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HOMOLOGY MODELLING AND STRUCTURE EVALUATION OF HUMAN GRIN 1 PROTEIN

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Abstract

Human immune deficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) is a disease of human immune system caused by infection with human immunity. HIV targets the T-cells in the human body. The virus begins its infection by first binding itself to the receptor protein(CD4)s on a human cell, which enables the membranes to fuse and allows the virus to enter the cell. Once inside the cell, HIV generated DNA using reverse transcriptase integrates with human DNA by the enzyme integrase that is present in the viral core. Glutamate [NMDA]receptor subunit zeta-1 is a protein that in humans is encoded by the GRIN1 gene.The protein encoded by this gene is a critical subunit of N-methyl-D-aspartate receptors, members of the glutamate receptor channel super family which are heteromeric protein complexes with multiple subunits arranged to form a ligand-gated ion channel. These subunits play a key role in the plasticity of synapses, which is believed to underlie memory and learning. The gene consists of 21 exons and is alternatively spliced, producing transcript variants differing in the C-terminus. Although the sequence of exon 5 is identical in human and rat, the alternative exon 5 splicing in rat has yet to be demonstrated in human. Cell-specific factors are thought to control expression of different isoforms, possibly contributing to the functional diversity of the subunits.

GRIN suppress infection by cell HIV-1 strains tested has equivalent or reduced effects on divergent similar immunodeficiency viruses. The primary step towards better understanding of the protein function is to determine the structure of the protein. The model was generated using CPH3 server using the template sequence 5fxi. Thecorrectness of the predicted structures are evaluated using Errat server and Ramachandran plot.

Keywords **:** *Homology modeling, Human GRIN 1 protien, NCBI, Genbank, FASTA, Query sequence, CPH model 3.2 server, Stride server, Ramachandran plot, Errat server.*

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Introduction

Human immuno deficiency virus infection (HIV/AIDS) is a disease of the human immune system caused by infection with human immunodeficiency virus (HIV). AIDS was first recognized by the Centers for Disease Control and Prevention (CDC) in 1981 and its cause-HIV infection-was identified in the early part of the decade[1]. During the initial infection, a person may experience a brief period of influenza-like illness[2]. This is typically followed by a prolonged period without symptoms. One of the unique properties of HIV is that it is a retrovirus; it carries its genetic material as RNA and creates viral DNA with the help of an enzyme called reverse transcriptase[3]. It targets the T-cells in the human body. The virus begins its infection by first binding itself to the receptor protein (CD4)s on a human cell, which enables the membranes to fuse and allows the virus to enter the cell. Although not as effective as the viral propagatory mechanism, there are potent HIV entry inhibitors within the cell. For entry into a cell, HIV has to interact with the specific co-receptor called CCR5.

He protein encoded by this gene is a critical subunit of N-methyl-D-aspartate receptors. Cell-specific factors are thought to control expression of different isoforms, possibly contributing to the functional diversity of the subunits,and the block to infection occurs at a late post-entrystep, with both the nuclear accumulation and chromosomal integration of nascent viral complementary DNA suppressed. Homology modeling, also known as comparative modeling of protein, refers to constructing an atomic resolution model of the "target" protein from its amino acid sequence and an experimental three dimensional structure of a related homologous protein (the"template"). The method of homology modeling is based on the observation that protein tertiary structure is better conserved than amino acid sequence. Human GRIN1 protein serves as a first line defense against HIV-1 in humans by inhibiting the nuclear transport of the virus.

Materials and Method

The GRIN 1 protein FASTA sequence of the protein was taken from GenBank (http://www.ncbi.nlm.nih.gov/genbank/).

Model building using CPHmodels-3.2 web server

The FASTA sequence of GRIN1 is submitted to the server by pasting the sequence in the corresponding field of CPH models 3.2 server. The following methodologies are followed in the modeling program.

Identification of template protein

A position-specific scoring matrix (PSSM) is generated for a query sequence by searching for up to five iterations with default settings, against a local version of the Uniprot database using PsiBlast (1). The PSSM generated by Blast is saved and

used to search for a template in PDB. The blast procedure identified GRIN1 protein with PDB id [3szr A]as the most related protein for our query sequence. Next, the query is aligned to the template.

Modeling

Once the best template has been found, Cα-atom coordinates are extracted according to the sequence alignment and used as a starting point for the homology-modeling process. Missing atoms were added using the segmod program and the structure was refined using the encadprogram[4], both from the GeneMine package (www.bioinformatics.ucla.edu/genemine/).

Structure Evaluation

The correctness of the predicted structures are evaluated using errat server and stride server. Ramachandran plot has been generated to check the validity of the structure.

Results and Discussion

Prior to the modelling, the server made an alignment of both the target and template protein sequences for identification of structurally conserved and variable regions between them[5].

Figure 1: The alignment between the sequence of GRIN 1 sequence (query) and the sequence of template.

The success of the homology model depends upon the quality of the alignment between the two protein sequences. Since the identity between the two proteins is above 94.8 %, homology modeling of our target protein is not an issue here.

. The strand structure of GRIN 1 protein thus generated through homology modeling is shown in figure 2.

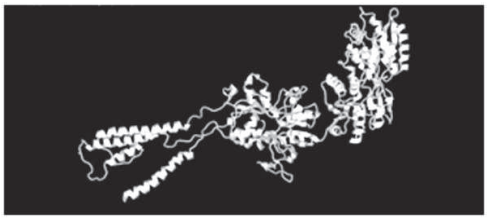

Figure 2: Figure showing the modeled structure of human GRIN 1 protein

Secondary structural analysis of the protein was done at the stride server. It produces a visual output of various secondary structural features occupied by all the residues in the proteins in a diagrammatic view (Figure 3).

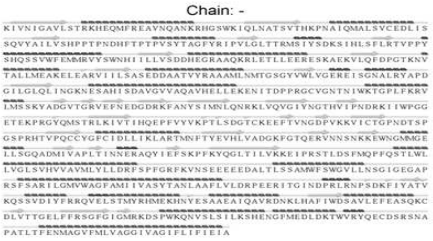

Figure 3: Secondary structure analysis of modeled human GRIN1 protein

The structure shows that there are 21 alpha helix, 34 beta helix and 69coiled (loop) regions.The 3-dimensinal arrangement of secondary structures of human GRIN1 protein is given in figure 4[6].

Figure 4: Three dimensional arrangement of different secondary structures in the modeled human GRIN1 proteins

Stereochemical quality of the modeled human GRIN 1 protein is calculated using the Errat [7] and Ramachandran Plot analysis [8].

Ramachandran plot analysis was employed to evaluate the stereo chemical quality of the protein.985.0% residues were in most favoredregions.12.9% residues in additional allowed regions. Only 0.7% are in the disallowed regions. The structure also shows trans-membrane and nuclear regions very clearly.

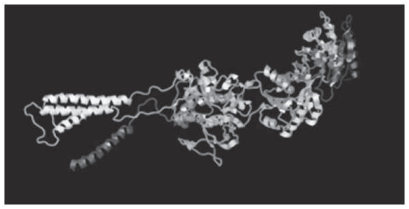

Figure 4: Three dimensional arrangement of different secondary structures in the modeled human GRIN1 proteins

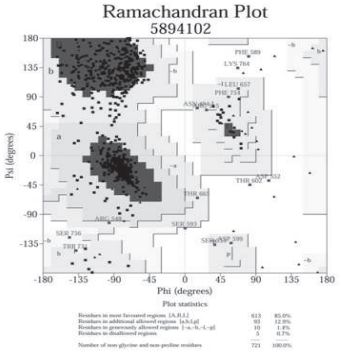

Figure 5: Ramachandran plot analysis data of GRIN 1 Protein

Errat is a programe for verifying protein structures determined by X-ray crystallography. The over- all quality factor for GRIN 1 protien is 86.318.

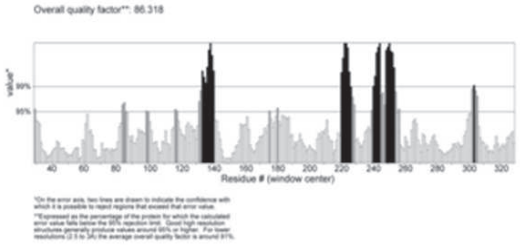

Figure 6: Errat analysis data of human GRIN 1 protein.

Our model of GRIN 1 protein from the human beings is found very much confined to the secondary structural features of the template protein indicating the common structural features occupied by both and which in turn is an indication of the correctness of the homology modeling procedure. Thus our model in general showed the overall features of the GRIN 1 class of proteins as well as showed differences with the template to indicate their unique identity from the other members of the class.

The correctness of a proteins structure depends on satisfying the basic bio-physical parameters associated with the protein folding process such as correct bond lengths, bond angles, tetrahedral angles, phi angles, psi angles etc. Stereo chemical analysis by Errat followed by Ramachandran Plot analysis are in tune with the features of a correct macromolecular structural features. In effect, the modeled structure of GRIN 1 protein confined to the secondary structural and stereochemical features for a good quality structure.

Conclusion

Human GRIN 1 protein was modeled by CPH3.2 server using 5fxi as a template. The overall protein sequence identity between the protein model and template was around 94.8% and an E-value of 1e-108. Secondary structure prediction using Stride server identified 21 alpha helices , 34betastrands and 69coiled(loop) regions in the modeled human GRIN 1 protein. Ramachandran plot analysis was employed to evaluate the stereo chemical quality of the protein. 85% residues were in most favored regions, 12.9% residues in additional allowed regions, and only 0.7% are in the disallowed regions. Errat analysis determines correctness of protein structure and the overall quality factor is 86.318.The result indicates that the modeled GRIN 1 protein confines to allowed regions of the evaluation criteria. The generated structure can be used for further studies in future.

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