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Original Research Article

STRING analysis of beta-lactamase in *Salmonella enterica arizonae*: Identification and characterization of predicted functional partners

Sanjay Vijay[1], **Viveka T**[1], **Yuvashri Gobinathan**[2], **Prakash Balu**[1]*

[1]*Dept. of Biotechnology, Vels Institute of Science, Technology and Advanced Studies, Chennai, Tamil Nadu, India*
[2]*Dept. of Bioinformatics, Sathyabama Institute of Science and Technology, Chennai, Tamil Nadu, India*

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ABSTRACT

Introduction: This study investigates the functional roles and predicted interactions of the putative beta-lactamase STY4057 in *Salmonella typhi* using STRING database analysis. *S. typhi* is a pathogenic bacterium responsible for typhoid fever, presenting significant public health challenges.
Materials and Methods: We identified several key functional partners of STY4057 by exploring various interaction criteria, including gene fusion, co-occurrence, co-expression, and experimental data through STRING database analysis.
Results: The analysis revealed interactions with regulatory proteins, metabolic enzymes, and proteins involved in adhesion and biofilm formation. High-confidence interactions with STY4058 (a regulatory protein) and apeE (an outer membrane esterase) suggest significant roles in transcriptional regulation and lipid metabolism.
Discussion: The findings underscore the potential contribution of STY4057 to antibiotic resistance and pathogenicity in *S. typhi*. Interactions with regulatory proteins like STY4058 may influence beta-lactamase expression, while interactions with metabolic enzymes like apeE could affect membrane permeability and antibiotic influx, providing insights into *S. typhi*'s survival and resistance mechanisms.
Conclusion: This study lays the groundwork for future experimental validation and therapeutic target development, offering insights into *S. typhi*'s survival and resistance capabilities. Further research is needed to validate these interactions and explore their potential as therapeutic targets.

1. Introduction

Salmonella typhi (S. typhi), the causative agent of typhoid fever, poses a significant public health challenge, particularly in developing countries. The bacterium's ability to survive and proliferate within human hosts is attributed to various virulence factors and resistance mechanisms.[1] Among these mechanisms, the production of beta-lactamases is crucial for antibiotic resistance, which complicates treatment strategies.[2] Beta-lactamases are enzymes that hydrolyze beta-lactam antibiotics, rendering them ineffective and allowing the bacterium to withstand antibiotic pressure.[3] STY4057 is a putative beta-lactamase identified in *S. typhi* that shows significant similarity to metallo-beta-lactamases found in other bacterial species.[4] Understanding the functional interactions of STY4057 is essential for comprehending its role in antibiotic resistance and pathogenicity.

The STRING database provides a platform for analyzing protein-protein interactions and predicting functional partners based on various criteria such as gene fusion, co-occurrence, co-expression, and experimental data.[5] This study leverages STRING analysis to investigate the interaction network of STY4057 in *S. typhi*, aiming to

* *Corresponding author*.
E-mail address: prakazbt@gmail.com (P. Balu).

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identify its potential partners and elucidate their collective roles. By examining these interactions, we can gain insights into the molecular mechanisms that underlie the bacterium's survival and resistance capabilities.

Previous studies have demonstrated that beta-lactamases and their interacting partners can contribute to the overall virulence of pathogenic bacteria.[6] Identifying and characterizing these interactions in *S. typhi* may reveal novel targets for therapeutic intervention and aid in the development of more effective treatment strategies against typhoid fever. This study aims to build on this foundation by providing a comprehensive analysis of STY4057's functional network, thus advancing our understanding of its contribution to antibiotic resistance and pathogenicity in *S. typhi*.

2. Materials and Methods

STRING database was employed to analyze the protein-protein interaction network of STY4057 and predict its functional partners. The analysis included metrics such as gene fusion events, co-occurrence, co-expression, experimental data, databases, and text mining scores. Homology searches were performed using FASTA to identify sequence similarities.

3. Results

The STRING analysis (Figure 1) revealed a robust interaction network for the putative beta-lactamase STY4057 in *S. typhi*. The network includes multiple predicted functional partners based on various interaction criteria, such as gene fusion, co-occurrence, co-expression, and experimental data. Below, we elaborate on the key findings for each predicted partner.

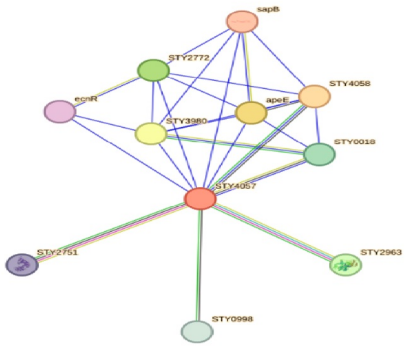

Figure 1: Interaction network for the putative beta-lactamase STY4057

4. Predicted Functional Partners

4.1. STY4058

1. *Function:* Regulatory protein similar to *Pseudomonas stutzeri* nahR.
2. *Interaction evidence:* High confidence score (0.715), significant sequence similarity (E-value: 2.4e-11), and co-occurrence in related bacterial species.
3. *Potential role:* May act as a transcriptional regulator influencing the expression of STY4057.

4.2. ApeE

1. *Function:* Outer membrane esterase similar to *Salmonella typhimurium apeE*.
2. *Interaction evidence:* High confidence score (0.666), perfect sequence match (E-value: 0), and co-expression data.
3. *Potential role:* Involved in lipid metabolism and may interact with STY4057 to affect membrane permeability or integrity.

4.3. STY3980

1. Function: Hypothetical protein, member of the glycosyl hydrolase 5 family.
2. Interaction evidence: Moderate confidence score (0.609), presence in similar genomic contexts.
3. Potential role: Possible involvement in carbohydrate metabolism and interaction with cell wall components.

4.4. STY2772

1. *Function:* Putative polyferredoxin.
2. *Interaction evidence*: Moderate confidence score (0.527), weak sequence similarity (E-value: 7.1e-05).
3. *Potential role:* Could play a role in electron transfer processes essential for bacterial respiration.

4.5. STY2963

1. *Function:* Putative rubredoxin reductase, accessory protein for anaerobic nitric oxide reductase.
2. *Interaction evidence:* Moderate confidence score (0.525), gene co-expression and fusion evidence.
3. *Potential role:* Facilitates anaerobic respiration by reducing nitric oxide, potentially interacting with STY4057 in redox reactions.

4.6. STY0018

1. *Function:* Putative chitinase.
2. *Interaction evidence:* Moderate confidence score (0.508), strong sequence similarity (E-value: 0).
3. *Potential role:* Degradation of chitin, which could be part of the bacterium's interaction with host organisms.

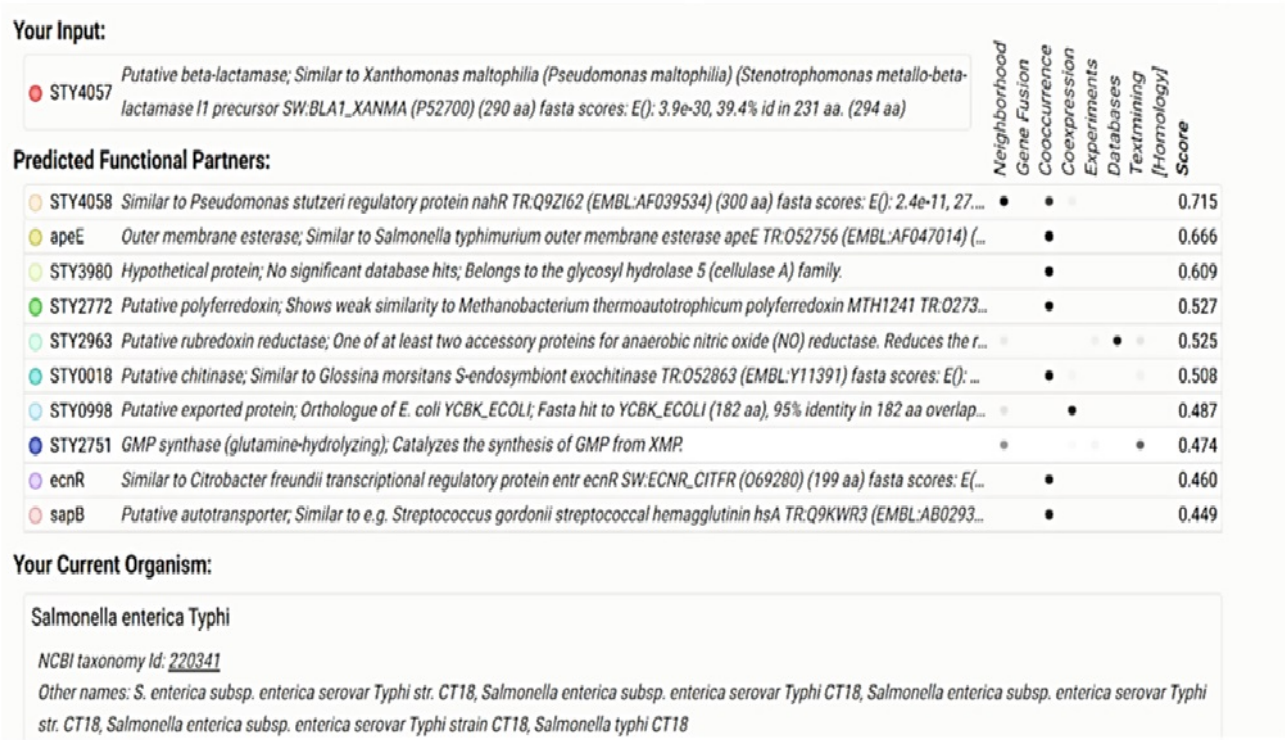

Figure 2: Predicted functional partners

4.7. STY0998

1. *Function:* Putative exported protein, orthologous to *E. coli* YCBK.
2. *Interaction evidence:* Lower confidence score (0.487), strong sequence similarity (95% identity).
3. *Potential role:* Involved in protein export and possibly interacts with STY4057 during transport processes.

4.8. STY2751

1. *Function:* GMP synthase (glutamine-hydrolyzing).
2. *Interaction evidence:* Lower confidence score (0.474), genomic neighborhood evidence.
3. *Potential role:* Catalyzes GMP synthesis, indicating a possible role in nucleotide biosynthesis.

4.9. EcnR

1. *Function:* Similar to *Citrobacter freundii* transcriptional regulatory protein ecnR.
2. *Interaction evidence:* Lower confidence score (0.460), significant sequence similarity (E-value: 0).
3. *Potential role:* Regulatory functions that may influence the expression of STY4057 or other related genes.

4.10. SapB

1. *Function:* Putative autotransporter, involved in adhesion.
2. *Interaction evidence:* Lower confidence score (0.449), sequence similarity (E-value: 2.5e-19).
3. *Potential role:* Adhesion and biofilm formation, possibly interacting with STY4057 in colonization processes.

5. Discussion

The interaction network constructed from the STRING analysis suggests that STY4057 is part of a complex functional landscape in *S. typhi*. The high confidence interactions, such as with STY4058 and apeE, indicate critical roles in regulatory and metabolic processes. The involvement of STY4057 in these interactions underscores its potential contribution to antibiotic resistance and

pathogenicity.

The interaction with regulatory proteins, particularly STY4058, suggests that STY4057 may be under tight transcriptional control, potentially responding to environmental signals or antibiotic pressure. Regulatory proteins like STY4058, which share similarities with nahR from *Pseudomonas*, are known to be involved in the response to environmental stressors, including antibiotics.[7] This regulatory mechanism could modulate the expression of beta-lactamases, contributing to resistance phenotypes observed in *S. typhi*.

The interactions with metabolic enzymes, such as apeE and STY2772, indicate a broader role for STY4057 beyond antibiotic resistance. ApeE, an outer membrane esterase, may interact with STY4057 to modify membrane permeability, thereby affecting antibiotic influx.[8] Similarly, interactions with polyferredoxins and rubredoxin reductases (e.g., STY2772 and STY2963) suggest a link between redox homeostasis and antibiotic resistance, where the maintenance of redox balance is crucial for bacterial survival under stress.[9]

Interactions with proteins involved in adhesion and biofilm formation, such as sapB, highlight the potential role of STY4057 in pathogenicity. Biofilm formation is a well-known factor in chronic infections and antibiotic resistance, as it provides a protective environment for bacterial communities.[10] The interaction with sapB suggests that STY4057 could contribute to the establishment and maintenance of biofilms in host tissues, facilitating persistent infections.

While the STRING analysis provides a comprehensive overview of potential interactions, experimental validation is essential to confirm these predictions.[11] Techniques such as co-immunoprecipitation, bacterial two-hybrid assays, and gene knockout studies could provide direct evidence of these interactions and elucidate their functional significance. Additionally, understanding the regulatory mechanisms controlling STY4057 expression could reveal new targets for antimicrobial therapy.

6. Conclusion

In conclusion, STRING-based analysis illuminates STY4057's intricate network of interactions in *S. typhi*, suggesting its role in regulatory circuits like with STY4058, potentially governing beta-lactamase expression under diverse conditions. Interactions with proteins like apeE imply involvement in membrane permeability and antibiotic resistance strategies. Connections to metabolic proteins STY2772 and STY2963 hint at roles in redox processes crucial for bacterial survival. Additionally, associations with adhesion proteins such as sapB underscore potential contributions to *S. typhi*'s pathogenicity via biofilm formation. Experimental validation is essential to substantiate these findings, emphasizing the significance of regulatory mechanisms in STY4057's function and its implications for therapeutic targeting in typhoid fever treatment. This study expands our understanding of *S. typhi*'s resistance mechanisms, laying the groundwork for future research and clinical interventions.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Author biography

Sanjay Vijay, Student https://orcid.org/0009-0005-6553-3435

Viveka T, Student https://orcid.org/0009-0006-0677-1297

Yuvashri Gobinathan, Student https://orcid.org/0009-0009-9666-4322

Prakash Balu, Associate Professor https://orcid.org/0000-0002-1040-3554

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