

# Estimates of the Mutation Rate per Year Can Explain Why the Molecular Clock Depends on Generation Time

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## Abstract

Rates of molecular evolution are known to vary across species, often deviating from the classical expectation of a strict molecular clock. In many cases, the rate of molecular evolution has been found to correlate to generation time, an effect that could be explained if species with shorter generation times have higher mutation rates per year. We investigate this hypothesis using direct estimates of the mutation rate for 133 eukaryotic species from diverse taxonomic groups. Using a phylogenetic comparative approach, we find a strong negative correlation between mutation rate per year and generation time, consistent across all phylogenetic groups. Our results provide a simple explanation for why generation time plays a pivotal role in driving rates of molecular evolution across eukaryotes.

**Keywords:** generation time, mutation rate, evolutionary rate

## Introduction

The concept of a “molecular clock,” whereby DNA sequence evolution proceeds at a constant, clock-like rate, was first introduced in the 1960s (Zuckerlandl and Pauling 1962). The molecular clock was initially heralded as a powerful tool for estimating evolutionary rates and divergence times of species across the tree of life. However, more recent tests of the strict clock hypothesis have revealed that the rate of molecular evolution (measured as the rate at which protein, RNA, or DNA sequences evolve per year) varies widely between species, especially when considering more distantly related lineages (Bousquet et al. 1992; Thomas et al. 2006). This was first discovered by Wu and Li (1985) in a comparison of protein-coding sequences from primates, rodents, and artiodactyls; they found that rodents were about twice as divergent from their common ancestor as primates. Studies have found this variation in rate to be correlated to several aspects of species biology, including body size, longevity, metabolic rate, DNA repair mechanisms, and generation time (Bromham 2002; Nabholz et al. 2008; Smith and Donoghue 2008; Thomas et al. 2010). Among these traits, generation time has emerged as a particularly strong correlate of molecular evolution rates, such that species with short generation times have higher rates of molecular evolution. This effect of generation time on the rate of evolution in both nuclear and mitochondrial DNA has been observed extensively in mammals (Ohta 1993; Bromham et al. 1996; Li et al. 1996; Rowe and Honeycutt 2002; Welch et al. 2008; Sayres et al. 2011), but also in diverse taxa including plants (Smith and Donoghue 2008), invertebrates (Thomas et al. 2010), and bacteria (Weller and Wu 2015).

It is thought that the association between the rate of molecular evolution and generation time is due to a correlation between the mutation rate and generation time. However, until

recently, there have been few direct estimates of the mutation rate available to confirm or refute this hypothesis. The advent of next-generation sequencing has enabled direct estimation of mutation rates through parent–offspring sequencing and mutation accumulation experiments, offering an opportunity to test this hypothesis directly. A number of studies comparing the mutation rates of individual mammalian species to humans have observed that species with shorter generation times tend to have higher mutation rates per year (Wu et al. 2020; Bergeron et al. 2021; Wang et al. 2022b). Bergeron et al. (2023) further showed that the relationship between the mutation rate per generation and generation time across species has a positive intercept, implying that a negative correlation between the mutation rate per year and generation time should exist. However, the relationship between the mutation rate per year—the fundamental determinant of rates of molecular evolution—and generation time remains underexplored across a more extensive phylogeny. In this study, we leverage a growing data set of directly estimated mutation rates to investigate whether the mutation rate per year is correlated to generation time across a wide range of species.

## Methods

The germline mutation rate estimates used in this study were primarily compiled from an existing meta-analysis by Wang and Obbard (2023). An additional literature search was performed using Clarivate Web of Science following the search strategy described in Wang and Obbard (2023) for the period from 2022 September 22 to 2024 April 15 to ensure inclusion of more recent data. This yielded an additional 30 estimates and brought the total number of species with genome-wide mutation rate estimates to 156 (supplementary table S1, Supplementary Material online). All estimates were based on

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sequencing of closely related individuals in pedigrees or mutation accumulation lines.

Generation time estimates for 146 of these species were sourced from the literature ([supplementary table S2, Supplementary Material](#) online). In the context of this analysis, the generation time is the average age of parents. Unfortunately, most species lack sufficiently detailed reproductive data to estimate this directly. As a result, most generation time estimates are modeled based on available life history traits such as age at first breeding and reproductive life span (full details of how these estimates were made can be found in [supplementary table S2, Supplementary Material](#) online). Although this approach may introduce a level of error into estimates of generation time—particularly for iteroparous species, for which age at first breeding likely underestimates average parental age—indirect generation time estimates should still provide a reasonable approximation for large-scale comparative studies such as this. Prior work has demonstrated that such estimates correlate well with empirical data for species where direct measurements are available ([Pacifi et al. 2013](#)), and given the scope and diversity of species included in this study, indirect generation time estimates offer a practical means of addressing gaps in reproductive data while ensuring the feasibility of analyzing broad evolutionary trends.

Mutation rates per year ( $\mu_y$ ) were subsequently calculated as  $\mu_G$ /generation time, where  $\mu_G$  is the mutation rate per site per generation.  $\mu_y$  estimates ranged from  $1.51 \times 10^{-6}$  mutations per site per year in *Saccharomyces cerevisiae* down to the lowest estimate of  $1.26 \times 10^{-10}$  per year in the snowy owl ([supplementary table S2, Supplementary Material](#) online). Since these values vary over orders of magnitude, all analyses following the initial calculation of  $\mu_y$  were performed on  $\log(\mu_y)$  and  $\log(\text{generation time})$ , though for simplicity we refer to these variables as  $\mu_y$  and generation time, respectively.

[Bergeron et al. \(2023\)](#) note that estimating  $\mu_y$  as  $\mu_G$ /generation time may lead to a biased estimate of the mutation rate per year if the average age of parents in the experiment used to determine the mutation rate differs from the generation time in the wild. They propose a method to control for this, but they assume that the number of mutations per site at birth is the same across all species. While this assumption may be reasonable for the vertebrates they have considered, it seems less likely to be the case for our more diverse selection of species. Our estimates are only likely to be substantially biased if the parental age in the experiment differs significantly from the generation time in the wild and mutation rates increase substantially with parental age. The available evidence suggests that many mutations occur before birth ([Gao et al. 2014](#); [Lindsay et al. 2019](#)), and although there is evidence that the mutation rate increases with parental age in many species ([Lindsay et al. 2019](#); [Wang et al. 2022b](#); [Bergeron et al. 2023](#)), in most cases, the slope is shallow relative to the intercept—i.e. in those species that show a parental age effect, the total number of mutations at reproductive age is often dominated by those that occurred before birth, not those that occurred post-puberty.

To test for an association between  $\mu_y$  and generation time, phylogenetic comparative methods were employed to account for the shared evolutionary history between species ([Felsenstein 1985](#)). A phylogenetic tree was constructed using <https://timetree.org/> ([Kumar et al. 2022](#)), and phylogenetic generalized least squares (PGLS) regressions were performed using the R package *caper* ([Orme et al. 2023](#)) to correct for

phylogenetic nonindependence when fitting regression lines. Phylogenetic generalized linear mixed models (PGLMM) were performed using the R package *phyr* ([Li et al. 2020](#)). Thirteen species were lost from our analysis since TimeTree had no data on them or a closely related species; this meant that the following analyses were ultimately performed on a final set of 133 species.

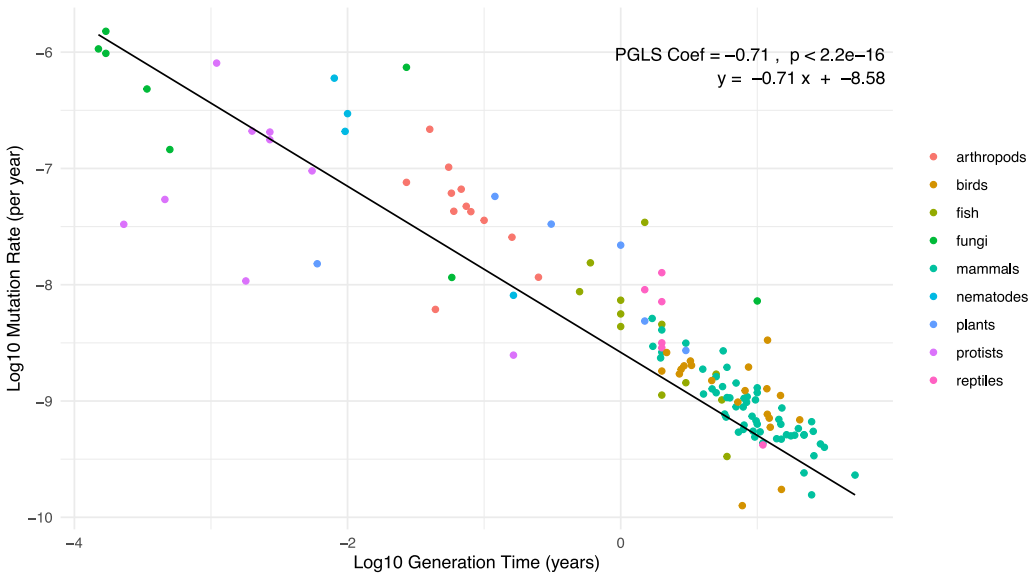
To investigate whether the relationship between  $\mu_y$  and generation time might be due to estimation error in the generation time, we performed a simulation in which we assumed that the mutation rate per year was independent of the generation time. We sampled  $\log(\mu_{y\_true})$  and  $\log(GT\_true)$  from normal distributions, along with a normally distributed error term. We calculated  $\log(\mu_{G\_true}) = \log(\mu_{y\_true}) + \log(GT\_true)$  and  $\log(GT\_obs) = \log(GT\_true) + e$ , where  $e$  is the error in the generation time. The estimated mutation rate per year is then  $\log(\mu_{y\_obs}) = \log(\mu_{G\_true}) - \log(GT\_obs)$ . We considered the regression between  $\log(\mu_{y\_obs})$  and  $\log(GT\_obs)$  for data sets of 133 species. We repeated the regression 100 times for each set of parameters varying the error variance across simulations.  $\log(GT\_obs)$  was constrained to equal the variance observed in the data we have analyzed.

## Results and Discussion

Using our data set of 133 species, we find that the mutation rate per year ( $\mu_y$ ) is significantly negatively correlated to generation time (PGLS slope =  $-0.71$ ,  $P < 0.01$ ; [Fig. 1](#); [supplementary fig. S2, Supplementary Material](#) online), such that species with shorter generation times are estimated to have higher mutation rates per year. The slope of the regression implies that doubling the generation time will reduce the mutation rate per year by approximately 39%.

This relationship appears to be consistent across diverse phylogenetic groups. Classifying species into nine arbitrary taxonomic groups, we find that the relationship between  $\mu_y$  and generation time is negative in all cases, with many groups showing statistically significant correlations ([Table 1](#)). To investigate whether the nature of the relationship differed among groups, we used a PGLMM of  $\mu_y$  on generation time, incorporating phylogenetic group as a fixed effect. This model allowed us to test whether the intercept and slope of the relationship between  $\mu_y$  and generation time vary across groups, while accounting for the nonindependence of species due to their phylogenetic relationships by specifying a phylogenetic tree as a covariance structure for the species as a random effect term. In our analysis, we found no evidence that adding phylogenetic group, or an interaction between the slope and phylogenetic group, improved the fit of the model. While some groups contained relatively few species, potentially limiting the power of our analyses, we detected no significant difference in the intercept of the relationship when comparing the two largest groups, mammals and birds, using a two-sample  $t$ -test ( $P = 0.33$ ); likewise, we found no significant difference in the slopes ( $P = 0.66$ ).

The negative relationship identified between  $\mu_y$  and generation time could potentially be a consequence of error in the generation time estimates, which are only approximations for species with complex life histories or incomplete ecological data. The fact that  $\mu_y$  is estimated as the mutation rate per generation divided by generation time means that sampling error in the generation time estimates could generate an artifactual negative correlation between the two. To investigate this, we ran a simulation in which we assumed that  $\mu_y$  was independent



**Fig. 1.** PGLS regression of mutation rate per year ( $\mu_y$ ) on generation time (in years) on a log10 scale. After controlling for phylogenetic inertia, mutation rate per year remains significantly negatively correlated to generation time. Adjusted  $R^2 = 0.50$ . Standard error associated with the slope = 0.062.

**Table 1** Summary of PGLS regressions of mutation rate per year ( $\mu_y$ ) on generation time (in years) within individual phylogenetic groups

Phylogenetic group	Number of species	PGLS slope	P-value	Adjusted $R^2$
Arthropods	12	−0.84	0.0980	0.17
Birds	20	−0.63	0.0242 <sup>a</sup>	0.21
Fish	12	−1.20	0.0027 <sup>b</sup>	0.57
Fungi	8	−0.57	0.0057 <sup>b</sup>	0.70
Mammals	56	−0.80	<2.2e-16 <sup>b</sup>	0.76
Nematodes	4	−1.31	0.0071 <sup>b</sup>	0.98
Plants	6	−0.26	0.3160	0.06
Protists	9	−0.47	0.1703	0.14
Reptiles	6	−1.67	0.0261 <sup>a</sup>	0.69

<sup>a</sup> $P < 0.05$ . <sup>b</sup> $P < 0.01$ .

of generation time, with both generation time values and the error in these values being sampled from independent normal distributions. We find that the error variance in generation time would need to be approximately 2.2 times greater than the systematic variance in generation time to produce the observed slope (supplementary fig. S1, Supplementary Material online). A similar result can also be derived analytically (see supplementary text S1, Supplementary Material online). Given that it is unrealistic for the error in our generation time estimates to substantially exceed the systematic variation in generation time, we conclude that there is a genuine negative relationship between  $\mu_y$  and generation time.

We have shown that  $\mu_y$  is negatively correlated to generation time. This provides an intuitive explanation as to why the rate of molecular evolution is correlated to generation time, as we expect this rate to depend on the mutation rate under almost every model of molecular evolution. However, *why*  $\mu_y$  is negatively correlated to generation time is less clear. Mutations can occur due to errors in DNA replication or from DNA damage that is either unrepaired or incorrectly repaired prior to the next round of replication. Although the relative contributions of these processes to the overall level of mutation remain unclear and actively debated (Gao et al. 2016; Wang et al. 2020; Wu et al. 2020; Hahn et al. 2023), there are various models incorporating different mutational processes that could account for the negative relationship between  $\mu_y$  and generation time.

One simple model is that the mutation rate during early gametogenesis is higher than in later stages. If early rounds of cell division are significantly more mutagenic, regardless of whether those mutations are replicative or nonreplicative in origin, then  $\mu_y$  will decrease with increasing generation time. First, it has been shown in both *Drosophila* (Gao et al. 2011, 2014) and mice (Lindsay et al. 2019) that the mutation rate is elevated during early germ cell development, with 24% of all germline mutations in mice found to occur during the first three cell divisions. Second, as several authors have noted, the intercept of a regression of the number of mutations against parental age typically has a positive intercept, implying that a significant number of mutations have accumulated before birth (Lindsay et al. 2019; Wang et al. 2022b; Bergeron et al. 2023). If this pattern holds across species, then organisms with shorter generation times will have higher  $\mu_y$  due to a higher frequency of mutagenic developmental cycles per unit time.

An alternative hypothesis that is commonly invoked to explain the generation time effect is that organisms with shorter generation times have a faster rate of cell division and therefore accumulate more mutations due to replication errors (Li et al. 1996). However, evidence in mammals increasingly supports a decoupling of the mutational burden from cell division. Firstly, a modest but significant maternal age effect has been observed in humans, with older mothers found to transmit more germline mutations despite the absence of ongoing

cell division in the female germline (Goldmann et al. 2016; Wong et al. 2016; Jónsson et al. 2017). Secondly, the paternal mutation bias in mammals—whereby most germline mutations are transmitted from the father—has been found to be present by the age of puberty despite similar numbers of cell divisions occurring in the male and female germ lines up until this point (Drost and Lee 1995; Forster et al. 2015; Gao et al. 2019). Finally, the degree of male mutation bias appears to be relatively consistent across species with very different generation times (Lindsay et al. 2019; Wu et al. 2020; Wang et al. 2022a), casting further doubt on the assumption that germline mutations track cell divisions. In the absence of a clear link between cell division rates and mutation rates, replication-driven mutations cannot fully account for the negative correlation between  $\mu_y$  and generation time.

It could instead be that organisms with shorter generation times experience greater levels of nonreplicative damage, either due to higher rates of lesion formation or more error-prone DNA repair processes. This could explain the observed negative relationship without having to invoke replication-dependent mutations. A similar hypothesis has been proposed to account for the male mutation bias in mammals, with the suggestion that males have less robust DNA repair and/or protection mechanisms than females (de Manuel et al. 2022; Hahn et al. 2023). An analogous model whereby species with shorter generation times accumulate more damage-induced mutations due to a reduced capacity to protect their germline could help to explain the observed negative correlation between  $\mu_y$  and generation time. This effect could be complemented by longer generation times inducing stronger selection against “mutator alleles”, such as those reducing the efficiency of DNA repair (Lindsay et al. 2019; Zhu et al. 2024). This heightened selection pressure could help to counteract the weaker purifying selection expected in species with smaller effective population sizes (Lynch 2010), ultimately favoring lower  $\mu_y$  to limit the accumulation of germline mutations within each generation.

As it stands, the timings and absolute contributions of replicative and nonreplicative mutations in the germline remain largely unknown, so we cannot definitively explain the negative correlation between  $\mu_y$  and generation time. However, regardless of the underlying mechanism behind this correlation, it still provides a simple explanation as to why the widely observed relationship between rates of molecular evolution and generation time exists. By identifying systematic correlates of rates of molecular evolution, such as generation time, it becomes possible to increase the flexibility and accuracy of the molecular clock by integrating these variables into relaxed clock models (Lartillot et al. 2016). Overall, these findings highlight the importance of generation time as a predictor of mutation rates, providing valuable insights for refining evolutionary models and improving our understanding of how life history traits shape molecular evolution across the tree of life.

## Supplementary Material

Supplementary material is available at *Molecular Biology and Evolution* online.

## Data Availability

All data and scripts used in this study are available on GitHub at <https://github.com/lovedayel/mutation-generation-evolution>.

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