What is the human germline mutation rate?

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Abstract

Germline mutations are the ultimate source of heritable genetic variation, driving evolution, enabling adaptation, and underlying certain diseases. Despite their fundamental importance, key questions remain unanswered: How frequently do germline mutations arise? Do mutation rates vary systematically across individuals, populations, and local genomic context? And what determines whether a mutation arising in a germ cell is ultimately transmitted to offspring? Historically, mutation rates were assumed to be relatively uniform within species, but recent advances in sequencing and computational methods now allow direct measurement of *de novo* mutations in families and gametes, revealing unexpected variation. We review evidence for variation in human germline mutation rates and spectra, considering sources ranging from molecular mechanisms and life-history traits to developmental processes and evolutionary forces. A central theme is the distinction between factors shaping mutation occurrence in germ cells and those influencing mutation detection in sampled individuals and populations. We highlight major sources of uncertainty, including methodological heterogeneity across studies, confounding between molecular and developmental effects, and limited sampling diversity. We argue that resolving these questions requires technical standardization, broader sampling across diverse ancestries and environments, and explicit theoretical frameworks that account for the multiple scales—cellular, organismal, and populational—at which mutation rates vary. Understanding the origins and extent of germline mutation rate variation is essential for reconstructing human evolutionary history, predicting disease risk, and interpreting the genetic architecture of complex traits.

Main text

Ninety years ago, J.B.S. Haldane suggested that “taking the generation as the unit of time, man is a rather more mutable species than Drosophila”, after attempting, for the first time, to measure the rates of spontaneous germline mutations in members of our species (Haldane, 1935) (but see Danforth, 1923) for an earlier discussion of the same approach). Given that this was still two decades before

understanding the structure of DNA (Franklin & Gosling, 1953; Watson & Crick, 1953), Haldane lacked the technical and conceptual foundations to estimate mutations based on changes in DNA sequences as we do today. Thus, he needed to rely on an indirect method based on the principle of mutation-selection-balance, or the idea that deleterious alleles exist in populations because their purging via purifying selection is counterbalanced by a continual influx of new mutations (Haldane, 1927). Although our understanding of genetics has dramatically expanded since Haldane´s initial estimations, through the deepening of our understanding of molecular biology, the increasing availability of DNA sequencing technologies and important conceptual advances in our understanding of mutational processes and population genetics, answers to the question of *how frequently new mutations arise* in the human germline are far from definite.

Genetic mutations are the ultimate source of heritable variation in populations, and their rate and spectrum shape the tempo of evolution at molecular, phenotypic, and adaptive levels. Understanding how and why mutation rates vary is therefore central to evolutionary biology, including the evolution of our own species, as well as to human health, disease, and the heritability of traits. Germline mutations originate in cell lineages capable of differentiating into gametes and thus constitute the source of novel genetic variation transmitted between generations. Therefore, insights into both the frequency with which new mutations arise (the mutation rate) and the types of mutations that occur (the mutational spectrum), are key for understanding heritable variation within our species. Although research over the past few decades suggests that germline mutation rates and spectra might vary within and between populations due to an interplay of genetic, environmental, and life-history factors, many analyses in genomics, population genetics, and phylogenetics still rely on simplifying assumptions about mutation rates, which can massively affect our inference (e.g.Bromham, 2024; Ritchie et al., 2022). Consequently, vast uncertainties still exist in relation to just how variable germline mutation rates are across and within human populations, what drives differences in such variation, and how have those differences evolved throughout our evolutionary history.

In this perspective, we examine recent findings on variation in both the rate and spectrum of human germline mutations—within and across populations—and consider their possible causes. We also highlight major sources of uncertainty and key research gaps (For recent reviews covering somatic mutations or broader taxonomic comparisons, see (Beichman et al., 2024; Solís-Moruno et al., 2023). A central theme is the importance of distinguishing between three questions: (1) what determines the probability that particular mutations occur in an individual's germline, (2) what determines the probability that mutations enter the gene pool of a population, and (3) what determines the probability that such mutations are present in a population at the time we measure them. For this it is important to distinguish between the molecular mutation rate ($\hat{\mu}_{mol}$), and the generational mutation rate, at which new alleles are added to the gene pool of a population (μ_{pop}) and substitution rates(Drake et al., 1998;

Kimura, 1987; Majic et al., 2026; Neville et al., 2025). In other words, we argue that disentangling the causes of mutation occurrence from the forces that shape their probability of persisting, such that they are present in a successful gamete, as well as through development and over evolutionary time is key to reconciling disparate findings—and to guiding future research. We also argue that, as for most aspects of genetics research, diversifying the samples we use in human genetic research is necessary in order to disentangle potential drivers and variability in mutation rates within our species (see(Fatumo et al., 2022; Flegontov et al., 2023; Padilla-Iglesias & Derkx, 2024) for a more general discussion).

1. Quantifying human germline mutation rates

The quantification of human mutation rates has a long history that has seen many conceptual and technological developments (Table 1). Together with these developments, the precise question of how many new mutations arise each generation has provided a diversity of estimations, sometimes with notorious discrepancies, sometimes with surprising consistency (see Table S1 for a comprehensive summary, details and numerical estimates of such studies).

Some of the earliest attempts to estimate mutation rates go back to Haldane's work on haemophilia, a recessive X-linked disorder. Haldane reasoned that if haemophiliacs typically did not reproduce, that is, if the strength of selection s was close to 1, the mutation rate could be approximated by dividing the frequency of haemophiliac males by 3, since males carry one-third of the X chromosomes in the population (Haldane, 1935). Using data from haemophilia cases in London, he estimated a mutation rate of about one mutation per 50,000 generations (Haldane, 1935; Kondrashov, 2003). Following this seminal work, these genetic principles were widely applied to estimate spontaneous per-generation mutation rates by counting individuals affected by autosomal dominant or X-linked recessive disorders born to unaffected parents (Cooper & Krawczak, 1995), yielding per-locus, per-generation estimates ranging from 10^{-6} to 10^{-4} (Vogel & Motulsky, 1997).

This **disease-based approach**, however, inherently biases results toward mutations with significant phenotypic impact, typically those causing severe and easily identifiable disease symptoms(Pfeifer, 2020), and requires estimating both the mutational target size (the size of the genomic region where mutations yield the observable phenotype) and the strength of selection, both of which carry substantial uncertainty. Accounting for mutational target size across 20 known disease-causing loci, Kondrashov (2003) estimated a human mutation rate of about 2×10^{-8} per site per generation, while Lynch (2010) combined data from a broader set of loci to arrive at a lower estimate of 1.28×10^{-8} per site per generation.

As an alternative to these disease-based approaches, other methods were developed during the molecular revolution that followed the deciphering of the DNA structure and genetic code. In 1968, Kimura introduced the neutral theory of molecular evolution, under which the rate of neutral substitutions equals the neutral mutation rate (Kimura, 1968). For a single lineage, the expected number of substitutions (K) accumulating over a time interval of (T) years equals $(\mu/G)T$, where μ is the per-generation mutation rate (equivalent to μ_{pop}) and G is generation time. For pairwise divergence between two species, however, the observed sequence divergence reflects substitutions accumulated independently along both descendant lineages, such that $\mu = DG/(2T)$, where D is the observed divergence and T is the time since their common ancestor. This provided the theoretical foundation for **the "phylogenetic method,"** where mutation rates are estimated by dividing observed sequence divergence in orthologous neutral genomic regions between species using independently estimated divergence times, typically calibrated from the fossil record, together with estimates of generation time (Drake et al., 1998; Kondrashov & Crow, 1993; Nachman & Crowell, 2000). Using this approach, Nachman and Crowell (2000) estimated a human mutation rate of 2.5×10^{-8} per site per generation. Despite the methodological differences this strikingly matches closely Kondrashov's (2003) per-site estimate and is compatible with Haldane's earlier per-locus estimate, assuming ~10^3 coding sites per gene (Haldane, 1935).

In recent decades, whole-genome or exome **sequencing-based pedigree designs** (including trio-based approaches) have offered a more direct route to estimating germline mutation rates (Bergeron et al., 2023), and have been complemented by methods that sequence single gametes, allowing mutations to be observed in the very cells that transmit DNA to the next generation (Axelsson et al., 2024; Melamed et al., 2025; Shoag et al., 2025; Kaplanis et al., 2022). Genome-wide sequencing in family pedigrees (Garcia-Salinas, Hwang, et al., 2025; Jónsson et al., 2017; O'Roak et al., 2011; Porubsky et al., 2025; Rahbari et al., 2016; Roach et al., 2010), has yielded estimates of germline mutation rates by relying on the assumption that any mutations present in the offspring whilst not in the parents must be the product of a *de novo* mutation (DNM) in the parental germline. These estimates typically fall around $1.1–1.3 \times 10^{-8}$ mutations per site per generation (Awadalla et a l., 2010; Besenbacher et al., 2015; Jónsson et al., 2017; Kong et al., 2012; Michaelson et al., 2012; Roach et al., 2010; W. S. Wong et al., 2016).

Unlike trio-based approaches that infer DNMs by comparing parents and offspring, direct **sperm sequencing** provides a complementary approach by measuring mutations present in the male germline without requiring transmission to an offspring. Current studies have largely used highly accurate sequencing of bulk sperm DNA in men, allowing rare mutations to be detected directly in sperm but not resolving which individual gametes carry them (Axelsson et al., 2024; Kunisaki et al., 2024; Neville et al., 2025; Shoag et al., 2025). Longitudinal sampling of sperm from the same men in New York City

have revealed substantial variation in mutation accumulation both among individuals and across age (Shoag et al., 2025).

Identity-by-descent (IBD) analyses of whole-genome data offer an alternative to trio-based inference and should, in principle, reduce confounding from post-zygotic mosaicism (Campbell et al., 2012; Palamara et al., 2015). Instead of detecting de novo mutations directly in parent–offspring trios, they identify chromosomal segments shared from a recent common ancestor in pedigrees (Campbell et al., 2012; Getseva et al., 2026; Palamara et al., 2015) or unrelated individuals (Tian et al., 2019) and use the sequence differences that have accumulated on those shared haplotypes to infer mutation rates. However, estimates can be inflated by biased gene conversion and IBD calling error. These studies, too, produce variable estimates (1.66×10^{-8}, 1.24×10^{-8}, and 1.20×10^{-8} per bp per generation, respectively).

2. *Quantifying human germline mutation rates: discrepancies*

Overall, the methods described above estimate a genome-wide germline mutation rate for human between 1.1 and 2.5×10^{-8} per bp per generation. Yet, these advances have not so much resolved the question of how fast the human germline mutates as each of them carry with them their own baggage of epistemological and biological puzzles. Estimates of mutation rates from whole-genome sequencing in family pedigrees are often lower than estimates derived from exome sequencing also in pedigrees (see. Narasimhan et al., 2017) for estimates of 1.45×10^{-8} among British Pakistani individuals, or (Brozou et al., 2023) for much higher estimates among trios with haematological conditions). And generally, both these estimates are lower than those from phylogenetic and older disease incidence studies (Neale et al., 2012; Ségurel et al., 2014; Zaidi et al., 2013).

Part of this discrepancy, especially with phylogenetic approaches, may reflect problems in phylogenetic calibration. Fossil dates constrain speciation times only imperfectly, whereas sequence divergence reflects the average coalescence time between lineages and may therefore substantially predate speciation, especially when ancestral effective population sizes are large. However, calibration issues are unlikely to explain the entire gap, which is particularly puzzling given that if anything, one would expect pedigree-based estimates to be slightly higher (as they include deleterious mutations that would eventually be weeded out by selection). To illustrate the issue, Wu et al. (2020), using multigeneration pedigrees of humans and baboons, estimated mutation rates of 1.23×10^{-8} and 0.58×10^{-8} per base pair per generation, respectively. Under simple molecular-clock assumptions, these rates imply an ape–baboon average divergence time of as much as 63–67 million years, which is closer to the Cretaceous–Paleogene (KPG) extinction rather than the ~35 million years indicated by fossil evidence (Elango et al., 2009; Seiffert, 2012). Although the precise degree of mismatch depends on

assumptions about ancestral population sizes and generation intervals (Rivas-González et al., 2023), the question is not how much lower pedigree-based estimates are relative to phylogenetic or disease-incidence methods, but what is driving remaining discrepancies?

Sequencing-based mutation-rate estimates are themselves conditional on the sequencing technology, depth, reference genome and bioinformatic pipeline used. (See Wang et al., 2026) for a recent systematic comparison of how sequencing technologies, depths and variant-calling pipelines substantially affect mutation-rate estimates). Short-read approaches exclude regions that cannot be reliably sequenced or mapped, meaning that estimates are effectively calculated over a technology-dependent 'callable' fraction of the genome. This matters because difficult-to-access regions are likely not mutationally representative of the rest of the genome. For example, using five complementary sequencing technologies in a four-generation pedigree, Porubsky et al. (2025) increased the callable genome by approximately 260 Mb relative to previous short-read datasets and revealed elevated mutation rates in repetitive regions, including segmental duplications and centromeres. Similarly, Noyes et al. (2026) found that long-read sequencing increased DNM discovery by 20–40% across 42 human families and revealed substantially elevated germline and postzygotic mutation rates in highly repetitive DNA.

The calling of mutations also has the potential of confounding mutations that may have arisen during offspring development, such as those from early embryonic mosaicism and somatic mutations in blood or saliva. A conundrum in the estimation of mutation rates comes from the timing of the germline-soma separation. A clear example comes from a potential downward bias in germline mutation-rate estimates from family trio studies. Such studies generally compare somatic tissue from parents and offspring, rather than germ cells directly. An early post-zygotic mutation occurring before germline specification in either parent will be present in both in part of the parent's soma (and thus maybe in the sampled tissue) and in their germline, and so also in the offspring. Under standard short-read approaches, an early post-zygotic mutation arising before germline specification in a parent may be present in both the parent's soma and germline, and therefore also in the offspring, causing the site to be classified as shared rather than de novo and omitted from the estimate (Garcia-Salinas, Hwang, et al., 2025; Palamara et al., 2015; Scally, 2016). This problem was initially partly addressed using three-generation pedigrees, in which transmission to a third generation can help distinguish inherited variants from parental post-zygotic mosaic mutations (Sasani et al., 2019). Recent long-read pedigree studies, have provided a further advance by phasing mutations to parental haplotypes and distinguishing inherited variants from early embryonic/postzygotic mutations more directly (Porubsky et al., 2025; Noyes et al., 2026).

A further source of uncertainty is intrinsic to the rarity and stochasticity of mutational events themselves. Even if individuals shared an identical underlying mutation rate, the number of de novo mutations observed in any one offspring would vary simply because mutations are rare, discrete events. Consequently, estimates based on small numbers of individuals can be sensitive to unusually high or low mutation counts, while distinguishing genuine biological heterogeneity from stochastic variation requires large sample sizes.

Furthermore, adding to the puzzle of explaining variation in human germline mutation rates, García-Salinas et al.(2025) recently analysed over 10,000 trios from the 100,000 Genomes Project using a unified pipeline and reported that individuals of African ancestry had germline mutation rates 3–4% higher than those of European, South Asian, or American ancestry—even after controlling for maternal and paternal age (see also Kohailan et al., 2022) for results in a similar direction; but Getseva et al., 2026 for recent contradictory findings). If this difference holds across generations, it will substantially influence our estimates of the timing of evolutionary events, as well as risk models in medical genomics. This begs the question, beyond discrepancies in methodological techniques, what may be driving the differences in mutation rates detected among different individuals and populations of our own species?

3. *Causes of germline mutations at the molecular level*

Identifying potential sources of variation in mutation rate requires identifying the sources of mutations, both in cell lineages that may produce gametes (where all heritable mutations emerge), as well as in individuals and/ or populations – which is what we ultimately sample when obtaining estimates (Majic et al., 2025).

We will focus first on the causes of mutations at a molecular level, which can be classified under two main types of processes: The first one is copying errors that arise during DNA replication. The second are DNA changes that occur spontaneously (i.e., nonreplicatively) because of the instability of the structure of DNA (Bena et al., 2024; Lindahl, 1993) or are induced by endogenous or exogenous sources (i.e., UV radiation or other chemical or biological agents)(Gao et al., 2019; Wu et al., 2020). Both types of errors lead to mutations if they are either not repaired or repaired wrongly before the next round of replication. Hence, mutation rate variation reflects a complex balance between lesion formation and DNA repair efficacy. Differences in either component could explain variation in mutation rates between sexes, individuals, and populations (Ségurel et al., 2014).

For decades, the predominant view was that replication errors primarily drove variation in human germline mutation rates (Gao et al., 2019; Kong et al., 2012). Evidence supporting this notion included the significant excess of mutations of paternal origin compared to maternal origin, which was

documented in early research by Haldane[1] and also subsequent studies (Heller & Clermont, 1963; Kong et al., 2012; Michaelson et al., 2012; Porubsky et al., 2025), and which is consistent with a higher number of replication cycles in males. In humans, by the onset of puberty, each primary oocyte has undergone approximately 31 cell divisions whilst in males, before spermatogenesis there are 34. However, through adulthood, sperm is produced continuously via the asymmetric division of spermatogonial stem cells every 16 days, with five additional cell divisions per cycle. Thus, by the age of 30, approximately 429 germ cell divisions occur in males, rising to about 659 by age 40 (Gao et al., 2019; Ségurel et al., 2014). Continued cell division throughout adulthood also predicts an increase in paternally derived mutations with paternal age, known as the **paternal age effect.**

Recent research, however, has called into question the dominance of replication-driven mutations. Studies have shown a significant maternal age effect on mutation rates, although less pronounced than the paternal age effect, indicating that maternal age also contributes substantially to germline mutations (Garcia-Salinas, Hwang, et al., 2025; Jónsson et al., 2017; Wu et al., 2020). Furthermore, young fathers contribute roughly three times more mutations than young mothers, a ratio that surprisingly remains relatively constant rather than increasing markedly with paternal age, as would be expected if replication cycles were the sole driving factor(Gao et al., 2019; Spisak et al., 2024). An explanation for this pattern is that damage-induced mutations that may be independent of replication events play a significant role in shaping germline mutation patterns (De Manuel et al., 2022; Hahn et al., 2023).

Differences in mutagenesis at the molecular level may not only be relevant to differences in mutation rates between sexes, but also for differences among populations. This could be due to the presence of alleles for genes involved in DNA damage and repair. For instance, a recent study (Wu et al., 2026) identified a variant in the DNA-repair gene *NHEJ1* associated with a 27% increase in maternal germline mutation rates and a shift towards A-to-T mutations; notably, this allele is particularly frequent in East Asian populations, potentially contributing to population differences in mutation rates and spectra.

Differences in damage and repair mechanisms that lead to spontaneous mutations arising independently from replication may be of various sources. One striking example is the prevalence of C>T transitions at methylated CpG sites. Despite CpGs comprising less than 2% of the genome, they account for nearly 20% of observed germline mutations (Gao et al., 2019). This disproportionate frequency is largely due to the spontaneous deamination of methylated cytosines. When unmethylated cytosines deaminate, they form uracil, which is efficiently recognized and excised by uracil-DNA glycosylase as part of the base excision repair pathway. In contrast, deamination of methylated cytosines produces thymine, resulting in T:G mismatches that are less effectively repaired (Lindahl, 1993; Schmutte et al., 1995; Ségurel et al., 2014). As a result, methylated CpG sites are especially prone to

C>T transitions (Gao et al., 2019; but see Spisak et al., 2024; Tomkova et al., 2024) for an argument about how this may also be explained by replicative errors). The frequency of damage and repair efficiency are further influenced by local sequence context. DNA in AT-rich regions, held together by fewer hydrogen bonds, is more easily unwound, facilitating repair by exonuclease enzymes (Bloom et al., 1994; Petruska & Goodman, 1985). At a functional scale, In recent years it has been proposed that, at least in some organisms, the binding of transcription factors may shield novel mutations from repair mechanisms (Sabarinathan et al., 2016; Zhu et al., 2025), that the amount of transcriptional activity influences the frequency of mutations (Jinks-Robertson & Bhagwat, 2014) and that certain epigenetic marks may differentially recruit repair mechanisms, thus locally decreasing mutation rates (Li et al., 2013).

In population-level studies, a consistent enrichment of TCC>TTC mutations—up to 20% higher in individuals of European ancestry compared to those of African or Asian ancestry—has been documented in phylogenetic analyses and sometimes attributed to UV exposure (Gao et al., 2023; Harris, 2015; Harris & Pritchard, 2017; Speidel et al., 2021). However, Amos (2019) has proposed a role of local sequence context in explaining this difference. Specifically, that flanking heterozygosity promotes extra rounds of repair/replication that slightly elevate mutation rates. Analysing 1000 Genomes data, he showed that as flanking heterozygosity increases, the relative probability of some triplet changes consistently rises while others fall, with broadly similar slopes across Africa, Europe, South/Central Asia, East Asia and the Americas. Because the "Out-of-Africa" bottleneck reduced heterozygosity outside Africa, this framework predicts a demographic, genome-wide shift in mutation spectra that could explain African vs. non-African spectrum differences (e.g. the well-known TCC→TTC contrast) without invoking population-specific modifiers for each triplet class (note however, that this does not explain why individuals from certain ancestries, namely East Asian and Amerindian lack this signature despite experiencing a stronger bottleneck than Europeans). Amos extended this reasoning to propose that mutability might be overall higher in Africans (Amos, 2020). And in fact, a recent study relying on the TOPMed research program – across 1,465 trios from diverse human populations living in the United States, that tested the relationship between heterozygosity and DNM rate across all individuals, found a significant positive correlation even after accounting for parental age (Kessler et al., 2020). However, heterozygosity only explained ~0.3% of the variation in DNM count. Crucially, however, this mechanism cannot straightforwardly account for the elevated mutation rates in African-ancestry individuals reported by García-Salinas et al. (2025), whose African-descent sample actually showed *lower* genomic diversity and heterozygosity than their European-descent sample.

4. *The role of development and life-history on shaping generational mutation rates*

Molecular mutation rates are not the only factors that may vary such that they can explain differences in between-population mutation rates. For instance, García-Salinas et al. (2025) found no difference in mutation spectra between individuals of African and European ancestry, despite a small but consistent difference in overall DNM rates, suggesting perhaps that different populations may experience similar mutagenic processes, even if mutation rates differ. So, what other processes could account for the differences observed within and between human populations?

De novo mutations inevitably arise in single cells in the organismal context of each individual. For this reason, developmental attributes and the life history of each individual has the potential of shaping the repertoire of new alleles each individual may produce (Majic et al., 2026). These factors, while not necessarily altering the *molecular* mutation rate of germ cells ($\hat{\mu}_{mol}$), can strongly influence the *generational* mutation rate per individual (μ_{pop}) (i.e. the probability of sampling a mutant gamete upon reproduction) and, ultimately, the number of genetic variants present in populations —the substrate on which natural selection acts (Majic et al., 2025; Otto & Orive, 1995)(Figure 2).

This reasoning predicts that species or populations with longer developmental time may show higher per-generation *de novo* mutation input, even if the underlying molecular mutation rate per cell division or per unit time is unchanged (Majic et al., 2025). In this view, developmental duration can increase the probability that a gamete derives from a mutant cell lineage, thereby elevating the effective mutation rate observed at the population level. This is also true of mutagenesis in the mature germline – such that a longer time to reproduction may derive in higher mutation rates. Indeed, Zhu et al. (2025) argue that this positive relationship between developmental time and measured mutation counts could mask an actual *negative* relationship between the true gametic mutation rate and generation time. In their framework, embryonic mutations reflect the action of genetic drift on mutation-rate modifiers (i.e. drift-barrier dynamics (Lynch, 2010), but for gamete-derived mutations, molecular mutation-rate modifiers are constrained by both effective population size and generation time—making selection against mutator alleles more efficient in long-lived species, even if their N_e is smaller. Regardless of the mechanism, this example is helpful to illustrate how distinguishing whether we measure mutations in cells, individuals or populations is key to investigate variation in rates and its evolutionary explanations.

Characteristics of the germline architecture, not only its timing, could also drive differences in the mutational output from developmental causes. If mutations are of a replicative origin, then a larger pool of germline cells undergoing divisions in parallel could contribute to a larger mutational output from the germline. This may be reflected in gonad size: for example, if chimpanzees have proportionally more germline stem cells than humans—as would be suggested by their much larger testes—this could contribute to their higher measured mutation rate relative to humans(Besenbacher et al., 2019; A. Wong, 2014). This may also be extrapolated to differences between individuals in human populations.

Germline architecture may also reflect differences in the paternal biases reported for *de novo* mutations. The pronounced excess of paternally derived DNMs may partly reflect the far greater number of cell divisions in the male germline throughout the lifetime of individuals.

Furthermore, within the germline of individual organisms there may be selection at the cellular level (Arnheim & Calabrese, 2016; Hodge & Bach, 2024; Majic et al., 2025; Otto & Hastings, 1998; Haig, 2023; Majic & Payne, 2023). For instance, Majic et al. (2025) reported that in *Drosophila*, heterozygous flies carrying a mutation that increased cell proliferation produced a biased proportion of offspring inheriting that mutation, implying overrepresentation in the gametes at the time of reproduction right after development and upon sexual maturity. In humans, while such experiments are not feasible, convergent evidence points to a similar process. Clinical studies have long shown that certain pathogenic mutations undergo clonal expansion in the male germline and rise in frequency with paternal age (Choi et al., 2008; Yoon Cho et al., 2013). More recently, large-scale analyses of human sperm have shown that positive selection on driver variants in spermatogonia creates apparent mutation hotspots, elevating the effective transmission rate at specific loci far above baseline expectations. These studies identified dozens of genes involved in such clonal expansions, and can produce a roughly 2–3-fold enrichment of likely disease-causing variants in sperm, with 3–5% of sperm from middle-aged to older individuals carrying a pathogenic mutation across the exome (Neville et al., 2025; Seplyarskiy et al., 2025).

Although differences in development and life history may affect μ_{pop} independently of $\hat{\mu_{\text{mol}}}$, this effect may also interact with $\hat{\mu_{\text{mol}}}$. Molecular mutation rates are especially high during the earliest embryonic cell divisions. Increased early mutation loads are biologically plausible: for example, two key components of base excision repair are missing in spermatozoa, meaning DNA lesions accumulated late in spermatogenesis can only be repaired post-fertilization in the zygote (Gao et al., 2019; Smith et al., 2013). At the same time, mammalian zygotes depend almost entirely on the maternal protein and mRNA complement until the four-cell stage (Braude et al., 1988; Dobson et al., 2004; Zhang & Smith, 2015). If oocyte replication or repair capacity declines with maternal age (Karabulut et al., 2025; Sun et al., 2024), early embryonic mutation counts could increase, providing one mechanistic explanation for the maternal-age effect observed in recent trio studies (albeit this doesn't account for a measurable maternal-age effect even at young maternal ages (Gao et al., 2019; Garcia-Salinas, Hwang, et al., 2025; Wong et al., 2016). More generally, it has been suggested that different developmental periods may differentially employ repair mechanisms, that may result in stage-specific mutation rates (Lindsay et al., 2019).

These possibilities relating molecular mutation rates, developmental and life-history parameters, the fitness effects of mutations at the cellular level and socio-cultural backgrounds highlight a broader

point: observed inter-population differences in mutation rates may partly reflect *which* individuals are measured, rather than intrinsic, population-wide genetic differences. This further highlights the need of careful study designs when attempting to explore inter-population or inter-individual differences in mutation rates or spectra.

5. *Evolutionary explanations*

Mutation rates are an evolving trait that varies broadly across the tree of life (Bergeron et al., 2023; Lewin & Eyre-Walker, 2025; Lynch et al., 2023; Y. Wang & Obbard, 2023). In the specific case of humans, measured mutation rates per generation appear to be comparatively high among mammals (Beichman et al., 2024; Lynch, 2010; Lynch et al., 2016). As we have been discussing, variation in mutation rates may arise from either changes in the molecular mutation rates or changes in developmental and life-history traits. Explanations for differences in molecular germline mutation rates across species, populations, and individuals have generally been framed in two ways: selectionist theories, which posit that mutation rates are shaped by natural selection, and neutralist theories, which emphasise the role of genetic drift and other stochastic forces.

In **selectionist theories**, mutation rates are treated as the product of natural selection acting on traits such as long-term survival, reproductive fitness, or evolvability (Galhardo et al., 2007; F. Li et al., 2013; Martincorena et al., 2012; Paul et al., 2013; Payne & Wagner, 2019; Rosenberg, 2001). One such theory, named the cost of fidelity model, proposes that the germline mutation rate reflects a trade-off between the benefits of avoiding deleterious mutations and the energetic and/or time costs of achieving accurate DNA replication. While this model is well supported in viruses and bacteria, its explanatory power in multicellular organisms remains uncertain (Lynch et al., 2016).

A related idea treats mutation rates as an evolvability trait (Pal et al., 2007; Payne & Wagner, 2019), as low mutation rates can impose a second-order fitness cost by slowing adaptation to changing environments. In bacteria, certain mutagenic pathways are upregulated under stress conditions(Foster, 2005). If a similar mechanism operated in our lineage, it could plausibly have been advantageous during periods of environmental instability. Paleoclimate records indicate that after ~270 ka a relatively stable phase in Africa gave way to marked climatic cyclicity, which coincides with the ecological diversification and wider dispersal of early *Homo sapiens* populations (Foerster et al., 2022; Scerri et al., 2018). Whether selection favoured slightly higher baseline mutation rates as part of a broader adaptive strategy for flexibility is therefore an untested, but intriguing possibility (Hallett et al., 2025; Timbrell et al., 2022; but see Barnett et al., 2025 for experimental evidence in bacteria).

Another selectionist hypothesis links germline and somatic mutation rates through shared DNA repair pathways. If long-lived, large-bodied species experience strong selection to reduce somatic mutation rates, for instance, to limit cancer risk, then improved DNA repair could incidentally lower germline mutation rates as well (Beichman et al., 2024; Cagan et al., 2022; Tollis et al., 2017). However, available data complicates this link. Baleen whale generation times and per-generation germline mutation rates are comparable to those humans (1.11×10^{-8}), which are already high for mammals (Suárez-Menéndez et al., 2023), even though some species (e.g., bowhead whales) can live up to ~200 years. These data imply that selection against somatic mutations (and thus their low cancer incidence) might not always be correlated to a reduction in germline mutation rates.

Relatedly, somatic maintenance may be favoured by selection for longevity in species that are social or have high parental investment. Under this scenario, all other things being equal, cooperative breeders should lie toward the lower end of the mutation-rate continuum. Cooperative breeders such as marmosets (*Callithrix jacchus*)—which rely heavily on biparental and alloparental care and show a low per-generation mutation rate (0.43×10^{-8}; Yang et al., 2021)—can be contrasted with taxa in which parental investment is more limited, including owl monkeys (0.81×10^{-8}; Thomas et al., 2018); a closely related species), many Old World monkeys (e.g., green monkeys or macaques; Gao et al., 2023; Pfeifer, 2017), and most great apes (Besenbacher et al., 2019). However, this prediction does not map cleanly onto apes: humans are arguably the most cooperative breeders among great apes (Hrdy, 2009; Marlowe, 2005), yet human per-generation mutation rates are amongst the highest (e.g.Beichman et al., 2024; Besenbacher et al., 2019) - implying that parental investment alone cannot explain interspecific differences, though within-human variation in parental investment remains an interesting candidate for population-level differences to test.

When it comes to **neutralist theories** of mutation rate evolution, one of the most influential is the drift-barrier hypothesis (Lynch, 2010, 2011; Lynch et al., 2016; Sung et al., 2012). This framework builds on Ohta's nearly neutral theory (Ohta, 1973), and it proposes that since most mutations are expected to be deleterious, natural selection would tend to minimize mutation rates. However, this reduction is ultimately limited either by the cost of extremely high-fidelity replication or by the power of genetic drift. In species with small effective population sizes (N_e), selection against weakly deleterious "mutator" alleles (i.e. alleles that increase mutation rates) is therefore less effective, allowing higher mutation rates to persist. Yet this logic also presumes a supply of heritable modifier variants affecting mutation rate. If such variants arise rarely, or if mechanistic changes to replication and repair are strongly constrained, mutation rates may evolve more slowly, or over a narrower range, than drift-barrier arguments alone would suggest (Majic et al., 2025).

The drift-barrier counts with empirical support from significant negative correlations between per-generation mutation rates and N_e from species across the tree of life(Lynch et al., 2023; Sung et al., 2012), after controlling for phylogenetic non-independence. A recent study providing support for the drift-barrier hypothesis was that from Bergeron et al. (2023), which found this anticorrelation comparing germline mutation rates from family trios across 68 vertebrate species. The authors found a significant negative correlation between per-generation mutation rates and N_e, independent of phylogenetic autocorrelation. Traits that are typical of species with low N_e (i.e. slow life history strategies), such as low fecundity and long generation times were also independently associated with higher mutation rates. However, Majic et al. (2025) demonstrated how the association between *Ne* and generational mutation rates in this dataset could also result from the evolution of developmental and life-history traits. More recently, reinforcing this interpretation, Weinstein and Roy (2026) reanalysed the same dataset used by Bergeron et al. (2023) using a phylogenetic, causal inferential framework explicitly controlling for six life-history traits, and showed that the apparent effect of N_e on per generation mutation rates was strongly mediated by generation time. The trends used in support of the drift-barrier hypothesis may therefore represent a neutral byproduct of the diversification of developmental and life-history traits in what has been called the "life-history hypothesis" (Majic et al., 2026).

If mutation rates track the number of germline cell divisions, then life-history traits that affect the number of cell divisions may indirectly influence mutation rates. The generation time effect (Li et al., 1996; Ohta, 1993) predicts that species—or populations—with shorter generation times have higher per-year mutation rates because they undergo more germline replications per unit time. Longer reproductive ages should also increase the *proportion* of replication-driven, male-biased mutations (Chang et al., 1994). Generation time changes have also been invoked to explain the discrepancy between trio-based and phylogenetic mutation rate estimates, as generation times have lengthened over the course of primate evolution—from Old World monkeys, to apes, to hominins, and finally to modern humans (Elango et al., 2006; Langergraber et al., 2012; Wang et al., 2023). However, if longer generation times are accompanied by later puberty onset (which seems to be the case across human evolution, see Dean, 2016; Fenner, 2005), the total number of germline divisions may not scale linearly with generation time. In recent centuries, nonetheless age at puberty has fallen sharply in many Western populations (Bellis et al., 2006), even as generation time has increased, raising the possibility of population-specific shifts in mutation rate components.

Besides developmental parameters and generation time, another relevant life-history trait is mating system. Mating systems may influence mutation rates indirectly through sperm production. In species with high sperm competition, males produce more sperm, increasing the number of germline cell divisions, and speed of cell division and thus the potential for mutations (Parker, 1970; Ramm et

al., 2014; Whitlock & Agrawal, 2009). Humans are largely (historically) monogamous with intermediate relative testis size, while chimpanzees are promiscuous, with larger testes and faster sperm turnover (every 14 days vs every 16 days in humans (Heller & Clermont, 1963; Kelly, 1995; Smithwick et al., 1996)). This may contribute to a pronounced paternal age effect in chimpanzees, although current pedigree-based estimates remain imprecise because they are based on small sample sizes (Venn et al., 2014). In fact, in Weinstein and Roy's (2026) analyses of mutation rates across the vertebrate phylogeny, the authors found that after controlling for generation time, polygynous vs. monogamous mating systems was the strongest predictor of per-generation mutation rates, possibly due to differences in sperm competition. Within humans, Auger et al. (2022) reported variation in the rate of sperm production exists across and even within populations across relatively short geographic distances, but whether these differences are large enough to influence mutation rates is unknown.

Within our own species, archaeological, ethnographic, and historical data indicate that both contemporary and prehistoric human populations vary widely in life-history traits (Kelly, 1995; Mace, 2000; Robson & Wood, 2008; Schwartz, 2012; R. J. Wang et al., 2023). Although such variation could, in principle, produce inter-population differences in mutation rates, its explanatory power in humans is debated (Thomas & Hahn, 2014). Future work should therefore explore whether human populations with historically small N_e (e.g., long-term isolated groups) may have slightly higher baseline mutation rates than those with larger N_e. Under the life-history hypothesis of mutation rate variation it is expected that at shorter microevolutionary scales the negative correlation between μ_{pop} and *Ne* would emerge readily, while in the case of the drift-barrier hypothesis the effect pf selection would play out over longer evolutionary times (Majic et al., 2026). Studies on human populations, and the increasingly rich paleogenomic record would help shed light on the relative explicative power of each of these hypotheses. However, carrying out these analyses requires the explicit acknowledgement that mutation rates may have diversified not only over time, but also within the populations of our ancestors.

6. *So, is there a human mutation rate?*

Many reported population-level differences in mutation-rate estimates for our species come from studies of groups with small effective population sizes, high levels of isolation, or cultural practices that increase consanguinity. These contexts are expected to alter the genomic background of individuals, and amplify the role of drift acting on modifiers of the *molecular* mutation rate itself, but they can also confound interpretation by intersecting with developmental and life-history factors that influence the *number of mutations we measure in adult individuals* (Figure 2). In other words, it is important to recognise that biases in sampling can affect *both* the processes that genuinely alter the probability of new mutations per cell division, and processes that alter how many of those mutations are ultimately observed in offspring.

Importantly, the environment may interact with molecular, developmental and life-history factors, thus helping shape generational mutation rates (Figure 2). For example, UV-light and radiation are well known mutagens, while environmentally induced stress could increase mutation rates, as has been shown for nematodes (Matsuba et al., 2013), and speculated in male germline in humans (Aitken, 2017; Gidron et al., 2006). Furthermore, socio-cultural background and inhabited locations may impact key life-history traits, such as time to reproduction, which would repercuss in the number of mutations that arise each generation in a population. These possibilities relating molecular mutation rates, developmental and life-history parameters, and environmental context highlights a broader point: observed inter-population differences in mutation rates may partly reflect *which* individuals are measured and the environments they experienced, rather than intrinsic, population-wide genetic differences. This further highlights the need of careful study designs when attempting to explore inter-population or inter-individual differences in mutation rates or spectra.

Examples of populations in which these complexities arise, yet have been used to claim inter-population differences in mutation rates include immigrant groups in Europe and North America (Garcia-Salinas, Hwang, et al., 2025), isolated religious communities (Kessler et al., 2020), societies with high levels of consanguineous marriage (Kohailan et al., 2022), and countries with exceptionally small effective populations (Bataillon et al., 2006; Jónsson et al., 2017). Thus, observed inter-population differences may reflect population-specific (adaptive or neutral) evolution of germline mutation rates, short-term effects of environmental damage, but also environmental and developmental effects on measured counts in sampled individuals.

Any attempt to disentangle the above-mentioned possibilities must first recognize that grouping individuals into broad continental ancestry categories often complicates the task. For instance, Africa harbours more genetic diversity than all populations outside Africa combined (Bergström et al., 2020). Treating African-descent individuals as a single category is therefore unjustified when trying to understand the evolutionary trajectories of mutation rates and spectra (Lewis et al., 2022; Padilla-Iglesias & Derkx, 2024). Hunter-gatherer and former hunter-gatherer groups in Central and Southern Africa descend from lineages that are estimated to have diverged from all other human populations as far as 250–300 kya (Fan et al., 2023; Lipson et al., 2025; Padilla-Iglesias et al., 2025; Schlebusch et al., 2020)—four to five times older than the deepest divergence between any African and non-African populations (Bergström et al., 2020). This raises the question of what we really mean by "population-specific evolution of the human mutation rate" (cf. Harris, 2015) in studies relying on broad continental groupings, when some lineages diverged close to the origins of our species. It may also help explain the large within-group variance in mutation-rate estimates observed in datasets such as García-Salinas et al.(2025).

Another key issue is whether the samples used to calculate human mutation rates are truly representative—not only of more or less "valid" continental groups but even of the specific populations they are meant to represent. For example, although African-descent women in the UK typically give birth at younger ages than women of European descent (Rivers et al., 2024), the African-descent parents in García-Salinas et al.'s(2025) dataset were significantly older, implying longer generation times. Moreover, while African populations generally harbour the highest levels of global genetic diversity (Gomez et al., 2014), the African-descent participants in that study showed only about one-quarter of the genetic variation observed among the European-descent participants, indicating unusually low N_e and high levels of homozygosity. This suggests that observed differences between "ancestry groups" may instead reflect drift-barrier effects or even gene × environment interactions affecting mutation rate probabilities at a molecular level, but also developmental or environmental effects affecting the probability of sampling mutant cells from individuals.

If mutation rates had undergone stable, population-specific evolution driven by variants still segregating within populations, one expectation would be that mutation rate is highly heritable. Empirical evidence to date does not support this. The two largest trio-based studies—García-Salinas et al.(2025), which estimated SNP heritability of parent-of-origin DNM burdens after adjusting for parental age and covariates, and Kessler et al.(2020), which estimated narrow-sense heritability using genome-wide relatedness—both found near-zero heritability. This indicates minimal additive genetic contribution (particularly from common variants) to variation in DNM counts. However, low within-population heritability does not rule out population-specific genetic evolution of mutation rate more broadly: heritability estimates are uninformative about loci that are rare, fixed, or nearly fixed within the sampled populations, or that differ mainly in frequency between rather than within populations-exactly the pattern expected if a mutation-rate modifier had already swept toward fixation along a specific lineage.

A further complication is that mutation-rate estimates depend on the timescale over which they are measured. Trio studies quantify mutations transmitted in a single generation, often after controlling for parental age and related covariates, whereas IBD-based approaches integrate mutation accumulation across several generations and thus reflect the realized number of mutations added along recent lineages. Unsurprisingly, the two approaches may yield different patterns. For example, Huang et al.(2025), using IBD-based methods, reported significant differences in per-generation mutation-rate estimates across human populations, including higher estimates in European than African populations, seemingly contradicting the study by Garcia-Salinas et al.(2025). Such discrepancies may indicate that historical differences in parental age structure, environmental mutagen exposure, or other transient factors can leave measurable signatures in lineage-specific mutation accumulation even when present-day

molecular mutation rates are similar. Yet for evolutionary and demographic inference, those accumulated differences may be precisely the relevant quantity, since they determine how many mutations were actually added along ancestral lineages.

A clearer illustration of the kind of signal that heritability and rate-based comparisons can miss comes from mutation spectra rather than absolute rates. The enrichment of TCC→TTC changes, strongest in Europeans and weaker in South Asians (Harris, 2015; Harris & Pritchard, 2017), has been localized in time and population history using genealogy-based methods. Speidel et al.(2021), relying on a dataset of 278 present-day and 430 ancient DNA human samples quantified the TCC→TTC "pulse" via an integrated mutation-intensity metric. The authors showed it is absent >34 kya, widespread by the Late Glacial Period, strongest in Neolithic farmers, and highly correlated with coalescence to a ~10 kya Anatolian genome, consistent with spread by gene flow rather than a locus-specific driver, and shedding light on the evolutionary history of a mutational pattern (albeit not its source; see also Gao et al., 2023).

Although still rare, new studies relying on multi-generational pedigrees may allow us to get one step closer to the question of heritability of mutation rates. Porubsky et al.(2025) found that *de novo* mutations tended to appear repeatedly within the same 32 genomic regions. Yet because this was a single family, this raises the question: would the same regions re-occur in others? In fact, even something like the extent of a paternal age effect has been shown to differ across human families (Rahbari et al., 2016; Sasani et al., 2019). A larger number of families will be needed to pinpoint why mutation rates differ between lineages and to what extent such variation is heritable or transient and environmentally modulated.

7. A way forward?

So where do we go from here? Broadly speaking - despite ever-better sequencing—we still measure human germline mutations at a rate not too different from Haldane's first attempts almost a century ago. Yet variability in that rate is often treated as a given. We have conclusive evidence that paternal and maternal contributions to offspring *de novo* mutations differ, that paternal age (and to a lesser degree maternal age) shapes mutational load, and that ancestry groups may show distinct mutational profiles. But most of those inferences rest on Global-North datasets, modest sample sizes, and highly heterogeneous bioinformatic pipelines. And in many pedigree studies, germline and post-zygotic variants are lumped together, despite the fact that even within the germline lineage, theory gives us good reasons to expect different evolutionary forces acting on mutations accumulated during prepubertal germline development versus those accumulated post pubertally in dividing spermatogonia and oocytes (Zhu et al., 2025). These limitations are compounded by the rarity and stochasticity of mutations: in modest samples, whether or not single events are observed can heavily influence

estimates. As a result, it remains unclear in each case whether reported variation reflects molecular processes (neutral or adaptive), environmental/developmental factors that affect the likelihood of sampling mutant cells, or methodological discrepancies between studies—or, most likely, some complex interaction of all three (Figure 1-2).

The first thing we need to be able to disentangle between the above possibilities is to increase and diversify our samples. Not just in terms of the ancestry composition of individuals, but in terms of the environments they inhabit – social, ecological and economic. Whist studies of *de novo* mutation rates have recently been performed on trio data from the UK Biobank (Getseva et al., 2026; Hujoel et al., 2026), the *All of Us* Research Program, a US-based biobank (one of the largest in the world), now includes >414k whole-genome sequences, yet the number of trios in the dataset is extremely small and parental ages at conception are not recorded (Getseva et al., 2026; Biobank & A. 15, 2024a). Therefore, the potential to investigate questions concerning germline mutation rates is limited (Biobank & A. 15, 2024b). Similarly, the UK's Newborn Genomes "Generation Study" will sequence ~100,000 newborns and their mothers, but not their fathers. Whilst this design might be useful for early diagnostics, it makes it impossible to trace where mutations come from, or how often they arise, and thus, the heritability of DNMs.

Second, we need to explicitly acknowledge and propagate both the uncertainty and the relevant underlying variation captured by mutation-rate estimates through downstream analyses of population history and historical relationships between populations and species, rather than collapsing this information into single point estimates treated as fixed constants. Which sources of variation should be retained will depend on the inference being made: estimates used to reconstruct the history of a particular population, for example, should ideally reflect the range of mutation-rate variation relevant to the individuals, environments and life histories represented in that population. Flexible simulation-based approaches increasingly provide ways to propagate distributions of plausible mutation rates and richer patterns of variation directly through downstream inference, rather than reducing them to a single summary value.

Third, we must combine human data and theoretical studies with experiments in model systems. Mutation accumulation experiments remain one of the most powerful tools for identifying sources of mutations, and for disentangling mutational inputs from selective filters (Keightley et al., 2014, 2015; Monroe et al., 2022; Mukai, 1964; Mukai et al., 1972; Muller, 1928; Ohnishi, 1977; K. Wu et al., 2024). Therefore, manipulating exposure to mutagens, genomic background, life-history timing, and environments directly could allow us to directly test hypotheses with regards to their role in shaping mutagenesis.

Fourth, we need to create unified wet-lab and bioinformatic protocols to make sure "mutation rate" means the same across studies, species and contexts (c.f. Bergeron et al., 2022). For instance, whilst promising recent studies claim an ability to distinguish postzygotic mutations arising post-fertilisation, prior to primordial germ cell specification and *de novo* mutations in the Genomics England 100,000 genomes project (Garcia-Salinas, Sanghvi, et al., 2025), it remains to be determined whether such pipeline is applicable to other datasets. Similarly, as recent comparisons across sequencing technologies, depths and variant-calling pipelines demonstrate, differences in callable genome size and error rates alone can generate systematic differences in mutation-rate estimates (Wang et al., 2026).

Fifth, we should take advantage of technologies that let us measure germline mutations more directly and confidently. High-accuracy long-read sequencing (PacBio HiFi; ONT duplex(Charmouh et al., 2025)) and error-corrected Duplex Sequencing (Axelsson et al., 2024; Neville et al., 2025) now permit ultra-rare variant detection in sperm (Shoag et al., 2025) with far fewer false positives than short-read pipelines. Most current approaches sequence bulk sperm samples rather than individual gametes (Shoag et al., 2025) but, when combined with longitudinal sampling and matched somatic tissues, could provide insight into when mutations arise and how they accumulate across the male germline. These methods can be applied both genome-wide and at specific loci, allowing targeted tests of evolutionary hypotheses. Importantly, they do not just yield "better numbers" to plug into population history models—they enable asking genuinely new questions about when and where mutations arise, and how ancestry, environment, and life history modulate both their occurrence and fate.

One example comes from recent sperm-sequencing studies. Melamed et al.(2022) showed that the HbS mutation (20A→T in *HBB*), which is associated with malaria resistance, arises de novo at higher rates in donors of African descent. A follow-up study (Melamed et al., 2025) found a similar pattern for the *APOL1 G1* variant (1024A→G), long known to protect against *Trypanosoma brucei gambiense*. The authors suggest that some conditionally adaptive mutations may originate more frequently in populations where they have been beneficial—seemingly at odds with the canonical view that mutations are random with respect to fitness (Lenski & Mittler, 1993). Whether this claim holds up will depend on replication across labs, loci and methodologies, but the point is that this research illustrates how evolutionary principles and hypotheses can be tested directly.

The sequencing of single gametes could also enable scientists to track mutations across the lifespan of individual germ cells. This would help pinpoint not just exactly when and where mutations occur, but also how lifestyle, ancestry or the environment individuals are exposed to at different moments in life might shape both the occurrence and the fate of such mutations (Neville et al., 2025; Seplyarskiy et al., 2025). However, these approaches remain technically challenging, particularly for oocytes, which are rare and difficult to isolate. At the same time, whether and to what extent the mutational processes

characterised in the male germline can be extrapolated to females remains an open question. Meanwhile, if at least in part, lineage specific evolution of mutation rates is driven by the emergence of "mutator alleles" new computational tools, combined with the rapidly increasing availability of ancient DNA, could help scientists trace when such "mutator" alleles emerged and spread in human history(Speidel et al., 2021).

So, perhaps, "what is *the* human mutation rate" is the wrong question – and looking for a number is the wrong thing to look for. Mutations differ across genomic contexts (Porubsky et al., 2025), across developmental stages (Shoag et al., 2025), and across individuals living in different environments. A more useful framework may be to ask: "what factors make certain mutations more likely to occur in particular germlines, at particular moments, and which of these factors are heritable? And, how have these forces shifted over and affected the evolutionary history of our species?"

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Figure legends.

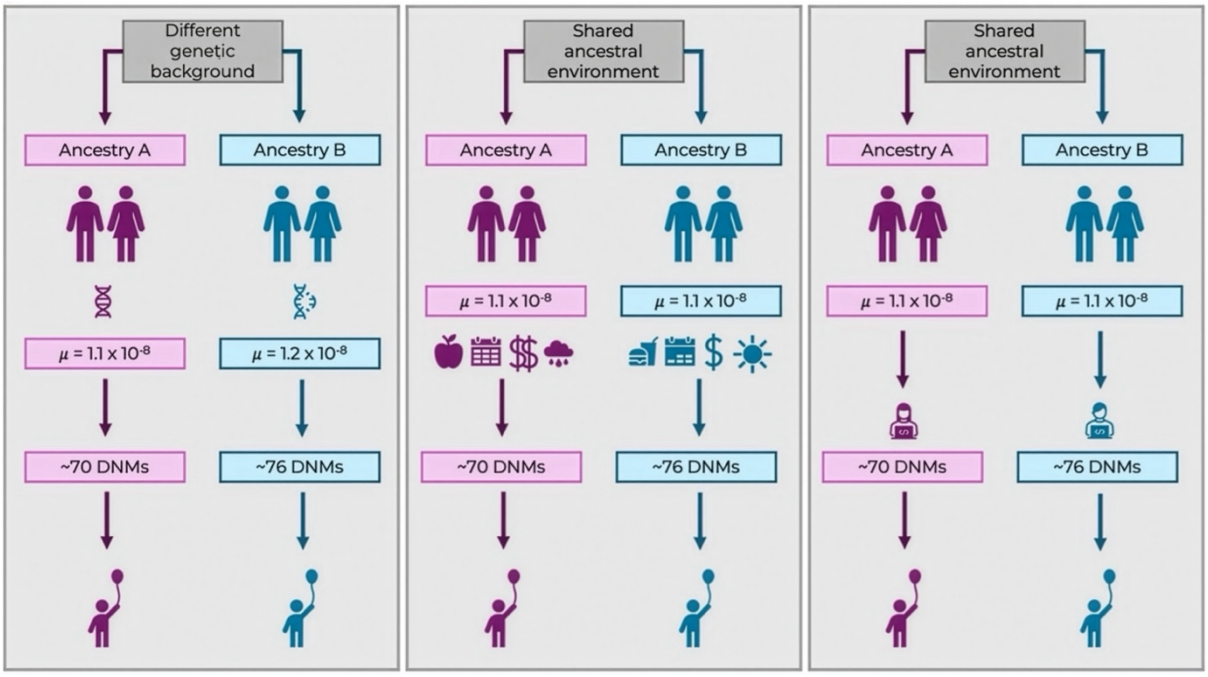


Figure 1. **Pathways generating observed differences in measured germline mutation rates between populations from pedigree (trio) studies**. Three distinct mechanisms that can produce between-population differences in measured de novo mutation (DNM) counts. Left panel: True differences in molecular mutation rates (μ) arise through lineage-specific evolution via selection or genetic drift, resulting in heritable differences in the per-generation mutation rate at the germline

level. Middle panel: Shared molecular mutation rates can yield different measured DNM counts when populations experience distinct developmental, environmental, or life-history conditions (represented by icons: diet, life-history, socio-economic status, external environment). These factors alter the probability of sampling mutations in offspring without affecting the underlying per-cell mutation probability. Right panel: Identical molecular and developmental processes can produce apparent rate differences through variation in study design, laboratory protocols, or bioinformatic pipelines. Distinguishing among these scenarios is essential for interpreting reported mutation rate variation and requires careful experimental design, standardized methodologies, and representative sampling across diverse populations and environments.

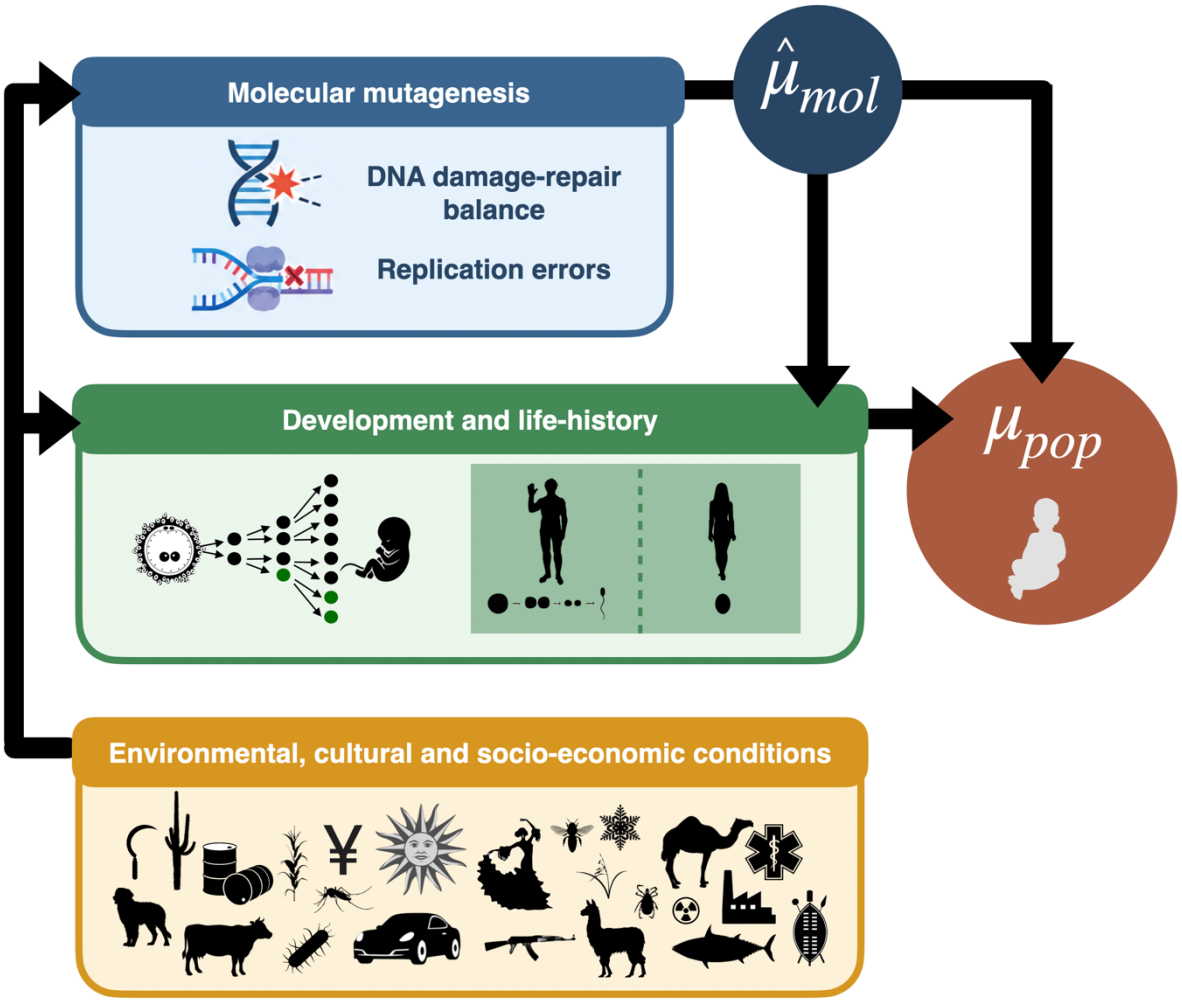


Figure 2. Determinants of the generational mutation rate. The generational mutation rate (μ_{pop}) is the number of de novo mutations arising per locus per offspring. It is shaped by both molecular and organismal processes. Molecular causes, including DNA damage and repair, as well as replication errors during cell division, jointly determine the molecular mutation rate ($\hat{\mu}_{mol}$). Organismal determinants include developmental and life-history traits such as the number of germline cell divisions, age at reproduction, germline stem-cell turnover, and cell-lineage selection. Environmental, cultural, and

socio-economic factors can influence both molecular and organismal processes—for example through exposure to mutagens, nutrition, stressful environments or social and reproductive structure—and thereby indirectly affect generational mutation rates.

Table 1. Main methods for quantifying human mutation rates, and representative estimates. See Table S1 for additional details on studies cited in the manuscript employing each of these methods.

Method	Representative estimate/ range	Biological material/data	Quantity most directly measured	Timescale	Major sources of uncertainty/ limitations
Disease incidence	1.28-2 × 10^{-8}/site/generation	Disease incidence, affected individuals, population frequencies	Rate of mutations entering the population at disease-associated loci, inferred indirectly	One generation to population equilibrium	Strong phenotype ascertainment; uncertainty in mutational target size and selection; severe disease loci are not representative of the whole genome
Phylogenetic method	~2.5 × 10^{-8}/site/generation	Orthologous DNA sequences across species	Substitution/divergence accumulated along lineages, converted into a mutation rate	Millions of years	Fossil calibration; speciation versus coalescence; ancestral polymorphism/ILS; generation-time assumptions; evolutionary filtering
Sequencing-based pedigree designs: WGS, two-generations	~1.1–1.3 × 10^{-8}/site/generation	Usually blood/saliva DNA from parents and offspring	DNMs transmitted to one offspring and detectable as absent from parental somatic samples	One generation	Parental age; callable genome; sequencing/calling thresholds; postzygotic mosaicism; early mutations shared between parental soma and germline can be missed
Sequencing-based pedigree designs: exomes, two-generations	~1.45 × 10^{-8}/site/generation	Parent–offspring exomes, often disease cohorts	Exonic DNM burden/rate	One generation	Restricted genomic target; disease ascertainment; exome-specific denominator; not necessarily representative of genome-wide mutation
Sequencing-based pedigree designs: WGS, several generations	~1.23 × 10^{-8}/site/generation	Multiple generations/family members	Mutation transmission and timing across several generations	Multiple generations	Small numbers of families; family-specific effects; still dependent on sequencing/calling strategy
IBD-based methods: recent shared ancestry	~1.20-1.66 × 10^{-8}/site/generation	Shared IBD haplotypes in relatives or unrelated individuals	Realized mutations accumulated along recent genealogical lineages	Several to many generations	IBD detection; recombination/gene conversion; demographic assumptions; integrates historical parental ages and environments
IBD-based methods: siblings	~1.28 × 10^{-8}/site/generation	Shared IBD haplotypes in relatives or unrelated individuals	Realized mutations accumulated along recent genealogical lineages	One generation	IBD detection/dating; recombination/gene conversion
Direct sperm sequencing: bulk duplex sequencing, once	2.5 × **10^{-8}/site/generation**	Human sperm	Mutations present directly in male gametes	Contemporary germline	Male-only; sampled gamete frequencies need not equal transmission probability; clonal selection can alter observed frequencies
Direct sperm sequencing: bulk duplex sequencing, sequential	5.74 × 10^{-10}/site/year	Repeated sperm samples from the same men	Within-individual accumulation/dynamics of mutations in the male germline	Across reproductive lifespan	Male-only; limited individuals; clonal expansion and sampling dynamics

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Data availability statement

No new data were generated or analysed in support of this research.