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The Location of the Bacterial Origin of Replication is Critical for Initial Ciproflaxcin Antibiotic Resistance[1] JULIA BOS, Princeton University, RALPH NEHRING, DIANE CRUZ, Baylor College Medicine, DOUG AUSTIN, Boston University, SUSAN ROSENBERG, Baylor College Medicine, ROBERT AUSTIN, Princeton University — By using *E. coli* cells in which the unique origin of replication has been moved to a ectopic chromosome location distant from the native one, we probe how perturbation of gene order near the origin of replication impacts genome stability and survival under genomic attack. We find that when challenged with sub-inhibitory doses of ciprofloxacin, an antibiotic that generates replication fork stalling, cells with the ectopic origin show significant fitness loss. We show that genes functionally relevant to the cipro-induced stress response are largely located near the native origin, even in distantly related species. We show that while cipro induces increased copy number of genes proximal to the origin of replication as a direct consequence of replication fork stalling, gene copy number variation was reduced near the ectopic origin. Altered gene dosage in cells with an ectopic origin resulted in impaired replication fork repair and chromosome instability. We propose that gene distribution in the origin region acts as a fundamental first line of defense when the integrity of the genome is threatened and that genes proximal to the origin of replication serve as a mechanism of genetic innovation and a driving force of genome evolution in the presence of genotoxic antibiotics.

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