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Title:

Genomic Analysis of the Polyvalent Bacteriophage FP01

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ABSTRACT

Recently the polyvalent bacteriophage FP01, isolated from wastewater in Valparaiso, Chile, was described to have lytic activity across species against *Escherichia coli* and *Salmonella enterica* serovars. Due to it polyvalent nature the bacteriophage FP01 could have potential application in food and agri-industry. Also, fundamental aspects of polyvalent bacteriophage biology are not well known. In this study we sequenced and describe the complete genome of the polyvalent phage FP01 (MH745368) using the nanopore technology. The bacteriophage FP01 genome has a 44,900 bp, double-stranded DNA with an average G+C content of 49.41% and 90 coding sequences (CDSs). We found that the phage FP01 critically depends on host factors for replication and transcription. Also, it has a critical lysogenic repressor pseudogene. Phylogenetic analyses indicated that the phage FP01 is closely related to phages lambda and P22. These results suggest that the phage FP01 could be a lytic variant of a lysogenic phage or acquired genes from lysogenic phages during host infection.

Keywords: polyvalent bacteriophage FP01, *Escherichia coli*, *Salmonella*, genome

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INTRODUCTION

Bacteriophages or phages are bacterial viruses characterized by their obligatory bacterial parasitism, influencing bacterial ecology and evolution [1, 2]. Since the early 1900s, lytic bacteriophages have been utilized as prophylactic and therapeutic agents against bacterial infectious diseases [3, 4]. There is a large amount of research that proves the effective and safe utilization of bacteriophages [5, 6]. Nowadays, the utilization of bacteriophages has public acceptance and government approval [7]. Commercial bacteriophage cocktails are currently utilized in human and animal health, and in the Agri-food industry to prevent bacterial infectious diseases [4, 8]. Bacteriophage host-range is typically narrow, and lytic bacteriophages are usually species specific or even strain specific [9]. Most of the bacteriophages possess a tail that allows specific recognition and subsequent adsorption to a receptor at the surface of the host bacterium [10, 11]. Because of phage host specificity, phage cocktails or mixes that offer a broad host-range are frequently utilized in commercial preparations [12, 13].

Polyvalent phages that are able to infect different species or serotypes are very attractive for industrial applications. Polyvalent phages offer the possibility of increasing bacterial species coverage in the design of phage cocktails [12, 13] and to propagate the bacteriophages in non-pathogenic hosts, reducing the risk of accidental contamination of preparations with the target pathogen. Polyvalent phages have been described since 1933 [14], including phages of Enterobacteria [11] and staphylococci [15], *Aerobacter aerogenes* [16], and *Pseudomonas* spp [17].

The polyvalent bacteriophage FP01 was isolated from wastewater in the V region of Chile, using *Salmonella enterica* serotype Choleraesuis VAL201 as host [18]. The phage FP01 belongs

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to the order *Caudoviridae*, family *Siphoviridae*, which are bacterial viruses of double-strand DNA [18]. The bacteriophage FP01 is able to proliferate in *E. coli* C, *E. coli* B, *E. coli* K12, and *Salmonella enterica* serovars Typhi, Paratyphi B, and Choleraesuis [18], indicating that FP01 has a common attachment site on the susceptible bacterial species [18, 19]. A better understanding of the mechanisms and evolution of polyvalent bacteriophages can be gained by comparative genomic analysis. Here, we sequence and describe the whole genome of the polyvalent bacteriophage FP01 using the MinION nanopore technology. We found that the phage FP01 critically depends on host factors for replication and transcription. Phylogenetic analyses indicated that the phage FP01 is closed related to phages lambda and P22. These results suggest that the phage FP01 could be a lytic variant of a lysogenic phage or, alternatively, that it acquired genes from other lysogenic phages during host infection.

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MATERIALS AND METHODS

DNA extraction. The bacteriophage FP01 was propagated in *S.* Choleraesuis VAL201 using standardized methods [20, 21]. Genomic DNA (gDNA) from concentrated phage lysates was purified according to the method described by Kaiser et al [22].

Nanopore library preparation and sequencing. The MinION (Oxford Nanopore Technologies) is the smallest sequencing device technology currently available (Lu et al., 2016). The MinION is an USB-portable and low-cost device, which is able to generate reads of 2-10 Kb on average, with an error range of 2-13% [23-26], ideal for sequencing small genomes like the bacteriophage FP01. The MinION sequencing library was prepared using the SQK-RAD003 kit according to the manufacturer's instructions and sequenced using an R9.Spot-On flow cell (FLO-MIN106). The FP01 gDNA library was added to a MinION sequencer and run for 22 h with a coverage of X29,68. Coverage was calculated by the Lander-Waterman equation [27]. The resulting FAST5 files were based called and demultiplexed using Albacore v2.0.2. The FAST5 files were converted into FASTA format using Poretools [8]. The contigs were analyzed and visualized using CLC genomics workbench 12 (Qiagen).

Annotation and Genome Mapping. The genome was initially annotated with the PHage Search Tool (PHAST) [28] and refined with the Rapid Annotation Subsystem Technology (RAST) [29]. The whole genome was submitted to NCBI data using the whole genome shotgun submission pipeline (WGS) (https://www.ncbi.nlm.nih.gov/genbank/wgs/). The phage FP01 genome was

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deposited in DDBJ/EMBL/GenBank under the Bioproject (PRJNA450422) and the gene bank accession number (MH745368.1). The phage FP01 genome was visualized using the DNAplotter software [30] and easyfig [31].

Phylogenetic analysis. Sequence alignments were performed using the CLC Genomics Workbench 12 (Qiagen). The evolutionary analyses of the whole genome of the phage FP01 were conducted using MEGA7 [32]. The Neighbor-Joining method [33] with a bootstrap test of 1000 replicates and the p-distance method [34] were utilized to determine the evolutionary distances. The bacteriophage genomes used in this analysis were *Salmonella* phage SE2 (JQ007353.1); *Salmonella* phage ST4 (JX233783.1); *Salmonella* phage vB SenS-Ent2 (HG934469.1); *Salmonella* phage vB SenS-Ent1 (HE775250.1); *Salmonella* phage vB SenS-Ent3 (HG934470.1); *Salmonella* phage SETP3 (EF177456.2); *Salmonella* phage vB SenS AG11 (JX297445.1); *Salmonella* phage SETP13 (KF562864.1); *Salmonella* phage SETP7 (KF562865.1); *Salmonella* phage FSL SP-101 (KC139511.1); *Salmonella* phage LSPA1 (KM272358.1); *Salmonella* phage Jersey (KF148055.1); *Escherichia* phage K1G (GU196277.1); *Escherichia* phage K1H (GU196278.1); *Escherichia* phage K1ind1 (GU196279.1); *Escherichia* phage K1ind2 (GU196280.1); *Escherichia* phage K1ind3 (GU196281.1); *Salmonella* phage ST4 (JX233783.1); *Shigella* phage EP23 (JN984867.1); *Salmonella* phage STsAS (MH221128.1); *Salmonella* phage FSL SP-031 (KC139518.1); *Salmonella* phage E1 (AM491472.1); Enterobacteria phage lambda (J02459.1); *Salmonella* phage SS3e (AY730274.2); *Salmonella* phage wksl3 (JX202565.1); *Salmonella* phage *f*SE1C (KT962832.1); *Salmonella* phage *f*SE4S (KT881477.1); *Salmonella* phage *f*18S (KR270151.1); *Salmonella* phage *f*2SE (KU951146.1); *Salmonella* phage *f*3SE (KU951147.1); Enterobacteria phage P22 (NC_002371.2); and Enterobacteria phage M13

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(NC_003287.2).

Comparative genomics. A multiple genome alignment was made to compare the whole genome of the bacteriophage FP01 to the bacteriophages P22 (NC_002371.2) and lambda (J02459.1). The alignment was analyzed by Mauve software [35] and a Easyfig [31].

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RESULTS AND DISCUSSION

Sequencing. The total analyzed bacteriophage FP01 reads were 2,067 with 7,546 nucleotides in average (Fig. S1A). The library was sequenced during 22 h and only 12 of 2,067 reads that did not pass the quality control were removed (Figs. S1B-C). The percentage of successful sequencing was 99.4% (Fig. S1B). The genome of the bacteriophage FP01 was obtained in a single contig of 44,900 bp (Fig. 1), coincident with the previous description of the gDNA molecular weight of the phage FP01 [18]. The genome of the phage FP01 has a total of 90 CDSs with a 49.41% G+C content (Fig. 1).

Annotation, Genome mapping and Sequence Analysis. The RAST analysis showed a unique subsystem related to phage, prophages, transposable elements, and plasmids (Fig. S2A). The PHAST analysis showed 4 type CDSs related to tail shaft, phage–like protein, tail fiber and coat (capsid and scaffold proteins), respectively (Fig. S2B). A total of 90 coding genes, among them 56 hypothetical genes, 25 structural and virion assembly associated genes, 3 encoding genes related to DNA packaging, 3 genes related to cell lysis, 2 genes related to the lambda lysogenic cycle (Table S1). These genes are partially similar to the CII repressor and integrase, hypothetically encoding for a mutated shorted version of these proteins. The genome of the bacteriophage FP01 does not present DNA polymerase, RNA polymerase, and helicase genes, in contrast to the *Salmonella enterica* monovalent bacteriophages previously isolated from the same location [36, 37].

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We found several genes that encode for structural proteins, including three capsid related genes, a major and two minor tail encoding genes, seven tail fiber encoding genes, seven tail length tape-measure encoding genes, and a tail and a fiber assemble encoding genes (Table S1). These structural genes correlate with the virion structure of the phage FP01 [18]. The tail of the bacteriophage lambda is made of at least 6 proteins with other 7 required for assembly [38], which is also coincident with the FP01 phage genes.

Regarding to the lysis we found that FP01 presents a Kil protein, a holin, a host specificity protein, and an attachment and invasion protein precursor (Table S1). This could be related to the high lytic activity that FP01 possess with titers of $5.5x10^{11}$ pfu/ml [18].

Phylogeny analysis. The phylogenetic analyses were made and computed by the MEGA7 software, using the p-distance method to compute the evolutionary distance between the phages that were selected from different families (*Myoviridae*, *Podoviridae*, and *Siphoviridae*) and genera within the *Siphoviridae* family, like *Jerseyviridae*, *K1glikevirus*, *Spn3virus*, and *Sp3unalikevirus*. The phage FP01 is closed related to the Enterobacteria phage lambda (Fig. 2), in correlation with the previously described virion shape [18]. The phylogenetic analyses suggested that the phage FP01 could be a variant of the phage lambda representing a different species of lytic viruses.

Comparative genome analysis. The gene repertoire of FP01 is very different from other lytic members of the family *Siphoviridae*, but similar to lambda and P22 (Fig. 3). Therefore, our comparative analysis focused on these phages. We noticed that the phage FP01 (44,900 bp) has a bigger genome than the phage P22 (NC_002371.2) (41,724 bp) but smaller than the phage lambda

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(J02459.1) (48,502 bp). Although these phages share similar blocks of genes, its arrangements are different in each phage. For instance, the genes related to the lysogenic cycle are mostly absent from the phage FP01 genome, and the few that remain are mutated (Table 1). The genes related to cell lysis also are located in different segments of the phage genomes (Figs. 3 and 4). The most conserved blocks of genes shared between these three phages are structural genes. The capsid related genes are shared between FP01, lambda, and P22, and the tail related genes are shared between lambda and FP01 (Fig. 4).

The bacteriophage FP01 is closely related to the phage lambda, and distant from the monovalent *Salmonella* Typhi and Paratyphi A bacteriophage STsAS (MH221128). The complete genome of FP01 presented structural genes related to lambda-like virus particles that correlated with its previous characterization [18]. The critical dependency of host factors for bacteriophage replication and transcription perhaps gives phage FP01 the flexibility to multiply in *E. coli* and different *Salmonella enterica* serovars. The receptor of the phage lambda in the *E. coli* membrane is the protein LamB, which does not work as a lambda receptor in *S. enterica* [39, 40]. This suggests that a common receptor for *E. coli* and the susceptible *S. enterica* serovar is present in these hosts. The phage FP01 could represent a novel phage species but more analyses are needed to establish this.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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FIGURE LEGENDS

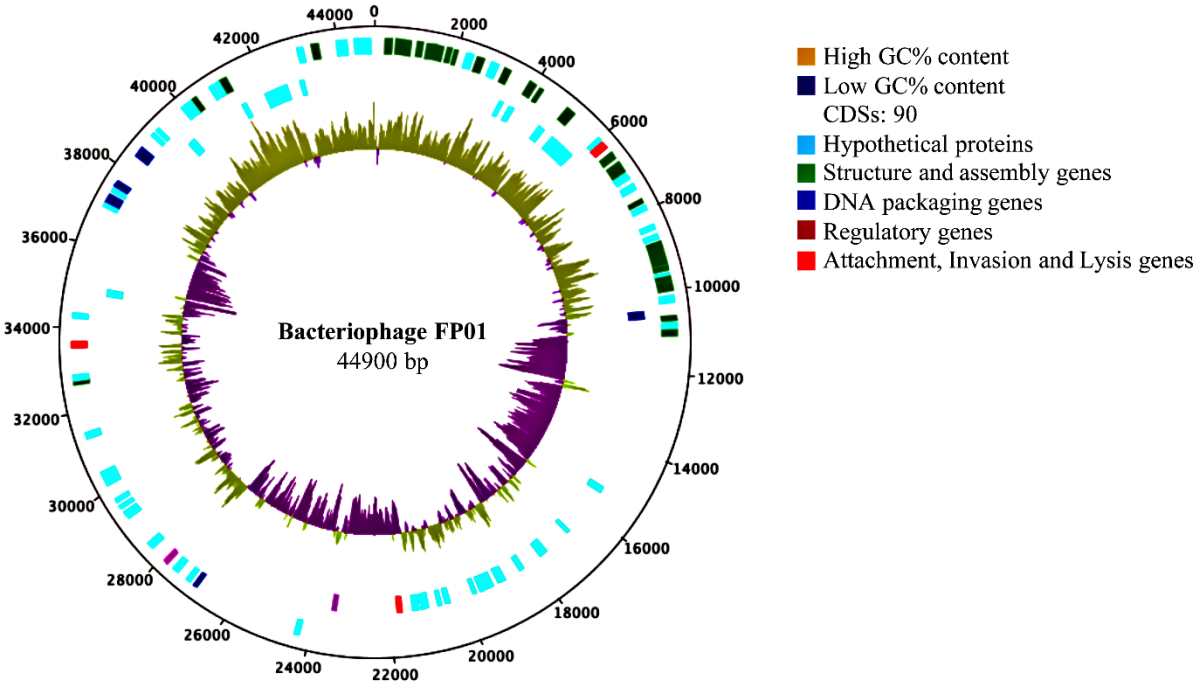

Figure 1. Bacteriophage FP01 genome map. DNAplotter software was used to visualize and generate a whole genome map of bacteriophage FP01. The genome sequence is represented by a gray color circle, the yellow and purple color represent the G+C content distributed along the genome. The predicted coding sequences were identified; hypothetical genes are indicated in light blue, structure and assembly associated genes are indicated in green, DNA packaging genes are indicated in blue, and lysis related encoding genes are indicated in red.

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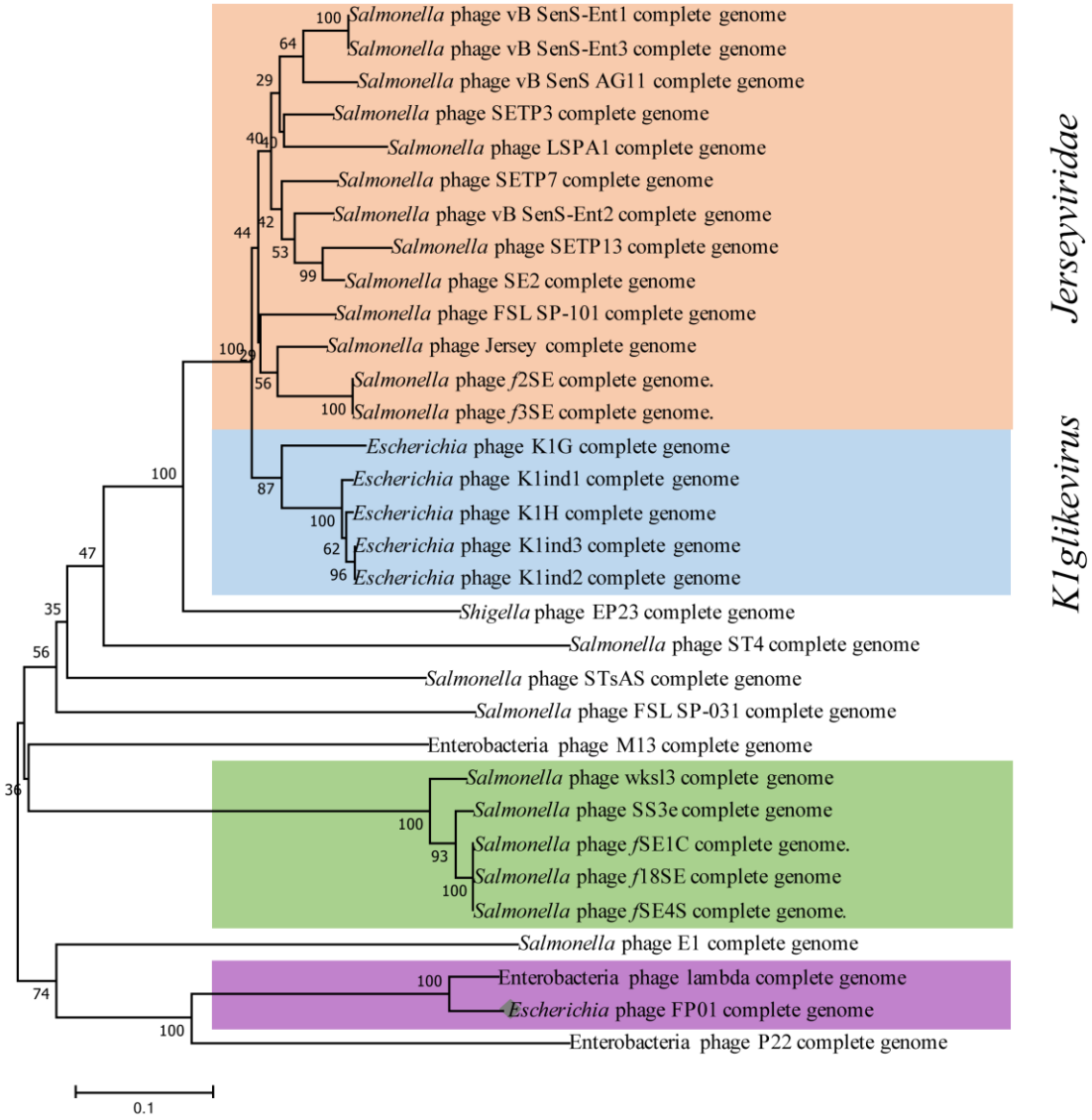

Figure 2. Phylogenetic tree using the complete genome sequence. The evolutionary history of the phage FP01 was inferred by using the Neighbor-Joining method. The percentage of replicate trees was calculated with a bootstrap test of 1000 replicates. The evolutionary distances were computed using the p-distance method. The analyses involved 32 phage genome sequences. Evolutionary analyses were conducted in MEGA7.

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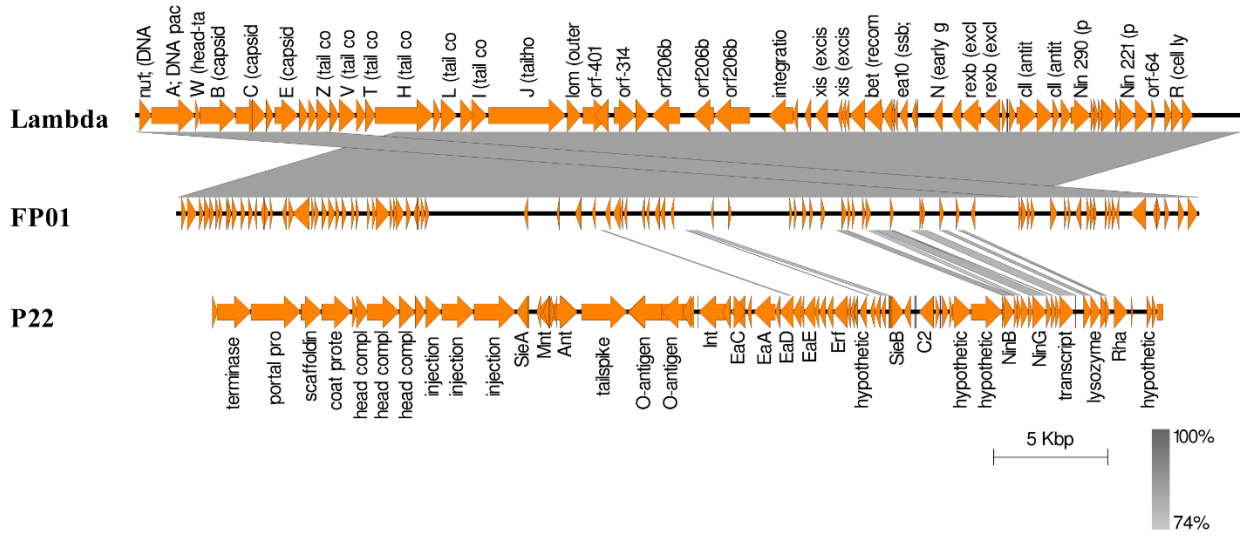

Figure 3. Genome comparison of FP01, Lambda and P22 phages. Alignment and figure were computed using the Easyfig 2.2.3 software.

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SUPPLEMENTARY FIGURE LEGENDS

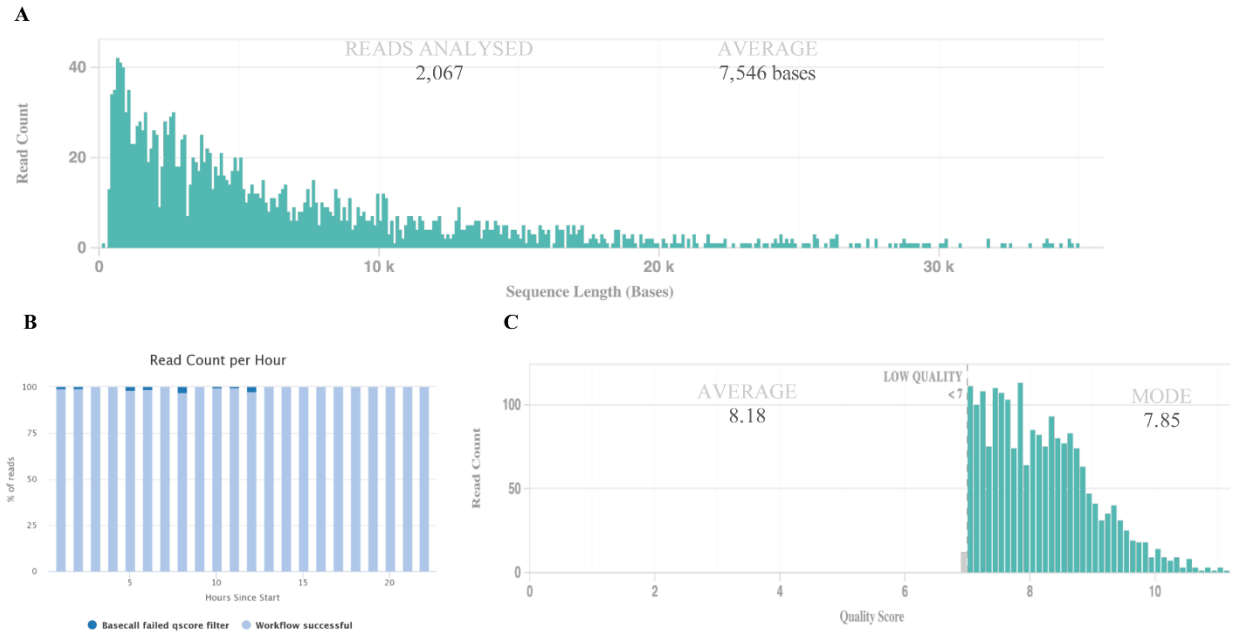

Figure S1. EPI2ME Basecalling QScore. **A.** Representative graph of analyzed reads (green bars) by sequences length (bases) with an average of 7,546 bases. **B.** Percentage of reads count per hour that workflow was successful (light blue bars) and percentage of reads count per hour that failed the quality score filter (Blue bars). **C.** Representative graph of quality score by read count, failed reads are < 7 score value (gray bars) and successful reads are > 7 score value (green bars) with a mode of 7.85 score value.

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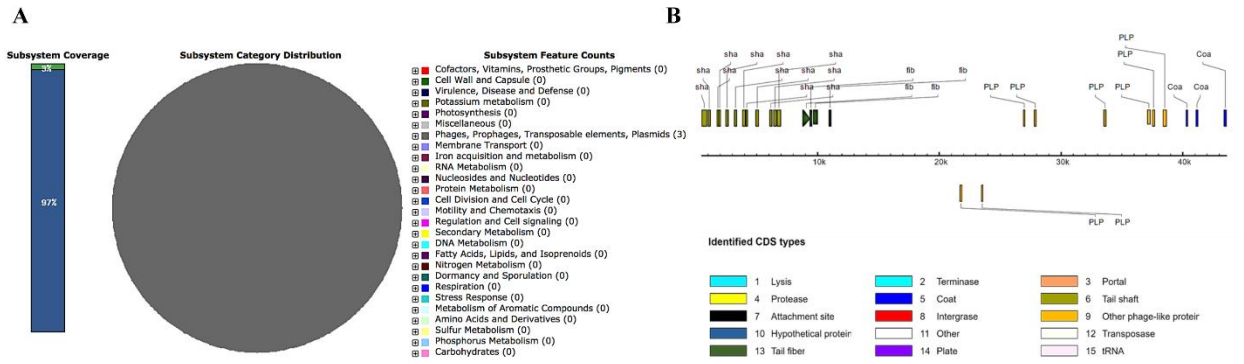

Figure S2. Distribution of subsystems founds in the polyvalent bacteriophage FP01 genome. **A.** Rapid Annotation System Technology (RAST) annotation subsystems percentage coverage in green bar (protein included) and in blue bar (non-included), subsystem is represented by grey color (Phages, Prophages, Transposable elements, Plasmid). **B.** Phage Search Tool (PHAST) annotation CDS type distribution along the complete genome of phage FP01. Specific phage CDSs types are described by numbers (1-15) and colors for each type. The graph presents only annotated proteins for: tail shaft (sha); tail fiber (fib); other phage-like protein (PLP) and coat (Coa).

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