ORIGINAL ARTICLE

# ANALYSIS OF INHIBITORY EFFECT OF TRANSCRIPTIONAL REGULATORY PROTEIN (STY 4289) OF *SALMONELLA TYPHI* CT18BY HOMOLOGY MODELLING

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**Background:** *Salmonella typhi* cause typhoid fever which is life threatening disease. It affects approximately 600,000 people per annum around the world. Food and water are the integral components through which this disease is transmitted and becomes base of typhoid. It spreads widely where cleanliness is very poor. Objective was to analyse three-dimensional structure of transcriptional regulator of *Salmonella typhi* CT18 by homology modelling to inhibit virulent effect of *Salmonella typhi*. **Methods:** Bioinformatics tools and programs like comprehensive Microbial resource (CMR). Interproscan, Basic Local Alignment Search tool (BLAST), Modeller 9.10, Procheck and Prosa were used as bioinformatic tools for effective study of protein. **Results:** Homology modelling is an appropriate and precise method to find three-dimensional transcriptional regulator to stop its virulency. **Conclusion:** Homology modelling is computational and accurate method to find 3D structure of transcriptional regulator to inhibit its virulence effect of causing disease.

**Keywords:** Homology modelling; Transcriptional regulator; Typhoid fever; Modeller

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## INTRODUCTION

*Salmonella typhi* is the basis of typhoid fever. Typhoid vaccine contributes 50–90% safety for 5–6 years.[1] *Salmonella typhi* is usual pollutant and acquires resistant to a lot of bactericides. It is one of human host restricted bacteria which causes typhoid fever in approximately 10.9 million people annually.[2] Transcriptional regulators are one of the chief family of transcription factors. These proteins are linked with different metabolic processes.[3] Transcriptional regulator is a protein that coheres to definite DNA sequence which takes part in regulating the flux of genetic information from DNA to messenger RNA. It contains DNA domains which binds to precise DNA sequence. They are present in all living organisms. The number of transcriptional regulators extend with the genomic size. In *Salmonella typhi*, transcriptional regulators aid the cell to rapidly accept different events arising in close around. Operators are firmed with repressors which lies downstream the promotor portion.[4] In host cell, Salmonella performs its metabolic functions through its effector proteins which are concerned with Salmonella pathogenicity.[5]

Transcription factor binds to specific DNA site to regulate gene expression.[6] Virulency of bacteria depends upon keen balance of signals between host and microbe.[7]Homology modelling is a computational access to build three-dimensional structure of protein targets when experimental conclusions about similar proteins are attainable. Nuclear magnetic resonance (NMR) spectroscopy and X-ray crystallography found out the structure of approximately 150,000 macromolecules but in our structural study, there is still a space. This space is fulfilled by computational study which includes homology modeling.[8] Homology modelling has wide applications. It has been emerged as considerable aspect to approach 3-dimensional structure of target. 3D structure of the target through homology modelling became contributively intense study of the target to compose drug.[9] Recent research showed that homology modelling lead in detecting the 3D structure of proteins of coronavirus, useful for antiviral drug designing against 2019.nCov.[10] Homology modelling aids in breaking the resistance of organophosphate (pesticide) on insects.[11]Homology modelling plays very important role in structural applications and protein characterization and function.[12] Homology modelling of TMPRSS2 produces candidate drugs that can inhibit entrance of SARS.CoV-2 in living cells.[13] Homology modelling consists of particular stops that are genuine and manageable to practice. It has diverse uses in drug discovery as drugs contact with receptors which are almost entirely proteins. Computer aided drug design methodologies are playing important part in drug discovery.[14] To learn and understand biological functions of proteins, three-dimensional structure of proteins is beneficial and valuable fount of knowledge.

Homology modelling was considered the best technique to give 3D structure with perfect accuracy.[15]

## MATERIAL AND METHODS

Accurate sequence of *Salmonella typhi* CT18 was downloaded from Comprehensive Microbial Resource (CMR). The comprehensive microbial resource or CMR (http://cmr.jcvi.org) is bioinformatic technique for viewing, analysing and examining of the sequence and illustrating the complete bacterial genome.[16] It tells that more than 4000 proteins are present in *Salmonella typhi* bacterium. Inter proscan helped in retrieving the function of proteins. Among these proteins, transcriptional regulation has been selected to study its structure. Homology modelling was brought to build three-dimensional structure of transcriptional regulator. Basic Local Alignment Search tool (BLAST), helped in obtaining template which causes pairwise alignment between template and target.[17] Modeller 9.10 was run to build 10 different models. One authentic and finest model was selected among them. The reliability of the models was checked through Procheck web application (http://www.ebi.ac.uk/thornton-srv).[18] The Procheck gives rise to Ramachandran plot. Through this plot, different residues of proteins can be analysed in different regions. The energy of transcriptional regulator was calculated through Prosa. Prosa served in proof reading and refinement of protein structure.[19]

## RESULTS

Total 4934 proteins are present in *Salmonella typhi* CT18. Six hundred were hypothetical proteins which were (12.16%). The analysis of function of hypothetical proteins of *Salmonella typhi* CT18 was done by interproscan and structure was analysed by modeller. 362 proteins (60.3% of total hypothetical proteins) were functional and 120 (20%) hypothetical proteins were proteins of unknown function as no hits were observed for 118 proteins (19.6% of total hypothetical proteins) among 600 hypothetical proteins. The functionally predicted proteins were grouped on the basis of particular conserved enzymatic domain. Kinases, transferases, peptidases, ligases, hydrolases, reductases, synthetases, ligases, carboxylase and phosphatases transcriptional regulators are some groups The proteins with similar functions were placed in one group.

**Table-1: Total proteins and their percentages**

| Proteins | Numbers | Percentage |
|---|---|---|
| Total proteins | 4934 | 100 |
| Hypothetical proteins | 600 | 12.16 |
| Functionally detected | 362 | 60.3 |
| Uncharacterized proteins | 120 | 20 |
| No hits were found for remaining proteins | 118 | 19.6 |

| Alignments | Description | Max score | Total score | Query cover | E value | Ident | Accession |
|---|---|---|---|---|---|---|---|
| Chain A, Solution Structure Of E.Coli Protein Yhgg: The Northeast Structural Genomics Consortium Target Et95 | | 143 | 143 | 100% | 2e-45 | 90% | 1XN7_A |
| Chain A, Solution Structure Of Putative Ferrous Iron Transport Protein C (Feoc) Of Klebsiella Pneumoniae | | 115 | 115 | 100% | 2e-34 | 71% | 2K02_A |
| Chain B, Moonlighting Functions Of Feoc In The Regulation Of Ferrous Iron Transport In Feo | | 115 | 115 | 100% | 3e-34 | 71% | 4AWX_B |
| Chain X, Crystal Structure Of The Anti-Hiv B12 Scaffold Protein >pdb\|3RPT\|A Chain A, Crystal Structure Of The Anti-Hiv F | | 29.3 | 29.3 | 55% | 0.22 | 33% | 3RPT_X |
| Chain X, Structure Of An Hiv Epitope Scaffold In Complex With Neutralizing Antibody B12 Fab | | 29.3 | 29.3 | 55% | 0.22 | 33% | 3RU8_X |

**Figure-1: Blast results of transcriptional regulator protein (STY4289)**

**Alignment results**

| Score | Expect | Method | Identities | Positives | Gaps | Frame |
|---|---|---|---|---|---|---|
| 143 bits (361) | 2e-45() | Compositional matrix adjusts. | 70/78(90%) | 72/78(92%) | 0/78(0%) | |

**Features:**

```
Query 1  MASLIQVRDLLALRGRMEATQISHTLHAPQPMIDAMLNQLEIMGKAVRIPEEPDGCLSGS 60
         MASLIQVRDLLALRGRMEA QIS TL+ PQPMI+AML QLE MGKAVRI EEPDGCLSGS
Sbjct1   MASLIQVRDLLALRGRMEAAQISQTLNTPQPMINAMLQQLESMGKAVRIQEEPDGCLSGS 60

Query 61 CKSCPEGKACLREWWALR 78
         CKSCPEGKACLREWWALR
Sbject 61 CKSCPEGKACLREWWALR 78
```

**Figure-2: Sequence alignment of transcriptional regulator (STY 4289)**

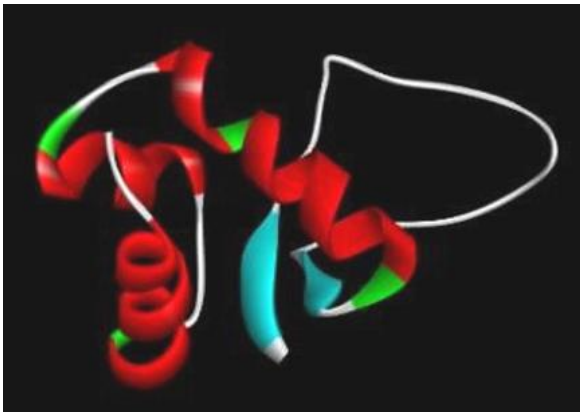


**Figure-3: Three-dimensional model of transcriptional regulator (STY4289)**

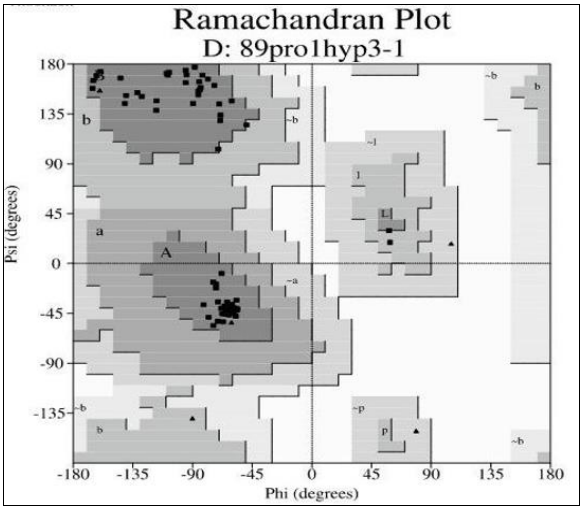



**Figure-4: Sterio-chemical analysis of transcriptional regulator (STY4289) using Procheck**

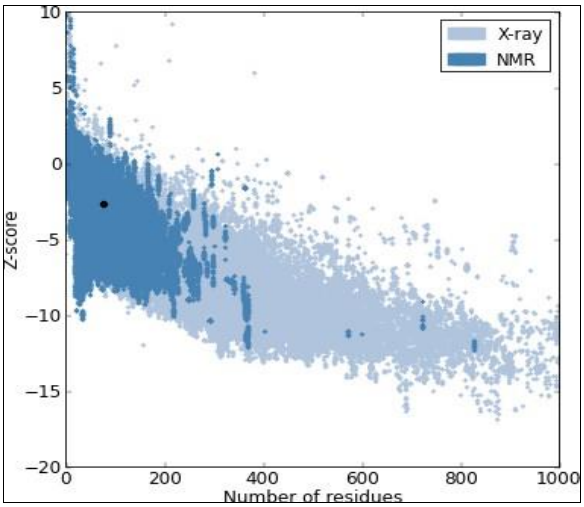
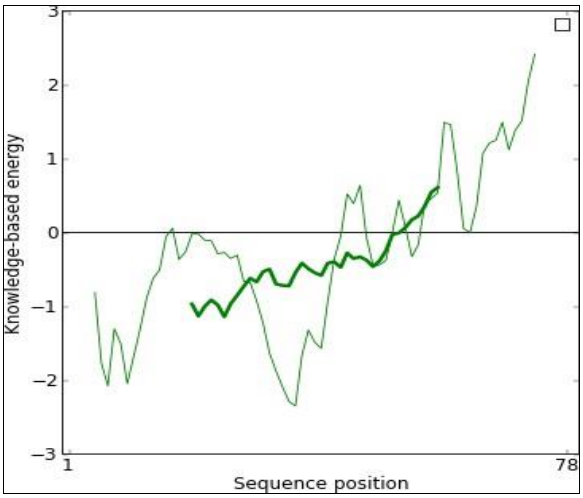



**Figure-5: Z-score results of transcriptional regulator obtained through Prosa-web**




**Figur-6: Energy peaks of transcriptional regulator obtained through Prosa-web**

## DISCUSSION

*Salmonella typhi* causes typhoid fever which is life threatening disease. It causes typhoid in approximately 10.9 million people annually. It becomes serious problem all over the world. My finding was on the structural analysis transcriptional protein of *Salmonella typhi* which plays crucial role in spreading disease. I have studied transcriptional regulator protein (STY 4289) structure in detail. Homology modelling was performed to find the 3d structure of protein. Alignment was proceeded with BLAST (Figure-2). Template like *E. coli* protein yhgg having accession no 1XN7 was chosen. Target and template have 90% identity. Modeller 9.10 was set out to construct model. Construction of 10 models was carried out. On the basis of stereochemistry, one best model was selected. DS viewer helped in visualizing the model. Helices ere 4 in numbers (red) and β-sheets were 2 in numbers (blue) as shown in (Figure-3). Evaluation of model was carried out through Procheck. Ramachandran plot was derived from Procheck. The Plot demonstrated that in favoured region, 95% residues were present, 4.5% debris in additional allowed portion and no residues were found in fewer and disallowed portion (Figure-4). Estimation of energy was done by Prosa-web. Z-score results illustrated highly negative value (-2.69) which approves that structure is highly stable (Figure-5).

## CONCLUSION

This study has shown by knowing the 3D structure of transcriptional regulatory protein (STY 4289) by homology modelling, we can be able to design anti receptor which binds to the virulent site of the protein thus inhibits its disease pathogenesis.

## AUTHORS' CONTRIBUTION

AF: Literature research, conceptualization of study design. SS: Data collection. RR: Data analysis. GR: Data interpretation. AH: Write up. MF: Proof reading

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