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The author declares no competing interests.

Genetics

Important genomic regions mutate less often

Jianzhi Zhang

Genomic regions that are crucial for the viability and reproduction of the model plant *Arabidopsis thaliana* are enriched with molecular features that are associated with a reduced rate of mutation. **See p.101**

Salvador Luria and Max Delbrück made a profound discovery in 1943 that won them a Nobel prize, shared with Alfred Hershey, 26 years later. What they found was that bacterial mutations that confer resistance to a virus arise at the same rate, regardless of whether the virus is present[1]. That the generation of mutations (a process called mutagenesis) is blind to its consequence has since become an established principle of genetics. Monroe *et al.*[2] report on page 101 that, in stark contrast to this tenet, the rate of mutation in the model plant *Arabidopsis thaliana* is lower in genomic regions that are functionally more important, and in regions where mutations are more frequently harmful.

By analysing thousands of mutations collected in mutation-accumulation experiments, the authors find that the mutation rate is 58% lower inside genes than in regions immediately outside them, and 37% lower in essential genes (those indispensable for viability or fertility) than in non-essential genes. Furthermore, the authors observe a negative correlation between the proportion of mutations in a gene that are deleterious and the mutation rate of the gene.

Monroe *et al.* are not the first to describe such apparently advantageous patterns of variation in the rate of mutation across a genome. For example, a previous study[3] reported that highly expressed genes in the bacterium *Escherichia coli* have relatively low mutation rates. This trend has been suggested to be an evolutionary 'risk-management' strategy[3], because the detriment imposed by a mutation tends to increase with the expression level of the mutated gene[4]. Similarly, another study[5] proposed that gene expression in the human testes is regulated to optimize gene-specific rates of mutations that are transmitted to the next generation. However, the results of both of these studies have been contested, owing to confounding factors in mutation-rate estimation, and a lack of viable mechanisms[6–8].

What mechanisms cause crucial genomic regions to mutate less in *A. thaliana*? Monroe *et al.* noticed that the mutation rate of a given genomic region (in the study, a stretch of 1,000 nucleotide bases) is correlated with several genomic features. Among these are the percentage of nucleotides in the region that are guanine or cytosine, and epigenetic features of the region — molecular modifications that affect gene activity without changing the DNA sequence. These include various modifications to histone proteins that bind to DNA and affect gene regulation, DNA replication and DNA packaging. Monroe *et al.* propose that these genomic features and (especially) epigenetic features together form part of the machinery that is shaped by natural selection to reduce mutagenesis of important genomic regions.

The evolutionary selective pressure for mutagenesis-reducing machinery should be weak, because the machinery does not directly affect the fitness of the organisms that carry it. Rather, it affects the fitness of their offspring, owing to differences in their numbers of newly generated mutations[9]. In organisms such as *A. thaliana* that reproduce by selfing (the union of male and female sex cells from the same organism), the strength of selection for this machinery approximates the number of deleterious mutations per individual per generation that the machinery prevents[9,10]. Monroe *et al.* estimate that, in the face of genetic drift (random fluctuation of frequencies of genetic variants in a population), a machinery that lowers the mutation rate of essential genes by 30% must influence at least one-third of all coding sequences of all essential genes in *A. thaliana* for it to be established by natural selection. Hence, a mutagenesis-reducing machinery is unlikely to have emerged through adaptive evolution unless it has large and broad effects.

The suppression of mutagenesis in important genomic regions could, in theory, originate

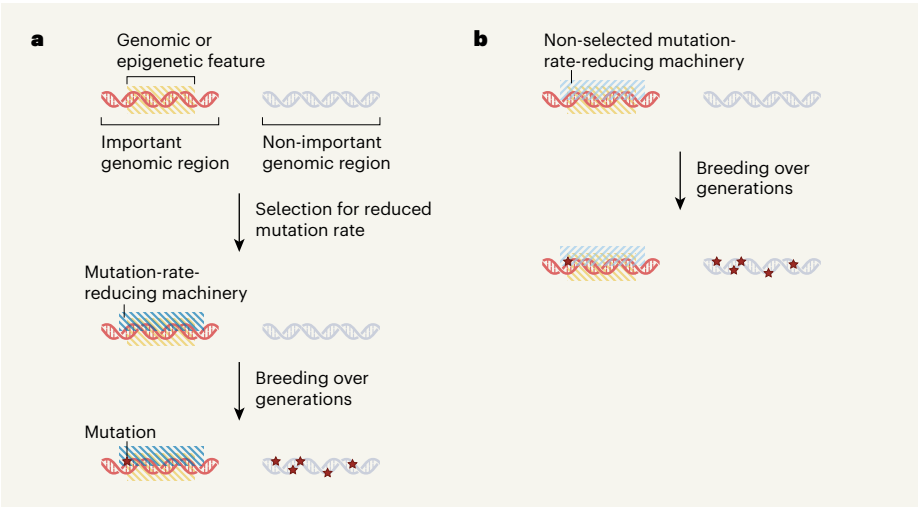

Figure 1 | Routes to lower mutation rates in more-important genomic regions. Monroe *et al.*[2] analysed mutations in the model plant *Arabidopsis thaliana*, and found that genomic regions important for plant viability and reproduction mutate less often (show reduced mutagenesis) than do other regions. This variation in mutation rate could originate in one of two ways. **a**, If a genomic feature or an epigenetic feature (a modification that affects gene activity without changing the DNA sequence) is present at important genomic regions, but not at non-important regions, natural selection could drive the emergence of a mutation-rate-reducing machinery that is associated with the feature. This would reduce the number of mutations that occur in the important regions over multiple generations. **b**, Alternatively, the association between the feature and reduction in mutation rate could be intrinsic or a by-product of some other biological processes, without selection.

in two ways. First, because epigenetic modifications regulate gene expression, epigenetic features probably differ between genomic regions within and outside genes, and also between genes that show drastically different expression levels or regulation (for example, those that are continuously expressed and those that are expressed only in certain tissues or in response to certain environmental factors). The relationship between the expression or regulation of a genomic region and the functional importance of the region might thus create a correlation between the epigenetic feature of a region and the probability that a mutation in the region would be deleterious. Consequently, selection might lead to the evolution of machinery that lowers mutagenesis in regions that exhibit an epigenetic feature that correlates with high probability of a mutation being deleterious (Fig. 1a).

Second, the association between a genomic or epigenetic feature and mutation rate might not be a result of selection for lower mutagenesis. Instead, it might be intrinsic to the feature (owing to its chemical nature) or a by-product of some other biological processes[11] (Fig. 1b). Intriguingly, although selection for lower mutagenesis should be orders of magnitude weaker in the non-selfing forest tree *Populus trichocarpa* than in the selfing *A. thaliana*[9,10], Monroe and colleagues present evidence suggesting similar mutation-rate profiles between the two species. This finding supports this second approach to explaining the origin of suppressed mutagenesis in important genomic regions.

It is worth emphasizing that, in both scenarios, the enrichment of certain genomic or epigenetic features at important regions occurs not because these regions have a high probability of deleterious mutations, but because of some correlates of that probability, such as gene expression or regulation. Hence, some variations in mutation rate across the genome might merely reflect these correlates. For example, Monroe *et al.* find that the outermost coding parts of a gene mutate more than other coding parts do. Moreover, genes that lack untranslated regions in their messenger RNAs have higher coding mutation rates than do other genes. And genes with few non-coding segments (introns) have higher coding mutation rates than do genes with more introns. Whether these mutational patterns are beneficial to the plant is unclear.

Even when mutagenesis-reducing machinery recognizes a particular genomic or epigenetic feature, selection for lower mutagenesis cannot drive the acquisition of the feature at an important genomic region. This is because the feature's beneficial effect on mutation rate in that one region is too small to overcome the effect of genetic drift[6,8].

Monroe *et al.* propose that, because *A. thaliana*'s mutation-rate profile reduces the overall chance that a new mutation is deleterious, the profile increases the chance that a mutation is beneficial. This statement, however, need not be true, because lowering mutagenesis in crucial genomic regions could reduce the proportion of mutations that are deleterious as well as the proportion of those that are beneficial – provided that these types are concentrated, and neutral mutations under-represented, in important regions.

Mutation and selection are generally considered to be distinct evolutionary forces. But if mutation rate is shaped by selection to different extents in genomic regions of different importance, as Monroe *et al.* suggest, this distinction would be blurred, and many evolutionary phenomena would require reinterpretation. Most notably, differences between genomic regions in DNA-sequence variation within a species (known as polymorphism) and between species have been commonly explained by a variation in selection – but they might also be caused by a variation in mutation rate. Indeed, the authors observe a striking similarity between mutation-rate variation and polymorphism variation among genomic regions in *A. thaliana*, suggesting that the latter is largely attributable to the former.

Although I am not ready to throw out the fundamental tenet of Luria and Delbrück, the intriguing mutation-rate pattern of *A. thaliana* makes me wonder whether the same pattern exists in many other species – and, if so, what the underlying mechanism is, and how it originated in evolution.

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The author declares no competing interests.
This article was published online on 12 January 2022.

Particle physics

Single magnetic charges in the largest of fields

Sonia Kabana

Collisions between lead ions have produced the largest measured magnetic field in the Universe, enabling a search for elusive exotic particles that carry an isolated magnetic charge. **See p.63**

Break a magnet into smaller pieces, and each part will have its own north and south pole. But in the subatomic realm, an exotic particle called a magnetic monopole can possess an isolated magnetic charge – existing as only a north pole or a south pole. On page 63, Acharya *et al.*[1] report the results of a search for these extraordinary particles using a very strong magnetic field.

The implications of the existence of magnetic monopoles are far reaching. For example, theories that attempt to unify the various forces in the Universe predict the existence of these particles, and such predictions motivated development of the most popular cosmological model, which holds that the early Universe underwent a period of inflation during which the volume of space expanded exponentially. Many investigations have looked for evidence of magnetic monopoles – by searching in the cosmos, and by attempting to produce and detect them in high-energy particle collisions.

The Scottish mathematician James Clerk Maxwell offered the first hint of a possible unification of forces, by incorporating the electric and magnetic forces into a set of beautiful equations. These equations allow the existence of isolated electric charges in the Universe, but prohibit isolated magnetic charges. The discovery of an isolated magnetic charge would therefore motivate an update that provides symmetry to Maxwell's equations.

The idea of isolated magnetic charges was first mentioned formally in 1894 by French physicist Pierre Curie[2], and the English physicist Paul Dirac was the first to come up with a theory for a point-like particle (meaning a particle lacking a substructure) that could possess an isolated magnetic charge[3]. Remarkably, he