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Reply to: Mutation rate variation in eukaryotes: evolutionary implications of site-specific mechanisms

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King and Kashi bring attention to the phenomenon of intragenomic variability in mutation processes, the elevated rates of simple sequence repeat (SSR) mutations in particular, and suggest that the widespread use of a single average mutation rate does not reflect the biological realities and consequences of intragenomic mutational variation. We agree with King and Kashi that the historical use of a single mutation rate fails to capture the complexities of genomic mutation processes and that understanding the causes that underlie this variation is highly important — the impact of SSR abundance variation was discussed in the "DNA replication" section of the Review (page 621), and another later section (page 624) was titled "Within-genome variation in mutation rates". However, we also believe that a single mutation rate serves a valuable and necessary role in evolutionary biology, for two reasons. First, single (that is, average) mutation rates have been crucial to the historical development of classic evolutionary theories, concepts and tools such as the neutral theory of molecular evolution[1] and the Tajima's *D* statistic[2]. Furthermore, single mutation rates have proved essential for estimating effective population sizes on the basis of within-species nucleotide diversity data; this use of single mutation rate values was crucial to the recent development of a powerful and broadly applicable population genetic theory on the origins and evolution of genome complexity[3]. Second, fitness in its usual context is a property of the whole organism, and every nucleotide in the genome potentially contributes to fitness. Therefore, the genomic mutation rate for fitness (U) is properly integrated over the entire genome. Nonetheless, we agree that understanding the causes (including site-specific mechanisms) and consequences of intragenomic mutational variation is key to a more broad-based and realistic knowledge of genomic mutation properties, and is certainly deserving of a sixth future direction.

King and Kashi also reference work suggesting that the hypermutable nature of particular SSRs is associated with adaptive processes and posit that SSR mutations are commonly associated with adaptive rather than deleterious effects. Although we agree that there are likely to be special contexts in which elevated mutation rates at SSRs are selectively advantageous, their strong underrepresentation in protein-coding gene sequences in all eukaryotic genomes examined[4] is indicative of a strong general role for purifying natural selection in preventing SSR accumulation in most gene sequences. Despite a few special cases, a century of investigation[5–8] continues to support the idea that most new mutations have deleterious effects on fitness.

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