UNIVERSITY OF CALIFORNIA SAN DIEGO

Viral-host interactome evolution compensates for an array of host gene deletions

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by

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Abstract of the Thesis

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In order to carry out successful infections, bacteriophage λ depends on many proteins in its host, the bacterium *Escherichia coli*. λ proteins and λ DNA interact with host molecules to facilitate infection and replication. These interactions form a molecular network known as the interactome. Viral evolution is therefore largely governed by changes that optimize the productivity of the interactome. Here, I present studies where we perturbed λ's interactome and allowed it to regain functionality through adaptive evolution. These studies provide insight into how viruses adapt, and more generally, how gene networks evolve. Previous studies have identified host genes used by λ during infection. We used this knowledge in order to perturb the

interactome by culturing λ on a variety of host strains with one of these genes deleted. We proceeded to study λ evolution to the 16 KOs and a wild type control to distinguish between specialized adaptations to specific KOs, or general adaptations to suboptimal laboratory conditions. Overall, most perturbations to the interactome could be solved with generic mutations that improve λ growth, although, there are a few host gene deletions that require specialized mutations. Our study shows that viruses can easily adapt to perturbations in their interactomes through different adaptive solutions. While mutations with general benefits aid the correction of node deletions by providing disproportionate benefits for especially destructive deletions, some host gene deletions require specialized mutations.

Introduction:

As microscopic parasites that lack the fundamental components of a living cell, viruses are fully dependent on their host's cellular machinery to reproduce (Holmes and Drummond, 2007; Pybus and Rambaut, 2009). During an infection, viruses must rewire their host's innate programming that is optimized for cellular reproduction and survival, to replicate new viral particles and ultimately triggering cellular self-destruction. To accomplish this, viruses have evolved the ability to manipulate massive host molecular networks with a minimal set of viral genes (Chisari, 2005; Pybus and Rambaut, 2009; Stebbing and Gazzard, 2011; Trkola, 2004;).

Even though it is thought that viruses have evolved highly specialized interactions with their host molecular network, viruses seem to be flexible and able to adopt new molecular interactions. As viruses are dependent on a specific set of host molecular interactions, in order for a virus to infect a novel host the virus must adapt to efficiently manipulate the novel host's molecular machinery by evolving a new virus-host interaction network that compensates for missing interactions that were previously present in the natural host (Jones *et al*., 2008; Longdon *et al*., 2014; Parrish *et al*., 2008). For example, studies have shown that influenza strains which jump into a new host species must adapt to regulate a novel host's interferon immune response through NS1 mutations (Parrish *et al*. 2008). By studying how viruses evolve to exploit new molecular interactions we are able to better understand and predict emerging infectious diseases (Kuiken *et al*., 2006). Thus, it is important to understand the evolutionary dynamics that lead to changes in virus-host molecular interactions.

Shifts in pathogen-host molecular interactions are also a common theme in coevolutionary arms races (Beutler *et al*., 2008; Forde *et al*., 2008; Meyer *et al*., 2012; Scanlan *et al*., 2011). Viruses that face resistant host strains must adapt to compensate for missing or even

deleterious host interactions through mutations which allow the virus to gain novel interactions within the host's molecular network (Hertz *et al*., 2011; Marques and Carthew, 2007). Previous studies have shown that λ readily adapted to exploit a new receptor on its host, *Escherichia coli,* in response to the host decreasing the expression of its primary receptor, indicating that λ is highly evolvable and can easily adapt new molecular interactions to compensate for missing host components of the interactome (Meyer *et al*., 2012). Similarly, many antiviral therapeutics inhibit viral replication by preventing certain virus-host molecular interactions that are necessary for infection to occur (De Clercq, 2002; Lou *et al*., 2014). This creates a selection pressure for the virus to accumulate mutations that allow the virus to exploit novel interaction to overcome the antiviral block, leading to the rise of a resistant viral strain which is no longer dependent on the previous interaction (Kimberlin *et al*., 1995; Lipsitch *et al*., 2007 Strasfeld and Chou, 2011). Understanding how the molecular interactions between a virus and its host evolves under different evolutionary challenges provides major insights into better methods for the development of novel antiviral therapies that both mitigate evolution of antiviral resistance and attenuate effects of immune-mediated pathogenesis resulting from infection (Strasfeld and Chou, 2011; Rambaut *et al*., 2004; Karlsson *et al*., 2014).

In these scenarios, the virus has to evolve novel molecular interactions in response to new host opportunities or to perturbations within its host molecular network (i.e. antivirals and resistant hosts). Typically, these circumstances cause the virus to experience selective pressure to evolve adaptations that compensate for a changing host molecular interaction network (Lipsitch *et al*., 2007; Pybus and Rambaut, 2009). In this work, I explore the process of viral adaptation by seeing how a non-pathogenic model virus, bacteriophage λ, evolves solutions to deletions in host proteins that are used for viral replication. Bacteriophage λ is a well-studied phage that infects

the bacterium, *Escherichia coli* and has been used as model for viruses for decades (Barrick and Lenski, 2013; Casjens and Hendrix, 2015; Longdon *et al*., 2014). Moreover, λ evolution has been documented in many laboratory studies, and is an ideal model system to test evolutionary theories (Meyer *et al*., 2012; Refardt and Rainey, 2010; Shao and Wang, 2008).

Like all viruses, λ depends on a set of *E. coli* genes that consists of multifaceted and single molecular interactions (Balsche *et al*., 2013; Mariano *et al*., 2015; Maynard *et al*., 2010). The network of molecular interactions (i.e. protein-protein or DNA-DNA interactions) that occur between a virus and its host during infection and facilitate viral replication is known as the interactome (Rodrigo *et al*., 2017; Schneider *et al*., 2016). Studies from the last half century have identified over 100 host proteins (*i.e. dnaK, lamB, nusB, etc.)* which make up the bacterial components of the λ-*E. coli* interactome network; many of which have been recently identified through high throughput screens (Cumby *et al*., 2014; Balsche *et al*., 2013; Esquinas-Rynchen and Erni, 2001; Maynard *et al*., 2010). Because of this, our understanding of the members of the λ-*E. coli* interactome is well established. Yet it is not well known how λ can evolve to deal with alterations in the host components of its interactome.

As previously mentioned, viruses have evolved highly specialized interactome networks with their hosts yet evidence supports that interactomes are adaptable. Studies show that λ possesses additional qualities that may enhance its interactome adaptability. First, both the genome and interactome of λ is quite large relative to other phage, suggesting that it may have evolved genetic redundancies. Redundancies within the interactome may facilitate evolution since λ would be able to repurpose unnecessary interactions with host components for new operations (Hauser *et al*., 2012; Scandella and Arber, 1976). Moreover, λ has a unique interactome with few similarities to the interactome of other phage that infect *E. coli,* such as T7,

which indicates that there exists a number of alternative interactions that λ could evolve to exploit (Hauser *et al*., 2012). These observations suggest that λ should have the evolutionary capacity to compensate for different perturbations in host components of the interactome.

To study how λ evolves to perturbations in host components of its interactome we screened a library of single gene knockouts *Escherichia coli* to identify the host genes that most affected λ's ability to replicate (Baba *et al*., 2006; Balsche *et al*., 2013; Maynard *et al*., 2010). We were able to test how λ evolves to compensate for deletions in its host interactome and whether there are any perturbations which λ is unable to overcome. Overall, studying how λ adapts to single deletions in host components of its interactome allows us to better understand many different scenarios of viral evolution and determine if there are common themes in virus-host interactome evolution and λ evolvability.

Materials and Methods:

E. coli strains:

Two *E. coli K-12* strains were used as hosts when culturing or plating our phage populations. The *KEIO* knockout (*KO*) collection consists of a library of single knockout mutants in which a non-essential gene is replaced with a kanamycin resistance cassette. We screened 67 different *KEIO KO* strains in our preliminary study (supplemental table 1). The 14 with the greatest effects on viral fitness plus *ΔdnaJ* and *ΔnusB* were selected as hosts for the parallel evolution experiments along with *WT KEIO E. coli BW25113*, as our control host (table 2, Baba *et al*., 2006). *DH5α* was primarily used as the host for infused plates during our competitive growth rate experiments (Invitrogen).

K12 MG1655 derivative, HWEC106 (provided by Harris Wang, Columbia University, New York, New York), was used for producing lysogens and editing lambda genomes. Notable modifications in this strain include the addition of λ red recombineering genes provided on plasmid pKD46 and the deletion of *mutS* to improve allelic replacement of single nucleotide substitutions. All *E. coli* strains were stored at -80°C with 15% w/v glycerol.

Bacteriophage λ strains:

We used two λ strains that have different mutations in the gene that dictates the switch between life cycles, *cI* (Meyer *et al*., 2010). Typically, λ has two stages in its life cycle, a lytic phase in which the phage rapidly replicates and kills the cell or a lysogenic phase in which the phage integrates into the host genome and remains dormant (Casjens and Hendrix, 2015). To start our evolution experiment we used *cI26*, a strictly lytic λ genotype (Meyer *et al*., 2010). For competition assays we used a marked *strain, cI26lacZ* that has the *lacZ* gene fused to λ's gene *R,* allowing it to produce differentiable plaques when infecting DH5α in the presence of X-gal

(Burmeister, 2016; Shao and Wang, 2008). *cI26* stocks were made by co-culturing cI26 with fresh *E. coli* host in modified LBM9 overnight, phage were isolated by chloroform extraction and preserved at 4°C or -80°C with 15% w/v glycerol (Sambrook and Russell, 2001).

We used a second λ base strain, *cI857* (*provided by Ing-Nang Wang, State University of New York at Albany*) that has a mutation in *cI* which causes temperature controlled lysogeny. *cI857* remains integrated in the *E. coli* host's genome at low temperatures, but the lytic phase can be triggered by heat shock. This strain was used for genetic engineering because modifications are easier to introduce during the lysogenic phase (Meyer *et al*., 2016). When measuring the competitive fitness of mutant *cI857* lysogens we used a marked *cI857* strain as the ancestor, *cI857lacZ*, which like *cI26lacZ* is used for the same purpose and was created in a similar fashion.

Lysogens were produced by inoculating 140 μL of fresh lysogen culture into 4-mL of modified LBM9 and grown at 30°C shaking at 220 rpm for 2 hours. After the incubation period, lysogens were heat shocked in a water bath for 15 minutes at 42.5°C and transferred to a 37°C incubator shaking at 220 rpm until the culture cleared, ~1.5 hours (Meyer *et al*., 2016). The cultures were then filtered (0.22 μm) to isolate the phage and stored at 4°C or -80°C with 15% w/v glycerol.

Culture conditions:

In order to maintain consistent culturing conditions for the duration of the experiment *E. coli* cultures were started daily from freezer stocks. We inoculated 4 mL of Luria Bertani (LB) Broth and 5 μL of 10 mg/mL Kanamycin with a sample of host cells taken from representative freezer stocks and incubated overnight shaking at 220 rpm and at a temperature of 37°C (Sambrook and Russell, 2001). To grow up *HWEC106* for MAGE we inoculated a tube of 4 mL LB and 5 μL of 20mg/mL ampicillin then incubated overnight at 30°C, 220 rpm. The same

media conditions were used throughout the evolution rounds and phage fitness assays, with the only varying condition being the host cells used. When propagating λ phage on its respective host, the phage and host cells were inoculated into 50 mL flasks containing 10 mL of modified LBM9 with 12.5 μL of 10 mg/mL kanamycin (20 g tryptone and 10 g yeast extract per liter water, supplemented with a final concentration of 47.7 mM disodium phosphate, 22.0 mM potassium phosphate monobasic, 18.7mM ammonium chloride, 8.6 mM NaCl, 0.2 mM calcium chloride and 10 mM magnesium sulfate) and incubated for 4 hours at a temp of 37°C while shaking at 120 rpm (adapted from, Sambrook and Russell, 2001). Similar media conditions were used when growing up clonal phage populations, except these populations were incubated shaking at 220 rpm in 4 mL of modified LBM9 with 5 μL of 10 mg/mL Kanamycin overnight (~16 hours) at 37°C.

Determining phage stock density:

Spot assays were performed by either spotting 2 μL of a diluted or "full-strength" sample of a phage population on a bacterial lawn of the corresponding host *E. coli* cells suspended in soft agar (LB w/ 0.8% w/v agar supplemented with 2 mM Calcium Chloride, 10 mM Magnesium Sulfide, and 0.1 g/L glucose) on the surface of an LB plate (LB broth with 1.6% w/v agar; Sambrook and Russell, 2001). Spot assays were used to confirm the presence of viable phage particles during the evolution experiment and when determining the density of phage stocks throughout the duration of the study. Infused plates were made by suspending 100 μL of overnight culture of *DH5*α, diluted mixed phage population and X-gal in soft agar and spreading it on an LB plate, these were primarily used to calculate phage density during competition experiments and for clonal isolation. All Plates were incubated overnight (~16hrs) at 37°C (Sambrook and Russell, 2001).

KO host screen to determine effects on λ plaquing efficiency:

Putative *E. coli* members of the *λ- E. coli* interactome were identified from a physical protein-protein interaction screen (Blasche *et al*., 2013) and a functional host dependency screen (Maynard *et al*., 2010). Two additional candidates (*ΔmanY & ΔmanX)* were identified from the literature (Cumby *et al*., 2014; Esquinas-Rynchen and Erni, 2001). Of these candidate genes, 74 have knockout strains in the KEIO collection (Baba *et al*., 2006). Omitting the well-studied lambda receptor (*lamB*) (Esquinas-Rynchen and Erni, 2001; Meyer *et al*., 2012), its regulators (*cyaA, yneJ, malI, and malt*), and two genes already shown to affect infection (*nusB, and dnaJ*) (*Meyer lab unpublished data*), these 67 candidates were screened for their effect on replication of our λ strain, cI26.

Bacterial lawns of each candidate *E. coli* knockout strain and a *WT* control were prepared in soft-agar overlays (Sambrook and Russell, 2001). A serial dilution of an isogenic *cI26* phage stock was prepared and 5 μL of each dilution were applied to every plate in discrete spots, ensuring that single plaques would be visible at some dilution after incubation at 37°c overnight.

The number and appearance of plaques on each knockout strain was compared to their number and appearance on the *WT* strain. The knockouts' effect was classified as follows: 4=completely blocked plaque formation, 3=reduced the number of plaques compared to wild-type, 2&1=produced same number of plaques but with altered appearance (2=substantially smaller than plaques on *WT*, 1=possibly smaller that plaques on *WT*) and 0=indistinguishable in both number and appearance from plaques on *WT* host. All candidates with a score of 4 or 3, and some candidates with a score of 2, were used for further study

Evolution experiment:

In order to study how λ adapts to cope with perturbations within the interactome, we used evolution experiments to provide λ with an environment in which there exists a selective advantage for the use of the specific *KO* host provided. Our evolution rounds began by co-culturing λ populations from an isogenic stock of *cI26* (Meyer *et al*., 2010) with a respective mixture of *WT* and *a* single *KO* host (supplemental table 2). *WT* host was initially provided and λ was slowly weaned from it as they developed adaptations to use the *KO*. λ was co-cultured with its *KO host* for twenty incubation periods of four hours, roughly 200 generations (figure 1).

In addition to the 16 *KOs*, we also studied λ's evolution to *WT* as a control to distinguish responses to missing host proteins from general improvements to suboptimal laboratory conditions. The evolution experiment was broken up into 6 different blocks and for each we ran a separate *WT* control (table 1). λ evolution to each host was studied in 6 replicate lines. In total 132 separate lines of evolution were carried out (supplemental table 2). After each round of evolution, a 1 mL sample was taken from each flask and treated with chloroform to kill all bacterial cells and isolate the representative evolved phage population which were stored at 4°C.

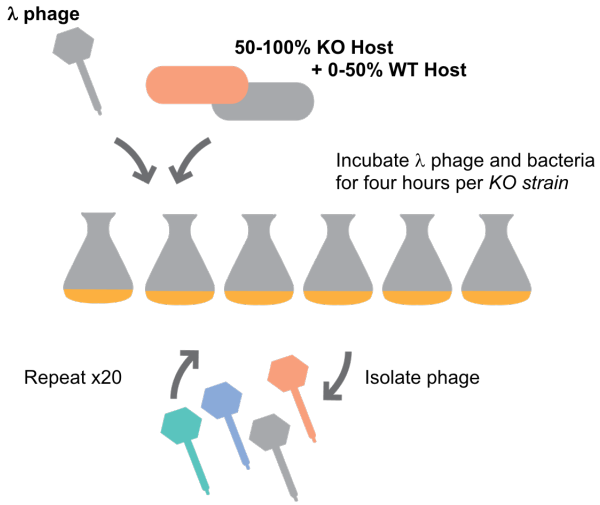

Figure 1: schematic of the evolution experiment.

Table 1: experimental block design for parallel evolution experiment. The sixteen *KO* hosts were divided as shown below because this portion of the experiment was run by six different experimenters.

Block:	1	2	3	4	5	6
E. coli Hosts:	*WT-1*	*WT-2*	*WT-3*	*WT-4*	*WT-5*	*WT-6*
	dnaJ	*clpX*	*nuoG*	*hsds*	*hldD*	*dnaK*
	nusB	*crr*	*ompC*	*manX*	*tpx*	*recA*
	-	*gmhA*	*rfaF*	*manY*	-	*rfaC*

Before proceeding to the next round of evolution, spot assays were done for each population to check for viable phage. If the population formed a full clearing on their respective host, such as the *WT* control, then the next round of evolution was done using 100% of their respective *KO* host. The ratio of *KO* host to *WT* host was adjusted with respects to whether the phage population was able to form a clearing on a lawn of their respective *KO* host after a round of evolution (supplementary table 2).

After round twenty of evolution, phage populations were isolated by chloroform extraction. A dilution series spot assay was done for each population using *WT E. coli* to determine the population's density (*pfu/mL*). Once determining the density of each phage stock, we diluted them to make infused plates with their corresponding bacterial host for clonal isolation. We then picked a plaque from each plate to serve as a clonal representative. All clones were grown on their corresponding *KO* or *WT* host to produce phage stocks. Freezer stocks were made of all clonal populations and the evolved populations from round 5, 10, 15, and 20, and stored at -80°c in 15% v/v glycerol.

Genome Sequencing:

Genomic DNA was isolated from clonal phage lysates using phenol-chloroform extraction. Filtered lysates were freshly prepared from overnight infections on the host each

isolate evolved on, except for *ΔmanY* replicates *a* and *e* which were grown on *WT*. Briefly, to 500 μL of lysate, 6.25 μL of 1 $MgCl_2$, 0.8 units of DNAseI, and 1 μL of 100 mg/mL RNaseA were added to remove unencapsidated nucleic acids. After incubation at room temperature for 30 minutes, 20 μL 0.5M EDTA was added to quench the reaction, and 2.5 μL 10 mg/mL Proteinase K and 25 μL of 10% SDS were added and the mixture was incubated at 55°C for 1 hour with occasional vortexing to break down viral capsid proteins. Genomic DNA was isolated from the mixture by extracting the protein components successively with 500 μL phenol chloroform isoamyl alcohol (24:25:1) and 500 μL chloroform. The aqueous fraction was then ethanol precipitated in sodium acetate and washed, then resuspended in 100 μL H_20.

Genomic DNA was quantified using the Quant-iT dsDNA HS reagent (Thermofisher), and between 60 and 2350 ng of each isolate were submitted to the UC San Diego Institute for Genomic Medicine for multiplex library preparation and single-read 50 bp sequencing using an Illumina HiSeq4000. Evolved phage from the project were sequenced in two batches.

Identification of mutations in evolved phage isolates:

In order to analyze the *Ilumina* sequence data files, we used *BreSeq* under default settings to identify mutations present in the evolved clone with respect to the ancestor cI26's genome (Baym *et al*., 2015). *BRESEQ* was also used to construct *FASTA* sequence files, using cI26 as a reference genome, for the populations with evidence of insertions/recombination events (*i.e. those with high numbers of mutations*) via the built in *gdtools* feature (Baym *et al*., 2015). *CLC Sequence Viewer 8* was used to analyze these files and to align them to *BW25113* genome to determine the site of recombination (QIAGEN Aarhus A/S, 2015). *BLAST* was also used to further determine the origin of these recombination events (NCBI).

Competitive fitness experiments:

We measured evolved fitness gains of each strain on the *KO* it adapted to by running competition experiments against a genetically marked ancestor λ. For each λ isolate we ran three replicate competition experiments. The experiment was run identically for all phage, however the studies had to be broke into a block design. Such that the competitive fitness of the evolved isolates from a particular *KO* were measured in one block or two blocks. To account for *lacZ's possible* marker effect on phage fitness, three separate replicates of *c126* λ phage were competed against *c126lacZ* on the corresponding *KO* host for each block.

We began each assay by inoculating a flask with ~1E5 pfu/mL of the corresponding evolved or ancestral phage being tested and ~1E5 pfu/mL *cI26lacZ* along with ~1E8 cfu/mL of the corresponding bacterial host, the same culturing conditions were used as the parallel evolution experiment. We determined the density for each replicate before the hour incubation period and after using infused plates with *DH5α* and supplementary *X-gal* (Supplemental table 3, Sambrook and Russell, 2001).

Due to the fact that some of the evolved populations outnumbered the marked ancestor by about three-fold after four hours of competition, we had to adjust the timing of a few competitions to two hours (*i.e. ΔrfaF, ΔhldD, Δtpx)* in order to record reliable measurements.

Calculation of λ growth rate and fitness:

To calculate the fitness of our phage we used the difference of the competitors' growth rate from the competition experiments. The growth rate, *r*, of each competing phage was calculated using the initial and final density measurements from infused plates.

$$r = \frac{\ln\left[\left(\frac{p.f.u.}{mL}\right)_{final} \Big/ \left(\frac{p.f.u.}{mL}\right)_{initial}\right]}{time}$$

The difference of two competitor's growth rates is more commonly known as the selection rate, *S (*Travisano and Lenski, 1996*)*.

$$S_{phage\ isolate} = r_{unmarked\ phage} - r_{marked\ phage}$$

Although similar to the ratio of the competitive growth rates (*i.e. relative fitness*) this value provides a more reliable method for quantifying fitness especially in circumstances in which one competitor declines in abundance as seen for some KOs. To account for the marker effect on *cI26lacZ's* growth rate we established a correction in the calculations for the selection rate of our evolved populations. This correction consists of taking the difference of the selection rate of the evolved population and the selection rate of the ancestor on a particular *KO*.

$$S_{evolved\ isolate} - S_{ancestral\ phage}$$

The correction to our fitness calculations allows us to make a direct comparison between evolved phages measured in different blocks.

Host Range Experiment:

To test the host range of each evolved λ isolate we performed a dilution series spot assay on all 16 *KO* hosts as well as on *WT*. The purpose of this assay was to quantify each evolved isolates' ability to infect each host genotype. Using a 96-pinner tool we plated each population's dilution series on all 16 *KO* hosts, and *WT* as a control to determine the phages infectivity on an optimal host. We plated a dilution series of the ancestral strain, *cI26,* on all the *hosts* as reference to identify improvements or losses in the evolved populations. After an overnight incubation at 37°C we measured the plating efficiency (pfu/mL) of each evolved phage isolate and ancestor on

all hosts. The plaquing or plating efficiency of λ represents the relative number of plaques a phage stock is able to produce on a particular host and is calculated by dividing the number of plaques by the amount of sample plated multiplied by the dilution factor (Travisano and Lenski, 1996*)*

To quantify an isolate's change in infectivity on a given *KO*, we took the natural log of the isolate's plating efficiency on a *KO* relative to the natural log of its plating efficiency on *WT*, subtracted by the natural log of the ancestor's plating efficiency on the same *KO* relative to the natural log of its plating efficiency on *WT*.

$$\left[\left(\left(\ln\left(\frac{p.f.u}{ml}\right)_{on\ KO} \Big/ \ln\left(\frac{p.f.u}{ml}\right)_{on\ WT}\right)_{evolved\ isolate}\right) - \left(\left(\ln\left(\frac{p.f.u}{ml}\right)_{on\ KO} \Big/ \ln\left(\frac{p.f.u}{ml}\right)_{on\ WT}\right)_{ancestral\ phage}\right)\right]$$

Genome Engineering:

We engineered six different *cI857* lysogens with specific single point mutations using multiplex automated genome engineering (MAGE) with the same protocol described by *Meyer et al., 2016*. Oligo sequences used for genome engineering and sanger sequencing verification of mutants are in supplemental table 3 and 4.

Competitive Fitness Experiments for Engineered λ Strain:

We ran competitive growth rate experiments, using a similar protocol as above, for each mutant lysogen on both *WT E. coli* and the *KO* host on which the mutation evolved. Few modifications were made with regards to the protocol, but in place of *cI26* and *cI26lacZ* we used *cI857* and *cI857lacZ* (Meyer *et al., 2016)*. This is because *cI857* is the base strain of our lysogens

and both vary from the genetic composition of *cI26*. Fitness was also calculated in the same fashion as described above.

Statistical Analysis:

All statistical tests were run using *PAST 3.16 (2017)* with standard settings and parameters while running the different analysis. Refer to the results for further specifications on what type of statistical test were used for the analysis of our data. Heat maps were made using ClustVis, all pre-data processing and PCA were done under default settings (Metsalu and Vilo, 2015).

Results:

Our preliminary screen of the 67 knockout *E. coli* hosts revealed that only 16 of the *KO* hosts had observable deleterious effects on λ's replication (table 2*)*. We estimated a decline in λ's fitness on each *KO* strain, and confirmed that λ's growth rate on the *KO* strains was less than λ's growth rate compared to the *WT* control (*$p<0.005$, figure 2).

Table 2: candidate KEIO E. coli strains used as hosts for λ during the evolution experiment. Effect on λ plaque morphology was based on a preliminary observational screen and is relative to plaque morphology on WT host. (key: 0=no effect, 1=possible, 2=minimal, 3=moderate, 4=no viable infection detected)

	E. coli Gene	Function	KO effect on lambda plaque production
1	*nusB*	transcription anti terminator	4
2	*dnaJ*	chaperone hsp40	4
3	*tpx*	lipid metabolism	3
4	*crr*	phospho transport system	2
5	*gmhA*	LPS isomerase	3
6	*rfaC*	LPS transferase	3
7	*rfaF*	LPS transferase	3
8	*hldD*	LPS metabolism	4
9	*recA*	DNA repair	2
10	*ompC*	membrane protein	2
11	*clpX*	protease specificity	2
12	*dnaK*	chaperone hsp70	4
13	*nuoG*	NADH-quinone oxidoreductase	2
14	*hsdS*	restriction-modification	2
15	*manX*	mannose PTS permease	1
16	*manY*	mannose PTS permease	3

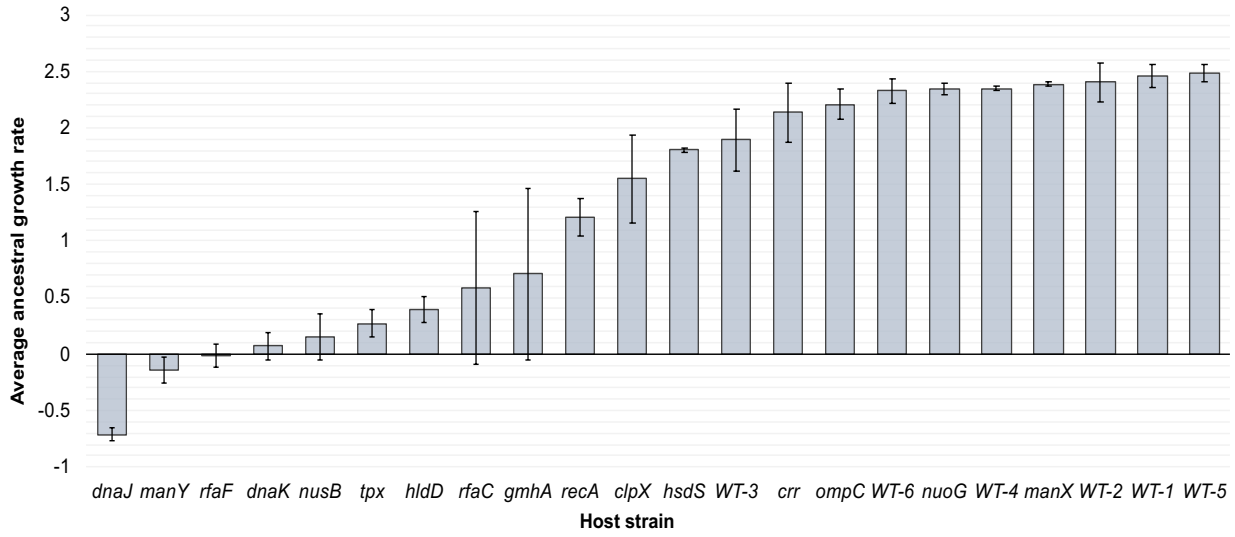

Figure 2: growth rate measurements of the ancestral λ on candidate KEIO KO strains reveal a spanning range of deleterious effects on λ replication. The average ancestral growth rate represents measurements from the three replicates that were run in parallel during the competition experiments, the error bars depict the standard deviation from the replicate measurements.

Almost all λ isolates experienced an increase in fitness on their particular *KO* host, relative to the ancestral λ's fitness on the same *KO* (*paired T-Test, two-tailed, df=21, p<0.0001*, figure 3a). Each *KO* yielded at least one isolate which was able to infect 100% of the *KO*. Interestingly, we observed that the relative fitness varied between lines that were adapted to different host conditions (*one-way ANOVA, F=5.887, p<0.0001)* as well as between the replicates from the same host condition (*one-way ANOSIM, r=0.23, p=0.0001)* suggesting that there is genotypic variation among replicates of the same condition and variation in response between host conditions.

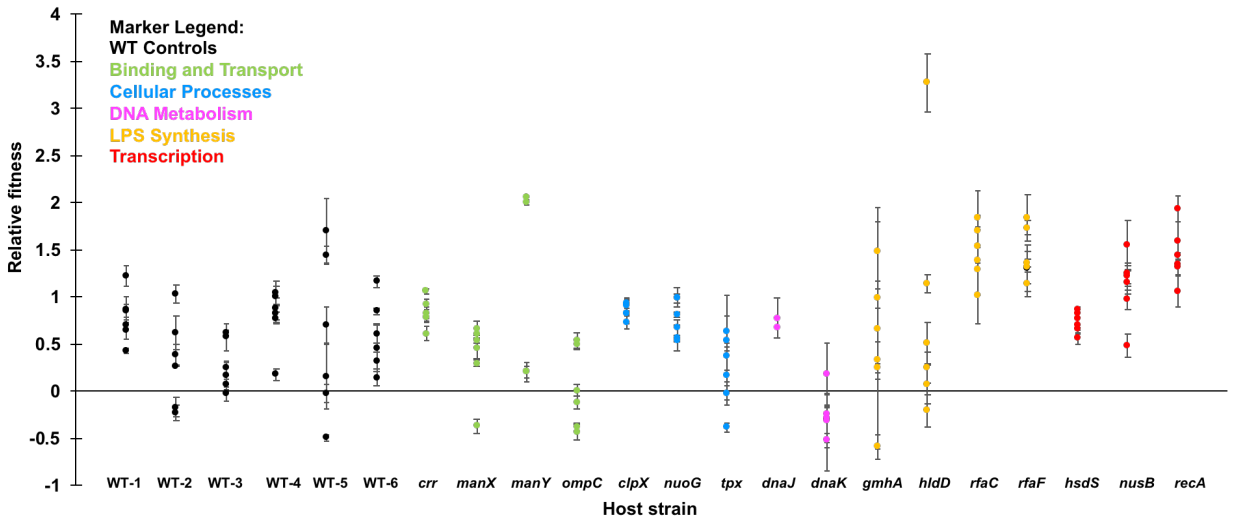

Figure 3a: relative fitness measurements of evolved isolates reveal a common pattern of improvement across all conditions with variation in the degree of improvement. Relative fitness was measured by taking the difference in Malthusian growth rates of the evolved isolate and ancestral isolate on the host condition which the evolved isolate was adapted to during the evolution experiment. The error bars show the standard deviation of three replicate measurements for each data point.

In general, the degree to which λ's growth rate improved was greater in the lines adapted to *KO*'s that initially most reduced λ's ancestral growth rate (figure 3b). For example, we see that the host strains in which λ's ancestral growth rate was approximately between -0.1<x<1.5 had the largest increases in growth rate. While, those adapted to hosts that minimally perturbed λ's ancestral growth rate (i.e. samples between 1.5<x< 2.5) did not experience such a large increase in growth rate. Interestingly, λ was unable to improve its growth rate on some *KO* hosts, seen in the lines adapted to *ΔdnaK* (figure 3a-b).

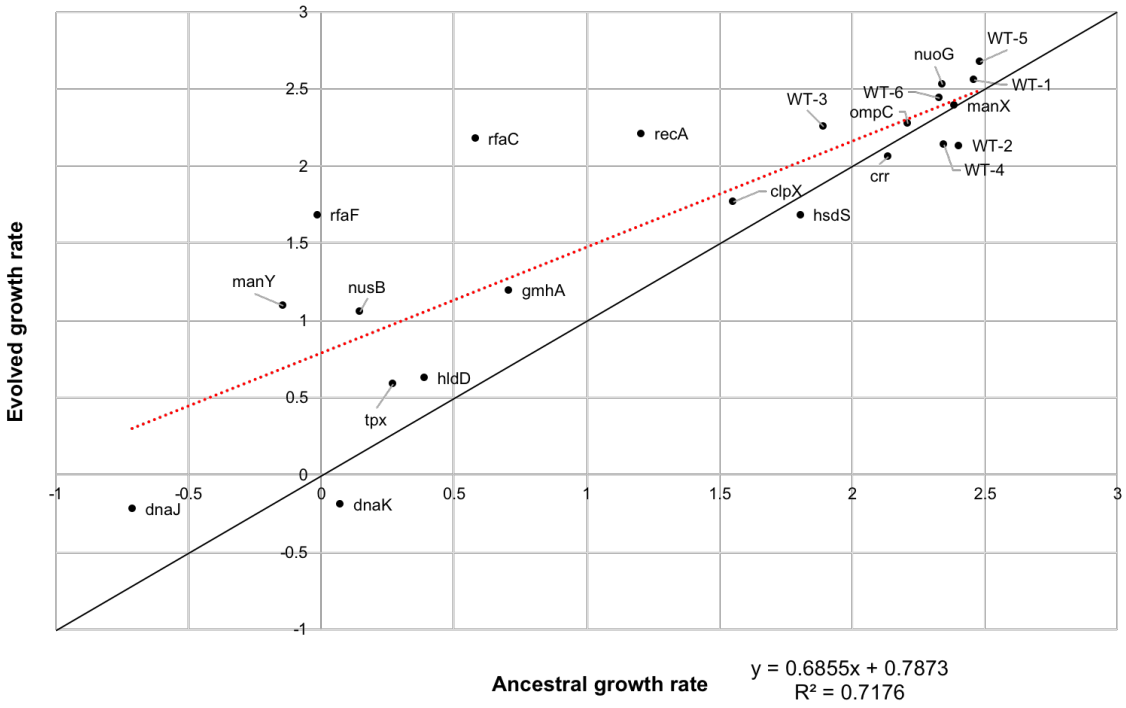

Figure 3b: comparison of ancestral and evolved λ growth rates on 17 host genotypes reveals that λ evolved greater improvements when faced with larger challenges. Each data point represents the average evolved growth rate (y-axis) versus the growth rate of the ancestor (x-axis). The colors of each data point show the average number of SNP's for the evolved population of a particular condition. The red line is a representative trend line which has a slope less than one. Data points above the 1:1 dashed line show improvement in growth rate.

We proposed three hypotheses to explain why λ gained more on poorer hosts. The first hypothesis that could explain this pattern is that hosts that have a large deleterious effect on λ's fitness may apply more selection pressure on λ that drives more rapid molecular evolution. The second is similar however λ responds to the increased pressure by evolving mutations with greater benefit. The third is that each population will have evolved similar mutations, yet they have larger positive effects on fitness when infecting *KO*'s with larger growth rate consequences and smaller when λ's growth penalty is not as steep (diminishing returns).

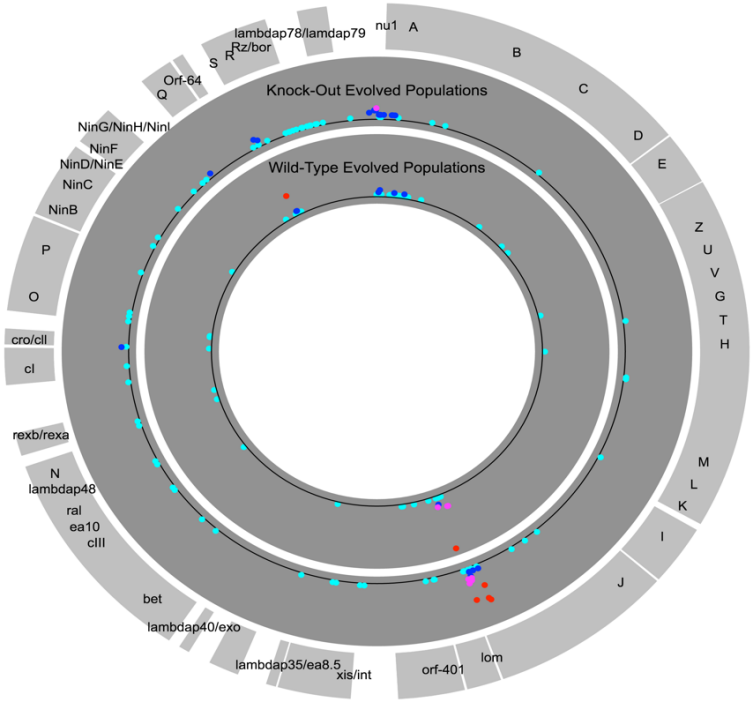

Figure 4a key:
● = 10+
● = 5-9
● = 2-4
● = 1
(no. of SNP's)

Figure 4a: genomic analysis of λ evolution show similar patterns of adaptation between KO and WT evolved populations. The outer light grey ring represents the λ genome and its ORF's, while the inner rings show the distribution of SNP's found in populations either evolved to a *KO* host or *WT* host. The colors of the points representing unique SNP's denotes the number of populations with that SNP.

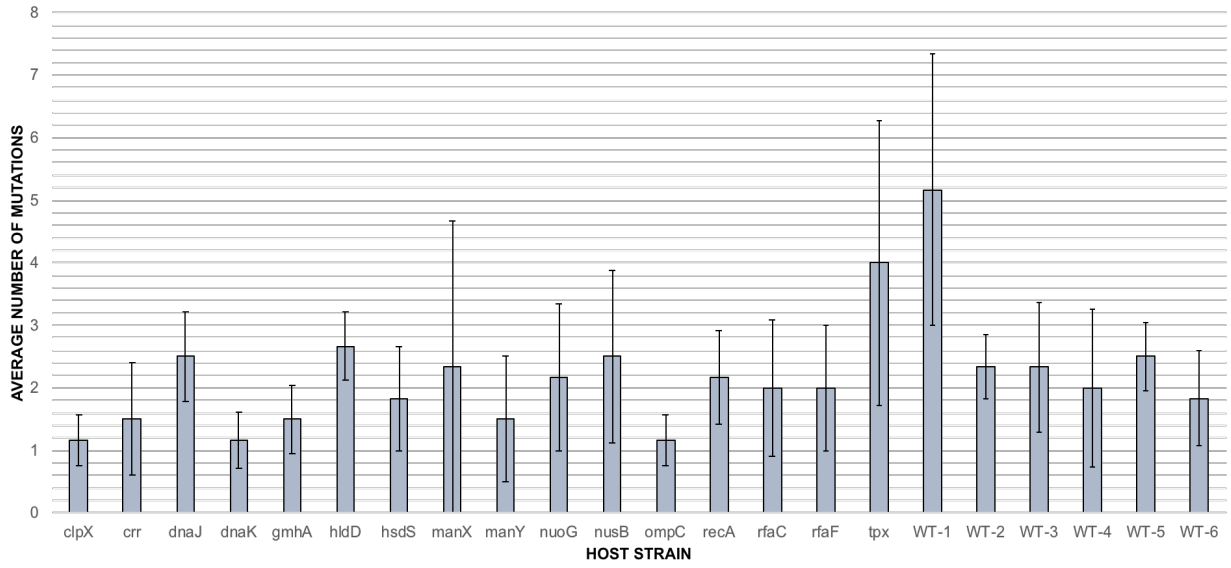

Figure 4b: more rapid molecular evolution is observed in WT evolved isolates than in KO evolved isolates. The number of single point mutations was measured for all isolates and the average was taken of the isolates adapted to the same *KO*, the standard deviation of the averages is shown by the error bars.

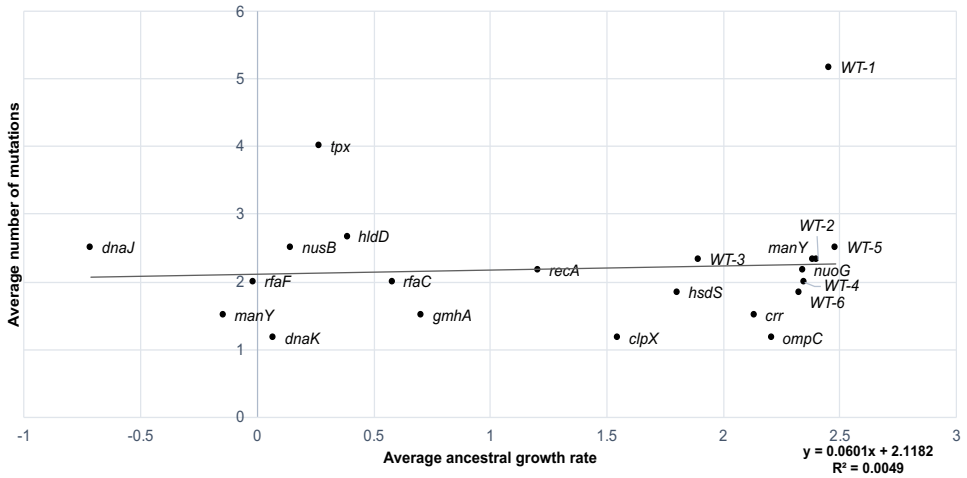

Figure 4c: extreme KOs that attenuate viral growth rate do not show to select for increased rapid molecular evolution. The average ancestral growth rate is the average of three replicate control growth rate measurements from the competition experiments. The average number of mutations for each KO condition was taken from the mutation profiles of each evolved isolate.

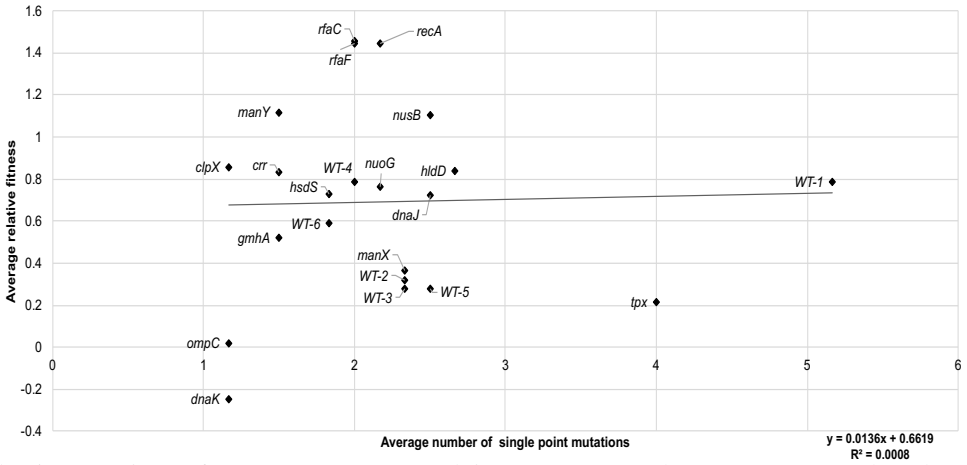

Figure 4d: the number of mutations acquired by any one isolate is not correlated to increased improvement in fitness of an evolved isolate relative to the ancestral strain. The fitness of each evolved isolate was measured on the host they adapted to, relative to *cI26's* fitness on the same host. The average number of mutations for each KO condition was taken from the mutation profiles of each evolved isolate.

To test these hypotheses, we sequenced the full genome of each evolved λ isolate and identified their mutations. We predicted that if hosts with large deleterious effect on λ fitness select for more rapid molecular evolution then isolates adapted to more challenging hosts would have acquired more mutations. The mutation profile of each isolate revealed that on average *KO* evolved lines acquired fewer mutations than the *WT evolved* lines (*corresponding means of 2 and 2.611, comparison of KO and WT evolved mutation profiles, one-way ANOVA, F=6.416, p=0.01*, figure

4b). Additionally, the more extreme KOs did not evolve more mutations ($x^2(21) = 15.645$, $df=21$, $p=0.79$, figure 4c) and there is no significant relationship between the number of single point mutations acquired by an isolate and its improvement in relative fitness (*no association*, $x^2(21)=13.314$, $df=21$, $p=0.89$, figure 4d). Taken together we can reject the first hypothesis.

To test the second hypothesis, we compared the mutation profile of *KO* evolved isolates to the *WT* evolved isolates in order to determine if unique mutations evolved in the different host conditions (figure 4a). The mutations acquired among all *KO* evolved isolates and all *WT* evolved isolates significantly overlapped in a few key genes that control tail synthesis, lysis, and DNA synthesis. Almost all evolved λ isolates appeared to have mutations in the reactive region of gene *J* and in the regulatory region, upstream of gene *S*, suggesting they provide generic adaptation to laboratory conditions (figure 4a). The overlap in mutation profiles between the *WT and KO* evolved lines is inconsistent with the second hypothesis.

To test the third hypothesis, we first identified a common mutation acquired by isolates adapted to different hosts. We found a mutation in gene *J* at genome position 18,824 relative to start, which arose in both *KO* (i.e. *ΔhldD, Δcrr*) and *WT* evolved λ isolates. We chose this mutation because the hosts in which the mutation arose spanned the range of effect sizes on the ancestral λ's growth rate and the mutation was in a region of the genome which was under selection in both *KO* and *WT* adapted strains *(*figure 1 and 4a*)*. All evolved lines (*i.e. WT-2a & b, crr-c, hldD-a & b)* with this mutation had varying returns on growth rate on their particular host (figure 2a). If the benefit of the mutation has diminishing returns then it should have a higher return on growth rate on more challenging *KO* strains. In other words, we would observe that the modified λ would experience larger growth rate pay offs when infecting *ΔhldD* versus when infecting *Δcrr* because the mutation is expected to have more benefit on more extreme *KOs*. Next, we engineered λ to

have this single mutation. A comparison of the modified and unmodified λ's Malthusian growth rate (r) on each of the three strains (*i.e. ΔhldD, Δcrr, WT)*, revealed that this common *J mutation* increased λ's growth rate significantly on both *KO* strains *(*p-value<0.05,* figure 5*)*. In agreement with our third hypothesis, the *J mutation* had a larger relative effect on λ's growth rate when presented with the more challenging host condition, *ΔhldD (one sample t-test, t=30.32, p=0.001) than with Δcrr (one sample t-test, t=22.01, p=0.002)*. The *J mutant* doubled the growth rate on *Δcrr* relative to the unmodified λ, and it caused an astounding growth rate improvement of 12 times better on *ΔhldD (*p<0.05)*. As expected, the modified and unmodified λ's had indistinguishable growth rates when cultured on *WT* host showing no significant improvement when presented with an optimal host (*one sample t-test, t=1.1204, p=0.379)*. The diminishing returns on fitness we observed lends support to the third hypothesis.

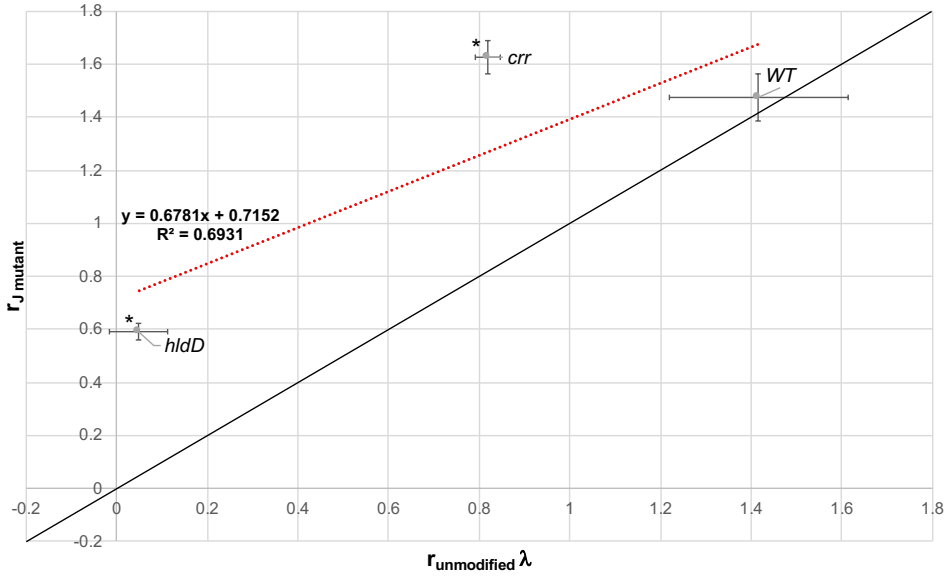

Figure 5: intergenomic diminishing returns epistasis produces large variation in λ fitness improvements. Above is a comparison of Malthusian growth rates of our modified and unmodified phage on *ΔhldD, Δcrr and WT*. The hosts used for this experiment were the conditions in which the mutation arose. The red line is a representative trendline with a slope less than 1.
**P-value <0.05 (Solid black line represents 1:1, null hypothesis)*

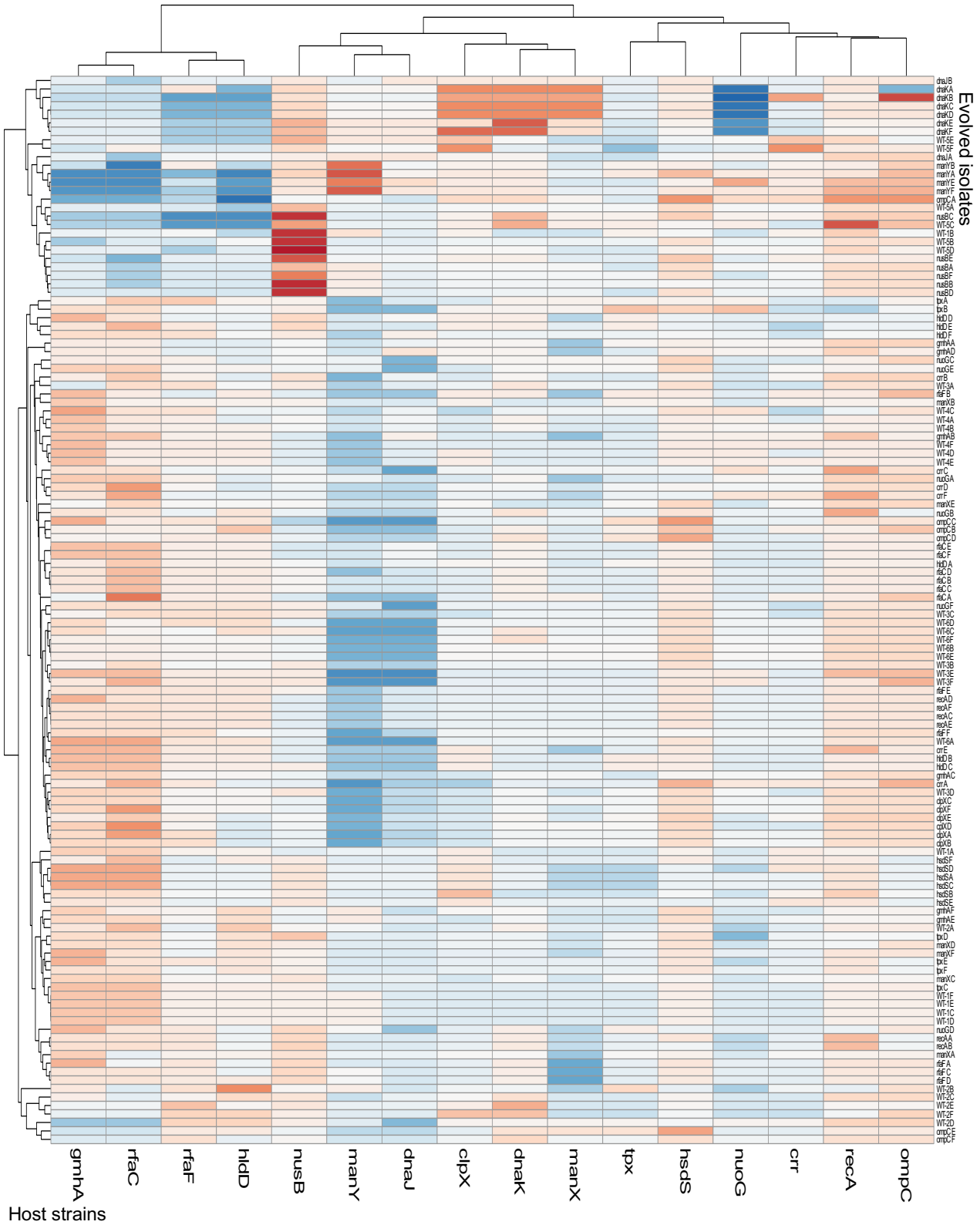

Figure 6: phenotypic analysis of evolved isolates' host range profile reveals two general patterns of adaptation. The color represents how much better any given population is at forming plaques on a particular host compared to the ancestor and relative to its efficiency of plaquing on *WT* host. Red signifies an improvement relative to the ancestor and blue indicates a decline in plaquing efficiency. *(x-axis = KO strain, y-axis=virus isolates)*

Given that most λ isolates evolved similar mutations, regardless of their host condition during the evolution experiment, we hypothesized that adapting to any given *KO* host will have a correlated positive effect on λ's ability to infect other *KO* hosts. We quantified each evolved isolates' ability to infect each host and found that in general most of our evolved λ isolates tended to have improved their ability to infect specifics groups of KOs (figure 6). Correlation clustering of λ host range profiles revealed that in general most isolates improved on *ΔrecA, ΔompC, and ΔhsdS*, while few gained infectivity on *ΔnuoG, ΔtpX, and Δcrr* relative to the ancestor. We also observed two major modules of evolved phage and KOs (figure 6). The largest module is made up of the phage that improved on *KO*'s that have a single deletion in a host gene associated with LPS synthesis (i.e. *ΔhldD, ΔgmhA, ΔrfaF and ΔrfaC*) *but* did poorly on *ΔdnaK, ΔdnaJ, ΔmanY, and ΔnusB* (figure 6). The second module is comprised of isolates that have improved plaquing efficiency on *ΔdnaK, ΔdnaJ, ΔmanY, ΔclpX, ΔmanX and ΔnusB, but* do poorly on *ΔgmhA, ΔrfaC, ΔrfaF, andΔ hldD*. Interestingly we observed that isolates within the second module had stronger one to one interactions with the host they evolved on, we hypothesized that these isolates had evolved unique adaptations in response to their specific host.

We observed that lines evolved to *ΔdnaJ, ΔnusB, and ΔmanY* had unique mutations which were not seen in any other isolate (figure 7). For example, both λ isolates that evolved on *ΔdnaJ,* had a single mutation near the start of gene S. The first being at position 39,212 and the second mutation at position 39,170 both arose in a single *ΔdnaJ* evolved isolate. Moreover, almost all *ΔnusB* evolved isolates had mutations within the *nin* genes. Two of the isolates shared the same mutation at position 37,640. The others had distinct mutations that were within 2,000 base pairs of each other. Finally, two out of the four λ isolates that survived the evolution experiment and

showed improvement on *ΔmanY* had unique mutations in gene H, and both isolate's mutations were within 60 base pairs of each other.

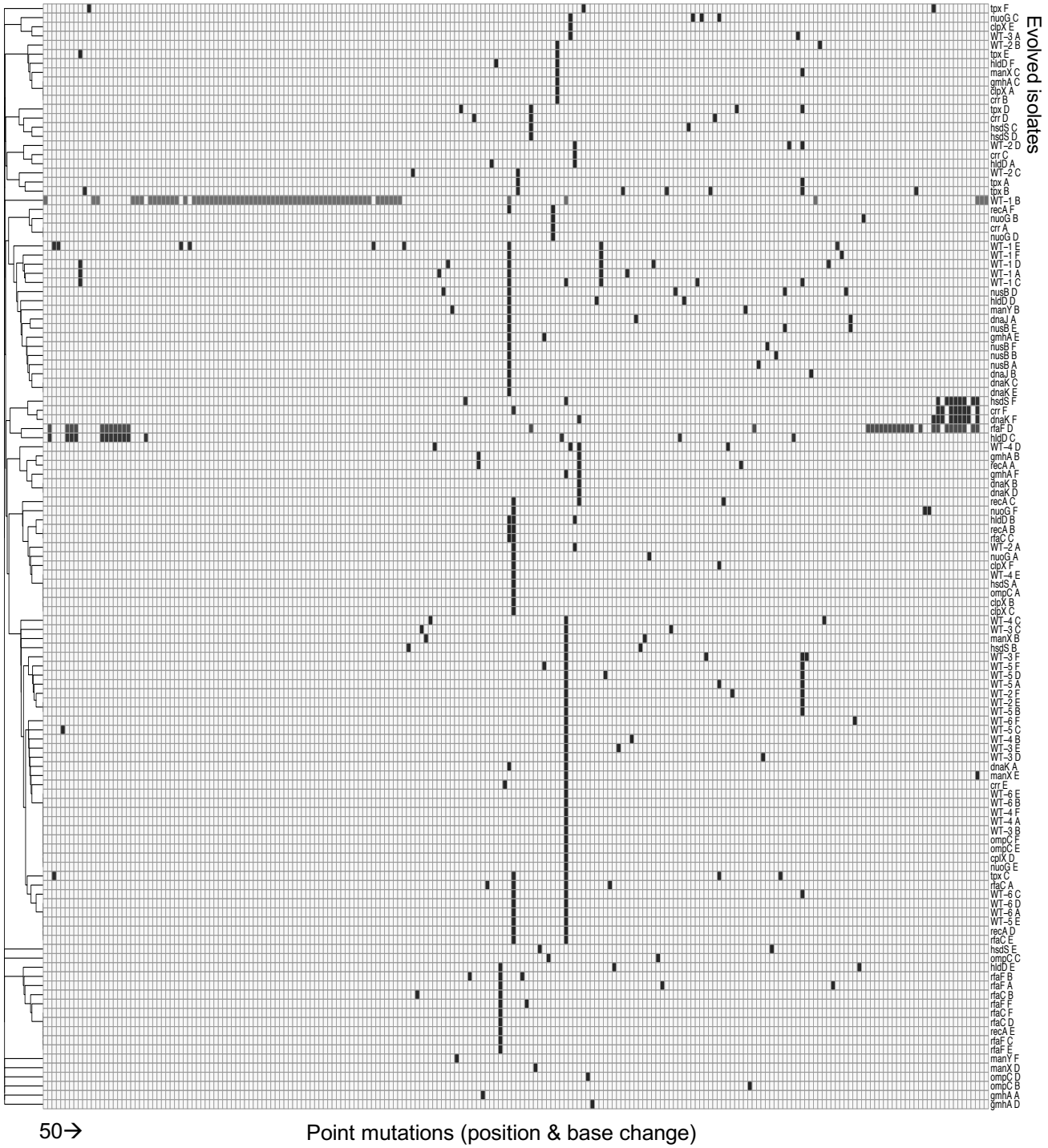

Figure 7: correlation clustering and unit variance scaling of the evolved isolates' mutation profiles reveals unique lineages with specialized adaptations. This heat map shows all phage isolates on the *y-axis, with their corresponding* base pair changes on the *x-axis*. Supplemental table 8 contains data for the mutation position and base change acquired by each isolate (x-axis values).

We proceeded to test whether these unique mutations preferentially improved λ fitness on the *KO* strains they evolved on. Indeed, we observed that the mutations improved fitness on the *KO* that they arose on, but most had varying effects on *WT*. The λ's with a single *H* mutation had a significantly higher fitness relative to the unaltered λ, on *ΔmanY (**p<0.001),* but no significant effect was detected when on *WT* (*one-sample t-test, t=-0.25, p=0.8154, figure 8a*). Similarly, the λ we engineered with a mutation in gene *ninI* at position 37,640 showed to have an improved fitness on *ΔnusB (**p<0.001),* and no significant effect on λ's fitness on *WT* host (*one-sample t-test, t=1.64, p=0.241, figure 8b*). On the other hand, we observed that although the two S mutations seen in both *ΔdnaJ* adapted isolates had improved relative fitness on the *KO*, both had varying effects on λ's fitness on *WT*. The modified λ with the mutation in gene S, at position 39,212 had an improved growth rate on *ΔdnaJ* but had a notable deleterious effect on the modified λ's growth rate when *on WT* compared to the unaltered λ *(*p<0.05*, figure 8c). Next, we observed that the λ engineered with the S intergenic mutation at position 39,170 had an improved fitness on both *WT* and *ΔdnaJ* (*p<0.05,* figure 8d). Thus, we observed unique mutations arising in isolates adapted to some of the most challenging KO strains.

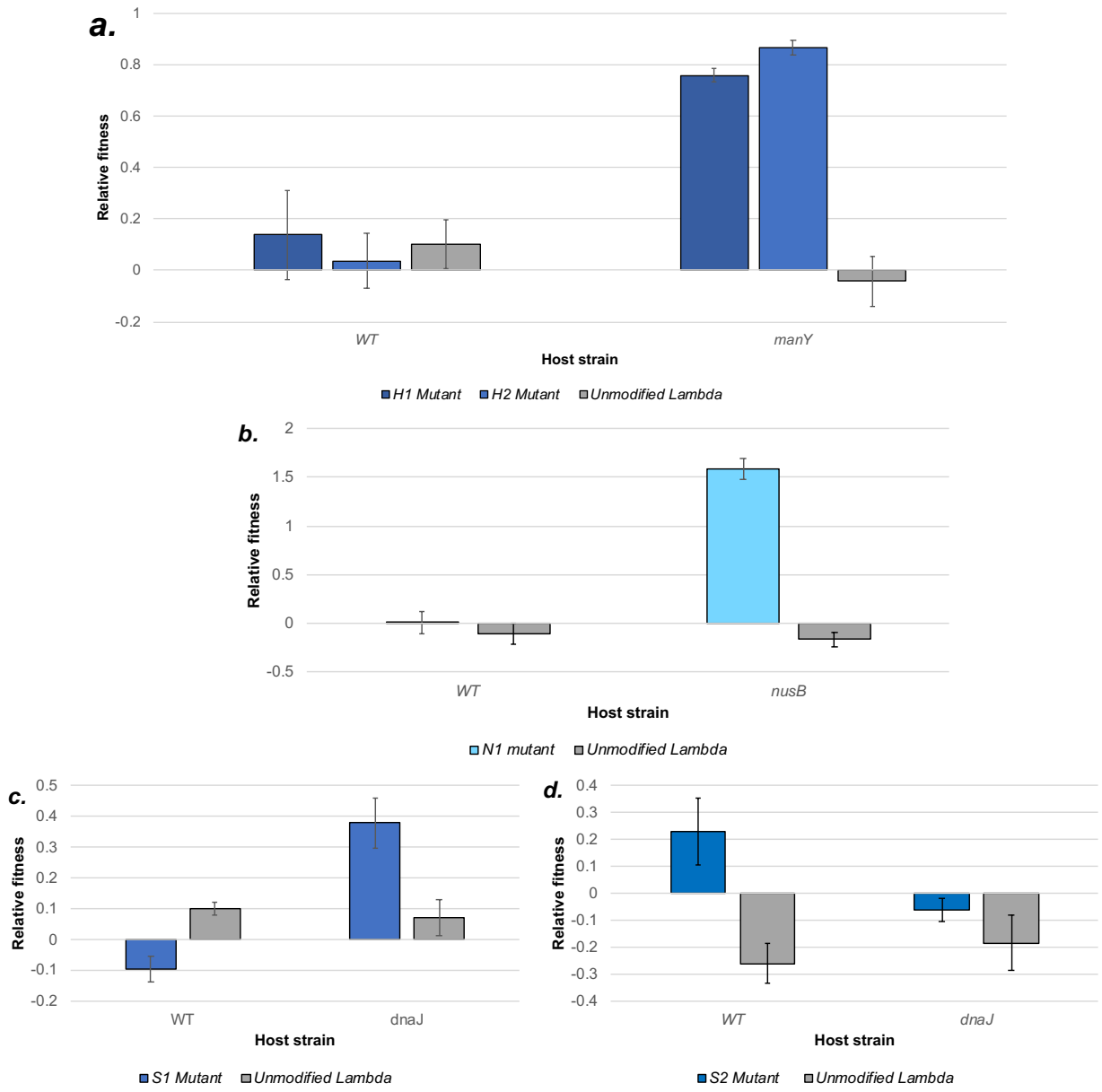

Figure 8: relative fitness measurements of engineered λ strains reveal that some KOs selected for specialized adaptive solutions. a: mutations in gene H give large returns on ΔmanY. H1 mutant has a base change from T→C at position 11378 and H2 mutant has a base modification from G → A at position 11432. These mutations arose in isolates *manY*-B&F, respectively. *b: mutation in nin region compensates for ΔnusB.* N1 mutant was modified to have a base change from G → T at position 37460, this mutation was taken from isolate *nusB*-D&E. The grey bars represent the unmodified cI857's relative fitness to the marked ancestor, *cI857 lacZ* and the error bars represent the standard deviation of the three replicate measurements takes for each condition. *c: relative fitness of S1 mutant on WT, and dnaJ reveals negative fitness returns on less challenging hosts.* S1 mutant has a modification at position 39212 (GAC→GGC) and arose in isolate *dnaJ*-A. *d: relative fitness of S2mutant on WT and ΔdnaJ shows general improvement on both KO and WT hosts.* S2 mutant has a base change from C to A and arose in isolate *dnaJ-B*.

Discussion:

Preliminary KO screen reveals large redundancies within the λ-E. coli Interactome:

Unlike previously documented, our study shows that only 16 of the *KO hosts* appeared to have a significant deleterious effect on λ replication, some having stronger consequences than others. *Only 4 of the 16 KO's*, completely prevented λ infection, suggesting that *dnaJ, dnaK, nusB, and hldD are* host components of the interactome network that are most essential for λ infection. Interestingly, the *KO's* that prevented or significantly impeded λ replication were host components that carried out important functions in λ DNA replication, transcription, LPS synthesis and protein transport (Blasche *et al*., 2013; Casjens and Hendrix, 2015; Maynard *et al*., 2010; NCBI*)*. The fact that we observed only a fraction of *KO hosts* having detrimental effects on λ replication can have two explanations. First, previous high-throughput studies aimed at identifying all the host components of the λ-*E. coli* interactome were prone to false positive results for certain interactions (Balsche *et al*., 2013; Maynard *et al*., 2010). On the other hand, we may have not been able to detect effects on λ because redundancies within the interactome likely buffered the effects of the different host component deletions (Hauser *et al*., 2012).

Intergenomic diminishing returns epistasis drives large variation in fitness improvements:

Nearly all λ trials yielded strains that could replicate on their *KO*, moreover almost all had improved fitness on their host compared to the ancestral λ. Our data suggests λ is able to rapidly evolve to compensate for genetic perturbations in its host interactome (Wiser *et al*., 2013). The *KO host's* initial effect on λ replication affected the extent of its improvement. We found evidence for a 'fitness ceiling', in which there is a limit to how much λ can improve at infecting its host before its reproduction is constrained by universal rate-limiting host processes (Bull *et al*., 2003).

Based on the variation in fitness improvements we suggested three hypothesis that could explain such a pattern. The first being that more challenging *KO's* pose stronger selection for rapid molecular evolution. Previous studies have found that viruses can undergo selection for increased substitution rates is favored in response to a host counter adaptation, so we would assume that *more challenging KOs* would produce this type of environment in which rapid molecular evolution is under positive selection (Paterson *et al*., 2010).

The overlap of mutation profiles contradicts the second hypothesis that more difficult KOs would select for unique mutations with greater fitness effects. Instead most mutations tended to occur in a few key λ genes. We observed mutations in genes *cII, nu1*, *S, and J*. Supporting the idea that these are generic mutations to laboratory conditions that have been observed in previous evolution studies (Meyer *et al*., 2012; Chuo *et al*., 2011; Wang, 2006).

In accordance with our third hypothesis, a mutation was observed to evolve in both *KO* and *WT* evolved lines which provided different returns on fitness depending on the difficulty of the host challenge, this pattern of fitness returns is similarly seen in diminishing returns epistasis. Many studies have found examples of diminishing returns in which mutations have varying returns on fitness depending on the selective pressures such that a beneficial mutation is observed to have higher returns on fitness in harsher environments than in optimal conditions (Chuo *et al*., 2011; Khan *et al*., 2011). Yet no examples exist of intergenomic diminishing returns epistasis as observed here, in which a mutation has different effects on fitness depending on the genome of the host.

Host range profiles of evolved isolates reveal a modular pattern of adaptation:

We determined that most bacteria-phage interactions observed were not completely specialized to one *KO* but rather evolving to one *KO* selected for adaptions which allowed λ to compensate for functionally related *KOs* and/or to *KOs* with similar adaptive solutions. This

created a modular pattern of adaptation in which blocks of phage better infected specific groups of *KOs'* that are missing functionally similar host components of the interactome. A module is a group of phage and bacteria in which the phage preferentially interacts with hosts from within the group more than hosts from another module. For example, we see that evolving to one LPS synthesis *KO* allows λ to improve on other LPS synthesis *KOs'* yet this adaptation has pleiotropic effects resulting in decreased infectivity on DNA metabolism, and intracellular transport gene *KOs'*. Interestingly we observed another module in which a group of phages selectively interacted with a group of KOs' that seem functionally unrelated.

Adaptive solutions to specific KOs:

A few of the *KOs* we studied selected for adaptive solutions which greatly improved λ's fitness on the *KO*, showing evidence of greater specialization suggesting that some interactome perturbation require more specialized mutations.

First, we observed that *ΔdnaJ* selected for isolates with mutations in gene S, which is responsible for controlling host cell lysis time. Previous studies have found that λ's S gene is highly adaptable and is under constant selection to be optimized for λ's host environment. Typically, it is seen that prolonged lysis times are beneficial in an environment in which a relatively large adaptive solution is required to compensate for a change in the host and could potentially improve the odds of an adaptive mutation arising in the population (Goldhill and Turner, 2014; Heineman and Bull, 2007). In contrast, short cell lysis times are selected for in an environment with abundant host cells and is not prevalent in "harsh environments". A prolonged lysis time was perhaps selected for by *ΔdnaJ* since it likely requires a more complex adaptive solution which had not been evolved in the original phage population (Goldhill and Turner, 2014; Heineman and Bull, 2007). Even if a mutation that conferred the ability to grow well on *ΔdnaJ* had

arisen in the population there was no evidence of it having spread through the population. Thus, this mutation's benefit must be due to secondary effects from delaying lysis time which likely improves λ's odds of evolving an adaptive solution to compensate for *ΔdnaJ*.

Next, we observed that the isolates adapted to *ΔmanY* evolved unique mutations in gene H, the tail tape measure gene, that compensated for the absence of *manY*. After λ binds to a cell, λ's tail tape measure protein along with other tail components interact with an inner membrane mannose transporter complex that contains *manY* in order to import its genome into the host cell (Cumby *et al*., 2014). Studies have also shown that the tail tape measure protein of different phage, including λ, can form a channel through the host cell membrane (Hu *et al*., 2013; Roessner and Ihler, 1984). Like us, other studies observed that deleting a component of *E. coli's* mannose transport system is deleterious for a different phage, and mutations in its tail tape measure protein are sufficient for determining a phage's dependency on *manY* (Cumby *et al*., 2014). So, the mutations in λ gene H that we observed likely allowed λ to either form a channel through the membrane of the host or allowed λ to use a mutated mannose transporter protein. Adaptation to *ΔmanY* was evidently very challenging (*i.e*. only two *ΔmanY* lines had significant improvements on the *KO*) and required a specialized adaptive solution, indeed the two isolates which showed to have the most significant improvements on *ΔmanY* had a mutation in the tail tape measure protein gene. This finding is in line with similar studies and proves to be an adaptive solution that is perhaps repeatedly evolved under these similar selective pressures.

Third, we observed that the *ΔnusB* evolved lines with the largest fitness improvements had acquired a mutation in the nin regulatory region, which has a role in the transcriptional regulation of λ genes. The *E. coli* protein *nusB* interacts with other host and λ proteins to form the N-mediated transcription antitermination complex which functions as a termination-resistant RNA polymerase,

and disruptions in host components of this complex results in an inefficient anti-termination transcription complex (Leason and Friedman, 1988). Studies have shown that deletions in the nin region make transcription of λ genes independent of the N transcription anti-terminator system (Cheng *et al*., 1995; Herskowitz, 1973). This suggests that the large fitness reward provided by the *ninI* mutation observed in two of our *ΔnusB* evolved isolates were selected as unique adaptations that exclusively improved λ's growth rate on the focal host most likely by modifying λ's dependency on the N transcription anti-terminator system. Further studies are required to identify the molecular mechanisms behind these adaptive solutions and how they compensate for the absence of these specific host components of the interactome.

Conclusion:

Overall, most interactome 'challenges' could be solved with general adaptations that improve λ growth variably depending on the host strain, yet a few host gene deletions required specialized adaptations. This supports the idea that viruses are good at dealing with suboptimal host conditions by selecting for adaptive solutions that generally improve fitness in turn providing an advantage in dealing with a variety of suboptimal hosts without any cost on *WT* host.

Supplemental materials:

Supplemental table 1: list of 67 Keio KO strains used as hosts for the preliminary screen and their effect on λ replication. (key: 1 = possible effect, 2= minimal effect, 3= moderate effect, 4= total inhibition)

	E. coli gene	Effect on lambda plating efficiancy		*E. coli gene*	Effect on lambda plating efficiancy
1	*pdxH*	0	35	*cchB*	0
2	*hldE*	3	36	*fhuF*	1
3	*tpx*	3	37	*fdoH*	1
4	*manZ*	0	38	*yohN*	1
5	*crr*	2	39	*chaC*	1
6	*ihfA*	2	40	*proQ*	0
7	*ihfB*	2	41	*yeiW*	0
8	*gmhA*	3	42	*yfcQ*	0
9	*rfaF*	3	43	*yohH*	1
10	*rfaC*	3	44	*yehD*	0
11	*hldD*	4	45	*yjdI*	0
12	*spr*	0	46	*yqhC*	1
13	*RecA*	2	47	*rmf*	0
14	*rpoD*	0	48	*PriC*	1
15	*hslV*	2	49	*cobB*	1
16	*hslU*	2	50	*soxS*	0
17	*clpA*	2	51	*ycbG*	0
18	*clpP*	2	52	*hcr*	0
19	*HflD*	0	53	*nuoG*	2
20	*lon*	0	54	*yebR*	0
21	*ompC*	2	55	*envR*	0
22	*fis*	0	56	*minC*	0
23	*sbcC*	0	57	*rpoS*	0
24	*recB*	0	58	*PpyrF*	2
25	*hsdM*	0	59	*yhdW*	1
26	*hsdS*	2	60	*Slp*	0
27	*clpX*	2	61	*hycG*	0
28	*clpP*	2	62	*sdiA*	1
29	*dnaK*	4	63	*paaC*	1
30	*dcrB*	0	64	*caiF*	1
31	*nohA*	0	65	*ybcW*	0
32	*nohB*	1	66	*manX*	1
33	*ydgH*	1	67	*manY*	3
34	*fixB*	1			

Supplemental table 2: host ratio and spot assay data for parallel evolution experiments. (Key: NC= no clearing, SP= single plaques, FC= full clearing)

	round 1		round 2		round 3		round 4		round 5	
phage strain	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay
clpX A	90:10	SP	90:10	FC	90:10	SP	90:10	NC	90:10	SP
clpX B	90:10	SP	90:10	FC	90:10	SP	90:10	NC	90:10	SP
clpX C	90:10	SP	90:10	FC	90:10	SP	90:10	NC	90:10	SP
cplX D	90:10	SP	90:10	FC	90:10	SP	90:10	NC	90:10	SP
clpX E	90:10	SP	90:10	FC	90:10	SP	90:10	NC	90:10	SP
clpX F	90:10	FC	90:10	FC	90:10	SP	90:10	NC	90:10	SP
crr A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
gmhA A	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
gmhA B	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
gmhA C	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
gmhA D	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
gmhA E	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
gmhA F	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK A	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK B	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK C	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK D	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK E	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK F	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
recA A	100:0	NC	100:0	SP	100:0	FC	100:0	FC	100:0	SP
recA B	100:0	NC	100:0	SP	100:0	FC	100:0	FC	100:0	SP
recA C	100:0	NC	100:0	SP	100:0	FC	100:0	FC	100:0	SP
recA D	100:0	NC	100:0	SP	100:0	FC	100:0	FC	100:0	SP
recA E	100:0	NC	100:0	SP	100:0	FC	100:0	FC	100:0	SP
recA F	100:0	NC	100:0	SP	100:0	FC	100:0	FC	100:0	SP
rfaC A	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
rfaC B	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
rfaC C	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
rfaC D	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
rfaC E	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
rfaC F	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
nuoG A	100:0	SP	100:0	SP	100:0	FC	100:0	FC	100:0	FC
nuoG B	100:0	SP	100:0	SP	100:0	FC	100:0	FC	100:0	FC
nuoG C	100:0	SP	100:0	SP	100:0	FC	100:0	FC	100:0	FC
nuoG D	100:0	SP	100:0	SP	100:0	FC	100:0	FC	100:0	FC
nuoG E	100:0	SP	100:0	SP	100:0	FC	100:0	FC	100:0	FC
nuoG F	100:0	SP	100:0	SP	100:0	FC	100:0	FC	100:0	FC
ompC A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF A	90:10	PC	90:10	PC	90:10	PC	90:10	FC	100:0	FC
rfaF B	90:10	PC	90:10	PC	90:10	PC	90:10	FC	100:0	FC
rfaF C	90:10	PC	90:10	PC	90:10	PC	90:10	FC	100:0	FC
rfaF D	90:10	PC	90:10	PC	90:10	PC	90:10	FC	100:0	FC
rfaF E	90:10	PC	90:10	PC	90:10	PC	90:10	FC	100:0	FC
rfaF F	90:10	PC	90:10	PC	90:10	PC	90:10	FC	100:0	FC
hldD A	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
hldD B	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
hldD C	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
hldD D	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
hldD E	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
hldD F	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
tpx A	90:10	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx B	90:10	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx C	90:10	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx D	90:10	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx E	90:10	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx F	90:10	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS A	100:0	PC	100:0	PC	100:0	FC	100:0	FC	100:0	FC
hsdS B	100:0	PC	100:0	PC	100:0	FC	100:0	FC	100:0	FC
hsdS C	100:0	PC	100:0	PC	100:0	FC	100:0	FC	100:0	FC
hsdS D	100:0	PC	100:0	PC	100:0	FC	100:0	FC	100:0	FC
hsdS E	100:0	PC	100:0	PC	100:0	FC	100:0	FC	100:0	FC
hsdS F	100:0	PC	100:0	PC	100:0	FC	100:0	FC	100:0	FC
manX A	100:0	PC	100:0	PC	100:0	FC	100:0	FC	100:0	FC
manX B	100:0	PC	100:0	PC	100:0	FC	100:0	FC	100:0	FC
manX C	100:0	PC	100:0	PC	100:0	FC	100:0	FC	100:0	FC
manX D	100:0	PC	100:0	PC	100:0	FC	100:0	FC	100:0	FC
manX E	100:0	PC	100:0	PC	100:0	FC	100:0	FC	100:0	FC
manX F	100:0	PC	100:0	PC	100:0	FC	100:0	FC	100:0	FC
manY A	50:50	SP	50:50	SP	50:50	SP	50:50	SP	50:50	NC
manY B	50:50	SP	50:50	SP	50:50	SP	50:50	SP	50:50	NC
manY C	50:50	SP	50:50	SP	50:50	SP	50:50	SP	50:50	NC
manY D	50:50	SP	50:50	SP	50:50	SP	50:50	SP	50:50	NC
manY E	50:50	SP	50:50	SP	50:50	SP	50:50	SP	50:50	NC
manY F	50:50	SP	50:50	SP	50:50	SP	50:50	SP	50:50	NC

Supplemental table 2 continued: host ratio and spot assay data for parallel evolution experiments. (Key: NC= no clearing, SP= single plaques, FC= full clearing)

	round 6		round 7		round 8		round 9		round 10	
phage strain	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay
clpX A	90:10	FC	90:10	FC	90:10	FC	90:10	FC	90:10	FC
clpX B	90:10	FC	90:10	FC	90:10	FC	90:10	FC	90:10	FC
clpX C	90:10	FC	90:10	FC	90:10	FC	90:10	FC	90:10	FC
cplX D	90:10	FC	90:10	FC	90:10	FC	90:10	FC	90:10	FC
clpX E	90:10	FC	90:10	FC	90:10	FC	90:10	FC	90:10	FC
clpX F	90:10	FC	90:10	FC	90:10	FC	90:10	FC	90:10	FC
crr A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
gmhA A	90:10	PC	90:10	PC	90:10	PC	90:10	NC	90:10	NC
gmhA B	90:10	PC	90:10	PC	90:10	PC	90:10	NC	90:10	NC
gmhA C	90:10	PC	90:10	PC	90:10	PC	90:10	NC	90:10	NC
gmhA D	90:10	PC	90:10	PC	90:10	PC	90:10	NC	90:10	NC
gmhA E	90:10	PC	90:10	PC	90:10	PC	90:10	NC	90:10	NC
gmhA F	90:10	PC	90:10	PC	90:10	PC	90:10	NC	90:10	NC
dnaK A	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK B	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK C	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK D	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK E	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK F	90:10	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
recA A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaC A	90:10	NC	90:10	PC	100:0	PC	100:0	FC	100:0	FC
rfaC B	90:10	NC	90:10	PC	100:0	PC	100:0	FC	100:0	FC
rfaC C	90:10	NC	90:10	PC	100:0	PC	100:0	FC	100:0	FC
rfaC D	90:10	NC	90:10	PC	100:0	PC	100:0	FC	100:0	FC
rfaC E	90:10	NC	90:10	PC	100:0	PC	100:0	FC	100:0	FC
rfaC F	90:10	NC	90:10	PC	100:0	PC	100:0	FC	100:0	FC
nuoG A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hldD A	90:10	PC	90:10	PC	90:10	PC	90:10	PC	90:10	FC
hldD B	90:10	PC	90:10	PC	90:10	PC	90:10	PC	90:10	FC
hldD C	90:10	PC	90:10	PC	90:10	PC	90:10	PC	90:10	FC
hldD D	90:10	PC	90:10	PC	90:10	PC	90:10	PC	90:10	FC
hldD E	90:10	PC	90:10	FC	90:10	FC	90:10	FC	90:10	FC
hldD F	90:10	PC	90:10	PC	90:10	PC	90:10	PC	90:10	FC
tpx A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manY A	50:50	NC	50:50	NC	50:50	NC	50:50	NC	50:50	NC
manY B	50:50	NC	50:50	NC	50:50	NC	50:50	SP	50:50	SP
manY C	50:50	SP	50:50	NC	50:50	NC	50:50	NC	50:50	NC
manY D	50:50	NC	50:50	NC	50:50	NC	50:50	NC	50:50	NC
manY E	50:50	NC	50:50	NC	50:50	NC	50:50	NC	50:50	NC
manY F	50:50	NC	50:50	NC	50:50	NC	50:50	SP	50:50	SP

Supplemental table 2 continued: host ratio and spot assay data for parallel evolution experiments. (Key: NC= no clearing, SP= single plaques, FC= full clearing)

	round 11		round 12		round 13		round 14		round 15	
phage strain	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay
clpX A	90:10	FC	90:10	FC	90:10	FC	90:10	FC	90:10	FC
clpX B	90:10	FC	90:10	FC	90:10	FC	90:10	FC	90:10	FC
clpX C	90:10	FC	90:10	FC	90:10	FC	90:10	FC	90:10	FC
cplX D	90:10	FC	90:10	FC	90:10	FC	90:10	FC	90:10	FC
clpX E	90:10	FC	90:10	FC	90:10	FC	90:10	FC	90:10	FC
clpX F	90:10	FC	90:10	FC	90:10	FC	90:10	FC	90:10	FC
crr A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
gmhA A	90:10	NC	90:10	PC	90:10	PC	90:10	FC	90:10	FC
gmhA B	90:10	NC	90:10	PC	90:10	PC	90:10	FC	90:10	FC
gmhA C	90:10	NC	90:10	PC	90:10	PC	90:10	FC	90:10	FC
gmhA D	90:10	NC	90:10	PC	90:10	PC	90:10	FC	90:10	FC
gmhA E	90:10	NC	90:10	PC	90:10	PC	90:10	FC	90:10	FC
gmhA F	90:10	NC	90:10	PC	90:10	PC	90:10	FC	90:10	FC
dnaK A	90:10	NC	100:0	NC	100:0	NC	100:0	NC	100:0	NC
dnaK B	90:10	NC	100:0	NC	100:0	NC	100:0	NC	100:0	NC
dnaK C	90:10	NC	100:0	NC	100:0	NC	100:0	NC	100:0	NC
dnaK D	90:10	NC	100:0	NC	100:0	NC	100:0	NC	100:0	NC
dnaK E	90:10	NC	100:0	NC	100:0	NC	100:0	NC	100:0	NC
dnaK F	90:10	NC	100:0	NC	100:0	NC	100:0	NC	100:0	NC
recA A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaC A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaC B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaC C	100:0	PC	100:0	NC	100:0	NC	100:0	NC	100:0	NC
rfaC D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaC E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaC F	100:0	PC	100:0	SP	100:0	SP	100:0	FC	100:0	FC
nuoG A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hldD A	90:10	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hldD B	90:10	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hldD C	90:10	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hldD D	90:10	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hldD E	90:10	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hldD F	90:10	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manY A	50:50	SP	50:50	SP	50:50	SP	50:50	SP	50:50	NC
manY B	50:50	FC	50:50	SP	100:0	SP	100:0	FC	50:50	FC
manY C	50:50	NC	50:50	NC						
manY D	50:50	NC								
manY E	50:50	SP	50:50	SP	50:50	SP	50:50	SP	50:50	NC
manY F	50:50	SP	50:50	FC	50:50	SP	50:50	FC	50:50	FC

Supplemental table 2 continued: host ratio and spot assay data for parallel evolution experiments. (Key: NC= no clearing, SP= single plaques, FC= full clearing)

	round 16		round 17		round 18		round 19		round 20	
phage strain	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay
clpX A	90:10	FC	90:10	FC	100:0	FC	100:0	FC	100:0	FC
clpX B	90:10	FC	90:10	FC	100:0	FC	100:0	FC	100:0	FC
clpX C	90:10	FC	90:10	FC	100:0	FC	100:0	FC	100:0	FC
cplX D	90:10	FC	90:10	FC	100:0	FC	100:0	FC	100:0	FC
clpX E	90:10	FC	90:10	FC	100:0	FC	100:0	FC	100:0	FC
clpX F	90:10	FC	90:10	FC	100:0	FC	100:0	FC	100:0	FC
crr A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
crr F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
gmhA A	90:10	FC	90:10	FC	100:0	FC	100:0	FC	100:0	FC
gmhA B	90:10	FC	90:10	FC	100:0	FC	100:0	FC	100:0	FC
gmhA C	90:10	FC	90:10	FC	100:0	FC	100:0	FC	100:0	FC
gmhA D	90:10	FC	90:10	FC	100:0	FC	100:0	FC	100:0	FC
gmhA E	90:10	FC	90:10	FC	100:0	FC	100:0	FC	100:0	FC
gmhA F	90:10	FC	90:10	FC	100:0	FC	100:0	FC	100:0	FC
dnaK A	100:0	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK B	100:0	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK C	100:0	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK D	100:0	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK E	100:0	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
dnaK F	100:0	NC	90:10	NC	90:10	NC	90:10	NC	90:10	NC
recA A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
recA F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaC A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaC B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaC C	100:0	NC	90:10	NC	90:10	FC	90:10	FC	90:10	FC
rfaC D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaC E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaC F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
nuoG F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
ompC F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
rfaF F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hldD A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hldD B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hldD C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hldD D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hldD E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hldD F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
tpx F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
hsdS F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX A	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX B	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX C	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX D	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX E	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manX F	100:0	FC	100:0	FC	100:0	FC	100:0	FC	100:0	FC
manY A	50:50	NC	50:50	NC	50:50	NC	50:50	NC	50:50	NC
manY B	50:50	FC	90:10	FC	90:10	FC	90:10	FC	100:0	FC
manY C										
manY D										
manY E	50:50	NC	50:50	NC	50:50	NC	50:50	NC	50:50	NC
manY F	50:50	FC	90:10	FC	90:10	FC	90:10	FC	100:0	FC

Supplemental table 2 continued: host ratio and spot assay data for parallel evolution experiments. (Key: NC= no clearing, SP= single plaques, FC= full clearing)

	round 1		round 2		round 3		round 4		round 5	
phage strain	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay
WT-1 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC

Supplemental table 2 continued: host ratio and spot assay data for parallel evolution experiments. (Key: NC= no clearing, SP= single plaques, FC= full clearing)

	round 6		round 7		round 8		round 9		round 10	
phage strain	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay
WT-1 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC

Supplemental table 2 continued: host ratio and spot assay data for parallel evolution experiments. (Key: NC= no clearing, SP= single plaques, FC= full clearing)

	round 11		round 12		round 13		round 14		round 15	
phage strain	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay
WT-1 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC

Supplemental table 2 continued: host ratio and spot assay data for parallel evolution experiments. (Key: NC= no clearing, SP= single plaques, FC= full clearing)

	round 16		round 17		round 18		round 19		round 20	
phage strain	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay	KO:WT Host	Spot Assay
WT-1 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-1 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-2 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-3 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-4 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-5 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 A	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 B	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 C	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 D	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 E	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC
WT-6 F	0:100	FC	0:100	FC	0:100	FC	0:100	FC	0:100	FC

Supplemental table 3: initial and final phage densities for competitive growth assay experiments (pfu/mL).

Sample	Initial evolved isolate concentration	Final evolved isolate concentration	Initial cI26lacZ concentration	Final cI26lacZ Concentration
crr A1	4.64E+06	5.54E+09	4.14E+06	8.00E+07
crr A2	5.40E+06	6.16E+09	3.48E+06	1.10E+08
crr A3	4.96E+06	6.54E+09	3.58E+06	8.00E+07
crr B1	2.82E+06	6.74E+09	3.46E+06	1.00E+08
crr B2	2.64E+06	9.36E+09	3.36E+06	1.30E+08
crr B3	2.66E+06	7.44E+09	3.26E+06	1.70E+08
crr C1	1.66E+06	8.50E+09	2.56E+06	4.60E+08
crr C2	2.02E+06	7.58E+09	3.18E+06	8.20E+08
crr C3	1.40E+06	1.01E+10	2.84E+06	8.60E+08
Control A	1.76E+06	2.58E+09	4.12E+06	3.28E+09
Control B	1.50E+06	3.50E+09	3.10E+06	3.32E+09
Control C	1.26E+06	3.06E+09	2.54E+06	3.92E+09
crr D1	3.94E+06	1.50E+10	5.10E+06	2.00E+08
crr D2	2.66E+06	1.50E+10	4.34E+06	4.40E+08
crr D3	2.78E+06	1.71E+10	4.30E+06	3.70E+08
crr E1	1.56E+06	1.14E+10	5.36E+06	2.10E+08
crr E2	9.60E+05	1.06E+10	5.54E+06	2.60E+08
crr E3	1.16E+06	1.19E+10	5.50E+06	2.30E+08
crr F1	3.16E+06	1.51E+10	4.72E+06	2.70E+08
crr F2	4.30E+06	1.36E+10	4.40E+06	2.40E+08
crr F3	3.84E+06	1.27E+10	4.68E+06	2.00E+08
Control A	1.70E+06	3.00E+10	3.32E+06	1.40E+10
Control B	1.92E+06	1.70E+10	4.62E+06	1.90E+10
Control C	2.14E+06	2.90E+10	5.50E+06	2.10E+10
clpx A1	3.72E+07	1.05E+10	6.48E+07	6.60E+08
clpx A2	3.36E+07	1.25E+10	6.32E+07	5.60E+08
clpx A3	2.80E+07	1.03E+10	7.48E+07	5.40E+08
clpx B1	4.34E+07	8.34E+09	9.76E+07	5.40E+08
clpx B2	4.10E+07	8.26E+09	9.18E+07	4.80E+08
clpx B3	3.90E+07	1.22E+10	9.40E+07	5.60E+08
clpx C1	3.32E+07	8.44E+09	1.00E+08	1.04E+09
clpx C2	2.64E+07	6.72E+09	8.00E+07	1.60E+09
clpx C3	3.00E+07	7.24E+09	8.96E+07	9.20E+08
Control A	3.78E+07	4.38E+09	8.78E+07	9.68E+09
Control B	3.96E+07	4.76E+09	8.98E+07	1.12E+10
Control C	3.78E+07	4.56E+09	8.74E+07	9.48E+09
clpx D1	1.22E+06	6.57E+09	5.32E+06	2.30E+08
clpx D2	1.28E+06	5.71E+09	4.46E+06	3.10E+08
clpx D3	1.36E+06	4.44E+09	5.08E+06	3.70E+08
clpx E1	8.60E+05	6.93E+09	6.14E+06	5.90E+08
clpx E2	8.40E+05	7.30E+09	5.66E+06	7.20E+08
clpx E3	8.60E+05	7.21E+09	5.64E+06	7.80E+08
clpx F1	2.48E+06	9.10E+09	4.10E+06	1.90E+08
clpx F2	2.10E+06	8.36E+09	5.96E+06	1.80E+08
clpx F3	2.26E+06	8.13E+09	5.38E+06	1.60E+08
Control A	1.96E+06	4.20E+09	5.02E+06	3.96E+09
Control B	2.20E+06	3.92E+09	5.02E+06	3.44E+09
Control C	2.06E+06	4.52E+09	4.56E+06	4.06E+09

Supplemental table 3 continued: initial and final phage densities for competitive growth assay experiments (pfu/mL).

Sample	Initial evolved isolate concentration	Final evolved isolate concentration	Initial cI26lacZ concentration	Final cI26lacZ Concentration
gmhA A1	6.60E+05	2.07E+08	2.81E+06	6.00E+07
gmhA A2	6.20E+05	1.78E+08	3.38E+06	4.40E+07
gmhA A3	7.00E+05	2.28E+07	3.06E+06	6.90E+06
gmhA B1	5.50E+05	3.58E+09	2.82E+06	2.00E+07
gmhA B2	4.50E+05	3.08E+09	2.81E+06	2.00E+07
gmhA B3	5.60E+05	4.98E+09	3.14E+06	2.00E+06
gmhA C1	1.16E+06	1.97E+09	3.05E+06	1.00E+07
gmhA C2	1.40E+06	8.50E+08	2.98E+06	1.00E+07
gmhA C3	1.21E+06	1.63E+09	2.55E+06	1.00E+07
Control A	1.10E+06	1.53E+07	2.52E+06	6.00E+06
Control B	1.19E+06	1.03E+07	2.97E+06	4.70E+06
Control C	9.30E+05	1.02E+07	3.08E+06	4.50E+06
gmhA D1	4.90E+05	3.40E+07	2.35E+06	1.00E+06
gmhA D2	7.20E+05	1.70E+08	2.01E+06	2.00E+07
gmhA D3	4.70E+05	1.50E+08	1.75E+06	1.00E+07
gmhA E1	1.27E+06	3.37E+09	2.10E+06	0.00E+00
gmhA E2	1.31E+06	4.39E+09	2.03E+06	3.16E+04
gmhA E3	1.13E+06	3.40E+08	1.96E+06	1.00E+07
gmhA F1	7.00E+05	7.69E+03	1.78E+06	6.32E+03
gmhA F2	6.40E+05	5.75E+03	1.57E+06	1.58E+04
gmhA F3	5.70E+05	6.45E+03	1.79E+06	1.58E+04
Control A	5.70E+05	2.20E+07	1.71E+06	4.30E+06
Control B	7.40E+05	2.04E+07	1.67E+06	2.70E+06
Control C	6.90E+05	0.00E+00	2.31E+06	
manX A1	9.80E+05	8.96E+09	3.90E+05	8.00E+07
manX A2	9.60E+05	1.15E+10	4.00E+05	5.00E+07
manX A3	8.90E+05	9.40E+09	2.20E+05	9.00E+07
manX B1	1.50E+05	8.12E+09	2.20E+05	7.80E+08
manX B2	1.30E+05	6.50E+09	2.40E+05	1.03E+09
manX B3	1.20E+05	8.18E+09	2.10E+05	9.40E+08
manX C1	7.00E+04	5.60E+08	2.20E+05	1.25E+09
Manx C2	1.00E+05	5.50E+08	1.40E+05	1.20E+09
manX C3	9.00E+04	4.90E+08	1.40E+05	7.70E+08
manX D1	9.10E+05	1.05E+10	2.60E+05	1.30E+08
manX D2	8.20E+05	8.82E+09	2.20E+05	5.00E+07
manX D3	9.00E+05	8.88E+09	1.90E+05	1.10E+08
manX E1	1.62E+06	1.21E+10	3.20E+05	4.00E+07
manX E2	1.29E+06	1.12E+10	2.10E+05	2.00E+07
manX E3	1.28E+06	1.27E+10	2.60E+05	6.00E+07
manX F1	4.90E+05	9.86E+09	1.30E+05	8.00E+07
manX F2	4.60E+05	1.08E+10	2.20E+05	1.40E+08
manX F3	4.20E+05	1.01E+10	1.80E+05	1.10E+08
Control A	7.60E+05	1.13E+10	2.80E+05	9.20E+08
Control B	8.70E+05	1.24E+10	1.40E+05	5.90E+08
Control C	8.60E+05	1.09E+10	2.50E+05	6.20E+08
manY A1	7.40E+05	8.00E+05	3.69E+06	3.30E+06
manY A2	8.90E+05	1.50E+06	3.49E+06	3.40E+06
manY A3	8.40E+05	6.00E+05	3.40E+06	2.60E+06
manY B1	1.80E+06	1.98E+10	4.00E+06	2.00E+07
manY B2	1.75E+06	1.84E+10	3.96E+06	2.00E+07
manY B3	1.72E+06	3.54E+10	4.03E+06	4.00E+07
manY E1	1.51E+06	1.50E+06	4.54E+06	3.80E+06
manY E2	1.73E+06	2.00E+06	4.68E+06	2.50E+06
manY E3	1.91E+06	8.00E+05	4.63E+06	2.40E+06
manY F1	2.53E+06	8.70E+09	4.92E+06	1.00E+07
manY F2	2.20E+06	8.50E+09	4.98E+06	1.00E+07
manY F3	2.42E+06	9.72E+09	3.55E+06	1.00E+07
Control A	1.75E+06	1.40E+06	3.78E+06	4.60E+06
Control B	2.00E+06	1.30E+06	3.90E+06	3.40E+06
Control C	2.02E+06	7.00E+05	3.96E+06	3.90E+06

Supplemental table 3 continued: initial and final phage densities for competitive growth assay experiments (pfu/mL).

Sample	Initial evolved isolate concentration	Final evolved isolate concentration	Initial cI26lacZ concentration	Final cI26lacZ Concentration
tpx A1	2.80E+05	1.83E+06	3.90E+05	1.81E+06
tpx A2	4.20E+05	2.41E+06	3.40E+05	1.62E+06
tpx A3	2.40E+05	1.61E+06	2.80E+05	1.70E+06
tpx B1	1.60E+05	1.56E+06	3.00E+05	1.47E+06
tpx B2	1.30E+05	1.64E+06	2.60E+05	1.45E+06
tpx B3	1.20E+05	1.71E+06	3.40E+05	1.35E+06
tpx C1	3.30E+05	4.00E+07	3.20E+05	1.35E+06
tpx C2	4.60E+05	1.00E+07	3.70E+05	1.35E+06
tpx C3	5.50E+05	1.00E+07	2.50E+05	1.61E+06
tpx D1	7.80E+05	3.00E+07	4.20E+05	1.20E+06
tpx D2	9.60E+05	2.00E+07	4.60E+05	1.57E+06
tpx D3	1.01E+06	1.10E+07	4.70E+05	5.00E+05
tpx E1	4.70E+05	3.60E+06	7.10E+05	8.00E+05
tpx E2	3.60E+05	3.30E+06	3.00E+05	4.00E+05
tpx E3	6.60E+05	1.60E+06	7.70E+05	5.00E+05
tpx F1	1.70E+05	9.00E+05	2.90E+05	2.00E+05
tpx F2	3.30E+05	1.10E+06	3.00E+05	4.00E+05
tpx F3	2.80E+05	1.00E+06	3.80E+05	5.00E+05
Control A	2.60E+05	1.00E+06	4.80E+05	5.00E+05
Control B	4.80E+05	8.00E+05	7.70E+05	5.00E+05
Control C	2.80E+05	1.10E+06	4.60E+05	9.00E+05
hldD A1	5.10E+05	1.00E+07	5.00E+05	3.00E+05
hldD A2	4.50E+05	1.00E+07	8.30E+05	6.10E+05
hldD A3	4.60E+05	4.43E+06	8.50E+05	1.70E+05
hldD B1	3.08E+06	3.40E+09	5.30E+05	1.00E+05
hldD B2	2.82E+06	9.00E+08	6.70E+05	1.00E+05
hldD B3	2.54E+06	1.50E+09	4.60E+05	2.00E+05
hldD C1	6.00E+05	2.32E+06	5.70E+05	2.90E+05
hldD C2	5.10E+05	9.90E+05	4.90E+05	3.10E+05
hldD C3	4.40E+05	4.50E+05	6.20E+05	1.90E+05
hldD D1	1.65E+06	1.00E+07	9.20E+05	6.90E+05
hldD D2	1.68E+06	2.00E+07	7.80E+05	4.80E+05
hldD D3	1.79E+06	1.00E+07	6.10E+05	4.80E+05
hldD E1	2.66E+06	2.00E+07	7.90E+05	8.10E+05
hldD E2	2.07E+06	2.00E+07	5.10E+05	6.20E+05
hldD E3	1.66E+06	1.00E+07	4.70E+05	7.40E+05
hldD F1	5.90E+05	2.65E+06	5.70E+05	8.50E+05
hldD F2	7.40E+05	1.77E+06	5.50E+05	8.70E+05
hldD F3	5.50E+05	1.42E+06	5.70E+05	4.50E+05
Control A	3.20E+05	1.22E+06	7.10E+05	5.30E+05
Control B	2.20E+05	1.76E+06	5.40E+05	9.30E+05
Control C	4.60E+05	1.59E+06	6.10E+05	9.80E+05
ompC A1	1.40E+05	5.76E+09	9.00E+05	2.48E+09
ompC A2	5.00E+04	1.50E+10	2.80E+05	5.52E+09
ompC A3	1.80E+05	9.28E+09	8.90E+05	4.56E+09
ompC B1	4.80E+05	7.64E+09	4.30E+05	5.16E+09
ompC B2	4.50E+05	4.80E+09	6.50E+05	3.76E+09
ompC B3	4.40E+05	5.40E+09	6.70E+05	3.28E+09
ompC C1	7.00E+05	3.52E+09	6.40E+05	6.80E+09
ompC C2	7.20E+05	3.00E+09	7.10E+05	9.16E+09
ompC C3	7.80E+05	2.96E+09	6.90E+05	6.76E+09
Control A	1.06E+06	4.40E+09	7.70E+05	3.28E+09
Control B	7.70E+05	1.15E+10	6.50E+05	3.48E+09
Control C	8.60E+05	7.00E+09	8.40E+05	3.28E+09

Supplemental table 3 continued: initial and final phage densities for competitive growth assay experiments (pfu/mL).

Sample	Initial evolved isolate concentration	Final evolved isolate concentration	Initial cI26lacZ concentration	Final cI26lacZ Concentration
ompC D1	1.10E+05	4.00E+08	7.30E+05	9.20E+09
ompC D2	8.00E+04	4.00E+07	7.90E+05	1.51E+09
ompC D3	6.00E+04	9.00E+07	7.60E+05	2.00E+09
ompC E1	6.00E+04	1.50E+08	1.01E+06	1.92E+09
ompC E2	8.00E+04	1.70E+08	8.10E+05	1.95E+09
ompC E3	3.00E+04	6.00E+08	6.50E+05	7.56E+09
ompC F1	3.70E+05	7.96E+09	8.70E+05	7.20E+08
ompC F2	5.00E+05	4.92E+09	6.50E+05	6.00E+08
ompC F3	5.10E+05	9.20E+09	8.00E+05	8.00E+08
Control A	9.50E+05	3.92E+09	6.80E+05	1.00E+09
Control B	1.09E+06	5.12E+09	7.60E+05	1.88E+09
Control C	8.70E+05	9.32E+09	5.30E+05	3.72E+09
rfaF A1	1.32E+06	2.06E+07	8.70E+05	1.10E+06
rfaF A2	1.27E+06	2.15E+07	1.08E+06	1.20E+06
rfaF A3	1.18E+06	2.51E+07	8.80E+05	1.30E+06
rfaF B1	8.40E+05	3.24E+07	7.70E+05	6.00E+05
rfaF B2	8.70E+05	4.84E+07	9.80E+05	3.00E+06
rfaF B3	8.50E+05	4.30E+07	8.60E+05	8.00E+05
rfaF C1	4.00E+05	8.00E+06	8.90E+05	8.00E+05
rfaF C2	5.30E+05	7.50E+06	9.90E+05	1.10E+06
rfaF C3	5.50E+05	7.10E+06	7.30E+05	1.40E+06
Control A	9.10E+05	4.00E+05	9.90E+05	5.00E+05
Control B	8.50E+05	6.00E+05	8.80E+05	9.00E+05
Control C	9.10E+05	6.00E+05	9.80E+05	5.00E+05
rfaF D1	1.26E+06	1.93E+07	9.20E+05	1.00E+06
rfaF D2	1.16E+06	2.04E+07	1.00E+06	7.00E+05
rfaF D3	1.05E+06	2.04E+07	9.10E+05	1.20E+06
rfaF E1	4.30E+05	9.50E+06	8.70E+05	7.00E+05
rfaF E2	4.10E+05	6.62E+07	8.60E+05	8.80E+06
rfaF E3	4.00E+05	8.30E+06	1.02E+06	6.00E+05
rfaF F1	7.80E+05	5.34E+07	1.00E+06	1.30E+06
rfaF F2	8.20E+05	3.70E+07	1.03E+06	9.00E+05
rfaF F3	6.90E+05	5.32E+07	7.40E+05	8.00E+05
Control A	8.30E+05	1.10E+06	7.80E+05	9.00E+05
Control B	1.05E+06	2.10E+06	1.10E+06	6.00E+05
Control C	8.40E+05	1.30E+06	8.90E+05	1.00E+06
nuoG A1	8.70E+05	9.16E+09	5.90E+05	1.10E+08
nuoG A2	8.00E+05	1.08E+10	6.20E+05	1.40E+08
nuoG A3	8.30E+05	9.90E+09	5.70E+05	9.00E+07
nuoG B1	5.00E+04	7.88E+09	5.70E+05	3.76E+09
nuoG B2	6.00E+04	9.56E+09	6.20E+05	5.00E+09
nuoG B3	5.00E+04	8.52E+09	6.60E+05	5.60E+09
nuoG C1	1.83E+06	9.68E+09	4.70E+05	5.00E+07
nuoG C2	2.02E+06	1.14E+10	5.00E+05	7.00E+07
nuoG C3	4.14E+06	1.08E+10	5.30E+05	6.00E+07
nuoG D1	4.00E+04	7.16E+09	6.70E+05	5.60E+09
nuoG D2	2.00E+04	7.80E+09	7.10E+05	5.96E+09
nuoG D3	6.00E+04	5.78E+09	5.70E+05	4.30E+09
nuoG E1	4.30E+05	5.04E+09	7.00E+05	5.00E+07
nuoG E2	5.60E+05	5.22E+09	7.50E+05	7.00E+07
nuoG E3	7.10E+05	4.86E+09	7.10E+05	4.00E+07
nuoG F1	5.30E+05	9.64E+09	7.40E+05	6.00E+07
nuoG F2	5.90E+05	9.72E+09	7.90E+05	1.00E+08
nuoG F3	6.30E+05	9.40E+09	5.70E+05	1.10E+08
Control A	7.10E+05	6.72E+09	6.10E+05	2.64E+09
Control B	7.60E+05	9.60E+09	6.90E+05	3.52E+09
Control C	8.10E+05	1.09E+10	8.10E+05	4.04E+09

Supplemental table 3 continued: initial and final phage densities for competitive growth assay experiments (pfu/mL).

Sample	Initial evolved isolate concentration	Final evolved isolate concentration	Initial cI26lacZ concentration	Final cI26lacZ Concentration
nusB A1	1.06E+06	4.46E+07	2.80E+05	1.00E+05
nusB A2	8.30E+05	3.80E+07	3.90E+05	4.00E+05
nusB A3	1.01E+06	3.32E+07	8.50E+05	3.00E+05
nusB B1	4.80E+05	6.00E+07	4.90E+05	4.00E+05
nusB B2	4.60E+05	6.24E+07	2.30E+05	1.00E+05
nusB B3	5.10E+05	6.72E+07	2.90E+05	4.00E+05
nusB C1	8.30E+05	3.80E+06	3.50E+05	1.00E+05
nusB C2	6.80E+05	3.40E+06	3.20E+05	1.00E+05
nusB C3	9.10E+05	3.70E+06	2.80E+05	2.00E+05
nusB D1	8.70E+05	8.44E+07	4.70E+05	3.00E+05
nusB D2	5.90E+05	5.32E+07	3.60E+05	2.00E+05
nusB D3	5.40E+05	5.00E+07	4.50E+05	1.00E+05
nusB E1	3.80E+05	1.87E+08	3.10E+05	1.00E+05
nusB E2	4.20E+05	1.91E+08	4.00E+05	1.00E+05
nusB E3	4.70E+05	1.32E+08	3.20E+05	5.00E+05
nusB F1	4.20E+05	4.20E+07	2.80E+05	2.00E+05
nusB F2	5.00E+05	5.92E+07	2.10E+05	1.00E+05
nusB F3	4.80E+05	5.72E+07	3.50E+05	1.00E+05
Control A	3.50E+05	6.00E+05	4.00E+05	4.00E+05
Control B	6.10E+05	5.00E+05	3.20E+05	2.00E+05
Control C	4.10E+05	1.70E+06	3.70E+05	8.00E+05
dnaJ A1	4.10E+05	2.76E+05	3.50E+05	7.00E+03
dnaJ A2	5.00E+05	1.43E+05	3.70E+05	5.00E+03
dnaJ A3	6.00E+05	9.70E+04	4.50E+05	6.00E+03
dnaJ B1	3.00E+05	8.80E+04	3.50E+05	1.00E+04
dnaJ B2	2.70E+05	1.40E+05	3.10E+05	2.00E+03
dnaJ B3	1.90E+05	1.80E+05	3.90E+05	1.04E+04
Control A	5.50E+05	3.10E+04	3.20E+05	1.20E+04
Control B	4.80E+05	3.50E+04	4.30E+05	1.50E+04
Control C	6.30E+05	3.00E+04	3.20E+05	1.80E+04
dnaK A1	2.41E+06	4.00E+05	1.16E+06	1.50E+06
dnaK A2	2.43E+06	1.00E+05	1.09E+06	6.00E+05
dnaK A3	2.65E+06	4.30E+05	1.20E+06	1.20E+05
dnaK B1	2.10E+05	2.00E+05	1.44E+06	1.20E+06
dnaK B2	1.90E+05	5.00E+05	1.15E+06	1.20E+05
dnaK B3	3.00E+05	7.00E+04	1.27E+06	1.40E+05
dnaK C1	1.02E+06	1.20E+06	8.50E+05	1.00E+06
dnaK C2	1.13E+06	8.00E+05	8.40E+05	1.10E+06
dnaK C3	1.20E+06	9.00E+05	1.07E+06	1.00E+06
dnaK D1	4.80E+05	1.50E+05	7.30E+05	7.40E+05
dnaK D2	3.10E+05	1.00E+05	8.30E+05	5.00E+05
dnaK D3	4.10E+05	4.00E+05	1.06E+06	8.00E+05
dnaK E1	8.20E+05	2.00E+05	1.01E+06	1.20E+06
dnaK E2	7.40E+05	7.00E+05	1.25E+06	5.00E+05
dnaK E3	7.60E+05	3.00E+05	6.30E+05	5.00E+05
dnaK F1	4.00E+05	3.00E+05	7.10E+05	4.00E+05
dnaK F2	7.50E+05	1.00E+05	9.80E+05	1.20E+06
dnaK F3	4.40E+05	1.00E+06	9.50E+05	1.80E+06
Control A	6.70E+05	6.00E+05	1.02E+06	5.00E+05
Control B	3.50E+05	8.00E+05	8.80E+05	7.00E+05
Control C	6.80E+05	8.00E+05	1.09E+06	9.00E+05

Supplemental table 3 continued: initial and final phage densities for competitive growth assay experiments (pfu/mL).

Sample	Initial evolved isolate concentration	Final evolved isolate concentration	Initial cI26lacZ concentration	Final cI26lacZ Concentration
rfaC A1	5.20E+05	6.00E+07	5.40E+05	1.00E+05
rfaC A2	1.70E+05	6.00E+07	3.50E+05	2.00E+05
rfaC A3	8.00E+04	4.00E+07	1.30E+05	1.00E+05
rfaC B1	3.40E+05	1.60E+09	2.10E+05	5.00E+05
rfaC B2	7.00E+04	2.10E+09	1.60E+05	9.00E+05
rfaC B3	3.60E+05	2.90E+09	2.90E+05	2.00E+05
rfaC C1	7.50E+05	4.01E+09	6.40E+05	1.00E+05
rfaC C2	2.40E+05	7.10E+09	4.50E+05	1.00E+08
rfaC C3	2.50E+05	2.90E+09	3.50E+05	3.00E+06
rfaC D1	6.40E+05	2.29E+09	3.40E+05	2.00E+05
rfaC D2	4.30E+05	3.70E+09	3.20E+05	5.00E+05
rfaC D3	3.90E+05	3.24E+09	3.00E+05	1.00E+05
rfaC E1	4.20E+05	1.41E+10	4.50E+05	2.00E+05
rfaC E2	3.20E+05	7.90E+09	5.80E+05	3.00E+06
rfaC E3	7.10E+05	1.49E+10	5.90E+05	1.00E+06
rfaC F1	4.10E+05	2.00E+09	2.10E+05	2.00E+05
rfaC F2	2.90E+05	4.50E+09	2.60E+05	4.00E+05
rfaC F3	3.40E+05	2.65E+09	4.70E+05	1.00E+07
Control A	3.90E+05	9.00E+07	7.10E+05	5.00E+05
Control B	3.50E+05	8.00E+05	5.00E+05	9.00E+05
Control C	3.00E+05	6.00E+05	5.80E+05	4.00E+05
hsds A1	6.92E+06	1.11E+10	6.50E+06	1.90E+08
hsds A2	6.86E+06	9.72E+09	7.78E+06	2.40E+08
hsds A3	7.54E+06	9.44E+09	7.18E+06	1.30E+08
hsds B1	6.48E+06	8.64E+09	7.68E+06	3.30E+08
hsds B2	5.42E+06	6.52E+09	9.34E+06	1.80E+08
hsds B3	4.44E+06	7.28E+09	8.98E+06	3.10E+08
hsds C1	5.84E+06	3.30E+09	6.82E+06	1.30E+08
hsds C2	6.28E+06	2.68E+09	6.80E+06	1.10E+08
hsds C3	6.76E+06	3.95E+09	7.66E+06	1.50E+08
hsds D1	5.84E+06	3.02E+09	6.86E+06	1.60E+08
hsds D2	5.96E+06	5.86E+09	3.76E+06	1.20E+08
hsds D3	6.02E+06	6.16E+09	4.62E+06	9.00E+07
hsds E1	1.36E+07	6.52E+09	4.58E+06	1.10E+08
hsds E2	1.32E+07	6.06E+09	4.94E+06	1.60E+08
hsds E3	1.43E+07	5.00E+09	5.64E+06	8.00E+07
hsds F1	4.26E+06	4.29E+09	6.00E+06	8.00E+07
hsds F2	3.98E+06	3.87E+09	5.42E+06	9.00E+07
hsds F3	6.06E+06	5.75E+09	6.34E+06	9.00E+07
Control A	3.74E+06	4.84E+09	6.48E+06	4.76E+09
Control B	3.24E+06	4.74E+09	7.46E+06	5.14E+09
Control C	3.78E+06	5.08E+09	7.90E+06	4.66E+09
recA A1	1.25E+06	6.90E+09	9.30E+05	1.30E+07
recA A2	1.57E+06	7.10E+09	1.18E+06	1.10E+07
recA A3	1.22E+06	5.30E+09	1.10E+06	1.40E+07
recA B1	9.30E+05	8.10E+09	8.00E+05	3.00E+07
recA B2	1.01E+06	4.40E+09	8.70E+05	2.00E+07
recA B3	9.90E+05	4.80E+09	9.70E+05	1.00E+07
recA C1	3.30E+05	5.90E+09	1.25E+06	1.00E+07
recA C2	3.20E+05	2.70E+09	1.49E+06	2.00E+07
recA C3	4.00E+05	2.90E+09	1.29E+06	3.00E+07
recA D1	3.00E+04	1.20E+09	1.07E+06	3.00E+07
recA D2	1.50E+05	4.00E+09	1.27E+06	1.00E+07
recA D3	7.00E+04	4.00E+09	1.04E+06	1.10E+07
recA E1	8.00E+05	2.50E+09	1.23E+06	2.00E+07
recA E2	6.30E+05	1.50E+09	9.70E+05	6.00E+07
recA E3	9.10E+05	2.00E+09	8.30E+05	2.00E+07
recA F1	1.32E+06	4.40E+09	9.80E+05	2.00E+07
recA F2	1.54E+06	6.60E+09	1.10E+06	2.00E+07
recA F3	1.52E+06	5.10E+09	1.16E+06	1.00E+07
Control A	6.60E+05	9.00E+07	1.13E+06	1.30E+08
Control B	7.90E+05	1.80E+08	1.70E+06	1.10E+08
Control C	8.00E+05	5.00E+07	1.58E+06	1.90E+08

Supplemental table 3 continued: initial and final phage densities for competitive growth assay experiments (pfu/mL).

Sample	Initial evolved isolate concentration	Final evolved isolate concentration	Initial cI26lacZ concentration	Final cI26lacZ Concentration
WT-1 A1	8.50E+05	1.87E+10	4.00E+05	2.40E+08
WT-1 A2	7.30E+05	1.20E+10	4.90E+05	1.50E+08
WT-1 A3	7.70E+05	1.42E+10	4.90E+05	1.60E+08
WT-1 B1	1.80E+05	1.58E+10	4.70E+05	6.00E+07
WT-1 B2	2.10E+05	1.58E+10	4.50E+05	1.20E+08
WT-1 B3	2.90E+05	1.63E+10	5.00E+05	1.00E+08
WT-1 C1	8.10E+05	1.82E+10	4.60E+05	1.60E+08
WT-1 C2	8.80E+05	1.34E+10	6.10E+05	1.20E+08
WT-1 C3	9.70E+05	2.06E+10	5.90E+05	1.00E+08
WT-1 D1	4.10E+05	1.06E+10	3.90E+05	2.40E+08
WT-1 D2	4.00E+05	1.57E+10	5.30E+05	1.60E+08
WT-1 D3	3.10E+05	1.13E+10	5.80E+05	1.50E+08
WT-1 E1	4.00E+05	1.30E+10	5.10E+05	4.30E+08
WT-1 E2	5.70E+05	9.80E+09	7.10E+05	2.10E+08
WT-1 E3	5.10E+05	1.53E+10	4.60E+05	5.70E+08
WT-1 F1	8.60E+05	1.66E+10	5.90E+05	6.10E+08
WT-1 F2	9.10E+05	1.63E+10	4.20E+05	5.20E+08
WT-1 F3	7.50E+05	1.58E+10	4.10E+05	5.60E+08
Control A	8.80E+05	2.18E+10	3.40E+05	3.20E+09
Control B	9.80E+05	1.16E+10	4.00E+05	1.64E+09
Control C	8.60E+05	1.88E+10	4.50E+05	3.12E+09
WT-2 A1	5.44E+06	4.65E+09	6.20E+05	9.00E+06
WT-2 A2	4.74E+06	5.12E+09	7.10E+05	5.00E+06
WT-2 A3	5.50E+06	5.43E+09	6.50E+05	7.00E+06
WT-2 B1	1.35E+07	1.11E+10	2.60E+05	3.00E+07
WT-2 B2	1.20E+07	1.06E+10	4.40E+05	1.00E+07
WT-2 B3	1.13E+07	1.14E+10	4.20E+05	2.00E+07
WT-2 C1	2.60E+05	1.72E+09	9.20E+05	9.66E+09
WT-2 C2	2.40E+05	1.42E+09	6.60E+05	8.92E+09
WT-2 C3	1.90E+05	9.20E+08	5.90E+05	6.22E+09
Control A	1.60E+05	4.82E+09	7.10E+05	6.62E+09
Control B	1.30E+05	5.36E+09	7.60E+05	6.92E+09
Control C	2.10E+05	6.60E+09	7.60E+05	5.36E+09
WT-2 D1	2.00E+04	6.00E+07	2.60E+05	1.02E+09
WT-2 D2	1.00E+04	6.00E+07	2.90E+05	1.26E+09
WT-2 D3	1.00E+04	5.00E+07	3.20E+05	9.70E+08
WT-2 E1	1.10E+05	1.37E+09	2.80E+05	4.00E+08
WT-2 E2	7.00E+04	1.06E+09	2.70E+05	4.80E+08
WT-2 E3	8.00E+04	1.07E+09	2.80E+05	4.10E+08
WT-2 F1	6.00E+04	1.32E+09	2.50E+05	7.40E+08
WT-2 F2	4.00E+04	1.64E+09	2.90E+05	5.50E+08
WT-2 F3	4.00E+04	1.64E+09	2.90E+05	6.70E+08
Control A	1.00E+05	6.80E+08	4.50E+05	9.00E+08
Control B	7.00E+04	6.30E+08	4.40E+05	9.80E+08
Control C	9.00E+04	6.00E+08	4.00E+05	1.30E+09
WT-3 A1	1.26E+06	1.22E+10	1.26E+06	1.16E+10
WT-3 A2	5.00E+05	1.37E+10	5.00E+05	9.72E+09
WT-3 A3	4.50E+05	1.14E+10	4.50E+05	1.06E+10
WT-3 B1	1.58E+06	1.45E+10	1.58E+06	7.20E+08
WT-3 B2	1.70E+06	1.21E+10	1.70E+06	9.20E+08
WT-3 B3	1.70E+06	1.17E+10	1.70E+06	6.80E+08
WT-3 C1	5.30E+05	1.34E+10	5.30E+05	6.80E+08
WT-3 C2	8.10E+05	1.06E+10	8.10E+05	1.72E+09
WT-3 C3	8.40E+05	1.54E+10	8.40E+05	1.64E+09
Control A	8.20E+05	1.04E+09	8.20E+05	7.60E+08
Control B	1.18E+06	1.12E+09	1.18E+06	5.60E+08
Control C	9.50E+05	2.68E+09	9.50E+05	1.20E+09
WT-3 D1	1.20E+05	1.55E+09	1.20E+05	7.50E+08
WT-3 D2	2.40E+05	1.15E+09	2.40E+05	6.40E+08
WT-3 D3	1.90E+05	6.90E+08	1.90E+05	5.10E+08
WT-3 E1	2.40E+05	1.61E+09	2.40E+05	2.60E+08
WT-3 E2	2.10E+05	1.41E+09	2.10E+05	4.40E+08
WT-3 E3	5.50E+05	1.68E+09	5.50E+05	2.90E+08
WT-3 F1	5.10E+05	1.08E+09	5.10E+05	9.00E+08
WT-3 F2	3.30E+05	1.35E+09	3.30E+05	1.20E+09
WT-3 F3	1.20E+05	9.30E+08	1.20E+05	6.10E+08
Control A	1.50E+05	9.60E+08	1.50E+05	7.20E+08
Control B	2.90E+05	9.80E+08	2.90E+05	6.50E+08
Control C	8.20E+05	6.30E+08	8.20E+05	3.10E+08

Supplemental table 3 continued: initial and final phage densities for competitive growth assay experiments (pfu/mL).

Sample	Initial evolved isolate concentration	Final evolved isolate concentration	Initial cI26lacZ concentration	Final cI26lacZ Concentration
WT-4 A1	7.30E+05	8.66E+09	3.10E+05	8.00E+07
WT-4 A2	1.31E+06	1.00E+10	4.30E+05	1.20E+08
WT-4 A3	1.26E+06	7.32E+09	4.00E+05	8.00E+07
WT-4 B1	1.55E+06	9.06E+09	4.80E+05	4.00E+07
WT-4 B2	1.50E+06	6.40E+09	5.20E+05	8.00E+07
WT-4 B3	1.38E+06	4.68E+09	5.10E+05	5.00E+07
WT-4 C1	9.00E+05	2.42E+10	7.60E+05	5.96E+09
WT-4 C2	9.50E+05	1.92E+10	6.90E+05	3.60E+09
WT-4 C3	1.03E+06	1.86E+10	5.60E+05	4.68E+09
WT-4 D1	1.60E+06	3.83E+09	3.80E+05	1.00E+07
WT-4 D2	1.49E+06	1.34E+09	5.50E+05	1.00E+07
WT-4 D3	1.19E+06	3.54E+09	4.50E+05	1.00E+07
WT-4 E1	1.73E+06	8.12E+09	5.40E+05	4.00E+07
WT-4 E2	1.85E+06	2.56E+09	5.20E+05	1.00E+07
WT-4 E3	2.09E+06	6.42E+09	6.20E+05	1.00E+07
WT-4 F1	1.64E+06	8.16E+09	5.70E+05	1.00E+08
WT-4 F2	1.52E+06	5.48E+09	4.10E+05	3.00E+07
WT-4 F3	1.67E+06	8.82E+09	4.90E+05	3.00E+07
Control A	7.80E+05	8.52E+09	4.90E+05	2.56E+09
Control B	6.90E+05	8.96E+09	3.30E+05	3.46E+09
Control C	7.30E+05	8.92E+09	3.80E+05	3.64E+09
WT-5 A1	1.40E+05	3.00E+09	3.40E+05	5.40E+09
WT-5 A2	2.50E+05	3.40E+09	7.40E+05	8.10E+09
WT-5 A3	1.90E+05	4.00E+09	3.70E+05	8.10E+09
WT-5 B1	2.80E+05	8.60E+09	8.00E+05	2.20E+09
WT-5 B2	4.90E+05	1.16E+10	7.30E+05	3.90E+09
WT-5 B3	1.80E+05	8.50E+09	5.00E+05	2.60E+09
WT-5 C1	3.20E+05	2.70E+09	6.50E+05	1.00E+08
WT-5 C2	9.00E+04	3.10E+09	4.10E+05	1.00E+08
WT-5 C3	2.30E+05	2.20E+10	3.60E+05	1.00E+08
WT-5 D1	3.60E+05	6.80E+09	4.40E+05	1.00E+09
WT-5 D2	2.50E+05	7.00E+09	4.40E+05	2.70E+09
WT-5 D3	1.80E+05	1.38E+11	4.00E+05	2.90E+09
WT-5 E1	2.70E+05	5.60E+10	4.30E+05	2.00E+07
WT-5 E2	1.80E+05	1.80E+10	2.70E+05	1.50E+07
WT-5 E3	2.80E+05	3.80E+09	3.30E+05	1.70E+06
WT-5 F1	1.20E+05	4.10E+10	4.00E+05	1.00E+07
WT-5 F2	1.90E+05	1.10E+10	5.50E+05	2.90E+07
WT-5 F3	1.90E+05	5.10E+09	2.40E+05	2.30E+05
Control A	1.10E+05	1.80E+09	3.90E+05	6.00E+08
Control B	1.20E+05	3.40E+09	2.00E+05	4.00E+08
Control C	1.80E+05	3.40E+09	1.90E+05	9.00E+08
WT-6 A1	5.40E+05	4.00E+09	5.00E+05	4.00E+07
WT-6 A2	8.10E+05	4.80E+09	8.70E+05	4.00E+07
WT-6 A3	6.20E+05	3.80E+09	8.60E+05	5.00E+07
WT-6 B1	6.40E+05	8.70E+09	4.50E+05	1.30E+08
WT-6 B2	5.60E+05	8.80E+09	5.90E+05	1.74E+09
WT-6 B3	7.10E+05	9.00E+09	4.50E+05	1.20E+08
WT-6 C1	2.90E+05	7.40E+09	5.70E+05	1.47E+09
WT-6 C2	3.90E+05	6.20E+09	6.80E+05	1.23E+09
WT-6 C3	1.00E+05	1.20E+10	3.80E+05	2.00E+09
WT-6 D1	3.40E+05	6.70E+09	6.70E+05	4.00E+07
WT-6 D2	4.40E+05	5.70E+09	1.15E+06	5.00E+07
WT-6 D3	2.40E+05	1.00E+10	1.04E+06	8.00E+07
WT-6 E1	8.70E+05	6.90E+09	3.70E+05	1.20E+08
WT-6 E2	8.50E+05	1.02E+10	6.20E+05	1.20E+08
WT-6 E3	7.00E+05	1.01E+10	5.20E+05	1.70E+08
WT-6 F1	4.00E+05	9.40E+09	4.00E+05	1.50E+09
WT-6 F2	2.60E+05	1.80E+10	4.20E+05	2.90E+09
WT-6 F3	4.40E+05	8.90E+09	4.20E+05	2.00E+09
Control A	7.90E+05	9.80E+09	5.10E+05	1.70E+09
Control B	9.50E+05	6.60E+09	5.90E+05	1.10E+09
Control C	9.40E+05	1.50E+10	5.30E+05	2.50E+09

Supplemental table 4: host range experiment raw plating efficiency data (pfu/mL). (Y-axis= λ isolates; X-axis= KO strain) strain).

bacterial strain																		
phage strain	*clpX*	*crr*	*gmhA*	*dnaK*	*recA*	*rfaC*	*nuoG*	*ompC*	*rfaF*	*hldD*	*tpx*	*hsdS*	*manX*	*manY*	*dnaJ*	*nusB*	*WT*
clpX A	1.00E+05	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+04	1.00E+06	1.00E+06	1.00E+06	0.00E+00	1.00E+01	1.00E+01	1.00E+06
clpX B	1.00E+05	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+04	1.00E+06	1.00E+06	1.00E+06	0.00E+00	1.00E+01	1.00E+01	1.00E+06
clpX C	1.00E+05	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+05	1.00E+05	1.00E+06	1.00E+06	1.00E+06	0.00E+00	1.00E+01	1.00E+01	1.00E+06
cplX D	1.00E+05	1.00E+05	1.00E+05	0.00E+00	1.00E+06	1.00E+06	1.00E+05	1.00E+06	1.00E+05	1.00E+04	1.00E+06	1.00E+06	1.00E+06	0.00E+00	1.00E+01	1.00E+01	1.00E+06
clpX E	1.00E+05	1.00E+06	1.00E+04	0.00E+00	1.00E+06	1.00E+05	1.00E+05	1.00E+06	1.00E+05	1.00E+04	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+01	1.00E+01	1.00E+06
clpX F	1.00E+05	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+05	1.00E+05	1.00E+06	1.00E+05	1.00E+06	0.00E+00	1.00E+01	1.00E+01	1.00E+06
crr A	1.00E+04	1.00E+06	1.00E+04	0.00E+00	1.00E+05	1.00E+05	1.00E+06	1.00E+06	1.00E+05	1.00E+04	1.00E+05	1.00E+06	1.00E+05	0.00E+00	1.00E+01	1.00E+01	1.00E+05
crr B	1.00E+05	1.00E+06	1.00E+04	0.00E+00	1.00E+06	1.00E+05	1.00E+05	1.00E+06	1.00E+05	1.00E+04	1.00E+05	1.00E+05	1.00E+05	0.00E+00	1.00E+02	1.00E+02	1.00E+06
crr C	1.00E+05	1.00E+05	1.00E+04	0.00E+00	1.00E+06	1.00E+04	1.00E+06	1.00E+05	1.00E+04	1.00E+04	1.00E+05	1.00E+04	1.00E+05	1.00E+01	0.00E+00	1.00E+01	1.00E+05
crr D	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+05	1.00E+04	1.00E+06	1.00E+05	1.00E+05	1.00E+01	1.00E+01	1.00E+01	1.00E+06
crr E	1.00E+06	1.00E+05	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+04	1.00E+01	1.00E+01	1.00E+01	1.00E+05
crr F	1.00E+05	1.00E+06	1.00E+04	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+05	1.00E+04	1.00E+04	1.00E+05	1.00E+04	1.00E+04	1.00E+01	1.00E+01	1.00E+01	1.00E+05
gmhA A	1.00E+06	1.00E+06	1.00E+04	0.00E+00	1.00E+06	1.00E+04	1.00E+06	1.00E+06	1.00E+06	1.00E+04	1.00E+04	1.00E+06	1.00E+05	1.00E+04	1.00E+01	1.00E+02	1.00E+06
gmhA B	1.00E+05	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+04	1.00E+01	1.00E+03	1.00E+01	1.00E+05
gmhA C	1.00E+05	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+05	1.00E+05	1.00E+05	1.00E+06	1.00E+01	1.00E+01	1.00E+01	1.00E+06
gmhA D	1.00E+06	1.00E+06	1.00E+04	0.00E+00	1.00E+06	1.00E+04	1.00E+06	1.00E+05	1.00E+04	1.00E+04	1.00E+05	1.00E+05	1.00E+04	1.00E+01	1.00E+03	1.00E+01	1.00E+06
gmhA E	1.00E+05	1.00E+06	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+06	1.00E+05	1.00E+06	1.00E+05	1.00E+03	1.00E+02	1.00E+01	1.00E+06
gmhA F	1.00E+06	1.00E+05	1.00E+05	0.00E+00	1.00E+05	1.00E+04	1.00E+05	1.00E+05	1.00E+05	1.00E+06	1.00E+05	1.00E+06	1.00E+05	1.00E+03	1.00E+01	1.00E+01	1.00E+06
dnaK A	1.00E+02	1.00E+01	0.00E+00	0.00E+00	1.00E+01	0.00E+00	0.00E+00	0.00E+00	1.00E+01	0.00E+00	1.00E+01	1.00E+01	1.00E+02	0.00E+00	0.00E+00	0.00E+00	1.00E+02
dnaK B	1.00E+02	1.00E+02	0.00E+00	0.00E+00	1.00E+01	0.00E+00	0.00E+00	1.00E+02	0.00E+00	0.00E+00	1.00E+01	1.00E+01	1.00E+02	0.00E+00	0.00E+00	0.00E+00	1.00E+02
dnaK C	1.00E+02	1.00E+01	0.00E+00	0.00E+00	1.00E+01	0.00E+00	0.00E+00	1.00E+01	0.00E+00	0.00E+00	1.00E+01	1.00E+01	1.00E+02	0.00E+00	0.00E+00	0.00E+00	1.00E+02
dnaK D	1.00E+02	1.00E+01	0.00E+00	0.00E+00	1.00E+01	0.00E+00	0.00E+00	1.00E+01	0.00E+00	0.00E+00	1.00E+01	1.00E+01	1.00E+02	0.00E+00	0.00E+00	0.00E+00	1.00E+02
dnaK E	1.00E+02	1.00E+01	0.00E+00	0.00E+00	1.00E+01	0.00E+00	0.00E+00	1.00E+01	0.00E+00	0.00E+00	1.00E+01	1.00E+01	1.00E+02	0.00E+00	0.00E+00	0.00E+00	1.00E+03
dnaK F	1.00E+03	1.00E+01	0.00E+00	0.00E+00	1.00E+01	0.00E+00	0.00E+00	1.00E+01	0.00E+00	0.00E+00	1.00E+01	1.00E+01	1.00E+02	0.00E+00	0.00E+00	0.00E+00	1.00E+03
recA A	1.00E+05	1.00E+05	1.00E+04	0.00E+00	1.00E+06	1.00E+04	1.00E+04	1.00E+04	1.00E+05	1.00E+04	1.00E+05	1.00E+05	1.00E+04	1.00E+01	1.00E+01	1.00E+02	1.00E+06
recA B	1.00E+05	1.00E+05	1.00E+04	0.00E+00	1.00E+06	1.00E+04	1.00E+04	1.00E+04	1.00E+05	1.00E+04	1.00E+05	1.00E+04	1.00E+04	1.00E+01	1.00E+01	1.00E+02	1.00E+06
recA C	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+01	1.00E+02	1.00E+01	1.00E+06
recA D	1.00E+06	1.00E+06	1.00E+06	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+02	1.00E+03	1.00E+01	1.00E+06
recA E	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+01	1.00E+02	1.00E+01	1.00E+06
recA F	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+01	1.00E+02	1.00E+01	1.00E+06
rfaC A	1.00E+05	1.00E+06	1.00E+03	0.00E+00	1.00E+05	1.00E+06	1.00E+05	1.00E+06	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+06	0.00E+00	0.00E+00	0.00E+00	1.00E+06
rfaC B	1.00E+06	1.00E+06	1.00E+05	1.00E+01	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+02	1.00E+02	1.00E+02	1.00E+06
rfaC C	1.00E+06	1.00E+06	1.00E+05	1.00E+01	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+02	1.00E+02	1.00E+02	1.00E+06
rfaC D	1.00E+06	1.00E+06	1.00E+05	1.00E+01	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+01	1.00E+02	1.00E+02	1.00E+06
rfaC E	1.00E+06	1.00E+06	1.00E+06	1.00E+01	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+02	1.00E+03	1.00E+01	1.00E+06
rfaC F	1.00E+06	1.00E+06	1.00E+05	1.00E+01	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+02	1.00E+03	1.00E+01	1.00E+06
nuoG A	1.00E+05	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+05	1.00E+04	1.00E+05	1.00E+04	1.00E+04	1.00E+02	1.00E+01	1.00E+01	1.00E+06
nuoG B	1.00E+04	1.00E+04	1.00E+03	0.00E+00	1.00E+05	1.00E+03	1.00E+04	1.00E+03	1.00E+03	1.00E+04	1.00E+04	1.00E+04	1.00E+04	0.00E+00	0.00E+00	0.00E+00	1.00E+05
nuoG C	1.00E+06	1.00E+05	1.00E+04	0.00E+00	1.00E+05	1.00E+04	1.00E+05	1.00E+06	1.00E+05	1.00E+04	1.00E+06	1.00E+06	1.00E+06	1.00E+02	0.00E+00	1.00E+01	1.00E+06
nuoG D	1.00E+05	1.00E+05	1.00E+05	0.00E+00	1.00E+04	1.00E+04	1.00E+05	1.00E+05	1.00E+05	1.00E+04	1.00E+06	1.00E+04	1.00E+04	1.00E+02	0.00E+00	1.00E+02	1.00E+06
nuoG E	1.00E+05	1.00E+06	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+02	0.00E+00	1.00E+01	1.00E+06
nuoG F	1.00E+06	1.00E+05	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+02	0.00E+00	1.00E+02	1.00E+06
ompC A	1.00E+06	1.00E+06	0.00E+00	0.00E+00	1.00E+06	0.00E+00	1.00E+06	1.00E+06	1.00E+06	1.00E+04	1.00E+06	1.00E+06	1.00E+05	1.00E+01	0.00E+00	0.00E+00	1.00E+06
ompC B	1.00E+04	1.00E+05	1.00E+03	0.00E+00	1.00E+04	1.00E+03	1.00E+04	1.00E+05	1.00E+04	1.00E+05	1.00E+05	1.00E+05	1.00E+04	0.00E+00	0.00E+00	0.00E+00	1.00E+05
ompC C	1.00E+04	1.00E+04	1.00E+04	0.00E+00	1.00E+04	1.00E+03	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+05	1.00E+05	1.00E+04	0.00E+00	0.00E+00	0.00E+00	1.00E+04
ompC D	1.00E+03	1.00E+03	1.00E+02	0.00E+00	1.00E+03	1.00E+02	1.00E+03	1.00E+03	1.00E+03	1.00E+03	1.00E+04	1.00E+04	1.00E+03	0.00E+00	0.00E+00	0.00E+00	1.00E+04
ompC E	1.00E+03	1.00E+03	1.00E+01	0.00E+00	1.00E+03	1.00E+01	1.00E+03	1.00E+03	1.00E+03	1.00E+03	1.00E+04	1.00E+04	1.00E+04	0.00E+00	0.00E+00	0.00E+00	1.00E+04
ompC F	1.00E+03	1.00E+03	1.00E+01	0.00E+00	1.00E+03	1.00E+01	1.00E+03	1.00E+03	1.00E+03	1.00E+02	1.00E+03	1.00E+03	1.00E+03	0.00E+00	0.00E+00	0.00E+00	1.00E+04
rfaF A	1.00E+06	1.00E+06	1.00E+06	1.00E+01	1.00E+06	1.00E+04	1.00E+06	1.00E+06	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+04	1.00E+02	1.00E+02	1.00E+03	1.00E+06
rfaF B	1.00E+06	1.00E+06	1.00E+05	1.00E+01	1.00E+05	1.00E+04	1.00E+06	1.00E+06	1.00E+06	1.00E+05	1.00E+06	1.00E+05	1.00E+04	1.00E+01	1.00E+01	1.00E+01	1.00E+05
rfaF C	1.00E+06	1.00E+06	1.00E+05	1.00E+01	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+05	1.00E+06	1.00E+04	1.00E+03	1.00E+02	1.00E+03	1.00E+06
rfaF D	1.00E+06	1.00E+06	1.00E+05	1.00E+01	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+04	1.00E+03	1.00E+02	1.00E+03	1.00E+06
rfaF E	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+01	1.00E+02	1.00E+02	1.00E+06
rfaF F	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+05	1.00E+06	1.00E+05	1.00E+06	0.00E+00	1.00E+01	1.00E+01	1.00E+06
hldD A	1.00E+06	1.00E+05	1.00E+04	0.00E+00	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+06	1.00E+05	1.00E+01	1.00E+02	1.00E+01	1.00E+06
hldD B	1.00E+06	1.00E+05	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+06	1.00E+05	1.00E+01	1.00E+01	1.00E+01	1.00E+05
hldD C	1.00E+06	1.00E+05	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+06	1.00E+05	1.00E+01	1.00E+01	1.00E+02	1.00E+05
hldD D	1.00E+06	1.00E+05	1.00E+05	0.00E+00	1.00E+04	1.00E+04	1.00E+05	1.00E+04	1.00E+04	1.00E+04	1.00E+06	1.00E+06	1.00E+04	1.00E+01	1.00E+02	1.00E+02	1.00E+06
hldD E	1.00E+06	1.00E+04	1.00E+04	0.00E+00	1.00E+04	1.00E+05	1.00E+05	1.00E+04	1.00E+05	1.00E+04	1.00E+06	1.00E+04	1.00E+05	1.00E+01	1.00E+01	1.00E+02	1.00E+06
hldD F	1.00E+06	1.00E+05	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+06	1.00E+05	1.00E+06	1.00E+05	1.00E+06	1.00E+05	1.00E+06	1.00E+01	1.00E+03	1.00E+02	1.00E+06
tpx A	1.00E+05	1.00E+05	1.00E+04	1.00E+01	1.00E+04	1.00E+05	1.00E+06	1.00E+05	1.00E+06	1.00E+05	1.00E+06	1.00E+05	1.00E+06	1.00E+01	1.00E+02	1.00E+02	1.00E+05
tpx B	1.00E+05	1.00E+04	1.00E+04	1.00E+01	1.00E+03	1.00E+04	1.00E+06	1.00E+04	1.00E+04	1.00E+04	1.00E+06	1.00E+05	1.00E+05	1.00E+01	1.00E+01	1.00E+02	1.00E+04
tpx C	1.00E+05	1.00E+05	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+02	1.00E+02	1.00E+02	1.00E+05
tpx D	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+04	1.00E+05	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+05	1.00E+02	1.00E+02	1.00E+03	1.00E+06
tpx E	1.00E+06	1.00E+06	1.00E+06	0.00E+00	1.00E+06	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+02	1.00E+02	1.00E+02	1.00E+06
tpx F	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+05	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+02	1.00E+02	1.00E+02	1.00E+06
hsdS A	1.00E+06	1.00E+05	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+05	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+02	1.00E+02	1.00E+02	1.00E+05
hsdS B	1.00E+06	1.00E+05	1.00E+04	0.00E+00	1.00E+05	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+02	1.00E+02	1.00E+02	1.00E+04
hsdS C	1.00E+06	1.00E+05	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+05	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+02	1.00E+02	1.00E+02	1.00E+05
hsdS D	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+02	1.00E+02	1.00E+02	1.00E+05
hsdS E	1.00E+06	1.00E+06	1.00E+04	0.00E+00	1.00E+05	1.00E+04	1.00E+05	1.00E+04	1.00E+04	1.00E+04	1.00E+05	1.00E+04	1.00E+05	1.00E+02	1.00E+02	1.00E+02	1.00E+05
hsdS F	1.00E+06	1.00E+06	1.00E+04	0.00E+00	1.00E+05	1.00E+05	1.00E+05	1.00E+04	1.00E+04	1.00E+04	1.00E+05	1.00E+05	1.00E+05	1.00E+02	1.00E+02	1.00E+02	1.00E+05
manX A	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+05	1.00E+04	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+04	1.00E+02	1.00E+02	1.00E+02	1.00E+06
manX B	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+05	1.00E+04	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+06	1.00E+05	1.00E+05	1.00E+02	1.00E+02	1.00E+02	1.00E+05
manX C	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+06	1.00E+05	1.00E+05	1.00E+02	1.00E+02	1.00E+02	1.00E+06
manX D	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+05	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+05	1.00E+02	1.00E+02	1.00E+02	1.00E+06
manX E	1.00E+06	1.00E+06	1.00E+04	0.00E+00	1.00E+06	1.00E+05	1.00E+05	1.00E+06	1.00E+05	1.00E+05	1.00E+06	1.00E+06	1.00E+05	1.00E+02	1.00E+02	1.00E+02	1.00E+05
manX F	1.00E+06	1.00E+06	1.00E+06	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+05	1.00E+02	1.00E+02	1.00E+02	1.00E+06
manY A	1.00E+06	1.00E+06	0.00E+00	0.00E+00	1.00E+05	0.00E+00	1.00E+06	1.00E+06	1.00E+02	1.00E+01	1.00E+06	1.00E+06	1.00E+05	1.00E+05	1.00E+02	1.00E+02	1.00E+06
manY B	1.00E+06	1.00E+06	1.00E+02	0.00E+00	1.00E+05	0.00E+00	1.00E+05	1.00E+06	1.00E+03	1.00E+06	1.00E+06	1.00E+05	1.00E+05	1.00E+05	1.00E+02	1.00E+02	1.00E+06
manY C	1.00E+04	1.00E+04	0.00E+00	0.00E+00	1.00E+04	0.00E+00	1.00E+05	1.00E+04	1.00E+02	1.00E+01	1.00E+03	1.00E+03	1.00E+03	1.00E+03	1.00E+02	1.00E+01	1.00E+04
manY D	1.00E+05	1.00E+05	0.00E+00	0.00E+00	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+02	1.00E+01	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+02	1.00E+01	1.00E+05
manY E	1.00E+04	1.00E+04	1.00E+02	0.00E+00	1.00E+04	1.00E+01	1.00E+04	1.00E+04	1.00E+03	1.00E+03	1.00E+03	1.00E+03	1.00E+03	1.00E+02	1.00E+02	1.00E+01	1.00E+04
manY F	1.00E+05	1.00E+04	1.00E+02	0.00E+00	1.00E+04	1.00E+01	1.00E+04	1.00E+04	1.00E+03	1.00E+04	1.00E+04	1.00E+04	1.00E+05	1.00E+01	1.00E+02	1.00E+01	1.00E+05
nusB A	1.00E+06	1.00E+06	1.00E+03	0.00E+00	1.00E+06	1.00E+02	1.00E+06	1.00E+06	1.00E+04	1.00E+04	1.00E+05	1.00E+06	1.00E+06	1.00E+03	1.00E+02	1.00E+03	1.00E+06
nusB B	1.00E+06	1.00E+06	1.00E+03	0.00E+00	1.00E+06	1.00E+02	1.00E+06	1.00E+06	1.00E+04	1.00E+04	1.00E+06	1.00E+05	1.00E+06	1.00E+03	1.00E+02	1.00E+05	1.00E+06
nusB C	1.00E+03	1.00E+03	1.00E+00	0.00E+00	1.00E+03	0.00E+00	1.00E+03	1.00E+03	0.00E+00	0.00E+00	1.00E+03	1.00E+03	1.00E+03	0.00E+00	0.00E+00	0.00E+00	1.00E+04
nusB D	1.00E+06	1.00E+06	1.00E+03	0.00E+00	1.00E+06	1.00E+03	1.00E+06	1.00E+06	1.00E+04	1.00E+04	1.00E+05	1.00E+06	1.00E+06	1.00E+03	1.00E+02	1.00E+05	1.00E+06
nusB E	1.00E+06	1.00E+06	1.00E+02	0.00E+00	1.00E+05	1.00E+01	1.00E+05	1.00E+05	1.00E+04	1.00E+04	1.00E+05	1.00E+06	1.00E+05	1.00E+02	1.00E+02	1.00E+04	1.00E+06
nusB F	1.00E+06	1.00E+06	1.00E+03	0.00E+00	1.00E+06	1.00E+02	1.00E+05	1.00E+06	1.00E+04	1.00E+04	1.00E+06	1.00E+06	1.00E+06	1.00E+03	1.00E+02	1.00E+04	1.00E+06
	clpX	*crr*	*gmhA*	*dnaK*	*recA*	*rfaC*	*nuoG*	*ompC*	*rfaF*	*hldD*	*tpx*	*hsdS*	*manX*	*manY*	*dnaJ*	*nusB*	*WT*

Supplemental table 4 continued: host range experiment raw plating efficiency data (pfu/mL). (Y-axis= λ isolates; X-axis= KO strain) strain).

bacterial strain																	
phage strain	*clpX*	*crr*	*gmhA*	*dnaK*	*recA*	*rfaC*	*nuoG*	*ompC*	*rfaF*	*hldD*	*tpx*	*hsdS*	*manX*	*manY*	*dnaJ*	*nusB*	*WT*
WT-1 A	1.00E+05	1.00E+05	1.00E+04	0.00E+00	1.00E+05	1.00E+05	1.00E+04	1.00E+05	1.00E+04	1.00E+06	1.00E+05	1.00E+05	1.00E+05	1.00E+02	1.00E+01	1.00E+01	1.00E+06
WT-1 B	1.00E+04	1.00E+04	1.00E+03	0.00E+00	1.00E+03	1.00E+02	1.00E+03	1.00E+04	1.00E+04	1.00E+05	1.00E+05	1.00E+03	1.00E+03	1.00E+02	1.00E+01	1.00E+01	1.00E+04
WT-1 C	1.00E+05	1.00E+04	1.00E+03	0.00E+00	1.00E+05	1.00E+02	1.00E+04	1.00E+05	1.00E+04	1.00E+05	1.00E+04	1.00E+04	1.00E+04	0.00E+00	1.00E+01	1.00E+01	1.00E+06
WT-1 D	1.00E+04	1.00E+04	1.00E+01	0.00E+00	1.00E+04	1.00E+01	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+03	1.00E+04	1.00E+01	0.00E+00	1.00E+01	1.00E+04
WT-1 E	1.00E+03	1.00E+02	1.00E+01	0.00E+00	1.00E+02	1.00E+01	1.00E+02	1.00E+02	1.00E+03	1.00E+02	1.00E+02	1.00E+02	1.00E+02	0.00E+00	0.00E+00	0.00E+00	1.00E+04
WT-1 F	1.00E+04	1.00E+02	1.00E+01	0.00E+00	1.00E+02	1.00E+01	1.00E+02	1.00E+03	1.00E+03	1.00E+03	1.00E+02	1.00E+02	1.00E+02	0.00E+00	0.00E+00	0.00E+00	1.00E+04
WT-2 A	1.00E+06	1.00E+06	1.00E+06	0.00E+00	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	0.00E+00	0.00E+00	1.00E+01	1.00E+06
WT-2 B	1.00E+06	1.00E+06	1.00E+04	0.00E+00	1.00E+06	1.00E+04	1.00E+06	1.00E+06	1.00E+05	1.00E+05	1.00E+06	1.00E+06	1.00E+06	0.00E+00	0.00E+00	1.00E+01	1.00E+06
WT-2 C	1.00E+06	1.00E+06	1.00E+05	1.00E+01	1.00E+06	1.00E+04	1.00E+06	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+06	0.00E+00	0.00E+00	1.00E+02	1.00E+06
WT-2 D	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+06	1.00E+04	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	0.00E+00	0.00E+00	1.00E+01	1.00E+06
WT-2 E	1.00E+06	1.00E+06	1.00E+04	0.00E+00	1.00E+06	1.00E+04	1.00E+06	1.00E+06	1.00E+05	1.00E+05	1.00E+06	1.00E+06	1.00E+06	0.00E+00	0.00E+00	1.00E+01	1.00E+06
WT-3A	1.00E+06	1.00E+06	1.00E+04	1.00E+01	1.00E+06	1.00E+04	1.00E+06	1.00E+06	1.00E+05	1.00E+05	1.00E+06	1.00E+06	1.00E+06	0.00E+00	0.00E+00	1.00E+01	1.00E+06
WT-3 B	1.00E+06	1.00E+05	1.00E+03	1.00E+01	1.00E+06	1.00E+05	1.00E+05	1.00E+06	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+01	1.00E+02	1.00E+02	1.00E+06
WT-3 C	1.00E+06	1.00E+06	1.00E+04	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+05	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+01	1.00E+01	1.00E+02	1.00E+06
WT-3 D	1.00E+05	1.00E+05	1.00E+04	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+06	1.00E+01	1.00E+01	1.00E+02	1.00E+06
WT-3 E	1.00E+05	1.00E+05	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+05	1.00E+05	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+01	1.00E+02	1.00E+06
WT-3 F	1.00E+05	1.00E+05	1.00E+05	0.00E+00	1.00E+06	1.00E+05	1.00E+06	1.00E+06	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	0.00E+00	0.00E+00	1.00E+02	1.00E+05
WT-4 A	1.00E+05	1.00E+05	1.00E+04	0.00E+00	1.00E+05	1.00E+05	1.00E+06	1.00E+06	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	0.00E+00	0.00E+00	1.00E+02	1.00E+05
WT-4 B	1.00E+06	1.00E+06	1.00E+03	0.00E+00	1.00E+06	1.00E+03	1.00E+06	1.00E+06	1.00E+04	1.00E+03	1.00E+06	1.00E+06	1.00E+06	1.00E+02	1.00E+02	1.00E+03	1.00E+06
WT-4 C	1.00E+06	1.00E+06	1.00E+02	0.00E+00	1.00E+06	1.00E+03	1.00E+06	1.00E+06	1.00E+04	1.00E+05	1.00E+06	1.00E+06	1.00E+06	1.00E+02	1.00E+02	1.00E+05	1.00E+06
WT-4 D	1.00E+03	1.00E+02	0.00E+00	0.00E+00	1.00E+04	0.00E+00	1.00E+03	1.00E+03	0.00E+00	0.00E+00	1.00E+03	1.00E+02	1.00E+03	0.00E+00	0.00E+00	1.00E+01	1.00E+04
WT-4 E	1.00E+06	1.00E+06	1.00E+03	0.00E+00	1.00E+06	1.00E+03	1.00E+06	1.00E+05	1.00E+03	1.00E+04	1.00E+05	1.00E+05	1.00E+05	1.00E+02	1.00E+02	1.00E+05	1.00E+06
WT-4 F	1.00E+05	1.00E+05	1.00E+02	0.00E+00	1.00E+04	1.00E+02	1.00E+04	1.00E+03	1.00E+02	1.00E+02	1.00E+03	1.00E+03	1.00E+03	1.00E+02	1.00E+02	1.00E+02	1.00E+04
WT-5 A	1.00E+06	1.00E+06	1.00E+02	0.00E+00	1.00E+04	1.00E+03	1.00E+04	1.00E+04	1.00E+03	1.00E+03	1.00E+03	1.00E+03	1.00E+04	1.00E+02	1.00E+02	1.00E+02	1.00E+04
WT-5 B	1.00E+05	1.00E+05	1.00E+05	0.00E+00	1.00E+05	1.00E+04	1.00E+06	1.00E+05	1.00E+05	1.00E+04	1.00E+05	1.00E+05	1.00E+05	1.00E+01	1.00E+02	1.00E+01	1.00E+06
WT-5 C	1.00E+05	1.00E+06	1.00E+05	0.00E+00	1.00E+05	1.00E+04	1.00E+06	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+01	1.00E+02	1.00E+01	1.00E+06
WT-5 D	1.00E+04	1.00E+04	1.00E+05	0.00E+00	1.00E+04	1.00E+04	1.00E+06	1.00E+05	1.00E+05	1.00E+04	1.00E+05	1.00E+05	1.00E+05	1.00E+01	1.00E+02	1.00E+01	1.00E+05
WT-5 E	1.00E+06	1.00E+05	1.00E+05	0.00E+00	1.00E+05	1.00E+04	1.00E+06	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+01	1.00E+02	1.00E+01	1.00E+05
WT-5 F	1.00E+06	1.00E+06	1.00E+05	0.00E+00	1.00E+05	1.00E+04	1.00E+06	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+01	1.00E+02	1.00E+01	1.00E+05
WT-6 A	1.00E+05	1.00E+06	1.00E+05	0.00E+00	1.00E+05	1.00E+04	1.00E+06	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+01	1.00E+02	1.00E+01	1.00E+05
WT-6 B	1.00E+05	1.00E+05	1.00E+04	0.00E+00	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+04	1.00E+02	1.00E+02	1.00E+01	1.00E+04
WT-6 C	1.00E+05	1.00E+05	1.00E+03	0.00E+00	1.00E+05	1.00E+03	1.00E+04	1.00E+04	1.00E+04	1.00E+03	1.00E+05	1.00E+04	1.00E+04	1.00E+03	1.00E+02	1.00E+04	1.00E+04
WT-6 D	1.00E+05	1.00E+05	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+03	1.00E+02	1.00E+02	1.00E+05
WT-6 E	1.00E+05	1.00E+05	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+03	1.00E+02	1.00E+02	1.00E+05
WT-6 F	1.00E+05	1.00E+05	1.00E+05	0.00E+00	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+05	1.00E+03	1.00E+02	1.00E+02	1.00E+05
c126	1.00E+05	1.00E+05	1.00E+03	0.00E+00	1.00E+04	1.00E+03	1.00E+05	1.00E+04	1.00E+04	1.00E+04	1.00E+05	1.00E+04	1.00E+05	1.00E+02	1.00E+02	1.00E+01	1.00E+05
	clpX	*crr*	*gmhA*	*dnaK*	*recA*	*rfaC*	*nuoG*	*ompC*	*rfaF*	*hldD*	*tpx*	*hsdS*	*manX*	*manY*	*dnaJ*	*nusB*	*WT*

Supplementary table 5: oligos for λ modification using MAGE

Mutation	Oligo Sequence
H_11378	5' GTCTGCCCAGGTCTCCAGCGTGCCCATGTTCTCTTTCAGGCGGCGGGTCTGGTCATCAAGCCCTTTCGTTGCGGCCTCGTTCGCCGCCTG 3'
H_11432	5' CATCCCACATGGATTTGAATGCCCGCGCAGTCCTGTCTGTCCAGGTCTCCAGCGTGCCCATGTTCTCTTTCAGGCGGCGGGTCTGGTCAT 3'
ninI_37640	5' TTTCCAAACTCGTATTCGTCAAAGGGATAATCGGCGTGGAAGATAACATATTTTTTATCTTTGCTCACCAGTTCGATGATTAACGGAAGT 3'
S_39212	5' CGCAAGGATTGCCCCGATGCCTTGTTCCTTTGCCGCGAGAATGGCGGCCAACAGGCCATGTTTTTCTGGCATCTTCATGTCTTACCCCCAA 3'
S_39170	5' GGTCATGTTTTTCTGGCATCTTCATGTCTTACCCCCAATAAGGGtATTTGCTCTATTTAATTAGGAATAAGGTCGATTACTGATAGAACA 3'
J_18824	5' CTGTTTCTTAATCACCATAACCTGCACATCGCTGGCAAACGTATACGGCGGAATACCTGCCGAATGCCGTGTGGACGTAAGCGTGAACGT 3'

Supplementary table 6: primers for sanger sequencing verification of mutation incorporation in post MAGE isolates

Mutation	Direction	Primer Sequence	Direction	Primer Sequence
H_11378	FWD	5' ACTCAACCCTGTCCGATTTC 3'	REV	5' CTGCGCCTCTTCGGTATATT
H_11432	FWD	5' ACTCAACCCTGTCCGATTTC 3'	REV	5' CTGCGCCTCTTCGGTATATT 3'
ninI_37640	FWD	5' GGAGTGAAAGAGATGCGCTATTA 3'	REV	5' TTGCCACACCACGGTATTT 3'
S_39212/S_39170	FWD	5' TAGAGCCTGCATAACGGTTTC 3'	REV	5' GGGTGATCGGAGTAATCAGTAAAT 3'

Supplemental table 7: initial and final concentrations for modified λ competitive growth rate experiments.

Modified lambda strain/host strain	Initial modified lambda concentration	Final modified lambda concentration	Initial cI857lacZ concentration	Final cI857lacZ Concentration
H11378/WT 1	2.80E+06	5.09E+09	3.00E+06	9.50E+08
H11378/WT 2	2.28E+06	5.12E+09	1.80E+06	2.68E+09
H11378/WT 3	2.76E+06	6.52E+09	2.68E+06	3.08E+09
H11378/manY 1	2.92E+06	2.94E+08	2.96E+06	1.50E+07
H11378/manY 2	2.44E+06	4.44E+08	1.80E+06	1.90E+07
H11378/manY 3	2.48E+06	4.88E+08	2.28E+06	2.80E+07
H11432/WT 1	1.20E+06	3.40E+09	1.20E+06	2.83E+09
H11432/WT 2	1.04E+06	3.24E+09	1.76E+06	1.96E+09
H11432/WT 3	1.40E+06	3.27E+09	2.04E+06	3.03E+09
H11432/manY 1	1.84E+06	8.40E+08	1.60E+06	3.00E+07
H11432/manY 2	1.24E+06	8.32E+08	1.96E+06	4.30E+07
H11432/manY 3	1.44E+06	7.80E+08	2.32E+06	4.80E+07
cI857/WT 1	2.00E+06	3.84E+09	2.64E+06	3.44E+09
cI857/WT 2	1.44E+06	3.28E+09	1.60E+06	4.24E+09
cI857/WT 3	1.60E+06	5.04E+09	2.72E+06	3.20E+09
cI857/manY 1	1.36E+06	2.52E+07	1.44E+06	3.96E+07
cI857/manY 2	1.12E+06	2.76E+07	1.76E+06	4.20E+07
cI857/manY 3	1.20E+06	3.24E+07	1.52E+06	4.72E+07

Modified lambda strain/host strain	Initial modified lambda concentration	Final modified lambda concentration	Initial cI857lacZ concentration	Final cI857lacZ Concentration
ninI37640/nusB 1	4.40E+05	4.76E+06	2.14E+06	1.20E+05
ninI37640/nusB 2	3.30E+05	6.76E+06	2.60E+06	1.20E+05
ninI37640/nusB 3	3.00E+05	5.64E+06	1.84E+06	1.20E+05
ninI37640/WT 1	2.20E+05	1.24E+09	2.64E+06	1.41E+10
ninI37640/WT 2	3.60E+05	7.20E+08	2.40E+06	1.12E+10
ninI37640/WT 3	3.00E+05	1.24E+09	2.06E+06	1.24E+10
cI857/nusB 1	1.10E+06	9.60E+03	1.50E+06	3.60E+04
cI857/nusB 2	9.80E+05	8.80E+03	2.58E+06	3.56E+04
cI857/nusB 3	1.12E+06	8.20E+03	2.10E+06	2.68E+04
cI857/WT 1	1.12E+06	2.72E+09	2.40E+06	5.56E+09
cI857/WT 2	9.50E+05	2.38E+09	2.14E+06	8.56E+09
cI857/WT 3	1.54E+06	2.16E+09	2.64E+06	8.28E+09

Modified lambda strain/host strain	Initial modified lambda concentration	Final modified lambda concentration	Initial cI857lacZ concentration	Final cI857lacZ Concentration
S39212/WT 1	1.40E+06	2.08E+09	1.25E+06	1.59E+09
S39212/WT 2	1.23E+06	2.08E+09	1.11E+06	2.21E+09
S39212/WT 3	2.05E+06	2.13E+09	1.64E+06	1.61E+09
S39212/dnaJ 1	1.77E+06	1.21E+05	1.29E+06	1.80E+04
S39212/dnaJ 2	1.80E+06	1.28E+05	1.57E+06	2.20E+04
S39212/dnaJ 3	1.58E+06	1.80E+05	1.15E+06	1.50E+04
S39212/nusB 1	2.19E+06	3.72E+04	1.65E+06	1.32E+04
S39212/nusB 2	1.69E+06	1.72E+04	1.67E+06	1.04E+04
S39212/nusB 3	2.17E+06	2.08E+04	1.86E+06	9.60E+03
cI857/WT 1	1.17E+06	1.80E+09	1.38E+06	1.45E+09
cI857/WT 2	1.01E+06	7.70E+08	1.63E+06	7.60E+08
cI857/WT 3	1.21E+06	7.20E+08	2.01E+06	8.60E+08
cI857/dnaJ 1	1.20E+06	1.68E+04	2.30E+06	2.20E+04
cI857/dnaJ 2	1.15E+06	1.20E+04	1.94E+06	2.00E+04
cI857/dnaJ 3	1.13E+06	1.56E+04	2.30E+06	2.04E+04
cI857/nusB 1	1.03E+06	1.48E+04	1.99E+06	8.80E+03
cI857/nusB 2	8.80E+05	1.00E+04	1.41E+06	1.28E+04
cI857/nusB 3	1.08E+06	1.40E+04	1.93E+06	7.60E+03

Modified lambda strain/host strain	Initial modified lambda concentration	Final modified lambda concentration	Initial cI857lacZ concentration	Final cI857lacZ Concentration
S39170/WT 1	4.00E+07	1.70E+09	1.40E+07	6.40E+08
S39170/WT 2	3.70E+07	3.30E+09	1.90E+07	1.21E+09
S39170/WT 3	5.50E+07	2.34E+09	1.10E+07	8.90E+08
S39170/dnaJ 1	4.20E+07	2.82E+07	8.00E+06	1.72E+07
S39170/dnaJ 2	4.00E+07	6.28E+07	7.00E+06	2.92E+07
S39170/dnaJ 3	3.50E+07	6.04E+07	8.00E+06	3.12E+07
cI857/WT 1	1.70E+07	2.64E+09	1.30E+07	5.16E+09
cI857/WT 2	1.20E+07	2.12E+09	9.00E+06	3.60E+09
cI857/WT 3	2.10E+07	3.48E+09	8.00E+06	5.20E+09
cI857/dnaJ 1	1.80E+07	5.20E+06	1.10E+07	1.02E+07
cI857/dnaJ 2	1.80E+07	8.00E+06	1.90E+07	1.20E+07
cI857/dnaJ 3	1.60E+07	6.00E+06	1.10E+07	8.20E+06

Supplemental table 8: mutation profiles of all evolved isolates from BreSeq output files.

Sample	Total reads	Position	Base change	Gene	Predicted or marginal	Frequency (if marginal)
clpX A	4816125	18751	A→G	J→	predicted	
clpX B	4671959	18535	A→G	J→	predicted	
clpX C	3606338	18535	A→G	J→	predicted	
clpX E	4763246	18824	A→C	J→	predicted	
clpX F	3932627	18535	A→G	J→	predicted	
clpX F	3932627	32003	A→G	cI ← / → cro	predicted	
cplX D	5041887	18823	G→A	J→	predicted	
crr A	4646270	18737	A→G	J→	predicted	
crr B	3893381	18751	A→G	J→	predicted	
crr C	4132576	18824	A→G	J→	predicted	
crr D	5451409	17419	G→T	J→	predicted	
crr D	5451409	18730	G→A	J→	predicted	
crr D	5451409	31455	C→A	cI←	predicted	
crr E	4578574	18501	G→T	J→	predicted	
crr E	4578574	18823	G→A	J→	predicted	
crr F	3727090	18535	A→G	J→	predicted	
crr F	3727090	42432	C→G	lambdap79→ / -	predicted	
crr F	3727090	42434	2bp→AG	lambdap79→ / -	predicted	
crr F	3727090	42437	C→T	lambdap79→ / -	predicted	
crr F	3727090	42449	T→C	lambdap79→ / -	predicted	
crr F	3727090	42464	C→T	lambdap79→ / -	predicted	
crr F	3727090	42472	C→T	lambdap79→ / -	predicted	
crr F	3727090	42476	2bp→GT	lambdap79→ / -	predicted	
crr F	3727090	42491	T→C	lambdap79→ / -	predicted	
dnaJ A	450113	18,503	C→T	*J* →	predicted	
dnaJ A	450113	21,595	G→T	*orf-401* → / ← int	predicted	
dnaJ A	450113	39,212	A→G	*S* →	predicted	
dnaJ B	637988	18,503	C→T	*J* →	predicted	
dnaJ B	637988	39,170	C→A	*orf-64* → / → S	predicted	
dnaK A	4286465	18503	C→T	J→	predicted	
dnaK A	4286465	18823	G→A	J→	predicted	
dnaK B	5705760	18835	T→C	J→	predicted	
dnaK C	4491146	18503	C→T	J→	predicted	
dnaK D	4985869	18835	T→C	J→	predicted	
dnaK E	4468036	18503	C→T	J→	predicted	
dnaK F	3261467	18835	T→C	J→	predicted	
dnaK F	3261467	42300	C→A	lambdap79 → /-	predicted	
dnaK F	3261467	42432	C→G	lambdap79 → /-	predicted	
dnaK F	3261467	42434	2bp→AG	lambdap79 → /-	predicted	
dnaK F	3261467	42437	C→T	lambdap79 → /-	predicted	
dnaK F	3261467	42449	T→C	lambdap79 → /-	predicted	
dnaK F	3261467	42464	C→T	lambdap79 → /-	predicted	
dnaK F	3261467	42472	C→T	lambdap79 → /-	predicted	
dnaK F	3261467	42476	2bp→GT	lambdap79 → /-	predicted	
dnaK F	3261467	42491	T→C	lambdap79 → /-	predicted	
gmhA A	3861960	18481	A→G	J→	predicted	
gmhA B	4685134	18473	C→T	J→	predicted	
gmhA B	4685134	18835	T→C	J→	predicted	
gmhA C	4243117	18751	A→G	J→	predicted	
gmhA D	4432104	18877	C→G	J→	predicted	
gmhA E	3818269	18503	C→T	J→	predicted	
gmhA E	3818269	18734	T→C	J→	predicted	
gmhA F	4510047	18823	G→A	J→	predicted	
gmhA F	4510047	18835	T→C	J→	predicted	
hldD A	3954016	18,493	A→G	*J* →	predicted	
hldD A	3954016	18,824	A→G	*J* →	predicted	
hldD B	4718258	18,503	C→T	*J* →	predicted	
hldD B	4718258	18,535	A→G	*J* →	predicted	
hldD B	4718258	18,824	A→G	*J* →	predicted	
hldD C	3422662	53	C→T	– / → *nu1*	predicted	
hldD C	3422662	73	A→G	– / → *nu1*	predicted	
hldD C	3422662	85	T→A	– / → *nu1*	predicted	
hldD C	3422662	102	T→C	– / → *nu1*	predicted	
hldD C	3422662	186	2 bp→TG	– / → *nu1*	predicted	
hldD C	3422662	398	G→T	*nu1* →	predicted	
hldD C	3422662	412	G→A	*nu1* →	predicted	
hldD C	3422662	429	A→G	*nu1* →	predicted	
hldD C	3422662	474	C→T	*nu1* →	predicted	
hldD C	3422662	483	A→G	*nu1* →	predicted	
hldD C	3422662	489	G→A	*nu1* →	predicted	
hldD C	3422662	583	C→A	*nu1* →	predicted	
hldD C	3422662	18,752	T→C	*J* →	predicted	
hldD C	3422662	27,689	G→T	*ea10* ←	predicted	
hldD C	3422662	39,017	A→G	*orf-64* → / → S	predicted	
hldD D	4023301	18,503	C→T	J →	predicted	
hldD D	4023301	18,878	A→G	J →	predicted	
hldD D	4023301	28,476	A→G	orf28 ← / → lambdap48	predicted	
hldD E	3607313	18,500	A→C	*J* →	predicted	
hldD E	3607313	19,710	A→G	*orf-401* →	predicted	
hldD E	3607313	39,443	A→G	*S* →	predicted	
hldD F	3339056	18,495	T→G	*J* →	predicted	
hldD F	3339056	18,751	A→G	*J* →	predicted	

Supplemental table 8 continued: mutation profiles of all evolved isolates from BreSeq output files.

Sample	Total reads	Position	Base change	Gene	Predicted or marginal	Frequency (if marginal)
hsdS A	553727	18535	A→G	J →	predicted	
hsdS B	538398	1506	A→C	A →	predicted	
hsdS B	538398	18823	G→A	J →	predicted	
hsdS B	538398	21711	A→G	orf-401 → / ← int	predicted	
hsdS C	639878	18730	G→A	J →	predicted	
hsdS C	639878	28585	A→G	lambdap48 →	predicted	
hsdS D	387080	18730	G→A	J →	predicted	
hsdS E	338840	18733	G→A	J →	predicted	
hsdS E	338840	36964	A→G	NinG →	predicted	
hsdS F	465074	16572	G→A	J →	predicted	
hsdS F	465074	18823	G→A	J →	predicted	
hsdS F	465074	42432	C→G	lambdap79 → / –	predicted	
hsdS F	465074	42434	2 bp→AG	lambdap79 → / –	predicted	
hsdS F	465074	42437	C→T	lambdap79 → / –	predicted	
hsdS F	465074	42449	T→C	lambdap79 → / –	predicted	
hsdS F	465074	42464	C→T	lambdap79 → / –	predicted	
hsdS F	465074	42472	C→T	lambdap79 → / –	predicted	
hsdS F	465074	42476	2 bp→GT	lambdap79 → / –	predicted	
hsdS F	465074	42491	T→C	lambdap79 → / –	predicted	
manX A	2408	1	Δ42,507 bp	nu1–lambdap79	predicted	
manX B	54388	18823	G→A	J →	predicted	
manX B	54388	4755	T -> C	C	marginal	0.579
manX B	54388	22360	C .	int	marginal	0.2
manX B	54388	13891-13904	New junction	L	predicted	0.398
manX B	54388	22377-22387	new junction	int	predicted	0.374
manX B	54388	41110-41122	new junction	lambdap78	predicted	0.38
manX B	54388	41107-41127	new junction	lambdap78	marginal	0.139
manX C	517076	18751	A→G	J →	predicted	
manX C	517076	39127	T→C	orf-64 → / → S	predicted	
manX D	105641	18731	C→T	J →	predicted	
manX E	273764	18823	G→A	J →	predicted	
manX E	273764	42491	T C	lambdap79/–	marginal	0.226
manX F	48	1	Δ42,507 bp	nu1–*lambdap79*		
manY A	248627					
manY B	525188	11378	T→C	H →	predicted	
manY B	525188	18503	C→T	J →	predicted	
manY B	525188	33010	A→G	O →	predicted	
manY E	595090					
manY F	901928	11432	G→A	H →	predicted	
nuoG A	4500330	18535	A→G	J →	predicted	
nuoG A	4500330	22456	T→C	int ←	predicted	
nuoG B	4248874	18737	A→G	J →	predicted	
nuoG B	4248874	39982	A→G	Rz →	predicted	
nuoG C	4534567	18824	A→C	J →	predicted	
nuoG C	4534567	29697	$(G)_{6\rightarrow7}$	N ← / ← rexb	predicted	
nuoG C	4534567	29830	T→G	rexb ←	predicted	
nuoG C	4534567	32003	A→G	cI ← / → cro	predicted	
nuoG D	4229787	18737	A→G	J →	predicted	
nuoG E	4446838	18823	G→A	J →	predicted	
nuoG F	3596079	18535	A→G	J →	predicted	
nuoG F	3596079	41037	A→C	bor ← / ← lambdap78	predicted	
nuoG F	3596079	41785	A→G	lambdap79 →	predicted	
nusB A	702263	18503	C→T	J →	predicted	
nusB A	702263	35319	+TAT	NinC →	predicted	
nusB B	818244	18503	C→T	J →	predicted	
nusB B	818244	37305	G→T	NinI →	predicted	
nusB C	528989					
nusB D	598935	18503	C→T	J →	predicted	
nusB D	598935	37640	G→T	NinI →	predicted	
nusB D	598935	9745	T C	G	marginal	0.537
nusB D	598935	39212	A G	S	marginal	0.338
nusB D	598935	27600	T C	ea10	marginal	0.258
nusB E	553926	18503	C→T	J →	predicted	
nusB E	553926	37640	G→T	NinI →	predicted	
nusB E	553926	39212	A→G	S →	predicted	
nusB F	684211	18503	C→T	J →	predicted	
nusB F	684211	36305	A→T	NinF →	predicted	
ompC A	3345819	18535	A→G	J →	predicted	
ompC B	5892769	34206	T→C	P →	predicted	
ompC C	4897093	18734	T→G	J →	predicted	
ompC C	4897093	23327	T→C	lambdap35 ← / ← *ea8.5*	predicted	
ompC D	4339920	18872	A→G	J →	predicted	
ompC E	4214.667	18823	G→A	J →	predicted	
ompC F	4303427	18823	G→A	J →	predicted	
recA A	4619255	18473	C→T	J→	predicted	
recA A	4619255	18835	T→C	J→	predicted	
recA A	4619255	32900	A→G	O→	predicted	
recA B	4613527	18503	C→T	J→	predicted	
recA B	4613527	18535	A→G	J→	predicted	
recA C	3620450	18535	A→G	J→	predicted	
recA C	3620450	18835	T→C	J→	predicted	
recA C	3620450	32015	G→A	cI ← / → cro	predicted	
recA D	5169558	18535	A→G	J→	predicted	
recA D	5169558	18823	G→A	J→	predicted	
recA E	4330027	18500	A→C	J→	predicted	
recA F	3871885	18503	C→T	J→	predicted	
recA F	3871885	18737	A→G	J→	predicted	

Supplemental table 8 continued: mutation profiles of all evolved isolates from BreSeq output files.

Sample	Total reads	Position	Base change	Gene	Predicted or marginal	Frequency (if marginal)
rfaC A	3600676	18535	A→G	J→	marginal	0.649
rfaC A	3600676	18823	G→A	J→	marginal	0.642
rfaC A	3600676	19683	G→A	orf-401→	marginal	0.332
rfaC A	3600676	18491	A→C	J→	marginal	0.301
rfaC B	4650434	1868	G→T	A→	predicted	
rfaC B	4650434	18500	A→C	J→	predicted	
rfaC C	4489428	18503	C→T	J→	predicted	
rfaC C	4489428	18535	A→G	J→	predicted	
rfaC D	4006284	18500	A→C	J→	predicted	
rfaC E	4272075	18535	A→G	J→	predicted	
rfaC E	4272075	18823	G→A	J→	predicted	
rfaC F	4382434	18500	A→C	J→	predicted	
rfaF A	3349176	18500	A→C	J →	predicted	
rfaF A	3349176	25980	T→C	exo ←	predicted	
rfaF A	3349176	39183	(G)5→6	orf-64 → / → S	predicted	
rfaF B	3889186	16983	T→C	J →	predicted	
rfaF B	3889186	18500	A→C	J →	predicted	
rfaF B	3889186	18649	A→C	J →	predicted	
rfaF C	4120286	18500	A→C	J →	predicted	
rfaF D	4170859	53	C→T	– / → *nu1*	predicted	
rfaF D	4170859	73	A→G	– / → *nu1*	predicted	
rfaF D	4170859	85	T→A	– / → *nu1*	predicted	
rfaF D	4170859	102	T→C	– / → *nu1*	predicted	
rfaF D	4170859	186	2 bp→TG	– / → *nu1*	predicted	
rfaF D	4170859	398	G→T	nu1 →	predicted	
rfaF D	4170859	412	G→A	nu1 →	predicted	
rfaF D	4170859	429	A→G	nu1 →	predicted	
rfaF D	4170859	474	C→T	nu1 →	predicted	
rfaF D	4170859	483	A→G	nu1 →	predicted	
rfaF D	4170859	489	G→A	nu1 →	predicted	
rfaF D	4170859	18730	G→A	J →	predicted	
rfaF D	4170859	35038	G→T	NinB →	predicted	
rfaF D	4170859	40073	C→T	Rz →	predicted	
rfaF D	4170859	40107	G→A	Rz →	predicted	
rfaF D	4170859	40194	T→G	Rz →	predicted	
rfaF D	4170859	40290	C→G	Rz →	predicted	
rfaF D	4170859	40434	T→C	Rz → / ← *bor*	predicted	
rfaF D	4170859	40437	C→A	Rz → / ← *bor*	predicted	
rfaF D	4170859	40468	G→T	bor ←	predicted	
rfaF D	4170859	40592	G→A	bor ←	predicted	
rfaF D	4170859	40672	C→T	bor ←	predicted	
rfaF D	4170859	40674	G→T	bor ←	predicted	
rfaF D	4170859	40694	C→T	bor ←	predicted	
rfaF D	4170859	40867	T→C	bor ← / ← *lambdap78*	predicted	
rfaF D	4170859	42300	C→A	lambdap79 → / –	predicted	
rfaF D	4170859	42432	C→G	lambdap79 → / –	predicted	
rfaF D	4170859	42434	2 bp→AG	lambdap79 → / –	predicted	
rfaF D	4170859	42437	C→T	lambdap79 → / –	predicted	
rfaF D	4170859	42449	T→C	lambdap79 → / –	predicted	
rfaF D	4170859	42464	C→T	lambdap79 → / –	predicted	
rfaF D	4170859	42472	C→T	lambdap79 → / –	predicted	
rfaF D	4170859	42476	2 bp→GT	lambdap79 → / –	predicted	
rfaF D	4170859	40668		bor	marginal	0.189
rfaF D	4170859	37104		NinH	marginal	0.189
rfaF D	4170859	2679/12680		H	marginal	0.156
rfaF D	4170859	42491	T→C	lambdap79 → / –	predicted	
rfaF E	4153404	18500	A→C	J →	predicted	
rfaF F	3604925	18500	A→C	J →	predicted	
rfaF F	3604925	18651	C→A	J →	predicted	
tpx A	3480745	18622	A→G	J →	predicted	
tpx A	3480745	39127	T→C	orf-64 → / → S	predicted	
tpx B	4742092	39165		orf-64/S	marginal	0.265
tpx B	4742092	117	A→G	– / → *nu1*	predicted	
tpx B	4742092	18622	A→G	J →	predicted	
tpx B	4742092	19929	A→C	orf-401 →	predicted	
tpx B	4742092	26477	A→G	bet ←	predicted	
tpx B	4742092	30986	T→C	rexa ←	predicted	
tpx B	4742092	39127	T→C	orf-64 → / → S	predicted	
tpx B	4742092	40831	T→G	bor ← / ← lambdap78	predicted	
tpx C	4515269	61	T→G	– / → *nu1*	predicted	
tpx C	4515269	18535	A→G	J →	predicted	
tpx C	4515269	18823	G→A	J →	predicted	
tpx C	4515269	32003	A→G	cI ← / → cro	predicted	
tpx C	4515269	37446	T→C	NinI →		
tpx D	4617814	13798	A→G	L →	predicted	
tpx D	4617814	18730	G→A	J →	predicted	
tpx D	4617814	32749	T→C	O →	predicted	
tpx D	4617814	39127	T→C	orf-64 → / → S	predicted	
tpx E	4434768	116	A→G	– / → *nu1*	predicted	
tpx E	4434768	18751	A→G	J →	predicted	
tpx F	3654198	118	Δ1 bp	– / → *nu1*	predicted	
tpx F	3654198	18842	T→C	J →	predicted	
tpx F	3654198	42300	C→A	lambdap79 → / –		

Supplemental table 8 continued: mutation profiles of all evolved isolates from BreSeq output files.

Sample	Total reads	Position	Base change	Gene	Predicted or marginal	Frequency (if marginal)
WT-1 A	1150485	116	A→G	– / → *nu1*	predicted	
WT-1 A	1150485	9067	T→C	V →	predicted	
WT-1 A	1150485	18503	C→T	J →	predicted	
WT-1 A	1150485	18884	T→C	J →	predicted	
WT-1 A	1150485	20200	A→G	orf-401 →	predicted	
WT-1 B	143924	531	T→C	nu1 →	predicted	
WT-1 B	143924	534	T→G	nu1 →	predicted	
WT-1 B	143924	597	G→T	nu1 →	predicted	
WT-1 B	143924	606	T→C	nu1 →	predicted	
WT-1 B	143924	609	T→C	nu1 →	predicted	
WT-1 B	143924	615	A→G	nu1 →	predicted	
WT-1 B	143924	631	G→A	nu1 →	predicted	
WT-1 B	143924	678	C→T	nu1 →	predicted	
WT-1 B	143924	691	C→A	nu1 →	predicted	
WT-1 B	143924	832	G→C	A →	predicted	
WT-1 B	143924	838	A→G	A →	predicted	
WT-1 B	143924	841	C→G	A →	predicted	
WT-1 B	143924	844	A→C	A →	predicted	
WT-1 B	143924	874	C→G	A →	predicted	
WT-1 B	143924	880	G→A	A →	predicted	
WT-1 B	143924	883	G→C	A →	predicted	
WT-1 B	143924	886	C→G	A →	predicted	
WT-1 B	143924	904	C→T	A →	predicted	
WT-1 B	143924	906	G→A	A →	predicted	
WT-1 B	143924	916	C→A	A →	predicted	
WT-1 B	143924	925	G→C	A →	predicted	
WT-1 B	143924	958	C→A	A →	predicted	
WT-1 B	143924	965	C→T	A →	predicted	
WT-1 B	143924	982	C→G	A →	predicted	
WT-1 B	143924	985	C→T	A →	predicted	
WT-1 B	143924	991	2 bp→TC	A →	predicted	
WT-1 B	143924	997	T→C	A →	predicted	
WT-1 B	143924	1006	C→A	A →	predicted	
WT-1 B	143924	1009	2 bp→TT	A →	predicted	
WT-1 B	143924	1045	G→A	A →	predicted	
WT-1 B	143924	1057	2 bp→GT	A →	predicted	
WT-1 B	143924	1060	C→G	A →	predicted	
WT-1 B	143924	1063	C→T	A →	predicted	
WT-1 B	143924	1075	T→G	A →	predicted	
WT-1 B	143924	1081	T→C	A →	predicted	
WT-1 B	143924	1093	G→A	A →	predicted	
WT-1 B	143924	1096	G→T	A →	predicted	
WT-1 B	143924	1111	G→C	A →	predicted	
WT-1 B	143924	1183	C→T	A →	predicted	
WT-1 B	143924	1189	C→T	A →	predicted	
WT-1 B	143924	1201	A→G	A →	predicted	
WT-1 B	143924	18503	C→T	J →	predicted	
WT-1 B	143924	18823	G→A	J →	predicted	
WT-1 B	143924	39172	C→A	orf-64 → / → S	predicted	
WT-1 B	143924	42491	T→C	lambdap79 → / –	predicted	
WT-1 B	143924	42498	A→C	lambdap79 → / –	predicted	
WT-1 B	143924	42500	2 bp→TT	lambdap79 → / –	predicted	
WT-1 B	143924	928	T C	A	marginal	0.797
WT-1 B	143924	931	G T	A	marginal	0.797
WT-1 B	143924	934	G T	A	marginal	0.797
WT-1 B	143924	1039	T C	A	marginal	0.79
WT-1 B	143924	868	A G	A	marginal	0.788
WT-1 B	143924	869	C T	A	marginal	0.788
WT-1 B	143924	910	C T	A	marginal	0.786
WT-1 B	143924	510	A G	nu1	marginal	0.779
WT-1 B	143924	693	G A	nu1	marginal	0.775
WT-1 B	143924	949	C T	A	marginal	0.766
WT-1 B	143924	642	G C	nu1	marginal	0.759
WT-1 B	143924	952	T C	A	marginal	0.753
WT-1 B	143924	52	G C	–/nu1	marginal	0.75
WT-1 B	143924	736	C G	A	marginal	0.741
WT-1 B	143924	737	A G	A	marginal	0.741
WT-1 B	143924	1120	C A	A	marginal	0.741
WT-1 B	143924	176	C G	–/nu1	marginal	0.733
WT-1 B	143924	177	C T	–/nu1	marginal	0.733
WT-1 B	143924	1022	T C	A	marginal	0.725
WT-1 B	143924	1027	G T	A	marginal	0.708
WT-1 B	143924	29749 =/29769 =	new junction	N/rexb	marginal	0.172
WT-1 B	143924	22791 =/22813 =	new junction	int	marginal	0.142
WT-1 B	143924	32308 =/32330 =	new junction	cro/cII	marginal	0.145
WT-1 B	143924	29036=/29042 =	new junction	lambdap48, N	marginal	0.144
WT-1 B	143924	33172/33186	new junction	O	marginal	0.136
WT-1 B	143924	33165/33171	new junction	O	marginal	0.173
WT-1 B	143924	33161/33172	new junction	O	marginal	0.151
WT-1 B	143924	33166-33180	new junction	O	predicted	0.521

Supplemental table 8 continued: mutation profiles of all evolved isolates from BreSeq output files.

Sample	Total reads	Position	Base change	Gene	Predicted or marginal	Frequency (if marginal)
WT-1 C	684372	18503	C T	J	marginal	0.61
WT-1 C	684372	18884	T C	J	marginal	0.592
WT-1 C	684372	39127	T C	orf-64/S	marginal	0.562
WT-1 C	684372	116	A G	–/nu1	marginal	0.4
WT-1 C	684372	18823	G A	J	marginal	0.36
WT-1 C	684372	29786	. G	N/rexb	marginal	0.342
WT-1 D	572119	116	A→G	– / → *nu1*	predicted	
WT-1 D	572119	10636	T→C	H →	predicted	
WT-1 D	572119	18503	C→T	J →	predicted	
WT-1 D	572119	18884	T→C	J →	predicted	
WT-1 D	572119	22852	T→G	int ←	predicted	
WT-1 D	572119	39182	G→A	orf-64 → / → S	predicted	
WT-1 E	420530	39198	G T	S	marginal	0.688
WT-1 E	420530	1263	A G	A	marginal	0.635
WT-1 E	420530	62	T C	–/nu1	marginal	0.581
WT-1 E	420530	61	T G	–/nu1	marginal	0.291
WT-1 E	420530	1096	G T	A	marginal	0.245
WT-1 E	420530	693	G A	nu1	marginal	0.24
WT-1 E	420530	691	C A	nu1	marginal	0.238
WT-1 E	420530	18503	C→T	J →	predicted	
WT-1 E	420530	18884	T→C	J →	predicted	
WT-1 F	1246537	18503	C→T	J →	predicted	
WT-1 F	1246537	18884	T→C	J →	predicted	
WT-1 F	1246537	39198	G→A	S →	predicted	
WT-2 A	3462693	18535	A→G	J→	predicted	
WT-2 A	3462693	18824	A→G	J→	predicted	
WT-2 B	3741124	18751	A→G	J→	predicted	
WT-2 B	3741124	39172	C→T	orf-64 →/→S	predicted	
WT-2 C	4546103	1802	T→C	A→	predicted	
WT-2 C	4546103	18622	A→G	J→	predicted	
WT-2 D	3718619	18824	A→G	J→	marginal	0.672
WT-2 D	3718619	38636	C→T	orf-64 →	marginal	0.672
WT-2 D	3718619	39127	T→C	orf-64 →/→S	marginal	0.672
WT-2 E	3944544	18823	G→A	J→	predicted	
WT-2 E	3944544	39127	T→C	orf-64 →/→S	predicted	
WT-2 F	4404135	18823	G→A	J→	mariginal	0.787
WT-2 F	4404135	32547	(G)6→7	cII→	mariginal	0.787
WT-2 F	4404135	39127	T→C	orf-64 →/→S	mariginal	0.787
WT-3 A	2038559	18824	A→C	J →	predicted	
WT-3 A	2038559	39092	C→A	orf-64 → / → *S*	predicted	
WT-3 B	4664174	18823	G→A	J →	predicted	
WT-3 C	5349633	4428	G→A	B →	predicted	
WT-3 C	5349633	18823	G→A	J →	predicted	
WT-3 C	5349633	27447	A→T	cIII ←	predicted	
WT-3 D	4543718	18823	G→A	J →	predicted	
WT-3 D	4543718	35478	A→G	NinC →	predicted	
WT-3 E	5167935	18823	G→A	J →	predicted	
WT-3 E	5167935	19747	T→C	orf-401 →	predicted	
WT-3 F	5100901	18823	G→A	J →	predicted	
WT-3 F	5100901	30200	C→A	rexb ←	predicted	
WT-3 F	5100901	39127	T→C	orf-64 → / → *S*	predicted	
WT-3 F	5100901	39142	A→C	orf-64 → / → *S*	predicted	
WT-4 A	643331	18823	G→A	J →	predicted	
WT-4 B	539710	18823	G→A	J →	predicted	
WT-4 B	539710	20255	T→C	orf-401 →	predicted	
WT-4 C	489613	5667	A→G	C →	predicted	
WT-4 C	489613	18823	G→A	J →	predicted	
WT-4 C	489613	39181	G→T	orf-64 → / → S	predicted	
WT-4 D	1310033	6039	A→G	D →	predicted	
WT-4 D	1310033	18824	A→C	J →	predicted	
WT-4 D	1310033	18835	T→C	J →	predicted	
WT-4 D	1310033	32500	A→G	cII →	predicted	
WT-4 E	449512	18535	A→G	J →	predicted	
WT-4 F	409563	18823	G→A	J →	predicted	
WT-5 A	3666622	18823	G→A	J →	predicted	
WT-5 A	3666622	32003	A→G	cI ← / → *cro*	predicted	
WT-5 A	3666622	39127	T→C	orf-64 → / → *S*	predicted	
WT-5 B	3801784	18823	G→A	J →	predicted	
WT-5 B	3801784	39127	T→C	orf-64 → / → *S*	predicted	
WT-5 C	4080224	62	T→C	– / → *nu1*	predicted	
WT-5 C	4080224	18823	G→A	J →	predicted	
WT-5 D	2758261	18823	G→A	J →	predicted	
WT-5 D	2758261	19149	A→G	lom →	predicted	
WT-5 D	2758261	39127	T→C	orf-64 → / → *S*	predicted	
WT-5 E	3838658	18535	A→G	J →	predicted	
WT-5 E	3838658	18823	G→A	J →	predicted	
WT-5 F	3443382	18734	T→C	J →	predicted	
WT-5 F	3443382	18823	G→A	J →	predicted	
WT-5 F	3443382	39127	T→C	orf-64 → / → *S*	predicted	
WT-6 A	4315618	18535	A→G	J→	predicted	
WT-6 A	4315618	18823	G→A	J→	predicted	
WT-6 B	4424663	18823	G→A	J→	predicted	
WT-6 C	4218933	18535	A→G	J→	predicted	
WT-6 C	4218933	18823	G→A	J→	predicted	
WT-6 C	4218933	39127	T→C	orf-64→/→S	predicted	
WT-6 D	3744760	18535	A→G	J→	predicted	
WT-6 D	3744760	18823	G→A	J→	predicted	
WT-6 E	4107342	18823	G→A	J→	predicted	
WT-6 F	4510712	18823	G→A	J→	predicted	
WT-6 F	4510712	39343	G→T	S→	predicted	

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