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COMPUTATIONAL MODELLING AND FUNCTIONAL CHARACTERIZATION OF HDAC-11

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ABSTRACT: In eukaryotes, DNA is packaged into chromatin structures, whose basic unit is the nucleosome. A principle component of chromatin that plays an important role in the regulation of DNA is the modification of histones. Since histones are post-translationally modified, there inludes a large number of different histone post-translational modifications. These histone modifications create a repressive environment for gene expression, which in case of histone acetylation, are controlled by competing activities of two families of enzymes, histone acetyltransferases (HAT's) and histone deacetylases (HDACs). HDAC11 is a class IV protein of the HDAC family. The present aim of this study is to develop a model of HDAC11 by using bioinformatics applications. The design of the model is based on thorough evaluation of the HDAC-11 query sequence, Q96DB2, which was retrieved from UniProtKB. The physiochemical and primary analysis were computed using ExPASy Protparam tool. Functional characterization was computed using RaptorX, HMMTOP and Softberry Server's CYS_REC tool (Cysteine Recognition Server) which predicted the secondary structure composition, presence of transmembrane proteins and the presence of cysteine residues respectively. The molecular model was generated using PHYRE2 server, since it was best suited as it provided higher query sequence coverage and confidence. Model refinement was computed using UCSF Chimera V1.9 and validation was performed using RAMPAGE server which explains the feature of Psi and Phi angle orientation. Verify 3D Structure Evaluation Server was used to determine the 3D-profiling of the residues in the model. The overall quality score of the model was calculated by ProSA Web Server.

INTRODUCTION: In eukaryotes, DNA is packaged into chromatin structures, whose basic unit is the nucleosome. Histones are highly conserved basic proteins which associate with DNA to constitute the nucleosome, each nucleosome consists of ~148 bp DNA, wrapping around a core histone octamer, which contains copies each of H2A, H2B, H3, and H4. Also a H1 linker histone is associated, which binds externally with the nucleosome and helps in further compaction of the chromatin structure.

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Within a nucleosome, these exist as two dimers of (H2A-H2B) and a complex of (H32-H42) ultimately forming an octamer.[1, 2].

A principle component of chromatin that plays an important role in the regulation of DNA is the modification of histones. It is clear from recent studies, that histone modifications play fundamental roles in most biological processes that are involved in the manipulation and expression of DNA.[3] Since histones are post-translationally modified, there involves a large number of different histone post-translational modifications which include Histone acetylation, Histone Methylation, Histone phosphorylation and other modifications, of which Histone Acetylation is the best understood modification.[3] Hypoacetylated chromatin is associated with gene silencing, whereas hyperacetylation correlates with gene activation.

However, recent studies have shown that histone deacetylation can also play a significant role in transcriptional activation [3]

These histone modifications create a repressive environment for gene expression, which in case of histone acetylation, are controlled by competing activities of two families of enzymes, histone acetyltransferases (HAT's) and histone deacetylases (HDACs).[1]

The HATs utilize acetyl CoA as cofactor and catalyse the transfer of an acetyl group to the epsilon-amino group of lysine side chains in the NH2-terminal tails of core histones. In doing so, they neutralize the lysine's positive charge and this action has the potential to weaken the interactions between histones and DNA. The HATs are classified into two classes: type-A and type-B. The type-B HATs are predominantly cytoplasmic, acetylating free histones but not those that are already deposited into chromatin. The type B-HAT's also acetylate newly synthesize histones. The type-A HATs are a more diverse family of enzymes than the type-Bs. Nevertheless, they can be classified into at least three separate groups depending on amino-acid sequence homology and conformational structure: GNAT, MYST and CBP/p300 families [3]

HDAC enzymes oppose the effects of HATs and reverse lysine acetylation, an action that restores the positive charge of the lysine. This potentially stabilizes the local chromatin architecture thus allowing the DNA to wrap more tighty and is consistent with HDACs being predominantly transcriptional repressors [3]

HDAC's based on their homology to yeast orthologues Rpd3, HdaI and Sir2, respectively, comprise a family of 18 genes, which are grouped into classes I–IV. The Classes I, II, and IV consist of 11 family members, which are referred to as classical HDAC's, whereas the class II, which consists of 7 members are called Sirtuins.[4]

Classes I and II contain enzymes that are most closely related to yeast scRpd3 and scHda1, respectively, Class I being closely related to yeast scRpd3, comprise of HDAC1, HDAC2, HDAC3 and HDAC8. Class II having closely related to yeast scHda1 and are divided into subclass IIA (HDAC4, HDAC5, HDAC7 and HDAC9) and subclass IIB (HDAC6 and HDAC10). [3, 4]

Class IV has only a single member, HDAC11, while class III (sirtuins) are homologous to yeast scSir2.[3] The sirtuins have a catalytic domain, unique to this family characterized by its requirement for nicotine adenine dinucleotide (NAD) as a cofactor.[5]

Classical HDACs are Zn^{2+}-dependent enzymes which harbour a catalytic pocket with a Zn^{2+} ion at its base that can be inhibited by Zn^{2+} chelating compounds such as hydroxamic acids. In contrast, these compounds are not active against sirtuins. Taking into consideration, Classical HDAC's being a promising novel class of anti-cancer drug target [4], also histone modifications like DNA methylation and histone acetylation play an important role in a wide range of brain disorders,

From recent research, Histone Deacetylase Inhibitors are suggested to act as neuroprotectors by enhancing synaptic plasticity and learning and memory in a wide range of neurodegenerative and psychiatric disorders, such as Alzheimer's disease and Parkinson's disease [6]. The present study aims at developing fully modelled structures of HDAC11 as its 3D structure is currently not available The development of these structures may provide information related to functional mechanisms and also help us in further docking studies and aid in anticancer and neuroprotector drugs.

MATERIALS AND METHODS:

Sequence Retrieval:

Since the 3D structure for our interested protein HDAC11 is not available on UniProtKB database, its FASTA sequence was retrieved from UniProtKB (Q96DB2) consisting of 347 aminoacids and was subjected for physiochemical characterization

Physiochemical Characterization:

The physiochemical characterization of our protein Q96DB2 consisting of 347AA residues is computed by ExPASy-ProtParam tool [7]. The tool

provides sequence fragment analysis also, but here the entire sequence analysis is computed. This tool allows the computation of various physical and chemical parameters for a given protein. The computed parameters include the molecular weight, theoretical pI (isoelectric point), amino acid composition, atomic composition, extinction coefficient, estimated half-life, instability index, aliphatic index and grand average of hydropathicity (GRAVY).

Secondary structure Analysis:

The secondary structure prediction of our protein Q96DB2 was computed by using various online softwares, which included RaptorX, HMMTOP and CYS_REC.

The RaptorX is a protein structure prediction server which was used to predict secondary structures[8], excelling at predicting 3D structures for protein sequences without close homologs in the Protein Data Bank (PDB). The FASTA sequence of our protein was retrieved and was submitted to the RaptorX server. Using RaptorX server, number of secondary structure components such as α-helix, β-sheets, turns, random coils were predicted.

The presence of Transmembrane Proteins was predicted by using HMMTOP [9]. HMMTOP is an automated server which predict's transmembrane helices and topology of proteins. The submission of our protein was done by submitting the FASTA sequence of our protein Q96DB2.

Also the presence of Di-sulphide bonds was computed by using Softberry server's CYS_REC tool [10], which predicts SS-bonding States of Cysteines and disulphide bridges in Protein Sequences. These predictions are computed by submitting the FASTA sequence. It predicted the absence of Di-sulphide bonds.

Molecular Modelling:

The molecular modelling of our protein Q96DB2 was carried out using multiple Protein Homology structure prediction servers. The best results were found in PHYRE2 with the highest query sequence coverage and confidence. [11] The best template which provided the maximum query coverage and confidence based on the ranking of raw alignment score was selected. The modelled HDAC11 is shown in **Picture 1**. Using RasMol software.

Model Refinement:

The model refinement and energy minimization was carried out using UCSF Chimera V1.9 [12].
UCSF Chimera is a highly extensible program for interactive visualization and analysis of molecular structures and related data, including density maps, supramolecular assemblies, sequence alignments, docking results, trajectories, and conformational ensembles. [13]

An initial model built will usually contain errors, In order to produce an accurate model, it is necessary to carry out model refinement, which includes the addition of H-bonds, in the expected regions. Then is the energy minimization of the extended atomic model using a combination of physics and knowledge based force fields. The energy minimized model is the final refined model.

Model Validation and Verification:

The model validation was carried out using multiple servers. The model thus generated was subjected to a series of analysis to determine its stability and reliability. The Backbone conformation of the refined model was computed by the Rampage web server which explains the feature of Psi and Phi angle orientation [14]. Verify 3D Structure Evaluation Server was used to determine the 3D-profiling of the residue in the model [15]. The overall quality score of the model was calculated by ProSA Web server.[16, 17]

RESULTS AND DISCUSSIONS:

Sequence Retrieval and Primary Sequence Analysis:

Initial analysis was to identify the query sequence of HDAC-11 (Q96DB2) which was retrieved from UniProtKB (**Table 1**), which consisted of 347 AminoAcid residues.

The primary analysis of the query was computed using Expasy proteomics server ProtParam tool and the physicochemical properties were analyzed. In Protparam, no additional information was required about the query protein. The query sequence can either be specified as Swiss-Prot/TrEMBL accession number or ID, or in the form of a raw

sequence. The header of the sequence was removed.

The molecular weight of our protein HDAC11 (Q96DB2) was found to be 39183.1, consisting of 347AA residues. Theoretical pI (Isoelctric point) was found to be 7.17, thus helping out the purification of the protein by efficient buffer systems. The Extinction coefficients are in units of M^{-1} cm^{-1}, at 280 nm measured in water provides a value of 44015. The extinction coefficient indicates how much light a protein absorbs at a certain wavelength.

Two values are produced by ProtParam based on the above equations, both for our protein measured in water at 280 nm. The first one shows the computed value based on the assumption that all cysteine residues appear as half cystines (i.e. all pairs of Cys residues form cystines), and the second one assuming that no cysteine appears as half cystine (i.e. assuming all Cys residues are reduced). Experience shows that the computation is quite reliable for proteins containing Trp residues; however there may be more than 10% error for proteins without Trp residues. Extinction Coefficient is calculated on the basis of Trp and Tyr that help us in the quantitative study of the protein-protein and protein-ligand interactions in solution.

Our value here indicates higher concentration of Trytophan and Tyrosine. The predictive charged residues (+R, -R) indicate that our interested protein is neutral in nature with equal number of charged residues of (Asp + Glu) and (Arg + Lys) that is 44. The instability index indicates less than 40, i.e. 39.10, which represents that our protein is stable.

The estimated half life period was derived for the prediction of the time it takes for half of the amount of protein in a cell to disappear after its synthesis in the cell. The aliphatic index (AI), a positive factor for the increase of thermal stability of globular proteins was found to be high- 96.05%, indicates greater amount of aliphatic to aromatic residues. Thus, both proteins appear to be stable over a wide range of temperatures.

The High Grand Average hydropathy (GRAVY) value of the protein was calculated to predict its solubility and a positive score indicates hydrophobicity while a negative score indicates hydrophilicity. The very low GRAVY indices of both proteins indicate they could interact well with water. Our computed value is -0.209, which concludes to be hydrophilic in nature. All the parameter values are represented in (**Table 2**). Detailed amino acid composition of HDAC11 protein is shown (**Table 3**).

TABLE 1: HDAC11 QUERY SEQUENCE RETREIVED FROM UNIPROTKB.

>sp|Q96DB2|HDA11_HUMAN Histone deacetylase 11 OS=Homo sapiens GN=HDAC11 PE=1 SV=1

MLHTTQLYQHVPETRWPIVYSPRYNITFMGLEKLHPFDAGKWGKVINFLKEEKLLSDSMLVEAREASEED
LLVVHTRRYLNELKWSFAVATITEIPPVIFLPNFLVQRKVLRPLRTQTGGTIMAGKLAVERGWAINVGGGF
HHCSSDRGGGFCAYADITLAIKFLFERVEGISRATIIDLDAHQGNGHERDFMDDKRVYIMDVYNRHIYPGD
RFAKQAIRRKVELEWGTEDDEYLDKVERNIKKSLQEHLPDVVVYNAGTDILEGDRLGGLSISPAGIVKRDE
LVFRMVRGRRVPILMVTSGGYQKRTARIIADSILNLFGLGLIGPESPSVSAQNSDTPLLPPAVP

TABLE 2: EXPASY PROTPARAM RESULT OF OUR PROTEIN HDAC11

Parameters	Values
Lengh (Aminoacid residues)	347
Molecular Weight	39183.1
Theoretical pI (Isoelctric point)	7.17
Positively charged residues (Asp + Glu) (+R)	44
Negatively charged residues (Arg + Lys) (- R)	44
Extinction Coefficient (M^{-1} cm^{-1})	44015
Estimated Half life	30 hours (mammalian reticulocytes, in vitro) >20 hours (yeast, in vivo). >10 hours (Escherichia coli, in vivo)
Instability Index	39.10
Aliphatic Index (AI)	96.05%
GRAVY	-0.209

TABLE 3: AMINO ACID COMPOSITION OF HDAC11

ALA (A)	21	6.1%
ARG (R)	27	7.8%
ASN (N)	11	3.2%
ASP (D)	21	6.1%
CYS (C)	2	0.6%
GLN (Q)	9	2.6%
GLU (E)	23	6.6%
GLY (G)	29	8.4%
HIS (H)	10	2.9%
ILE (I)	25	7.2%
LEU (L)	35	10.1%
LYS (K)	17	4.9%
MET (M)	8	2.3%
PHE (F)	14	4.0%
PRO (P)	18	5.2%
SER (S)	17	4.9%
THR (T)	17	4.9%
TRP (W)	5	1.4%
TYR (Y)	11	3.2%
VAL (V)	27	7.8%
PHY (O)	0	0%
SEC (U)	0	0%
(B)	0	0%
(Z)	0	0%
(X)	0	0%

Secondary Structure Analysis and Functional Characterization:

As percentage of Cysteine (Cys) is very low in our HDAC11 protein under study (**Table 3**), also none of these proteins have disulphide bond linkages, as indicated by CYS_REC result which indicates the instability of the protein. (**Table 4a, 4b**). The extensive hydrogen bonding may provide stability to these proteins in absence of disulphide bonds.

Secondary structures of our query protein were predicted using RaptorX. Secondary structure prediction is provided in 3 state secondary structure mode, which are abbreviated as H, E, and C, which represent helix, beta-sheet and loop, respectively. (**Table 5**)

HMMTOP which is an automatic server for predicting transmembrane helices and topology of proteins, this tool is used to analyze the number of transmembrane domain in our given protein. The orientation of the helices may be present from 87-106, 119-136, and 149-166. (**Table 6**)

TABLE 4a: CYS_REC RESULT PROVIDING THE NUMBER OF CYSTEINE RESIDEUS AND ITS POSITIONS.

No. Of Cysteines	Position of Cysteine
2	144 , 153

TABLE 4b: CYS_REC RESULT PROVIDING THE SCORE OF CYSTEINE RESIDEUS.

CYS	144 is probably not SS-bounded	Score: -2.8
CYS	153 is probably not SS-bounded	Score: -1.8

TABLE 5: PREDICTION OF SECONDARY STRUCTURES USING RAPTORX

Secondary Structure	Percentage of Secondary Structure
H (Alpha Helix)	37%
E (Beta- Sheet)	12%
C (Loop)	50%

TABLE 6: PREDICTION OF TRANSMEMBRANE HELICES USING HMMTOP

Protein	Length	N-Terminus	No. of Transmembrane helices	Transmembrane helices
HDAC11	347	Out	3	87-106, 119-136, 149-166.

Molecular Modelling Studies:

Our query protein HDAC11 was subjected for modelling using PHYRE2 ((Protein Homology/AnalogY Recognition Engine). Phyre2 is a major update to the original Phyre server with a range of new features, accuracy is improved, using the alignment of hidden Markov models via HH search to significantly improve accuracy of alignment and detection rate.

PHYRE2 works on the algorithm of PSI-BLAST in which the target sequence is subjected to PSI-BLAST iterations which detects the evolutionary relationships between the homologous sequences.

From the PSI-BLAST results, a HMM (Hidden Markov Model) is made out of the evolutionary patterns among the homologous sequences, thus making an evolutionary fingerprint.

When an unknown sequence is submitted, the algorithm which has already made HMM of known structures are compared with our sequence to make a 3-D model. PHYRE2 provides accurate results even in >15% sequence identity An HTML link is provided, which gives the result summary. The top ranked models generated by Phyre2 are represented in (**Table 7**)

TABLE 7: TOP 5 RANKED MODELS GENERATED FOR OUR QUERY PROTEIN USING PHYRE2

Template	Alignment Coverage	Confidence	Percentage Identity	Template Information
c1zz0C	93% (15-341 residues of the sequence aligned)	100	20	Chain: C: PDB Molecule:histone deacetylase-like amidohydrolase;
c3maxB	95% (15-347 residues of the sequence aligned)	100	24	Chain: B: PDB Molecule:histone deacetylase 2
c4a69A	95% (15-347 residues of the sequence aligned)	100	23	Chain: A: PDB Molecule:histone deacetylase 3
d3c10a1	92% (13-335 residues of the sequence aligned)	100	20	Fold:Arginase/deacetylase Superfamily:Arginase/deacetylase Family: Histone deacetylase, HDAC
d1c3pa	90% (15-330 residues of the sequence aligned)	100	24	Fold:Arginase/deacetylase Superfamily:Arginase/deacetylase Family:Histone deacetylase, HDAC

The matches are ranked by a raw alignment score (not shown) that is based on the number of aligned residues and the quality of alignment. This in turn is based on the similarity of residue probability distributions for each position, secondary structure similarity and the presence or absence of insertions and deletions. The Percentage Identity determines the accuracy of the model. Even with low Percentage Identity (<15%), the models can be useful as far as the confidence is high. Confidence represents the probability (from 0 to 100) that the match between our protein and the template is homologous.

The template which was best suited for the generation of the model of our protein HDAC11 was c1zz0C- Histone deacetylase-like amidohydrolase, Chain C, since it provided 93% of the query sequence coverage (15-341 residues of our sequence aligned). The modelled structure of HDAC11 is viewed in RasMol tool (**Figure 1**)

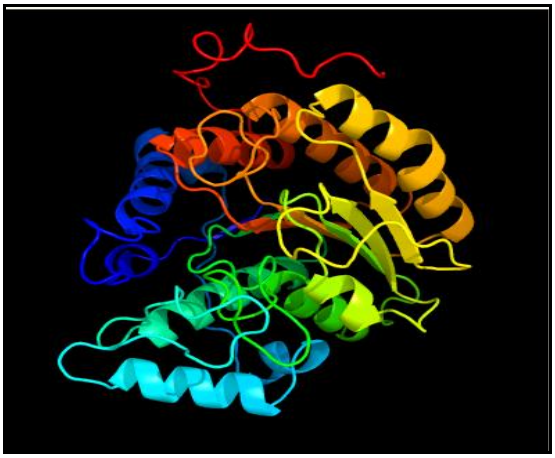

FIG. 1: MODELLED STRUCTURE OF HDAC11 GENERATED FROM PHYRE2 VIEWED IN RASMOL.

Other Modelling servers which are available for model building include SWISS-MODEL Workspace – ExPASy, I-TASSER, M4T server, ModWeb, HMM Modellor, RaptorX etc. These servers were not used for the generation of the model of our protein HDAC11, since the template identity and the total sequence coverage were low (<50%) As a result, these models were no longer beneficial for futher scope. Due to this limitation, PHYRE2 was used for the generation of the model.

Model Refinement:

Model refinement was carried by using UCSF Chimera V1.9. UCSF Chimera is a highly extensible program for interactive visualization and analysis of molecular structures and related data, including density maps, supramolecular assemblies, sequence alignments, docking results, trajectories, and conformational ensembles.

In model refinement, the addition of Hydrogen bonds takes place, which aids to the stability of the model, as the absence of Di-sulphide bonds resulted in the instability of the model.

The addition of charge is done, which associate atoms with partial charges and other force field parameters, which included the assignment of Amber residue names, Amber atom types, and atomic partial charges from an Amber force field. Energy Minimization is intended for cleaning up small molecule structures and improving localized interactions within larger systems. The minimization procedure occurs in a vary of steps which include Steepest descent minimization,

which is performed first to relieve highly unfavourable clashes, followed by conjugate gradient minimization, which is much slower but more effective at reaching an energy minimum after severe clashes have been relieved. [17]

The minimized structure is represented in (Picture 2) viewed in UCSF Chimera V1.9

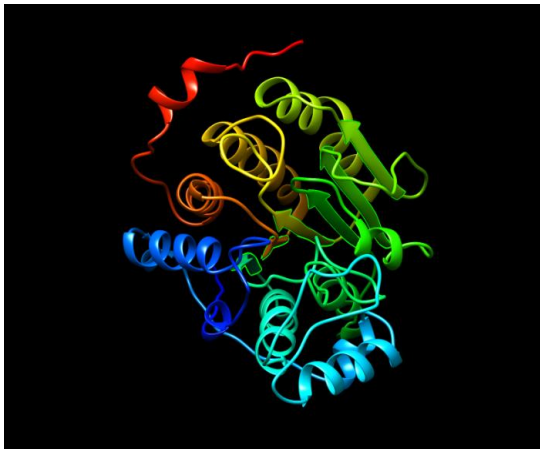

FIG. 2: REFINEMENT AND MINIMIZATION OF OUR PROTIEN HDAC11 PERFORMED IN UCSF CHIMERA V1.9

Model Validation and Verification:

Our interested protein was validated using RAMPAGE server, verifying the parameter of Ramachandran plot quality. (**Figure 3)** The models were tested for φ and ψ torsion angles using the Ramchandran plot, and the plot analysis (**Table 8**) showed that 88.6% (288) of the residues are in the favoured region, 7.7% (25) are in the allowed region and 3.7% (12) are in the outlier region.

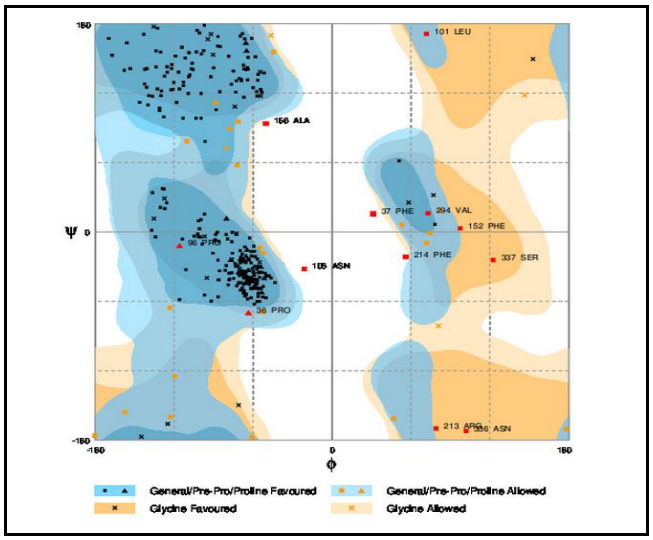

FIGURE 3: RAMACHANDRAN PLOT OF OUR MODELLED PROTEIN HDAC11

TABLE 8: RAMPAGE SERVER PLOT ANALYSIS OF OUR COMPUTED HDAC11 PROTEIN MODEL

Plot Analysis	Score
Number of residues in favoured region (~98.0% expected)	288 (88.6%)
Number of residues in allowed region (~2.0% expected)	25 (7.7%)
Number of residues in outlier region	12 (3.7%)

The model was verified using Verify3D; it analyzes the compatibility of an atomic model (3D) with its own amino acid sequence (1D). Each residue is assigned a structural class based on its location and environment (alpha, beta, loop, polar, nonpolar, etc). A collection of good structures is used as a reference to obtain a score for each of the 20 amino acids in this structural class. The scores of a sliding 21-residue window (from -10 to +10) are added and plotted for individual residues.

From the results obtained from Verify3D, The residues falling in the area where the orange line crosses 0.0 have low prediction accuracy and less stable conformation, since none of the residues fall in the orange line region and all the residues are in the region between 0.13-0.65, we can say that our model is of good quality (**Figure 4**)

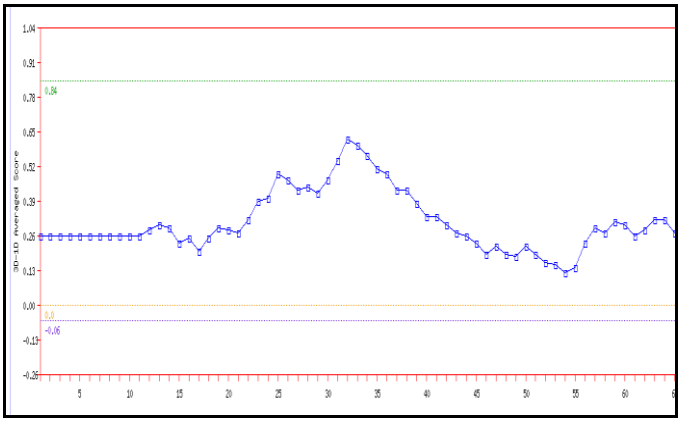

FIGURE 4: VERIFY3D PLOT ANALYSIS OF OUR COMPUTED HDAC11 PROTEIN MODEL

The quality of the model was checked by ProSA-Web Server. In order to facilitate interpretation of the z-score of the specified protein, its particular value is displayed in a plot that contains the z-scores of all experimentally determined protein chains in current Structure. Groups of structures from different sources (X-ray, NMR-Nuclear Magnetic Resonance) are distinguished by different

colours (NMR with dark blue and X ray with light blue). This plot can be used to check whether the z-score of the protein in question is within the range of scores typically found for proteins of similar size belonging to one of these groups.

It can be seen in (**Figure 5**) that Z-scores value of the obtained model is located within the space of proteins determined By X ray. This value is close to the value of the template (-7.01) which suggests that the obtained model is reliable and close to experimentally determined structures.

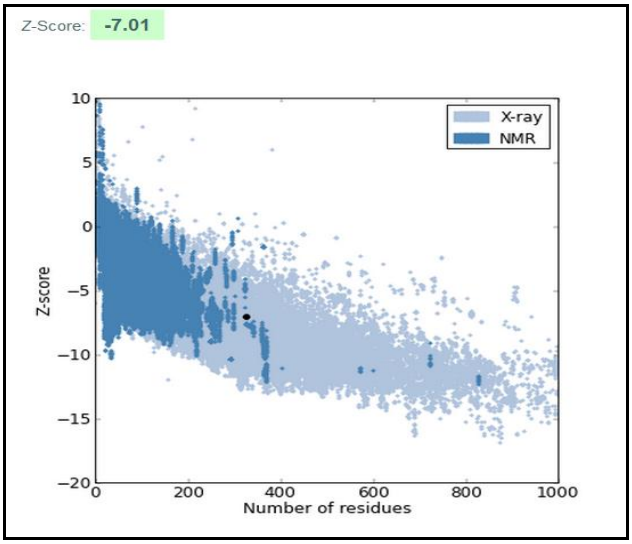

FIGURE 5: PROSA-WEB SERVER, Z-SCORE PLOT

CONCLUSION: The modelling of our protein was computed by using various Bioinformatics applications and this effort can aid in further research on HDAC11 and Histone Deacetylase family**.** From the current study, it was evident that our protein is stable and neutral in nature. The predicted secondary results showed the dominant coil regions. Validation and evaluation result of 3-D structure of our protein HDAC11 shows that predicted model is a stable structural model and of good quality because it shows maximum residues (88.6%) in favoured region.

Our effort of modelling HDAC11 protein may provide information related to functional mechanisms and also help us in further docking studies and aid in anticancer and neuroprotector drugs.

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REFERENCES:

1. Gao L, Cueto MA, Asselbergs F and Atadja P: Cloning and Functional Characterization of HDAC11, a Novel Member of the Human Histone Deacetylase Family. The Journal of Biological Chemistry 2002; 277:25748-25755.
2. Khare SP, Habib F, Sharma R, Gadewal N, Gupta S and Galande S; HIstome: a relational knowledgebase of human histone proteins and histone modifying enzymes. Nucleic Acids Research Database issue, 2011
3. Bannister AJ and Kouzarides T: Regulation of chromatin by histone modifications. Cell Research 2011; 21(3):381–395.
4. Witt O, Deubzer HE, Milde T and Oehme I: HDAC family: What are the cancer relevant targets? Cancer Letters 2008; 277(1):8–21
5. North BJ and Verdin E: Sirtuins: Sir2-related NAD-dependent protein deacetylases. Genome Biology 2004; 5:5-224
6. Xu K, Dai XL, Huang HC, and Jiang ZF: Targeting HDACs: A Promising Therapy for Alzheimer's Disease. Oxidative Medicine and Cell Longevity. 2011; 2011: 143269.
7. Gasteiger E., Hoogland C., Gattiker A., Duvaud S, Wilkins M.R., Appel RD and Bairoch A: Protein Identification and Analysis Tools on the ExPASy Server; (In) John M. Walker (ed): The Proteomics Protocols Handbook, Humana Press 2005.
8. Källberg M, Wang H, Wang S, Peng J, Wang Z, Lu H, Xu J: Template-based protein structure modeling using the RaptorX web server. Nature Protocols 2012; 7:1511–1522,
9. http://www.enzim.hu/hmmtop.(Last accessed on 21st July 2014, 16:15)
10. http://www.softberry.com/berry.phtml?topic=cys_rec&group=programs&subgroup=prot (last accessed on 17th July 2014, 08:31)
11. Kelley LA, Sternberg MJ: Protein structure prediction on the Web: a case study using the Phyre server, Nature Protocols, 2009; 4: 363 - 371
12. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, Ferrin TE: UCSF Chimera--a visualization system for exploratory research and analysis. J Comput Chem. 2004; 13:1605-12
13. http://www.cgl.ucsf.edu/chimera
14. Lovell SC, Davis IW, Arendall WB, de Bakker PI, Word JM, Prisant MG, Richardson JS, Richardson DC: Structure validation by Calpha geometry: phi, psi and Cbeta deviation. Proteins: Structure. Function & Genetics 2003; 3:437-50
15. Eisenberg D, Lüthy R, and Bowie JU: VERIFY3D: assessment of protein models with three-dimensional profiles. Methods in Enzymol.1997; 277:396-404

16. Wiederstein, M. & Sippl M.J: ProSA-web: interactive web service for the recognition of errors in three-dimensional structures of proteins. Nucleic Acids Research.2007; 35: W407–W410
17. Sippl, M.J: Recognition of Errors in Three-Dimensional Structures of Proteins. Proteins Proteins 1993;17:355-362
18. https://www.cgl.ucsf.edu/chimera/docs/ContributedSoftware/minimize/minimize.html

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