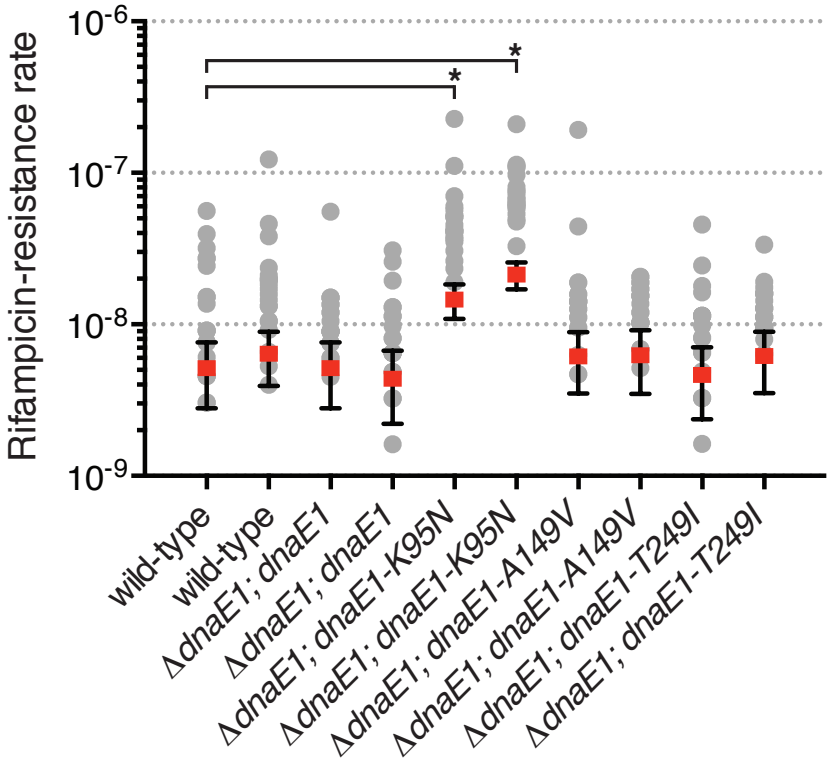
A

Genome Coordinate	Reference Base	Alternative Base	Effect	SNP Prevalence
1747837	C	G	silent_T46	1 in 1725
1747972	C	T	silent_D91	6 in 1725
1747984	G	T	K95N	1 in 1725
1747987	C	G ; T	silent_A96 ; silent_A96	22 in 1725 ; 1 in 1725
1748131	C	T	silent_L144	6 in 1725
1748145	C	T	A149V	1 in 1725
1748152	C	T	silent_G151	1 in 1725
1748445	C	T	T249I	52 in 1725

B



Supplemental Figure 7. Loss-of-function mutations in the *dnaE1* PHP domain are rarely found in clinical *M. tuberculosis* isolates.
(A) *dnaE1* (*Rv1547*) PHP domain single nucleotide polymorphisms (SNPs) observed in clinical Mtb isolates. SNP prevalence refers to the number of clinical strains containing the indicated SNP as compared to the total number of clinical strains analyzed. See Supplemental Table 3 for additional information. **(B)** Fluctuation analysis was used to determine the rates at which the indicated *M. smegmatis* strains acquired resistance to rifampicin. With the exception of wild-type *M. smegmatis*, these strains harbor a deletion of the endogenous *dnaE1* (*Ms3178*) gene and have been complemented with the indicated *M. tuberculosis dnaE1* (*Rv1547*) gene. Circles represent mutant frequency (number of rifampicin-resistant mutants per cell plated in a single culture). The red bar represents the estimated mutation rate (mutations conferring rifampicin resistance per generation), with error bars representing the 95% confidence interval (CI). * $P < 0.05$ in comparison of mutant frequencies by Wilcoxon rank-sum test.