Broad host range *Brockvirinae* phages infect *Enterococcus* and drive evolution of exopolysaccharide synthesis genes.

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**ABSTRACT**

Phages infecting the diverse bacteria that colonize humans could be a valuable resource for treating antibiotic-resistant infections. *Enterococcus* is an opportunistic pathogen with rising rates of antibiotic resistance, but few phages that infect *Enterococcus* have been isolated and studied. We characterized the *Brockvirinae* sub-family (formerly *Spounavirinae*) of phages that infect *Enterococcus* and present eight new phages within the sub-family*.* Genomic characterization revealed that *Brockvirinae* phages represent two genera with distinct host range patterns. *In vitro* experimental evolution showed that, as *Brockvirinae* phages co-evolved with their hosts, they selected for *Enterococcus* with mutations in exopolysaccharide synthesis genes. Further, by searching the SRA, we showed that these phages were found globally in human and animal microbiomes. Characterizing the host ranges and molecular evolution of these and other phages could lead to more efficient strategies for the therapeutic use of phages against antibiotic resistant bacteria.

**INTRODUCTION**

Bacteriophages (phages) are ubiquitous in the environment and important members of microbial communities. In the years following their discovery in 1915, phages were exploited to treat bacterial infections, which is referred to as phage therapy. The discovery of antibiotics led to the abandonment of phage therapy in most of the western world, however the recent epidemic of antibiotic resistant bacterial infections has caused renewed interest in phage therapy. Phages are much more host-specific than antibiotics, therefore a diverse collection of phages would be needed to ensure that that a wide range of infections can be treated. This is a major hurdle for phage therapy to overcome because few phages that infect human pathogens are well characterized.

*Enterococcus* is a genus of gram-positive bacteria that is commonly found in low abundance in the guts of humans and other animals.1 *Enterococcus faecalis* and *Enterococcus faecium* are the most common species commensally associated with humans, though they have recently emerged as a major health crisis due to their opportunistic pathogenicity. These species are considered high-priority pathogens by the WHO due to high rates of antibiotic resistance and adaptation to the hospital environment.2,3 The National Healthcare Safety Network reported that of hospital acquired *Enterococcus* infections, about 80% of *E. faecium,* and 8% of E. *faecalis* isolates demonstrated Vancomycin resistance. Phage therapy could offer an alternative approach to treating antibiotic resistant infections, and *Enterococcus* phages have shown promise as therapeutics *in vitro*.4,5 However, few phages infecting *Enterococcus* have been isolated and characterized.

Phages in the family *Herelleviridae* (formerly the sub-family *Spounavirine*) exclusively infect Firmicutes bacteria, are tailed with *Myoviridae* morphology, and have double-stranded DNA genomes between 127-157 kb in length.6,7 *Enterococcus*-infectingphages within the *Herelleviridae* family are classified in the subfamily *Brockvirinae* and have been noted for their broad host ranges and potential as therapeutics.8–10

Here, we present the genomes of eight newly isolated *Enterococcus* phages in the *Brockvirinae* subfamily. These represent two genera with distinct host ranges for *E. faecalis* and *E.* *faecium*. Like other members of *Brockvirinae*, these phages have a broad host range within their host genus. Further, we show that *in vitro* growth with susceptible *Enterococcus* hosts resulted in predictable evolutionary outcomes, with the phages evolving mutations in their capsid and tail fiber genes, while the *Enterococcus* hosts evolved mutations in exopolysaccharide synthesis genes. Understanding the evolutionary pressure these phages exert on exopolysaccharide synthesis genes could provide insight into therapies that would combine these exopolysaccharide-targeting phages with antibiotics that target the cell wall.

**RESULTS**

Genomics of new *Enterococcus* phages in the *Brockvirinae* sub-family

Eight novel *Enterococcus* phages in the *Brockvirinae* sub-family were isolated from sewage and their genomes sequenced (**Figure 1**). Average nucleotide identity (ANI) of core genes clearly divided the phages into two groups with ~95% ANI within each group and ~74 % ANI between the groups. Phages vB\_OCPT\_Car, vB\_OCPT\_Carl, and vB\_OCPT\_Bob fit into the *Kochikohdavirus* genus, and phages EfV12-phi1, vB\_OCPT\_Bop, vB\_OCPT\_Bill, vB\_OCPT\_Ben, vB\_OCPT\_Tex, and vB\_OCPT\_CCS1 fit into an Unassigned second genus, which we propose to call *Wandervirus*. Further, phages in the *Wandervirus* genus were split between two groups based on core genome nucleotide identity (97 % ANI within groups and ~94 % ANI between groups) and accessory genome content.

*Brockvirinae* phage genomes encoded around 210 ORFs divided into two opposite facing blocks. The first block of genes encoded short hypothetical ORFs (average 450 bp) of unknown function. These ORFs were often shared among phages within the phage genus, and not shared between the two genera. The second block of ORFs was twice as long on average (900 bp) and encoded recognizable structural genes, lysins, and genes involved in genome replication. Most of these ORFs were conserved among all eleven *Brockvirinae* phages. Between these two gene blocks was a cluster of tRNA genes. Phages in the *Kochikohdavirus* genus carried 24 tRNAs on average while phages in the *Wandervirus* genus carried 7 tRNAs on average (F**igure S1**).

*Brockvirinae* phages are globally distributed and found in phage cocktails

To assess the environmental distribution of *Brockvirinae* phages, we queried a representative genome from both genera against 67,429 publicly available metagenomes in NCBI’s SRA (**Table 1**) 11. Metagenomes with positive hits were downloaded and aligned to representative *Brockvirinae* genomes to ensure most of the genome was covered. *Brockvirinae* phages were found to be globally distributed in fecal metagenomes. Sequences matching *Brockvirinae* genomes were found in eight SRA projects from the United States, Europe, the Middle East, and Asia. Matching sequences were also found in non-human fecal metagenomes from condors, pigs, and bats. *Brockvirinae* phages were also found to be highly abundant in two phage cocktails from the Eliava Institute designed to treat intestinal issues. The first phage cocktail is the Intestiphage cocktail, which contains an isogenic *Brockvirinae* phage in the *Kochikohdavirus* genus. The second phage cocktail is the PYO phage cocktail developed by the Eliava institute. These phage cocktails contain many different phages targeting a wide range of bacterial hosts, and their efficacy in treating *Enterococcus* infections remains to be tested.

*Brockvirinae* phages have broad host ranges

The host range for each of the eight novel *Brockvirinae* phages was tested against a collection of 36 *E. faecalis* strains and 29 *E. faecium* strains using a drop assay. *Brockvirinae* phages demonstrated broad lytic activity within the two *Enterococcus* species (**Figure 2**). No lysis was seen against any *Streptococcus* strains (data not shown). In general, *Kochikohdaviruses* infected *E. faecalis* strains but not *E. faecium*. Phages within *Wandervirus* A generally infected both *E. faecium* and *E. faecalis* strains, while phages belonging to *Wandervirus B* infected mostly *E. faecium* strains. These patterns indicate that genetic similarity among *Brockvirinae* phages is a good indicator of potential *Enterococcus* host species. Conversely, knowing the species of *Enterococcus* would provide insight into susceptibility to *Brockvirinae* phages. However, at the strain level, neither genetic similarity nor accessory genome content were predictive of susceptibility to *Brockvirinae* phages.

*Brockvirinae* phages drive evolution of *Enterococcus* exopolysaccharide synthesis genes

To understand the selective pressures exerted between *Brockvirinae* phages and their *Enterococcus* hosts, pairs of bacteria and phage were experimentally coevolved *in vitro*, followed by whole genome sequencing. Coevolution was performed by growing bacteria and phage together in semi-continuous liquid culture for four weeks. Cultures were started at an initial MOI of 0.01 so that not all *Enterococcus* cells were lysed immediately. During the coevolution experiments, *Brockvirinae* phages evolved mutations in the same three genes regardless of host strain (**Table S4**). These genes encoded a “tail fiber gene”, a “capsid and scaffold gene”, and one ORF of unknown function. The ORF of unknown function contained a predicted ATPase domain and was homologous to genes in a wide range of phages and bacteria. The consistent mutations in the tail fiber gene and capsid and scaffold gene indicate that mutations in structural genes are the primary route for adapting to hosts in these conditions.

*Enterococcus* strains grown with *Brockvirinae* phages consistently evolved mutations in genes involved in exopolysaccharide synthesis (**Figure 3, S2, Table S3**). All three *E. faecalis* strains acquired point and nonsense mutations in three of the nineteen genes in the Epa exopolysaccharide synthesis locus. Host control cultures lacking phage never acquired mutations in these genes. In contrast to *E. faecalis*, when *E. faecium* TX1330 coevolved with *Brockvirinae* phages, the Yqw exopolysaccharide synthesis locus was consistently mutated. Mutations in the Yqw locus mutations also occurred in the host control cultures; these cultures showed signs of prophage induction based on an increase in sequencing coverage of a predicted prophage, and therefore it was unclear if mutations in the Yqw locus could be attributed to phage evolutionary pressure. Mutations in other genes occurred, but not with the same frequency or consistency as genes involved in exopolysaccharide synthesis (**Table S3**). Therefore, mutations in capsule synthesis genes are a consistent feature of E*nterococcus* coevolution with *Brockvirinae* phages.

**DISCUSSION**

Here, we present a characterization oftwo genera of *Brockvirinae* phages infecting two species of *Enterococcus*. These two genera displayed distinct infectivity patterns for *E. faecium* and *E. faecalis* and were found to be globally distributed in fecal metagenomes of humans and several animals. Experimental coevolution of these phages with their host bacteria consistently resulted in bacterial mutations in exopolysaccharide synthesis loci and phage mutations in structural genes.

The *Brockvirinae* family contains phages that infect *Firmicutes*. While the genome nucleotide identity and amino acid identities were extremely low when comparing the *Spounaviridae* genera, they share a common morphology and genome organization.7,12 Phages are often thought to exchange genes sufficiently frequently to have highly mosaic genomes, thereby hindering inference of their phylogenetic relationships. However, little mosaicism has been seen in *Herelleviridae* phages, and genome nucleotide identity tracks with host range down to the phage sub-genus level.7,13 Similarly, our data did not show mosaicism in *Enterococcus*-infecting *Herelleviridae* phages in either gene content or nucleotide identity.

*Herelleviridae* phages have been previously observed to have broad host ranges within the genus they infect.8–10 Likewise, our data are consistent with *Enterococcus*-infecting *Brockvirinae* phages having broad host ranges for *E. faecium* and *E. faecalis*. The lysin from an *Enterococcus*-infecting *Brockvirinae* phage, EfV12-phi1, has been shown to lyse different genera, including *Staphylococcus* and *Streptococcus*.14 However, there is no evidence that *Spounaviridae* phages can infect non-host genera.

*Herelleviridae* phages were confidently found in twelve sequencing projects out of the thousands of human gut metagenomes from the SRA. Since *Enterococcus* is present in the guts of most people, this suggests that either *Herelleviridae* phages are uncommon members of the human gut, or they are usually at a low enough abundance that they would not be seen with a normal depth of shotgun sequencing. We are inclined to the second explanation given the high frequency with which we have isolated *Herelleviridae* phages from sewage. Even one of the most abundant phages in the human microbiome, crAssphage infecting *Bacteroides*, is only found at 1% read abundance in human metagenomes, so a phage infecting a minority community member such as *Enterococcus* would be much less abundant.15

Structural gene mutations were a consistent feature seen during phage evolution. Two phages in the *Wandervirus* genus were seen to mutate the same genes when evolving with different *E. faecium* and *E. faecalis* hosts. These genes were primarily structural genes encoding the capsid and tail fibers and likely were involved in the initial binding of phage to the bacterial surface. A common way bacteria evolve resistance to phage infection is to prevent binding to the cell surface, and mutations in genes such as the tail fiber can overcome that resistance. Mutations in phage structural genes are commonly seen when phages co-evolve *in vitro* with their host.16,17 Tail fibers mediate host binding, and thus, mutations in tail fiber genes could change binding affinity to certain hosts.16–18 The binding target of *Brockvirinae* phages has not been characterized, but related *Spounaviridae* phages have been shown to bind teichoic acids in the cell wall.19

When under selective pressure from *Brockvirinae* phages, *Enterococcus* evolved mutations primarily in exopolysaccharide synthesis genes. These mutations suggest resistance evolved by preventing phage recognition and initial binding. *E. faecium* and *E. faecalis* both contain the highly conserved Epa capsule synthesis locus, in which mutations were observed consistently for *E. faecalis* strains. Mutations in the Epa locus have been observed previously during coevolution with *Brockvirinae* phages and other phages; these mutations impaired *Enterococcus* host colonization and increased antibiotic sensitivity.20 *E. faecium* encodes a second exopolysaccharide synthesis locus known as the Yqw locus, which is not present in *E. feacalis*. It is in this Yqw locus that mutations were observed in *E. faecium* TX1330. Various mutations in a single gene of this locus have been previously seen during coevolution in the same phage-host pair.16 Since mutations in Yqw locus genes also occurred in *E. faecium* TX1330 host control cultures lacking phage, we cannot attribute these mutations to phage evolutionary pressure. However, prophage induction was observed in all *E. faecium* TX1330 cultures, indicating that mutations in exopolysaccharide synthesis genes may be a consistent phage resistance mechanism in *Enterococcus*.

The broad host range of *Brockvirinae* phages and predictable outcomes of coevolution with their hosts make them ideal candidates for use in phage therapy to treat *Enterococcus* infections. Multiple commercial phage therapy cocktails already include *Brockvirinae* phages. Although *Enterococcus* are seen to evolve resistance to infection, including a diverse set of phages in a phage cocktail could lessen that effect.21,22 Further, there may be trade-offs where mutations that lead to phage resistance also reduce fitness for *Enterococcus*.20 Phage therapy is a promising avenue of research for treating antibiotic resistant infections, but more work needs to be put into isolating and characterizing collections of phages that infect important pathogens.

**MATERIALS AND METHODS**

Bacteria and phage strains and growth conditions

*Enterococcus* isolates were either ordered from BEI or obtained from UC San Diego clinical microbiology laboratory (**Table S2**). *Enterococcus* was grown statically at 37 °C in brain heart infusion (BHI) media in all experiments. Phage EfV12-phi1 was ordered from Felix d’Herelle Reference Center for Bacterial Viruses (HER# 339). All other phages were isolated from sewage (**Table S1**).

Phage isolation propagation and storage

Phages were isolated from sewage using three rounds of plaque assays. Raw sewage influent was collected from wastewater treatment plants in Redwood Shores and Escondido, California. Sewage was stored at 4 °C and used for phage isolation for several months. Sewage was centrifuged for 10 minutes at 10,000 g to remove particulates and the supernatant was used in plaque assays with various strains of *Enterococcus*. 100 ul sewage supernatant was added to 100ul exponentially growing *Enterococcus* in BHI media and incubated at 37 °C for 15 minutes. 5 mL of warm BHI containing 0.3 % UltraPure Low Melting Point Agarose (ThermoFisher #16520050) was then added and the mixture poured on a BHI agar plate and incubated overnight at 37 °C. The next day, plates were examined for plaques and any plaques were picked with a pipette tip and suspended in 50 ul SM buffer. Picked plaques underwent two more rounds of plaque assays in the same manner to ensure purity of the phage isolate. Pure phages were propagated by performing a plaque assay to create a plate displaying webbed lysis that was then flooded with 3 mL SM buffer and incubated for 1 hour. The SM buffer was then collected and centrifuged at 10,000 g for 10 minutes. For long term storage, phages were stored at -80 °C with 25% glycerol.

Genomic sequencing

DNA was extracted from *Enterococcus* and phage using Quick-DNA Microprep Kit (Zymo #D3020). Before *Enterococcus* DNA extraction, lysozyme was added to lysis buffer at a concentration of 100ug/ml and incubated at 37 °C for 30 minutes. For DNA extraction from coevolution cultures containing both bacteria and phage, the extractions were performed without lysozyme. Libraries were prepared using scaled down reactions with the Illumina Nextera enzyme.23 Paired-end sequencing with a 75 bp read length was performed on the Illumina NextSeq using the Mid Output v2 reagents. Approximately 2.5 million reads were obtained for each sample.

Genomic characterization

Phage and *Enterococcus* genomes were assembled *de novo* using the SPAdes assembler.24 Core genomes were determined and aligned using Anvio.25 Genomes were manually examined using Geneious. Visualizations were made using Anvio, R (using the ggplo2 package) and Easyfig.

SRA search

All metagenomes in the SRA were searched for *Brockvirinae* *Enterococcus* phages using the Searching SRA tool using the core genome as the query sequence.11 Briefly, the Searching SRA tool searches for the query sequence in all 111,156 metagenomes currently on the SRA by subsampling 100,000 sequences from each metagenome. From the metagenome hit list, we selected only metagenomes where the average read length matching our query was over 50 bp.

Host range assay

Phage host ranges were tested using a spot assay. 5 mL of warm BHI containing 0.3 % UltraPure Low Melting Point Agarose (ThermoFisher #16520050) was added to 100 ul of exponentially growing *Enterococcus* and poured on a BHI agar plate. After allowing the agarose to solidify for approximately 30 minutes, 5 ul droplets of each concentrated phage was spotted on top of the agarose. As a negative control, SM buffer was spotted in the same fashion. Spots were allowed to dry for 30 minutes and then the plates were incubated overnight at 37 °C. The next day, each spot was checked for clearing.

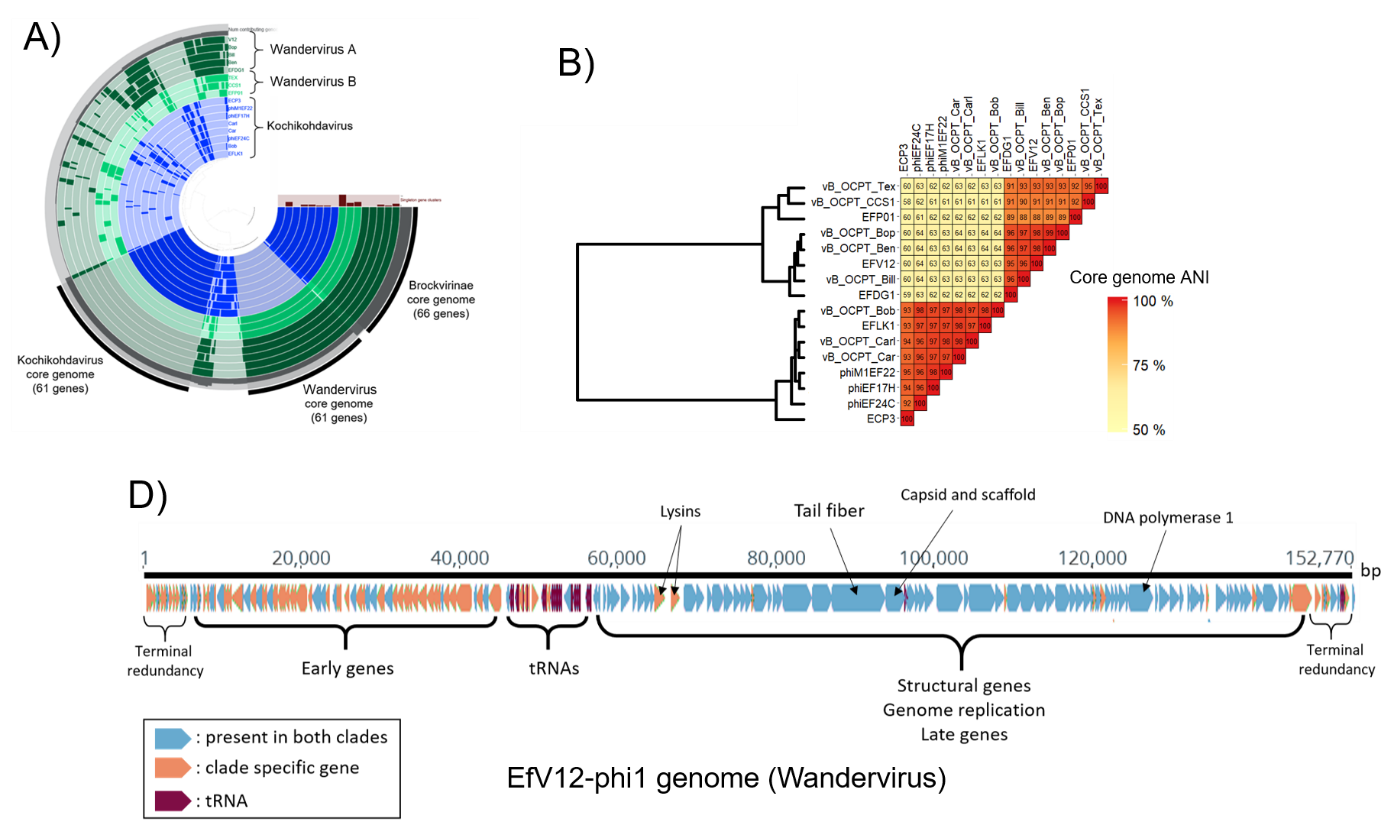
Coevolution of *Enterococcus* and phage

Pairs of *Enterococcus* strains and phage isolates were co-evolved in liquid media for 28 days with once daily dilution. To start the culture, phage was added to exponentially growing *Enterococcus* at an MOI of approximately 0.01 in 200 ul BHI liquid media in a 96-well plate. The plate was incubated statically for 24 hours at 37 °C, then 10 ul of each well was diluted into 190 ul fresh BHI media in a new 96-well plate. This process was repeated for 28 days. At the end of the experiment, 150 ul of the final cultures were pipetted into a new 96-well plate and 150 ul of 50 % glycerol was added and the plate was stored at -80 °C prior to DNA extraction.

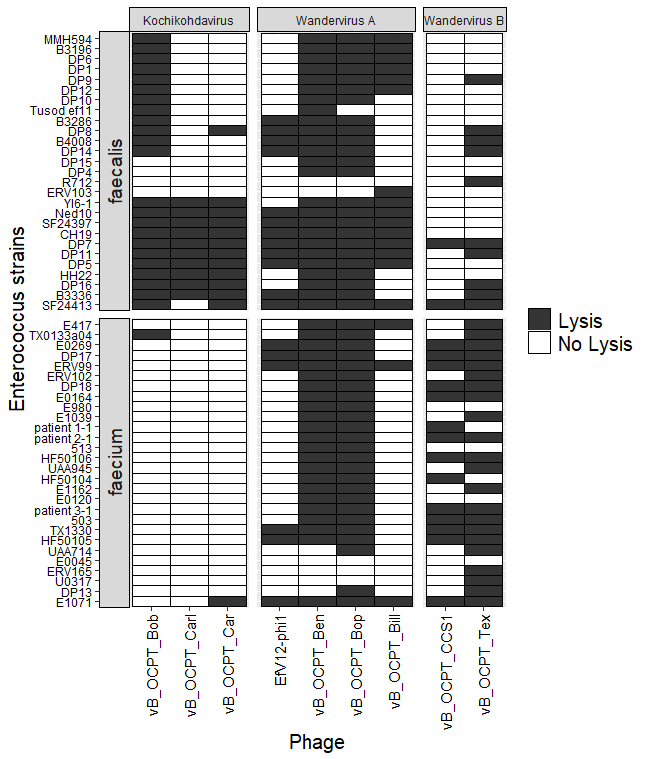
**ACKNOWLEDGEMENTS**

Thank you to Heather \_\_\_ for helping with editing

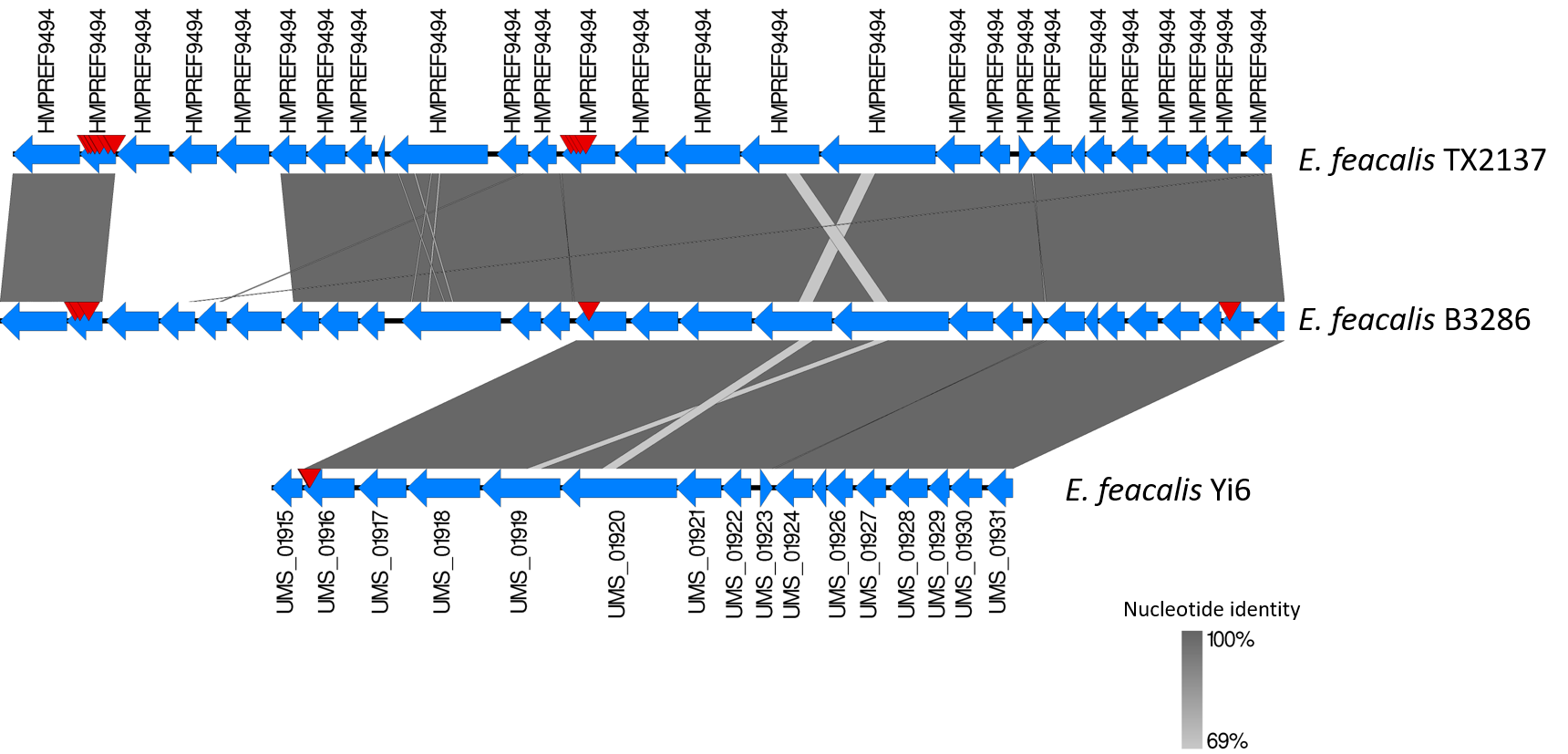
**FIGURES AND TABLES**



**Figure 1.** Genomics of *Enterococcus Brockvirinae* phages. **A)** Shared gene content of *Brockvirinae* phages. Each ring represents a phage genome, and each dark tick represents a gene. Genes that are shared among phages appear in the same column. The colors indicate the phage genus. **B)** Core genome average nucleotide identity of all *Brockvirinae* phages. Dendrogram represents hierarchical clustering of phages based on core genome average nucleotide identity. **C)** Genome of phage EfV12-phi1 showing some genes in *Brockvirinae* phages are conserved at the genus level and some are present in both genera.



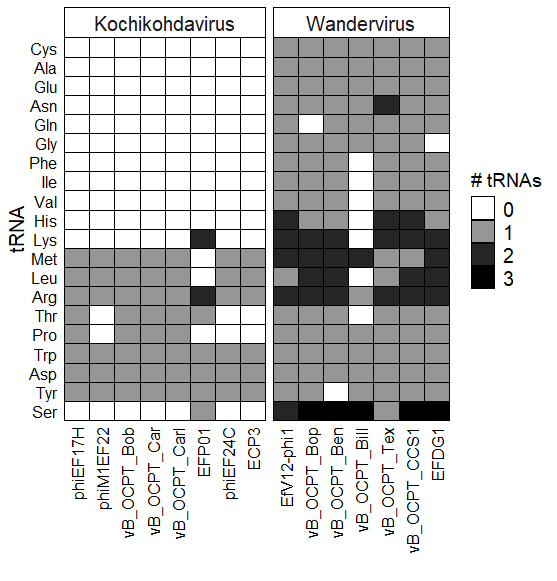
**Figure 2.** Host range of *Brockvirinae Enterococcus* phages.Host range was determined by a drop assay with visual scoring. Partial clearings were counted as lysis.



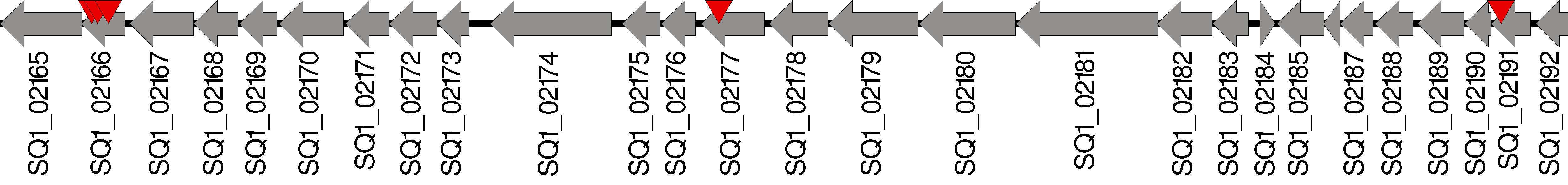
**Figure** **3.** *E. faecalis* strains evolved to resist phage through mutations in genes at the Epa locus.The genes comprising the Epa locus of *E. faecalis* strains TX2137, B3286, and Yi6 are shown. Red ticks represent the locations of non-synonymous mutations observed in *E. faecalis* B3286, TX2137, and Yi6 respectively as they coevolved with *Brockvirinae* phages. Detailed information about these mutations can be found in **Table S3**.

**Table 1.** *Brockvirinae* *Enterococcus* phages from the Sequence Read Archive.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| SRA | | Title | Location | Sample type |
| SRP077952 | The INTESTI bacteriophage cocktail genome sequencing and assembly | | Georgia | Phage cocktail |
| PRJEB23244 | PYO phage cocktail | | Georgia | Phage cocktail |
| ERP017091 | The gut microbiome in Crohn's disease and modulation by exclusive enteral nutrition | | Guangdong, China | human fecal |
| ERP006678 | Gut and Oral Microbiome Dysbiosis in Rheumatoid Arthritis | | Beijing China | human fecal |
| SRP071229 | Gymnogyps californianus microbiome raw sequence reads | | Los Alamos National Laboratory | California condor fecal |
| ERP006046 | Virus\_Discovery\_for\_Vietnam\_Initiative\_on\_Zoonotic\_Infections\_\_VIZIONS\_ | | Vietnam | viral metagenome |
| ERP001956 | Diagnostic Metagenomics: A Culture-Independent Approach to the Investigation of Bacterial Infections | | Germany | human fecal |
| SRP051511 | New York City MTA subway samples Metagenome | | New York City | subway samples |
| ERP012929 | Towards personalized nutrition by prediction of glycemic responses | | Israel | human fecal |
| SRP040146 | Clostridium difficile FMT | | Massachusetts | human fecal |
| SRP115494 | Longitudinal Multi'omics of the Human Microbiome in Inflammatory Bowel Disease | | Massachusetts | Human fecal |
| SRP099123 | Metagenomic analysis of gut microbiota in sows and piglets | | Freie University of Berlin | Pig fecal |

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**Figure S1.** tRNAs in phage genomes.

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**Figure S2.** Locus tags for Epa genes that mutated in *E. faecalis* B3286. Red arrows indicate genes that mutated when *E. faecalis* evolved resistance to *Brockvirinae* phages.

**Table S1.** *Brockvirinae*phage information.

|  |  |  |  |
| --- | --- | --- | --- |
| **Phage** | **genus** | **isolation source** | **Genbank** |
| vB\_OCPT\_Bob | Kochikohdavirus | Escondido sewage |  |
| vB\_OCPT\_Car | Kochikohdavirus | Escondido sewage |  |
| vB\_OCPT\_Carl | Kochikohdavirus | Escondido sewage |  |
| EfV12-phi1 | Wandervirus A | Canadian sewage | MH880817.1 |
| vB\_OCPT\_Ben | Wandervirus A | Escondido sewage | MN027503.1 |
| vB\_OCPT\_Bop | Wandervirus A | Escondido sewage |  |
| vB\_OCPT\_Bill | Wandervirus A | Escondido sewage |  |
| vB\_OCPT\_CCS1 | Wandervirus B | Escondido sewage |  |
| vB\_OCPT\_Tex | Wandervirus B | Escondido sewage |  |

**Table S2.** *Enterococcus* strain information.

|  |  |  |  |
| --- | --- | --- | --- |
| **Species** | **Strain** | **Genbank** | **Source** |
| Enterococcus faecalis | B3319 | GCA\_000396325.1 | HMP |
| Enterococcus faecalis | B3196 | GCA\_000396345.1 | HMP |
| Enterococcus faecalis | B3286 | GCA\_000396365.1 | HMP |
| Enterococcus faecalis | B3336 | GCA\_000396385.1 | HMP |
| Enterococcus faecalis | B4008 | GCA\_000396405.1 | HMP |
| Enterococcus faecalis | CH19 | GCA\_000394255.1 | HMP |
| Enterococcus faecalis | HH22 | GCA\_000394775.1 | HMP |
| Enterococcus faecalis | MMH594 | GCA\_000394795.1 | HMP |
| Enterococcus faecalis | Ned10 | GCA\_000394875.1 | HMP |
| Enterococcus faecalis | R712 | GCA\_000163815.1 | HMP |
| Enterococcus faecalis | S613 | GCA\_000163795.1 | HMP |
| Enterococcus faecalis | SF105 | GCA\_000394895.1 | HMP |
| Enterococcus faecalis | SF24397 | GCA\_000394075.1 | HMP |
| Enterococcus faecalis | SF24413 | GCA\_000394095.1 | HMP |
| Enterococcus faecalis | SF28073 | GCA\_000394195.1 | HMP |
| Enterococcus faecalis | Tusod ef11 | GCA\_000175015.1 | HMP |
| Enterococcus faecalis | TX1322 | GCA\_000159275.1 | HMP |
| Enterococcus faecalis | TX2137 | GCA\_000147595.1 | HMP |
| Enterococcus faecalis | V587 | GCA\_000394175.1 | HMP |
| Enterococcus faecalis | YI6-1 | GCA\_000395095.1 | HMP |
| Enterococcus faecalis | DP1 |  | David Pride hospital isolate |
| Enterococcus faecalis | DP2 |  | David Pride hospital isolate |
| Enterococcus faecalis | DP12 |  | David Pride hospital isolate |
| Enterococcus faecalis | DP14 |  | David Pride hospital isolate |
| Enterococcus faecalis | DP15 |  | David Pride hospital isolate |
| Enterococcus faecalis | DP16 |  | David Pride hospital isolate |
| Enterococcus faecalis | ERV103 | GCA\_000294005.2 | HMP |
| Enterococcus faecalis | DP3 |  | David Pride hospital isolate |
| Enterococcus faecalis | DP4 |  | David Pride hospital isolate |
| Enterococcus faecalis | DP5 |  | David Pride hospital isolate |
| Enterococcus faecalis | DP6 |  | David Pride hospital isolate |
| Enterococcus faecalis | DP7 |  | David Pride hospital isolate |
| Enterococcus faecalis | DP8 |  | David Pride hospital isolate |
| Enterococcus faecalis | DP9 |  | David Pride hospital isolate |
| Enterococcus faecalis | DP10 |  | David Pride hospital isolate |
| Enterococcus faecalis | DP11 |  | David Pride hospital isolate |
| Enterococcus faecium | E0120 | GCA\_000321485.1 | HMP |
| Enterococcus faecium | E0164 | GCA\_000321505.1 | HMP |
| Enterococcus faecium | E0269 | GCA\_000321525.1 | HMP |
| Enterococcus faecium | ERV102 | GCA\_000295355.2 | HMP |
| Enterococcus faecium | ERV99 | GCA\_000295175.2 | HMP |
| Enterococcus faecium | HF50104 | GCA\_000396685.1 | HMP |
| Enterococcus faecium | HF50105 | GCA\_000396705.1 | HMP |
| Enterococcus faecium | HF50106 | GCA\_000396725.1 | HMP |
| Enterococcus faecium | patient 1-1 | GCA\_000394755.1 | HMP |
| Enterococcus faecium | patient 2-1 | GCA\_000394655.1 | HMP |
| Enterococcus faecium | patient 3-1 |  | HMP |
| Enterococcus faecium | TX0133a04 | GCA\_000147235.1 | HMP |
| Enterococcus faecium | TX1330 | GCA\_003583905.1 | HMP |
| Enterococcus faecium | UAA714 | GCA\_000395445.1 | HMP |
| Enterococcus faecium | 503 | GCA\_000295055.2 | HMP |
| Enterococcus faecium | 513 | GCA\_000295575.2 | HMP |
| Enterococcus faecium | E0045 | GCA\_000321465.1 | HMP |
| Enterococcus faecium | E1071 | GCA\_000172655.1 | HMP |
| Enterococcus faecium | E1039 | GCA\_000174935.1 | HMP |
| Enterococcus faecium | UAA945 | GCA\_000396845.1 | HMP |
| Enterococcus faecium | U0317 | GCA\_000172915.1 | HMP |
| Enterococcus faecium | E417 | GCA\_000295415.2 | HMP |
| Enterococcus faecium | DP13 |  | David Pride hospital isolate |
| Enterococcus faecium | DP17 |  | David Pride hospital isolate |
| Enterococcus faecium | DP18 |  | David Pride hospital isolate |
| Enterococcus faecium | DP19 |  | David Pride hospital isolate |
| Enterococcus faecium | E1162 | GCA\_000172675.1 | HMP |
| Enterococcus faecium | ERV165 | GCA\_000295235.2 | HMP |
| Enterococcus faecium | E980 | GCA\_0001726151 | HMP |
| Enterococcus avium | DP0 |  | David Pride hospital isolate |

**Table S3.***Enterococcus* mutations. List of all mutations that occurred in *Enterococcus* genomes during coevolution with phage for 28 days.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Species | Strain | Coevolving Phage | Rep | Freq. | Locus | Gene name | Type |
| E. faecalis | B3286 | vB\_OCPT\_Bop | 1 | 1.00 | Epa | NAD-dependent epimerase/dehydratase | SNP |
| E. faecalis | B3286 | vB\_OCPT\_Bop | 1 | 1.00 | Epa | glucose-1-phosphate thymidylyltransferase | SNP |
| E. faecalis | B3286 | vB\_OCPT\_Bop | 2 | 1.00 |  | endonuclease III | SNP |
| E. faecalis | B3286 | vB\_OCPT\_Bop | 2 | 1.00 | Epa | NAD-dependent epimerase/dehydratase | SNP |
| E. faecalis | B3286 | EfV12-phi1 | 1 | 1.00 | Epa | exopolysaccharide biosynthesis polyprenyl glycosylphosphotransferase | SNP |
| E. faecalis | B3286 | EfV12-phi1 | 1 | 0.61 | Epa | NAD-dependent epimerase/dehydratase | SNP |
| E. faecalis | B3286 | EfV12-phi1 | 1 | 1.00 |  | ATP-dependent Clp protease ATP-binding subunit ClpE | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Ben | 1 | 1.00 |  | DNA gyrase subunit A (EC 5.99.1.3) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Ben | 2 | 1.00 |  | DNA-directed RNA polymerase beta' subunit (EC 2.7.7.6) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Ben | 2 | 0.94 | Yqw | Tyrosine-protein kinase EpsD (EC 2.7.10.2) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Ben | 3 | 0.50 | Yqw | Tyrosine-protein kinase EpsD (EC 2.7.10.2) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Ben | 3 | 1.00 |  | DNA-directed RNA polymerase beta subunit (EC 2.7.7.6) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Bill | 1 | 1.00 | Yqw | Tyrosine-protein kinase EpsD (EC 2.7.10.2) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Bill | 2 | 0.22 | Yqw | Tyrosine-protein kinase EpsD (EC 2.7.10.2) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Bob | 1 | 0.26 | Yqw | Tyrosine-protein kinase transmembrane modulator EpsC | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Bob | 1 | 0.15 |  | Phosphate regulon sensor protein PhoR (SphS) (EC 2.7.13.3) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Bob | 2 | 0.22 |  | Phosphate regulon sensor protein PhoR (SphS) (EC 2.7.13.3) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Bob | 3 | 0.11 |  | Pyruvate dehydrogenase E1 component alpha subunit (EC 1.2.4.1) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Bob | 3 | 1.00 |  | Two-component transcriptional response regulator, LuxR family | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Bop | 1 | 1.00 |  | UDP-N-acetylglucosamine 4,6-dehydratase (EC 4.2.1.135) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Bop | 1 | 1.00 | Yqw | Tyrosine-protein kinase EpsD (EC 2.7.10.2) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Bop | 2 | 1.00 | Yqw | Tyrosine-protein kinase EpsD (EC 2.7.10.2) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Bop | 2 | 0.30 |  | Neopullulanase (EC 3.2.1.135) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Bop | 2 | 0.29 |  | hypothetical protein | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Car | 1 | 0.41 |  | Phosphate regulon sensor protein PhoR (SphS) (EC 2.7.13.3) | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Car | 1 | 0.26 |  | Bacterial ribosome SSU maturation protein RimP | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Carl | 2 | 1.00 | Yqw | Tyrosine-protein kinase transmembrane modulator EpsC | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Carl | 2 | 0.26 |  | Xanthine/uracil/thiamine/ascorbate permease family protein | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Carl | 2 | 0.21 |  | Oxidoreductase, short-chain dehydrogenase/reductase family | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Carl | 2 | 0.20 |  | Excinuclease ABC subunit A paralog of unknown function | SNP |
| E. faecium | TX1330 | vB\_OCPT\_Carl | 3 | 0.34 | Yqw | Tyrosine-protein kinase transmembrane modulator EpsC | SNP |
| E. faecium | TX1330 | No phage | 1 | 1.00 | Yqw | Tyrosine-protein kinase transmembrane modulator EpsC | SNP |
| E. faecium | TX1330 | No phage | 1 | 0.27 |  | Transcriptional regulator, repressor of the glutamine synthetase, MerR family | SNP |
| E. faecium | TX1330 | No phage | 1 | 0.26 |  | Two-component sensor kinase SA14-24 | SNP |
| E. faecium | TX1330 | No phage | 1 | 0.24 |  | Cyclic-di-AMP phosphodiesterase GdpP | SNP |
| E. faecium | TX1330 | No phage | 1 | 0.24 |  | Ribonuclease PH (EC 2.7.7.56) | SNP |
| E. faecium | TX1330 | No phage | 1 | 0.23 |  | Two-component system YycFG regulatory protein YycH | SNP |
| E. faecium | TX1330 | No phage | 2 | 1.00 | Yqw | Tyrosine-protein kinase transmembrane modulator EpsC | SNP |
| E. faecium | TX1330 | No phage | 2 | 0.23 |  | Teichoic acid glycosylation protein | SNP |
| E. faecium | TX1330 | No phage | 3 | 0.70 | Yqw | Tyrosine-protein kinase EpsD (EC 2.7.10.2) | SNP |
| E. faecium | TX1330 | No phage | 3 | 0.30 | Yqw | Tyrosine-protein kinase EpsD (EC 2.7.10.2) | SNP |
| E. faecium | TX1330 | No phage | 4 | 0.24 |  | ABC transporter, permease protein YckA (cluster 3, basic aa/glutamine/opines) | SNP |
| E. faecium | TX1330 | V12 | 1 | 1.00 | Yqw | Tyrosine-protein kinase transmembrane modulator EpsC | SNP |
| E. faecalis | TX2137 | Bop | 1 | 0.63 | Epa | NAD dependent epimerase/dehydratase family protein | SNP |
| E. faecalis | TX2137 | Bop | 1 | 0.31 |  | UDP-N-acetylglucosamine 1-carboxyvinyltransferase | SNP |
| E. faecalis | TX2137 | Bop | 1 | 0.12 | Epa | NAD dependent epimerase/dehydratase family protein | SNP |
| E. faecalis | TX2137 | Bop | 2 | 1.00 |  | phosphocarrier protein HPr | SNP |
| E. faecalis | TX2137 | Bop | 2 | 1.00 | Epa | NAD dependent epimerase/dehydratase family protein | SNP |
| E. faecalis | TX2137 | Bop | 3 | 0.90 | Epa | exopolysaccharide biosynthesis polyprenyl glycosylphosphotransferase | SNP |
| E. faecalis | TX2137 | Bop | 3 | 0.89 | Epa | exopolysaccharide biosynthesis polyprenyl glycosylphosphotransferase | SNP |
| E. faecalis | TX2137 | Bop | 4 | 0.25 | Epa | exopolysaccharide biosynthesis polyprenyl glycosylphosphotransferase | SNP |
| E. faecalis | TX2137 | Bop | 4 | 0.25 | Epa | exopolysaccharide biosynthesis polyprenyl glycosylphosphotransferase | SNP |
| E. faecalis | TX2137 | Bop | 4 | 0.20 | Epa | NAD dependent epimerase/dehydratase family protein | SNP |
| E. faecalis | TX2137 | Bop | 5 | 0.17 |  | UDP-N-acetylglucosamine 1-carboxyvinyltransferase | SNP |
| E. faecalis | TX2137 | Bop | 6 | 0.25 | Epa | NAD dependent epimerase/dehydratase family protein | SNP |
| E. faecalis | TX2137 | Bop | 6 | 0.25 | Epa | NAD dependent epimerase/dehydratase family protein | SNP |
| E. faecalis | TX2137 | Bop | 6 | 0.17 | Epa | NAD dependent epimerase/dehydratase family protein | DEL |
| E. faecalis | TX2137 | Bop | 7 | 0.82 | Epa | NAD dependent epimerase/dehydratase family protein | SNP |
| E. faecalis | TX2137 | Bop | 7 | 0.17 | Epa | NAD dependent epimerase/dehydratase family protein | SNP |
| E. faecalis | TX2137 | Bop | 8 | 1.00 | Epa | NAD dependent epimerase/dehydratase family protein | SNP |
| E. faecalis | TX2137 | Bop | 8 | 0.59 |  | UDP-N-acetylglucosamine 1-carboxyvinyltransferase | SNP |
| E. faecalis | TX2137 | V12 | 1 | 0.71 | Epa | exopolysaccharide biosynthesis polyprenyl glycosylphosphotransferase | SNP |
| E. faecalis | TX2137 | V12 | 1 | 0.71 | Epa | exopolysaccharide biosynthesis polyprenyl glycosylphosphotransferase | SNP |
| E. faecalis | TX2137 | V12 | 2 | 0.69 |  | DNA ligase (NAD+) | SNP |
| E. faecalis | TX2137 | V12 | 2 | 0.55 | Epa | exopolysaccharide biosynthesis polyprenyl glycosylphosphotransferase | DEL |
| E. faecalis | TX2137 | V12 | 2 | 0.31 | Epa | exopolysaccharide biosynthesis polyprenyl glycosylphosphotransferase | SNP |
| E. faecalis | Yi6 | Bop | 1 | 1.00 | Epa | exopolysaccharide biosynthesis polyprenyl glycosylphosphotransferase | SUB |
| E. faecalis | Yi6 | Bop | 1 | 1.00 | Epa | exopolysaccharide biosynthesis polyprenyl glycosylphosphotransferase | SNP |
| E. faecalis | Yi6 | Bop | 1 | 1.00 | Epa | exopolysaccharide biosynthesis polyprenyl glycosylphosphotransferase | SNP |
| E. faecalis | Yi6 | Bop | 1 | 0.19 | Epa | exopolysaccharide biosynthesis polyprenyl glycosylphosphotransferase | SNP |
| E. faecalis | Yi6 | Bop | 2 | 1.00 |  | UTP-glucose-1-phosphate uridylyltransferase | DEL |
| E. faecalis | Yi6 | Bop | 2 | 1.00 |  | UDP-N-acetylglucosamine 1-carboxyvinyltransferase 1 | SNP |
| E. faecalis | Yi6 | Bop | 3 | 1.00 |  | isoleucyl-tRNA synthetase | DEL |
| E. faecalis | Yi6 | Bop | 3 | 0.87 | Epa | exopolysaccharide biosynthesis polyprenyl glycosylphosphotransferase | DEL |
| E. faecalis | Yi6 | V12 | 1 | 0.53 |  | 30S ribosomal protein S7 | SNP |
| E. faecalis | Yi6 | V12 | 2 | 0.50 |  | DNA-directed RNA polymerase subunit alpha | SNP |

**Table S4.**Phagemutations. List of all mutations that occurred in phagegenomes during coevolution with *Enterococcus* for 28 days.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Phage | Rep | Host species | Host strain | Freq | Type | Gene |
| EfV12-phi1 | 1 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| EfV12-phi1 | 1 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| EfV12-phi1 | 1 | E. faecalis | B3286 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| EfV12-phi1 | 1 | E. faecalis | B3286 | 0.90 | SNP | Phage recombination related exonuclease (EC 3.1.11.-) |
| EfV12-phi1 | 1 | E. faecalis | B3286 | 1.00 | DEL | Phage protein |
| EfV12-phi1 | 1 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| EfV12-phi1 | 1 | E. faecalis | B3286 | 0.65 | SNP | Phage protein |
| EfV12-phi1 | 1 | E. faecalis | B3286 | 0.91 | SNP | Protein RtcB |
| EfV12-phi1 | 1 | E. faecalis | B3286 | 0.40 | SNP | Phage protein |
| EfV12-phi1 | 1 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| EfV12-phi1 | 1 | E. faecalis | B3286 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| EfV12-phi1 | 2 | E. faecalis | B3286 | 0.44 | SNP | hypothetical protein |
| EfV12-phi1 | 2 | E. faecalis | B3286 | 0.84 | SNP | Phage capsid and scaffold |
| EfV12-phi1 | 2 | E. faecalis | B3286 | 0.51 | SNP | Phage protein |
| EfV12-phi1 | 2 | E. faecalis | B3286 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| EfV12-phi1 | 2 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 3 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 3 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 3 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 3 | E. faecalis | B3286 | 0.22 | SNP | Protein RtcB |
| vB\_OCPT\_Bop | 3 | E. faecalis | B3286 | 1.00 | SNP | Phage protein |
| vB\_OCPT\_Bop | 3 | E. faecalis | B3286 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 4 | E. faecalis | B3286 | 0.46 | SNP | Phage protein |
| vB\_OCPT\_Bop | 4 | E. faecalis | B3286 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 4 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 4 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 4 | E. faecalis | B3286 | 0.24 | SNP | Phage protein |
| vB\_OCPT\_Bop | 4 | E. faecalis | B3286 | 0.53 | SNP | Phage protein |
| vB\_OCPT\_Bop | 4 | E. faecalis | B3286 | 1.00 | SNP | hypothetical protein |
| vB\_OCPT\_Bop | 4 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 5 | E. faecalis | B3286 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 5 | E. faecalis | B3286 | 1.00 | SNP | Phage protein |
| vB\_OCPT\_Bop | 5 | E. faecalis | B3286 | 0.80 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 5 | E. faecalis | B3286 | 0.81 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 5 | E. faecalis | B3286 | 0.80 | SNP | Serine/threonine protein phosphatase (EC 3.1.3.16) |
| vB\_OCPT\_Bop | 5 | E. faecalis | B3286 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 0.19 | SNP | hypothetical protein |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 0.11 | SNP | hypothetical protein |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 1.00 | SNP | Phage protein |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 0.18 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 0.56 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 0.23 | SNP | Nicotinamide-nucleotide adenylyltransferase, NadR family (EC 2.7.7.1) / Ribosylnicotinamide kinase (EC 2.7.1.22) |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 0.13 | SNP | Phage protein |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 0.21 | SNP | DNA helicase, phage-associated |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 0.19 | SNP | Nicotinamide-nucleotide adenylyltransferase, NadR family (EC 2.7.7.1) / Ribosylnicotinamide kinase (EC 2.7.1.22) |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 0.15 | SNP | Phage major tail sheath |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 6 | E. faecalis | B3286 | 0.25 | SNP | Deoxyadenosine kinase (EC 2.7.1.76) / Deoxyguanosine kinase (EC 2.7.1.113) |
| vB\_OCPT\_Bop | 7 | E. faecalis | B3286 | 1.00 | SNP | Phage protein |
| vB\_OCPT\_Bop | 8 | E. faecalis | B3286 | 0.22 | SNP | Phage baseplate |
| vB\_OCPT\_Bop | 8 | E. faecalis | B3286 | 1.00 | INS | Phage protein |
| vB\_OCPT\_Bop | 8 | E. faecalis | B3286 | 1.00 | SNP | Phage protein |
| vB\_OCPT\_Bop | 8 | E. faecalis | B3286 | 0.25 | SNP | hypothetical protein |
| vB\_OCPT\_Bop | 8 | E. faecalis | B3286 | 0.22 | SNP | Phage protein |
| vB\_OCPT\_Bop | 8 | E. faecalis | B3286 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 8 | E. faecalis | B3286 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 8 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 8 | E. faecalis | B3286 | 1.00 | SNP | Phage protein |
| vB\_OCPT\_Bop | 8 | E. faecalis | B3286 | 1.00 | SNP | Phage protein |
| vB\_OCPT\_Bop | 8 | E. faecalis | B3286 | 0.18 | SNP | hypothetical protein |
| vB\_OCPT\_Bop | 8 | E. faecalis | B3286 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 8 | E. faecalis | B3286 | 0.22 | SNP | NrdR-regulated deoxyribonucleotide transporter, PnuC-like |
| vB\_OCPT\_Bop | 8 | E. faecalis | B3286 | 0.24 | SNP | Phage protein |
| EfV12-phi1 | 1 | E. faecalis | TX2137 | 0.38 | SNP | Phage capsid and scaffold |
| EfV12-phi1 | 1 | E. faecalis | TX2137 | 0.40 | SNP | Phage capsid and scaffold |
| EfV12-phi1 | 1 | E. faecalis | TX2137 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| EfV12-phi1 | 2 | E. faecalis | TX2137 | 0.58 | SNP | hypothetical protein |
| EfV12-phi1 | 2 | E. faecalis | TX2137 | 0.92 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| EfV12-phi1 | 3 | E. faecalis | TX2137 | 0.80 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 4 | E. faecalis | TX2137 | 0.17 | SNP | Phage protein |
| vB\_OCPT\_Bop | 4 | E. faecalis | TX2137 | 0.39 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 4 | E. faecalis | TX2137 | 0.91 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 4 | E. faecalis | TX2137 | 0.17 | SNP | hypothetical protein |
| vB\_OCPT\_Bop | 4 | E. faecalis | TX2137 | 0.84 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 5 | E. faecalis | TX2137 | 0.17 | SNP | hypothetical protein |
| vB\_OCPT\_Bop | 6 | E. faecalis | TX2137 | 0.38 | SNP | Ribonucleotide reductase of class III (anaerobic), activating protein (EC 1.97.1.4) |
| vB\_OCPT\_Bop | 6 | E. faecalis | TX2137 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 6 | E. faecalis | TX2137 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 6 | E. faecalis | TX2137 | 0.40 | SNP | Phage protein |
| vB\_OCPT\_Bop | 7 | E. faecalis | TX2137 | 0.95 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 7 | E. faecalis | TX2137 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 8 | E. faecalis | TX2137 | 0.98 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 8 | E. faecalis | TX2137 | 0.99 | SNP | Phage protein |
| vB\_OCPT\_Bop | 8 | E. faecalis | TX2137 | 0.36 | SNP | Phage protein |
| vB\_OCPT\_Bop | 8 | E. faecalis | TX2137 | 0.11 | SNP | Thioredoxin, phage-associated |
| vB\_OCPT\_Bop | 8 | E. faecalis | TX2137 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 9 | E. faecalis | TX2137 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 9 | E. faecalis | TX2137 | 0.57 | SNP | Phage protein |
| vB\_OCPT\_Bop | 9 | E. faecalis | TX2137 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 10 | E. faecalis | TX2137 | 0.66 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 10 | E. faecalis | TX2137 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 10 | E. faecalis | TX2137 | 0.97 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 11 | E. faecalis | TX2137 | 0.84 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 11 | E. faecalis | TX2137 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 11 | E. faecalis | TX2137 | 0.18 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 12 | E. faecalis | TX2137 | 0.21 | SNP | DNA primase (EC 2.7.7.-) / DNA helicase (EC 3.6.1.-), phage-associated |
| vB\_OCPT\_Bop | 12 | E. faecalis | TX2137 | 0.97 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 12 | E. faecalis | TX2137 | 0.16 | SNP | Phage protein |
| vB\_OCPT\_Bop | 12 | E. faecalis | TX2137 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 12 | E. faecalis | TX2137 | 0.11 | SNP | Phage protein |
| vB\_OCPT\_Bop | 13 | E. faecalis | TX2137 | 0.25 | SNP | Phage protein |
| vB\_OCPT\_Bop | 13 | E. faecalis | TX2137 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 13 | E. faecalis | TX2137 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 13 | E. faecalis | TX2137 | 0.38 | SNP | Phage protein |
| vB\_OCPT\_Bop | 1 | E. faecalis | Yi6 | 0.54 | SNP | Phage protein |
| vB\_OCPT\_Bop | 1 | E. faecalis | Yi6 | 0.38 | SNP | Phage protein |
| vB\_OCPT\_Bop | 1 | E. faecalis | Yi6 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 2 | E. faecalis | Yi6 | 0.98 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 2 | E. faecalis | Yi6 | 1.00 | SNP | Phage protein |
| vB\_OCPT\_Bop | 2 | E. faecalis | Yi6 | 0.96 | SNP | Phage protein |
| vB\_OCPT\_Bop | 2 | E. faecalis | Yi6 | 1.00 | SNP | Phage protein |
| vB\_OCPT\_Bop | 2 | E. faecalis | Yi6 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 2 | E. faecalis | Yi6 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 3 | E. faecalis | Yi6 | 0.96 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 3 | E. faecalis | Yi6 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 3 | E. faecalis | Yi6 | 1.00 | SNP | Phage protein |
| vB\_OCPT\_Bop | 3 | E. faecalis | Yi6 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 4 | E. faecalis | Yi6 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 4 | E. faecalis | Yi6 | 0.95 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 4 | E. faecalis | Yi6 | 0.12 | SNP | Phage protein |
| vB\_OCPT\_Bop | 4 | E. faecalis | Yi6 | 0.40 | SNP | Phage protein |
| vB\_OCPT\_Bop | 4 | E. faecalis | Yi6 | 0.79 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 4 | E. faecalis | Yi6 | 0.99 | SNP | Phage protein |
| vB\_OCPT\_Bop | 4 | E. faecalis | Yi6 | 1.00 | SNP | Phage protein |
| vB\_OCPT\_Bop | 5 | E. faecalis | Yi6 | 0.64 | SNP | Phage protein |
| vB\_OCPT\_Bop | 5 | E. faecalis | Yi6 | 0.32 | SNP | Phage protein |
| vB\_OCPT\_Bop | 5 | E. faecalis | Yi6 | 0.13 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 5 | E. faecalis | Yi6 | 0.16 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 5 | E. faecalis | Yi6 | 0.49 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 5 | E. faecalis | Yi6 | 0.76 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 5 | E. faecalis | Yi6 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 5 | E. faecalis | Yi6 | 0.82 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 5 | E. faecalis | Yi6 | 0.24 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 5 | E. faecalis | Yi6 | 0.10 | SNP | hypothetical protein |
| vB\_OCPT\_Bop | 6 | E. faecalis | Yi6 | 0.82 | SNP | Phage protein |
| vB\_OCPT\_Bop | 6 | E. faecalis | Yi6 | 0.13 | SNP | Phage protein |
| vB\_OCPT\_Bop | 6 | E. faecalis | Yi6 | 1.00 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 6 | E. faecalis | Yi6 | 1.00 | SNP | Phage protein |
| vB\_OCPT\_Bop | 6 | E. faecalis | Yi6 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 7 | E. faecalis | Yi6 | 0.99 | SNP | Phage protein |
| vB\_OCPT\_Bop | 7 | E. faecalis | Yi6 | 0.98 | SNP | Phage capsid and scaffold |
| vB\_OCPT\_Bop | 7 | E. faecalis | Yi6 | 1.00 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 7 | E. faecalis | Yi6 | 0.20 | SNP | Phage protein |
| vB\_OCPT\_Bop | 7 | E. faecalis | Yi6 | 0.91 | SNP | Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46), phage variant |
| vB\_OCPT\_Bop | 8 | E. faecalis | Yi6 | 1.00 | SNP | Phage capsid and scaffold |