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Feedforward loop for diversity

Michael Lynch

Department of Biology, Indiana University, Bloomington, Indiana 47405, USA.

milynch@indiana.edu

Abstract

DNA-sequence analysis suggests that genetic mutations arise at elevated rates in genomes harbouring high levels of heterozygosity — the state in which the two copies of a genetic region contain sequence differences.

The rate at which genetic mutations arise is relevant to every area of biology. Evidence indicates that mutation rates vary almost 1,000-fold between species, from 10^{-11} mutations per nucleotide site per generation in some unicellular organisms to approximately 10^{-8} in primates¹. These figures represent genome-wide averages, but mutation rates can vary between nucleotide sites^{2–4} and between members of the same species⁵. Intraspecies differences have long been assumed to be a consequence of genetic variation at discrete regions, or loci, containing genes involved in genome-wide aspects of DNA replication and repair. But on page 463 of this issue, Yang *et al.*⁶ suggest something quite different: that mutation rates are elevated in individuals with high genome-wide levels of heterozygosity (sequence variation between the two copies, called alleles, of each genetic locus).

Yang and colleagues' gold-standard analyses compared whole-genome sequences of parents and offspring for two plants and an insect. They found that mutation rates are elevated in individuals with higher overall heterozygosity, particularly in regions close to heterozygous sites and regions in which there are high rates of DNA exchange between chromosomes (recombination). The authors therefore propose a positive-feedback loop, whereby high levels of molecular variation in an individual facilitate the production of more variation.

It is accepted that recombination is mutagenic⁷, but the implications of Yang and co-workers' results for population-level genetic analyses, which rely on measures of heterozygosity, could be substantial. For example, average levels of variation are often assumed to directly reflect recent population sizes — independent of the mutation rate — because large population sizes enhance the maintenance of variation. But such an assumption is compromised if a transient boost in heterozygosity, for whatever reason, also boosts the rate of mutational production of variation. Furthermore, a feedforward effect might help to explain the clustering of variation at adjacent sites⁸, which may in turn relate to the fact that closely spaced sites have elevated levels of linkage disequilibrium (a measure of the statistical association between specific alleles at different genetic loci)⁹.

Some forms of natural selection that favour the maintenance of variation — for example, to promote avoidance of specialized pathogens — might also be associated with elevated mutation rates¹⁰. As Yang and colleagues note, their results bear on this controversial idea.

Whether natural selection is efficient enough to modulate gene-specific mutation rates is questionable¹¹. But if loci under diversifying selection (which favours variation) passively acquire elevated mutation rates as variation grows, gene-specific modifiers of the mutation rate need not be invoked to explain this model.

Although the authors' results concerning the mutagenic effect of heterozygosity are surprising, the mutation rate that they calculate for inbred strains of the plant *Arabidopsis* is not greatly different from that reported previously¹², so the results do not seem to be artefactual. But what biological peculiarities could elevate mutation rates in heterozygotes? Much goes wrong in inbred organisms owing to an increase in homozygosity (in which the two alleles of a gene are identical), which increases the exposure of an organism to deleterious 'recessive' alleles¹³. One might therefore expect the mutation rate to be higher in inbred than outcrossed individuals — the opposite pattern to that observed by Yang and colleagues. However, outcrossing between distantly related strains can sometimes lead to outbreeding depression, in which offspring have lower fitness than those from intra-strain crosses.

The parental strains used in this study might have been divergent enough to generate incompatibilities that influence the mutation rate. For instance, many proteins involved in DNA replication and damage repair operate as multimeric complexes, and the mixture of subunits from divergent strains might lead to malfunctioning complexes. Physiological effects on a cellular level, such as the production of free radicals that damage DNA, might also be a factor.

One argument against the involvement of outbreeding depression is the authors' observation that mutation rates are not uniformly elevated across the genomes of first-generation offspring from outcrossing, but are concentrated near heterozygous sites. However, the elevation in mutation rate near heterozygous sites is less than two-fold, and an outbreeding-depression effect cannot be entirely ruled out. For example, when a heterozygous site is part of a locus that is involved in a recombination event, the 'mismatch-repair' pathway used to resolve the difference at the site also engages with the surrounding DNA. Because this pathway is relatively error-prone¹⁴, if the repair complex is made up of a mixture of subunits from the different parents, this could specifically elevate the mutation rate near heterozygous sites.

The authors show that mutation rates decline in the third and fourth generation after outcrossing, consistent with expectations based on the associated decline in heterozygosity, but care must be taken with this interpretation. Immediately after outcrossing, each gene has an allele from each parental line, whereas in later descendent generations, offspring tend towards 50% mixtures of homozygous and heterozygous allele complements (Fig. 1). It then becomes difficult to determine whether a reduction in mutation rate is a direct consequence of the decline in heterozygosity, or whether changes in outbreeding depression or in its counterpart, outbreeding enhancement, are partially or wholly responsible¹³.

It should be straightforward to test whether heterozygosity per se is a direct determinant of the mutation rate by focusing on species such as the honeybee, in which males contain only

a set of chromosomes inherited from their mothers — if the authors' hypothesis is correct, mutation rates should be lower in males than in their heterozygous sisters. Moreover, if recombination magnifies the mutation rate, rates should be reduced on chromosomes that cannot recombine, such as the X and Y of human males and all the chromosomes of male fruit flies.

Under the authors' proposed scenario, might runaway magnification of both the mutation rate and population-level heterozygosity be possible? This would seem to require a rather implausible set of conditions, but there are reports of extraordinarily high levels of heterozygosity in organisms such as the urochordate *Ciona savignyi*¹⁵ and the nematode *Caenorhabditis brenneri*¹⁶. Whether these taxa actually reflect stable alternative states of heterozygosity could be answered by evaluating whether individuals engineered to be more homozygous show reduced mutation rates.

Finally, it is worth considering how the approximately 3.5-fold difference in mutation rate between inbred and outbred strains found in the current study compares with variation among individuals in normal populations. The mutation rates in two inbred lines of fruit fly differ by around 2.3-fold⁵, and these rates are slightly higher than those of outbred flies¹⁷. Self-fertilizing organisms with exceptionally low heterozygosity do not have unusually low mutation rates compared with outcrossing species with similar genome sizes¹. Furthermore, humans and chimpanzees, which are highly homozygous, have extremely high mutation rates^{1,18}. Of course, there are many biological differences between these species, so caution must be taken not to overinterpret these observations.

Overall, this study raises several intriguing questions. Even if the results are eventually found to reflect outbreeding depression or simply natural variation in replication fidelity, Yang and colleagues have done us a service, encouraging a focus on variation in the process that itself generates variation.

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Figure 1. Generating variation

This simplified schematic demonstrates the changes in diversity that arise in intercrosses of a diploid organism, which has two sets of chromosomes, one from each parent. In inbred organisms, most genetic regions are homozygous — they are identical on both chromosomes (completely homozygous chromosomes are depicted here for simplicity). When inbred plants self-fertilize, levels of homozygosity remain the same in offspring. But in the first generation of a cross between two inbred strains, the offspring have two different copies of each gene (heterozygosity). Further intercrossing of offspring leads to a decrease in levels of

heterozygosity, because some regions become homozygous once again. Yang *et al.*⁶ report that levels of heterozygosity correlate with the rate at which genetic mutations arise.

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