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Pathogenicity Island in *Salmonella*

Sarika Kombade and Navneet Kaur

Abstract

Considering a complex set of interplay with its host, *Salmonella* needs numerous genes for its full virulence. These genes responsible for invasion, survival, and extra intestinal spread are located on pathogenicity islands known as *Salmonella* pathogenicity islands (SPIs) that are thought to be acquired by horizontal gene transfer. A total of 17 SPIs (1–17) are recognized so far. The type III secretion system (T3SS) encoded by SPI-1 is considered as the most important virulence factor for *Salmonella* that delivers effector proteins necessary for invasion and production of enteritis. Among various SPIs, the role in virulence is well proven for SPI1 and SPI2 and further insight into the complex regulatory network of SPIs can contribute to drug investigation and prevention of infection.

Keywords: *Salmonella*, virulence genes, *Salmonella* pathogenicity islands, Type III secretion system

1. Introduction

Salmonellae are gram-negative bacteria and members of the family Enterobacteriales. They are chiefly intestinal parasites of human and a wide variety of animals including wild birds, domestic pets, rodents, chickens etc. They are also found in sewage, rivers and waters and soil. The genus *Salmonella* is divided into two species: *Salmonella enterica* that encompasses six subspecies (I, II, IIIa, IIIb, IV, and VI), and *Salmonella bongori*, which was earlier subspecies V [1]. Members of the seven *Salmonella* species can be serotyped into more than 2500 serotypes (serovars) based on somatic O and H antigens [1].

2. Pathophysiology of *Salmonella*

Salmonella is noted to cause diverse disease spectrum in humans and animals, varying from localized inflammation and gastroenteritis to typhoid fever which can lead to life-threatening systemic infection. The prime issue is that of asymptomatic healthy carriers who possibly shed bacteria in feces causing risk to community. There is diversity seen among certain *Salmonella* serovars based on host adaptation, such as *Salmonella* Typhi, *Salmonella* Paratyphi, and *Salmonella* Sendai are known to be very well adapted to only human host while *Salmonella* Typhimurium and *Salmonella* Enteritidis has a broad host range infecting animals and humans. Others produce diseases in farm animals like S. Choleraesuis in swine, S. Gallinarum in fowl. *Salmonella* Dublin (cattle) and Arizonae (reptiles) are mainly adapted to an animal species and seldom infect humans [1].

3. Pathogenesis of *Salmonella*

For the *Salmonella* infection to commence the bacteria is ingested through contaminated food and water. The infectious dose varies considerably ranging between 10^3–10^6 colony-forming units [2].

The first hurdle to *Salmonella* colonization is acidity of stomach and certain situations which either decreases stomach acidity (antacids, proton pump inhibitors, achlorhydric disease) or integrity of intestine (previous surgery of gastrointestinal tract, altered intestinal flora due to antibiotic use, inflammatory bowel disease) increases the chances of *Salmonella* infection [3].

Salmonellae exhibit an adaptive acid tolerance response on exposure to acid in vitro that possibly eases its survival in the stomach and movement to the small intestine.

When it reaches the small intestine, it attaches to the mucosal epithelial cells by fimbriae. Now, the penetration of the mucosal epithelium is achieved by *bacteria-mediated endocytosis* (BME) [4].

When the bacteria adheres to the apical epithelial surface, an extensive cytoskeletal rearrangements is followed shortly which disturbs the normal epithelial brush border prompting the configuration of membrane ruffles. These membrane ruffles reach out and encloses adherent bacteria in large vesicles. M cells (specialized cells overlying the Peyer's patches) are probably considered the primary portal of entry in case of Enteric fever and the generalized intrusion of enterocytes is thought to play a prominent role in enteritis caused by Non-Typhoidal *Salmonella* (NTS) serotypes [5].

There are several large insertions in the genome of *Salmonella* that are considered to arise from bacteriophages or plasmids, called as the *Salmonella* pathogenicity islands (SPIs). These SPIs encode genes that are crucial for survival in the host. The virulence genes are responsible for invasion, survival, and extra intestinal spread. For instance, Salmonellae encode a type III secretion system (T3SS) within *Salmonella* pathogenicity island 1 (the SPI-1 T3SS), which is necessary for bacteria-mediated endocytosis and epithelial invasion in the intestine.

4. Definitions

4.1 Genomic Island

Genomic islands (GIs) such as integrative and conjugative elements (ICEs) and integrative mobilizable elements (IMEs) are clusters of genes inside a bacterial genome which seems to be acquired by horizontal gene transfer [6]. Initially noticed in pathogenic bacteria, designated as pathogenicity islands because they carried virulence genes or other pathogenicity factors, now are also identified in various non-pathogenic bacteria. Therefore, GIs are frequently named based on the adaptive properties they bestow such as metabolic islands, antibiotic resistance islands, symbiosis islands, pathogenicity islands etc. [7]. Furthermore, GIs bless their hosts with new traits, like resistance to antimicrobials and enhanced virulence.

4.2 Pathogenicity island (PAI)

Pathogenicity islands are a definite class of GIs acquired by microorganisms by horizontal gene transfer. They constitute large genomic regions (10–200 kilobases in size) that are integrated in the genome of pathogenic bacteria and are not seen in non-pathogenic bacteria of the same or closely related species [6]. The concept of

S.No.	Characteristic features of Pathogenicity Islands
1.	Carrying of one or more genes of virulence
2.	Present in pathogenic bacteria and not seen in non-pathogenic ones of the same or closely related species
3.	Constitute large genomic regions (10–200 kilobases in size)
4.	Possess DNA content that varies markedly from the rest of the host genome, especially percentage of G + C content and codon usage
5.	Commonly situated adjacent to tRNA genes
6.	Frequent association with mobile genetic elements, often flanked by direct repeats Presence of integrase gene at one end of the island
7.	Genetic instability that can lead to loss of the Pathogenicity islands

Table 1.
Features of Pathogenicity Islands.

pathogenicity islands was established in the late 1980s by Jorg Hacker and his colleagues while probing the genetic grounds of virulence of uropathogenic *Escherichia coli* strains 536 and J96 [8]. The important features of PIs are summarized in **Table 1** [8].

5. *Salmonella* Pathogenicity Islands

Pathogenicity islands in *Salmonella* spp. are generally known as '*Salmonella* Pathogenicity Island' or SPI. They are found in large number and are the central elements for virulence in *Salmonella.* A total of 17 SPIs (1–17) are recognized so far [9].

5.1 SPI1

Salmonella species has the capability to penetrate non-phagocytic host cells. For the penetration or invasion to take place, there is requirement of several genes which were first identified for *S. typhimurium* [10]. At the later stages of research, it was established that all the genes responsible for invasion were bunched within a region at centisome 63 of the *Salmonella* chromosome [11]. After that, the second cluster of genes were identified which were required because of the ability of *Salmonella* to proliferate in different organs of the infected host, lead the researchers to designate Invasion Locus *Salmonella* Pathogenicity Island 1 and accordingly newly identified locus as *Salmonella* Pathogenicity Island 2 [12].

The size of SPI-1 is nearly 40 kilo bases in size and encodes a type III secretion system (T3SS) that is needed for BME and intestinal epithelial invasion (**Figure 1**). T3SS are considered as complex macromolecule machines that emerge to bring down the function of host cell by translocation of virulence proteins straight from the bacterial cytoplasm into the host cell. T3SS are also known as injectisomes' or 'molecular needles because of their capability to translocate proteins in a cell contact-dependent manner [13]. T3SS is also found in several species of several Gram-negative bacteria (e.g. *Salmonella*, *Yersinia, Shigella, E. coli, Pseudomonas*) and encompasses at least 20 different subunits that enables these bacteria to translocate specific substrates (or 'effectors') directly into the host cell cytoplasm which exerts a broad range of virulence functions [14]. The mutants of *Salmonella* not having a functional SPI-1 T3SS do not invade epithelial cells in tissue culture [15].
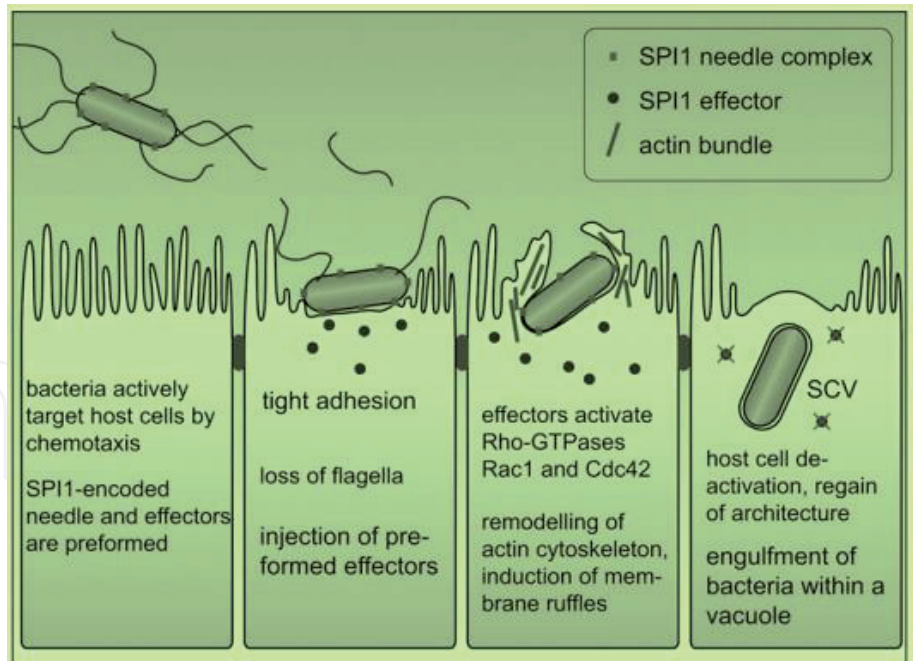
Figure 1.
Invasion of Salmonella *into non-phagocytic cells by SPI1. At the time of contact with host cell, there is injection of different effectors into cytoplasm of host cell by SPI1 encoded T3SS. This leads to stimulation of small rho GTPases that causes massive cytoskeleton rearrangements. This results in intake of bacteria by macropinocytosis. Now, bacteria live in vacuole and the host cells regain a normal architecture. (from Gerlach RG, Hensel M.* Salmonella *pathogenicity islands in host specificity, host pathogen-interactions and antibiotics resistance of* Salmonella enterica. *Berliner und Munchener tierarztliche Wochenschrift. 2007 Jul 1;120(7/8):317).*

There is requirement of at least five translocated proteins adequate invasion of cultured epithelial cells, whereas invasion is more complex and diverse in animal tissues [16]. Two subsets of effector proteins are generated by SPI-1 in which one subset mediates invasion by *Salmonella* of non-phagocytic cells through alteration of active cytoskeleton system of host cell and the other second subset is related with entero-pathogenesis and inflammation of cells of intestinal epithelium. The important effector proteins are summarized in **Table 2**.

Effector protein	Function	Mechanism
SipC & SipA	Promotes membrane ruffling and *Salmonella* invasion	By direct interactions with the actin cytoskeleton
SopE & SopE2	Promotes membrane ruffling ans *Salmonella* invasion	Directly activate Rac1 and Cdc42 in vitro by acting as GDP/GTP exchange factors (GEFs) and induce membrane ruffling and macropinocytosis after microinjection into epithelial cells
SopB (Additional SPI-1 translocated protein)	Promote membrane ruffling and *Salmonella* invasion	Targets inositol phosphate signaling within the host cell by acting as an inositol polyphosphatase.
SopA and SopD	Intestinal secretory and inflammatory responses	Recruitment of immune cells and secretion of fluid in intestinal lumen
SptP	Reverse the cytoskeletal rearrangements induced by SopE/E2 and SopB	GTPase activating protein (GAP) acts on Rac1 and Cdc42,

Table 2.
Important translocated proteins of SP-I of Salmonella.

5.2 The SPI1 regulon

The expression of SPI1 is driven by central transcription factor, SPI1 encoded HilA which is a member of OmpR/ToxR family of transcriptional regulators. The expression of SPI1 regulon is directed by specific blend of environmental signals such as osmolarity, antimicrobial peptides, oxygen, pH and other unidentified signals. These signals are perceived by a set of 2 component regulatory systems: BarA/SirA [17], OmpR/EnvZ [18], PhoBR [19] and PhoPQ [20]. The phosphorylated connected response regulators can promote the expression of either HilD or HilE that in turn either stimulates or represses SPI1-expression.

1. PhoB, PhoP and FimZY can activate hilE expression that can negatively impact hilA expression [21]

2. HilD along with HilC and RtsA make up a feed-forward loop, where each factor can promote the expression of itself, rtsA, hilC and hilA, thus integrating and greatly enhancing the signal [22]

3. Nucleoid proteins HU and Fis are essential for hilA expression [23]

4. HilA binds to cis-elements present in respective promoters that activates prg/org and inv./spa operons within SPI1 which in turn leads to production of InvF, a member of the AraC family of transcriptional regulators. Now, InvF along with the chaperone SicA induces expression of a set of genes encoded within SPI1 and on various loci elsewhere in the chromosome.

5. RtsA/HilD/HilC can activate the expression of dsbA required for the function of the SPI1-encoded T3SS [23] (**Figure 2**).

Figure 2.
The SPI1 regulon. The main regulatory factor of SPI1 expression is HilA whose activity is mainly controlled on the transcriptional level and relies on a complex network of transcription factors and two-component regulatory systems. Arrows indicate activation of gene expression. Positive feedback loop are highlighted by bold arrows. Repression is noted as lines with blunt ends. Solid lines represent direct transcriptional regulation. (from Gerlach RG, Hensel M. Salmonella *pathogenicity islands in host specificity, host pathogen-interactions and antibiotics resistance of* Salmonella enterica. *Berliner und Munchener tierarztliche Wochenschrift. 2007 Jul 1;120(7/8):317).*

5.3 SPI2

Salmonella has a second T3SS that is essential for survival within the macrophage and for establishment of systemic infection. Proteins delivered by both type III secretion systems are vital for intracellular survival. The second T3SS is encoded on *Salmonella* pathogenicity island 2 (SPI-2). The activity of SPI2 is needed to establish and maintain the *Salmonella-* containing vacuole (SCV) as an intracellular niche in which *Salmonella* can remain live and replicate.

SPI2 is of nearly 40 Kb in size and comprises of 2 distinct regions [24]:

1. The larger region relatively 25 Kb in size found exclusively in *S. enterica,* implicated in systemic pathogenesis. It encodes second T3SS.

2. The smaller region of 15 Kb in size was identified in *S. bongori. It* encodes the tetrathionate reductase (Ttr) that is involved in anaerobic respiration.

This second T3SS expressed by intracellular bacteria translocates proteins across the SCV membrane into the macrophage cytosol. With the help of these SPI2 translocated proteins, *Salmonella* escapes intracellular killing by altering the phagosome membrane to tubulate [25]. Phagosome tubulation is dynamic and rapid process and occurs to be dependent on the recruitment of microtubule motors, membrane lipid alteration and the activation of small GTPases, and membrane lipid alteration [25]. Phagosome tubulation is also correlated with the virulence by unknown mechanisms.

A total of seventeen effectors are recognized to be translocated over the SCV membrane into the host-cell cytoplasm, most of them being encoded outside the SPI2-locus [26]. Only 3 effectors are known to be encoded within SPI2 which includes SpiC, SseF and SseG. The SPI-2 translocated proteins, including SifA, SifB, SseJ, SopD2, PipB, and PipB2, localize to the surface of the SCV and either contributes to tubulation or other alterations of the phagosome [27]. The summary of important effectors has been given in **Table 3**.

5.4 The SPI2 regulon

The expression of SPI2 genes is controlled governed by global regulatory system: SsrAB system. It is a typical two-component system that is necessary for SPI2 regulon expression in intracellular bacteria. The main global regulatory systems that affect the expression levels of SPI2 genes are the EnvZ/OmpR and PhoPQ two-component systems, SlyA and Fis [23].

Effectors	Functons
SpiC	Block fusion of the SCV with lysosomes
Sif A	*Salmonella* containing vacuole membrane integrity
SseJ	Cytoskeleton rearrangements
SsPH2	Cytoskeleton rearrangements
Ttr genes	Tetrathionate respiration and outgrowth in the intestine
SseFG	Maintaining a juxtanuclear position of the SCV in HeLa cells
SpvB	*Salmonella* virulence protein that is secreted into the macrophage cytoplasm,

Table 3.
Functions of major effectors of SPI-2.

5.5 SPI3

The SPI3 locus is of size 17 kilobases and is inserted at the selC tRNA gene locus. The primary known virulence determinant is Mgt CB (Magnesium transport system) operon: MisL and Mar T. This determinant is necessary for survival of *Salmonella* in the intra-phagosomal habitat in nutritionally deprived conditions. Mis L, a anti-transport protein of SPI3, is identical to the autotransported AIDA-1 adhesin of enteropathogenic *E. coli* (EPEC) while Mar T shows resemblance with Tax R (Toxin gene regulator) of *Vibrio cholerae* and it is implicated in the activation of Mis L [28].

MisL is proved to work as an adhesion [29] and it is vital for the long term persistence of *Salmonella* in the intestine as observed in animal studies. Another autotransporter, ShdA is seen to have a function in adhesion and virulence in case of *S.* Typhimurium.

A high degree of sequential variation exists in SPI3 among different serovars; however it is conserved in cases of *S.* Typhi and *S.* Typhimurium.

5.6 SPI4

The size of SPI4 is identified as 27 Kb. Sequencing of the *Salmonella* Typhimurium genome anticipated that the pathogenicity island constitute of not more than six genes. Hence the genes of the locus SPI4 are named as siiA-F. SiiC, SiiD and SiiF encodes components of type I secretion system which secretes SiiE. This, SiiE is huge protein (approximately 600 kDa) that is known to colonize the bovine intestine [30]. The molecular functions of SPI4 encoded proteins are not known. The role of SPI4 in *Salmonella* virulence was investigated in one of the studies using refined cell culture and infection models, there it was observed that SPI4 contributes to gastrointestinal inflammation in murine colitis model and is also required for adhesion to epithelial cells [31]. De Keersmaecker et al. suggested a role for SPI4 in intra-macrophage survival as shown for SPI2 [32].

SPI4 seems to be highly conserved among different *Salmonella* serovars [33].

5.7 SPI5

The size of SPI5 locus is nearly 7.6 Kb. It encodes the effector proteins for both the T3SS that is encoded by SPI-1 and SPI-2. Pip A and Pip B are also known to be encoded by SPI5 locus. Pip A is implicated in the development of systemic infection and Pip B is involved in the accumulation of lipid rafts and is a translocated effector of SPI-2 encoded T3SS which is under the control of Ssr AB two-component systems. However, PipB is neither needed for bacterium's intracellular survival nor for systemic virulence as studied in mice [34, 35].

In enteropathogenicity in a cattle infection model, significant attenuation of SPI5-deficient *Salmonella* was observed. However SPI5 mutants showed only a minor virulence defect in mouse model [36].

5.8 SPI6

The SPI6 locus is also known as '*Salmonella* centisome 7 genomic island' or SCI [37]. It is of size 59 Kb and it has been recognized in *S.* Typhi and *S.* Typhimurium. It is investigated to contain [35]:

1. saf gene which codes for fimbriae

2. pag N gene which encodes for invasion protein

A microarray analysis indicated the conservation of SPI6 among serovars of S. enterica subspecies I serovars was indicated by microarray analysis.

Deletion of SPI6 had no influence on the systemic pathogenesis but decreased invasiveness of the bactetia in tissue cultured cells. SPI-6 was detected to be conserved among serovars of S. *enterica as* indicated by microarray analysis. Some of the portion of SPI-6 that was also identified in subspecies III b, IV, and VII. Further, SPI-6 has shown sequential homology with the genome of *P. aeruginosa* and *Y. pestis* [38].

5.9 SPI7 and SPI8

The size of SPI7 and SPI8 is approximately 133 Kb and 6.8 Kb respectively. SPI7, also termed as major Pathogenicity Island is specific to *S.* Typhi, *S.* Dublin and *S.* Paratyphi. It encodes for Vi antigen and constitute pil gene cluster that encodes for putative virulence factors. Its genetic organization is very complex and composed of several horizontally acquired elements. It also constitutes few genes of conjugative plasmid-like *tra* and *sam.*. The locus is said to not stable and loss of the capsule can be seen in *S.* Typhi isolates. Additionally SPI7 also encodes a type IV fimbrial adhesin. There exists a sequential homology with few other bacteria like *Xanthomonas axonopodis* and *Pseudomonas aeruginosa* in the case of SPI7 [39].

SPI8 has been identified in *Salmonella* Typhi and the genes located here encode for putative virulence factors, whose exact function has not been reported so far.

5.10 SP19

The size of SPI-9 locus is nearly 16,281 basepairs. SPI9 from S. Typhi harbors three ORFs (STY2876,STY2877,STY2878) presenting 98% identity with a type 1 secretory apparatus (T1SS) and a single ORF (STY2875) that is similar to a large RTX-like protein exhibiting repeated Ig domains. It encodes for virulence factors of type I secretion system. Furthermore, as it is functional in *S.* Typhi and encodes for adhesion which is induced under conditions of high osmolarity in culture. However it does not participate in biofilm formation [40].

5.11 SP110

SPI10 has a size of 32.8 Kb and is defined as an insertion at the tRNA leuX gene. It appears to be hyper variable and is a point of insertion for several different DNA fragments. Sef and pef gene clusters which encodes for fimbrial adhesions have been detected in *S.* Enteritidis and cryptic bacteriophage has been seen within this locus in case of *S.* Typhi and *S.* Paratyphi A. On the other hand, *S.* Typhimurium has entirely different gene content. Because of these findings, the leuX locus represents a hot spot for the insertion of various mobile genetic elements [41].

5.12 SPI11 and SPI12

The SPI11 and SPI12 were identified in *Salmonella choleraesuis.* Both these islands shows properties of PAI such as association with bacteriophage genomes and tRNA genes. The low G + C content of 41.32% was seen for SPI11. The proteins encoded by these SPIs contributes to virulence of *Salmonella* but exact role is still not clear and awaits further characterization [42].

5.13 SPI13 and SPI14

SPI13 and SPI14 were first identified in avian adapted S. Gallinarum which is causative agent of typhoid in fowls. SPI13 is close to the tRNA pheV gene and is

composed of 18 ORFs while SPI14 is not associated with a tRNA gene and constitutes 6 ORFs. Both these islands are not present in *S*. Typhi and *S*. Paratyphi A but are seen in *S*. Typhimurium and *S*. Enteritidis. This may indicate a possible role of the loci in host specificity. The role of proteins encoded by these SPIs is not clear yet and requires further molecular characterization [43].

5.14 SPI15, SPI16, and SPI17

SPI15, SPI16 and SPI17 were identified in S. Typhi using bioinformatics approach. All these exhibit association with tRNA genes. SPI16 and SPI17 encodes for genes that are responsible for LPS modification. There is presence of SPI15 in only S. Typhi isolate CT18 and role of its effecter proteins is not clear till date. SPI16 and SPI17 are seen in S. Typhi and most other S. enterica genome sequences [44].

Table 4 summarizes the various SPIs.

SPI & Insertion point	Distribution among *Salmonella* species	Variable or conserved	Function
SPI1			
flhA-mutS	*Salmonella* spp.	Conserved	T3SS, iron uptake
SPI2			
tRA val V	S.enterica	Conserved	T3SS, tetrathionate reductase
SPI3			
tRNA sel C	*Salmonella* spp.	Variable	Mg2+ uptake, Misc. adhesin
SPI4			
tRNA like	*Salmonella* spp.	Conserved	T1SS adhesin
SPI5			
tRNA ser T	*Salmonella* spp.	variable	T3SS effectors SopB, PipB
SPI6			
tRNA asp V	Subsp. I. parts in IIIB, IV, VII	Conserved In subsp. I	Saf fimbriae
SPI7			
tRNA pheU	Subsp. I serovars	Instable	Vi antigen, pilus assembly, SopE
SPI8			
tRNApheV	sv. Typhi	NK	NK
SPI9			
prophage	Subsp.. I serovars	NK	T1SS, adhesin BapA
SPI10			
tRNA leuX	subsp. I serovars	variable	Sef fimbriae
SPI11			
prophage	S.Choleraesuis	NK	NK
SPI12			
tRNA pro	S.Choleraesuis	NK	NK
SPI13			

SPI & Insertion point	Distribution among *Salmonella* species	Variable or conserved	Function
tRNA pheV	S.Gallinarum,S. Typhimurium	NK	NK
SPI14			
NK	S.Gallinarum,S. Typhimurium	NK	NK
SPI15			
tRNA gly	S. Typhi	NK	NK
SPI16			
tRNA arg S. Typhi, and others ? serotype conversion	S. Typhi, and others	NK	serotype conversion
SPI17			
tRNA arg	S. Typhi, and others	NK	serotype conversion
SGI1			
thdF–yidY	subsp. I serovars	variable	5 antibiotic resistance genes
CS54			
xseA-yfgK	subsp. I serovars	NK	adhesion

NK – Not Known.

Table 4.
Summary of various Salmonella *Pathogenicity Islands.*

5.15 SGI1

Strains showing resistance to multiple antibiotics is a usual phenomenon seen in pathogenic bacteria and is also mostly observed in S. enterica. Resistant *Salmonella* isolates harbor resistance plasmids of variable size and composition of resistance genes. A multidrug resistance phenotype conferred by 'Salmonella genomic island 1' or SGI1 was recognized in epidemic strain S. Typhimurium DT104 by molecular testing though It can also be present in other strains as well. The SGI1 confers resistance to the antibiotics such as ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracycline [23].

6. Conclusion

PAI phenomenon frequently identified in pathogenic bacteria and encodes virulence genes which help pathogens to establish infections. The molecular characterization of individual virulence genes and genome sequences demonstrated large numbers of PAI in S. *enterica* serovars. Among various *Salmonella* pathogenicity islands, only SPI1 and SPI2 have well proven role in virulence while knowledge of the molecular function of the rest of the SPIs is lacking. Furthermore, molecular analysis of SPI is vital for improvement of prevention and treatment of *Salmonella* infection in human and animals. Also the varied degrees of disease severity and of bacterial pathogenesis can be explained better by understanding SPI.

Author details

Sarika Kombade* and Navneet Kaur
Department of Microbiology, All India Institute of Medical Sciences (AIIMS),
Jodhpur, Rajasthan, India

*Address all correspondence to: spkombade@gmail.com

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