



Phage-mediated horizontal transfer of *Salmonella enterica* virulence genes with regulatory feedback from the host

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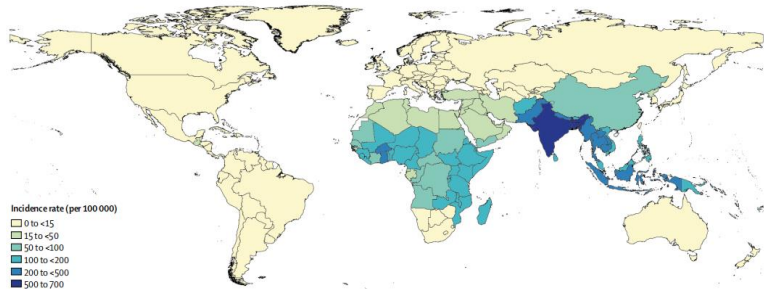
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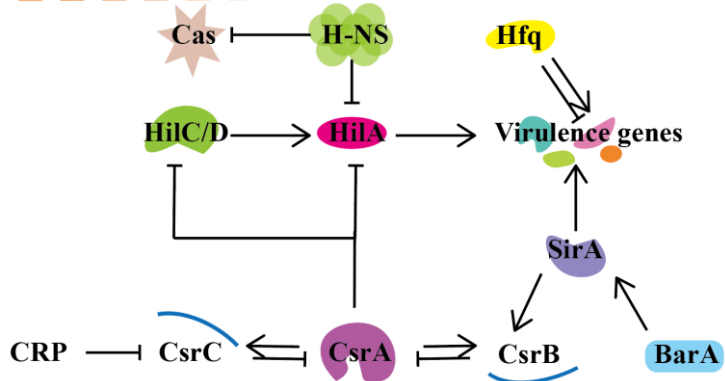
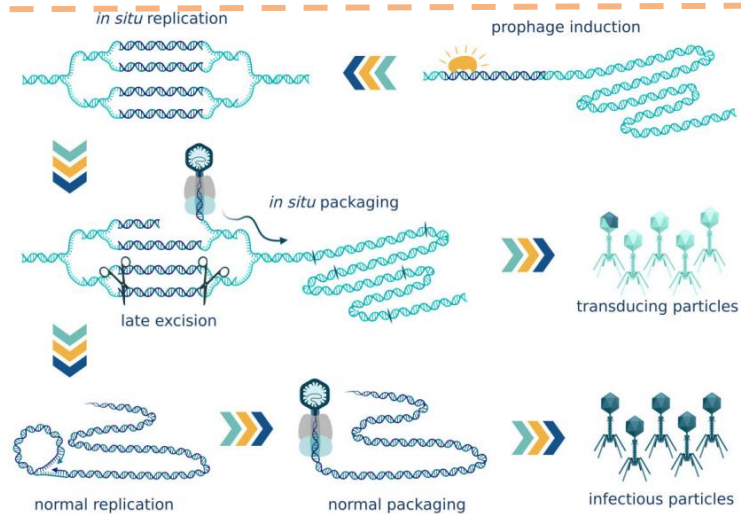
Introduction



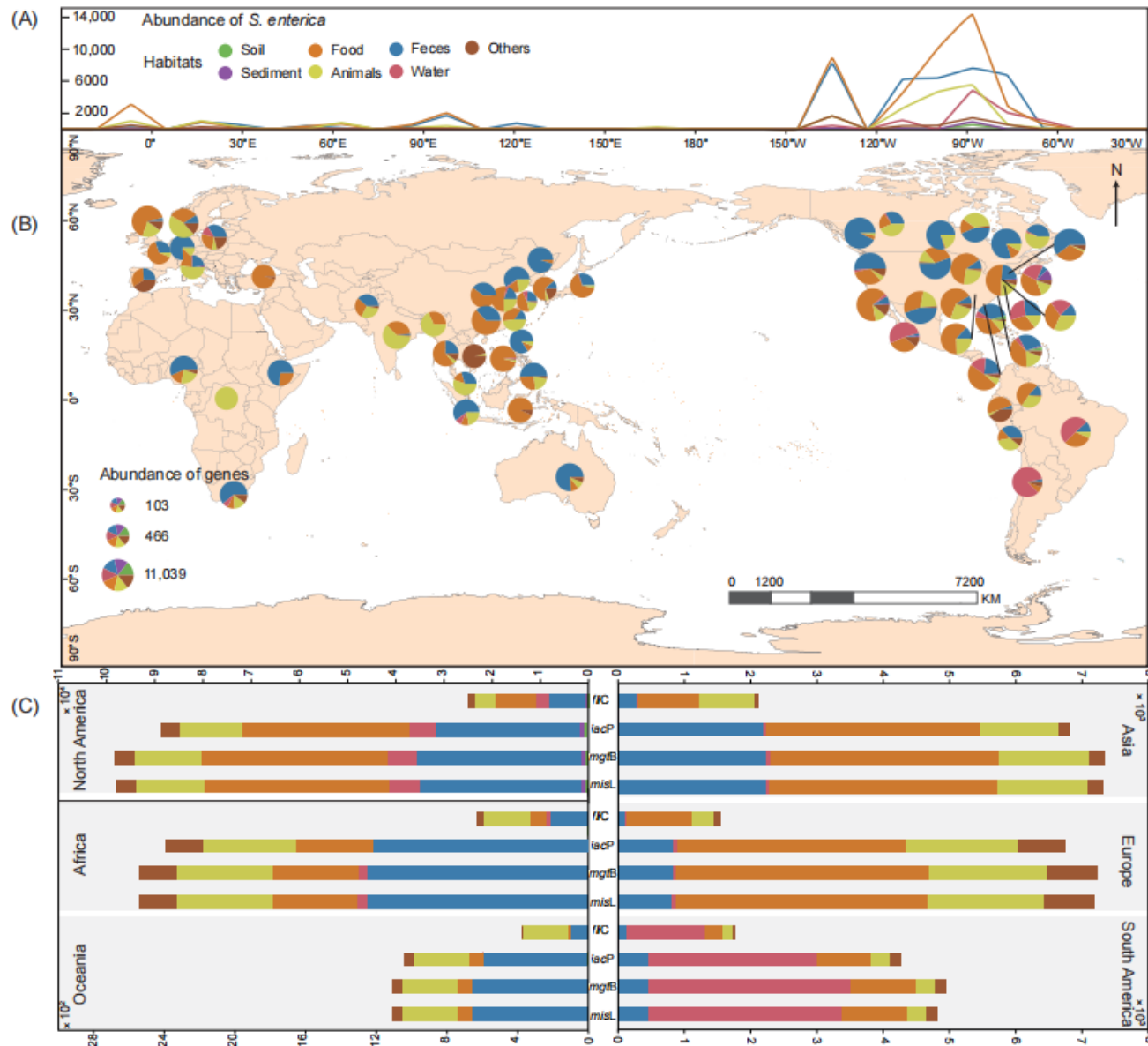
1. *Salmonella enterica* is a leading cause of foodborne illness worldwide, responsible for significant **public health concerns**. It causes typhoid fever, paratyphoid fever, and diarrheal illness, with an estimated 17.8 million cases annually in low- and middle-income countries.

2. Virulence factors such as virulence plasmids, toxins, pili, and flagella are essential for *Salmonella*'s pathogenicity. **Horizontal gene transfer (HGT)** is a key mechanism through which *Salmonella* acquires and spreads these **virulence factors**, enhancing its adaptability and survival in various environments.

3. *Salmonella* encodes various **regulatory genes** to modulate the expression of virulence genes, including *csrA*, *hns*, *hfq*, *crp*, *barA*, and *sirA*. These regulators may **influence HGT**, either promoting or repressing their expression upon entry into host cells, and play a crucial role in controlling bacterial infections.



The global distribution pattern of *S. enterica*



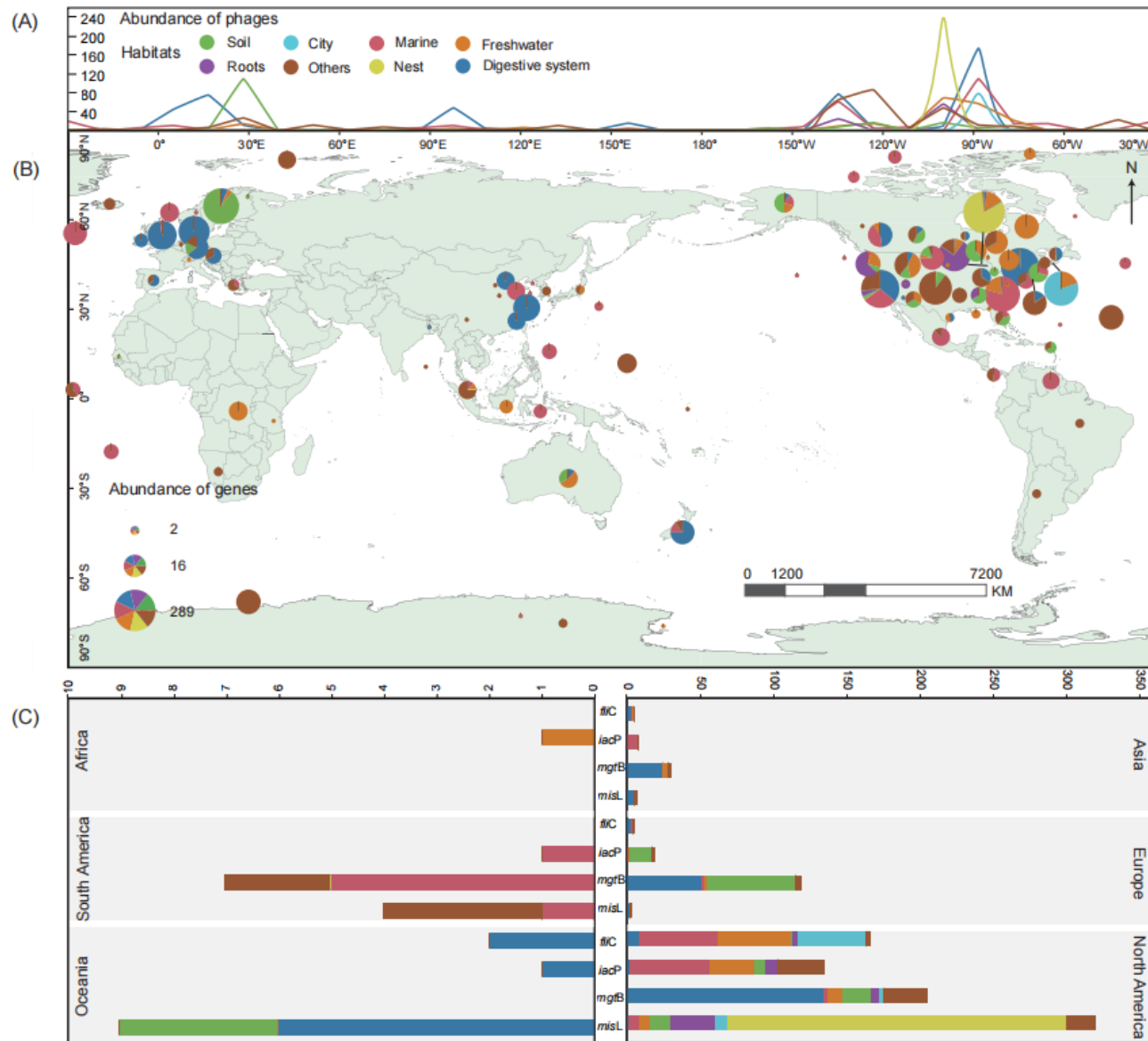
1. A total of **466,136** *S. enterica* genomes were obtained from EnteroBase. These strains were distributed across **548** serotypes and **66** countries.

2. *S. enterica* strains were mainly distributed in the **Americas, Europe, and Asia**, with North America having the highest abundance.

3. The main habitats of *S. enterica* included **food, human and animal feces, animals, water, sediments, and soil.**

Figure 1 Global geographical distribution of *S. enterica*.

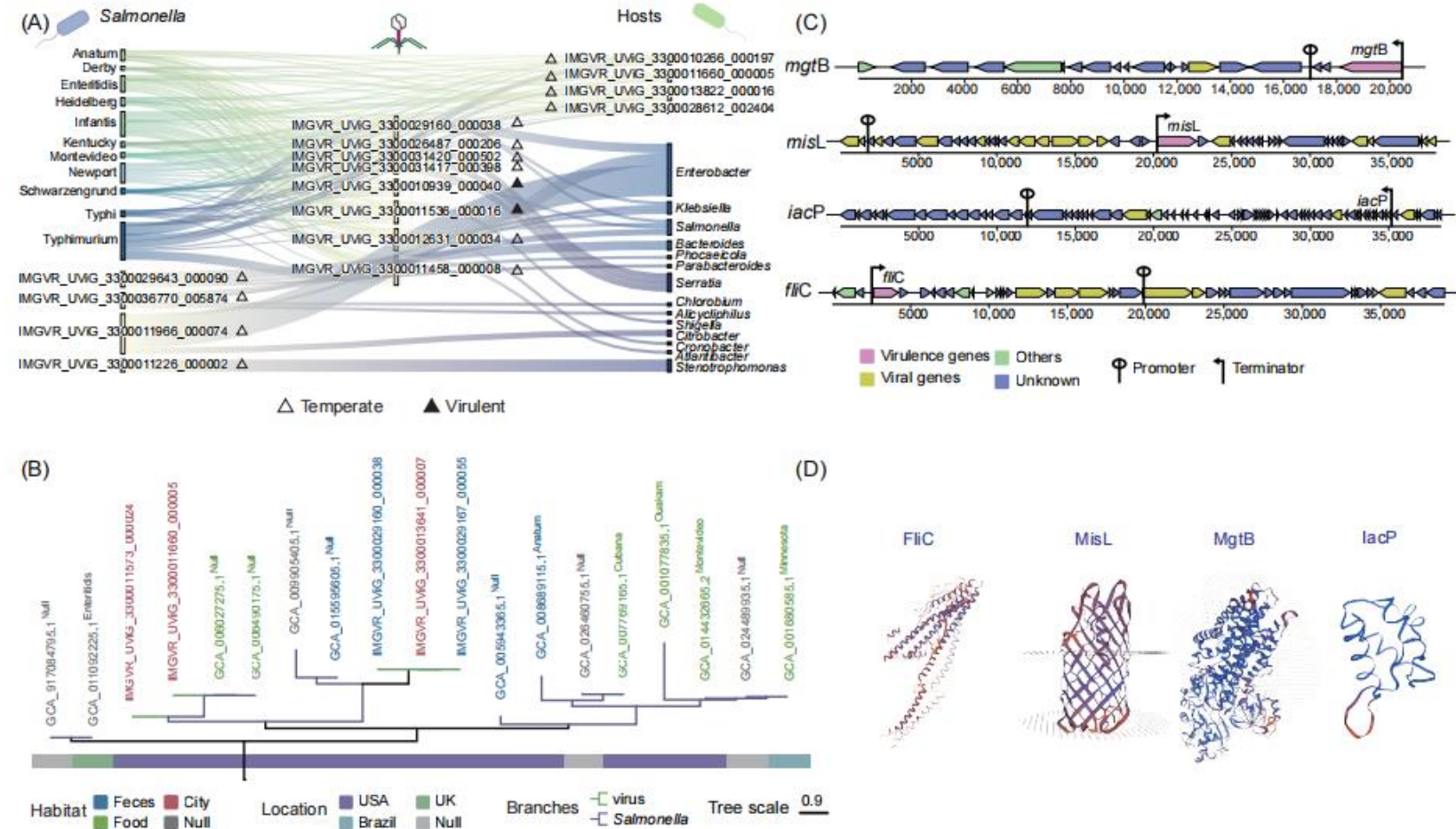
The global distribution pattern of phages



1. A total of **5178** such phages were identified from the IMG/VR database, primarily *Caudoviricetes*. Of these, **45.73%** were **temperate**, **33.49%** **virulent**.
2. The phages were most abundant in **North America, Europe, and Asia**.
3. The phages were mainly found in the mammalian **digestive system**, **marine** environments, nests, freshwater, soil, and roots.

Figure 2 Global distribution of phages encoding *S. enterica* virulence genes.

Phage-host interactions and HGT in *S. enterica*



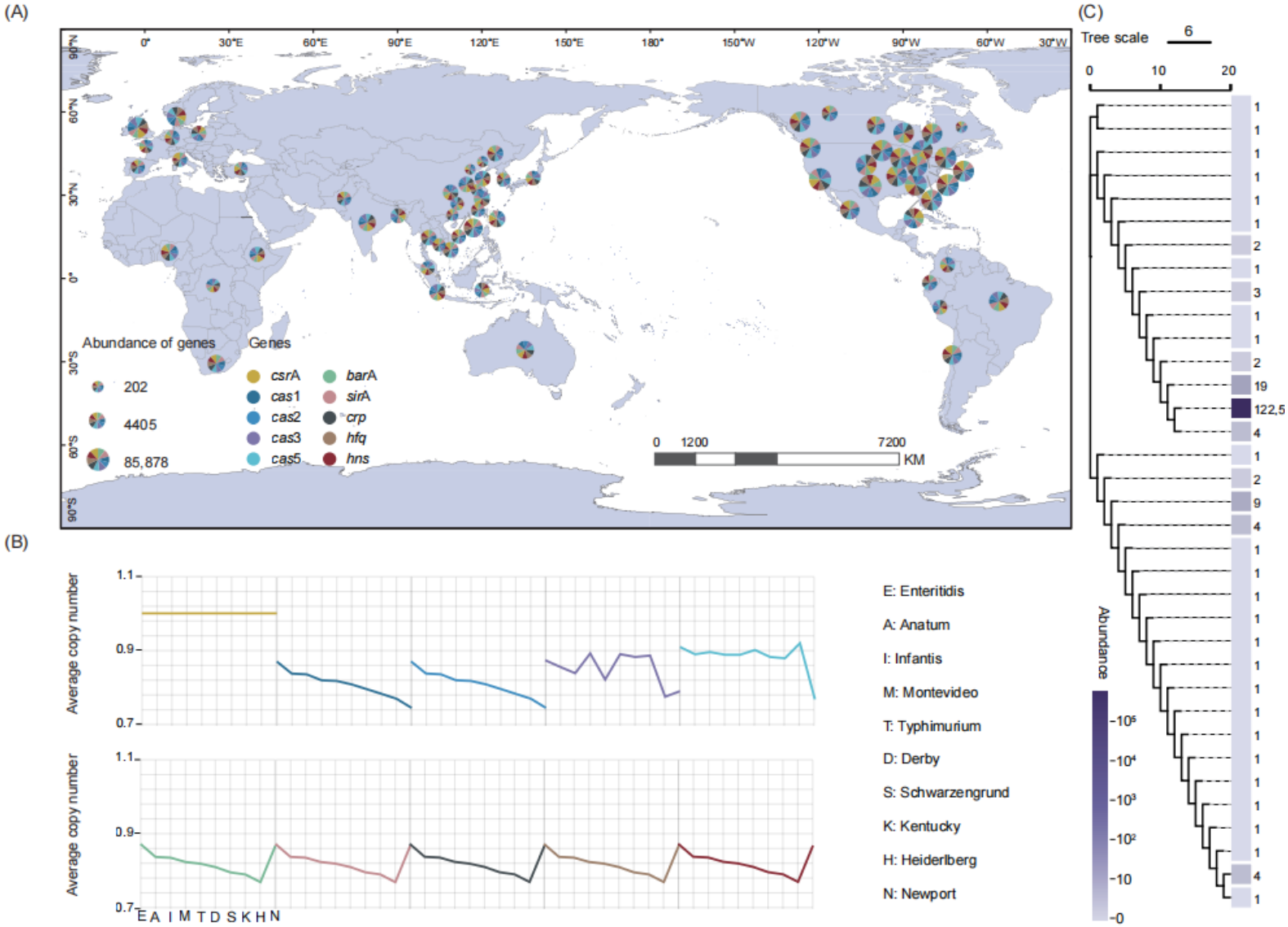
1. **Phages** were linked to diverse serotypes, indicating frequent gene exchange.

2. Phage-encoded virulence genes, such as *fliC*, *mgtB*, and *misL*, are genetically similar to those in *S. enterica*, suggesting historical **HGT** events.

3. **Promoter** and **terminator** analysis, along with **protein structure predictions**, confirmed the functional potential of these phage-encoded virulence genes.

Figure 3 Phage host prediction and phylogenetic analysis of virulence genes.

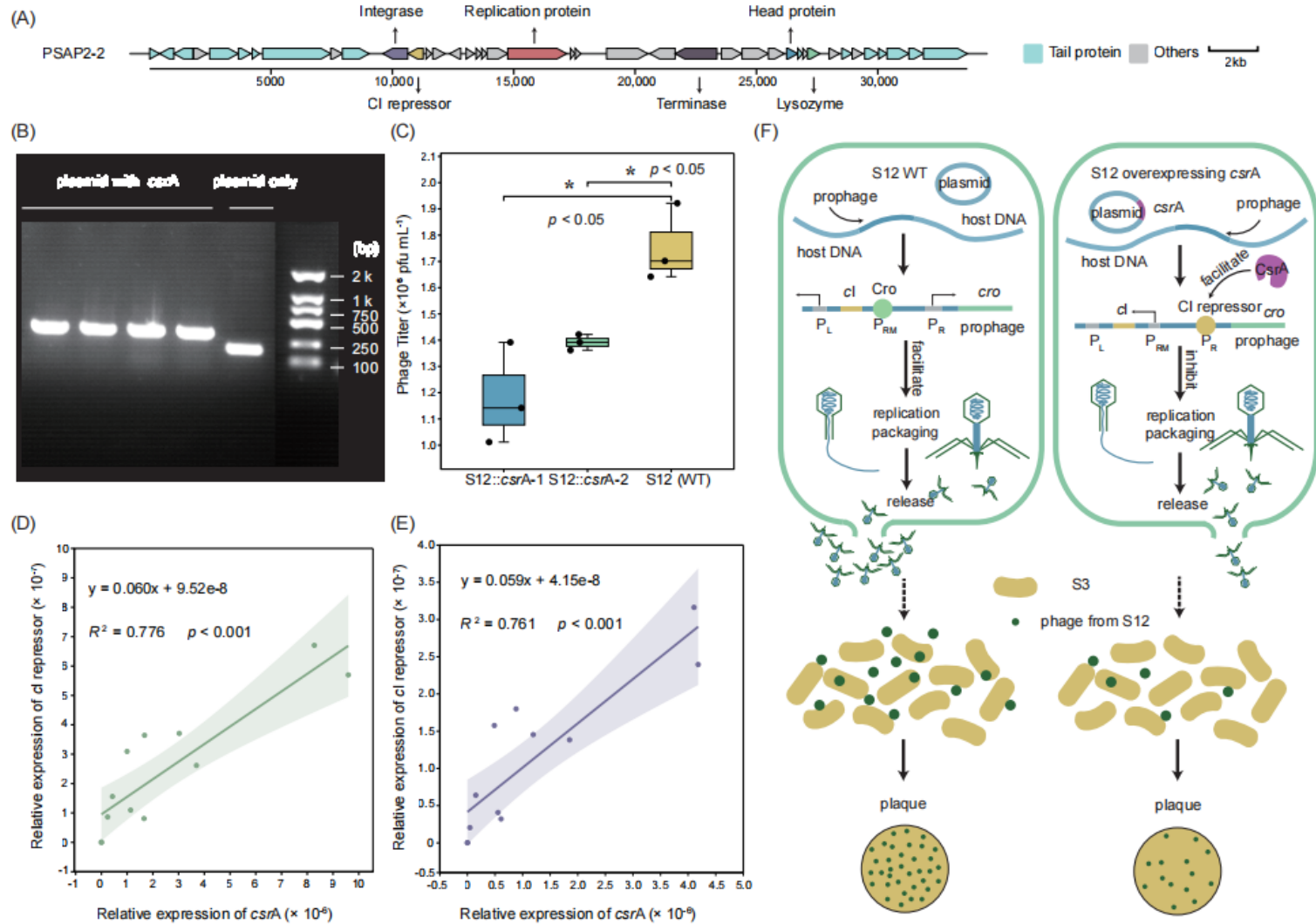
Distribution and conservation of regulatory genes



1. Ten key regulatory factors in *S. enterica* were predominantly found in **North America**, followed by **Asia** and **Europe**.
2. *csrA* was the most frequently detected and had the highest average copy number, nearly 100% across all serotypes.
3. 99.94% of *csrA* had identical amino acid sequences, indicating high conservation in *S. enterica*.

Figure 4 Global distribution of regulators in *S. enterica*.

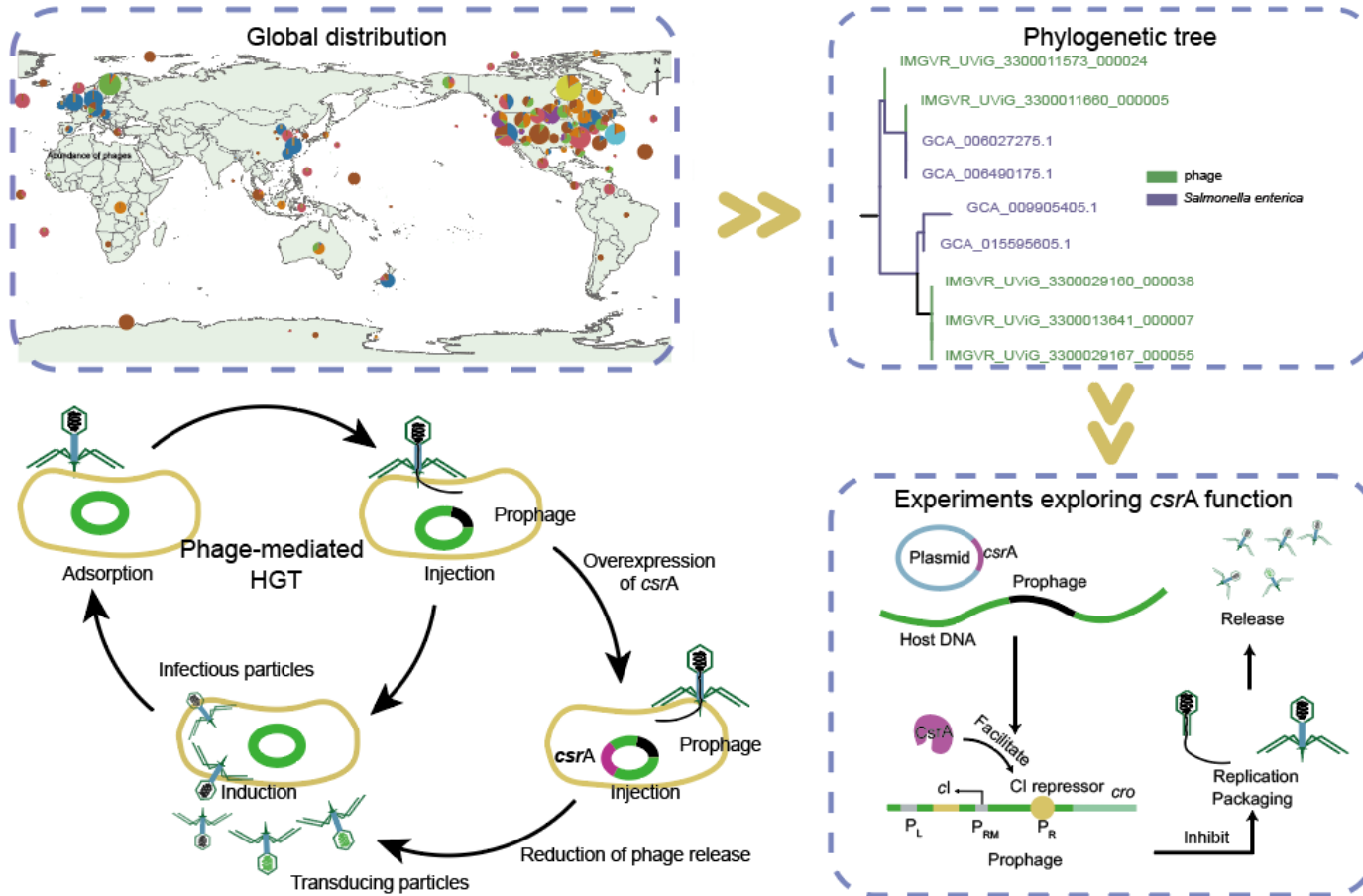
The effect of *csrA* on phage-mediated HGT



1. By introducing plasmids carrying *csrA* into *S. Typhimurium* strain S12, the prophage release was reduced compared to the wild-type strain, with **phage titers significantly lower** ($p < 0.05$).
2. Further analysis via **qPCR** revealed a strong positive correlation between ***csrA*** and ***cI* repressor** expression, indicating that *csrA* suppresses prophage cyclization by upregulating *cI*.

Figure 5 Experiments to validate the effect of *csrA* on phage cyclization and *cI* repressor.

Summary



In this study, we found evidence of **phage-mediated horizontal transfer** of virulence genes in *Salmonella enterica* in global habitats from a molecular evolutionary perspective. Notably, *csrA*, a global regulator in *Salmonella enterica*, curbed horizontal gene transfer by inhibiting the cyclization and release of **prophage**. This is a novel finding in phage-bacteria interactions that provides new ideas for controlling pathogenic bacteria in the environment.

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Data availability

Data for Phage-mediated global horizontal transfer of *Salmonella enterica* virulence genes (1)

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Dataset posted on 2024-08-11, 10:08 authored by [tianjing_she](#)

122,680 *Salmonella enterica* genomes were downloaded from Enterobase (<https://enterobase.warwick.ac.uk/>, accessed on 29 May 2023), and 2,186 phages encoding *S. enterica* virulence genes were download from IMG/VR database (<https://img.jgi.doe.gov/cgi-bin/vr/main.cgi>). This dataset under the web link contains the above phage genomes and some of *S. enterica* genomes.

USAGE METRICS

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CATEGORIES

- Microbial ecology

KEYWORDS

Salmonella outbreak

HISTORY

- 2024-08-11 - First online date, Posted date

1. *Salmonella enterica* genomes and phage genomes can be downloaded on **Figshare**.

<https://doi.org/10.6084/m9.figshare.26493310>

<https://doi.org/10.6084/m9.figshare.26527759>

<https://doi.org/10.6084/m9.figshare.26531836>

2. All figures and supporting information can be accessed via **GitHub**.

<https://github.com/TianjingShe/Salmonella-enterica>.

3. Supplementary materials (figures, tables, and graphical abstract) may be found in the **online DOI** or **iMeta Science** <http://www.imeta.science/>.

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