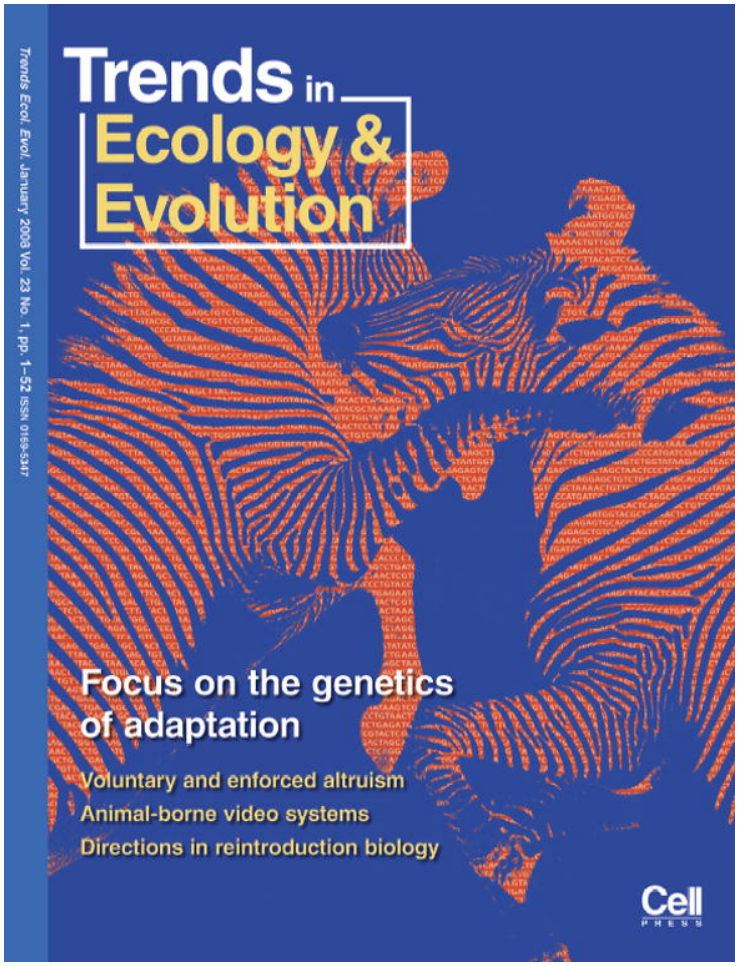

Review

Adaptation from standing genetic variation

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Populations adapt to novel environments in two distinct ways: selection on pre-existing genetic variation and selection on new mutations. These alternative sources of beneficial alleles can result in different evolutionary dynamics and distinct genetic outcomes. Compared with new mutations, adaptation from standing genetic variation is likely to lead to faster evolution, the fixation of more alleles of small effect and the spread of more recessive alleles. There is potential to distinguish between adaptation from standing variation and that from new mutations by differences in the genomic signature of selection. Here we review these approaches and possible examples of adaptation from standing variation in natural populations. Understanding how the source of genetic variation affects adaptation will be integral for predicting how populations will respond to changing environments.

Introduction

When a population colonizes a new environment or experiences a novel selective pressure, does it adapt mainly from standing genetic variation (see Glossary) or does it wait for new mutations? There are good reasons to ask this question. First, adaptation is likely to be faster from standing variation than from new mutation, not only because beneficial alleles are immediately available, but also because they usually start at higher frequencies [1]. As humans alter the biosphere, forcing many species to confront dramatically altered environments, it is becoming increasingly important to understand how rapidly populations can adapt [2–4].

Another reason is that a beneficial allele present as standing variation is older than a new mutation, and might have been pre-tested by selection in past environments, in another part of the species' range, or even in another species with which the population has exchanged genes [5]. Such alleles might have multiple advantageous genetic changes [6,7]. In contrast to new mutations, such standing variation has already passed through a 'selective filter', which increases the chance that large-effect alleles are advantageous, and the probability of parallel evolution [8].

A third reason is that the molecular signature of selection, which is often the only evidence available that a gene has recently fixed under directional selection, is not the same when a population adapts from standing variation instead of from new mutations [9]. Finally, understanding the source of variation for adaptation might tell us a great deal about the factors maintaining genetic variation in natural populations, still one of the most debated topics in evolution [10–13].

Of course, we already have part of the answer. A century of quantitative genetics has established the ubiquity of standing variation in natural populations, which successfully predicts the short-term response to selection [14,15]. At the other extreme, macroevolution would surely not be possible without a steady supply of new mutations over the long term. Yet these facts do not completely establish the relative roles of standing variation and new mutation during adaptation to an altered environment. The surest way to determine the source of beneficial alleles is to locate the genes themselves and establish their histories. Here we review the consequences of adaptation from standing genetic variation, contrast it with adaptation from new mutations, and identify ways in which it is possible to tell the difference.

Glossary

Directional selection: selection that favors the fixation of one particular allele in a population. In the absence of other factors, the frequency of this allele will increase at a rate proportional to the strength of directional selection.
Epistasis: an interaction in which an allele at one locus affects the phenotypic effect of an allele at another locus.
Fixation: a condition in which an allele attains a frequency of 100% in the population.
Frequency spectrum: the distribution of allele frequencies over many loci, specified by the proportion of alleles in different frequency ranges in a population.
Genetic drift: changes in gene frequency resulting from random sampling of offspring from the parental generation. Random sampling effects are more pronounced in smaller populations.
Hitchhiking: the process by which a neutral allele increases in frequency because it is linked to a beneficial allele under directional selection
Linkage disequilibrium: the amount by which haplotype frequencies in a population deviate from the frequencies they would have had if the genes at each locus were combined at random.
Mutation–selection balance: the equilibrium between the rate at which an allele arises by recurrent mutation and its elimination by natural selection.
Population structure: a departure from random mating as a consequence of factors such as geographical subdivision and overlapping generations. Population structure can distort the expected signature of selection.
Quantitative trait locus (QTL): a site in the genome containing one or more genes that underlie variation in a quantitative trait.
Selective sweep: the reduction or elimination of variation at sites that are physically linked to a site under directional selection.
Standing genetic variation: the presence of more than one allele at a locus in a population.

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How the source of beneficial alleles affects the genetics of adaptation

The process of adaptation from standing genetic variation is expected to differ in several ways from adaptation based on new mutations. We summarize several of these differences here. Our summary is not exhaustive, but then neither is the literature. Despite overwhelming observational and experimental evidence for the role of natural selection in phenotypic evolution, theoretical investigation of the selective effects of alleles contributing to adaptation is relatively new (reviewed in [16,17]). Most of the current theory on the genetics of adaptation assumes that adaptation occurs exclusively from new mutations rather than from standing variation. The theory for standing variation that we summarize below assumes that newly beneficial alleles are neutral or deleterious prior to the change of environment and are maintained in the ancestral population through a balance of recurrent mutation, selection and drift [9,18,19].

Probability of fixation

All else being equal, the chance that an advantageous allele becomes fixed in a population, rather than lost by genetic drift, is greater if it is present in multiple copies (standing variation) than if it appears as a single new mutation (Figure 1). The probability of fixation increases with the magnitude of the beneficial effect (s_b) and with increasing effective population size (N_e) in both scenarios; however, over a large range of selective effects, the probability of fixation is high for standing variation when it is negligible for a new mutation [18]. This increase in fixation probability from standing variation is especially great for small effect mutations, suggesting that small effect alleles should contribute more to adaptation from standing variation than from new mutation. The exact form of the curve in Figure 1 assumes that standing variation was previously neutral, but a greater probability of fixation from standing variation should be general.

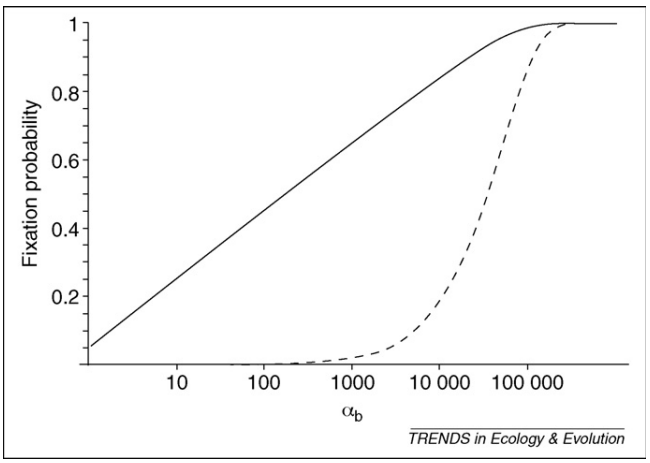

Figure 1. The probability of fixation of a single new mutation (dashed curve) compared with that of a polymorphic allele that arose in a single mutational event (solid curve). $\alpha_b = 2N_e s_b$, where N_e is the effective population size and s_b is the homozygous fitness advantage. The form of the curve for standing variation in this example assumes that $N = N_e = 25\,000$, the dominance coefficient (h) = 0.5 and that beneficial alleles were previously neutral. α_b is plotted on a logarithmic scale. Modified with permission from Ref. [18].

Speed of adaptation

Standing variation also leads to more rapid evolution in novel environments because it is available immediately at the time that selective conditions change, whereas waiting time is needed for a new beneficial mutation to arise. Furthermore, the initially higher frequency of beneficial alleles present as standing variation reduces the average fixation time [18]. Simulations of the process of fixation from standing variation nevertheless suggest that in the time it takes for an allele to fix from standing variation the allele will also arise by mutation, assuming that the mutation rate stays high before and after the environmental change [18]. Even in this case, most copies of the fixed allele are supplied from standing variation [18]. Consequently, alleles from standing variation should dominate in most cases when adaptation occurs over short timescales.

Dominance

There is a strong fixation bias against recessive mutations when adaptation occurs from new mutations because they experience weak selection when rare, a process known as Haldane's sieve [20–22]. However, the effect vanishes when adaptation occurs from standing variation [18,19]. This happens because, although a particular copy of a more dominant advantageous allele will carry a greater chance of fixation, on average there will have been fewer copies present at mutation–selection balance before the environment changed. Assuming that there is a correlation between the size of the deleterious effect before the environmental change and the size of the beneficial effect after the change, these tendencies roughly cancel each other out and, consequently, dominance has little effect on the probability of fixation for advantageous standing variation.

Mechanisms preserving standing variation

The previous section demonstrated that standing variation has a considerable advantage in the speed and probability of fixation. This advantage comes from an assumption that recurrent mutation and drift can maintain these neutral or deleterious alleles at a frequency higher than $1/2N$ in the ancestral environment. However, there are other factors that could also increase the frequency of alleles present as standing variation above the values predicted from these models. Gene flow from populations experiencing different environmental conditions, or even hybridization with other species, could preserve relatively high amounts of standing variation despite negative selection. Alternatively, alleles that are deleterious under specific environmental or genetic conditions might be hidden from selection because they do not have any effects on phenotype in the ancestral environment. This 'cryptic genetic variation' might await an environmental change or introduction of novel alleles before it manifests as a new phenotype [23].

A recent study of oldfield mice by Steiner *et al.* [24] shows how the genetic background in which alleles are present can mask the effects of ancestral standing variation. In the southeastern USA, *Peromyscus polionotus* has a dark coat, which matches the dark soils of mainland Florida. However, these mice have colonized barrier islands and coastal dunes of Florida's Gulf Coast. These

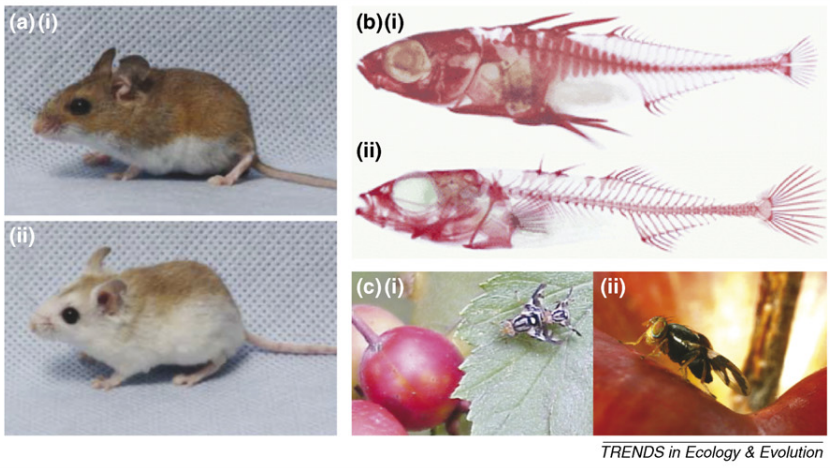

Figure 2. Candidates for adaptation from standing variation. **(a)** *Peromycus polionotus* subspecies. The mouse in (i) is a typical mainland mouse (*P.p. subgriseue*) and the mouse in (ii) is a typical Santa Rosa Island beach mouse (*P.p. leucocephalus*). Two candidate genes, the *melanocortin-1 receptor* (*Mc1r*) and its antagonist, the *Agouti signaling protein* (*Agouti*), control most of the difference in pigmentation between subspecies. **(b)** Threespine stickleback *Gasterosteus aculeatus*, cleared and stained with alazarin red to highlight bone structure. The fish in (i) has many bony lateral plates, a phenotype typically found in the ocean. The fish in (ii) has many fewer plates and is typically found in freshwater lakes. **(c)** Apple maggot fly *Rhagoletis pomonella*. The flies in (i) are from a host race specialized to feed on hawthorn. The fly in (ii) is from a host race specialized to feed on apple. Standing variation originating in Mexico is implicated in the evolution of overwintering pupal diapause in the apple race. Reproduced with permission from (a) H.E. Hoekstra and (c) J.L. Feder.

beach mice have a much lighter coat than their mainland conspecifics, presumably a result of selection for camouflage on pale sand dunes (Figure 2). The barrier islands are young, <6000 years old, and it is therefore likely that the ancestral population is the older mainland subspecies. Two candidate genes, the *melanocortin-1 receptor* (*Mc1r*) and its antagonist, the *Agouti signaling protein* (*Agouti*), map to independent regions of the genome and together control most of the difference in pigmentation between beach and mainland subspecies [24,25]. Derived alleles (i.e. alleles found in the beach mice) at both loci reduce the level of pigmentation. Moreover, there is a strong epistatic interaction between these two loci: mice homozygous for the dark pigment *Agouti* allele have fully pigmented hairs regardless of their *Mc1r* genotype. This suggests that the *Mc1r* allele producing light pigmentation, presumably deleterious on the darker mainland soil, could be maintained as standing variation in mainland populations, hidden by its epistatic interaction with *Agouti*. As the mice colonized the beach environment, the light pigment *Agouti* allele would be driven to higher frequency by positive selection. In turn, the light pigment *Mc1r* allele would also suddenly become visible to selection. Future population sampling will determine whether the light pigment *Mc1r* allele is present in the ancestral mainland environment (H.E. Hoekstra, personal communication).

Distinguishing standing variation from new mutations in adaptation

How does one determine whether evolution has used standing variation rather than new mutations? Here, we discuss three approaches that have been used with some success. The first is based on the 'signature of selection', which uses polymorphism data in the genome region linked to a fixed allele to identify a 'selective sweep'. The second involves a demonstration that a fixed allele in a new environment still occurs as standing variation in the ancestral population. The third approach uses a phylogenetic study of the DNA sequences of alternative alleles to determine their origins and their age. None of the approaches is infallible, and we identify possible difficulties with each.

The signature of selection on standing variation

Ever since J.B.S. Haldane's early efforts to determine mutation rates for hemophilia during the 1930s, mathematical models have been used to infer past evolutionary patterns from extant population data [26]. With the widespread availability of molecular polymorphism data, attention is now focused on identifying patterns in the genome that indicate a recent history of positive selection. The key idea is that the substitution of a beneficial allele at a site in the genome results in 'hitchhiking' by neutral alleles at nearby sites physically linked with the selected allele [27,28]. The beneficial allele will occur with only a subset of neutral variants at linked sites, creating a nonrandom association or 'linkage disequilibrium' between them. Unless recombination breaks down the association between the selected and neutral sites during the substitution process, a small subset of neutral variants will be fixed along with the selected allele. Thus, the fixation of a beneficial allele will produce a selective sweep that leaves a valley of low polymorphism as a signature in its vicinity in the genome. Although recombination can obscure this signature, potential targets of positive selection can be identified from polymorphism data for recent adaptive fixation events. This approach has been used extensively in *Drosophila* and humans, both of which experienced novel selection pressures after their recent expansion out of Africa (e.g. [29–37]). In addition, selective sweeps have been detected in genes associated with resistance to pest control, such as chloroquine resistance in malarial parasites and warfarin resistance in rats [38,39], and in several genes associated with cultivation of crop plants [40–46].

Fixed beneficial alleles that originate as standing variation will leave a different signature following a

selective sweep than that expected from a new mutation. Compared with new mutations, neutral or weakly deleterious alleles maintained as standing variation have a longer history in the population before becoming advantageous. One effect of this extra time is that it provides greater opportunity for recombination to break up the association between the soon-to-be-favored site and neutral variants at all but the nearest sites [9]. The result is that, on average, the valley of low polymorphism that accompanies fixation of a beneficial allele will be narrower compared with that in a standard sweep (Figure 3).

Another effect of the greater age of standing variation compared with new mutation is the increased chance that the same beneficial allele will originate more than once on different genetic backgrounds before becoming advantageous [18,47,48]. The result is that a sweep from standing variation will drag along more polymorphism at linked sites than will a sweep from a single new mutation, which must arise on a single background. The valley of low polymorphism characterizing a sweep from standing variation will be shallower on average compared with that of a standard sweep (Figure 3). Similarly, the strength of statistical associations between the selected site and nearby sites will be reduced [9,18]. Selective sweeps from standing variation will therefore be weaker on average than sweeps associated with new mutations. However, if there is a high mutation rate then repeated, independent origins of the advantageous allele can occur from new mutations arising after the environmental change, producing a similar weak sweep signal [47,48]. On the other hand, such a high mutation rate should also produce high levels of standing variation before the environmental change.

A possible example of a selective sweep from standing variation comes from a recent study on the *SCR* self-incompatibility locus in *Arabidopsis thaliana* [49]. Positive selection has driven the rapid fixation of an allele that inactivates self-incompatibility at *SCR*, which encodes a cysteine-rich protein found in the pollen coat. Simulations of different historical scenarios suggest that this event occurred during the post-Pleistocene expansion of *A. thaliana* from a glacial refuge, when a scarcity of pollinators might have provided an advantage to self-pollination, despite inbreeding depression. Patterns of linkage disequilibrium around *SCR* indicate that a considerable amount of recombination occurred after the origin of the allele but before its rapid fixation, resulting in differences in the evolutionary histories among sites in this region. As expected if the allele was present as standing variation, the selective sweep left a narrow signal in the region of DNA surrounding *SCR*.

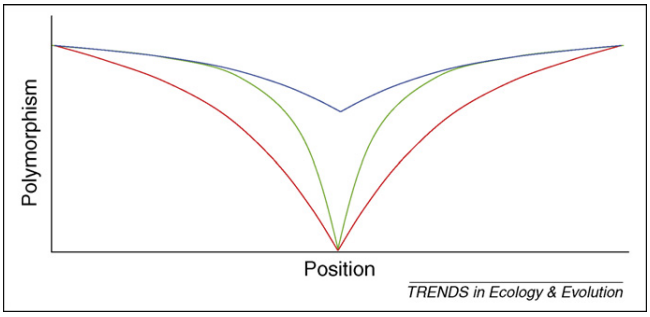

Figure 3. A schematic of differences between standing variation and new mutation in the expected signature of selection around a recently fixed beneficial allele (site at center of figure). Fixation of a new mutation eliminates polymorphism near the site (red lines) because the advantageous allele is linked from its time of origin to a single set of neutral variants nearby. Fixation of an allele present as standing variation can result in a narrower region of reduced polymorphism than in the case of a new mutation because its greater age has exposed it to more recombination events with nearby neutral sites before the selective period (green lines). Standing variation might also include multiple alleles that have arisen independently on different genetic backgrounds, in which case polymorphism will not be reduced as much in the selected region (blue lines).

Another potential example is the *Accord* insertion associated with DDT resistance in non-African populations of *D. melanogaster*. Schlenke and Begun [50] and Catania *et al.* [51] found evidence that *Accord* had recently undergone a selective sweep. Although the sweep did cause a detectable reduction in polymorphism around *Accord*, the width of the region of low polymorphism was reduced relative to expectations for a region under strong selection and of recent origin, as might be predicted if the insertion had been present as standing variation before application of DDT to the area.

A shallower and narrower selective sweep is not the only way to distinguish between adaptation from standing variation and that from new mutations. A perhaps more striking difference can be found in the allele frequency spectra at neutral sites linked to the selected allele. When linked sites are found to be polymorphic following a sweep from a new mutation, they usually harbor an excess of low- and high-frequency alleles [32]. This is because most recombination will occur once the mutation has reached high frequency [50,52–54]. Thus, recombination will usually incorporate only a few additional genetic backgrounds, each at low frequency, other than the one that first carried the beneficial allele (Figure 4). By contrast, recombination will put the advantageous allele on other genetic backgrounds before it becomes advantageous when a sweep originates as standing variation [1,9]. Thus, a distinguishing feature of sweeps from standing variation is an increase in the occurrence of linked neutral sites that have alleles at intermediate frequency (Figure 4). A potential example is the *Duffy* locus in humans, at which a null allele confers resistance to vivax malaria. This null allele is fixed in several populations exposed to malaria but is absent elsewhere. Despite evidence of a selective sweep, Hamblin and Di Rienzo [33] did not find that diversity levels were consistently reduced, and linked sites carried more intermediate frequency alleles than would be expected after fixation of a new beneficial allele.

Although the analysis of selective sweeps is a promising tool for detecting selection and distinguishing the origin of beneficial alleles, the approach is fraught with problems when demographic assumptions are violated [55–58], as is often the case for natural populations. Most methods assume that populations are randomly mating and have a constant size [28,32,52–54,58,59]. Departures from these conditions can make it difficult to determine the cause of sweep patterns (but see Ref. [60]). Some demographic events, such as population expansion, can lead to the same signal (e.g. an excess of rare alleles at linked neutral sites), as would positive selection on a new mutation. Other events, such as population subdivision, can distort the signal of a sweep from a new mutation and therefore could

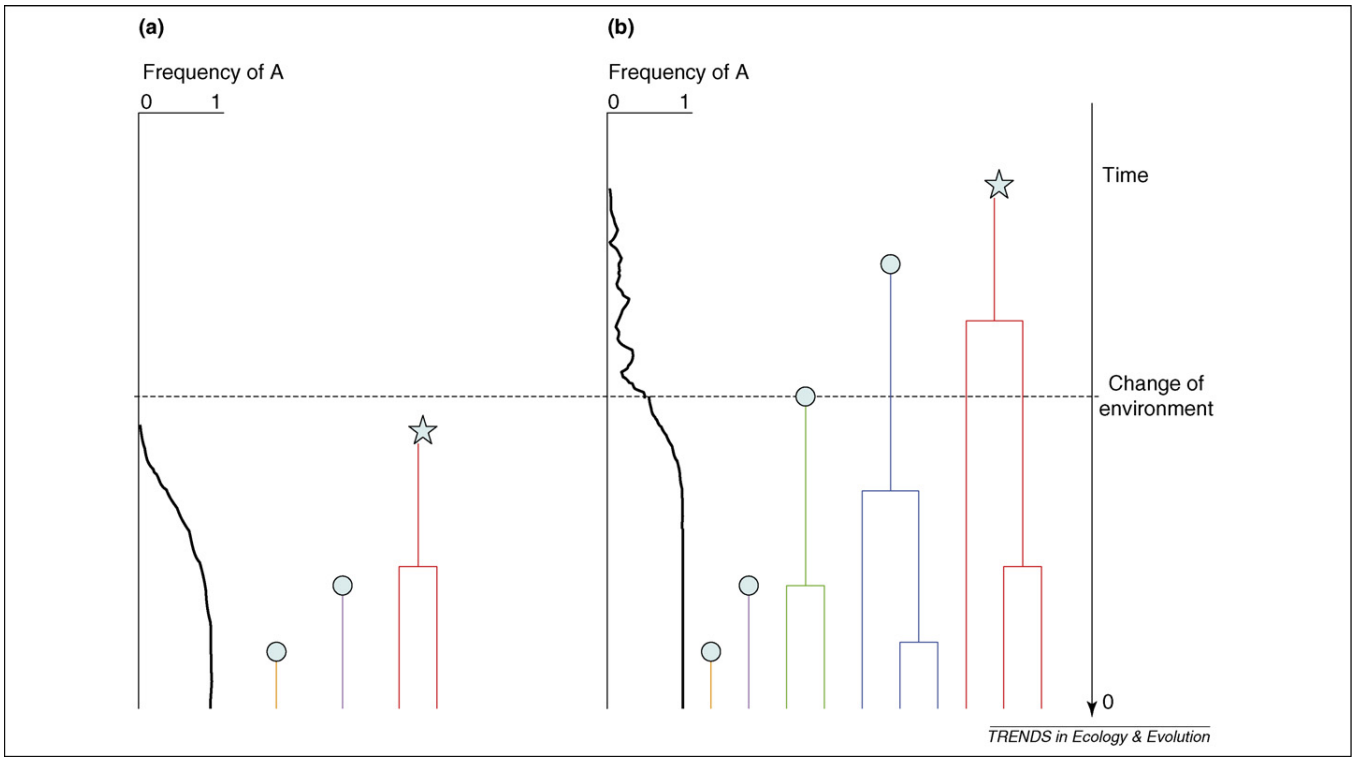

Figure 4. Genealogical trees of a segment of neutral DNA sequence linked to a beneficial allele that has fixed from **(a)** a new mutation and **(b)** standing variation. The star in each panel designates the time of unique origin of the favored allele, A. The subsequent frequency of the allele through time is illustrated on the left of each panel (thick black lines). As A increases in frequency, neutral mutations arise in the segment, leading to diversification of lineages (red lineages). Also, recombination events (indicated by filled circles) might link additional, independent neutral lineages with the favored allele (other colors). At fixation, these new lineages will be present at low frequency in the new mutation scenario, but might be at intermediate frequency in the standing variation scenario because they had more time to become associated with A when it was still relatively rare.

be confused with a sweep following selection on standing variation (e.g. both situations will result in more intermediate frequency alleles at linked neutral sites). As such, it will often be necessary to use additional complementary methods to determine whether standing variation has contributed to adaptation.

Finding the source of standing variation

Selection from standing variation can sometimes be inferred if a beneficial allele in a new environment is still present as standing variation in the ancestral population. For example, recent work on human populations has identified derived alleles that are associated with the ability to digest lactose, the main carbohydrate present in milk [61,62]. In most humans, this ability declines rapidly after weaning. However, in populations that have practiced cattle domestication, many individuals maintain the ability as adults [63]. An allele associated with adult lactose digestion has reached high frequency in European human populations over the past 8000–9000 years, which coincides with the spread of cattle domestication from the Middle East into Europe [64]. This allele is also present in Middle Eastern populations, suggesting that standing variation from these populations probably supplied the beneficial allele along with pastoralism into Europe [65]. However, this is not the whole story, because three separate alleles responsible for lactose digestion in adults arose recently in Sub-Saharan Africa and are not found elsewhere, an indication that these alleles probably arose *de novo* [61,65]. Thus, it is likely that new mutations and standing variation have both contributed to adaptation to pastoralism in different human populations.

A recent study by Pelz *et al.* [66] provides another example in which adaptive alleles have been found segregating in the ancestral environment. The brown rat *Rattus norvegicus* has evolved resistance to warfarin in just a few decades since the pesticide was introduced. Several different allelic variants of the gene *VKORC1* confer resistance to warfarin, and these variants are present in natural populations of brown rats throughout Europe [66].

One of the challenges of detecting adaptation from standing variation by looking for the presence of adaptive alleles in ancestral populations is determining which population is ancestral. In the case of alleles associated with adult lactose digestion in human populations, it was possible to use archeological and linguistic evidence to infer which populations practiced cattle domestication first, and it seems likely that these populations will also be the source of the lactose digestion allele. In other cases, geological data might be the most reliable way to determine which environment is ancestral. For instance, locations that were covered by glaciers during the last Ice Age are assumed to be new populations, whose ancestral populations resided in unglaciated areas. Another challenge is ruling out the possibility that a beneficial allele was secondarily introduced to the ancestral population by gene flow rather than having originated there. Therefore, additional evidence will be needed to confirm selection from standing variation. This problem could be resolved if several populations all independently derived

from the same ancestral population are fixed for the same adaptive allele, and if gene flow is not possible directly between derived populations. Although this allele might have arisen *de novo* in one of the populations, it is unlikely to have arisen *de novo* in all of them.

Determining the history of derived alleles

The phylogenetic history of alleles can also provide evidence of adaptation from standing variation or new mutation. If a beneficial allele that has fixed in a new environment pre-dates the origin or colonization of that environment, then we can be sure that it did not arise *de novo* under the current selective conditions. For example, Colosimo *et al.* [67] sequenced the alleles at the gene most responsible for the evolution of reduced defensive armor (bony lateral plates) in threespine stickleback *Gasterosteus aculeatus* populations that colonized freshwater from the sea at the end of the last Ice Age. The ancestral marine population has a complete set of 32–36 bony lateral plates, whereas freshwater populations have only 0–9 plates (Figure 2). The same gene, *Ectodysplasin* (*Eda*), was found to be responsible for armor reduction in all freshwater populations sampled. Phylogenetic analysis of the allele sequences in the freshwater and ancestral marine populations revealed that the allele that is beneficial in freshwater originated >2 million years ago. Given that the postglacial lakes inhabited by low-armor freshwater populations have existed for only ~10,000 years, the finding implies that evolution of the low-armor phenotype has occurred by recurrent local selection on an ancient allele brought repeatedly into freshwater environments by marine founders. The allele is indeed present at low frequency in marine populations today [67].

The two host races of the apple maggot fly, *Rhagoletis pomonella*, also provide an example in which ancient genetic changes might have led to much more recent adaptation under novel environmental conditions (Figure 2). Several inversion polymorphisms have been found to be strongly associated with the length of overwintering pupal diapause in *R. pomonella* [68]. This variation is significant because it differentially adapts apple and hawthorn races to the fruiting times of their hosts [69]. Although the North American apple race is only 150 years old, phylogenetic analysis shows that the inversions arose at least 1.5 million years ago in Mexico [68,70] and have recently been introduced to North America by gene flow [70]. The variation in diapause timing caused by these ancient inversions then contributed to the formation of an apple race adapted to the earlier fruiting time of introduced, cultivated apple orchards. Thus, life-history adaptation was due to introgression of standing variation that predated the latest environment where it was beneficial.

Conclusions

Here we have highlighted the evolutionary patterns and consequences that occur when a population makes use of standing genetic variation rather than new mutations when adapting to a new environment. We have little information about the relative importance of these two sources of beneficial alleles after a change of environment. Nevertheless, a few case studies of ecologically relevant genes suggest that standing variation has an important role in facilitating rapid adaptation to novel environments [24,61,66–68]. The dynamics and outcome of adaptation are distinct depending on the source of variation. Understanding these differences will be integral to predicting how populations will respond to changing environments. Rapid evolution will be necessary for the survival of many species as humans increasingly cause sudden and drastic environmental changes to the biosphere [2], and this will probably be fuelled largely from standing variation.

Many questions remain about the dynamics, circumstances and consequences of adaptation from standing variation. Because most of the theory on the genetics of adaptation has focused on adaptation from new mutations, there are still gaps in our knowledge concerning the theoretical predictions when adaptation instead occurs from standing variation. Only during the past few years have alternatives to the classic theory for selective sweeps been developed for adaptation from standing variation [9,18]. For example, theory for the distribution of fitness effect sizes produced during adaptation from new mutations is relatively well developed, but how does this change when adapting from standing variation? We have given some reasons why this distribution of fitness effect sizes might be different from standing variation, such as the greater fixation probability of small effect alleles, but a quantitative theory for standing variation is still needed. As we accumulate further examples of adaptive alleles in natural populations, it will become possible to undertake broad comparative analyses to discover the importance of standing variation across a diverse range of taxa and conditions. By considering the unique patterns and consequences of selection on standing variation, we will gain a more general understanding of how populations adapt to novel or changing environments.

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