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Commentary

Opportunities and challenges in assessing climate change vulnerability through genomics

Ary A. Hoffmann,[1] Andrew R. Weeks,[1] and Carla M. Sgrò[2,*]
[1]School of BioSciences, Bio21 Institute, The University of Melbourne, Parkville, VIC 3010, Australia
[2]School of Biological Sciences, Monash University, Clayton, VIC 3800, Australia
*Correspondence: carla.sgro@monash.edu
https://doi.org/10.1016/j.cell.2021.02.006

By investigating how past selection has affected allele frequencies across space, genomic tools are providing new insights into adaptive evolutionary processes. Now researchers are considering how this genomic information can be used to predict the future vulnerability of species under climate change. Genomic vulnerability assessments show promise, but challenges remain.

Introduction

Global climate change poses a significant threat to biodiversity. There is ample evidence of the effects of climate change on the distribution and abundance of animals and plants; there is also abundant evidence that organisms can respond to climate change through both phenotypic plasticity and evolutionary adaptation (Scheffers et al., 2016). Because of this, there is increasing focus on predicting the extent to which species could mitigate the negative effects of climate change via evolutionary adaptation. However, doing so is challenging because traditional ways of assessing the evolutionary adaptive capacity of organisms are cumbersome. They require transplant experiments (commonly used in plants), breeding experiments where genetic lineages are tracked across generations, selection experiments, and/or other approaches for assessing heritable variation that underlies traits linked to fitness and population persistence. These types of studies are difficult in many species due to long generation times, experimental intractability, low numbers of individuals available for phenotypic assessments (particularly for species of conservation concern), and the challenges of measuring the critical traits in meaningful ways (Shaw and Etterson, 2012).

This has resulted in attempts to develop ways of assessing evolutionary adaptive potential through modern genomic tools. Genetically variable populations are expected to respond more rapidly to natural selection because they are more likely to contain the alleles and genotypes required for adaptation to the new conditions (Willi et al., 2006), and modern genomic techniques can be used to accurately estimate the current level of variation in a population. Earlier molecular approaches assessing evolutionary capacity focused on neutral levels of genetic variation in populations. Studies were limited to tens and occasionally hundreds of genetic markers (allozymes, microsatellites), but variation in these markers was nonetheless assumed to represent variation across the whole genome and thus reflect adaptive capacity more generally. Advances in genomic technology mean that we can now score tens of thousands of genetic markers (single nucleotide polymorphisms, or SNPs) spread throughout the genome relatively easily and cheaply. Recent SNP studies on *Drosophila* point to how this detailed measure of genomic variation can predict rates of adaptation in selection experiments (Ørsted et al., 2019).

However, although there are millions of SNPs across the genome of any one species, only some of these will contribute to climatic adaptation; accurate estimates of adaptive capacity using genomic data could be achieved by only focusing on SNPs relevant to climatic adaptation, rather than general assessments of diversity based on all identified SNPs. The process of identifying those genetic variants that underpin climatic adaptation lies at the core of genomic vulnerability. Here, we describe the genomic vulnerability approach and its potential and also highlight the challenges in applying it.

Genomic vulnerability

Genomic vulnerability (GV) is defined through alleles and genotypes that are associated with the environment, i.e., genetic-environment associations (GEAs). The GV of a population is a measure of the amount of genomic change needed to track climate change via evolutionary adaptation, as determined from current GEAs. To estimate GV, allele frequencies are first compared among populations living in a range of climates throughout the species range; if populations are adapted to local climatic conditions, allele frequencies at loci under selection in a population are expected to be optimized to the local conditions. SNPs scattered throughout the genome therefore reflect optimal frequencies of the specific genetic variants responsible for climatic adaptation. To establish connections between these SNPs and climatic drivers of change, populations are compared across geographic space for association with climate variables such as high/low temperature or variable rainfall to generate GEAs. A matrix of environmental (dis)similarity is compared back to a matrix based on genetic distances between populations, by using different analytical approaches such as machine-learning tools or modeling approaches that allow the patterns of environmental and genetic distances to be compared (Fitzpatrick and Keller, 2015; Bay et al., 2018).

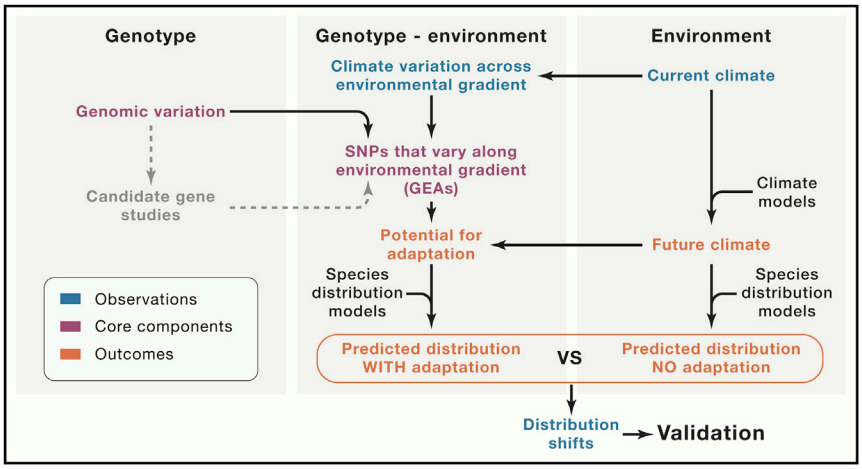

Figure 1. Outline of genomic vulnerability assessments and their connection to other relevant research areas

The three main elements of assessments of GV are genotype, genotype-environment interactions, and the environment, as highlighted in shaded panels. Observations (blue) are made on climate and on species distributions which validate predictions. Climate models and species distribution models (in black) are used to inform final assessments. Core components of GV (burgundy, bold) are the genomic variation and the identification of SNPs that vary along environmental gradients; patterns of variation can then be used to predict the extent to which adaptive responses to future environments (usually climate) are possible. The phenotypic effects of GEAs can be guided by experimental candidate gene studies (gray) that help identify putative adaptive SNPs. The outcomes (orange) are an assessment of how much adaptation will influence changes in species distributions. This can in turn be validated against observed distribution changes.

The GEAs identified with these approaches are assumed to have developed due to selection across many hundreds of generations. The GEAs are assumed to reflect the optimal outcome of this process. The spatial patterns of genetic variation are then projected forward in time to see how much genotype-environment mismatch might exist in the future, as defined by cumulative effects of allele frequencies. Thus, SNP frequencies in a focal population expected to experience hotter and drier conditions in the future can be compared back to SNP frequencies in a population from a different part of its range that is already experiencing variation in these conditions (Bay et al., 2018); the greater the mismatch in SNP allele frequencies between the two, the greater the vulnerability of the focal population to projected warming. GV can also be determined by assessing how close alleles that are linked to a climate gradient might be to fixation (i.e., when the alleles are favored and become fixed in a population, and no further allele change, and thus evolution, is possible). This is followed by a test of whether patterns of climate change would be expected to produce fixation of alleles that would limit evolutionary responses (Jordan et al., 2017).

In initial applications of the approach by Fitzpatrick and Keller (2015), the emphasis in such analyses was on candidate genes (Figure 1); in this case, those known to contribute to adaptive differentiation in flowering time of a poplar species among populations along climate gradients. These authors considered candidate genes from a previous analysis and their associated SNPs, one of which (*GIGANTEA-5*) was particularly well differentiated across populations in relation to climate. Such an approach is therefore built on direct connections between the SNPs and the trait under climatic selection. In other applications, SNPs might be identified initially based on allele frequency-climate associations but then tested further such as through considering other gradients or trait-based studies. In addition, more recent applications of the approach (Bay et al., 2018; Ahrens et al., 2020) do not restrict inferences about GV to known candidate genes. Rather, recent approaches use analytical methods (Hoban et al., 2016; van Boheemen and Hodgins, 2020) to identify SNPs that are not necessarily in candidate genes but nevertheless associated with specific environmental factors when evaluating GV. No further experiments might then be undertaken that explicitly link these SNPs to a known function and fitness.

The concept of GV is important because it has implications for management decisions. If threatened species are predicted to be close to the genetic composition required for the future based on GV analyses described above, there could be fewer concerns about their persistence under climate change. If keystone species that are ecologically important because they define entire ecosystems have the combinations of alleles needed to counter future climate change in at least part of their natural range, then the species might be expected to successfully adapt to future conditions if these combinations can be spread sufficiently to areas where the species is vulnerable. GV assessments could therefore help managers prioritize decisions to protect biodiversity against rapid climate change.

Overcoming challenges in generating GEAs

Before GV is widely used to predict climate change risk, there are analytical and methodological concerns that must be considered when establishing GEAs (Hoban et al., 2016; Fitzpatrick et al., 2018) (Table 1). First, demographic history can cause allele frequencies to vary across a species range in ways unconnected to local adaptation. Because GV assessments use large differences in SNP allele frequencies between populations to identify loci that underpin local adaptation, allele shifts due to demographic processes such as gene flow and random genetic drift could be interpreted incorrectly as supporting adaptive potential, especially if gene flow is spatially limited (Hoban et al., 2016). Demographic history can be controlled for analytically, although high rates of false positives—loci mistakenly identified as being adaptive (or linked to adaptive loci) when they are not—remain a problem (Hoban et al., 2016; van Boheemen and Hodgins, 2020).

When making GV assessments, it is important to use high-quality genomic data. Many genomic regions likely involved

Table 1. Limitations of currents assessments of GV and possible solutions

Limitation	Relationship to GV assessments	Solutions to address limitations
No direct link between SNPs and phenotypes under selection.	Demographic history, rather than selection, can result in SNPs that are differentiated across populations, resulting in SNPs mistakenly identified as under selection (adaptive).	Include neutral loci in the analysis of population differentiation. Test assumption that the population is in migration-selection balance; decoupling of neutral and phenotypic divergence will indicate that selection contributes to divergence irrespective of migration.
	SNPs are not under selection but only connected to polymorphisms under selection indirectly, such as through linkage.	Use SNPs with known function and link to fitness (phenotype). Perform functional assays with candidate loci to confirm link. Test for consistency of association across multiple gradients. Where possible, validate link between SNPs and phenotypes through reciprocal transplant or common garden experiments, functional assays, and association studies.
Methodological: Missing SNPs.	Poor sequencing depth, poor coverage of genome.	Use high-quality, high-depth genomic data
	Thousands of loci contribute to the traits that underpin climatic adaptation, which will not be captured by genomic data based on reduced representation sequencing methods, or low coverage sequencing.	Sequence entire genomes, include annotated reference genome in analysis, consider comparative analysis. Use multiple methods, including data from long read technologies, where possible, and appropriate; use multiple reference genomes.
	Copy number variants (CNVs) and structural variants such as inversions not scored despite being critical in adaptation	Explicitly consider structural variants in analyses, consider sequencing approaches that can identify structural variants (e.g., long-read sequencing for inversions).
Inaccurate assessment of future climate; no link with environmental variables used to identify adaptive SNPs.	Abiotic factors might not be the main drivers of species abundance, ignores biotic interactions.	Consider adding biotic interactions to initial SNP-environmental gradient associations. Use understanding of the natural history of the species/prior studies to formulate specific hypotheses to inform choice of variables.
	Future climate involves different selection pressures, happens faster, etc.	Test predictions experimentally, if possible in simulated contexts.
	Genetic-environment associations are not static through time.	Consider temporal sampling (e.g., across seasons) of populations to explicitly account for temporal variation in SNP allele frequencies and genetic-environment associations.
The complex and polygenic nature of adaptation is ignored. Pleiotropy, where a single gene affects multiple traits, might facilitate or constrain adaptation.	Interactions among genes might limit adaptive responses. This is not captured in current assessments of genomic vulnerability.	Compare predictions of adaptive capacity based on genomic vulnerability with those estimated directly using quantitative genetic analyses that explicitly account for pleiotropic interactions between key traits.
	The same phenotype can result from many different genotypes. This genetic redundancy is missed in current assessments of genomic vulnerability.	Assess redundancy in species, collate data across multiple populations and species. Consider experimental tests of genetic redundancy.
	The expression of adaptive genetic variation can be environment and sex specific.	Where possible, assess adaptive capacity across multiple environments and in both sexes. Where quantitative genetic breeding designs are not possible, common garden assessments of phenotypic divergence between populations sampled from across environmental gradients can shed light on adaptive genetic diversity.

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Table 1. *Continued*

Limitation	Relationship to GV assessments	Solutions to address limitations
Genomic vulnerability approaches less effective than other approaches based on genomic variability.	Adoption of genomic vulnerability tools could conflict with those based on assessments of overall genetic variation, leading to perverse outcomes.	Compare predictions and management based on measures of genome-wide variation to assess overall adaptive capacity with those based on subsets of putatively adaptive SNPs. Test approaches in generating successful outcomes.

Adapted from Hoban et al. (2016) and Hoffmann et al. (2015).

in local adaptation will be missed with the reduced-representation sequencing methods typically used in assessing GV (Hoban et al., 2016) (Table 1). For instance, RNA-seq and exome capture might fail to detect variation involved in gene regulation that underlies much of the phenotypic variation upon which selection acts. RAD-seq (restriction site associated DNA sequencing) and other related techniques, although useful for establishing neutral patterns of population structure and other population genetic parameters, represent only a small fraction of the genome (often much less than 1%); any gene not closely linked to one of the SNPs sequenced will be missed in tests for local adaptation/selection. Structural genomic variation, such as inversions, copy number variants, transposons, and insertions/deletions could also not be considered in assessments of GV. Yet structural variants are often associated with adaptive divergences in many taxa (Hoffmann et al., 2015).

Environmental effects on genotypic variation underlying phenotypes rather than just allelic variation might need to be considered when assessing adaptation and GV. Selection acts on phenotypic variation, and genotypic effects commonly interact with environmental conditions to affect traits and fitness. That is, adaptive genetic variation can be highly environment specific. Thus, genetic variation expressed and correlated with the current climate might not always reflect genetic variation expressed under climate change (Shaw and Etterson, 2012) (Table 1). So, putatively adaptive SNPs identified under current climatic conditions might not be the SNPs driving adaptation to future climate conditions.

Finally, assessments of GV identify putatively adaptive loci by using GEAs across the locations where a species currently occurs (Table 1). The ease of identifying GEAs will depend on how variable particular environmental parameters are across the geographical space being considered. So, more SNPs would be expected to associate with environmental variables that vary considerably rather than those that vary very little across space (and GV assessments would be based mostly on these SNPs). But vulnerability might depend on environmental variables that do not currently vary much across a species range but nevertheless change in the future. For instance, a species with a broad coastal distribution across a range of temperatures might still be vulnerable to climate change if conditions become drier across its current range, but this might not be evident if the current coastal range experiences similar rainfall. It is therefore important to consider how the future climate (environment) within a species' range will be altered irrespective of genomic variation—that is, separately consider whether the environmental variables to which a species will need to adapt show much variation across its current range. Predictions from GV assessments need to be tested by considering how well distribution changes match them in the future (Figure 1). Ongoing monitoring of both distribution shifts and genomic composition will therefore be crucial.

Linking GV to experimental data—validating the method

There is a huge amount of literature on testing for adaptation and identifying the genetic basis of adaptation, albeit not in the context of GV. What lessons can we take from relevant studies with respect to the types of data that might contribute to developing and validating the GV approach?

Experimental (reciprocal) transplant experiments are the gold standard in testing for adaptation across space because the transplanted populations experience different local conditions along a gradient. These are commonly undertaken in plants and can show evidence for strong local adaptation (Shaw and Etterson, 2012). However, signals of adaptation can be weak and not genetically based but rather due to plastic shifts in traits in response to different environmental conditions along a gradient. Nevertheless, plant fitness can be measured in the transplanted environments and linked to SNPs, which can be a way of validating adaptive alleles that vary across a gradient. Transplants with animals are more difficult because of their mobility, but they have been successfully undertaken with invertebrates such as *Drosophila* by housing them in cages.

Common garden experiments, where populations collected from a gradient are moved to a common controlled environment, are often more tractable for animals and are also widely used in plants. When these experiments control for non-genetic effects, they can shed light on the extent to which SNPs identified from GEAs are predictable. For instance, by combining genome scans with glasshouse experiments in an invasive plant along gradients in three continents, van Boheemen and Hodgins (2020) showed that 17%–26% of SNP loci with adaptive signatures were repeated among the gradients, despite different demographic histories shaping genetic variation on these continents. This suggests that a GV assessment based on one gradient could, to some extent, provide the basis for a GV in a different setting. However, many of the loci that underpinned adaptation in each continent were different, which begs the question of how often GV

assessments based on some populations from part of a species range can accurately assess vulnerability to climate change for a different part of the range (or in a related species).

The extent to which the same set of SNPs (or genes where SNPs are located) is useful in predicting evolutionary adaptation across different populations and species is an important issue because it dictates the extent to which one can generalize from one GV assessment to other situations. In the original Fitzpatrick and Keller (2015) paper used to inform GV (as applied in Bay et al., 2018), the focus was on genes involved in development and flowering in *Populus balsamifera*, but that could be linked to similar candidates in other species. However, even for these traits with strong candidates there could still be multiple sets of genes leading to the same phenotypic change, and this "genetic redundancy" will be larger for complex traits (Barghi et al., 2020). This redundancy is illustrated by numerous artificial selections that result in different sets of SNPs responding to selection across replicate selection lines exposed to the same selection pressures (Barghi et al., 2020). Thus, adaptation involving polygenic responses can typically be achieved by many different combinations of adaptive alleles, indicative of genetic redundancy (Table 1).

Related to the issue of genetic redundancy is the fact that pleiotropy, where a single gene affects more than one trait, could either facilitate or constrain climatic adaptation (Table 1). Genetic correlations between traits, which quantify pleiotropy, could oppose the direction of selection, slowing predicted responses to climate change (Shaw and Etterson, 2012), even when the individual traits under selection harbor abundant variation. Thus, adaptive variation could be present in a population, but the vulnerability of the population might remain because of pleiotropic interactions. When carrying out GV assessments, a focus on SNP variation in candidate genes known to have a link to trait function/fitness remains important, with the possibility that pleiotropic interactions involving these genes could be predictable, and that GEAs based on known candidates will likely be more repeatable across gradients and perhaps related species.

Challenges of applying GV in conservation

Although GV has potential as a tool in biodiversity conservation, there are some extra challenges in dealing with threatened species. At present, conservation genetics tends to focus on the maintenance of genetic variation in populations, as well as the consideration of population distinctiveness. Yet in threatened species, the genetic uniqueness of populations can be driven by the loss of genetic variation through random genetic drift (Weeks et al., 2016). Genetic mixing strategies are increasingly being considered for threatened species to increase the potential for adaptive evolution, particularly in the face of rapid climate change (Hoffmann et al., 2020). However, if a GV approach is used to select populations for genetic mixing, there is the danger that populations with low genomic variation might receive conservation priority, even though these could have a lower adaptive potential (Ørsted et al., 2019). Drift processes might then be overemphasized over adaptive evolution leading to population maladaptation. This becomes particularly important for short-lived species, where ongoing evolutionary changes could rapidly lead to new combinations of genes that speeds evolutionary changes in polygenic traits.

If sets of adaptive alleles are successfully identified, these could then be used to indicate source populations of a species that are pre-adapted to future environmental changes, particularly within the context of climate change. This is certainly attractive from a management perspective but could lead to perverse outcomes given that natural populations could appear to be genetically divergent from others solely as a consequence of demographic processes that have simultaneously reduced genetic variation—a situation that seems to exist in many threatened marsupials (Weeks et al., 2016). Other current methods are likely to be more tractable while GV approaches are developed further. For instance, source populations of plant species useful for countering the future effects of climate change can be identified through climatic provenancing, which is based mostly on matching future climate at a location with current climate at a different location where pre-adapted genotypes are expected to occur. These efforts can be reinforced by genomic information that points to populations being climatically adapted (Jordan et al., 2017), but climate matching rather than genetic matching is the main yardstick of such efforts. Similarly, focusing on increasing total genomic variation in plant and animal populations, which can now be more accurately measured by using genomic SNPs, should be the focus of genetic mixing strategies (Ørsted et al., 2019; Hoffmann et al., 2020).

GV assessments could be a powerful approach for applied conservation given the rapidity of climate change, but it is important to validate the approach by using the approaches described above in tracking putative adaptive alleles in transplants and across stressful periods. Although evidence of any GEAs is a useful way of demonstrating a past history of selection and evolutionary adaptation within a species, it might be too early to rely on GV assessments when making management decisions.

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