Invertible promoters mediate bacterial phase variation, antibiotic resistance, and host adaptation in the gut

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Phase variation, the reversible alternation between genetic states, enables infection by pathogens and colonization by commensals. However, the diversity of phase variation remains underexplored. We developed the PhaseFinder algorithm to quantify DNA inversion-mediated phase variation. A systematic search of 54,875 bacterial genomes identified 4686 intergenic invertible DNA regions (invertons), revealing an enrichment in host-associated bacteria. Invertons containing promoters often regulate extracellular products, underscoring the importance of surface diversity for gut colonization. We found invertons containing promoters regulating antibiotic resistance genes that shift to the ON orientation after antibiotic treatment in human metagenomic data and in vitro, thereby mitigating the cost of antibiotic resistance. We observed that the orientations of some invertons diverge after fecal microbiota transplant, potentially as a result of individual-specific selective forces.

ANTIBIOTIC RESISTANCE

Phase variation is a process that bacteria use to generate frequent and reversible changes within specific hypermutable loci, introducing phenotypic diversity into clonal populations. Such phenotypic diversity plays an important role in mediating preemptive adaptation to abrupt and severe selective events and is often crucial for infection by pathogens and colonization by commensals (1–5). In bacteria, phase variation often manifests through regions of DNA that invert between two states in a predictable, reversible manner (6). The mechanism of inversion involves enzymes called invertases, which recognize a set of inverted repeats flanking the invertible DNA region and catalyze its inversion in a reversible manner (7). Invertible regions commonly contain promoters oriented such that in the ON orientation, the promoter is poised to activate transcription of an operon (7). In the opposite OFF orientation, the promoter is oriented away from the operon, which is therefore not transcribed (7). Additional types of regulatory elements, such as terminators, may also be contained within these invertible DNA regions (8). Invertases catalyze frequent inversions—for example, one inversion in every 100 to 1000 Escherichia coli cells, a rate at least three orders of magnitude higher than the rate of point mutations (7, 9, 10). Thus, invertible promoters generate genetic diversity in populations, enabling rapid and reversible adaptation. Studies in specific pathogens and commensals have reported invertible promoters that regulate genes involved in virulence or colonization, such as those that encode fimbriae, flagella, and capsular polysaccharides (1, 2, 4, 7, II–17).

Phase variation mediated by DNA inversion is an underexplored mechanism with broad consequences for adaptation to abrupt and severe selective events. Here, we sought to systematically identify invertons, which we define as single intergenic invertible DNA regions flanked by inverted repeats likely recognized and inverted by invertase proteins in a reversible manner. The term inverton encompasses invertible promoters and intergenic invertible DNA regions containing alternate types of regulatory regions. Through our systematic search for invertons, we aimed to address three long-standing questions regarding this mechanism of regulation: (i) How prevalent are invertons? (ii) What are the functions of genes regulated by invertons? (iii) In the context of a host, do individual-specific selective pressures modulate inverton orientation? We found that invertons are widely distributed across bacteria, yielding fundamental insights into bacterial infection and colonization. We confirmed and expanded upon previous observations that the orientations of some invertons regulating capsular polysaccharide biosynthesis operons of human gut bacteria are stable within individuals and divergent between individuals (17). Using a fecal microbiota transplant (FMT) study to observe the orientation of invertons from the same strain in multiple individuals, we observed divergences in orientation between donor and patient. We also identified invertible promoters regulating antibiotic resistance genes. We observed that antibiotic treatment results in a shift from the OFF to ON orientation of these invertons in humans, and confirmed that antibiotic causes the orientation shift in vitro, which could mitigate the fitness cost of maintaining antibiotic resistance genes in the absence of antibiotics. We developed the PhaseFinder algorithm to computationally identify invertons and quantify their orientations with genomic or metagenomic sequencing reads by identifying regions flanked by inverted repeats, mimicking their inversion in silico, and identifying regions where sequencing reads support both orientations (figs. S1 and S2). Simulations to benchmark the performance of PhaseFinder reveal that given enough coverage, PhaseFinder can identify most invertons without a substantial rate of false positives. We reasoned that if inversion rates were high, both orientations of invertons would coexist, allowing for the identification of invertons in bacterial populations used for genome sequencing. Therefore, we used PhaseFinder to search for invertons in all available NCBI genomes from RefSeq that were sequenced using Illumina paired-end sequencing with data deposited in the NCBI Short Read Archive. In total, 54,875 bacterial genomes spanning the breadth of cultured bacterial diversity were searched, leading to the discovery of 4686 putative invertons in 2414 genomes (tables S1 and S2). Invertons were found in 10 of 19 bacterial phyla. Five phyla harbored invertons in at least 20% of their genomes (Table 1). The lack of a systematic method to identify invertons was the impetus for our study; however, the limited scope of known inverton examples may lead to biases in the PhaseFinder algorithm against invertons with features divergent from known invertible promoters. Additionally, the identification of invertons with PhaseFinder relies on the presence of both orientations of the inverton in sequenced samples. Therefore, applying the PhaseFinder algorithm to additional bacterial genomes derived from diverse conditions and sequenced at higher coverage or with longer reads will likely lead to the discovery of many more invertons. To explore how invertons are distributed across environmental niches, we used information from ProGenomes and the Joint Genome Institute to categorize species into aquatic, terrestrial, and host-associated habitats (18, 19). The prevalence of invertons was higher in host-associated species (Fisher exact test, host versus aquatic FDR (false discovery rate) P = 3.5 × 10−3, odds ratio = 6.4; host versus terrestrial FDR P = 0.0053, odds ratio = 4.8) (Fig. 1A and table S3). This overall enrichment in the prevalence of invertons is due to phyllum-level enrichment in Bacteroidetes (FDR P = 2.35 × 10−15) and Proteobacteria (FDR P = 8.51 × 10−8) and the fact that all Spirochaetes and Verrucomicrobia found with invertons were associated with vertebrate hosts. Additionally, we observed an increase in the number of invertons per genome
in host-associated species (Wilcoxon rank sum test, host versus aquatic FDR \(P = 0.00023, W = 361,190\); host versus terrestrial FDR \(P = 0.007, W = 180,680\) (Fig. 1B). The enrichment of invertors in host-associated species is not due to habitat-specific differences in coverage (fig. S3). Overall, our results suggest that diverse species likely use invertors to increase their fitness in host-associated niches.

We acquired detailed information on the niches inhabited by species from the phylum Bacteroidetes (table S4). In Bacteroidetes, the prevalence of invertors was higher in host-gut-associated species (Fisher exact test, host-gut versus aquatic FDR \(P = 3.3 \times 10^{-35}\), odds ratio = 328.4; host-gut versus terrestrial FDR \(P = 2.3 \times 10^{-34}\), odds ratio = 220.8; host-gut versus host-other; FDR \(P = 3.9 \times 10^{-27}\), odds ratio = 35.2) (Fig. 1C). The number of invertors per genome was also higher in host gut-associated isolates (Wilcoxon rank sum test, host-gut versus aquatic FDR \(P = 1.8 \times 10^{-30}\), \(W = 6991\); host-gut versus terrestrial FDR \(P = 2.3 \times 10^{-35}\), \(W = 6967\); host-gut versus host-other FDR \(P = 4.9 \times 10^{-33}\), \(W = 3956\) (Fig. 1D).

Because of the observed enrichment for invertors in gut species, we performed an in-depth analysis and curation of invertors in a non-redundant selection of 49 representative species from human stool using longitudinal metagenomic data instead of the reads used to assemble reference genomes (table S5). We identified 459 putative invertors (table S6), 87.6% of which were from species in the phylum Bacteroidetes, which had an average of 19 invertors per genome. We also identified invertors in additional phyla. We found 53 invertors from two Akkermansia species (phylum Verrucomicrobia), two invertors from a Eubacterium species (phylum Firmicutes), and one invertor from a Bifidobacterium species (phylum Actinobacteria) (fig. S4).

We categorized the invertors according to their flanking inverted repeats (IR) and identified four canonical motifs in Bacteroidetes; three corresponding to known IR motifs in B. fragilis and one uncharacterized motif (Fig. 2A and tables S7 and S8) (14). We also identified a distinctive motif class with tandem repeats within each

Table 1. Invertors per phylum identified in a systematic search of bacterial genomes with PhaseFinder.

<table>
<thead>
<tr>
<th>Phylum</th>
<th>Genomes searched</th>
<th>Genomes with invertors</th>
<th>Percentage of genomes with invertors</th>
<th>Total invertors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidobacteria</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Actinobacteria</td>
<td>5,262</td>
<td>67</td>
<td>1.3</td>
<td>200</td>
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<tr>
<td>Armatimonadetes</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bacteroidetes</td>
<td>491</td>
<td>160</td>
<td>32.6</td>
<td>1,254</td>
</tr>
<tr>
<td>Chloramycetes</td>
<td>45</td>
<td>3</td>
<td>6.7</td>
<td>5</td>
</tr>
<tr>
<td>Chloroflexi</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cyanobacteria</td>
<td>20</td>
<td>4</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Deinococcus-Thermus</td>
<td>14</td>
<td>1</td>
<td>71</td>
<td>1</td>
</tr>
<tr>
<td>Fibrobacteres</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Firmicutes</td>
<td>170,10</td>
<td>986</td>
<td>5.8</td>
<td>1,422</td>
</tr>
<tr>
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<td>10</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nitrospirae</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Proteobacteria</td>
<td>14,872</td>
<td>1,133</td>
<td>7.6</td>
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<td>Spirochaetes</td>
<td>138</td>
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<td>41.3</td>
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<td>Synergistetes</td>
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<td>25</td>
<td>2</td>
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<tr>
<td>Tenericutes</td>
<td>21</td>
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<td>0</td>
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<td>Thermodesulfovibrio</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thermotoga</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Verrucomicrobia</td>
<td>5</td>
<td>1</td>
<td>20</td>
<td>27</td>
</tr>
</tbody>
</table>

Fig. 1. Prevalence and number of invertors per genome are enriched in host-associated species. (A and B) The percentage of genomes identified with invertors (A) and the number of invertors per genome (B) from aquatic, terrestrial, and host-associated isolates. (C and D) In the phylum Bacteroidetes, the percentage of genomes identified with invertors (C) and the number of invertors per genome (D) from aquatic, terrestrial, host sites other than gut, and host gut–associated isolates. **P ≤ 0.01, ***P ≤ 0.001.
inverted repeat, which we call motif 0 (fig. S5). We found conserved promoter consensus motifs in 98% (231/235) of inverters with IR motifs 1 to 4 (Fig. 2B) (20). In contrast, promoter motifs were not observed in any of the invertible regions of IR motif 0-containing sequences (table S9). Because of the lack of promoter motifs combined with their location downstream of operons, inverters containing motif 0 may function as another type of regulatory element, such as a phase-variable terminator (8). In gut Bacteroidetes, we identified a total of 255 invertible promoters. On the basis of the orientation of the promoter consensus motif in relation to surrounding genes, we determined which genes or operons were regulated by invertible promoters and whether the promoter was in the ON or OFF orientation with respect to the downstream gene (tables S7 and S8). In both species of Akkermansia, all inverters are flanked by inverted repeats with the same motif (Fig. 2C), contain a promoter motif (Fig. 2D), and lack upstream inversions, which suggests that all invertible promoters are regulated by a single, master invertase (EAJ16-05345 in Akkermansia muciniphila; MK095134 in Akkermansia sp. aa_0143).

Through functional annotation, we found that 73% (228/312) of invertible promoters regulate genes involved in the biosynthesis of polysaccharides, fimbriae, outer membrane proteins, and autotransporters; genes involved in the utilization of polysaccharides; or genes encoding PEP-CTERM domain–containing proteins (Fig. 2A, tables S7 and S8, and fig. S4). All of these functional categories except polysaccharide utilization are enriched in genes regulated by invertible promoters (tables S10 and S11). Genes regulated by invertible promoters are enriched for cell surface products (e.g., GO:0016020, membrane, $P = 1.93 \times 10^{-15}$) (table S11). The most enriched functional class is capsular polysaccharide biosynthesis loci, for which we found at least one example regulated by an inverter in four of the five major gut phyla: Bacteroidetes, Actinobacteria, Verrucomicrobia, and Firmicutes (table S11). Previous studies show that a repertoire of phase-variable capsular polysaccharides is necessary for competitive gut colonization by Bacteroides species (2, 16, 21). Our data show that phase-variable capsular polysaccharide biosynthesis loci are not just a peculiarity of Bacteroides species but are likely a convergent response to a strong selective mechanism in the vertebrate gut that possibly originates from the immune response or phages (2, 21).

We found that invertible promoters could regulate antibiotic resistance genes, such as cmeABC/ermG, which is upstream of the macrolide resistance gene ermG in B. stercoris. To investigate this mechanism in vivo, we searched specifically for antibiotic resistance genes regulated by invertible promoters in a cohort of 39 Finnish children, 19 of whom had never been exposed to antibiotics and 20 of whom had been administered 9 to 15 antibiotic treatments over a 3-year period (22). By coupling PhaseFinder with metagenomic analysis and QPCR, we found three antibiotic resistance genes regulated by invertible promoters: (i) the same ermG macrolide resistance gene as IRIp32, (ii) a cmeABC multidrug resistance cassette conferring resistance primarily to macrolides and cephalosporins, and (iii) pmrEL genes conferring resistance to cationic antimicrobial peptides such as polymyxin B (Fig. 3A). At least one antibiotic resistance gene regulated by an invertible promoter was found in 38% (15/39) of individuals from the Finnish cohort: 40% (8/20) of individuals who were administered antibiotics and 37% (7/19) of individuals who were untreated. Inverters regulating antibiotic resistance genes were also detected in metagenomic data from healthy adults in the United States. All examples of inverters regulating antibiotic resistance were found in Bacteroides species, which are increasingly associated with multi–drug-resistant infections (23). Surprisingly, all cmeABC and ermG antibiotic resistance genes were regulated by an identical invertible promoter. On the basis of genomic context, the cmeABC/ermG invertible promoter is likely located on an integrative conjugative element homologous to CTNhyb, an antibiotic resistance–transmitting mobile element (fig. S6) (24).

We examined the orientation of the invertible promoters regulating antibiotic resistance genes in longitudinal metagenomic data from the Finnish children. The mean orientation of the cmeABC/ermG invertible promoter was 94% OFF in untreated individuals and 84% OFF in individuals administered antibiotics. We observed an individual in which the cmeABC/ermG invertible promoter was 99% OFF 7 days before the macrolide azithromycin was administered and 74% ON 27 days after treatment (Fig. 3B). The cmeABC/ermG invertible promoter reverted to 99% OFF within 5 months after azithromycin administration (fig. S3). A similar phenomenon was observed in a second individual (fig. S7). A permutation test revealed that macrodilide treatment was positively associated with the ON orientation of the cmeABC/ermG invertible promoter (quantitative polymerase chain reaction (qPCR) $P = 0.0005$, metagenomic $P = 0.0465$). Thus, it appears that macrolides may select for the ON orientation of the cmeABC/ermG invertible promoter, and the orientation of the invertible promoter drifts toward OFF after cessation of antibiotic treatment.

To test whether antibiotics select for resistance genes with invertible promoters in the ON orientation, we first verified that the genes regulated by the cmeABC/ermG invertible promoter confer macrolide resistance. We cultivated 13 B. stercoris isolates with and without the cmeABC/ermG invertible promoter upstream of the macrolide resistance gene ermG (table S12) (25). The invertible promoter was primarily ON (>75%) in 10 isolates derived from erythromycin-containing media and primarily OFF (>97%) in three isolates derived from media
without erythromycin (Fig. 3C). We established that all *B. stercoris* isolates with *ermG* regulated by the *cmeABC/ermG* invertible promoter were resistant to erythromycin, whereas the isolate without the *ermG* gene was susceptible (fig. S8).

Next, we showed that erythromycin treatment selects for the ON orientation of the *cmeABC/ermG* invertible promoter. To quantify changes in the relative abundances of cells with the *cmeABC/ermG* invertible promoter in ON and OFF orientations, we performed qPCR comparing relative amplification using a static primer downstream of the invertible promoter paired with either a primer that amplifies the ON orientation or one that amplifies the OFF orientation (fig. S9). We transferred *B. stercoris* isolates with the *cmeABC/ermG* invertible promoter

**Fig. 3. Invertible promoters regulate antibiotic resistance genes.** (A) Three classes of genes conferring antibiotic resistance are regulated by invertible promoters. The genomic contexts of the loci are shown with antibiotic resistance genes colored. Promoters are designated by hooked arrows; purple triangles represent inverted repeats. (B) An invertible promoter regulating the *cmeABC* multidrug efflux cassette in individual E011878 was 99% OFF before antibiotic treatment, shifted to 74% ON 7 days afterward, and then drifted back to 99% OFF over 5 months as measured by both qPCR and metagenomic (MGX) data. (C) The *cmeABC/ermG* invertible promoter is oriented ON in *B. stercoris* isolated in medium containing erythromycin (Erm+) and OFF in *B. stercoris* isolated in medium without erythromycin (Erm−). (D) The orientation of the *cmeABC/ermG* invertible promoter under antibiotic selection. Isolate s11 grown in Erm− medium remained OFF, whereas the same isolate transferred to Erm+ medium shifted to ON. Isolate s1 remained ON in Erm− and Erm+ media. (E) Growth of isolates under antibiotic selection. Isolate s1 grew in Erm+ medium without a lag phase relative to Erm− medium, whereas isolate s11 grew in Erm+ medium after an extended lag phase, consistent with a lower number of initially erythromycin-resistant cells. (F) Kinetics of the *cmeABC/ermG* invertible promoter. An isolate with the *cmeABC/ermG* invertible promoter initially in the OFF orientation, s12, was exposed to erythromycin. Half of the culture was then propagated in the presence of erythromycin and the other half in the absence of erythromycin for 24 1:1000 dilution transfers. In Erm+ medium, the promoter remained ON, whereas in Erm− medium, it drifted toward OFF. Error bars in (D) and (E) denote SD.
Fig. 4. The orientations of invertons are generally stable within individuals but divergent between individuals. (A) Examples of invertons from donor “am” found in the forward (F: IBP106, IBP124) or reverse (R: IBP60) orientation. (B) Examples of invertons from donor “am” (IBP129, IBP212, and IBP394) that are longitudinally stable. (C) Examples of invertons from donor “am” that are longitudinally unstable (IBP16, IBP199, and IBP353). (D) Selected examples of invertible promoters with different orientations among four individuals (“ae,” “am,” “an,” and “ao”). Numbers in each heat map cell represent the average counts in the F and R orientations (F:R); red and blue indicate F and R orientation, respectively. (E, G, and I) Phylogenetic trees produced by StrainPhlAn from metagenomic data from FMT donor (green) and patient (orange, pre-FMT; purple, post-FMT) as well as isolate genomes from the donor (green) and unrelated reference genomes from the same species (black). The phylogenetic trees demonstrate engraftment and persistence of B. fragilis (E), B. ovatus (G), and B. vulgatus (I) strains from the donor to the patient. Phylogenetic tree legends are the number of nucleotide substitutions per site. (F, H, and J) Examples of divergence of invertible promoter orientations after engraftment in a patient. Black circles denote invertible promoters whose orientation was significantly different between donor and patient after FMT. White circles denote invertible promoters whose orientation is not significantly different (Wilcoxon rank sum test, FDR P < 0.05). Numbers in each heat map cell represent the counts in the F and R orientations (F:R). (F) After engraftment, the orientations of IBP183 and IBP198 were reversed relative to the donor. (H) A strain of B. ovatus was present in Patient 14 before FMT but was outcompeted by the donor strain. After engraftment, the orientation of IBP155 and IBP198 was reversed relative to the donor. (J) After B. vulgatus engraftment, the orientation of IBP121 was only found in the F orientation, but over the course of 135 days, the orientation reversed.
oriented either primarily ON or OFF into media with (Erm+) or without (Erm–) erythromycin and quantified the percentage of cells in the ON or OFF orientation after 24 hours (Fig. 3D). The OFF cultures grew in Erm+ medium only after an extended lag phase relative to growth in Erm– medium, whereas ON cultures grew similarly in Erm+ and Erm– media (Fig. 3E). OFF isolates grown in Erm+ medium became predominantly ON, whereas OFF isolates grown in Erm– medium remained OFF. ON isolates remained predominantly ON in both Erm+ and Erm– media (Fig. 3D).

Finally, during serial transfers in both Erm+ and Erm– media, we monitored the ON:OFF ratio of the cmeABC/ermG invertible promoter in a B. stercoris OFF isolate that had previously been switched to ON in Erm+ medium. Over the course of 24 transfers at 1:1000 dilution, the orientation of the cmeABC/ermG invertible promoter remained ON in Erm+ medium but gradually drifted away from 100% ON in Erm– medium, recapitulating the in vivo observations from metagenomic data (Fig. 3F).

Although strongly favored in the presence of antibiotics, high expression of antibiotic resistance genes likely incurs a substantial fitness cost, which could explain the reversion to the OFF orientation after antibiotic treatment. Many compensatory mechanisms to maintain antibiotic resistance in the absence of antibiotics have been noted (26), but inverters are akin to catastrophe insurance; a certain percentage of the population is always prepared to resist future antibiotic treatment and reintroduce heterogeneity after antibiotic selection.

Dense longitudinal metagenomic data allow for a detailed view of the dynamics of inverters over time in the human gut. We analyzed a dataset of samples from 54 individuals, four of whom (“a,” “am,” “an,” “ao”) were extensively (Fig. 4D and fig. S10). The mean %R in the same individual were relatively stable over time (max-min %R > 95% and min > 75% for either the F or R orientation of the invertron in the reference genome, whereas the R orientation is the opposite orientation of the invertron in the reference genome. We identified 423 inverters with sufficient coverage to track their temporal dynamics in these individuals. Of these, 322 were predominantly found in one orientation within an individual with little or no fluctuation (mean > 95% and min > 75% for either the F or R orientation of the invertron in the reference genome). The orientations of 59 were relatively stable (max-min %R ≤ 50%) within an individual (Fig. 4B), whereas the orientations of 42 were unstable (max-min %R > 50%) within an individual (Fig. 4C and table S13).

Although the orientations of 90% of inverters in the same individual were relatively stable over time, the orientations between individuals varied extensively (Fig. 4D and fig. S10). The mean %R of 214 out of 423 of the inverters varied by more than 50% between individuals. In 122 examples, averaging across time, the inverter was predominantly (>95%) in the F orientation in at least one individual and predominantly (>95%) in the R orientation in another. Additionally, 119 out of 238 inverters were significantly different (Kruskal-Wallis test, FDR < 0.05) between the four individuals for whom we had dense longitudinal metagenomic data. The differences in the orientations of inverters between individuals could be explained by divergent selective forces between individuals, different optimal orientations between strains, or stochastic variation in orientation.

Sculpted by the individual’s diet, lifestyle, immune response, and genetics, the gut of every new host or severe perturbations. Overall, our study provides insights into a mechanism allowing adaptive tradeoffs in bacteria that have evolved to successfully colonize host-associated niches.

REFERENCES AND NOTES


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Switching ON resistance
Clonal bacterial colonies will often grow dissimilar patches, similar to a tortoiseshell pattern. These differing phenotypes arise by reversible mechanisms called phase variation. Jiang et al. developed an algorithm to survey bacterial genomes for invertible promoters that cause phase variation. Inverted repeats signal the presence of these promoters, which can flip between ON and OFF states catalyzed by phage integrase analogs called invertases. Invertible promoters linked to antibiotic resistance genes were widespread among vertebrate gut-associated organisms, including Bacteroidetes, Spirochaetes, and Verrucomicrobia. These bacteria are thus equipped and prepared for sudden environmental stress, including antibiotic exposure.

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