OXFORD GENETICS

GENETICS, 2026, 234(3), iyag262
https://doi.org/10.1093/genetics/iyag262
Advance Access Publication Date: 7 October 2026
Review

The dynamics of gene copy-number mutations: transient changes with long-lasting consequences

Isabella Tomanek [1,2,3,*], Călin C. Guet[4,*]

[1]Sir William Dunn School of Pathology, University of Oxford, South Parks Road, Oxford OX1 3RE, United Kingdom
[2]University of Vienna, Centre for Microbiology and Environmental Systems Science, Djerassiplatz 1, 1030 Vienna, Austria
[3]Present address: Faculty of Natural and Life Sciences, Department of Biosciences and Medical Biology, University of Salzburg, Hellbrunner Strasse 34, 5020 Salzburg, Austria
[4]Institute of Science and Technology Austria, Am Campus 1, 3400 Klosterneuburg, Austria

*Corresponding authors: Isabella Tomanek, Email: isabella.tomanek@plus.ac.at; Călin C. Guet, Email: calin@ist.ac.at

Gene copy-number mutations are frequent and prevalent yet often overlooked. While initially considered to be the neutrally evolving raw material needed for the emergence of new genes through the process of gene duplication and divergence, recent technical advances and renewed interest start to unravel a fundamentally different picture for duplications in bacteria: rather than being neutral, duplications have strong direct and indirect fitness effects, and rather than giving rise to evolutionary novelty through protein family expansions, duplications allow to transiently simply make more of the same. Tandem duplications arise at frequencies orders of magnitude higher than single nucleotide polymorphisms (SNPs), and they collapse at an even higher rate still. Understanding the biological idiosyncrasies of copy-number mutations is pivotal to understanding their fundamental role in bacterial evolution. Having multiple copies of a gene influences its evolutionary dynamics in surprising ways, slowing down divergence, acting along with purifying selection as a force of conservation, and facilitating "bet-hedging" in fluctuating environments or under diversifying selection. Paying careful attention to structural variation in genomic sequence analyses will yield a more comprehensive understanding of bacterial evolution, especially when it comes to the emergence of novel bacterial lineages, such as human pathogens.

Keywords: gene duplication; mutation rates; copy-number variation; duplication-divergence; bet-hedging; evolutionary dynamics; population genetics; microbiology

The process of duplication: underestimated rates and conflicting terminology across disciplines

The most easily measured and therefore also most commonly discussed mutations are point mutations—a change to a single nucleotide in the DNA sequence. The assumed random, uniform nature of point mutations is not only easy to glean from DNA sequence data but also convenient for our understanding of the process of evolution as the proverbial molecular clock (Bromham and Penny 2003). However, nature is full of mutations that take place on larger scales, such as inversions, deletions, and duplications (Darmon and Leach 2014) that form via a variety of molecular mechanisms (Darmon and Leach 2014; Yelin and Kishony 2026) and occur at a vast range of different rates. Their diversity in terms of size and their transient nature make them much harder to model, predict or even detect. Yet, the biological and medical importance of duplications cannot be overstated—they supply the raw material for much evolutionary novelty, provide a common mechanism of antibiotic resistance, and constitute one of the principal classes of driver mutations in cancer evolution (Wellenreuther et al. 2019; Raffaele Cosenza et al. 2025). This review aims to shed light on how the biological idiosyncrasies of copy-number mutations influence evolutionary trajectories in nontrivial ways. We review some intriguing recent findings that reveal how the properties of gene copy-number mutations not only grant rapid adaptation, but also how they give rise to counterintuitive evolutionary dynamics. While our account is focused on gene copy-number mutations in bacteria, we will compare their dynamics to examples from the whole tree of life.

To illustrate our points, we focus on one of the most common structural changes: tandem duplications, in which a DNA sequence is duplicated as a direct repeat in a head-to-tail manner. Tandem duplications form through a variety of different molecular mechanisms and can span from tens of base pairs up to half a bacterial chromosome (Darmon and Leach 2014). They most frequently arise through homologous recombination between existing sequence repeats, such as two copies of mobile genetic elements. At a lower rate, illegitimate duplications can form between any two sites of the genome sharing no homology at all or micro-homologies of just a few base pairs (Fig. 1a) (Reams et al. 2012; Reams and Roth 2015). Irrespective of their formation, all tandem duplications are genetically unstable (Andersson and Hughes 2009), as the repeated stretch of DNA sequence is prone

Received on 27 May 2026; accepted on 17 September 2026
© The Author(s) 2026. Published by Oxford University Press on behalf of The Genetics Society of America.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

Downloaded from academic.oup.com/genetics/article/234/3/iyag262/8875951 by Institute of Science and Technology Austria user on 17 November 2026

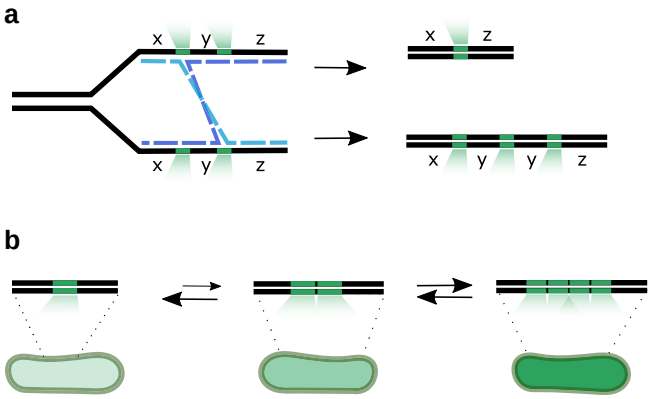


Fig. 1. a) Gene duplication or deletion occurs through homologous (or illegitimate) recombination between homologous (or nonhomologous) regions (highlighted) of replicating bacterial sister chromosomes. This unequal cross-over leads to the deletion of gene "y" in one chromosome and gain of an additional copy of gene "y" in the other chromosome. b) Schematic showing the highly reversible nature of gene duplication. The rate of initial duplication can vary considerably (small arrow), but once a duplication occurs, the sequence becomes more prone to recombination (large arrows) between the repeats that will lead to its deletion (reverting to the ancestral sequence) or its further duplication (also termed amplification). If a coding region (gene) is repeated, increases in gene copy-number will lead to increases in the gene product being expressed (cells with different degrees of shading).

to *recA*-dependent homologous recombination. In bacteria, duplications reverse back to the initial single copy (deletion) or duplicate further (amplification), at rates between 10^{-3} and 10^{-1} per cell per generation (Anderson and Roth 1977; Andersson and Hughes 2009; Pettersson et al. 2009; Reams and Roth 2015; Tomanek et al. 2020). Thus, one crucial difference between duplications and point mutations derives from the asymmetry of rates of formation and reversal: duplications reverse more frequently than they form. Their fleeting nature implies that tandem duplications provide transient adaptation: they form frequently and spread in the population if under positive selection; yet rapidly disappear once selection has subsided. The reversal of a duplication through homologous recombination restores the ancestral sequence and thus leaves no trace in the record of genomic sequence data (Fig. 1B) (Reams and Roth 2015).

Arguably, the relative neglect of structural mutations in comparison to singlenucleotide polymorphisms (SNPs) is not only a function of their hard-to-detect nature or plethora of mutation mechanisms but also due to marked differences in terminology and focus in different fields of biology. In genomics and evolutionary biology, the term copy-number variation (CNV) is used to refer to both tandem duplication as well as whole-chromosome duplication (Conrad and Hurles 2007), while microbiologists typically talk about gene duplications (two copies) and amplifications (that is, duplications of more than two copies in tandem). Adding to the confusion, different fields mean different things when they talk about the rate of duplication. In some contexts, such as bacterial genetics, duplication rate refers to the *de novo* mutation rate (Andersson and Hughes 2009; Reams et al. 2010; Tomanek and C. Guet 2022), with the majority of *de novo* mutations lost due to the high rate of reversal, selection, or drift, and therefore never making it into the "written" record of a species' genomic sequence data. However, in genomics, the rate of duplication often refers to the rate at which duplicates fix in the population, which ignores all mutations lost again shortly after their formation (Lynch and Conery 2000; Miller et al. 2011; Koonin 2015; Tria and Martin 2021). In addition to the ambiguous terminology, the error of confusing the rate of fixation (the molecular clock rate, μ, which is commonly low) with the rate of supply (formation) of potential mutations (the population mutation rate, μN_e, which is typically much higher) is common (Lieberman 2022; Torrillo and Lieberman 2024). Each bacterial cell residing within a population can supply random mutations created during DNA replication in every generation; however, only the surviving mutations along a single line of descent are taken into consideration when calculating molecular clock rates.

Due to their high reversibility and hard-to-detect nature, the rate of duplication formation (μN_e) is less straightforward to measure than that of point mutations. There are two standard ways to measure microbial mutation rates: the fluctuation test (Luria and Delbrück 1943) and mutation accumulation experiments (Muller 1928; Lynch et al. 2008; Halligan and Keightley 2009). In a fluctuation test, the number of individuals in a population carrying a mutation in a neutral marker gene depends on whether the mutation occurred early on during the first few generations of an expanding bacterial culture (most members will have inherited the mutation), or during later generations (only a small fraction will have inherited the mutation). Assaying many replicate populations allows one to estimate the mutation rate from the distribution of the frequency of point mutations (Foster 2006). However, in contrast to point mutations, the high rate of formation and loss of duplications means their frequency in a population rapidly reaches a steady state. Accordingly, replicate populations carry a similar number of duplications, irrespective of whether they formed early or late during outgrowth. It is thus immune to fluctuation tests (Reams and Roth 2015).

In mutation accumulation experiments, small laboratory populations are subjected to extreme bottlenecks to render selection extremely inefficient or abolish it to a large degree, meaning that all but extremely deleterious mutations will be transmitted to the next generations. The mutation rate can then be inferred from sequencing the individuals after a known number of generations. However, this approach is difficult with microorganisms, and the reason is illustrated in a recent publication: a mutation accumulation experiment attempted to estimate the rate of duplication by applying a strong population bottleneck through re-streaking single colonies of *Escherichia coli* (Zhou et al. 2023). While this method indeed introduces single-cell bottlenecks, the phase of colony outgrowth from a single cell to the 10^9 cells inside a typical colony imposes significant purifying selection for 30 generations (Korolev et al. 2012). During colony growth, cells that divide more rapidly can outcompete less fit individuals. For instance, individuals that lost a costly duplication expand in sectorized zones within a colony (Reams et al. 2010; Tomanek et al. 2020). Hence, rather than measuring the rate of duplication formation, the outcome of single colony experiments more accurately reflects the rate of formation of duplications with neutral fitness effects. Accordingly, due to their microscopic nature, the gold standard for mutation accumulation experiments in bacteria requires microfluidic devices to allow single-cell bottlenecks in every generation (Robert et al. 2018) without phases of outgrowth where the more competitive clones can overtake the population (Korolev et al. 2012). This is particularly crucial when aiming to capture highly reversible mutations. To the best of our knowledge, such experiments have only been conducted to estimate the rate of recombination of an existing duplication at a particular locus, but not the rate of *de novo* duplications (Tomanek et al. 2020).

Despite the difficulties with measuring the duplication rate, clever bacterial genetics experiments using a linear DNA

Downloaded from academic.oup.com/genetics/article/234/3/iyag262/8875951 by Institute of Science and Technology Austria user on 17 November 2026

fragment homologous to a marker gene were able to "trap" duplications in *Salmonella enterica* and inferred a duplication rate between 10^{-6} and 10^{-2} per locus per cell per generation (Reams et al. 2010; Reams and Roth 2015). Across experiments, the estimates for copy-number changes are orders of magnitude higher than the rate of point mutation (Drake et al. 1998; Elez et al. 2010), especially if a locus is flanked by existing repeat sequences such as mobile genetic elements (Steinrueck and Guet 2017). Not only are duplications more common, their mutational effect is likely larger, as the most common impact of a point mutation is no observable change in phenotype, while having additional gene copies is likely to affect the expression of the duplicated gene (Elde et al. 2012; Näsvall et al. 2012; Steinrueck and Guet 2017; Dulmage et al. 2018; Todd and Selmecki 2020; Tomanek and Guet 2022; Fritts et al. 2023).

In principle, the rate of duplication fixation is more straightforward to estimate than the rate of duplication formation, as it can be directly inferred from genomic sequence data. However, the prevalence of copy-number variations in genomic sequence data is likely an underestimate, and its interpretation is partially misleading. The reason is 3-fold: Firstly, in short-read sequencing data, structural variation is more challenging to detect than SNPs and, due to its more ambiguous interpretation, is often filtered out (Draper et al. 2017). Secondly, genome sequences are temporal snapshots and mostly capture the genome sequence of single bacterial clones isolated from large and potentially polymorphic populations (Draper et al. 2017; Wang et al. 2021; Vezina et al. 2024). Thirdly, and most importantly, because of the fleeting nature of duplications, even if they are adaptive temporarily, they are often lost fast when the environment changes (Tomanek et al. 2020), such as when bacterial isolates are grown in the absence of a selection pressure like antibiotics prior to DNA extraction. More generally, as any adaptation is context-dependent, changing conditions may select for the reversal of a once adaptive mutation. It has recently been argued that reversal conceals adaptive changes even for SNPs, if populations experience fluctuating directional selection as observed for members of the mammalian gut microbiome (Torrillo and Lieberman 2024) or human pathogens (Weissman et al. 2007; Morelli et al. 2010; Torrillo and Lieberman 2024). We would therefore expect this pattern to be more common for mutations with an even higher rate of reversal.

Detecting structural variants in the genomics era: overcoming a history of neglect

Our mathematical models and understanding of evolution have long been dominated by point mutations, due to rather mundane reasons such as "attention is shifted where the data are" (Kondrashov 2012). However, with the advent of long-read sequencing data, this is rapidly changing. Our current understanding of tandem duplications came from classical bacterial genetics experiments (Anderson and Roth 1977; Petes and Hill 1988). Later, microarrays allowed detection of repeats in human genomes, followed by short-read sequencing-based approaches, where detection was limited as it relies on algorithms to infer mutations that, by their very nature, span more than one read. Thus, inferring structural variation is ideally based on a combination of detecting several of its features such as (i) unique signature sequences at junction sites, (ii) altered read depth, and (iii) distance and direction of paired-end reads. The advance of long-read sequencing has solved all these shortcomings (Wellenreuther et al. 2019; Ho et al. 2020; Abrahams et al. 2022).

In recent years, the increased use of nanopore sequencing together with improvements in analysis pipelines is revolutionizing the detection of structural variation. Recent studies have unearthed a plethora of examples where copy-number variation between strains of the same species carries the signature of environmental selection (Waters et al. 2025). For instance, the copy-number of antibiotic resistance genes is increased when bacterial strains are isolated from humans and livestock as opposed to other environments. Copy-number variation in human gut commensals has been associated with host disease risk factors (Zeevi et al. 2019; Abrahams et al. 2022; Maddamsetti et al. 2024). Structural variation appears in species across diverse habitats, suggesting that a comprehensive picture of bacterial diversity can only be obtained by also including structural variants (Abrahams et al. 2022). For instance, *Bordetella pertussis* and *Mycobacterium tuberculosis* were believed to be surprisingly monomorphic pathogens based on SNP analyses. However, their broader genetic diversity and population structure only became apparent once analyses included copy-number variation (Abrahams et al. 2020; Abrahams et al. 2022). *B. pertussis* evolved from its nonpathogenic ancestor by accumulating repeats in the form of insertion sequence (IS) elements and ensuing rearrangements. Interestingly, the occurrence of amplification was dispersed throughout the genome, pointing to transient copy-number increases in different lineages. CNVs were also found in the cancerogenic pathogen *Helicobacter pylori* (Draper et al. 2017; Jang et al. 2017) and isolates of Methicillin-Resistant *Staphylococcus aureus* (MRSA) derived from patient samples. In the latter, the copy-number of genes with known immunomodulatory function varied considerably within a single bacterial population and increased significantly during infection (Belikova et al. 2020). However, while long-read sequencing improves our ability to detect tandem duplications that are present at the time of sampling, it cannot recover duplication events that have already reverted! As a result, the abundance of tandem duplications revealed currently by long-read sequencing studies is likely to represent only a lower bound on their true prevalence in nature.

Evolutionary dynamics of duplications: adaptive gene copy-number as a dominant force

Since Susumu Ohno's seminal work in the 1970s (Ohno 1970), gene duplications have mostly been viewed as the passive raw material necessary for the evolution of new genes through the process of gene duplication and divergence. Genomics data provided us with a rich fossil record of molecular evolution that paints a detailed picture of how two duplicated genes diverge over time as they accumulate point mutations. While Ohno posited that gene duplicates evolve neutrally, the last decades have provided many examples in which duplication has strong fitness effects, positive as well as negative.

As a first approximation, duplications increase the level of gene expression with every additional copy, and they do occur at a high rate compared to SNPs (Elde et al. 2012; Näsvall et al. 2012; Steinrueck and Guet 2017; Dulmage et al. 2018; Todd and Selmecki 2020; Tomanek and Guet 2022; Fritts et al. 2023). The fact that tandem gene duplications were discovered in bacteria is no coincidence. Handling them in the laboratory unintentionally or intentionally exposes microorganisms to strong selective pressures as conditions differ from what they encounter in their natural environments (Vezina et al. 2024). Above all, it is perhaps the fact that amplification is a common adaptation to the lab

Downloaded from academic.oup.com/genetics/article/234/3/iyag262/8875951 by Institute of Science and Technology Austria user on 17 November 2026

environment (Horiuchi et al. 1963; Adams 2004; Blount et al. 2012), that may lead to the view that copy-number increases are some sort of lab artifact warranting its filtering out of sequencing data sets in experimental evolution studies (Spealman et al. 2023), with most experimental evolution studies focusing on SNPs (Elena and Lenski 2003; Good et al. 2017). The interaction of growth, amplifications, single base pair mutations, and selection can create intricate dynamics, which need to be interpreted carefully rather than jumping to simple conclusions (Roth and Maisnier-Patin 2016). The first detailed description of tandem duplications emerged from classic experiments of *E. coli* grown on lactose as a single limiting nutrient (Horiuchi et al. 1963), leading to amplification of the *lac* operon (Anderson and Roth 1981). The reversible nature of duplications was noted by early bacterial geneticists, who described them as heritable yet very unstable phenotypes that returned to their original (ancestral) state at high frequency (Anderson and Roth 1977). This high intrinsic rate of deletion, in combination with often significant fitness cost (Bergthorsson et al. 2007; Pettersson et al. 2009; Reams et al. 2010), has one important implication: observing more than two copies of a certain gene or genomic region means they are most probably an adaptation, or at least have been one in the recent evolutionary past. Point mutations can fix via drift, but gene amplifications remain polymorphic and thus hardly ever fix even under strong positive selection (Reams et al. 2010; Tomanek et al. 2020; Tomanek and Guet 2022; Khomarbaghi et al. 2024). This feature has been of practical medical relevance and copy-number variation in human cancers is used to identify causative oncogenes (Albertson 2006). Consistent with this idea, recent bacterial genome-wide association studies have linked copy-number variation to adaptive phenotypes, further supporting the view that amplifications often reflect ongoing selection (Tam et al. 2024).

Gene amplification generates polymorphic populations

Unsurprisingly, a lot of our knowledge about gene duplication and amplification in the "wild", stems from studying them in the context of antibiotic resistance, where they are a common adaptation. Increases in copy-number increase the expression of resistance genes such as efflux pumps, drug targets, or antibiotic-modifying enzymes. By examining specific cases of resistance and their evolutionary trajectories, researchers have gained valuable insights into the dynamics of duplication and deletion more generally, as well as their broader evolutionary consequences (Andersson and Hughes 2009; Sandegren and Andersson 2009).

One intriguing example of how the biological idiosyncrasy of amplifications, in particular their instability, has important—but long overlooked-consequences for public health is hetero resistance (Nicoloff et al. 2024). During antibiotic treatment, high rates of copy gain and loss can lead to polymorphic populations where different levels of gene copies result in subpopulations of bacteria with varying levels of susceptibility to an antibiotic. Due to the cost often associated with both resistance and copy-number increases, additional copies are rapidly lost in the absence of selection. In *Klebsiella pneumoniae* and *Salmonella enterica*, for instance, tandem amplifications of efflux pumps or β-lactamase genes transiently confer resistance, allowing bacteria to survive antibiotic treatment but revert to susceptibility in the absence (Nicoloff et al. 2019). However, testing the antibiotic susceptibility of any bacterial sample in a clinical testing laboratory involves transferring only a small subset of a population to an antibiotic-containing medium. The population will appear susceptible, masking the subpopulation perfectly capable of growing in the presence of the antibiotic. The failure to recognize hetero-resistance driven by structural variation has led to underestimating resistance levels in clinical settings, which ultimately contributed to antibiotic treatment failures and the silent spread of resistant strains (Hjort et al. 2016; Nicoloff et al. 2019).

Polymorphisms, bet-hedging, and a primitive mechanism of gene regulation

The phenomenon of hetero-resistance highlights an intriguing consequence of the high rates of duplication gain and loss, which was pointed out almost 50 years ago (Anderson and Roth 1977): under transient directional selection, bacterial populations will rapidly and reversibly change their (average) gene expression level of a gene or genomic region, without "committing" to a different genotype in the long run. Microbial life is constantly exposed to such environmental fluctuations, and a population's survival critically depends on its ability to adapt to these changes.

Canonically, this feat is achieved with gene regulation at the level of the individual cell, where transcription factors bind to regulatory regions of a gene promoter. Thereby, populations of otherwise clonal individuals can rapidly access different phenotypic states in a manner responsive to the environment. Such pre-existing regulatory networks represent the primary mechanism by which bacteria respond to environmental change. However, if the environment shifts to a condition not previously met—such as exposure to a novel carbon source or antibiotic—population genetic theory predicts that new regulatory sequences are unlikely to evolve quickly enough to deal with it (Berg et al. 2004; Tuğrul et al. 2015). In this context, duplication and amplification, serving as "a rather crude regulatory mechanism" (Anderson and Roth 1977) at the population level, can provide an intermediate solution until more refined regulatory adaptations evolve. In situations where gene regulation has yet to evolve, copy gains and losses can direct gene expression levels up and down on time scales of a single day (Tomanek et al. 2020).

Initially, this "amplification-mediated gene expression regulation" (AMGET) was shown in a proof-of-principle study under controlled laboratory settings (Tomanek et al. 2020) (Fig. 2). More recently, it was found to occur in nature, in environments where strong selection varies on relatively short time scales. A study by Belikova et al. showed that gene amplifications contribute to the genetic and phenotypic diversity in *S. aureus* populations isolated from a community outbreak. The researchers identified several hotspots of gene copy-number variation in these isolates, notably the *csa1* gene cluster, which encodes immunogenic lipoproteins. They observed that the *csa1* locus can expand and contract during bacterial growth both in vitro and during systemic infection in mice, leading to rapid heterogeneity in initially clonal cultures. Strikingly, variation in *csa1* copy-number was found to alter the bacteria's immunostimulatory capacity (Belikova et al. 2020), suggesting that host immune response is the relevant selection pressure driving AMGET.

Could AMGET be a frequent type of evolutionary dynamics in natural bacterial populations despite canonical gene regulation being ubiquitous even in the simplest of organisms? Indeed, we know that *cis*-regulatory sequences seem to evolve faster than the coding regions they regulate (Surguchov 1991; Elena and Lenski 2003; Matus-Garcia et al. 2012; Nijveen et al. 2012; Oliver and Greene 2012; van Passel et al. 2014; Yona et al. 2018; Lagator et al. 2022). Why would bacteria rely on a mechanism that grants

Downloaded from academic.oup.com/genetics/article/234/3/iyag262/8875951 by Institute of Science and Technology Austria user on 17 November 2026

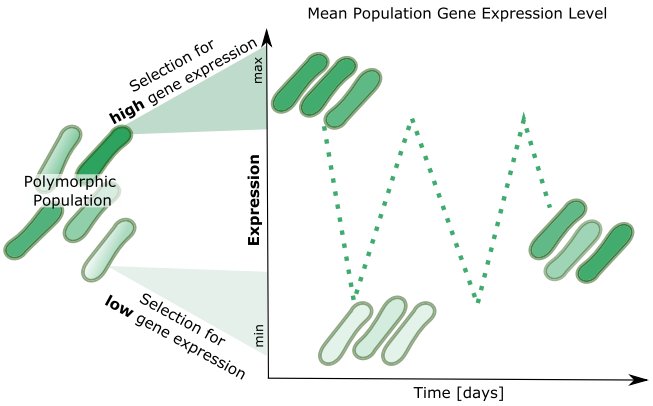


Fig. 2. Amplification-mediated gene expression regulation (AMGET) allows bacterial populations to rapidly and reversibly tune mean gene expression in response to selection. The high rate of gene duplication and deletion renders bacterial populations polymorphic with respect to the duplicated locus, harboring cells that differ in copy-number and, accordingly, gene expression levels. Directional selection for high gene expression favors cells with increased copy-number (dark shading, top), while selection for low expression favors cells with fewer copies (light shading, bottom) allowing gene expression to rise and fall reversibly on the timescale of days as the selective environment changes.

survival only to a fraction of a population, which is much less efficient than canonical gene regulation (once it has evolved)?

Intriguingly, between these two "classical" routes for altering gene expression—hard-wired promoter regulation (highly non-random and rapid) and adaptive mutation (random and slow)—a third, widespread category exists in bacteria. In this process, termed *phase variation*, changes in gene expression occur at rates that fall between the extremes of fast regulatory responses (in which all cells adjust expression within a single generation) and slow cis-regulatory mutations (in which only one cell in a large population acquires a change per generation). This intermediate timescale involves mutations that are, in a sense, partially hard-wired: genetically encoded mechanisms that generate reversible or repeatable changes in gene expression. The genomic loci at which these switches occur are known as *contingency loci* -sites with an elevated mutation rate, typically maintained by repeats or dedicated recombination hotspots, that generate a standing pool of phenotypic variants within a population. This strategy is a form of *bet-hedging*: rather than all cells sensing the environment and responding uniformly, a population pre-emptively diversifies into subpopulations with different phenotypic states, so that regardless of which environment materializes, some fraction of the population is already suited to it. Bacteria employ a striking array of such "specialized" mutational processes—ranging from highly frequent chromosomal breakpoints to catalyzed DNA inversions—to modulate their phenotypes in ways that can be entirely stochastic or more tightly programmed (Moxon et al. 1994, 2006).

This is true especially for pathogens, whose cell surface antigens are in direct contact with the immune system, and under constant selection to diversify (Hollingshead et al. 1987). For instance, in *Streptoccocus pyogenes*, antigenic variation is generated by high-frequency homologous recombination between short repeats within the M protein gene (Hollingshead et al. 1987) such that 1 in 2000 colonies harbor M proteins of a different size (a mutation rate of $5{\times}10^{-4}$ per cell per generation). Clinical isolates of *Streptococcus pneumoniae* and *Staphylococcus aureus* switch the expression of virulence factors via frequently occurring large-scale inversions. Importantly, recombination occurs at defined break points on opposite arms of the chromosome, resulting in a population with two otherwise isogenic subpopulations that differ in their colony morphology, antibiotic susceptibility, and hemolytic activity, among other things (Cui et al. 2012; Slager et al. 2018). Other classic examples include pathogens that carry an increased copy-number of virulence factors only when isolated from their human host: this is true for the cholera toxin of *Vibrio cholerae*, (Goldberg and Mekalanos 1986) and the *cap* locus of *Haemophilus influenzae* (Moxon et al. 1994). Worldwide isolates of *Haemophilus influenzae* carry an asymmetric tandem duplication of the *cap* locus, which activates it for duplication. *Cap* codes for the production of capsular polysaccharides and is amplified during invasive infection, but not in commensal isolates (Corn et al. 1993; Davis et al. 2011).

Unlike the above examples, where stochastic phenotype switching relies on "Sollbruchstellen" (German for meant-to-be breakpoints), frequent recombination at "dedicated" chromosomal hotspots or between existing repeats, the expression of pili in uropathogenic *E. coli* is controlled entirely by the enzymatically catalyzed inversion of a promoter fragment. The rates of this genetic switch also depend on the sensing of environmental factors (Tomasek et al. 2022) and, in the spectrum of tuning gene expression, lie closer to evolved canonical gene regulation than spontaneous mutation.

Moreover, this kind of genetic bet-hedging is by no means limited to pathogens. For instance, many species of the common soil bacterium *Streptomyces* carry linear chromosomes, which are highly unstable. Incidentally, most genes required for the production of secreted secondary metabolites, such as toxins and antibiotics, which presumably serve to interact with other species in its environment, are confined to the unstable chromosome arms (Leblond and Decaris 1994; Chen et al. 2002; Traxler and Kolter 2015). A 2023 study by Lowrey et al. investigated a bet-hedging strategy of another soil bacterium, the Beta-proteobacterium *Burkholderia thailandensis*. The authors show that RecA-mediated homologous recombination between two IS 2-like elements flanking a 208.6 kb genomic region allows stochastic switching between biofilm formation and planktonic growth.

In the above examples, dedicated genetic systems allow switching of genotypes and phenotypes at rates orders of magnitude higher than the point mutation rate (Moxon et al. 2006). A recent study employed an evolution experiment of ingenious design to show how second-order selection can indeed produce a contingency locus with an increased mutation rate, allowing the establishment of polymorphic populations for first-order selection to act on (Barnett et al. 2025). Given that duplication and deletion can occur at high rates in almost any region of the chromosome, and the fact that gene expression changes along with copy-number, it should not be surprising that AMGET dynamics occur in nature.

Interestingly, recent work has demonstrated that copy-number changes can also be achieved when mobile genetic elements move genes for antibiotic resistance onto multicopy plasmids (Yao et al. 2022), allowing reversible changes in gene dosage that track environmental conditions through a principle similar to AMGET (Ha et al. 2025; Maddamsetti et al. 2025). Plasmid copy-number itself, independent of any mobile element, can likewise generate phenotypic heterogeneity: stochastic fluctuations produce transient, nongenetic antibiotic resistance within isogenic populations (Hernandez-Beltran et al. 2024) and modulate virulence and resistance over infection (Wang and Joffré 2025). Such plasticity may also buffer costly new functions across multiple plasmid copies, easing evolutionary innovation until selection refines them (Rodriguez-Beltran et al. 2018).

Downloaded from academic.oup.com/genetics/article/234/3/iyag262/8875951 by Institute of Science and Technology Austria user on 17 November 2026

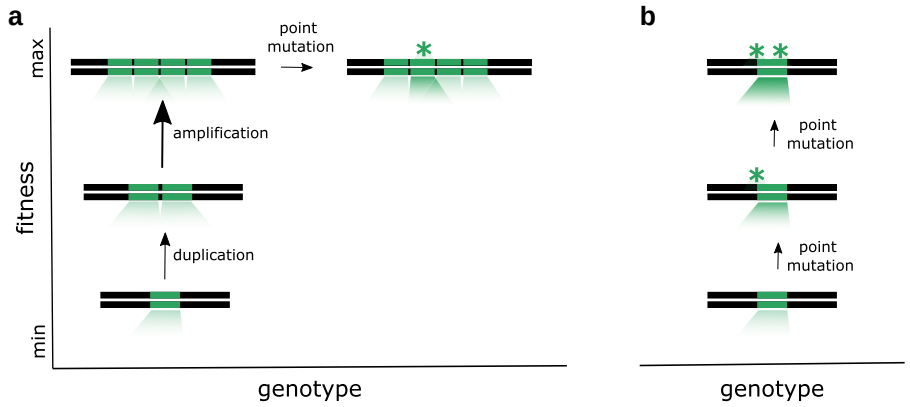


Fig. 3. Amplification hindrance. The scheme illustrates the fate of increasing copy-number mutations and single point mutations (asterisks) in a situation where growth is limited by an enzymatic reaction encoded by the gene shown in green. Fitness can be increased by increasing gene expression (either by duplication/amplification or a point mutation in the gene promoter region), or by improving catalytic activity (via a point mutation in the coding region of the gene). a) Amplification hindrance occurs when adaptive amplification occurs much more frequently (large arrows) than point mutations (small arrows) and allows the population to reach its fitness peak before adaptive point mutations can fix. If maximum fitness is reached by gene amplification, additional point mutations can only fix through drift, as they provide no additional fitness benefit. This contrasts with (b), where in the absence of duplication, point mutations in the promoter or coding sequence directly increase fitness and spread in the population.

The role of duplication in bacterial evolution: divergence, hindrance and horizontal gene transfer

As we have seen throughout this review, the high rates of duplication and deletion give rise to more transient evolutionary dynamics than observed for point mutations. However, it gets more interesting and rather counterintuitive, when both types of mutation interact. Together, copy-number and point mutations are responsible for the evolution of most functionally novel genes through the process of duplication and divergence of existing genes (Ohno 1970; Kacser and Beeby 1984; Conant and Wolfe 2008; Andersson et al. 2015).

Since most studies have focused on understanding the long-lasting process of how duplicate gene pairs diverge by accumulating point mutations (Lynch and Conery 2000; Teufel et al. 2015; Friedlander et al. 2017), we know less about the potentially short-lived initial duplication event itself (Innan and Kondrashov 2010). In part, this bias is also due to significant technical difficulties of studying transient copy-number variation experimentally (Lauer and Gresham 2019; Tomanek and Guet 2022; Mihajlovic et al. 2025).

However, a recent study was able to scrutinize how two duplicate gene copies diverge by constraining further recombination by intentionally placing the two copies in a head-to-tail manner (Mihajlovic et al. 2025). When two duplicate copies of a fluorophore gene were "frozen in place", both copies evolved higher genetic and phenotypic diversity and carried combinations of key beneficial mutations earlier than a single copy subjected to the same selection for increased fluorescence. This confirms one part of Ohno's hypothesis: selection is relaxed due to the redundancy provided by a second gene copy (Ohno 1970). However, the study also confirmed the flipside of this prediction, termed Ohno's dilemma (Bergthorsson et al. 2007): relaxed selection means that adaptive point mutations will accumulate rapidly, and so will deleterious point mutations. In Mihajlovic et al.'s experiments, the function of the second gene copy is lost after only a few generations.

While Ohno's original idea suggests that most gene duplicates evolve neutrally, in bacteria, selection for increased dosage is likely to play a crucial role in the evolution of paralogs (Andersson and Hughes 2009; Treangen and Rocha 2011; Copley 2020; Cisneros et al. 2026). As we have seen throughout this review, duplications rarely remain just duplications. Copies either contract or expand at high rates, and selection will direct population copy-number toward one or the other direction (Tomanek et al. 2020). For example, if having more copies is beneficial, as it increases expression of an enzyme whose activity is rate-limiting, populations will gain more than just two copies (Bergthorsson et al. 2007; Näsvall et al. 2012; Copley 2020). This principle also underlies the influential amplification model proposed by Andersson, Slechta and Roth (Andersson et al. 1998), in which amplification of a weakly beneficial allele provides an immediate fitness advantage until it is replaced by a more beneficial point mutation. The amplification subsequently collapses, leaving behind only the adaptive point mutation. This process of Innovation-Amplification-Divergence (IAD) (Näsvall et al. 2012) tied dosage selection to the intuition that additional gene copies speed up divergence (Andersson and Hughes 2009; Reams et al. 2010; Elde et al. 2012; Yona et al. 2015; Cone et al. 2017; Bayer et al. 2018; Lauer et al. 2018; Todd and Selmecki 2020), as, all else being equal, more copies should provide a bigger target for point mutations (San Millan et al. 2017). However, all else is not necessarily equal, as point and copy-number mutations have the potential to interact. If we let the copy-number mutation dynamics unfold, a more complex picture emerges (Tomanek 2024). When both point and copy-number mutations increase an enzyme's activity or expression, adaptive evolution will be dominated by the much more frequent copy-number increases (Fig. 3). If the fitness peak is reached with just amplification, additional point mutations will not contribute further to fitness. That means that point mutations which may have been adaptive in a gene present in single copy (such as mutations increasing enzyme activity) are not providing any extra benefit in a situation where the selective problem has already been optimized by copy-number increases. These potentially adaptive point mutations may still fix, but only exceedingly slowly, i.e., via genetic drift rather than selection (Fig. 3). This phenomenon, which we termed "Amplification Hindrance," is in essence a form of negative epistasis between copy-number and point mutations (Tomanek and C. Guet 2022) and was confirmed in the context of antibiotic resistance by a recent study (Jena et al. 2025). By hindering divergence, adaptive amplification could ultimately have long-lasting consequences not just *despite*, but *because* of its transient nature: if adaptation by amplification is the fastest and sufficient (De et al. 2025), other, less frequent, adaptive mutations, such as

Downloaded from academic.oup.com/genetics/article/234/3/iyag262/8875951 by Institute of Science and Technology Austria user on 17 November 2026

SNPs, may not have a chance to compete. In contexts where rapid amplification suffices for adaptation, it may act—alongside purifying selection—as a force conserving genes and their expression, paradoxically preventing even beneficial mutations from fixation!

The idea that amplification hinders the evolution of paralogous proteins aligns with the observation that gene duplication and divergence are not major drivers of protein family expansion in bacteria. Unlike eukaryotes, bacterial genomes are dominated by a strong deletion bias, selection for genome compactness, and high rates of horizontal gene transfer (Mira et al. 2001; Kuo and Ochman 2009; Koonin 2016). Hence, the majority of functionally novel genes in a bacterial lineage are orthologs, not paralogs. They have not evolved through duplications within the same genome, but enter through horizontal transfer after having evolved in the genome of another bacterial lineage (Ochman et al. 2000; Koonin et al. 2001; Treangen and Rocha 2011; Eme and Doolittle 2016; Hehemann et al. 2016). Interestingly, this pattern is evident when taking a zoomed-out view of the phylogenetic tree of all three domains of life: duplication and divergence become increasingly relevant in the archaeal lineage leading up to the eukaryotes (Makarova et al. 2005; Manzano-Morales and Gabaldón 2026), with paralogs occurring in conjunction with smaller population sizes and increased drift, both thought to play a crucial role in the evolution of eukaryotic complexity (Lynch and Conery 2003) (Fig. 4).

Beyond bacteria: a universal and underestimated force

Despite the different role tandem duplications play in eukaryotes, where they contribute to the evolution of evolutionary novelty in the form of paralogs and, with it, to organismal complexity, their rate of formation—like in bacteria—exceeds the rate of point mutation by orders of magnitude. In macroscopic organisms, mutation accumulation experiments are more straight forward, and the rate of duplication and deletion has been estimated to be around 10^{-5} per locus per generation in *Daphnia pulex* (Keith et al. 2016)), 10^{-7} per locus per generation in *Caenorhabditis elegans* and *Drosophila melanogaster* (Lipinski et al. 2011; Schrider et al. 2013), and 10^{-6} per locus per generation in *Saccharomyces cerevisiae* (Lynch et al. 2008), respectively.

Just as for bacteria, there is mounting evidence that gene copy-number changes also drive rapid evolutionary dynamics in eukaryotes. Examples include the independently evolved amplification of the salivary amylase enzyme gene AMY in humans and many other starch-consuming mammals (Perry et al. 2007; Pajic et al. 2019), the amplification of tumor suppressor gene TP53 as an adaptation to afford the increased body size of elephants (Sulak et al. 2016) or the *de novo* evolution of increased copy-number of a cholinesterase gene in humans upon insecticide exposure (Prody et al. 1989). More extreme examples of animals and plants illustrate that amplification provides appropriate gene expression levels in subpopulations of cells on time scales of a single generation. For instance, in species of frogs and flies, programmed gene amplification during development provides a mechanism to drastically increase the expression of certain gene products required at high levels, such as rRNA (Kafatos et al. 1985; Claycomb and Orr-Weaver 2005). The genome of the parasite *Leishmania tropica* is devoid of promoter-mediated regulation. Instead, gene expression is regulated through dosage in the form of structural variation, including tandem amplification (Iantorno et al. 2017). An even more intriguing form of gene amplification of multiple loci occurs in flax (*Linum usitatissimum*), where heritable copy-number variation can evolve in a subset of cells within a single organismal generation in a manner that is responsive to the current environmental conditions (Cullis 2005).

In a similar vein, *P. falciparum*, a eukaryotic parasite and causative agent of malaria, relies on high rates of recombination to adapt to the diversifying selection exerted by its host. In *P. falciparum*, duplications in the *var* genes generate diversity in hypervariable surface proteins that interact with the host immune system. These genes contain G4-quadruplex structures linked to recombination and replication stalling (Claessens et al. 2014; Ebel et al. 2023), indicating dedicated breakpoints, supplying mutations at a relatively high rate.

Copy-number variation can also drive rapid somatic evolution within the cells of a single organism. Akin to the parallels we drew between AMGET and plasmid copy-number variation in bacteria, circular DNA plays a role in animals too. In a substantial fraction of human cancers, oncogenes are amplified on extrachromosomal DNA (ecDNA). These circular elements lack centromeres and segregate randomly to daughter cells, generating copy-number heterogeneity within a tumor on timescales of days (Turner et al. 2017; Lange et al. 2022). This unequal segregation allows ecDNA copy-number to respond rapidly to selective pressure, including chemotherapy, and is associated with more aggressive disease and worse clinical outcomes across tumor types (Kim et al. 2020; Lange et al. 2022). Because ecDNA is inherited independently of the chromosomal genome, tumors can carry discordant chromosomal and extrachromosomal states within the same lineage, further amplifying intra-tumor heterogeneity (Decarvalho et al. 2018). The dynamics closely parallel AMGET: in both cases, gene dosage occurs in response to a changing selective environment, without committing the underlying change in nucleotide sequence.

Conclusions

We have focused our review on gene duplication and deletion in bacteria in order to shed light on the evolutionary dynamics that can arise with various types of copy-number mutations: rapid and reversible and potentially keeping SNP-based adaptation from happening (Tomanek and Guet 2022).

However, these dynamics are not unique to bacteria, nor do they rely on tandem duplication as a mechanism. Across the tree of life, gene copy-number mutations grant rapid but transient adaptation in situations where increased gene expression is favorable. We have argued that rather than limiting their importance, their transient nature causes it. This is because, firstly, unstable tandem arrays bring about a state of hypermutability (of increasing or decreasing the copy-number) of that specific locus under selection. Thus, once a gene is present in several copies, a population is equipped with a genetic way by which it can easily access different levels of gene expression on very short time scales (Tomanek et al. 2020). Secondly, because copy-number increases allow responding to selective pressures fast, they compete with and may ultimately hinder the slower, more permanent routes to the same phenotype: point mutations. The title of our review illustrates this paradox: changes that disappear as readily as they arise can nonetheless leave a lasting mark on genotypes, and on the evolutionary paths that were not taken, of the populations that carry them.

However, much of what we know about these dynamics still comes from a small number of tractable experimental systems, and the true extent of transient copy-number variation in nature likely remains underestimated. As we noted earlier, long-read sequencing has transformed our ability to detect tandem duplications and other structural variants directly, replacing indirect and error-prone inference from short reads. In addition,

Downloaded from academic.oup.com/genetics/article/234/3/iyag262/8875951 by Institute of Science and Technology Austria user on 17 November 2026

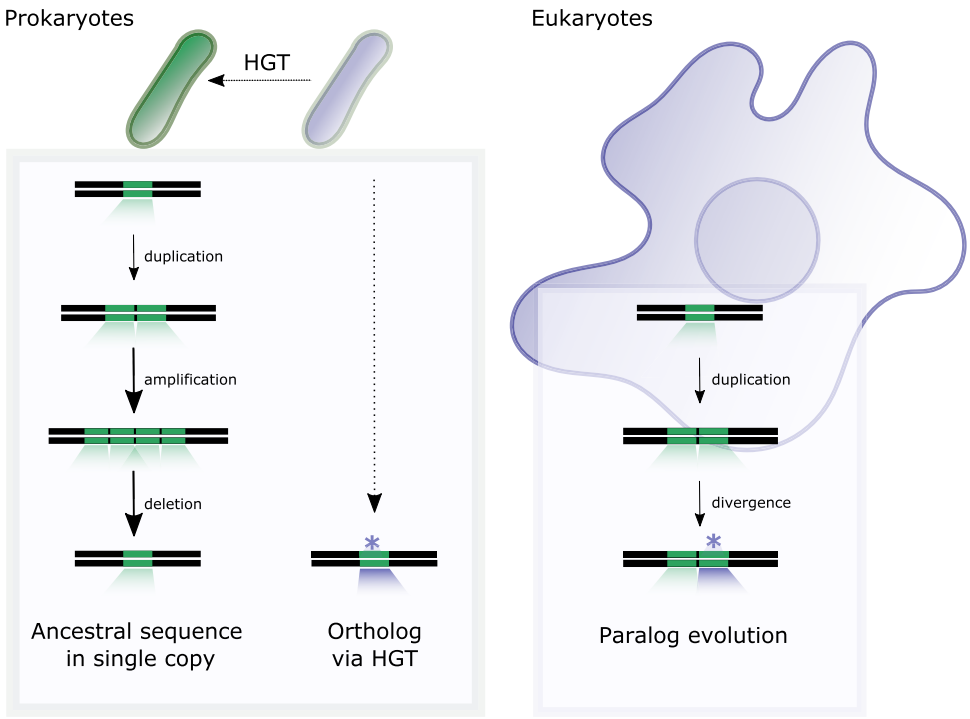


Fig. 4. Evolutionary dynamics of duplications in prokaryotes are often characterized by transient duplication and amplification events due to dosage selection (left scheme). In eukaryotes (right scheme), transient amplification may occur, but the evolutionary fate of duplications differs markedly. There, the divergence of duplicate gene copies through the accumulation of single nucleotide changes can lead to the evolution of paralogs. In prokaryotes, the long-term retention and divergence of tandem duplicates is much less common and gene families expand when genes diverge along with diverging bacterial lineages. These orthologs can be transferred horizontally (HGT), resulting in two diverged gene copies which do not originate from tandem duplication.

realizing this will also require a shift in standard bioinformatic and modeling practice: most pipelines remain SNP-centric by default, and tools that systematically screen for structural and copy-number variation are only beginning to emerge (Zabelkin et al. 2022). However, without dedicated experiments and time-resolved sampling, their transient dynamics may escape our attention despite these advances. Only then will we be able to fully capture how much of adaptive evolution—in bacteria and beyond—is currently invisible to us because it did not have to last.

Glossary

Adaptive mutation

A mutation that increases the fitness of an organism in a given environment. In this Review, the term refers solely to the fitness effect of a mutation and does not imply that mutations arise in response to selection.

Adaptive mutation controversy

A long-standing debate in bacterial genetics, initiated by the experiments of Cairns et al. (1988), over whether stressful conditions can induce beneficial mutations or whether adaptation is instead explained by conventional mutation and selection. The controversy was largely resolved by recognizing the role of gene duplication in amplifying small adaptive advantages that allow growth under selection and thereby increase the opportunity for subsequent beneficial mutations.

Bet-Hedging

An evolutionary strategy, formalized by Cohen (1966) and Slatkin (1974), in which a genotype reduces the variance in its fitness across generations at the cost of a lower arithmetic mean fitness. In unpredictably fluctuating environments, this tradeoff is favored because it raises the geometric mean fitness over time—the more relevant currency for long-term population persistence.

CNV (Copy-number variation)

A subset of structural mutations that only changes the number of copies of a genomic region (not its orientation), such as duplication (two copies), amplification (>two copies), or deletions (loss of a copy).

Contingency locus

A term coined by Moxon et al. (2006) for genomic regions with a localized mutation or recombination rate substantially elevated above the genome-wide background (conventionally, exceeding roughly 10^{-5} mutations per locus per division). These loci, which are often built from simple sequence repeats or specific recombination hotspots, generate a repertoire of genetic and phenotypic variants at a subset of genes, typically those interacting directly with a host or changing environment, allowing a population to adapt rapidly to conditions that cannot be anticipated in advance.

Gene dosage

The functional consequence of copy-number variation: as a first approximation, additional copies of a gene will result in more transcripts of the amplified gene(s) and hence increased expression.

Phase variation

The high-frequency switching of gene expression through reversible genetic changes at a contingency locus that allows clonal bacterial populations to rapidly generate phenotypic diversity. It is viewed a bet-hedging strategy to cope with fluctuating selection pressures.

Downloaded from academic.oup.com/genetics/article/234/3/iyag262/8875951 by Institute of Science and Technology Austria user on 17 November 2026

SNP (Single nucleotide polymorphism)

A genetic change affecting only a single nucleotide of the DNA sequence, also referred to as point mutation.

Structural mutation (Structural variation)

A larger-scale genomic alteration of hundreds or thousands of base pairs that occurs via a deletion, duplication, inversion, translocation, or large insertions of a DNA sequence fragment.

Acknowledgments

The authors would like to thank all three reviewers for their thoughtful comments and David Lanster for his helpful comments on an earlier version of the manuscript.

Funding

I.T. was funded by the Austrian Science Fund (FWF; Grant DOI: 10.55776/J4747).

Conflicts of interest

None declared.

Literature cited

Abrahams JS *et al.* 2022. Towards comprehensive understanding of bacterial genetic diversity: large-scale amplifications in *Bordetella pertussis* and *Mycobacterium tuberculosis*. Microb Genom. 8:000761. https://doi.org/10.1099/mgen.0.000761.

Abrahams JS, Weigand MR, Ring N, MacArthur I, Preston A. 2020. Duplications drive diversity in *Bordetella pertussis* on an underestimated scale [preprint]. bioRxiv 937284. https://doi.org/10.1101/2020.02.06.937284.

Adams J. 2004. Microbial evolution in laboratory environments. Res Microbiol. 155:311–318. https://doi.org/10.1016/j.resmic.2004.01.013.

Albertson DG. 2006. Gene amplification in cancer. Trends Genet. 22:447–455. https://doi.org/10.1016/j.tig.2006.06.007.

Anderson P, Roth J. 1981. Spontaneous tandem genetic duplications in *Salmonella typhimurium* arise by unequal recombination between rRNA (RRN) cistrons. Proc Natl Acad Sci USA. 78:3113–3117. https://doi.org/10.1073/pnas.78.5.3113.

Anderson RP, Roth JR. 1977. Tandem genetic duplications in phage and bacteria. Annu Rev Microbiol. 31:473–505. https://doi.org/10.1146/annurev.mi.31.100177.002353.

Andersson DI *et al.* 2015. Evolution of new functions de novo and from preexisting genes. Cold Spring Harb Perspect Biol. 7:a017996. https://doi.org/10.1101/cshperspect.a017996.

Andersson DI, Hughes D. 2009. Gene amplification and adaptive evolution in bacteria. Annu Rev Genet. 43:167–195. https://doi.org/10.1146/annurev-genet-102108-134805.

Andersson DI, Slechta SE, Roth JR. 1998. Evidence that gene amplification underlies adaptive mutability of the bacterial lac operon. Science (1979). 282:1133–1135. https://doi.org/10.1126/science.282.5391.1133.

Barnett M, Meister L, Rainey PB. 2025. Experimental evolution of evolvability. Science (1979). 387:eadr2756. https://doi.org/10.1126/science.adr2756.

Bayer A, Brennan G, Geballe AP. 2018. Adaptation by copy number variation in monopartite viruses. Curr Opin Virol. 33:7–12. https://doi.org/10.1016/j.coviro.2018.07.001.

Belikova D, Jochim A, Power J, Holden MTG, Heilbronner S. 2020. 'Gene accordions' cause genotypic and phenotypic heterogeneity in clonal populations of *Staphylococcus aureus*. Nat Commun. 11:3526. https://doi.org/10.1038/s41467-020-17277-3.

Berg J, Willmann S, Lässig M. 2004. Adaptive evolution of transcription factor binding sites. BMC Evol Biol. 4:42. https://doi.org/10.1186/1471-2148-4-42.

Bergthorsson U, Andersson DI, Roth JR. 2007. Ohno's dilemma: evolution of new genes under continuous selection. Proc Natl Acad Sci U S A. 104:17004–17009. https://doi.org/10.1073/pnas.0707158104.

Blount ZD, Barrick JE, Davidson CJ, Lenski RE. 2012. Genomic analysis of a key innovation in an experimental *Escherichia coli* population. Nature. 489:513–518. https://doi.org/10.1038/nature11514.

Bromham L, Penny D. 2003. The modern molecular clock. Nat Rev Genet. 4:216–224. https://doi.org/10.1038/nrg1020.

Cairns John, Overbaugh Julie, Miller Stephan. 1988. The origin of mutants. Nature. 335:142–145. 10.1038/335142a0.

Chen CW, Huang CH, Lee HH, Tsai HH, Kirby R. 2002. Once the circle has been broken: dynamics and evolution of Streptomyces chromosomes. Trends Genet. 18:522–529. https://doi.org/10.1016/S0168-9525(02)02752-X.

Cisneros AF *et al.* 2026. Evolutionary causes and consequences of gene duplication. Nat Rev Genet. 27:512–529. https://doi.org/10.1038/s41576-026-00935-5.

Claessens A *et al.* 2014. Generation of antigenic diversity in *Plasmodium falciparum* by structured rearrangement of Var genes during mitosis. PLoS Genet. 10:e1004812. https://doi.org/10.1371/journal.pgen.1004812.

Claycomb JM, Orr-Weaver TL. 2005. Developmental gene amplification: insights into DNA replication and gene expression. Trends Genet. 21:149–162. https://doi.org/10.1016/j.tig.2005.01.009.

Cohen D. 1966. Optimizing reproduction in a randomly varying environment. J Theor Biol. 12:119–129. https://doi.org/10.1016/0022-5193(66)90188-3.

Conant GC, Wolfe KH. 2008. Turning a hobby into a job: how duplicated genes find new functions. Nat Rev Genet. 9:938–950. https://doi.org/10.1038/nrg2482.

Cone KR, Kronenberg ZN, Yandell M, Elde NC. 2017. Emergence of a viral RNA polymerase variant during gene copy number amplification promotes rapid evolution of vaccinia virus. J Virol. 91:e01428-16. https://doi.org/10.1128/jvi.01428-16.

Conrad DF, Hurles ME. 2007. The population genetics of structural variation. Nat Genet. 39:S30–S36. https://doi.org/10.1038/ng2042.

Copley SD. 2020. Evolution of new enzymes by gene duplication and divergence. FEBS J. 287:1262–1283. https://doi.org/10.1111/febs.15299.

Corn PG, Anders J, Takala AK, Käyhty H, Hoiseth SK. 1993. Genes involved in *Haemophilus influenzae* type b capsule expression are amplified. J Infect Dis. 167:356–364. https://doi.org/10.1093/infdis/167.2.356.

Cui L, Neoh HM, Iwamoto A, Hiramatsu K. 2012. Coordinated phenotype switching with large-scale chromosome flip-flop inversion observed in bacteria. Proc Natl Acad Sci U S A. 109:5–9. https://doi.org/10.1073/pnas.1204307109.

Cullis CA. 2005. Mechanisms and control of rapid genomic changes in flax. Ann Bot. 95:201–206. https://doi.org/10.1093/aob/mci013.

Darmon E, Leach DRF. 2014. Bacterial genome instability. Microbiol Mol Biol Rev. 78:1–39. https://doi.org/10.1128/MMBR.00035-13.

Davis GS, Sandstedt SA, Patel M, Marrs CF, Gilsdorf JR. 2011. Use of bexB to detect the capsule locus in *Haemophilus influenzae*. J Clin Microbiol. 49:2594–2601. https://doi.org/10.1128/JCM.02509-10.

De T *et al.* 2025 Jul 24. Segmental copy number amplifications are stable in the absence of selection [preprint]. bioRxiv 665951. https://doi.org/10.1101/2025.07.21.665951.

Downloaded from academic.oup.com/genetics/article/234/3/iyag262/8875951 by Institute of Science and Technology Austria user on 17 November 2026

Decarvalho AC *et al.* 2018. Discordant inheritance of chromosomal and extrachromosomal DNA elements contributes to dynamic disease evolution in glioblastoma. Nat Genet. 50:708–717. https://doi.org/10.1038/s41588-018-0105-0.

Drake JW, Charlesworth B, Charlesworth D, Crow JF. 1998. Rates of spontaneous mutation. Genetics. 148:1667–1686. https://doi.org/10.1093/genetics/148.4.1667.

Draper JL *et al.* 2017. Fallacy of the unique genome: sequence diversity within single *Helicobacter pylori* strains. mBio. 8:e02321-16. https://doi.org/10.1128/mBio.02321-16.

Dulmage KA, Darnell CL, Vreugdenhil A, Schmid AK. 2018. Copy number variation is associated with gene expression change in archaea. Microb Genom. 4:e000210. https://doi.org/10.1099/mgen.0.000210.

Ebel ER *et al.* 2023. Antigenic diversity in malaria parasites is maintained on extrachromosomal DNA [preprint]. bioRxiv 526885. https://doi.org/10.1101/2023.02.02.526885.

Elde NC *et al.* 2012. Poxviruses deploy genomic accordions to adapt rapidly against host antiviral defenses. Cell. 150:831–841. https://doi.org/10.1016/j.cell.2012.05.049.

Elena SF, Lenski RE. 2003. Evolution experiments with microorganisms: the dynamics and genetic bases of adaptation. Nat Rev Genet. 4:457–469. https://doi.org/10.1038/nrg1088.

Elez M *et al.* 2010. Seeing mutations in living cells. Curr Biol. 20:1432–1437. https://doi.org/10.1016/j.cub.2010.06.071.

Eme L, Doolittle WF. 2016. Microbial evolution: xenology (apparently) trumps paralogy. Curr Biol. 26:R1181–R1183. https://doi.org/10.1016/j.cub.2016.09.049.

Foster PL. 2006. Methods for determining spontaneous mutation rates. Methods Enzymol. 409:195–213. https://doi.org/10.1016/S0076-6879(05)09012-9.

Friedlander T, Prizak R, Barton NH, Tkačik G. 2017. Evolution of new regulatory functions on biophysically realistic fitness landscapes. Nat Commun. 8:216. https://doi.org/10.1038/s41467-017-00238-8.

Fritts RK, Ebmeier CC, Copley SD. 2023 . The transcriptomic and proteomic ramifications of segmental amplification [preprint]. bioRxiv 568005. https://doi.org/10.1101/2023.11.21.568005.

Goldberg I, Mekalanos JJ. 1986. Effect of a recA mutation on cholera toxin gene amplification and deletion events. J Bacteriol. 165:723–731. https://doi.org/10.1128/JB.165.3.723-731.1986.

Good BH, McDonald MJ, Barrick JE, Lenski RE, Desai MM. 2017. The dynamics of molecular evolution over 60,000 generations. Nature. 551:45–50. https://doi.org/10.1038/nature24287.

Ha Y *et al.* 2025. Transposon-plasmid nesting enables fast response to fluctuating environments [preprint]. bioRxiv 657954. https://doi.org/10.1101/2025.06.04.657954.

Halligan DL, Keightley PD. 2009. Spontaneous mutation accumulation studies in evolutionary genetics. Annu Rev Ecol Evol Syst. 40:151–172. https://doi.org/10.1146/annurev.ecolsys.39.110707.173437.

Hehemann JH *et al.* 2016. Adaptive radiation by waves of gene transfer leads to fine-scale resource partitioning in marine microbes. Nat Commun. 7:12860. https://doi.org/10.1038/ncomms12860.

Hernandez-Beltran JCR *et al.* 2024. Plasmid-mediated phenotypic noise leads to transient antibiotic resistance in bacteria. Nat Commun. 15:2610. https://doi.org/10.1038/s41467-024-45045-0.

Hjort K, Nicoloff H, Andersson DI. 2016. Unstable tandem gene amplification generates heteroresistance (variation in resistance within a population) to colistin in Salmonella enterica. Mol Microbiol. 102:274–289. https://doi.org/10.1111/mmi.13459.

Ho SS, Urban AE, Mills RE. 2020. Structural variation in the sequencing era. Nat Rev Genet. 21:171–189. https://doi.org/10.1038/s41576-019-0180-9.

Hollingshead SK, Fischetti VA, Scott JR. 1987. Size variation in group A streptococcal M protein is generated by homologous recombination between intragenic repeats. Mol Gen Genet. 207:196–203.

Horiuchi T, Horiuchi S, Novick A. 1963. The genetic basis of hypersynthesis of beta-galactosidase. Genetics. 48:157–169. https://doi.org/10.1093/genetics/48.2.157.

Iantorno SA *et al.* 2017. Gene expression in *Leishmania* is regulated predominantly by gene dosage. mBio. 8:e01393-17. https://doi.org/10.1128/mBio.01393-17.

Innan H, Kondrashov F. 2010. The evolution of gene duplications: classifying and distinguishing between models. Nat Rev Genet. 11:97–108. https://doi.org/10.1038/nrg2689.

Jang S *et al.* 2017. Dynamic expansion and contraction of *cagA* copy number in *helicobacter pylori* impact development of gastric disease. mBio. 8:e01779-16. https://doi.org/10.1128/mbio.01779-16.

Jena C, Chinnaraj S, Deolankar S, Matange N. 2025. Proteostasis modulates gene dosage evolution in antibiotic-resistant bacteria. Elife. 13:RP99785. https://doi.org/10.7554/eLife.99785.

Kacser H, Beeby R. 1984. Evolution of catalytic proteins—on the origin of enzyme species by means of natural selection. J Mol Evol. 20:38–51. https://doi.org/10.1007/BF02101984.

Kafatos FC, Orr W, Delidakis C. 1985. Developmentally regulated gene amplification. Trends Genet. 1:301–306. https://doi.org/10.1016/0168-9525(85)90119-2.

Keith N *et al.* 2016. High mutational rates of large-scale duplication and deletion in *Daphnia pulex*. Genome Res. 26:60–69. https://doi.org/10.1101/gr.191338.115.

Khomarbaghi Z *et al.* 2024. Large-scale duplication events underpin population-level flexibility in tRNA gene copy number in *Pseudomonas fluorescens* SBW25. Nucleic Acids Res. 52:2446–2462. https://doi.org/10.1093/nar/gkae049.

Kim H *et al.* 2020. Extrachromosomal DNA is associated with oncogene amplification and poor outcome across multiple cancers. Nat Genet. 52:891–897. https://doi.org/10.1038/s41588-020-0678-2.

Kondrashov FA. 2012. Gene duplication as a mechanism of genomic adaptation to a changing environment. Proc R Soc Lond B Biol Sci. 279:5048–5057. https://doi.org/10.1098/rspb.2012.1108.

Koonin EV. 2015. The turbulent network dynamics of microbial evolution and the statistical tree of life. J Mol Evol. 80:244–250. https://doi.org/10.1007/s00239-015-9679-7.

Koonin EV. 2016. Horizontal gene transfer: essentiality and evolvability in prokaryotes, and roles in evolutionary transitions. F1000Res. 5:1805. https://doi.org/10.12688/f1000research.8737.1.

Koonin EV, Makarova KS, Aravind L. 2001. Horizontal gene transfer in prokaryotes: quantification and classification. Annu Rev Microbiol. 55:709–742. https://doi.org/10.1146/annurev.micro.55.1.709.

Korolev KS *et al.* 2012. Selective sweeps in growing microbial colonies. Phys Biol. 9:026008. https://doi.org/10.1088/1478-3975/9/2/026008.

Kuo C-H, Ochman H. 2009. Deletional bias across the three domains of life. Genome Biol Evol. 1:145–152. https://doi.org/10.1093/gbe/evp016.

Lagator M *et al.* 2022. Predicting bacterial promoter function and evolution from random sequences. Elife. 11:1–25. https://doi.org/10.7554/eLife.64543.

Lange JT *et al.* 2022. The evolutionary dynamics of extrachromosomal DNA in human cancers. Nat Genet. 54:1527–1533. https://doi.org/10.1038/s41588-022-01177-x.

Lauer S *et al.* 2018. Single-cell copy number variant detection reveals the dynamics and diversity of adaptation. PLoS Biol. 16:e3000069. https://doi.org/10.1371/journal.pbio.3000069.

Lauer S, Gresham D. 2019. An evolving view of copy number variants. Curr Genet. 65:1287–1295. https://doi.org/10.1007/s00294-019-00980-0.

Downloaded from academic.oup.com/genetics/article/234/3/iyag262/8875951 by Institute of Science and Technology Austria user on 17 November 2026

Leblond P, Decaris B. 1994. New insights into the genetic instability of streptomyces. FEMS Microbiol Lett. 123:225–232. https://doi.org/10.1111/j.1574-6968.1994.tb07229.x.

Lieberman TD. 2022. Detecting bacterial adaptation within individual microbiomes. Philos Trans R Soc B: Biol Sci. 377:20210243. https://doi.org/10.1098/rstb.2021.0243.

Lipinski KJ *et al.* 2011. High spontaneous rate of gene duplication in *Caenorhabditis elegans*. Curr Biol. 21:306–310. https://doi.org/10.1016/j.cub.2011.01.026.

Luria SE, Delbrück M. 1943. Mutations of Bacteria from virus sensitivity to virus resistance. Genetics. 28:491–511. https://doi.org/10.1093/genetics/28.6.491.

Lynch M *et al.* 2008. A genome-wide view of the spectrum of spontaneous mutations in yeast. Proc Natl Acad Sci U S A. 105:9272–9277. https://doi.org/10.1073/pnas.0803466105.

Lynch M, Conery JS. 2000. The evolutionary fate and consequences of duplicate genes. Science (1979). 290:1151–1155. https://doi.org/10.1126/science.290.5494.1151.

Lynch M, Conery JS. 2003. The origins of genome complexity. Science (1979). 302:1401–1404. https://doi.org/10.1126/science.1089370.

Maddamsetti R *et al.* 2024. Duplicated antibiotic resistance genes reveal ongoing selection and horizontal gene transfer in bacteria. Nat Commun. 15:1449. https://doi.org/10.1038/s41467-024-45638-9.

Maddamsetti R *et al.* 2025. Emergence of population-level feedback control by transposon-plasmid coevolution [preprint]. bioRxiv 683530. https://doi.org/10.1101/2025.10.20.683530.

Makarova KS, Wolf YI, Mekhedov SL, Mirkin BG, Koonin EV. 2005. Ancestral paralogs and pseudoparalogs and their role in the emergence of the eukaryotic cell. Nucleic Acids Res. 33:4626–4638. https://doi.org/10.1093/nar/gki775.

Manzano-Morales S, Gabaldón T. 2026. Phylogenomics of Asgard archaea reveals a unique blend of prokaryotic-like horizontal transfer and eukaryotic-like gene duplication. Nat Commun. 17:5103. https://doi.org/10.1038/s41467-026-71534-5.

Matus-Garcia M, Nijveen H, van Passel MWJ. 2012. Promoter propagation in prokaryotes. Nucleic Acids Res. 40:10032–10040. https://doi.org/10.1093/nar/gks787.

Mihajlovic L *et al.* 2025. A direct experimental test of Ohno's hypothesis. Elife. 13:RP97216. https://doi.org/10.7554/eLife.97216.

Miller SR, Wood AM, Blankenship RE, Kim M, Ferriera S. 2011. Dynamics of gene duplication in the genomes of chlorophyll c/-producing cyanobacteria: implications for the ecological niche. Genome Biol Evol. 3:601–613. https://doi.org/10.1093/gbe/evr060.

Mira A, Ochman H, Moran NA. 2001. Deletional bias and the evolution of bacterial genomes. https://doi.org/10.1016/S0168-9525(01)02447-7.

Morelli G *et al.* 2010. Microevolution of *Helicobacter pylori* during prolonged infection of single hosts and within families. PLoS Genet. 6:e1001036. https://doi.org/10.1371/journal.pgen.1001036.

Moxon ER, Rainey PB, Nowak MA, Lenski RE. 1994. Adaptive evolution of highly mutable loci in pathogenic bacteria. Curr Biol. 4:24–33. https://doi.org/10.1016/S0960-9822(00)00005-1.

Moxon R, Bayliss C, Hood D. 2006. Bacterial contingency loci: the role of simple sequence DNA repeats in bacterial adaptation. Annu Rev Genet. 40:307–333. https://doi.org/10.1146/annurev.genet.40.110405.090442.

Muller HJ. 1928. The measurement of gene mutation rate in Drosophila, its high variability, and its dependence upon temperature. Genetics. 13:279–357. https://doi.org/10.1093/genetics/13.4.279.

Näsvall J, Sun L, Roth JR, Andersson DI. 2012. Real-time evolution of new genes by innovation, amplification, and divergence. Science. 338:384–387. https://doi.org/10.1126/science.1226521.

Nicoloff H, Hjort K, Andersson DI, Wang H. 2024. Three concurrent mechanisms generate gene copy number variation and transient antibiotic heteroresistance. Nat Commun. 15:3981. https://doi.org/10.1038/s41467-024-48233-0.

Nicoloff H, Hjort K, Levin BR, Andersson DI. 2019. The high prevalence of antibiotic heteroresistance in pathogenic bacteria is mainly caused by gene amplification. Nat Microbiol. 4:504–514. https://doi.org/10.1038/s41564-018-0342-0.

Nijveen H, Matus-Garcia M, van Passel MWJ. 2012. Promoter reuse in prokaryotes. Mob Genet Elements. 2:279–281. https://doi.org/10.4161/mge.23195.

Ochman H, Lawrence JG, Groisman EA. 2000. Lateral gene transfer and the nature of bacterial innovation. Nature. 405:299–304. https://doi.org/10.1038/35012500.

Ohno S. 1970Evolution by gene duplicationBerlin (Germany): Springer-Verlag. https://doi.org/10.1007/978-3-642-86659-3

Oliver KR, Greene WK. 2012. Transposable elements and viruses as factors in adaptation and evolution: an expansion and strengthening of the TE-thrust hypothesis. Ecol Evol. 2:2912–2933. https://doi.org/10.1002/ece3.400.

Pajic P *et al.* 2019. Independent amylase gene copy number bursts correlate with dietary preferences in mammals. Elife. 8:1–22. https://doi.org/10.7554/eLife.44628.

Perry GH *et al.* 2007. Diet and the evolution of human amylase gene copy number variation. Nat Genet. 39:1256–1260. https://doi.org/10.1038/ng2123.

Petes TD, Hill CW. 1988. Recombination between repeated genes in microorganisms. Annu Rev Genet. 22:147–168. doi: 10.1146/annurev.ge.22.120188.001051.

Pettersson ME, Sun S, Andersson DI, Berg OG. 2009. Evolution of new gene functions: simulation and analysis of the amplification model. Genetica. 135:309–324. https://doi.org/10.1007/s10709-008-9289-z.

Prody CA, Dreyfus P, Zamir R, Zakut H, Soreq H. 1989. De novo amplification within a 'silent' human cholinesterase gene in a family subjected to prolonged exposure to organophosphorous insecticides. Proc Natl Acad Sci U S A. 86:690–694. https://doi.org/10.1073/pnas.86.2.690.

Raffaele Cosenza M, Rodriguez-Martin B, Korbel JO. 2025. Structural variation in cancer: role, prevalence, and mechanisms. Annu Rev Genomics Hum Genet. 66:34. https://doi.org/10.1146/annurev-genom-120121.

Reams AB, Kofoid E, Kugelberg E, Roth JR. 2012. Multiple pathways of duplication formation with and without recombination (RecA) in *Salmonella enterica*. Genetics. 192:397–415. https://doi.org/10.1534/genetics.112.142570.

Reams AB, Kofoid E, Savageau M, Roth JR. 2010. Duplication frequency in a population of *Salmonella enterica* rapidly approaches steady state with or without recombination. Genetics. 184:1077–1094. https://doi.org/10.1534/genetics.109.111963.

Reams AB, Roth JR. 2015. Mechanisms of gene duplication and amplification. Cold Spring Harb Perspect Biol. 7:a016592. https://doi.org/10.1101/cshperspect.a016592.

Robert L *et al.* 2018. Mutation dynamics and fitness effects followed in single cells. Science (1979). 359:1283–1286. https://doi.org/10.1126/science.aan0797.

Rodriguez-Beltran J *et al.* 2018. Multicopy plasmids allow bacteria to escape from fitness trade-offs during evolutionary innovation. Nat Ecol Evol. 2:873–881. https://doi.org/10.1038/s41559-018-0529-z.

Roth J, Maisnier-Patin S. 2016 Feb 16. Re-interpreting long-term evolution experiments: is delayed adaptation an example of historical contingency or a consequence of intermittent selection? J Bacteriol. 198:1009-12. https://doi.org/10.1128/JB.00110-16.

Downloaded from academic.oup.com/genetics/article/234/3/iyag262/8875951 by Institute of Science and Technology Austria user on 17 November 2026

Sandegren L, Andersson DI. 2009. Bacterial gene amplification: implications for the evolution of antibiotic resistance. Nat Rev Microbiol. 7:578–588. https://doi.org/10.1038/nrmicro2174.

San Millan A, Escudero JA, Gifford DR, Mazel D, MacLean RC. 2017. Multicopy plasmids potentiate the evolution of antibiotic resistance in bacteria. Nat Ecol Evol. 1:10. https://doi.org/10.1038/s41559-016-0010.

Schrider DR, Houle D, Lynch M, Hahn MW. 2013. Rates and genomic consequences of spontaneous mutational events in *Drosophila melanogaster*. Genetics. 194:937–954. https://doi.org/10.1534/genetics.113.151670.

Slager J, Aprianto R, Veening JW. 2018. Deep genome annotation of the opportunistic human pathogen *Streptococcus pneumoniae* D39. Nucleic Acids Res. 46:9971–9989. https://doi.org/10.1093/nar/gky725.

Slatkin M. 1974. Hedging one's evolutionary bets. Nature. 250:704–705. https://doi.org/10.1038/250704b0.

Spealman P, De T, Chuong JN, Gresham D. 2023. Best practices in microbial experimental evolution: using reporters and long-read sequencing to identify copy number variation in experimental evolution. J Mol Evol. 91:356–368 https://doi.org/10.1007/s00239-023-10102-7.

Steinrueck M, Guet CC. 2017. Complex chromosomal neighborhood effects determine the adaptive potential of a gene under selection. Elife. 6:1–26. https://doi.org/10.7554/eLife.25100.

Sulak M *et al.* 2016. TP53 copy number expansion is associated with the evolution of increased body size and an enhanced DNA damage response in elephants. Elife. 5:1–30. https://doi.org/10.7554/eLife.11994.

Surguchov A. 1991. Migration of promoter elements between genes: a role in transcriptional regulation and evolution. Biomed Sci. 2:22–38. https://pubmed.ncbi.nlm.nih.gov/1680476/

Tam YL, Cameron S, Preston A, Cowley L. 2024. *GWarrange*: a pre-and post-genome-wide association studies pipeline for detecting phenotype-associated genome rearrangement events. Microb Genom. 10:001268. https://doi.org/10.1099/mgen.0.001268.

Teufel AI, Masel J, Liberles DA. 2015. What fraction of duplicates observed in recently sequenced genomes is segregating and destined to fail to fix? Genome Biol Evol. 7:2258–2264. https://doi.org/10.1093/gbe/evv139.

Todd RT, Selmecki A. 2020. Expandable and reversible copy number amplification drives rapid adaptation to antifungal drugs. Elife. 9:e58349. https://doi.org/10.7554/eLife.58349.

Tomanek I *et al.* 2020. Gene amplification as a form of population-level gene expression regulation. Nat Ecol Evol. 4:612–625. https://doi.org/10.1038/s41559-020-1132-7.

Tomanek I. 2024. Shining a light on Ohno's dilemma. Elife. 13:e99318. https://doi.org/10.7554/eLife.99318.

Tomanek I, Guet C. 2022. Adaptation dynamics between copy-number and point mutations. Elife. 11:e82240. https://doi.org/10.7554/eLife.82240.

Tomasek K *et al.* 2022. Type 1 piliated uropathogenic *Escherichia coli* hijack the host immune response by binding to CD14. Elife. 11:e78995. https://doi.org/10.7554/ELIFE.78995.

Torrillo PA, Lieberman TD. 2024. Reversions mask the contribution of adaptive evolution in microbiomes. Elife. 13:e93146. https://doi.org/10.7554/eLife.93146.

Traxler MF, Kolter R. 2015. Natural products in soil microbe interactions and evolution. Nat Prod Rep. 32:956–970. https://doi.org/10.1039/c5np00013k.

Treangen TJ, Rocha EPC. 2011. Horizontal transfer, not duplication, drives the expansion of protein families in prokaryotes. PLoS Genet. 7:e1001284. https://doi.org/10.1371/journal.pgen.1001284.

Tria FDK, Martin WF. 2021. Gene duplications are at least 50 times less frequent than gene transfers in prokaryotic genomes. Genome Biol Evol. 13:evab224. https://doi.org/10.1093/gbe/evab224.

Tuğrul M, Paixão T, Barton NH, Tkačik G. 2015. Dynamics of transcription factor binding site evolution. PLoS Genet. 11:e1005639. https://doi.org/10.1371/journal.pgen.1005639.

Turner KM *et al.* 2017. Extrachromosomal oncogene amplification drives tumour evolution and genetic heterogeneity. Nature. 543:122–125. https://doi.org/10.1038/nature21356.

van Passel MWJ, Nijveen H, Wahl LM. 2014. Birth, death, and diversification of mobile promoters in prokaryotes. Genetics. 197:291–299. https://doi.org/10.1534/genetics.114.162883.

Vezina B *et al.* 2024. Wild-type domestication: loss of intrinsic metabolic traits concealed by culture in rich media. Microb Ecol. 87:144. https://doi.org/10.1007/s00248-024-02459-z.

Wang D *et al.* 2021. Characterization of gut microbial structural variations as determinants of human bile acid metabolism. Cell Host Microbe. 29:1802–1814.e5. https://doi.org/10.1016/j.chom.2021.11.003.

Wang H, Joffré E. 2025. Plasmid copy number as a modulator in bacterial pathogenesis and antibiotic resistance. NPJ Antimicrob Resist. 3:72. https://doi.org/10.1038/s44259-025-00145-9.

Waters EV, Cameron SK, Langridge GC, Preston A. 2025. Bacterial genome structural variation: prevalence, mechanisms, and consequences. Trends Microbiol. 33:875–886. https://doi.org/10.1016/j.tim.2025.04.004.

Weissman SJ *et al.* 2007. Differential stability and trade-off effects of pathoadaptive mutations in the *Escherichia coli* FimH adhesin. Infect Immun. 75:3548–3555. https://doi.org/10.1128/IAI.01963-06.

Wellenreuther M, Mérot C, Berdan E, Bernatchez L. 2019. Going beyond SNPs: the role of structural genomic variants in adaptive evolution and species diversification. Mol Ecol. 28:1203–1209. https://doi.org/10.1111/mec.15066.

Yao Y *et al.* 2022. Intra- and interpopulation transposition of mobile genetic elements driven by antibiotic selection. Nat Ecol Evol. 6:555–564. https://doi.org/10.1038/s41559-022-01705-2.

Yelin I, Kishony R. 2026. Non-canonical gene amplifications facilitate adaptive evolution in bacteria. Nat Microbiol. 11:2201–2212. https://doi.org/10.1038/s41564-026-02415-2.

Yona AH, Alm EJ, Gore J. 2018. Random sequences rapidly evolve into de novo promoters. Nat Commun. 9:1530. https://doi.org/10.1038/s41467-018-04026-w.

Yona AH, Frumkin I, Pilpel Y. 2015. A relay race on the evolutionary adaptation spectrum. Cell. 163:549–559. https://doi.org/10.1016/j.cell.2015.10.005.

Zabelkin A, Yakovleva Y, Bochkareva O, Alexeev N. 2022. Parebrick: PArallel REarrangements and BReaks identification toolkit. Bioinformatics. 38:357–363. https://doi.org/10.1093/bioinformatics/btab691.

Zeevi D *et al.* 2019. Structural variation in the gut microbiome associates with host health. Nature. 568:43–48. https://doi.org/10.1038/s41586-019-1065-y.

Zhou X *et al.* 2023. De Novo structural variations of *Escherichia coli* detected by nanopore long-read sequencing. Genome Biol Evol. 15:evad106. https://doi.org/10.1093/gbe/evad106.

Editor: M. Pespeni

Downloaded from academic.oup.com/genetics/article/234/3/iyag262/8875951 by Institute of Science and Technology Austria user on 17 November 2026