Southern Illinois University Carbondale **OpenSIUC**

Publications

Department of Anatomy

8-2007

Mutability and Evolvability: Indirect Selection for Mutability

David G. King Southern Illinois University Carbondale

Yechezkel Kashi Israel Institute of Technology

Follow this and additional works at: http://opensiuc.lib.siu.edu/anat_pubs Published in *Heredity*, Vol. 99, No. 2 (August 2007) at 10.1038/sj.hdy.6800998. News and Commentaries.

Recommended Citation

King, David G. and Kashi, Yechezkel. "Mutability and Evolvability: Indirect Selection for Mutability." (Aug 2007).

This Article is brought to you for free and open access by the Department of Anatomy at OpenSIUC. It has been accepted for inclusion in Publications by an authorized administrator of OpenSIUC. For more information, please contact opensiuc@lib.siu.edu.

News and Commentary Mutability and Evolvability

Indirect selection for mutability

DG King and Y Kashi

How readily does mutability evolve? Petrie and Roberts (2007) have recently described a theoretical example of increased mutation rate based on female choice. Mutator alleles can also be favored by strong selection for phenotypic variation, such as that imposed by immunological attack against pathogens, together with stable linkage to beneficial mutations, provided by haploidy in microorganisms. But the special conditions required for these examples highlight two assumptions that have framed discussion of mutationrate evolution for most of the past century (e.g., Bataillon, 2000; Bell, 2005; Cotton and Pomiankowski, 2007). First, although close linkage may allow a mutator to hitchhike on selection for a beneficial allele, recombination, at least in sexually reproducing populations, will eventually separate the two. Second, because most non-neutral mutations are deleterious, the net effect of any mutator must be fitness reduction. Thus, "natural selection of mutation rates has only one possible direction, that of reducing the frequency of mutation to zero" (Williams, 1966). Regrettably, this classic but overstated conclusion remains influential. Even well-established exceptions like the "contingency loci" of some bacteria are routinely marginalized as special cases that depend on extreme and/or unusual circumstances (Sniegowski and Murphy, 2006).

Contemporary discussion also often oversimplifies "mutation rate" as a single statistic rather than a cumulative total emerging from many distinct mutational mechanisms (e.g., Bataillon, 2000; Sniegowski and Murphy, 2006). However, although some mutator alleles may affect genome-wide accuracy of DNA processing, others have effects which are restricted to individual sites. Each site-specific mechanism may carry its own distinct rate and its own unique probability distribution for deleterious and beneficial effects. Such characteristics allow certain common mutagenic patterns to escape the reach of Williams's conclusion.

This is most clearly illustrated by the properties of simple sequence repeats (SSRs, also termed microsatellites and minisatellites). SSR "slippage" mutations, which increase or decrease the number of tandem repeats, occur at rates which may be orders of magnitude greater than those for single nucleotide substitutions. The particular mutation rate at each SSR depends on locus characteristics including motif length and purity of repetition. Because the rate-determining locus and the locus at which mutations occur are one and the same, there is no possibility for recombination to separate the two. Thus an SSR locus represents a "mutator allele" whose site for mutation is itself. Consequently, even in diploid, sexually reproducing genomes, an SSR mutator allele will always remain linked with its resulting mutations.

Although SSRs are often considered "junk", SSR repeat-number alleles can influence almost any aspect of genetic function from protein coding to exon splicing to regulatory interaction. Quantitative functional effects have been reported for SSRs located in exons, in introns, and in upstream and downstream regulatory domains (Kashi and King, 2006). Although harmful SSR mutations do exist (e.g., triplet repeat diseases), SSRs more typically yield "mutations of small effect". And "mutations of small effect" are potentially beneficial with probability approaching 50% (Fisher, 1930). Hence the genetic variation supplied by SSR mutator loci need not be predominantly deleterious.

At any given SSR locus, each allele encodes both a phenotypic effect, represented by the number of repeats, and a mutation rate, represented by purity of motif repetition, for example (Trifonov, 1989). Therefore, natural selection acting on the fitness effects of SSR alleles also indirectly selects their mutation rates. Eliminating a high-mutation-rate allele proceeds gradually through repeated rounds of selection against individual deleterious mutants as they arise. But if a high-mutation-rate allele gives rise to a beneficial mutant, selection that fixes the mutant will unavoidably fix the high mutation rate as well. Thus indirect selection can readily exploit the characteristic mutability of SSRs to minimize mutation rates at sites where variation is disadvantageous while assuring that variability remains present at sites that repeatedly experience directional selection.

A number of observations indicate that SSRs are distributed non-randomly with respect to gene function (Kashi and King, 2006). A surprisingly large proportion of genes are closely associated with one or more SSRs, with especially high prevalence in regulatory loci. Triplet repeats are most common in protein-coding domains where they allow adjustment of length of amino acid repeats. Non-triplet motifs predominate in other functional domains. The overall distribution of SSR motifs also varies among taxa, while SSRs in homologous locations may have different motifs in related species. Such patterns are readily interpretable as resulting from indirect selection for the site-specific mutability and allelic variation that SSRs provide.

Two common objections to the hypothesis of selection favoring mutability stem from an unfortunate conflation of "mutability" with "evolvability". First, since individual organisms do not evolve, a population-level property like evolvability can be favored only by some form of group selection (Williams. 1966). Thus the widely accepted implausibility of group selection also impugns selection for mutability (Sniegowski and Murphy, 2006). Second, selection for evolvability is often challenged simply because the advantages of future adaptation cannot be a selective force in the present (Sniegowski and Murphy, 2006). But in situations where variability offers immediate benefits, indirect selection for site-specific mutability, proceeding at the level of individual genes, is no less plausible than direct selection for fitness. Evolvability emerges as an epiphenomenon at the level of populations.

Williams (1966) wisely recognized that "our current picture of evolutionary adaptation is, at best, oversimplified and naive". Special conditions are certainly required before selection can favor mutability. But "special" does not necessarily imply "unusual". SSRs

illustrate just how readily appropriate conditions of site-specific mutability can obtain. Additional sources for genetic variation, such as transposable elements (e.g., Capy *et al.*, 2000), may also be amenable to indirect selection. Just as sexual recombination offers advantageous shuffling of preexisting variation, so too may new variations, if suitably constrained by site-specific mechanisms, accrue substantial advantage. As Darwin recorded, "some authors believe it to be as much the function of the reproductive system to produce individual differences . . . as to make the child like its parents". That point of view may be more pertinent to understanding the dynamic genome than Sturtevant's dismissive dictum that "mutations are accidents, and accidents will happen".

DG King is at the Department of Anatomy and the Department of Zoology, Southern Illinois University, Carbondale, IL 62901, USA and Y Kashi is at the Department of Biotechnology and Food Engineering, Israel Institute of Technology, Haifa 32000, Israel.

e-mail: dgking@siu.edu

- Bataillon T (2000). Estimation of spontaneous genome-wide mutation rate parameters: whither beneficial mutations? *Heredity* **84**: 497-501.
- Bell G (2005). The evolution of evolution. *Heredity* **94**: 1-2.
- Capy P, Gasperi G, Biémont C, Bazin C (2000). Stress and transposable elements: coevolution or useful parasites? *Heredity* **85**: 101-106.
- Cotton S, Pomiankowski A (2007). Sexually selected mutation rates. *Heredity* **98**: 185-186.
- Fisher RA (1930). *The Genetical Theory of Natural Selection*. Oxford University Press, Oxford
- Kashi Y, King DG (2006). Simple sequence repeats as advantageous mutators in evolution. *Trends Genet* **22**: 253-259.
- Petrie M, Roberts G (2007). Sexual selection and the evolution of evolvability. *Heredity* **98**: 198-205.
- Sniegowski PD, Murphy HA (2006). Evolvability. Current Biology 16: R831-R834.
- Trifonov EN (1989). The multiple codes of nucleotide sequences. *Bull Math Biol* **51**: 417–432.
- Williams G (1966). *Adaptation and Natural Selection*. Princeton University Press, Princeton.

Editor's Suggested Reading

- Caporale LH (2003). Natural selection and the emergence of a mutation phenotype: An update of the evolutionary synthesis considering mechanisms that affect genomic variation. *Ann Rev Microbiol* **57**: 465-485.
- Fondon III JW, Garner HR (2004) Molecular origins of rapid and continuous morphological evolution. *Proc Natl Acad Sci* USA **101**: 18058-18063.
- Kirschner M, Gerhart J (1998) Evolvability. Proc Natl Acad Sci USA 95: 8420-8427.
- Li Y-C, Korol AB, Fahima T, Beiles A, Nevo E (2002). Microsatellites: genomic distribution, putative functions and mutational mechanisms: a review. *Mol Ecol* 11:2453-65.
- Moxon ER, Thaler DS (1997). The tinkerer's evolving tool-box. Nature 387:659-662.
- Theodorou K and Couvet D (2006). Genetic load in subdivided populations: interactions between the migration rate, the size and the number of subpopulations. *Heredity* **96**: 69-78.
- Worobey M (2005). Genomics: Anthrax and the art of war (against ascertainment bias). *Heredity* **94**: 459-460.