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Elucidating the factors governing the functional compatibility of horizontally transferred genes is important to understand bacterial evolution, including the emergence and spread of antibiotic resistance, and to successfully engineer biological systems. In silico efforts and work using single-gene libraries have suggested that sequence composition is a strong barrier for the successful integration of heterologous genes. Here we sample 200 diverse genes, representing >80% of sequenced antibiotic resistance genes, to interrogate the factors governing genetic compatibility in new hosts. In contrast to previous work, we find that GC content, codon usage, and mRNA-folding energy are of minor importance for the compatibility of mechanistically diverse gene products at moderate expression. Instead, we identify the phylogenetic origin, and the dependence of a resistance mechanism on host physiology, as major factors governing the functionality and fitness of antibiotic resistance genes. These findings emphasize the importance of biochemical mechanism for heterologous gene compatibility, and suggest physiological constraints as a pivotal feature orienting the evolution of antibiotic resistance.

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