HHS Public Access

Author manuscript

Curr Opin Genet Dev. Author manuscript; available in PMC 2023 October 01.

Published in final edited form as:

Curr Opin Genet Dev. 2022 October ; 76: 101953. doi:10.1016/j.gde.2022.101953.

Recent insights into the evolution of mutation rates in yeast

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Abstract

Mutation is the origin of all genetic variation, good and bad. The mutation process can evolve in response to mutations, positive or negative selection, and genetic drift, but how these forces contribute to mutation rate variation is an unsolved problem at the heart of genetics research. Mutations can be challenging to measure, but genome sequencing and other tools have allowed for the collection of larger and more detailed datasets, particularly in the yeast model system. We review key hypotheses for the evolution of mutation rates and describe recent advances in understanding variation in mutational properties within and among yeast species. The multidimensional spectrum of mutations is increasingly recognized as holding valuable clues about how this important process evolves.

As the source of novel and heritable variation, spontaneous mutations play a fundamental role in genetics and development. While the occurrence of mutations is ubiquitous across the tree of life, there appears to be substantial variation among species and genotypes in both the rate and kinds of mutations that occur. Understanding how genomes have evolved and will change in the future requires that we characterize the sources of variation in the mutation process. Technological advances and lower costs associated with genome sequencing have accelerated progress in this area, particularly for fast-growing model organisms like yeast, where thousands of spontaneous mutations can readily be identified in laboratory experiments. Importantly, yeast are also used to explore many other dimensions of biological variation, providing opportunities to associate mutational patterns with other genomic and cellular features. Here we review recent studies that describe and explore variation in mutation patterns in yeast.

Models of mutation rate evolution

The simplest metric of mutation is arguably the rate of single-nucleotide mutation (SNM) per site per generation, μ. It has long been clear that μ varies by orders of magnitude among organisms [1,2], and we have multiple data points from several yeast species [3-13]. Such variation implies that the DNA replication and repair mechanisms that prevent or promote mutation must evolve [14,15]. Why should this be? One idea is that there could be some selective benefit to evolving a higher mutation rate if beneficial mutations are available;

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the optimal mutation rate would then depend on the balance between the benefits of rare adaptive mutations and the fitness costs of deleterious mutations. Theoretical investigations of this hypothesis ask whether a “mutator allele” that increases the mutation rate will be favored by selection. In the absence of sex, mutator alleles can hitchhike to high frequency along with beneficial alleles they generate, but this is unlikely in the presence of sexual reproduction, where recombination destroys this linkage. We therefore expect mutator alleles to be occasionally favorable in asexual populations, but generally disfavored in sexual populations [1,16-18], and empirical data support these predictions [19-26]. The benefits of mutator alleles may also be transient, disappearing once the population has adapted [27,28]. While a need for beneficial mutations may not be a sufficient explanation for broad taxonomic patterns of mutation rate evolution, there is still more to learn about when positive selection on mutation rates may occur, giving rise to mutation rate variation at some scales. For example, Raynes et al. [29-31] found that the nature of selection on mutation rate modifiers in yeast depends on the size and structure of populations and is not frequency-dependent. Continued investigations into the reproductive behavior and population structure of yeast in the wild [32-34] will therefore be important for predicting mutation rate evolution.

An alternative explanation for broad patterns of mutation rate diversity is that weak modifiers of the mutation rate, which have small and indirect effects on fitness, could be hidden from selection in finite populations, eventually becoming fixed at random due to genetic drift [2,35]. This “drift barrier” hypothesis predicts higher mutation rates in smaller populations, as well as low but non-zero mutation rates even in very large populations, and the data are broadly consistent with this prediction [2,36]. Detecting natural mutation rate modifiers within and among populations is challenging, but exciting evidence for such alleles in yeast strains is emerging [9,37-41]. Another prediction of the drift barrier hypothesis is that the effectiveness of each DNA replication or repair mechanism may be related to how frequently that mechanism is employed: rarely-used mechanisms will be subject to selection less often, such that their evolution is more likely to depend on genetic drift. This prediction is consistent with the observation that polymerases used infrequently to replicate small amounts of DNA are also error-prone [3,35]. Similarly, there is evidence that the SNM and mitochondrial mutation rates are higher in haploid *Saccharomyces cerevisiae* than in diploids of the same genetic background [11,42,43], suggesting that natural selection has had more opportunity to optimize DNA repair for the diploid cell state, which predominates in the wild [44]. We expect that continued efforts to characterize the natural genetic and genomic variation in this species will produce further insights into mutation rate evolution.

Experimental evolution is another strategy for studying the mutation process that is readily applied to yeast (see Jagdish and Ba, this issue). Liu and Zhang [9] predicted that, if selection always acts against mutator alleles, suppressing μ to the drift barrier limit, then a relaxation of selection should result in upward evolution of μ. Instead, they found that yeast mutation accumulation lines showed both increases and decreases in μ, indicating that the progenitor strain has a μ value above that predicted by the drift barrier hypothesis. A possible explanation is that the optimal mutation rate reflects a trade-off between the fitness costs of deleterious mutations and the “cost of fidelity”, meaning the energetic

requirements of minimizing errors in DNA replication [9,14,15]. Long-term evolution of small asexual yeast populations found little evidence for the emergence of mutator alleles [45] (unlike similar experiments in E. coli [25,26]), implying that there was little opportunity for second-order selection on μ to produce beneficial mutations. Clearly, multiple population genetic models of mutation rate evolution are still in play, and yeast will no doubt remain a key model system for testing these models.

Moving past μ –– the many dimensions of mutation

While much of the research on mutation rates has historically focused on μ, the rate of single-nucleotide mutation (SNM), there are many other dimensions of the mutation process that have been characterized, which reflect DNA replication and repair mechanisms and show evidence of evolution. Six types of SNM events are possible (Fig. 1), and the pattern of these changes appears to vary within and among species. For example, while the overall SNM rate of the haploid fission yeast *Schizosaccharomyces pombe* is similar to that of *S. cerevisiae* [3,5,11], these species show distinct biases towards different substitution types, as well as insertion/deletion biases [6,46]. There is also evidence that the substitution spectrum of *S. cerevisiae* varies among culture media conditions [8,47]. While this genetic and environmental variability is fascinating, it may complicate the task of finding general evolutionary explanations for mutation patterns, particularly since more complex aspects of the mutation spectrum will require greater empirical effort to characterize precisely.

Experiments with yeast also find evidence that local and regional genomic context can affect the rate of mutation [4-7,10-12,48-50]. For example, a common finding is that CpG sites show an elevated C→T mutation rate; in other organisms such a pattern has been attributed to spontaneous deamination of methylated cytosines, but fission and budding yeast seem to have little or no DNA methylation [51], so the explanation for this pattern remains unclear. There is evidence that the rate and spectrum of SNMs is altered in late-replicating regions of the budding yeast genome, possibly due to the use of alternative DNA repair mechanisms at different times [11,48,52]. Unique mutation patterns occur in yeast mitochondrial genomes [3,8,13,53], but relatively high levels of structural variation among these sequences has made it challenging to quantify complex types of mutation [53]. Several more patterns of context-dependent mutation have been reported, for which we often lack mechanistic and evolutionary explanations. Further research will ideally address the origins of specific context-dependent mutation patterns now that the prevalence of such patterns has become clear.

A recent study of mutation patterns in the plant *Arabidopsis thaliana* reports evidence that epigenomic factors substantially reduce SNM and indel rates in genes, particularly those under strong selective constraint [54]. Several MA studies with *S. cerevisiae* have examined the rate of mutation in genes as a measure of possible selection during the experiment; as reported previously [5,8,11], SNMs occur in genes at a rate that closely matches the null expectation (Fig. 2A), with a consistent pattern across genetic backgrounds, ploidy states, and environments. These experiments all show a bias of indel mutations away from genes, but this effect may be largely driven by the fact that low-complexity sequences and simple repeats are more common outside of genes in this species [11]. We extended these analyses

by considering whether each gene is classified as “essential” [55]; we find no evidence that the rate of SNMs or indels in essential genes differs from the null expectation (Fig. 2B). There is also evidence that mutations in essential genes are not more likely to affect yeast growth rates than mutations in non-essential genes [56]. These findings suggest that, while context-dependent mutation patterns exist in yeast, there is no substantial bias away from genic regions. Instead, highly-transcribed yeast genes seem to be subject to higher rates of DNA damage and mutation [57-59], though this effect may be partially counteracted by transcription-coupled repair or nascent RNA folding [60]. From a population genetic standpoint, it is perhaps surprising that targeted hypomutation [61] would evolve in *A. thaliana* but not *S. cerevisiae*, given the latter’s much larger effective population size, but yeast also have a much lower mutation rate overall [9]. We speculate that selection might act to prevent deleterious mutations by either reducing μ throughout gene-rich genomes, or alternatively by preferentially targeting DNA repair to functionally important regions.

Budding yeast has become a key model for studying large structural mutations, particularly aneuploidy and whole-genome duplication. Such changes often seem to be well-tolerated in this species and can contribute to adaptation [62-67], though there is also evidence that aneuploidy can cause fitness deficits and give rise to genome instability [11,68-70]. The spontaneous rate of aneuploidy events has been estimated based on mutation accumulation experiments [5,8,11,71], but because these events are rare relative to point mutations, consistent patterns of aneuploidy mutation have been harder to characterize. In particular, it is still unclear whether the observed variation in aneuploidy rates across chromosomes and the observed bias towards chromosome gains over chromosome losses (in diploids) stem from true differences in spontaneous mutation patterns, strong selection against mutant karyotypes, high rates of reversion to euploidy, or some combination of these effects. High-throughput methods to quantify spontaneous aneuploidy rates without the influence of selection would be valuable. Similarly, whole-genome duplication events are frequently observed in adapting populations of budding yeast, with huge consequences for adaptation (reviewed in [72]), but there have only recently been systematic attempts to quantify the spontaneous rate of such changes independently from their fitness effects [73-75]. Comparisons among experiments suggest there may be variation among haploid *S. cerevisiae* strains in the rate of spontaneous diploidization [76], so further study of the evolution of this unique mutation type may be fruitful, despite the challenges associated with its measurement.

The properties of yeast as a model system have made it possible to investigate a number of complex mutational mechanisms. A unique type of structural variation that has received recent attention in yeast is copy number at the highly-repetitive ribosomal DNA (rDNA) locus, where research has benefitted from technical advances like digital droplet PCR [77-79]. There is evidence for species diversity, standing genetic variation, and mutational variation in rDNA copy number [71,79-82]. The rDNA locus is particularly interesting because yeast seem to have evolved mutational mechanisms to maintain an optimal copy number in the face of recurrent copy loss and replication stress [78,83,84], so this genomic feature could serve as a model for the evolution of directed mutation. Transposable elements (TEs) can be a major source of mutations, and the facultatively-sexual nature of yeast has been leveraged to test the role of sexual reproduction in the evolution of TE activity [85,86].

Yeast strains and species can be hybridized in the lab as another way to study TE activity [87-92], as well as the mutation rate and spectrum generally [75,93,94], revealing mutation rate variation among genetic backgrounds. Yeast and their hybrids have also been used to identify genome-wide patterns of loss-of-heterozygosity mutations [33,44,75,93-95], an important form of genome evolution in many populations. This is only a brief overview, but yeast has clearly become a critical model for studying the amazing diversity of mutation mechanisms.

Mutation rates across yeast species

While the bulk of the work on mutation rate in yeast has been performed with *S. cerevisiae*, comparative insight into mutation rate evolution is also increasingly available from analyses of other yeast species. Given the close relation and undomesticated history of *S. paradoxus*, it is the species most often directly compared with *S. cerevisiae* [92,96]. In addition to comparing these species, recent studies have examined mutation patterns in their hybrids, revealing that specific genotypes rather than broad phylogenetic patterns often shape mutation rates and spectra [75,93,94]. Other types of phylogenetic comparison have been conducted between ascomycete and basidiomycete yeasts, the two largest phyla of fungi. This was done by comparing *Rhodotorula toruloides*, a basidiomycete yeast, to the ascomycete models *S. pombe* and *S. cerevisiae* which are themselves quite diverged within their clade [10]. This study found that while mutation rates are similar between clades, the types of mutations that occur vary greatly between groups, shaped by species-specific genomic architecture. Similar variation in mutation spectra has also been observed among species in the Saccharomycodaceae family [13], but much of this variation remains poorly understood. In yeast known as opportunistic human pathogens like *Cryptococcus*, genetic variation in DNA repair pathways are of particular interest due to the potential for mutator alleles to affect rapid adaptation and virulence [97,98]. Finally, in *Candida albicans*, the causal agent of human candidiasis, work has focused on understanding the interplay between (para)sexual reproduction and spontaneous genomic changes, including loss of heterozygosity and ploidy change [99,100]. We are only just beginning to uncover mutation patterns among the great diversity of yeast species; as more systems become genetically tractable, including species with industrial applications or health relevance, new dimensions of variation in mutation are likely to emerge.

Conclusion

Researchers increasingly recognize the importance of the broad spectrum of mutations, beyond the rate of single nucleotide substitution, and so we have tried to emphasize some of these traditionally-understudied patterns. Using yeast as a genetic model, including variation among species, genotypes, and environments, promises to shed new light on how DNA replication and repair systems evolve.

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* Of Special Interest

** Of Outstanding Interest

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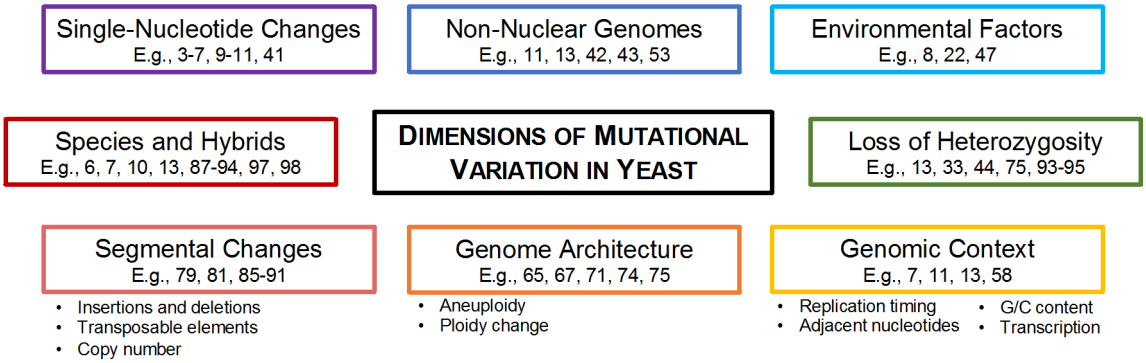

Figure 1.

Mutations in yeast occur on multiple scales, from single-nucleotide changes to whole genome duplication. There is evidence for variability in mutation patterns at every genomic scale, as well as among strains, species and environments. Example references are indicated for each type of variation.

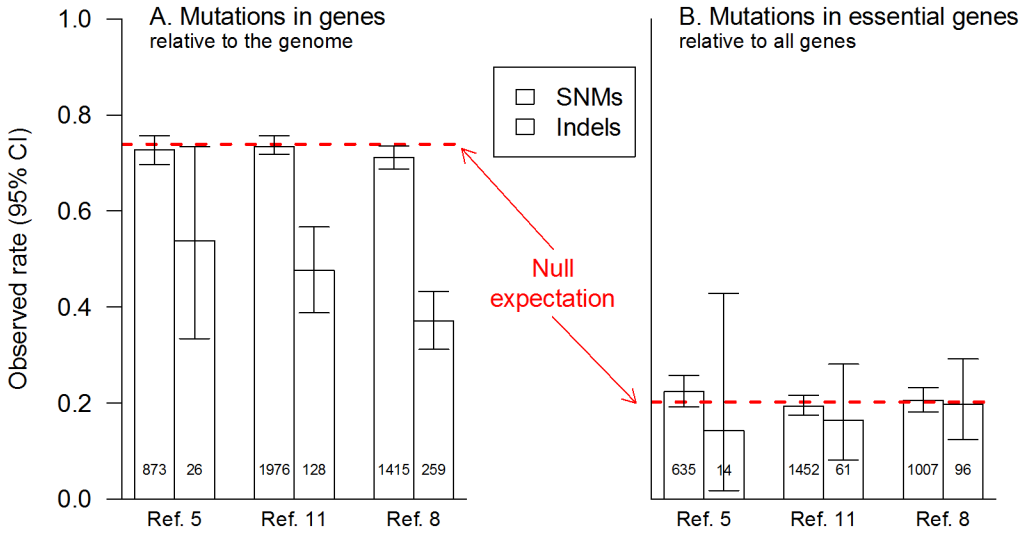

Figure 2. Mutation rates in yeast genes.

Bars show observed frequencies of mutations from three MA studies of *S. cerevisiae* (A) in genes, as a fraction of the whole genome, and (B) in essential genes relative to all genes. Dashed red lines represent the expected frequency if mutations occur in an unbiased fashion with respect to genes (A) or essential genes (B). These expected values account for gene length but do not incorporate other sources of mutation rate variation across the genome or variation in detection power. Values shown on bars indicate sample sizes, i.e., the total number of mutations observed in each category. Data from Ref. 11 are aggregated over ploidy levels and genotypes. Data from Ref. 8 are aggregated over environments; there is no evidence for a deviation from the null expectation in any individual environment. Indel mutations are observed in genes less often than expected, but are not observed in essential genes less often than expected; the deficit of genic indels may therefore reflect differences in sequence complexity between genic and intergenic regions. Overall, there is little evidence that mutations in this species occur less often in selectively-constrained regions.