor and Z-Score. By comparison of generated models, a comparative graph was generated (**Fig. 2**).

Table 1: The selected templates through BLASTp.

Description	Max Score	Total Score	Query Cover	E-Value	Per. Ident	Accession
Chain A, Rat synapsin I	864	864	59%	0.0	97.14%	1PK8
Chain A, Synapsin Ia	670	670	44%	0.0	98.39%	1AUX
Chain A, Synapsin Ia	637	637	44%	0.0	94.86%	1AUV
Chain A, crystal Structure Analysis of the complex of the C domain of Synapsin l	543	543	43%	0.0	77.92%	1I7L-A
Chain A, SYnapsin-3	498	498	42%	1e-172	70.72%	2P0A

ERRAT was utilized to evaluate quality factor of SYN1. The energy minimization on model forecast form of SYN1 was applied to refine the stereochemistry. The suitable structure was examined. The chosen structures after assessment restriction were subjected to UCSF Chimera 1.10 for minimization at 1000 steepest and conjugate slops runs (**Fig. 3**). String was applied to predict interacting part of SYN1. The structure has highest identity subjected with UCSF Chimera 1.10 and removed extra residues.

Protein-protein docking studies

The protein-protein docking analyses were performed through PatchDock. The receptor ligand (SYN1-1AUV) complex was examined onto the base of atomic contact energy and top ranked 10 complexes. Additionally, analyses were evaluated through FireDock and the complexes were examined on to the base of minimum binding global energy (**Table 2**) (**Fig. 4**).

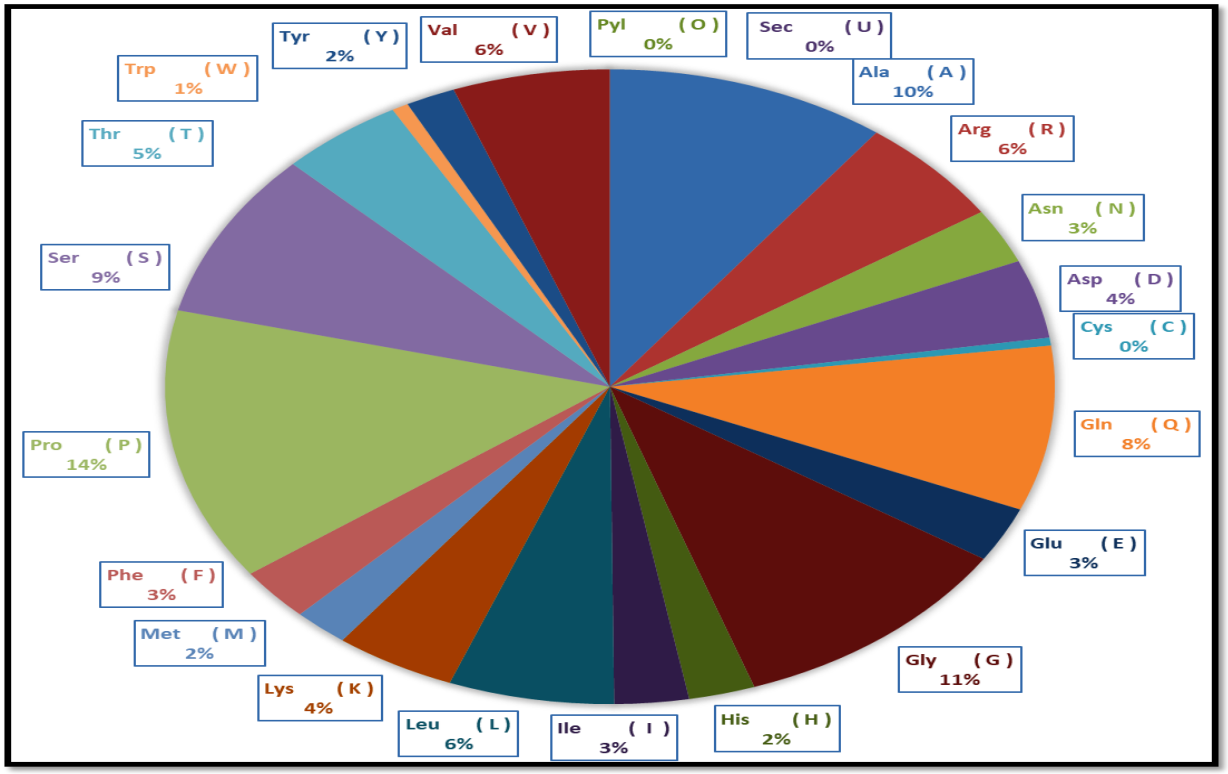

Fig. 1: Pie chart representation of composition amino acids and calculated percentage values of SYN1.

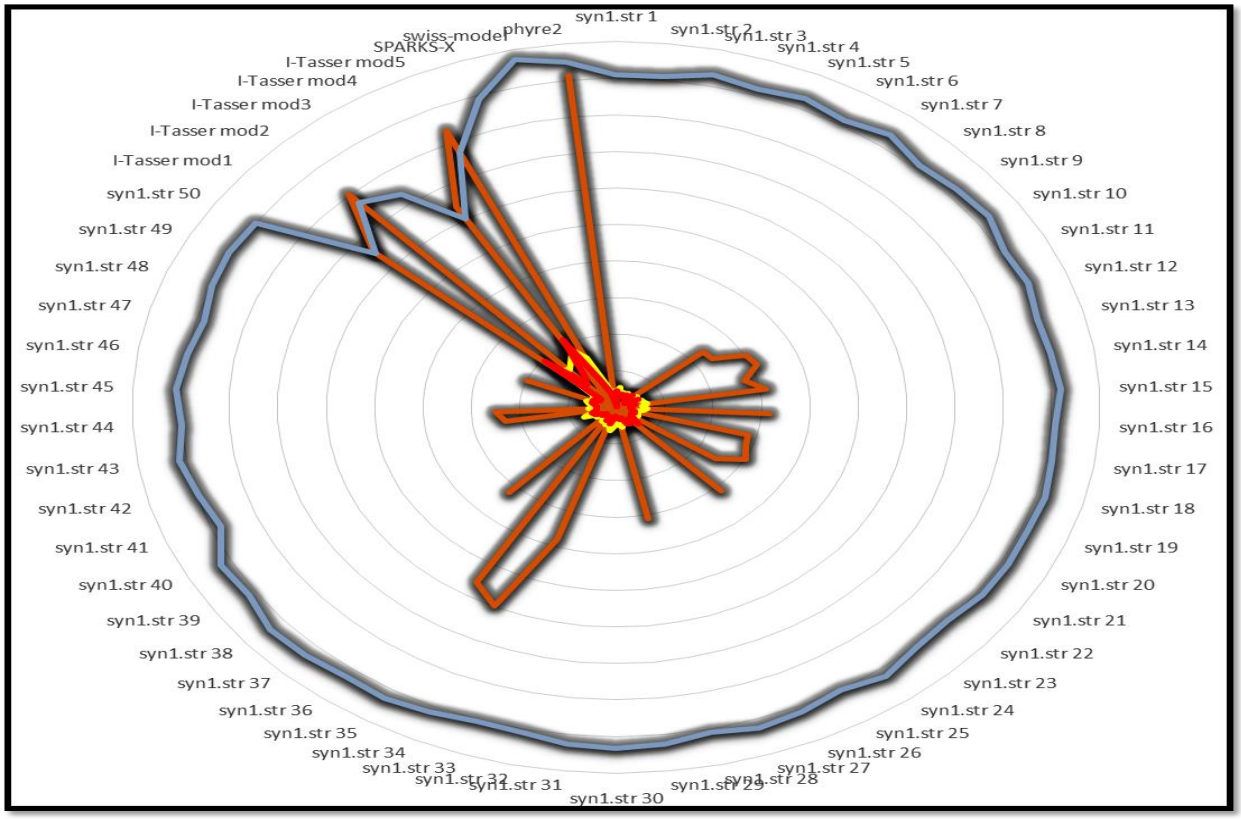

Fig. 2: Graph shows the quality factor (orange brown), allowed region (yellow), favored region (blue) and outlier region (red) *From all structures, most reliable structure was selected from graph.

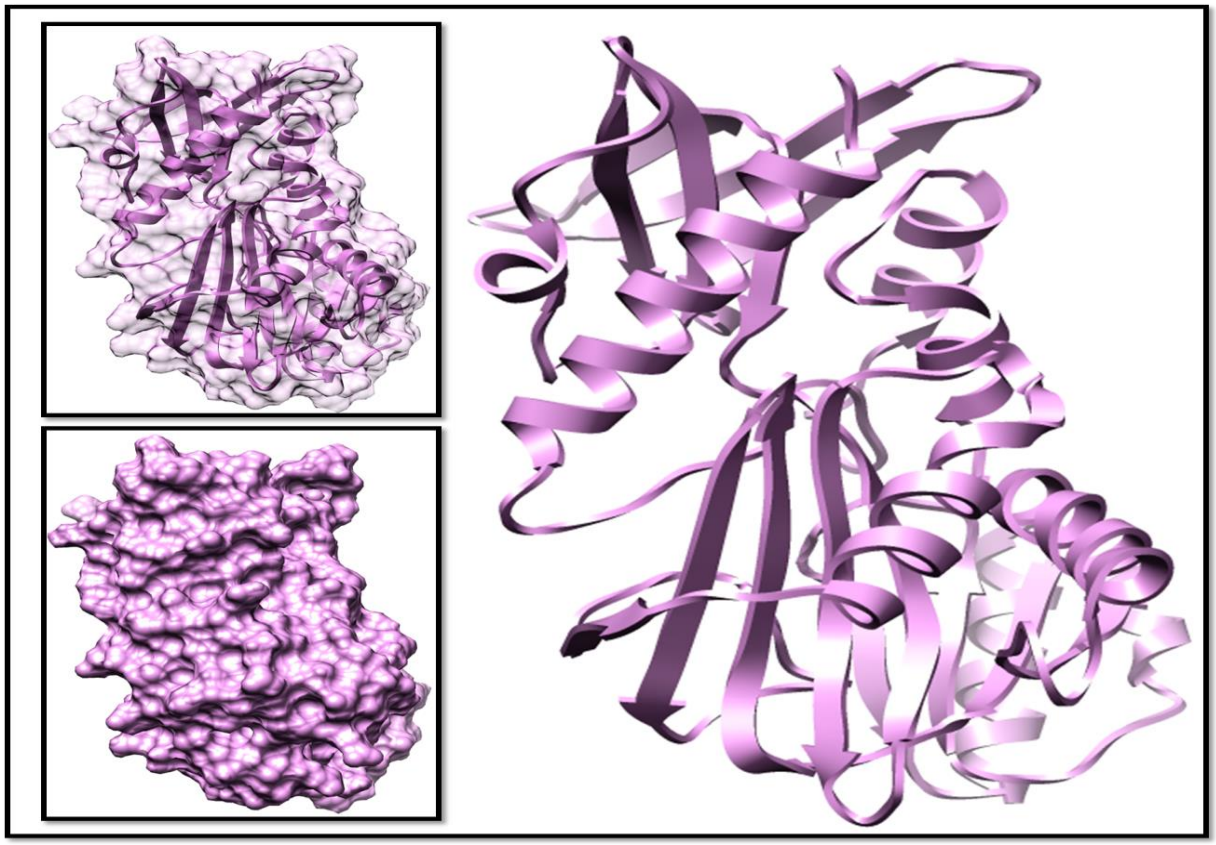

Fig. 3: The protein 3D structure of SYN1.

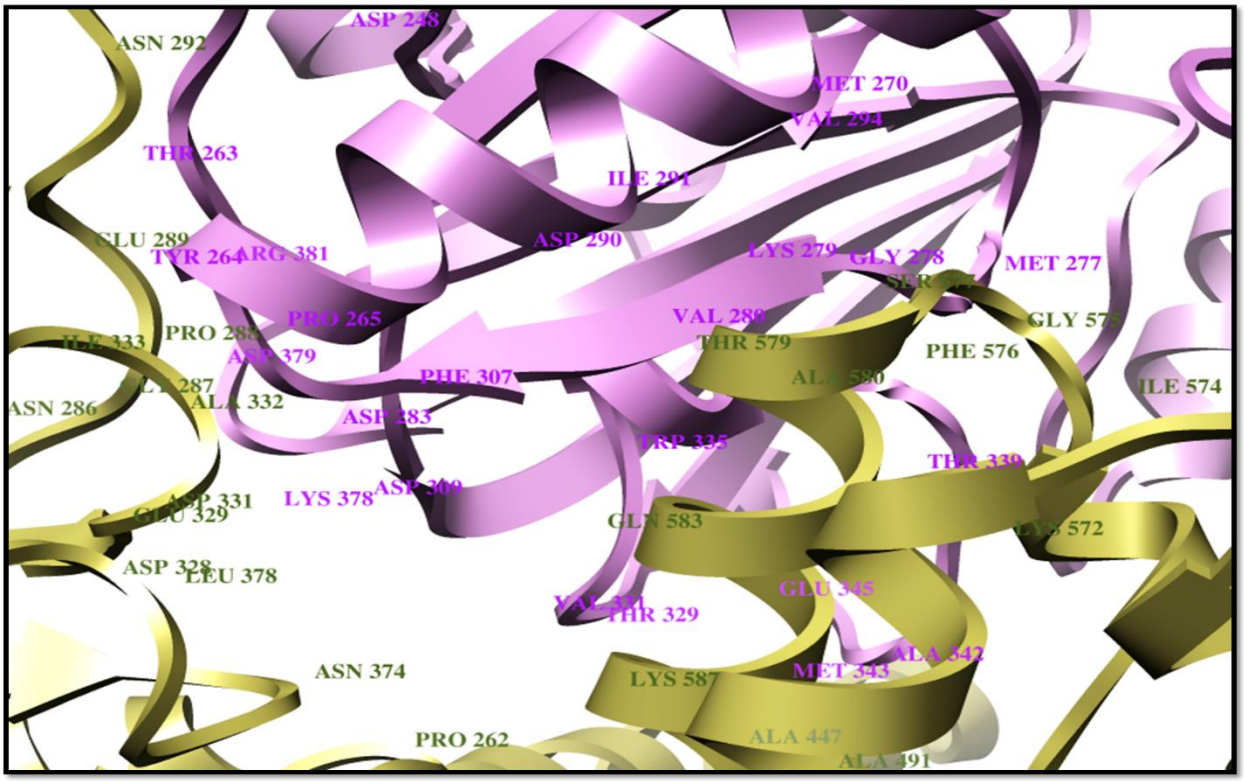

Fig. 4: The protein-protein docking structure analyses.

Table 2: The interacting residues of target protein and interacting protein

Target protein	Target Protein Residues	Interacting Protein	Interacting Protein Residues
SYN 1	GLU 289, GLY 287, PHE 492, PRO 262, ALA 491, THR 579, ALA 580, SER 577	1AUV	ARG 381, ASP 379, VAL 331, MET 343, ALA 342, VAL 280, MET 270ILE 291, VAL 294

Conclusion

Schizophrenia is considered as a complex disorder affects almost 1% of the total population. Computational techniques were utilized based on structural modeling docking analyses. The 3D structure prediction proposed the reliability of the structure. The docking analyses satisfied the least binding global energy and elucidating the target binding sites of SYN1 against schizophrenia.

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Conflict of interest

The authors declare no conflicts of interest.

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