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# Mutation Rate Variation in Eukaryotes: Evolutionary Implications of Site-specific Mechanisms

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

Baer *et al.*'s review<sup>1</sup> 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.*<sup>1</sup> 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 evolution<sup>2</sup>. Site-specific sources of germ line mutation are also familiar, as evidenced by prolific variation produced by simple sequence repeats (SSRs; microsatellites and minisatellites)<sup>3</sup>.

Although Baer *et al.*<sup>1</sup> 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 function<sup>3-8</sup>. Such effects need not be predominantly deleterious, especially when adaptation is suboptimal, as in variable environments<sup>9</sup>. 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 century<sup>1</sup>. 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 mutants<sup>1</sup>. 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 microorganisms<sup>10</sup>. In eukaryotes, the reported abundances, genomic distributions, phylogenetic conservation, and patterns of variation for SSRs are also strongly suggestive of positive selection<sup>4,6,7</sup>. The utility of SSR mutability for adaptive evolution has already been implicated in several cases, including skeletal evolution of domestic dogs<sup>5</sup>, temperature compensation of the *Drosophila* circadian clock<sup>11-13</sup>, and social behavior of voles<sup>14</sup>, among others<sup>7</sup>. 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<sup>8,9</sup>, 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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