Prediction of Toxin-Antitoxin system (TA system) as a Novel Potent Target in *Salmonella typhi* Using Bioinformatics Analysis

Mahsa Jalili[1,2], Sobhan Ghafourian[1,2,3]

1. Department of Microbiology, University of Medical Sciences, Ilam, Iran
2. Clinical Microbiology Research Center, Ilam University of Medical Sciences, Ilam, Iran
3. Department of Medical Microbiology and parasitology, Faculty of Medicine and Health Sciences, University Putra Malaysia, Malaysia

ABSTRACT

Background and Objective: *Salmonella typhi* is one of the major challenges for the human and animal health. *Salmonella* with high pathogenicity can be harmful factor for human health. The control of this pathogen is a big challenge as it can cause serious infectious diseases such as gastroenteritis, septicemia and typhoid fever. On the other side, there are many factors such as toxin-antitoxin (TA) system which may be a regulator for the virulence factors in bacteria. The TA system as a potent target for antimicrobial therapy is very important in this bacterium. Therefore, bioinformatics analyses are essential for identification of the potent TA loci. This system is potency for the antimicrobial therapy. In this study, we focused on the TA system as a regulon for the pathogenicity of *Salmonella typhi*.

Materials and methods: We analyzed the potent TA loci and assume the review of these potent TA loci can help us in the next experimental studies. We used RASTA (RASTA-Bacteria: a web-based tool for identifying toxin-antitoxin loci in prokaryotes) database and after that we analyzed TA system in all of the scores. Finally, all of the known and unknown TA loci were identified.

Results: By scrutiny different scores and excavate potent TA loci in *Salmonella typhi,* we were able to discover significant potent TA loci. We discovered several loci in scores 70-80%. In other hand, the potent TA loci were significant in scores 90-100%. A significant number of potent TA loci were discovered on this score. It is interesting that *hth-xre* exists in most scores and finally the highest number is compared to the other unknown potent TA loci in both strains of *Salmonella typhi.*

Conclusion: By studying all the scores in two different strains of *Salmonella typhi* including *P_stx_12_uid87001* and *Ty21a_uid201427*, *hth-xre* was shown in both strains as an unknown TA system which can be a great help for bioinformatics and experimental studies. Finally; we identified the potent TA loci in different *Salmonella typhi* strains.

Corresponding Information: Sobhan Ghafourian., *Department of Medical Microbiology and parasitology, Faculty of Medicine and Health Sciences, University Putra Malaysia, Malaysia*

Introduction

It is very obvious that low level of sanitation in human societies can be the cause of different diseases [1.2]. Among these diseases are typhoid fever and food poisoning which are transferred easily by consuming contaminated food or water and *Salmonella typhi* is of the great importance [3].

On the other hand, *Salmonella* family members have shown a great resistance to disinfectant agents which makes their removal difficult [4].

Unfortunately, nowadays the outspread of antibiotic resistance in *S. typhi* has become a huge problem [5]. Control and treatment *of S. typhi* infection has become a challenge [6]. On the other

side, according to the most recent studies, TA system is significant as a potent antimicrobial target and plays an important role as a basic principle in the pathogenesis of bacteria [7].

In this study, with the benefit of bioinformatics tools, we try to investigate the potent TA loci in this bacterium. Hence, various analyses were performed on *S. typhi* to identify novel TA loci.

Material and Methods
Bioinformatics analysis

To discover novel TA system, one should refer to the RASTA Database at:

(http://genoweb1.irisa.fr/duals/RASTA-Bacteria/) and then the analysis of various TA loci and potent TA loci can be performed.

Accessible bacterial strains from RASTA: Two strains were selected and analyzed:

*Salmonell aenterica_ serovar_typhi_* P_stx_12_ uid8700

*Salmonella_enterica_serovar_typhi_*Ty21a_uid20 1427

Results

As it is said in numerous studies, *S. typhi* has a high-power pathogenicity and also can be transferred quickly from one person to another. Therefore, typhoid fever is one of the most remarkable diseases in the world [8]. Many factors are involved in the pathogenesis of bacteria specially *S. typhi* [9]. One of these factors is toxin-antitoxin (TA) system which has been considered today [7].

Since the TA system plays an essential role in the pathogenesis of bacteria [10], we decided to analyze the potent TA loci by bioinformatics method.

After reviewing two different species of *S. typhi,* it was shown that both species have numerous and different potent TA loci. In species *S. typhi_P_stx* in different categories we can see potent TA loci (Table 2). But more importantly, this potent TA loci is in categories 50-60 % (Table 2).

The important issue is that among all unknown potent TA loci, *hth-xre* is present in most categories with the highest number compared to the other unknown potent TA loci (Table 2).

On the other hand, at categories 70-80%, numerous unknown potent TA loci were found. In the species *S. typhi_P_stx, hth-xre* is also seen in most categories.

This can be considered as a potent TA locus as it has the highest number (Table 1). These analyses were performed to identify the potent TA loci in different species of *S. typhi*, so that better prediction of TA loci and clinical experiments become possible (Table 3, Figure 1).

Table 1. Potent TA loci in Salmonella_enterica_serovar_typhi_P_stx_12_uid87001

Perecentage	known														unknown	Known + unknown
Conserved domain	HipB	HTH-XRE	HigB	COG3609	HicB	VagC	VapC	Doc-Doc	Hth-4	COG5499	Stbc	ParE	RelE	TOTAL		TOTAL
50 – 60 %	100% (n=1)	100% (n=4)	100% (n=1)	–	–	–	–	–	–	–	–	–	–	100% (n=6)	100% (n=476)	100% (n=482), Unknown 98.7% (n=476), Known 1.2% (n=6)
60- 70 %	–	100% (n=1)	–	100% (n=1)	100% (n=1)	–	–	–	–	–	–	–	–	100% (n=3)	100% (n=5)	100% (n=8), Unknown 62.5 % (n=5), Known 37.5 % (n=3)
70- 80 %	–	100% (n=2)	–	–	–	–	–	100% (n=1)	100% (n=1)	100% (n=1)	100% (n=1)	–	–	100% (n=6)	100% (n=4)	100 % (n=10),unknown 40% (n=4), Known 60% (n=6)
80 – 90 %	–	–	–	–	–	100% (n=1)	100% (n=2)	–	–	–	–	–	–	100% (n=3)	100% (n=2)	100% (n=5), unknown 40% (n=2), Known 60% (n=3)
90 – 100 %	–	–	–	–	–	–	–	–	–	–	–	100% (n=1)	100% (n=1)	100% (n=2)	100% (n=2)	100% (n=4), Unknown 50% (n=2). Known 50% (n=2)
Total	100% (n=1)	100% (n=7)	100% (n=1)	100% (n=1)	100% (n=1)	100% (n=1)	100% (n=2)	100% (n=1)	100% (n=1)	100% (n=1)	100% (n=1)	100% (n=1)	100% (n=1)	100% (n=20)	100% (n=4٨٩)	100% (n=5٠9) Unknown 96.7 %(n=489),3.9%Known (n=20)

Table 2. *Potent TA loci in Salmonella_enterica_serovar_Typhi_Ty21a_uid201427*

Percentage	known										unknown		Unknown + known
Conserved domain	Hth-xre	HipB	HtH-4	DOC-DOC	HtH-3	VapC	RelB	parE	VagC	Total known	unknown	Unknown Total	TOTAL
50 – 60 %	100% (n=4)	100% (n=1)	–	–	–	–	–	–	–	100% (n=5)	100% (n=439)	100% (n=439)	100% (n=444), Unknown 98.8% (n=439),known 1.1 % (n=5)
60 – 70 %	100% (n=1)	–	–	–	–	–	–	–	–	100% (n=1)	100% (n=10)	100% (n=10)	100% (n= 11), Unknown 90.9 % (n=10), Known 9.09 % (n=1)
70 – 80 %	100% (n=3)	–	100% (n=2)	100% (n=1)	100% (n=1)	–	–	–	–	100% (n=7)	100% (n=2)	100% (n=2)	100% (n= 9), Unknown 22 % (n=2), Known 77.7% (n=7)
80 – 90 %	100% (n=1)	–	–	–	–	100% (n=1)	–	–	–	100% (n=2)	100% (n=2)	100% (n=2)	100% (n=4), Unknown 50% (n=2), Known 50% (n=2)
90 – 100 %	–	–	–	–	–	–	100% (n=1)	100% (n=1)	100% (n=1)	100% (n=3)	100% (n=2)	100% (n=2)	100% (n=5), Unknown 40 % (n=2), Known 60% (n=3)
Total	100% (n=9)	100% (n=1)	100% (n=2)	100% (n=1)	100% (n=1)	100% (n=1)	100% (n=1)	100% (n+1)	100% (n=1)	100% (n=18)	100% (n=455)	100% (n=455)	100% (n=473) Unknown 96.1% (n=455), Known3.8% (n=۱۸)

Table 3. *Analysis of potent TA loci in both stains of S. typhi*

	Strain 1 (*S. typhi*_P_stx_12_uid87001)			Strin 2 (*S. typhi*_Ty21a_uid201427)			Total
Percent	unknown	known	Total strain 1	unknown	known	Total Strain 2	Total strain1,2
50 – 60 %	100% (n= 476)	100% (n=6)	100% (n=482), Unknown 98.7% (n=476), Known 1.2% (n=6)	100% (n=439)	100% (n=5)	100% (n=444), Unknown 98.8% (n=439),known 1.1 % (n=5)	100% (n=926) ,Unknown 98.81%(n=915) ,known 1.18% (n=11)
60 - 70 %	100% (n=5)	100% (n=3)	100% (n=8), Unknown 62.5 % (n=5), Known 37.5 % (n=3)	100% (n=10)	100% (n=1)	100% (n= 11), Unknown 90.9 % (n=10), Known 9.09 % (n= 1)	100% (n = 19), Unknown 78 % (n = 15), known 21 % (n = 4)
70 – 80 %	100% (n=4)	100% (n=6)	100 % (n=10),unknown 40% (n=4), Known 60% (n=6)	100% (n=2)	100% (n=7)	100% (n= 9), Unknown 22 % (n=2), Known 77.7% (n=7)	100 % (n = 19) Unknown 31.5 % (n = 6) Known 68.4 % (n = 13)
80 – 90 %	100% (n=2)	100% (n=3)	100% (n=5), unknown 40% (n=2), Known 60% (n=3)	100% (n=2)	100% (n=2)	100% (n=4), Unknown 50% (n=2), Known 50% (n=2)	100 % (n = 9) Unknown 44.4 (n = 4), Known 55.5 % (n = 5)

	Strain 1 (*S. typhi*_P_stx_12_uid87001)			Strin 2 (*S. typhi*_Ty21a_uid201427)			Total
90 – 100 %	100% (n=2)	100% (n=2)	100% (n=4), Unknown 50% (n=2). Known 50% (n=2)	100% (n=2)	100% (n=3)	100% (n=5), Unknown 40 % (n=2), Known 60% (n=3)	100 % (n = 9) Unknown 44.4 (n = 4), Known 55.5 % (n = 5)
Total	100% (n = 489)	100 % (n = 20)	100 % (n = 509) Unknown 96.2 % (n= 489). known 3.95 % (n = 20)	100 % (n = 455)	100 % (n = 18)	100% (n=473), Unknown 96.3% (n = 455) .known 3.8 % (n= 18)	100% (n = 982), unknown 96.3 % (n= 944), known 3.9% (n= 38)

Discussion

TA systems consist of a pair of specific genes which can be found on the chromosome or plasmid in various bacteria [11, 12]. The recent studies indicate that TA systems have been discovered to prevent loss of plasmids in bacteria and study its effect on bacterial pathogenicity [13,14]. Our findings demonstrated that we have different potent TA loci in several scores but the highest number of potent TA loci is in the score 70 - 80%.

On the other hand, among the scores of scurry that shines just the same 90 - 100 % its place is potent TA loci and the probability of identifying TA loci is high.

Therefore, the possibility of TA loci rises and it is likely that these bacteria have high capability of pathogenicity and the two strains that we have studied both are highly pathogenic.

Therefore, we can say that this problem is very serious and important on the pathogenicity of effective system that is very impressive.

On the other side, sometimes it can be seen that some unknown potent TA loci at score 90-100%cannot be neglected. Among all species, *hth-xre* has the highest frequency. Thus, *hth-xre* as a potent TA locus in both species of *Salmonella* including *P_stx_12_uid87001* and *Ty21a_uid201427* plays an important role. We investigated the likelihood of potent TA loci presence in both species of *S. typhi* with bioinformatics analysis which could prone them.

These results can be used in the further clinical experiments to explore the role of TA system in *S. typhi* pathogenicity.

Conflict of Interest

Authors declared no conflict of interest.

Acknowledgments

References

1. Prüss, A., D. Kay, et al. (2002). "Estimating the burden of disease from water, sanitation, and hygiene at a global level." Environmental health perspectives 110(5): 537-542.

2. Omran, A. R. (2005). "The epidemiologic transition: a theory of the epidemiology of population change." The Milbank Quarterly 83(4): 731-757.

3. Paniker, C. and K. Vimala (1972). "Transferable chloramphenicol resistance in Salmonella typhi." Nature 239: 109-110.

4. Randall, L., S. Cooles, et al. (2004). "Effect of triclosan or a phenolic farm disinfectant on the selection of antibiotic-resistant Salmonella enterica." Journal of Antimicrobial Chemotherapy 54(3): 621-627

5. Begum, K., S. J. Mannan, et al. (2017). "Antibiotic Resistance, Plasmids and Integron Profile of Salmonella Species Isolated from Poultry Farm and Patients." Dhaka University Journal of Pharmaceutical Sciences 15(2): 209-214.

6. Keddy, K. H., S. Takuva, et al. (2017). "An association between decreasing incidence of invasive non-*typhoidal salmonellosis* and increased use of antiretroviral therapy, Gauteng Province, South Africa, 2003–2013." PloS one 12(3): e0173091

7. Jaiswal, S., P. Paul, et al. (2016). "The Hha-TomB Toxin-Antitoxin System Shows Conditional Toxicity and Promotes Persister Cell Formation by

Inhibiting Apoptosis-Like Death in *S. Typhimurium*." Scientific Reports 6: 38204.

8. Elder, J. R., K. L. Chiok, et al. (2016). "The Salmonella pathogenicity island 13 contributes to pathogenesis in streptomycin pre-treated mice but not in day-old chickens." Gut pathogens 8(1): 16

9. Cronquist, A. (2016). Restaurant-Associated Outbreak of Typhoid Fever Traced to a Chronic Carrier–Colorado, 2015. 2016 CSTE Annual Conference, Cste.

10. Shidore, T. and L. Triplett (2017). "Toxin-Antitoxin Systems: Implications for Plant Disease." Annual Review of Phytopathology (0).

11. Yang, Q. E. and T. R. Walsh (2017). "Toxin–antitoxin systems and their role in disseminating and maintaining antimicrobial resistance." FEMS Microbiology Reviews 41(3): 343-353.

12. Stalder, T., L. M. Rogers, et al. (2017). "Emerging patterns of plasmid-host coevolution that stabilize antibiotic resistance." bioRxiv: 146118.

13. Yang, Q. E. and T. R. Walsh (2017). "Toxin–antitoxin systems and their role in disseminating and maintaining antimicrobial resistance." FEMS Microbiology Reviews 41(3): 343-353.

14. Yang, Q. E. and T. R. Walsh (2017). "Toxin–antitoxin systems and their role in disseminating and maintaining antimicrobial resistance." FEMS Microbiology Reviews 41(3): 343-353.

How to Cite This Article:

Jalili M, Ghafourian S. Prediction of Toxin-Antitoxin system (TA system) as a Novel Potent Target in Salmonella typhi Using Bioinformatics Analysis. Mod Med Lab J. 2020; 3 (1) :30-34