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Mutation rate variation in eukaryotes: Evolutionary implications of site-specific mechanisms

Baer *et al.*'s review¹ accurately conveys the tenor of most literature on mutation-rate evolution. Even while recognizing that mutation rates can vary dramatically from site to site within a genome, this literature mostly ignores or minimizes the special characteristics and consequences of site-specific mutational mechanisms. Therefore, to the authors' list of "five critical questions" for future investigation, we would like to propose a sixth: To what extent can elevated site-specific mutation rates vary (and evolve) independently from low average nucleotide substitution rates?

Following historical precedent, Baer *et al.*¹ consistently refer to "the mutation rate" as if a single value could adequately summarize the complex outcome of many diverse mutational mechanisms. However, such a simplistic statistic should no longer be tolerated, at least not without precise qualification such as "average rate of nucleotide substitutions within protein-coding sequences". Even then, somatic mutability of antibody genes demonstrates that localized hypermutation can be exploited by adaptive evolution². Site-specific sources of germ line mutation are also familiar, as evidenced by prolific variation produced by simple sequence repeats (SSRs; microsatellites and minisatellites)³.

Although Baer *et al.*¹ acknowledge SSRs' remarkably high mutation rates, they do not discuss the profound implications of such site-specific mutability for understanding mutation-rate evolution. Phenotypic effects of SSR mutations include reversible on-off switching as well as quantitative variation in many aspects of gene function³⁻⁸. Such effects need not be predominantly deleterious, especially when adaptation is suboptimal, as in variable environments⁹. Yet an assumption that "the vast majority of mutations with observable effects are deleterious" has informed most discussion of mutation-rate evolution throughout the past century¹. Traditionally, theoretical discussion also assumes that recombination in diploid organisms

must eventually separate "mutator alleles" from resulting mutations, thereby preventing mutators from "hitchhiking" on selection for beneficial mutants¹. However, recombination cannot unlink site-specific mutational mechanisms, such as those based on SSRs, from the mutations which they generate. Hence selection for any beneficial mutation at a mutable site must also, indirectly, favor the site's intrinsic mutability.

The best evidence for positive selection of sites with high mutation rates comes from the SSR-based contingency genes of haploid microorganisms¹⁰. In eukaryotes, the reported abundances, genomic distributions, phylogenetic conservation, and patterns of variation for SSRs are also strongly suggestive of positive selection^{4,6,7}. The utility of SSR mutability for adaptive evolution has already been implicated in several cases, including skeletal evolution of domestic dogs⁵, temperature compensation of the *Drosophila* circadian clock¹¹⁻¹³, and social behavior of voles¹⁴, among others⁷. Whether such mutable sites somehow prevail in spite of their high mutability (as conventional theory requires), or whether indirect selection for their high mutability is the reason for their prevalence^{8,9}, remains to be established. In either case, the special characteristics of site-specific mutational mechanisms deserve attention in any future consideration of mutation-rate evolution.

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