Evolutionary genetics

The mutation rate as an evolving trait

Mutations are the fundamental source of genetic variation but also the cause of deleterious effects on fitness. The mutation rate (the number of genetic changes within a given unit of time) is a central parameter in evolutionary biology. Thanks to the application of genomic sequencing technology, we can now precisely determine the exact number of de novo mutations arising in germ cells that are transmitted to offspring, as well as somatic mutations generated during somatic cell divisions. It has long been recognized that mutation rates vary substantially across taxa and even between populations within species. Although several hypotheses have been put forward to explain the proximal mechanisms that underlie the variations in mutation rate, including intrinsic and extrinsic environmental factors, the ultimate causes of evolutionary change on the mutation rate remain controversial even today.

This issue was first raised by the American geneticist Alfred H. Sturtevant in his seminal paper more than 80 years ago, well before DNA became recognized as the genetic material. Sturtevant noticed that most mutations with observable phenotypic effects were deleterious and wondered why the mutation rate had not evolved all the way to zero. He speculated that “the nature of genes does not permit such a reduction”. Surmising that mutations were unavoidable ‘accidents’, he proposed that some internal genetic factors might affect the general mutation rate. This hypothesis has since been bolstered by numerous reports in the literature that demonstrate that such accidents of nature occur by spontaneous DNA damage and replication errors, even under normal conditions. Defects in genes that encode proteins involved in DNA repair and replication can alter the efficiency of these essential processes, thereby increasing the genome-level mutation rate.

Sturtevant drew another influential conclusion: the mutation rate is an evolving parameter. This conclusion was based on his observations in fruitflies that mutation rates differed between closely related species, such as *Drosophila melanogaster* and *Drosophila funebris*, and among strains of the same species. In attempting to answer why this variation occurred, Sturtevant pointed to its ultimate cause: natural selection. He posited that genes that affect the mutation rate are subject to natural selection. There should therefore be a trade-off between selection that acts to favour the lowering of mutation rates (to avoid disadvantageous mutations) and a counter-acting process of selection that favours higher mutation rates (to maintain a flow of potentially advantageous mutations). This insight led to the hypothesis that variable optimal mutation rates could evolve across species over time.

In addition, Sturtevant proposed that the mutation rate could be affected by external agents. He hypothesized that, given time, natural populations could adapt to special ambient conditions by altering the general mutation rate. Although he acknowledged the difficulty in experimentally verifying this hypothesis, this prescient insight inspired the field of experimental evolution to examine the mutagenic effects of environmental agents in relation to both the mutation rate and mutation spectra.

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The nature of the non-zero mutation rate has been a constant focus for both the evolutionary and genomic research fields over the past few decades. The availability of genome sequences of many species has potentiated whole-genome comparisons to reveal variation in the mutation rate across genomes in a context-dependent manner, further supporting the idea of internal genetic effects on the general mutation rate as proposed by Sturtevant. More recently, it has become possible to measure mutation rates, in both the germ line and the soma, by genomic comparison of pedigree samples and different organs or cell lines.

To fully understand the evolutionary pattern of mutation rate variation across species, more empirical data of mutation rate estimation should be collected from a broader range of taxa. These data will be invaluable for untangling the complex interaction between life history traits and individual mutation rates, and for discerning the different selective forces to which mutation rates are subjected, leading to the emergence of an optimal mutation rate in each species. Sturtevant’s views on the evolution of mutation rates are likely to continue to influence future efforts to understand what remains a fundamental question in biology.

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Competing interests
The author declares no competing interests.

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