Genetics of Climate Change Adaptation

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Abstract

The rapid rate of current global climate change is having strong effects on many species and, at least in some cases, is driving evolution, particularly when changes in conditions alter patterns of selection. Climate change thus provides an opportunity for the study of the genetic basis of adaptation. Such studies include a variety of observational and experimental approaches, such as sampling across clines, artificial evolution experiments, and resurrection studies. These approaches can be combined with a number of techniques in genetics and genomics, including association and mapping analyses, genome scans, and transcription profiling. Recent research has revealed a number of candidate genes potentially involved in climate change adaptation and has also illustrated that genetic regulatory networks and epigenetic effects may be particularly relevant for evolution driven by climate change. Although genetic and genomic data are rapidly accumulating, we still have much to learn about the genetic architecture of climate change adaptation.

Climate change: changes in global climatic conditions, e.g., temperature, precipitation, and frequency of extreme events such as storms and droughts

Adaptive evolution: evolution via natural selection in which individuals with phenotypes of higher fitness pass on more genes to the next generation

Diapause: period of suspended development triggered by environmental cues that occurs in many insects and other animals

Photoperiod: amount of light versus dark during a day, dependent on latitude and time of year, and influential in biological clocks

INTRODUCTION

Global temperatures and patterns of precipitation are rapidly changing (53). Because these environmental conditions have strong effects on most organisms, it is not surprising that climatic changes are influencing the physiology, behavior, abundance, and distribution of many species. In contrast to such ecological effects of climate change, genetic effects of climate change have been less well studied, although there have been calls to change this (29, 82, 135). Recent research results in ecological genetics and advances in quantitative genetics and genomics are providing information on how climate change may have genetic consequences, but there are large gaps in our knowledge of the likelihood and rate of adaptive genetic changes, of the roles of regulatory and epigenetic effects, and of the evolution of plasticity in providing rapid selection responses, and more generally in our understanding of the genetic architecture of adaptive evolution.

Evidence is accumulating that climate change can cause genetically based adaptive evolution in traits such as body size (37), thermal responses (62), dispersal (48, 124), and diapause/reproductive timing (35). We are now starting to uncover the genetic basis of some of these traits, but whether evolution in these traits is controlled by many independently acting genes of small effect or by fewer key regulatory genes within genetic and metabolic networks remains an open question. Evolution can be caused by selection acting on standing genetic variation, but there is also the intriguing possibility that climate change can cause heritable epigenetic changes, potentially serving as an alternative and rapid mode of evolution (125). Although evolution could potentially rescue populations from the effects of climate change, there is not yet evidence that this will commonly occur and thereby circumvent a mass extinction and loss of genetic biodiversity. In fact, a recent meta-analysis predicted major losses in genetic diversity for northern plants owing to climate change (1).

Here, we review how climatic conditions and changes in these conditions can influence genes, how the genetic effects of climate change can be studied, and what the results of such studies might indicate about the genetic basis of evolution. We only briefly cover quantitative genetic and other models as well as evidence collected so far in support of evolutionary responses to climate change, as this information has been recently reviewed (40, 49, 112). These models are being applied to understand evolutionary processes and highlight the evolutionary responses needed to ensure persistence of populations and species under climate change, as in the case of spawning salmon (107) and pine/birch trees (67). Monitoring of adaptive genetic responses to environmental change (44) and approaches to study the genetic basis of adaptive evolution in plant systems have also been recently reviewed (3). Here, we focus on recent attempts to understand the underlying genetic basis of evolutionary responses to climate change. We present a conceptual model of the genetic basis of climate change adaptation, give examples of recent research, outline approaches to studies in this area, describe the usefulness and limitations of these various approaches, and point out areas out where future research is likely to be most fruitful. A goal of this review is to investigate how research on the genetic basis of climate change adaptation advances our understanding of the process of evolution in natural populations.

SELECTION TO EXPLOIT CONDITIONS OR TOLERATE STRESSES

A general framework for depicting how organisms may evolve in response to various changes in climate is given in **Figure 1**. In this framework, changes in climatic conditions, such as temperature, are separated from cues that indicate conditions such as photoperiod. Organisms perceive the changes in conditions either directly or through matching cues to new conditions. For example, when the cue is photoperiod, it remains the same with changing climatic conditions, but the way organisms respond to the cue is different (13). This point

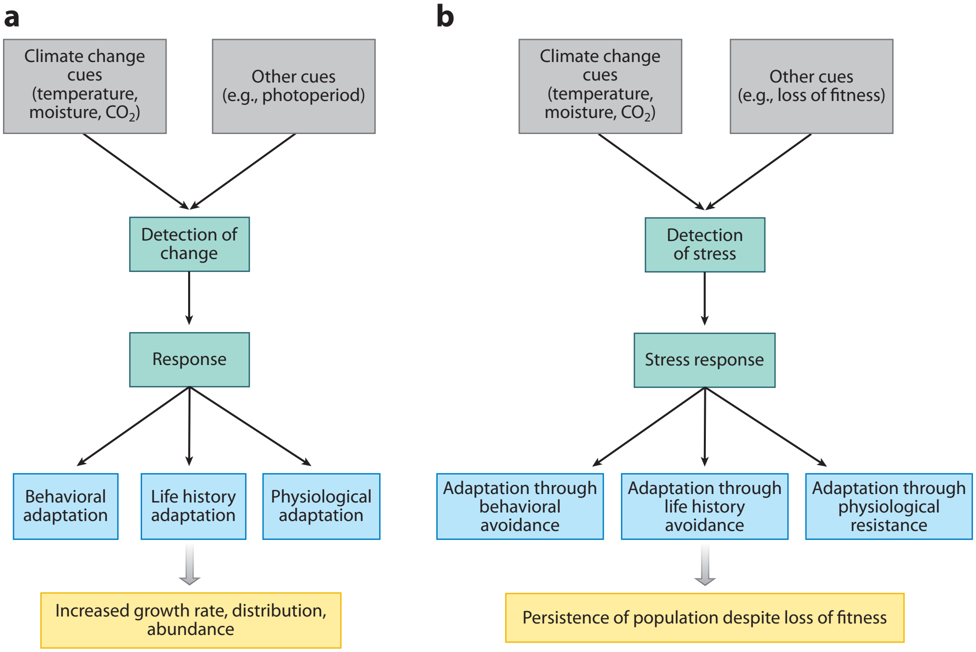

Figure 1

A framework for considering the direct evolutionary responses of organisms to climate change. Populations may be faced with (*a*) opportunities to take advantage of favorable climatic conditions for expanding distributions or (*b*) increasingly stressful conditions in which extinction is possible. Evolutionary changes in these situations may involve altered ways of detecting and responding to environmental conditions, leading to changes in life history traits, physiological resistance levels, and migration.

is illustrated by a recent study showing that in pitcher plant mosquitos, circadian clock genes and photoperiod response genes are linked, but selection can act to break down their genetic correlation and allow the cue and response pathways to evolve independently (12). A recent model has shown that activities stimulated by environmental cues are likely to evolve with climate change, with the outcome highly variable and dependent on the effects of the changes on the cues, responses, and their interactions (83).

The climatic changes detected by organisms act as agents of selection. Organisms evolve in response to climatic changes in one of two general ways: evolving to take advantage of the new conditions by exploiting novel or increased resources (**Figure 1*a***) or evolving to tolerate new conditions to which the population is not currently optimally adapted (**Figure 1*b***). Organisms can evolve to exploit new resources by expanding their range and/or the period across which they are active. Most animal range shifts correlate with climate and show expanding ranges at higher latitudes (123) and into high elevation areas in animals (6, 87) and plants (71). Geographic expansions may lead to selection for increased dispersal to take advantage of favorable conditions (48). Shorter and milder winters in temperate climates can select for earlier flowering in plants and earlier arrival of bird and insect migrants, particularly at temperate and boreal latitudes (97). This effect of increased season length has changed the migration and breeding patterns of many species (28, 85, 97, 130).

On the other hand, populations are also expected to encounter increasingly unfavorable conditions (**Figure 1*b***) associated with temperature extremes, ocean acidification, and extreme events, such as droughts, fires, and

Phenotypic plasticity: the expression of a different phenotype by the same genotype in a different environment

storms, which can influence species distributions (140). Extreme conditions can select for increased resistance to stressful conditions and/or ways of avoiding extremes, such as earlier flowering (35). These effects may be direct, as in the case of increased resistance to drought or heat stress, or indirect, such as when a reduction in food supply is countered by switching to another food source, as in Darwin's finches (42). Increased season length can potentially increase fitness by providing more time for resource acquisition in some species but decrease fitness in others. For example, increased spring temperatures can lead to early snowmelt in alpine areas, expanding the growing season but also subjecting some overwintering plants to lethal frost, with warming counterintuitively selecting for increased cold tolerance (52). Indirect effects can also occur via changes in sex ratio, which can be altered in species such as turtles in response to changes in temperature means as well as temperature variability (89).

Evolutionary changes to exploit or tolerate a resource can occur through behavioral traits such as migration (103), life-history traits such as diapause (13), and physiological traits such as water-use efficiency (33) (**Figure 1**). For instance, in pitcher plant mosquitoes there is an evolved change in response to photoperiod that allows mosquitoes to take advantage of longer favorable breeding conditions (13). As well as responding to altered seasonality, populations may also respond to increases in CO_2 and regional increases in precipitation when adapting to favorable effects of climate change. For example, *Arabidopsis thaliana* plants raised for five generations under CO_2 concentrations of 700 ppm evolved to take advantage of this increased resource and showed higher seed production than control lines (132). An increase in the frequency of extreme climatic events such as droughts could select for either escape or tolerance strategies (33).

These responses reflect the direct effects of climate change, which are the focus of this review. There are several indirect effects beyond the scope of this article that nevertheless may have important influences on genetic responses to climate change. These include altered selection pressures when climate change affects biotic interactions, triggering adaptive changes in competitive ability or parasite/predator resistance, and adaptive changes in host shifts, allowing organisms to evade biotic stresses (98). Climate change can also indirectly influence evolution by altering patterns of hybridization as a consequence of shifts in species distributions, with important genetic consequences (38).

EVOLUTIONARY MECHANISMS

Perhaps the simplest way that climate change can influence the genetic constitution of populations is shown in **Figure 2*a***. Suppose that there is a particular allele (α) at a locus influencing a trait such as thermal tolerance. Suppose also that individuals carrying this allele have an increased tolerance, improving their fitness (ability to survive and reproduce) at high temperatures. Any increase in thermal extremes over time should then favor allele α. To understand and predict the increase in allele frequency under this simple model, the alleles favored under climate change need to be identified, along with their effects on fitness in different climatic conditions. Organisms may also respond to climate change through phenotypic plasticity rather than evolution (31). However, in this case there would not be a genetic change in the population because plasticity involves the same genotypes expressing different phenotypes in different environments (114), in contrast to evolution, which involves changes in allele frequencies. It is also possible that climatic changes, particularly increases in the variances of climatic conditions, could influence the evolution of phenotypic plasticity. If variation in the degree of plasticity (rather than variation of the trait itself) is genetically based, alleles leading to increased plasticity could be favored with increased climatic variation if this allowed organisms to better match their more variable environment (78).

When climate change causes evolution through shifts in allele frequencies, allelic changes do not act in isolation but need to be

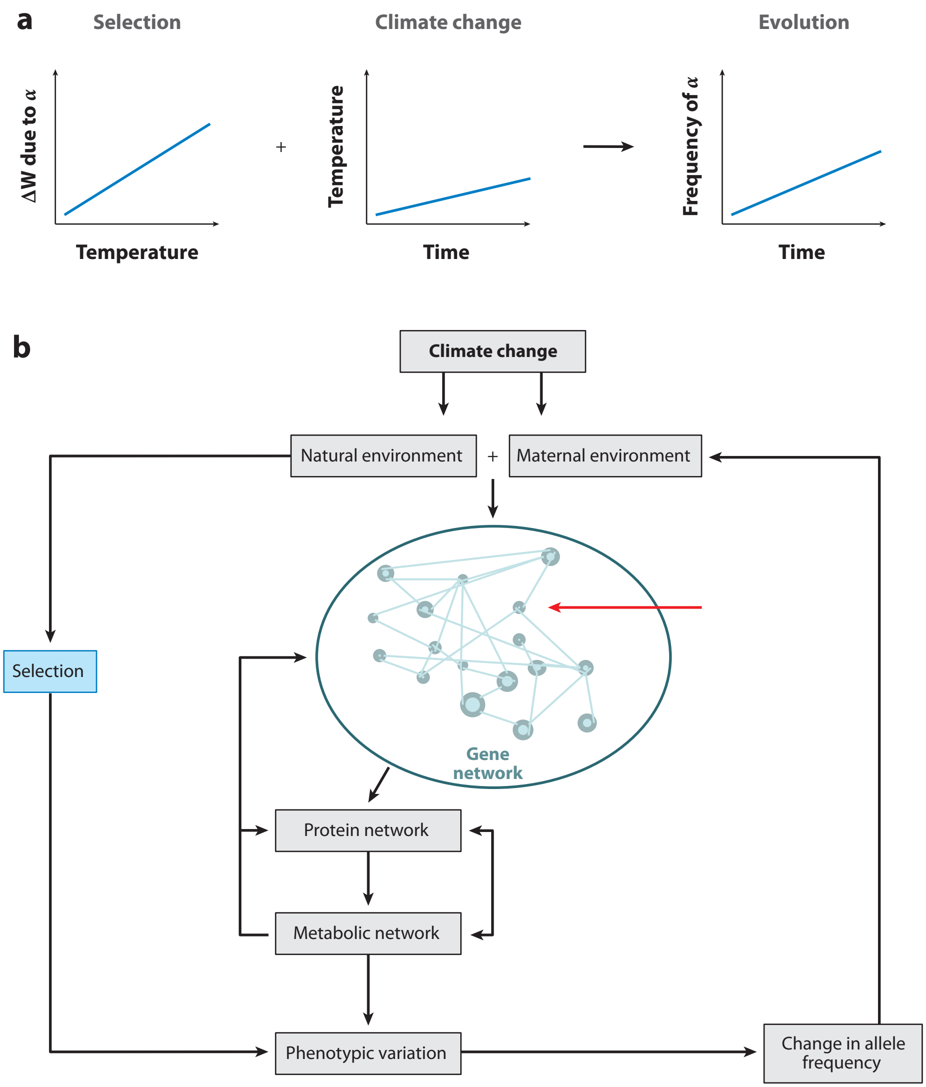

Figure 2

Genetic effects of climate change adaptation. (*a*) With evolution, the change in climate results in changes in allele frequencies. This can occur via natural selection: Suppose that the fitness of individuals carrying an allele α increases with some climatic factor such as temperature. This means that selection on α increases with increased temperature. Suppose that temperature increases with time. This climatic change should then lead to an increase in the frequency of the α allele, resulting in an evolutionary change via natural selection. (*b*) Allelic changes are embedded within networks. Allelic changes do not occur independently of other changes; combinations of alleles within gene networks may be required to produce adaptive phenotypes (90). These networks are affected by environmental and maternal inputs, and in turn influence protein and metabolic networks, although there are feedback loops and multiple points of environmental inputs. Selection acting on phenotypes therefore often influences allele frequencies at a specific gene (*red arrow*) only indirectly.

Maternal effect: the effect of maternal resources or environment on the phenotype of offspring

Resurrection studies: comparing phenotypes and/or genotypes of offspring of ancestors and descendants under common conditions to detect evolutionary change

considered within a gene network and within the context of environmental effects and the complex way that genotypes map onto phenotypes (**Figure 2*b*** and below). Allelic changes at a locus influence only one component of a gene network; this network also depends on maternal effects as well as the environment an individual experiences. Environmental effects include plastic changes such as thermal acclimation that can be triggered when temperature extremes influence the expression of particular genes. Protein and metabolic networks are the result of the gene network as well as further environmental inputs, and these in turn can impact the gene network, e.g., by affecting gene regulation. When genetic response networks are influenced by environmental conditions, such as temperature or CO_2 level, the networks could potentially facilitate adaptation by allowing for rapid responses to the changing conditions. However, if the genetic response networks are influenced by factors, such as photoperiod, that do not change with climatic conditions, then a network could potentially become out of sync with new conditions, and adaptive changes would require evolutionary shifts that alter the structure of the network (14).

APPROACHES AND TECHNIQUES

The genetic basis of evolutionary adaptation to stressful conditions related to climate change is still poorly understood (108). Although more and more genomes are being sequenced and annotated, patterns of molecular evolution are starting to emerge across gene families, and knockout studies are helping to indicate numerous connections between genes and traits, there remain large gaps in identifying the genetic basis of adaptive evolutionary shifts to different climatic conditions. This issue can be explored with a variety of experimental approaches and genetic techniques that can be broadly divided into those applicable to natural populations and those applicable to experimental populations (**Table 1**). The source material for studies of natural populations can come from those under different climatic conditions, such as elevation or latitudinal gradients, or from resurrection studies, in which ancestors and descendants in natural populations that have experienced climatic changes over contemporary time. Ancestors and descendants can also be compared in experimental evolution studies, which allow the genetic basis of evolutionary change under controlled conditions to be determined.

Comparing populations naturally occurring under different conditions, including clines, is a classic technique of ecological genetics (27). If gene flow among populations is limited, populations may become locally adapted to the climatic conditions experienced. Experiments, such as reciprocal transplants, used to determine the extent of local adaptation can also be applied to help predict evolutionary responses to climate change. For example, Etterson & Shaw (31) found local adaptation but evolutionary constraints caused by genetic correlations in an annual plant occurring in different climatic regions of the midwestern United States.

One of the most powerful ways to examine evolutionary changes in natural populations is to collect propagules of individuals before and after a change in conditions and compare ancestors and descendants reared under common conditions (34, 35). The advantage of this technique, known as the resurrection approach, is that it can show a definitive evolutionary change in a natural population, but the disadvantage is that thus far the technique has been possible only in rare circumstances (**Table 1**). There is now, however, an ongoing effort to build a collection of seeds that will make it possible to apply the resurrection approach to detect evolution in a variety of plant species (99). With this approach, ancestors and descendants can be compared to help elucidate the genetic basis of evolutionary change in natural populations.

Temporal changes have also been exploited to examine morphological evolution connected to climate change. Body color in tawny owls (*Strix aluco*) in Finland has changed, most likely as a consequence of altered selection associated with snow cover in winter (62). Morph color in this species has a high heritability (80%),

Table 1 Methods for isolating genes involved in adaptive genetic responses to climate change, their potential advantages, and their limitations

Source material	Description	Advantage	Limitation	Reference
Methods based mostly on comparisons of natural populations				
Clinal comparison	Comparisons of populations from along clines	Possible to collect data immediately, takes advantage of past evolution and local adaptation	Not always possible to determine if patterns reflect climate change or other factors	118
Natural evolution	Comparisons based on changes in natural populations across time	The only source material in which populations have actually adapted in contemporary time to changes in climate	Often difficult to find natural examples of rapid evolution	36
Genome scan of populations	Population comparisons involving a large number of markers to determine which markers are more differentiated than expected from neutrality	Relatively easy to apply, can use a number of different types of markers, allows a direct comparison between effects of selection and population processes	Differentiated marker may be distant from marker under selection depending on linkage disequilibrium	102
DNA sequence comparison of natural populations	DNA hybridization on microarrays or other techniques to identify highly diverged areas of the genome, often involving cline ends	Provides an unbiased assessment of parts of the genome involved in adaptive divergence (within the technical limits of the approach used)	Can be difficult to link to adaptive phenotypic variation; differences may also be related to historical processes	126
Known genetic polymorphisms	Follow polymorphisms connected to climate adaptation across time	Can indicate changes in polymorphisms with known adaptive functions	Polymorphisms considered may only have minor effects on traits; ignores most of genome	128
Known morphological polymorphisms	Follow changes in phenotypic morphs with a known genetic basis across time	Morphs are often easily related to adaptive functions, as in the case of changes in pigmentation	Only applicable to a specific class of polymorphisms	62
Methods based mostly on comparisons of manipulated populations				
Artificial selection and experimental evolution	Traits related to climate change adaptation selected directly (artificial selections), or populations are placed in environments simulating climate change effects (experimental evolution)	Traits can be accurately defined, selection pressures set, and crosses and sequence comparisons used to assess the genetic basis of selection reflecting natural environments; can assess potential rates of adaptation	Limited by base population for selection, may not reflect intermittent selection and tradeoffs, depends on species with short generation time	7
Candidate gene comparisons	Sets of genes that are candidates for adaptive divergence considered along gradients based on known polymorphisms or DNA sequencing	Provides a direct link to particular genes and polymorphisms; effects on traits can be confirmed through functional analysis	Can be difficult to isolate the critical polymorphisms, particularly if they are in promoter regions or if regulatory elements are involved; approach will miss many important genes not characterized	69

(*Continued*)

Table 1 ***(Continued)***

Source material	Description	Advantage	Limitation	Reference
Transcriptome comparisons	Gene expression microarrays (can also be used for some targeted genes)	Identifies genes and gene networks that are differentiated between populations and cline ends for further adaptive studies	Ignores adaptive responses that have no effect on gene expression	46
Quantitative trait locus mapping	Strains are made genetically homozygous and compared for quantitative traits	The same set of strains can be scored for multiple traits, including correlated responses, sequenced strains can be used for a variety of purposes, covers whole genome	Strains are typically inbred to make them homozygous before sequencing, which means that mapping may partly relate to effects of inbreeding depression; adaptive changes may have a different genetic basis, particularly if evolution acts as a filtering mechanism; difficult for species with long generation times	86
Association mapping	Genetic markers are compared with quantitative traits associated with climate change adaptation	Undertaken in outbred populations, does not depend on short generation times, covers whole genome	Most signals obtained when multiple markers available; can be biased towards detecting genes of large effect; proximity to genetic polymorphisms affecting trait depend on marker density	11

and crosses suggest a simple genetic basis with a brown morph dominant over a gray morph. In the past, there has been strong selection against the brown morph over winter, but this has weakened, and the brown morph has become much more common over the past three decades, increasing from 20% or less to almost 50%, although the exact reason for the fitness advantage of the brown morph remains unclear. Body color has also been implicated in thermal selection in periwinkle snails (*Littorina obtusata*), which have a shell color polymorphism with frequencies varying along the intertidal rocky shore and evidence for selection based on direct manipulations of shell color (100).

This temporal approach can be combined with clinal selection. For instance, there is clinal variation in the frequency of the common alleles at the *alcohol dehydrogenase* gene in *Drosophila melanogaster*, and the clinal pattern has changed over a period spanning >20 years; this change is consistent with thermal selection on the *alcohol dehydrogenase* polymorphism (128). The same approach continues to be used to explore selection on inversion polymorphisms in *Drosophila* species (109).

For individuals that can be raised under laboratory conditions and that have short generation times, it is possible to apply artificial selection or experimental evolution. With artificial selection, individuals are selected for breeding on the basis of traits related to climate change adaptation, such as thermal tolerance, drought tolerance, and dispersal ability (108). In experimental evolution studies, conditions are manipulated to represent changes in climatic conditions (such as increased temperature or CO_2 levels), and the populations are allowed to evolve in response to these conditions (7, 26). For example, Burke et al. (16) manipulated temperature conditions in which *Drosophila* were raised and identified many genes that changed expression patterns under common conditions after evolving under elevated temperature. Functional analysis of these genes suggested many that may be connected to thermal tolerance. An advantage of this approach is that treatments or selection criteria can be precisely defined, and a disadvantage is that changes may not reflect patterns of evolution under climate change in natural populations (**Table 1**) in which stressful conditions occur sporadically and unevenly within an area. In some cases, it may be possible to undertake selection directly in the field, as in sticklebacks (*Gasterosteus aculeatus*) transplanted from marine to colder freshwater environments; the transplanted populations evolved an increase in cold tolerance of more than 2°C despite only two rounds of selection (5), potentially allowing these populations to counter increased levels of thermal variability.

All of these sets of source material (collections from natural populations over space or time, or individuals from artificial selection or evolution experiments) can be combined with a variety of genomic and transcriptomic techniques to determine the genetic basis of evolutionary change (**Table 1**). To determine the genetic basis of variation in a trait, the standard approaches are quantitative trait locus (QTL) mapping or association mapping, both of which connect phenotypic variation in one or more traits to genetic variation at a number of loci (75). QTL mapping requires the use of recombinant inbred lines and can only map traits to a coarse scale but requires fewer individuals than association mapping. Association mapping can locate genes more precisely and does not depend on the development of inbred lines but requires more individuals and may be biased because of population structure (138), although statistical approaches can be used to help account for this (60). Both QTL and association mapping can be used to find a gene's underlying trait variation, but neither is designed to examine evolution directly; although variation at a particular locus might explain variation in a trait, this does not prove that the locus is necessarily involved in evolutionary responses in natural populations.

To identify the genetic basis of evolution following climate change, sets of source material from populations under different climatic conditions or before and after natural or artificial climatic changes can be compared at the level of the whole genome, the transcriptome, or individual candidate genes. By using massively parallel sequencing (such as 454 pyrosequencing or Illumina sequencing) or genome scans [genotyping with many single nucleotide polymorphisms (SNPs) or other markers], many genes throughout the genome can be assessed for variation and compared among populations (30, 93, 111, 117). For example, Prunier et al. (102) used genome scans of black spruce (*Picea mariana*) from populations varying in temperature and precipitation to identify SNPs. Genes that had outlier F_{ST} values were located in exons, had nonsynonymous polymorphisms, showed significant regression with climatic variables, had functional annotation consistent with climatic responses, were considered prime candidates for adaptation to climatic variation, and could potentially show responses to climate change. Another example involves the Antarctic clam, *Laternula elliptica*, a potential sentinel species for monitoring ocean acidification effects because it lives in a low calcium carbonate environment, and acidification is expected to affect shell formation. Through 454 sequencing of mantle tissue, a number of genes likely to be connected to shell deposition were identified particularly through making connections to model mollusk species such as mussels, providing gene targets for functional analysis and potential future monitoring (22).

Genomic comparisons and genome scans can provide useful information on differences among populations (particularly for species with a reference genome), but much of the genome is not expressed. By focusing on transcribed genes or on the full transcriptome, it is possible to narrow the set of genes of interest to those actually expressed as well as

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Quantitative trait locus (QTL) mapping: a technique used to map genetic regions associated with variation in traits of interest

Candidate gene: a gene putatively associated with a particular trait, phenomenon, or evolutionary change on the basis of genetic comparisons or function

Massively parallel sequencing (next-generation sequencing): techniques (Illumina, 454, SOLiD) in which DNA is sheared into millions of small fragments that are simultaneously sequenced

Genome scan: a technique of genotyping individuals at many loci throughout the genome, often accomplished through massively parallel sequencing

Single nucleotide polymorphisms (SNPs): loci showing variation at single nucleotides, used as genetic markers

F_{ST}: a measure in population genetics of genetic differentiation among populations, based on single or multiple loci

RNA-seq: a technique for transcription profiling of expressed genes by sequencing and quantifying products that cDNA derived from mRNA

to evaluate differences in levels of expression under different conditions. Analysis of transcribed genes involves extracting mRNA and measuring expression level. This can be done with techniques such as quantitative real-time PCR for a small number of genes, microarrays for a large number of genes, or massively parallel sequencing of expressed genes (RNA-seq) at the scale of the whole genome. One particular advantage of examining gene expression in a climate change adaptation context is that not only can different source material originating under different conditions be compared, but also the climatic factor can be experimentally manipulated and expression measured under the different treatments. For example, individuals could be collected from a warmer and a cooler area along a thermal cline and gene expression measured at both warm and cool temperatures. Genes that differed in expression between the source populations and between warm and cool temperature treatments might be particularly likely to play a role in thermal adaptation and evolution following changes in temperature, particularly if functional annotation points to connections with mechanisms involved in temperature or stress tolerance. Genome scans and genome-wide expression profiling have been highly successful in helping to elucidate the genetic basis of tolerance to high altitude conditions in vertebrates (20).

Tests such as the McDonald-Kreitman test compare the ratios of synonymous to nonsynonymous substitutions at polymorphic sites to look for genomic signatures of selection (79). Such tests can be used to help determine if past climatic changes may have left signatures of selection and are starting to be used in a variety of contexts, including adaptation of corals and *Drosophila* to thermal environments (119, 131). Identification of outlier F_{ST} values has also been useful in identifying genes involved in local adaptation and adaptive evolution, with recent advances making this technique even more effective (68).

These studies and comparisons could be further extended to include information on trait variation and trait interactions within a phylogenetic framework (112). So far one study has considered genetic variation that is phylogenetically controlled, showing that genetic variation for desiccation resistance is very low for sensitive rainforest species of *Drosophila*, whereas more-resistant widespread species tend to have higher levels of variability, a pattern that remained significant when species associations were controlled for phylogeny and also evident when species were compared for cold resistance (63). As argued by Salamani & Bell (112), phylogenetic analyses could be extended to encompass variability among populations and also interactions among traits, particularly when populations differ substantially in their thermal responses, as in the case of the copepod *Tigriopus californicus* (64).

IDENTIFYING CANDIDATE GENE SETS

There has been substantial progress in recent years identifying structural and regulatory genes that are potentially involved in adapting to climate change. This work has mostly proceeded through functional analysis of specific genes using under- and overexpression and through broad transcriptomic and genomic scans. Despite these efforts, there has been much less progress in identifying natural variation in genes linked to climate change adaptation, which is likely to require adaptation to a suite of environmental alterations, including changes in seasonality, thermal conditions, water availability, and biotic interactions.

In *Drosophila*, early lists of candidate genes were compiled for thermal tolerance on the basis of candidate gene work and transcriptomic studies (50). Additional genes and gene regions have subsequently been identified (23, 24, 91, 106), and there has been some progress in comparing candidate genes across studies, although results are mixed. Rand et al. (106) worked with *D. melanogaster* and successfully used QTL mapping to isolate the *shaggy* gene region of the X chromosome and demonstrate that this region is involved in differentiation of different temperatures. The alleles identified were also differentiated in lines selected for high-temperature knockdown and in a sample of populations from a natural thermal cline in North America, but not in a larger sample from Australia. These results point to the ways in which selection experiments can be used to find candidate genes relevant in nature. In the same way, experiments on laboratory thermal selection in *D. melanogaster* have implicated the *Hsr-omega* gene as being important in thermal adaptation (58), and these results have also been linked to clinal variation in natural populations (25).

Genomic comparisons can increase the list of candidates rather dramatically. Comparisons of tropical and temperate populations of *D. melanogaster* from Australia suggest a lot of genomic regions that are differentiated between these populations and most likely under selection (66), and this also matches genetic differentiation for a number of quantitative traits (51, 115), despite Australia being colonized by this species for just over 100 years. Some of the areas of substantial genomic differentiation are associated with a cosmopolitan inversion on the right arm of chromosome III (66), which shows a pattern of clinal differentiation that has substantially shifted in the past 20 years so that all populations have become more tropical in their constitution with respect to this chromosomal region (2, 128). Populations from the ends of climatic clines in Australia and North America are also differentiated for classes of transposable elements expected to be adaptive, which show stronger differentiation than transposable elements considered to be neutral (41).

Genome screens are starting to be employed to identify areas of the genome connected to climate adaptation in animals. Redband trout (*Oncorhyncus mykiss gairdneri*) from six montane and six desert environments were screened for 69 SNP polymorphisms, and five polymorphisms differentiated by climate (temperature) were identified, whereas the others appeared to show neutral patterns (88). Because these polymorphisms sampled only a small part of the genome, the results suggest that multiple loci are involved in thermal adaptation in this species. Across 61 human populations, SNPs have been identified that show strong associations with climate (43), including those associated with pigmentation.

Several screens of plant populations from different climates are starting to produce sets of candidate genes for climatic adaptation. In boreal black spruce (*Picea mariana*), a survey of more than 500 SNPs in genes potentially related to precipitation and thermal variability across 26 populations led to the eventual isolation of 26 SNPs in 25 genes that showed a strong association with the climate variables (102) These genes have a variety of putative functions, including phenology, growth, reproduction, wood formation, and stress response, many of which make sense in a climate change adaptation context.

A broad genome screen of SNPs and a geographically diverse set of almost 1,000 accessions of *A. thaliana* across environmental variables produced numerous candidate genes potentially involved in climatic adaptation (43). Signals of adaptive shifts were tested further by an enrichment of functional nonsynonymous changes and by growing plants in a common environment and then testing whether counts of putative adaptive alleles could predict fitness in this environment. This analysis showed a strong correlation between fitness in the common environment and the number of favored alleles, confirming the validity of the initial screen. In a different set of experiments with *Arabidopsis*, plants from multiple inbred lines were grown in four sites differing in climate, and SNPs at each location were associated with survival and reproductive output (32); SNPs with substantial effects were identified, and these proved to be locally abundant at two of the sites. The absence of strong selective sweeps suggested that local alleles were favored via selection on standing variation rather than through sweeps. Alleles affecting reproductive output were locally common (locally selected), and those affecting survival were more common across the species range, suggesting survival alleles were widely favored at multiple sites.

Hsp70: one of the heat shock proteins found in many organisms; genes coding for these proteins are typically upregulated when organisms are exposed to heat or other stressors

Several candidate loci involved in adaptation to different temperature and precipitation regimes were identified for future study.

Transcriptomic comparisons have usually involved a single population exposed to different climatic conditions to identify genes and gene ontogeny classes that tend to be differentially expressed and may point to candidates. Gene discovery from these efforts has proven challenging given the sheer number of genes that typically show altered expression patterns that may be indirectly related to the traits of interest (129). Recently, these types of studies have moved to consider multiple natural/selected populations or lines when reared under the same conditions and challenged by the same sets of stressful conditions. For example, Levine et al. (72) compared the plasticity of expression in *D. melanogaster* from tropical and temperate Australian populations when reared under warm and cool conditions, and they showed that plasticity in the expression of genes differed depending on origin, with greater expression of genes in the thermal home environment of the population. Cassone et al. (17) found that lines with one arrangement of a chromosome inversion polymorphism in *Anopheles gambiae* exhibited a higher level of upregulation of genes from several pathways following heat stress than lines with the alternative form; this could account for the higher level of heat/aridity resistance in one of the arrangements but could also lead to trade-offs if there is an increase in expression of genes unrelated to the provision of stress protection. By linking changes in expression across multiple populations to environmentally induced changes in expression, it is more likely that candidate loci for adaptive responses can be identified, particularly when multiple stresses are considered (18).

Nevertheless, linking gene expression patterns across populations or lines with adaptive changes is not straightforward. Changes in specific genes may be restricted to a particular life cycle stage; in *D. melanogaster*, variation in hsp70 expression levels among lines correlates with heat resistance at the larval stage, but at the adult stage no association is evident (57). Expression changes may also be unpredictable. Southern populations of the Atlantic killifish (*Fundulus heteroclitus*) are adapted to warm conditions and differ in heat shock protein expression from the cold-adapted northern population, but there is no consistency across the heat shock genes as to whether expression levels are increased or decreased in the southern population (46).

A challenge in transcriptomic studies of candidate genes is to move beyond simply describing patterns of up- and downregulation of genes, which can depend on background levels (113). This can be achieved by linking patterns to those evident from other ‘omics technologies, particularly metabolomics (129), and interpreting changes within a network context (see below). Once networks are known on the basis of studies of environmental responses, gene knockouts, and other approaches, researchers can begin considering the effects of genetic variants at different phenotypic levels.

Apart from genome and transcriptome scans, some very large genome-wide mapping efforts are starting to provide a detailed picture of the genes associated with changes in traits responding to environmental cues. In *A. thaliana*, an assessment of genome-wide diversity across more than 400 accessions planted in different climates and seasons led to the identification of 12 QTLs that affect flowering time in a season-location specific manner (73). For *D. melanogaster*, genome-wide deficiency mapping has recently been used to identify 19 QTLs influencing heat resistance (120), DNA-DNA hybridization between multiple selected and control lines was used to identify polymorphic regions responding to selection for desiccation resistance (121), and next-generation sequencing of pooled samples was used to identify SNP markers associated with novel thermal and photoperiodic conditions (93). Although *Drosophila* lines are typically measured under highly defined assays in laboratory environments, recent work points to ways in which identified QTLs can be linked to performance under different field conditions (74). Genomic approaches can also be used for nonmodel organisms when there is a reference genome available from a related species, as in the case of heat shock genes in Arctic charr, which were identified from association mapping following comparisons to the Atlantic salmon genome (104).

To summarize, a number of approaches are now available to isolate candidate genes involved in climate adaptation across model and nonmodel species. Genome scans and transcriptomic studies are starting to produce long candidate lists. However, moving from lists to validated candidates remains challenging and requires studies of model organisms in which genetic manipulations are possible.

NETWORKS AND REGULATION

Changes in genetic networks may play a large role in contemporary evolution and climate change responses. Traits important in climate change responses, such as the timing of flowering (133) or stress responses (129), are often controlled by genetic regulatory networks. These networks involve multiple genes and gene products, transcription factors, and proteins that interact with each other and with signals from the internal and external environment to produce a phenotype suited to given conditions (136). Changes in specific genes within genetic networks influence the expression of genes, and changes within biochemical pathways ultimately dictate how genetic changes influence phenotypes. In some cases, the connection between changes in genes and phenotypic effects involved in climatic responses may be relatively simple. For instance, an increase in the amount of Hsp70 produced by *Hsp70* genes may set the level of protection from denaturation during heat stress and influence survival in a range of organisms. However, even in this case a genetic regulatory network influences the expression of heat shock proteins through various interacting transcriptional factors that bind to the promoter region of *Hsp70* genes to influence expression (94). Moreover, alternative splicing, in which RNA transcripts are arranged in multiple ways so that a single gene can code for multiple proteins (15), can influence the tissue expression of heat shock genes such as *Hsr omega* from *D. melanogaster*, which influences the repression of protein synthesis (59).

Most adaptive changes in response to climate change occur within a regulatory network of genetic effects, and processes such as alternative splicing and the binding of transcription factors as well as posttranscriptional regulatory mechanisms and the expression and interaction of other elements could be key mechanisms of evolutionary responses to climate change. There is now a much greater appreciation of the different levels of gene and metabolite regulation that mediate stress responses (116). It is no longer considered particularly useful to split genetic variation into simple structural and regulatory categories. Changes in structural components of genes can affect expression, and regulatory elements now encompass a range of processes, including *cis*-acting control elements, transcription factors, and metabolites, whereas regulatory processes involve not only transcriptional control but also posttranscriptional modification and control of DNA through methylation (61, 129).

Some of these networks and interactions are quite well understood and can be linked to specific genetic variants. For instance, the pathway controlling flowering time and vernalization in plants (discussed below) involves the integration of a number of pathways associated with different environmental cues (134). Variation in abdominal pigmentation in *Drosophila*, which potentially influences resistance to multiple stressors (96), is affected by a well-characterized network of genes that includes regulatory elements that respond to environmental cues and thereby influence plastic responses (39).

When a large number of genes with variation in expression patterns are embedded in complex networks and there are strong patterns of correlations among the expression of the genes, it may be difficult to extract the effects of specific polymorphisms on traits involved in climate adaptation. Expression changes in genes upstream in networks might have large and multiple effects on traits, but expression

Methylation: the addition of a methylation group, for example, to cytosine, which is an important mechanism of epigenetic regulation

Vernalization: living through a cold period (winter), which acts as an important signal of time of year in many plants

Epigenetics: the study of gene regulation and inheritance via mechanisms other than changes in gene sequence, such as the methylation of cytosine

changes in these genes may be constrained because they are more likely to have detrimental effects on fitness. The combined effects of variation in numerous components of networks can mean that the effects of specific genes are lost unless there is a level of control of the natural genetic background (92).

Nevertheless, adaptive shifts in traits such as size across gradients can be influenced by major gene effects even when variation within populations has a complex basis; for example, in *Drosophila* much of the variation for body pigmentation seems associated with genetic variation in the expression of the *ebony* gene (122), even though numerous genes and interacting pathways could potentially be involved in pigmentation pathways (39).

An important question is whether networks are conserved or whether there are alternative pathways to the same evolutionary outcomes (and whether these are predictable). For instance, for flowering, the photoperiod response is conserved between *Arabidopsis* and cereals, but the vernalization response is not (see below). Another important issue is whether the nature of networks can facilitate or retard evolutionary rates; models suggest that small networks can enhance rates under rapid environmental change through increasing the expression of heritable variation (76). Adaptation to climate change may therefore be more likely to involve these networks, but this concept needs to be tested empirically.

EPIGENETICS: AN ALTERNATIVE MODE OF CLIMATE CHANGE ADAPTATION

It is now well established that the environment can influence gene expression, and thus phenotype, through epigenetic mechanisms (9, 54). In the contemporary sense, epigenetics refers to any inherited changes in the phenotype of an organism that are not directly due to variation in gene sequence (9, 110). Several epigenetic mechanisms have been established, including the methylation of cytosine, modification of chromatin structure, and alterations in gene regulation due to small RNAs (9).

At least in some cases, phenotypic traits can be passed on from parents (particularly the maternal parent) to offspring epigenetically for one or more generations without any change in gene sequence, providing a fundamentally distinct and potentially very rapid phenotypic change that is relevant to rapid adaptation to climate change (125). An extensive set of cases of transgenerational epigenetic inheritance is now known (54). This includes examples in which epigenetic mechanisms increase resistance to a range of stresses, including thermal extremes, in untreated F1 offspring (10, 45). Maternal effects that influence traits such as resistance to heat stress (56) are also likely to often reflect epigenetic mechanisms that act across one or two generations. Epigenetic mechanisms can also influence rates of recombination and mutation, leading to genetic changes that are passed to offspring (45). Stressful conditions may lead to epigenetic modifications that mobilize transposable elements, causing major genetic alterations and rearrangements (137). In these cases, epigenetic mechanisms can lead to permanent changes in traits.

Although it is known that epigenetic modifications can play an important role in gene regulation and expression, their role in adaptation to stressful conditions in natural populations is not yet clear (9). Epigenetic mechanisms passed across a generation that increase the fitness of offspring under stressful conditions may prevent populations from decreasing in size, losing genetic variation, and becoming extinct. Inherited epigenetic modifications that are passed on to offspring because of altered rates of recombination and mutation may permanently influence phenotypic variation and fitness of populations (125). However, the extent to which these modifications facilitate persistence and evolution of populations in changing climates is unknown.

CASE STUDIES

To uncover the genetic basis of an adaptive evolutionary change in a quantitative trait to a change in climate, we would ideally like to be able to show that a particular trait (*a*) is genetically based and heritable; (*b*) is under differential selection and has different fitness under different climatic conditions (changes in climate alter the pattern of selection); (*c*) varies geographically along latitudinal, altitudinal, or other gradients in a way consistent with climatic variation; and (*d*) has changed in mean value in a population following natural or experimental changes in climate. We would want to (*e*) identify genes and networks underlying variation in the trait and (*f*) show that allele frequencies of one or more of these genes have changed within a population following a change in climate. All six of these criteria have not yet been met within a single study or system, although some studies mentioned above have shown one or more of these components. We provide two examples of traits—flowering time and body size—that have often been linked to climate change adaptation. In the case of flowering time, we are close to meeting many of the criteria, whereas with body size we are only just starting to reach a very preliminary level of understanding.

Flowering Time

Flowering time is an important trait in plants and highly relevant for genetic adaptation to climate change. Climatic conditions have a strong effect on reproductive phenology and the relationship between flowering time and fitness (101). Previous studies have shown that flowering time meets several of the criteria described above to demonstrate the genetic basis of an evolutionary response to climate change. One study (35) found that in the annual plant *Brassica rapa*, flowering time was heritable, early flowering plants had greater fitness under drought conditions than late flowering plants, and average flowering time was earlier in plants following a natural drought than in plants from before the drought when ancestors and descendants were grown together under common conditions. In many other species flowering time is heritable (47), is under selection (52), and has shifted following changes in climate (85).

One feature of flowering time that makes it ideal for a study of the genetic basis of evolution under climate change is that a substantial amount of information already is known about genes, pathways, and processes involved in determining flowering time (84, 133). In *Arabidopsis*, flowering time is controlled by a genetic regulatory network involving four main pathways: photoperiod, temperature, gibberellin, and autonomous (**Figure 3**) (84). Internal (hormones such as gibberellins) and external (photoperiod, temperature) signals influence these pathways in a way that prevents a plant from flowering too early or too late. Although this regulatory network is quite complex; includes hundreds of genes, transcription factors, and receptor proteins; and involves variation in gene expression as well as epigenetic regulation;

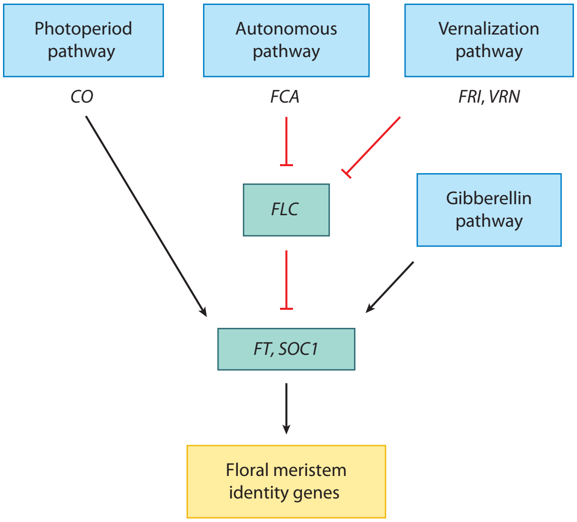

Figure 3

Summary of the flowering time genetic regulatory network. Shown are the four main genetic pathways influencing flowering time in *Arabidopsis thaliana*: photoperiod, autonomous, vernalization, and gibberellin. These pathways work in concert to regulate flowering time. Some of the major genes involved in these pathways are also indicated. Red lines indicate suppression, and black arrows indicate promotion. For example, the gene *FLC* suppresses the flowering time promoters FT and SOC1, preventing flowering until *FLC* is suppressed by gene products from the vernalization or autonomous pathways. The floral meristem identity genes cause meristem tissue to differentiate into floral rather than vegetative tissue, which causes flowering to begin. Evolutionary changes in flowering time due to climate change could be a result of changes in allele frequencies of these flowering time genes, changes in their expression or regulation, or changes in other genes with pleiotropic effects on flowering time.

only a relatively small number of genes appear to vary in the wild and to influence the flowering time phenotype in natural populations (70, 118). These are thus prime candidate genes for examining the genetic basis of flowering time variation and evolution across taxa in natural conditions.

Previous studies with *Arabidopsis* have found associations between flowering time, variations in candidate flowering time genes, and climate. One study showed a cline in flowering time in *Arabidopsis* from accessions from southern to northern Europe as well as a differential effect of loss-of-function mutations in the flowering time gene *FRIGIDA* across this cline (118). McKay et al. (80) showed that a natural cline in flowering time in *Arabidopsis* coincided with variation in the flowering time gene *FLOWERING LOCUS C*, which affected both flowering time and water use efficiency. Li et al. (73) conducted a genome-wide association mapping study in *Arabidopsis* and identified 12 candidate genes associated with flowering time, four of which were correlated with latitude of origin. Some of the QTLs had previously been identified, including the *FRIGIDA* locus, but the majority of QTLs mapped to novel areas of the genome. The QTLs that affected seasonal timing were associated with latitudinal variation and affected yield, suggesting an important role in local adaptation to climatic conditions. Another study with *A. thaliana* found that genetic variation at flowering time loci influenced climate niche breadth and that later flowering genotypes had more restricted range potentials than early flowering genotypes did (4), suggesting that the flowering time genotype will strongly influence response to climate change in this species. Flowering time genes linked to climate conditions have also been isolated in nonmodel plants. In pearl millet (*Pennisetum glaucum*), initially a genome scan was used to identify a signature of selection along a rainfall gradient in a MADS-box gene, *PgMADS11*, and association mapping was then used to link polymorphism in this gene to flowering time variation in a separate population (77).

It is therefore known that at least in some cases flowering time is heritable, is under selection by climatic factors, varies across climatic clines, and can evolve following changes in climatic conditions. Additionally, candidate genes have been identified that are linked to variation in flowering time as well as to climatic conditions, and the function of many of these genes is known. Further work on flowering time is likely to provide more information on the genetic basis of adaptive evolutionary responses to climate change.

Body Size

Body size has been associated with climate change adaptation and climate variation in both ectotherms and endotherms (37). In ectotherms, size variation may show Bergmann clines (increasing body size at higher latitudes/elevations) thought to reflect the advantage of large-bodied organisms in cold conditions and reverse Bergmann clines thought to reflect adaptation to seasonality in which small organisms have an advantage when favorable seasonal conditions for development are short (8, 21). In endotherms, size variation also often shows geographic patterns along climatic gradients, perhaps reflecting the energy and water needed to maintain body temperature and the surface area available for heat exchange (37). Climate may also influence size indirectly, such as by affecting the availability and nature of food sources, which dictate selection on body size in Darwin's finches during periods of drought (42). Changes in size in endotherms and ectotherms may have a genetic basis, although environmental effects can be enormous and of overriding importance in some cases (95).

Size variation can be highly heritable in endotherms and ectotherms, although this can depend on environmental conditions (19). The genetic basis of size is always assumed to be complex given that a large number of genes influence growth rate and development, and this conjecture is certainly supported by genetic analyses of *Drosophila* lines (127), with size mapping indicating contributions from all genomic regions (139). Yet in *D. melanogaster*, clinal variation in size (**Figure 4**) across multiple continents (55) is associated with the right arm of chromosome 3 (65). In Australian populations, approximately two-thirds of size variation in males maps to this region, which contains a large inversion (105) and in which association mapping indicates size genes located in two peaks. For wing size, at least 10% of the genetic variation is tightly associated with a promoter polymorphism in the *Dca* gene, which affects cell number (65, 69). Alleles in the *Dca* promotor region as well as *Dca* expression show clinal variation (**Figure 4**), and there is direct evidence from association studies and altered expression studies that increased expression of this gene is associated with decreased size (69, 81). Recent genomic analysis of *Drosophila* selection lines and population comparisons emphasize the role of allele shifts at multiple loci in changing traits (126), but adaptive changes might occur through only some of these loci, resulting in quite a different genetic basis for traits than indicated through mapping variation among lines.

Size therefore represents a trait with a complex relationship to fitness and potentially linked to climate change adaptation through multiple selective factors. Because size can be easily measured, it is an attractive trait for routine monitoring in relation to climate change. However, the heritable basis of size shifts has rarely been examined, and little is known about the genetic basis of adaptive variation in size potentially influenced by a complex of genes and regulatory pathways.

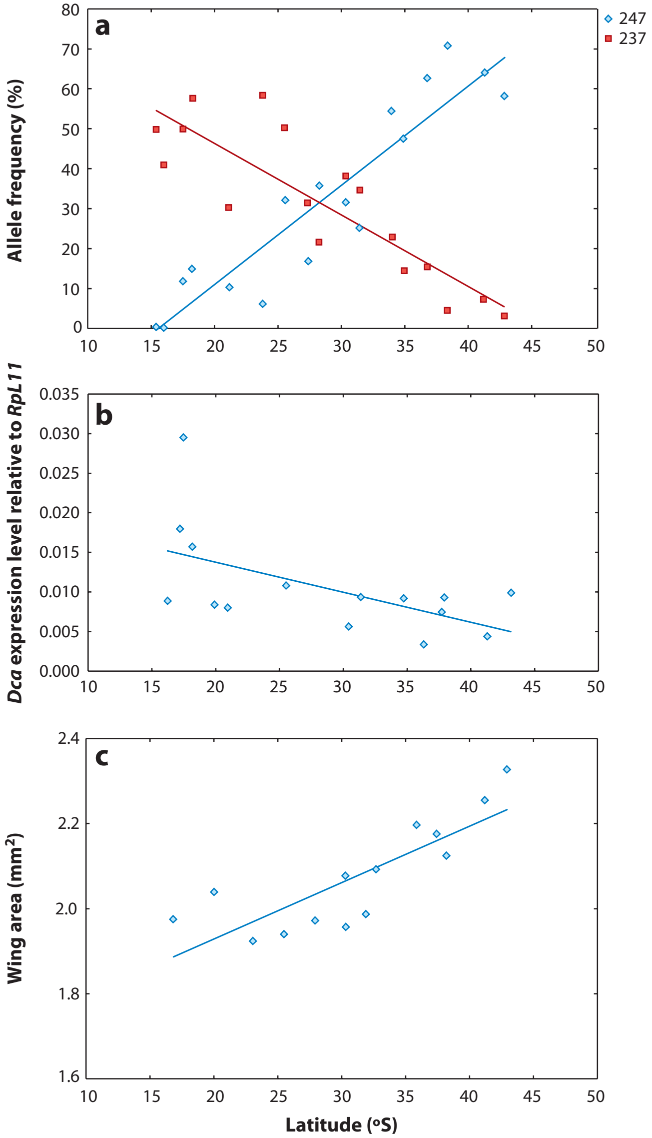

Figure 4

Associations between latitude and three interrelated variables measured across populations of *Drosophila melanogaster* from the eastern Australian coast. (*a*) Frequency of two indel alleles (237, 247) in the promoter region of the *Dca* gene (81). (*b*) Expression of *Dca* relative to a control gene, *RpL11* (69). (*c*) Wing area of females reared under controlled conditions (55).

CONCLUSIONS

Since the modern evolutionary synthesis, it has been a major goal of evolutionary biology to uncover the genetic basis of adaptive evolution. The rapid evolutionary responses of at least some organisms to current climate change indicates that studying contemporary evolutionary changes that result from climate change may provide opportunities to advance this goal. To do so, it is important to combine ecological approaches to studying responses to climate change with a variety of techniques in molecular and quantitative genetics and genomics. Recent advances, including genome sequencing and transcription profiling, help to uncover

Transcription profiling: a technique for measuring transcription levels through quantifying mRNA levels at expressed genes throughout the genome

the genetic basis of climate change adaptation. However, future studies need to be grounded in a thorough understanding of the ecological context of the environmental changes, need to use well-designed experiments, and need to draw on current knowledge of genetic regulation and interactions to avoid fishing expeditions involving enormous amounts of genetic information without clear questions. A better understanding of the genetic basis of adaptation to climate change will address such topics as the number and relative importance of genes involved in evolutionary changes, the degree to which changes in gene regulation result in evolution, and the role of additional mechanisms, such as epigenetics, in evolution in natural populations. Although recent research has increased understanding of links between genes and traits and how genes vary across environmental gradients, our understanding of the genetic basis of evolutionary responses to changes in climate is still quite limited.

SUMMARY POINTS

1. Climate change is occurring, affecting many organisms, and, at least in some cases, leading to evolutionary change that results in changed gene and allele frequencies in populations.
2. Studying evolutionary responses to climate change can help us to uncover the genetic basis of adaptive evolution.
3. Methods of studying the genetic basis of climate change adaptation involve a choice of source material (e.g., sampling along latitudinal or altitudinal gradients and before and after a natural or artificial environmental change) as well as a variety of possible genetic techniques (e.g., genome scans, transcriptome comparisons, candidate gene comparisons, and genetic mapping).
4. Substantial progress has been made recently in uncovering genes linked to traits of adaptive significance and genes associated with climatic variation. However, much less is known about genetic changes occurring as a result of climate change.
5. Body size in animals and flowering time in plants are two examples of areas in which further research into the genetic basis of climate change adaptation seems particularly promising.

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Errata

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