

# Landscape Genomics for Wildlife Research



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**Abstract** Landscape genomics investigates how spatial and environmental factors influence geographic patterns of genome-wide genetic variation. Adaptive landscape genomics focuses on how these spatial and environmental processes structure the amount and distribution of selection-driven genetic variation among populations, which ultimately determines how phenotypic variation is arrayed across landscapes. This adaptive landscape genomics approach can be used to identify the causal factors underlying local adaptation and has great potential to guide decision-making in applied wildlife research, especially in light of anthropogenic climate and land use change. Conservation and management applications include delineating conservation units, designing conservation monitoring programs, and predicting changes in the spatial distribution and potential loss of adaptive genomic variation under environmental change. However, there remains great untapped potential for the application of adaptive landscape genomics to wildlife research, including moving beyond correlative genotype-environment association tests. In this chapter, we explore and discuss the potential of adaptive landscape genomics for improving wildlife research, including case studies that illustrate its application in wildlife management and conservation. We also present a comprehensive workflow for adaptive landscape genomics studies in wildlife, including sampling design, genomic and environmental data production, and data analysis. We conclude with avenues and perspectives for future work and ongoing challenges in adaptive landscape genomics.

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## 1 Adaptive Landscape Genomics and Wildlife Research

For over three decades, the study of genetic variation in wildlife species has been used to investigate ecological and evolutionary questions, especially those related to management and conservation (e.g., Frankham 1995; Frankham et al. 2017). More recently, wildlife species have been a focus of landscape genetics research, including the investigation of functional connectivity in heterogeneous landscapes, the identification of source-sink dynamics and barriers to gene flow, and linkage of processes, such as land use change and degradation, to patterns of genetic variation (Storfer et al. 2010; Selkoe et al. 2015; Waits et al. 2015).

Prior to the development of next-generation sequencing (NGS), however, the examination of adaptive genetic variation in wildlife was relatively limited (Bensch and Åkesson 2005). In the past decade, NGS technologies, with their falling costs, improvements in genotyping yield and quality, and increasing accessibility (Goodwin et al. 2016), have created an unprecedented opportunity to study local adaptation and natural selection in wildlife populations. In an adaptive landscape genomics framework, these data allow for the explicit investigation of how environmental and spatial processes structure the amount and distribution of selection-driven genetic variation among wildlife populations. This, in turn, informs our understanding of the ecological and evolutionary processes at work, as well as how best to manage and conserve the adaptive capacity of wildlife populations in the face of complex and interacting environmental changes (Sgro et al. 2011; Harrisson et al. 2014; McMahan et al. 2014; Hoffmann et al. 2015; Funk et al. 2018).

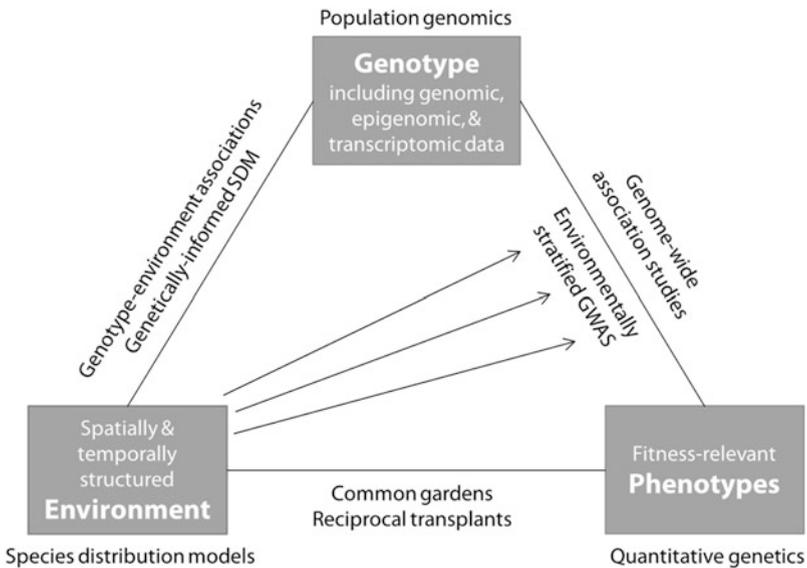
Despite these advances, there are many practical challenges of working with wildlife that limit the use of adaptive landscape genomics, as reflected in the small number of published empirical studies to date (see below). For many wildlife species, sampling can be a major obstacle, including obtaining adequate sample sizes, appropriate sample stratification across environmental gradients, and DNA of sufficient quality and quantity. Study inference can often be limited by a lack of basic ecological information including the proximal environmental drivers of natural selection. Finally, a lack of genomic resources and an inability to use experimental approaches in controlled environments (e.g., common gardens) for the majority of wildlife species limits validation of identified candidate adaptive variants. These issues are not insurmountable, however, and the integration of complementary data and analyses can be used to improve inference in many cases.

In the following sections, we present a workflow for adaptive landscape genomics studies in wildlife, including sampling design, genomic and environmental data production, and data analysis. We follow up with a discussion of the potential of

adaptive landscape genomics for wildlife studies, including case studies that illustrate the application of adaptive landscape genomics in wildlife management and conservation. We conclude with avenues and perspectives for future work and ongoing challenges in adaptive landscape genomics.

## 2 Data Production for Adaptive Landscape Genomics Research in Wildlife

Adaptive landscape genomics includes a range of techniques for identifying and analyzing spatially structured, selection-driven genetic variation, including correlative genotype-environment associations (GEA), phenotypic approaches like genome-wide association studies (GWAS) and quantitative trait locus mapping (QTL), candidate-gene methods, and exome and transcriptomic approaches (Storfer et al. 2015; Fig. 1). In this chapter, we focus on the identification of adaptive variants through GEA, because this is the analytical framework that explicitly incorporates environmental variation into the identification of selection-driven variation and is the most widely used landscape genomics approach in wildlife to date (Balkenhol et al. 2017). The reasons for this are practical and include (1) no requirement for



**Fig. 1** Expanded view of the adaptive landscape genomics framework, illustrating how multiple data types (boxes) can inform the relationships among spatially and temporally structured environmental heterogeneity, genotypes (including genomic, epigenomic, and transcriptomic data), and fitness-relevant phenotypes. Analytical approaches (black text) can be integrated to improve our understanding of adaptation in wildlife species. Figure adapted from Sork et al. (2013)

phenotypic data, which can be difficult to collect in the field on large numbers of individuals; (2) no requirement for manipulative experiments such as crosses, common gardens, and reciprocal transplants, which are impossible for many wildlife species; and (3) no requirement for prior genomic resources. While any landscape genomic study would be improved by the inclusion of complementary data sets and resources (Sect. 4), they are not essential to addressing many of the questions relevant to adaptive genetic variation in wildlife.

## 2.1 *Landscape Sampling Designs*

Sampling design is a fundamental component of robust research, but it is often unclear how different sampling strategies affect interpretation of landscape genomic results, including those obtained using GEA. So far, we know that the power of GEA methods can depend strongly on sampling design, which includes how samples are arrayed across the landscape, the total number of samples, and whether sampling is individual- or population-based. Generally, it is best to array samples across the maximum range of environmental variation that is thought to drive selection, for example, collecting samples from the lowest and highest elevation populations for a montane species. Though intermediate samples (i.e., along a transect) can be useful in addressing some questions (e.g., the spatial scale of local adaptation), for most GEA studies, intermediate samples will contribute little in terms of power (Lotterhos and Whitlock 2015). Paired sampling that maximizes environmental distance while minimizing geographic distance has shown high power and low false-positive rates in simulations, since this design maximizes environmental signal while minimizing the confounding effects of population structure (Lotterhos and Whitlock 2015). This sampling design may not be practical for many real species inhabiting complex landscapes, however.

Perhaps unsurprisingly, it is clear from simulation studies that increasing total sample size increases power to detect signatures of selection (De Mita et al. 2013; Lotterhos and Whitlock 2015). However, how those samples are arrayed, either within populations or as individuals, has complex trade-offs in power and false-positive rates. Population-based analyses combine individual genotypes into allele frequency estimates for the population, whereas individual-based analyses use individual genotypes as the response. Population-based sampling involves a compromise between the number of populations sampled and the number of individuals used within each population to estimate allele frequencies. Generally, fewer individuals sampled across more populations is the most effective approach for population-based GEA analysis (De Mita et al. 2013), though the impact of sample allocation can be method- and demography-dependent (Lotterhos and Whitlock 2015). Individual-based sampling and analysis tends to improve power due to the increase in the number of observations; however, this can also lead to increased false positives for univariate (though not multivariate) GEAs (de Villemereuil et al. 2014; Forester et al. 2018). Several studies have also revealed important impacts of

sampling design, including sample size, on characterizing the signal of IBD and other processes that influence spatial genetic patterns (Landguth et al. 2012; Oyler-McCance et al. 2013; Prunier et al. 2013). For example, a simulation study by Landguth et al. (2012) found that although the strength of environmental correlation values was not affected by sample size, the variance increased as sample size decreased. This suggests that an increase in noise of spatial genetic data could play a role in the ability to correctly identify loci under selection.

When possible, replicating sampling across multiple environmental gradients can improve the strength of inference (i.e., more evidence for true adaptive detection, Table 1), if the same candidate loci are identified (e.g., Hohenlohe et al. 2010; Swaegers et al. 2015; Brauer et al. 2016). While a lack of replicated detection can be indicative of false positives (Buehler et al. 2014), parallel adaptation through different genes and genetic architectures (i.e., the underlying genetic basis of a phenotypic trait) is also a possible explanation and one that can occur for a variety of reasons, including metapopulation dynamics, limited dispersal, and habitat heterogeneity (Ralph and Coop 2015a, b; Bernatchez 2016). Disentangling false positives from parallel adaptation involving different genes and architectures is not a simple task in species with limited genomic resources, so a lack of replicated detection should be interpreted cautiously. This complexity illustrates why GEA studies conducted in a small part of a species range should not be naively extrapolated to the entirety of the range, especially for species with strong geographic population structure (Hand et al. 2016).

There are still many avenues for research with regard to sampling protocol for GEA methods. Future work should explore simulations that evaluate sample allocation and effort for GEA method performance in both discrete populations and continuously distributed individuals (e.g., Prunier et al. 2013; Landguth and Schwartz 2014) and across spatially complex environments that control for both gene flow and selection. Most studies thus far have used a spatially random sample drawn from the population(s) to test GEA performance, but in reality, a truly random sampling design is not only difficult to achieve in the field but can also have reduced power relative to more strategic sampling strategies (Lotterhos and Whitlock 2015). Future simulations should consider different sampling designs as well as the number of loci sampled and the effect of missing data.

## ***2.2 Genomic Data Production***

Genomic data production begins with determining which molecular approach will be best suited to the questions under consideration, to the amount of data that will be needed to answer those questions, and to the budget available (Benestan et al. 2016; Hohenlohe et al. 2017). Because most wildlife species lack genomic resources, questions related to adaptive variation in wildlife will usually be best served with an anonymous reduced representation sequencing approach (though see Sect. 4 for a discussion of whole-genome resequencing in wildlife species).

**Table 1** Approaches to improve inference of local adaptation beyond anonymous NGS studies of genotype-environment associations

	Improvement in understanding of local adaptation	Data, logistical, and analytical requirements	General considerations for wildlife species	Examples
Replication of GEA	Identification of the same candidate adaptive loci across replicated gradients improves confidence; lack of replication can indicate parallel adaptation through alternate genetic architectures or false positives	Additional field work, sequencing, and bioinformatics required for additional samples	If possible, should be included in wildlife GEA studies due to relatively low cost and potentially high benefit	Hohenlohe et al. (2010), Buehler et al. (2014), Swaegers et al. (2015), Brauer et al. (2016), and Hand et al. (2016)
Simulation	Many uses including optimizing sampling design to maximize potential for identifying local adaptation; corroborating empirical findings; forecasting future distributions of adaptive variation; developing new theory	No additional data required; analytical efforts depend on the complexity of the simulation framework and scenarios	Given the logistical complexities and limitations of working with many wildlife species, there is considerable room for the creative application of simulation in adaptive studies of wildlife	Cooke et al. (2014), Landguth et al. (2015), Lotterhos and Whitlock (2015), and Creech et al. (2017)
Annotated genome	Can reduce data loss in anonymous NGS studies and improve data quality (e.g., genotyping accuracy) and inference (e.g., candidate validation); annotation can help with biological/ecological interpretation of candidate markers; can be used for targeted exon capture	Reference genome of focal or related species; quality of the reference and level of annotation will determine how useful it is; if producing a new genome, cost and effort may be high, depending on the size and complexity of the genome	Main uses to date have been in wildlife with genome-enabled domesticated relatives. There are few high-quality genomes for wildlife species, though that is changing as costs fall. Caution is needed if using genome of a distantly related species due to ascertainment bias	Roffler et al. (2016) and Ruegg et al. (2018)
Whole-genome resequencing	Identifies all genetic variation across sequenced individuals including structural variants (e.g., copy number variants) and mutations in regulatory elements. Increases power for detection of local adaptation and genetic basis of phenotypes	Requires a reference genome and large computational and storage capacity; greater expense than reduced representation sequencing but produces maximum information content	Not accessible for most wildlife species currently, especially those with large genome sizes (such as many amphibians); more information than is needed to address most conservation and management-related questions	Kardos et al. (2015) and Toews et al. (2016)

<p>Phenotypic data/GWAS</p>	<p>Identifying overlap in loci detected in environmentally stratified GWAS and loci detected by GEA improves strength of inference since independent detections are more likely to reflect true adaptive processes</p>	<p>GWAS requires dense genotyping to have sufficient power. Requires measurement of fitness-related phenotypic traits in many individuals</p>	<p>Unlike QTL mapping, GWAS does not require pedigree data or crosses, making it much more feasible for phenotypic studies in wildlife species</p>	<p>Wenzel et al. (2016) and Lasky et al. (2015)</p>
<p>Common gardens and reciprocal transplants</p>	<p>Provide direct evidence for local adaptation: common gardens establish the genetic basis of fitness (or related traits) while controlling for plasticity, while reciprocal transplants are a direct test of local adaptation</p>	<p>Logistically difficult, time-consuming, and labor-intensive, especially if experiments are replicated across many environments</p>	<p>Can only be used in species that can be reared under controlled conditions or in field-based experiments. Multiple generations raised in controlled conditions provides strongest inference. Have mainly been used in plants</p>	<p>De Kort et al. (2014) and Lasky et al. (2018)</p>
<p>Epigenetics</p>	<p>Extends our understanding of how the environment shapes phenotypic plasticity and local adaptation through non-genetic variation in gene expression. The extent of transgenerational transmission, especially in environmentally induced epigenetic responses, is very poorly understood</p>	<p>Reference-free data production methods are available. Many studies use a transcriptome or annotated genome for data production and/or interpretation</p>	<p>Feasible for studies of associations between environmental and epigenetic variation; establishing transgenerational inheritance requires experimental approaches that are not possible in many wildlife species</p>	<p>Dimond and Roberts (2016), Lea et al. (2016), and Trucchi et al. (2016)</p>
<p>Transcriptomics</p>	<p>Can be used to identify how environmental variation affects gene expression and functionally adaptive variation; can provide insight into the capacity of species to adapt to changing environmental conditions</p>	<p>Tissue requirements often involve sacrifice of animals. Especially in field-based studies, replicate sampling across treatments is required. RNA-specific lab spaces are required. Data can be produced de novo or by mapping to a reference genome</p>	<p>Requires careful experimental design and (for best inference) controlled, experimental treatments. Field-based investigations are possible, but inference of environmental processes driving differential gene expression is limited</p>	<p>Barshis et al. (2013), O'Neil et al. (2014), and Narum and Campbell (2015)</p>

Reduced representation methods require no prior genomic information and randomly subsample the genome to identify single nucleotide polymorphisms (SNPs). The most common anonymous sequencing family is restriction-site associated DNA sequencing (RADseq), which targets DNA adjacent to restriction enzyme cut sites (Andrews et al. 2016). While there are limitations to RADseq approaches (reviewed in Andrews et al. 2016), these methods are relatively inexpensive and produce data from both neutral and adaptive genomic regions which can be used to address a variety of management questions. Depending on genome size and levels of linkage disequilibrium, varying proportions of the genome will be sampled by RADseq methods (Lowry et al. 2016; McKinney et al. 2017). Most management questions related to adaptive variation, however, do not require a complete assessment of adaptive variation across the entire genome, nor the functional validation of candidate loci (Sect. 3). In many cases, characterizing the geographic and environmental patterns of potentially adaptive variation across populations will be sufficient (Catchen et al. 2017; Hohenlohe et al. 2017).

For species without genomic resources, downstream bioinformatics analyses of RADseq data (i.e., locus assembly, genotype, and SNP calling) are done *de novo* (e.g., Catchen et al. 2013). In cases where a high-quality reference genome is available for the focal or a closely related species (e.g., ~tens of millions of years divergent), RAD loci can be aligned to the reference, which can reduce data loss when compared to the stringent filtering required in a *de novo* framework (Table 1; Cosart et al. 2011). However, aligning to a poor quality or divergent reference genome can result in informative loci being lost. Current best practices for RADseq bioinformatics advise first building loci *de novo*, then aligning consensus loci to the reference (Paris et al. 2017).

When prior genomic resources are available (such as a previous RADseq assessment), targeted capture can be used to sequence data from a subset of previously identified regions (Jones and Good 2016). Recent developments that combine RADseq and capture methods (Ali et al. 2016; Hoffberg et al. 2016) have expanded the accessibility of targeted capture and can be used to optimize genotyping across individuals by ensuring consistent coverage of the same loci. In cases where a modest number of SNPs (50–500) are needed, genotyping in thousands by sequencing (GT-seq) can provide a means for genotyping SNPs in thousands of individuals in a single lane of sequencing (Campbell et al. 2015). These methods are especially useful for developing genetic monitoring panels (Flanagan et al. 2018; Schwartz et al. 2007) since they maximize coverage of targeted markers while minimizing cost per individual genotype. See Flanagan et al. (2018) and Benestan et al. (2016) for more detailed overviews of analytical pipelines for reduced representation and targeted sequencing methods, including data filtering, locus assembly and alignment, and genotype and SNP calling.

Finally, when a high-quality, well-annotated reference genome is available and the goal is to capture SNPs in genes of known function, exon capture can be used (e.g., Roffler et al. 2016) (Table 1), though it is often more costly than other approaches (Harvey et al. 2016; Manel et al. 2016). Exon capture can also target ultra-conserved elements and expressed sequence tags (e.g., McCartney-Melstad et al. 2016). Transcriptome sequencing is another option to identify transcribed

portions of the genome; however, rigorous transcriptomic studies will be challenging to implement in most wildlife species (Sect. 4, Table 1).

DNA requirements vary for these methods, though most anonymous and targeted NGS sequencing protocols require 50–100 ng of high-quality DNA, which can usually be satisfied with nonlethal blood or tissue samples. However, for very small animals, such as invertebrates, whole individuals may have to be sacrificed (e.g., Lozier 2014). Noninvasive genetic samples, including hair snags and fecal pellets, have been widely used in microsatellite studies of wildlife species that are difficult and/or expensive to capture (e.g., American black bear, Cushman et al. 2006). Unfortunately, the low levels of DNA present in these samples have posed a challenge for NGS methods, though new techniques are being developed to facilitate the use of these samples in genomic analyses (Andrews et al. 2018). For example, a recent study successfully used NGS on hair samples from American pika (*Ochotona princeps*), indicating that, with appropriate precautions and supporting information (a genomic scaffold in this case), even small amounts of DNA (as little as 1 ng) can be used for adaptive landscape genomics (Russello et al. 2015).

### 2.3 *Environmental Data Production*

Ideally, the environmental data component of GEA analysis should be developed based on the physiology and ecology of the focal species and known or hypothesized drivers of selection. When these factors are not well known, an exploratory approach will be required using available biotic and abiotic predictors. Because of its focus on local environmental conditions, adaptive landscape genomics does not necessarily require continuous environmental surfaces (e.g., interpolated raster layers created using a geographic information system, or GIS). However, these layers are often the default environmental data sources since they cover broad geographic areas (ensuring spatial coverage of sampled individuals and populations) and, for climate data, include long-term temporal resolution (Leempoel et al. 2017). Especially for long-lived wildlife species, sufficient temporal coverage in climate variables is important to capture interannual variability that matches long-term selective pressures. Most publicly available gridded data sets include data at these coarser annual and decadal scales (e.g., CHELSA; Karger et al. 2017). By contrast, high temporal resolution (e.g., daily data; TOPOFIRE; Holden et al. 2013) may be necessary for some species and questions, since extremes, cumulative exposure, and threshold events may be important selective pressures (e.g., Welbergen et al. 2008; Vasseur et al. 2014; Buckley and Huey 2016; Gardner et al. 2016). These data are available, but usually on reduced spatial scales. The relatively coarse spatial scale of these interpolated data sets (usually ~1 km resolution) can also be problematic for smaller species, since these data cannot capture relevant microclimates and can underestimate habitat and climatic heterogeneity (Nadeau et al. 2017). In these cases, field-based sensors for site-specific data collection (e.g., HOBOS, Onset Computer Corp.) and modeling may provide the highest spatial resolution (e.g., Peterman and Semlitsch 2013), but these data will be limited by their reduced

temporal component (i.e., limited to the time period during which data were collected). Exceptions to this temporal data issue include major catastrophic or selective events, such as severe drought or virulent disease (e.g., Grant and Grant 1993; Epstein et al. 2016). Finally, another option for site-specific climate data with potentially long temporal resolution is weather station data (e.g., RAWS; <https://raws.dri.edu/>); however, these data are typically sparse in space.

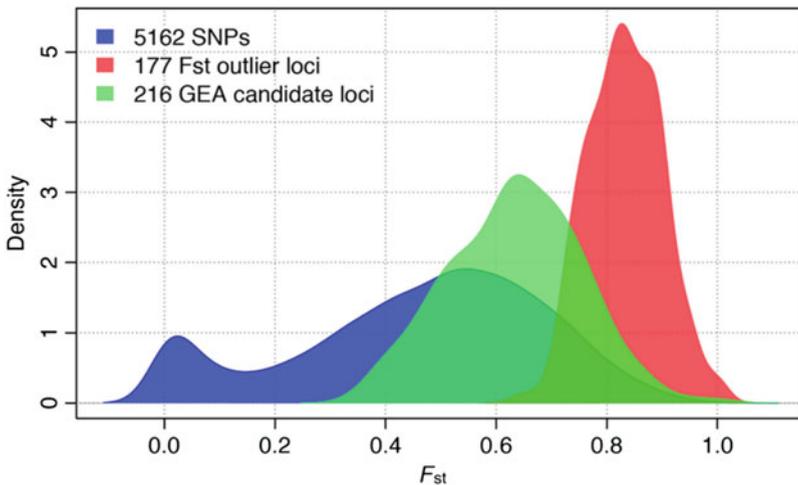
There are a large number of free climate and land cover GIS data sets available. Caution and skepticism are warranted, however, since these data sets can vary widely in their quality (Daly 2006). High-quality global data are available from CHELSA (Karger et al. 2017) and the Consortium for Spatial Information ([www.cgiar-csi.org/data](http://www.cgiar-csi.org/data)) for climate and water balance and from EarthEnv ([www.earthenv.org](http://www.earthenv.org)) for land cover and vegetation. Other regional climate resources (mostly North America) include TopoWx (Oyler et al. 2015), ClimateNA (Wang et al. 2016), and water balance data through AdaptWest (Dobrowski et al. 2013) for North America and Copernicus for global- to European-scale data (<http://climate.copernicus.eu> and <http://land.copernicus.eu>). In addition, the growing availability of environmental data from remotely sensed data products (e.g., <http://earthdata.nasa.gov>), including climate and land use time series datasets, offers unprecedented opportunities in landscape genomics to account for environmental variables (and changes in those variables) influencing local adaptation.

Once available data are identified, the next step is to extract and/or calculate relevant predictors. Whenever possible, it is best to use proximal (e.g., temperature, precipitation) as opposed to distal (e.g., elevation, latitude) predictors, since proximal variables are more ecologically relevant and may decouple from their distal proxies over time, for example, under climate change (Lookingbill and Urban 2005). Many environmental predictors will be highly correlated with each other (e.g.,  $|r| > 0.7$ , Dormann et al. 2013), which is statistically problematic for most GEA methods and confounds interpretation. Methods for dealing with collinearity include pruning predictors using a pairwise correlation matrix or variance inflation factor (retaining the variable most relevant or ecologically interpretable) or using PCA to reduce a large number of predictors into orthogonal synthetic predictors, though this can limit ecological interpretation. Finally, because GEAs are correlative models, environmental predictors identified as important by a GEA analysis may not be the driving selective pressures. Collinear predictors that were removed during pruning and other correlated but unmeasured biotic and abiotic conditions may also be important (Rellstab et al. 2015).

## ***2.4 Data Analysis with Genotype-Environment Associations***

Genotype-environment association (GEA) analysis (also called environmental association analysis) refers to a group of statistical analyses used in adaptive landscape genomics to partition neutral from potentially adaptive genetic variation. GEA methods identify candidate adaptive loci based on associations between allele

distributions and environmental variables hypothesized to drive selection, reflecting a pattern of selected alleles at higher frequency in certain environments (reviewed in Rellstab et al. 2015). This is in contrast to a population genomics approach, where adaptive loci are identified by differentiating locus-specific patterns (caused by locus-specific processes including selection) from the genome-wide pattern (caused by genome-wide processes, such as genetic drift, demographic processes, and gene flow; Luikart et al. 2003). These differentiation-based methods are useful for detecting strong divergent selection (Storz 2005) and are especially valuable when environmental predictors are not available or when the number of sampled populations is small. Limitations of differentiation-based approaches include a requirement for population-based sampling and a basis in theoretical population genetic models that are violated by many empirical systems. By contrast, many GEA methods can be used with either individual- or population-based sampling, which is advantageous when environmental gradients are continuous or when populations are not clearly distinguishable (Jones et al. 2013). Additionally, most GEA methods do not use an underlying population genetic model and so are not sensitive to the deviations common in empirical systems. GEA methods are not limited to detecting divergent selection, but can also detect weaker selective pressures, such as selection on standing genetic variation (Forester et al. 2018; Fig. 2). Finally, the inclusion of environmental predictors improves power when compared with differentiation-based methods (De Mita et al. 2013; de Villemereuil et al. 2014; Rellstab et al. 2015).



**Fig. 2** Density distribution of  $F_{ST}$  values for SNPs identified in southern pygmy perch (*Nannoperca australis*): 5,162 neutral and candidate adaptive SNPs (blue), 177 candidate loci identified using  $F_{ST}$  outlier/differentiation-based methods (red), and 216 candidate loci identified using GEA methods (green). The narrow  $F_{ST}$  distribution of outlier candidates with a high mean  $F_{ST}$  ( $\sim 0.8$ ) is indicative of divergent selection and allelic fixation, while the broader  $F_{ST}$  distribution of GEA candidates with a lower mean  $F_{ST}$  ( $\sim 0.6$ ) is indicative of polygenic selection from standing genetic variation. Figure from Brauer et al. (2016)

However, differentiation-based tests can provide complementary information to GEA results, since they can detect the impact of selective pressures that may not be captured by the selected environmental predictors.

Both sets of methods are sensitive to neutral genetic structure, which can produce spatial patterns that resemble selection, resulting in elevated false-positive rates in the absence of correction. Most GEA methods incorporate an approach for controlling for neutral genetic structure, including covariance matrices, the probability of membership from clustering or ordination analyses, spatial predictors, and other spatial analyses such as trend surface analysis (Rellstab et al. 2015). These corrections are applied in a diversity of GEA methods, most of which are univariate, meaning they test one locus and one predictor variable at a time. These methods include generalized linear models (e.g., Joost et al. 2007; Stucki et al. 2017), linear mixed effects models (e.g., Coop et al. 2010; Frichot et al. 2013; Lasky et al. 2014; Yoder et al. 2014), and nonparametric models (e.g., partial Mantel test, Hancock et al. 2011). Univariate GEAs can produce elevated false-positive rates due to the multiple comparisons required to test individual SNPs and predictors. Multiple test corrections, such as Bonferroni, can be overly conservative (potentially removing true-positive detections), while alternative correction methods, such as false discovery rate (Benjamini and Hochberg 1995), rely on an assumption of a null distribution of  $p$ -values, which may often be violated in empirical data sets. While these issues should not discourage the use of univariate methods (though corrections should be chosen carefully, see François et al. (2016) for an overview), other statistical approaches may be better suited to the high dimensionality of genomic data sets.

In particular, multivariate GEAs, which can analyze all loci and predictor variables simultaneously, are well suited to data sets comprising hundreds of individuals sampled at many thousands of genetic markers. These methods can more effectively detect multilocus selection since they consider how groups of markers covary in response to environmental predictors (Rellstab et al. 2015; Forester et al. 2018). This is important because many adaptive processes are expected to result in weak, polygenic molecular signatures. These include selection on standing genetic variation, recent or contemporary selection that has not yet led to allele fixation, and conditional neutrality (Yeaman and Whitlock 2011; Le Corre and Kremer 2012; Savolainen et al. 2013; Tiffin and Ross-Ibarra 2014). Multivariate GEAs include redundancy analysis (RDA), which was recently tested in a simulation framework and showed a superior combination of high true-positive and low false-positive rates while being robust to different demographic histories, sampling designs, and sample sizes (Forester et al. 2018). While additional testing is needed, multivariate GEAs show promise as a powerful complement to univariate detection approaches.

Finally, our understanding of the performance of GEA methods under realistic genomic architectures and sampling effects has been limited by the relatively simplistic simulation frameworks used to date. Additional testing of GEA methods on more complex genetic architectures (e.g., conditional neutrality vs. antagonistic pleiotropy, multilocus vs. polygenic selection) and realistic genomic sampling conditions is needed (e.g., Yoder and Tiffin 2017). In sum, it is important to realize that different approaches for detecting loci influenced by selection can yield different

conclusions, and a common standard for reporting the analysis of adaptive genomic data has yet to be developed (see Ahrens et al. 2018).

### **3 Applications and Potential of Adaptive Landscape Genomics in Wildlife Research**

Adaptive landscape genomics has been used in many studies to identify candidate adaptive variation, its environmental drivers, and spatial distribution. While these studies are important in that they provide a baseline for additional research, there are still a limited number of wildlife studies that move beyond data generation to directly address ecological and evolutionary questions and/or management issues. In this section, we discuss recent applications of adaptive landscape genomics in wildlife research and highlight notable case studies. We then follow up with areas for advancement that have not yet been implemented in wildlife genomics.

#### ***3.1 Current Applications of Adaptive Landscape Genomics in Wildlife Research***

##### **3.1.1 What Are the Ecological and Evolutionary Processes Underlying Spatial Patterns of Neutral and Adaptive Genetic Variation?**

Explicit investigation of how neutral and candidate adaptive genetic variation relate to spatial and environmental variation can provide insight into the ecological and evolutionary processes that generate observed genetic patterns. These patterns include isolation by distance (IBD) and isolation by environment (IBE), which can be explained by the processes of isolation by dispersal limitation and isolation by adaptation, respectively (Orsini et al. 2013; Wang and Bradburd 2014). These analyses can provide information on species biology, ecology, and evolutionary history, including estimates of dispersal distance, biased dispersal (e.g., due to fitness advantage or natal habitat preference), colonization history, natural or sexual selection against immigrants, and reduced hybrid fitness. In a recent application, Manthey and Moyle (2015) tested for patterns of IBD and IBE in white-breasted nuthatches (*Sitta carolinensis*) inhabiting the sky islands of the southeastern United States. By investigating both neutral and candidate adaptive markers, they identified IBE as the significant pattern structuring both neutral and adaptive markers, with an absence of IBD. Extremes of temperature and precipitation structured environmental adaptation due to nonrandom gene flow among populations, pointing to a generative process of isolation by adaptation as a result of biased dispersal (i.e., birds selecting more suitable environments).

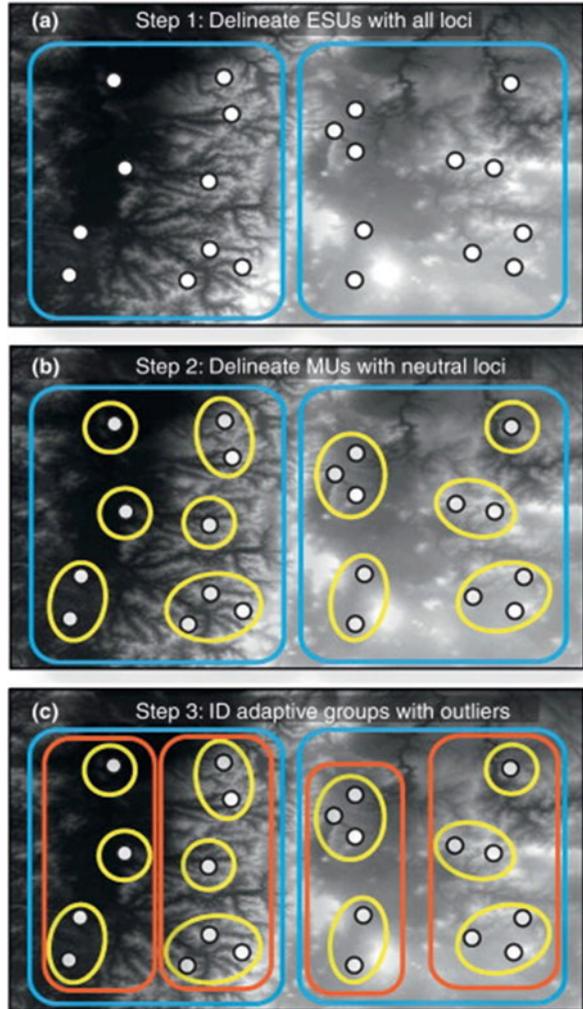
### 3.1.2 What Are the Relative Roles of Genetic Drift and Natural Selection in Structuring Genetic Variation in Small Populations?

Genetic drift is expected to be the dominant genetic process in populations with small effective sizes, constraining selection and lowering adaptive capacity (e.g., Lande 1988; Willi et al. 2006). However, recent studies have suggested that, while small populations show a decline in genetic variation due to drift, these declines may not overwhelm selection or necessarily lower adaptive capacity (Brauer et al. 2016; Funk et al. 2016; Wood et al. 2016). This could have important implications for conservation and management of these populations, including informing genetic rescue and assisted migration efforts (Sect. 3.2.1). Brauer et al. (2016) provide a compelling example of retained adaptive divergence in spite of strong genetic drift and geographic isolation in the threatened southern pygmy perch (*Nannoperca australis*). Using univariate and multivariate GEAs, they found signatures of parallel polygenic adaptation to environmental and physical gradients that were replicated across demographically independent populations (Fig. 2). The smaller and more isolated headwater populations had less standing genetic variation at candidate adaptive loci in comparison to larger downstream populations, pointing to these latter populations as sources for genetic rescue or assisted migration efforts into recently and anthropogenically isolated populations.

### 3.1.3 How Can Knowledge of Adaptive Differentiation Inform the Delineation of Conservation Units?

Genomic data can improve the delineation of conservation units through increased resolution into neutral differentiation (e.g., Lah et al. 2016; Peters et al. 2016) and characterization of adaptive differentiation (Funk et al. 2012; Prince et al. 2017; Ruegg et al. 2018) (Fig. 3). For example, genomic data were used to identify neutral and adaptive differentiation in Baltic Sea herring (*Clupea harengus*) where previous studies using smaller genetic datasets had found little evidence for differentiation (Guo et al. 2016). This study provided additional evidence that current herring management units may have negative impacts on fisheries yields since they are poorly aligned with biological units based on local adaptation to salinity and temperature. As this case illustrates, adaptive differentiation can inform the delineation of ecotypes: populations (or subspecies) that are adapted to local environmental conditions. Defining ecotypes can be especially important in conservation efforts where the emphasis is not only on maintaining neutral genetic diversity but also overall evolutionary potential (Harrisson et al. 2014). While adaptive differentiation can be characterized using differentiation-based approaches (e.g., Cooke et al. 2014; Moura et al. 2014), landscape genomics provides additional insight into the environmental drivers of local adaptation, which can better inform conservation efforts (e.g., Pavey et al. 2015). For example, a recent study of the willow flycatcher

**Fig. 3** Workflow for using genomic data to delineate and test for adaptive differentiation among conservation units. White circles are sampling locations, blue outlines are evolutionarily significant units (ESUs), yellow outlines are management units (MUs), and orange outlines are adaptively similar groups of MUs. The grayscale background is an elevation layer (low to high represented by black to white). (a) Step 1: Delineate ESUs with all loci. (b) Step 2: Delineate MUs with neutral loci. (c) Step 3: Identify adaptive groups with outliers. Figure from Funk et al. (2012)

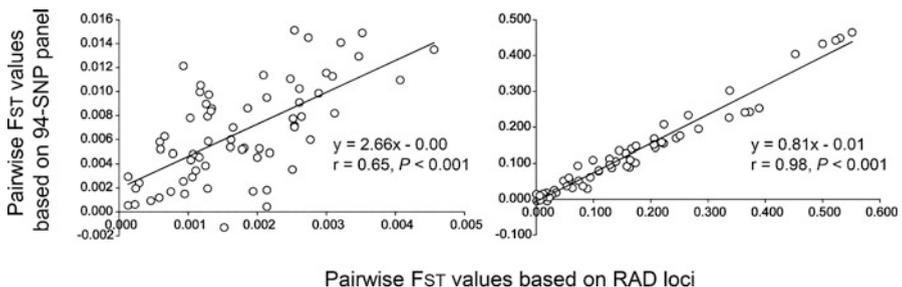


complex, including the endangered Southwestern willow flycatcher (*Empidonax traillii extimus*), supported the validity of this subspecies classification based on local adaptation related to temperature extremes (Ruegg et al. 2018). This study also found that the Southwestern subspecies was at the greatest risk for climate-mediated extinction due to high genomic vulnerability (a measure of the mismatch between adaptive genotypes and future environmental conditions).

### 3.1.4 How Can Adaptive Landscape Genomics Inform the Design of Conservation Monitoring Programs?

Depending on the conservation needs of a species, a genomic monitoring plan may be essential to effective management; however, there are few examples of genomic monitoring in the published literature. The best monitoring plans identify criteria for biologically significant change and develop a strategy for management intervention given detection of this change *prior* to initiating monitoring (Flanagan et al. 2018; Schwartz et al. 2007). This approach best ensures that monitoring will trigger timely management interventions, rather than just documenting decline and possibly extinction (Lindenmayer et al. 2013). An initial genomic assessment (e.g., RADseq study) can be used to identify a subset of neutral and candidate adaptive markers to be targeted for a monitoring panel using sequence capture or SNP arrays (e.g., Hohenlohe et al. 2011; Amish et al. 2012; Houston et al. 2014; Wright et al. 2015; Aykanat et al. 2016). While monitoring of neutral genetic variation can inform important parameters such as changes in genetic diversity and population size, monitoring of candidate adaptive variation can provide information on the status of adaptively divergent populations (Sect. 3.1.3) and management interventions such as assisted gene flow (Sect. 3.2.2).

For example, Hess et al. (2015) transitioned an initial NGS assessment (Hess et al. 2013) into a robust and multifaceted monitoring program for declining Pacific lamprey (*Entosphenus tridentatus*) (Fig. 4). They identified 96 neutral and candidate adaptive markers that were diagnostic for parentage analysis, cryptic species identification, and characterization of neutral and candidate adaptive genetic variation. These markers were incorporated into a SNP array and are currently being used to monitor the effectiveness of a diverse set of management actions including translocation, artificial propagation, and habitat restoration, as well as track population size, facilitate species identification at early life stages, and link adaptive markers to lamprey phenotypes (body size and migration timing). Appropriate sampling design for temporal monitoring of genetic change is still not well understood and will



**Fig. 4** Correlation between pairwise  $F_{ST}$  values from the full RADseq marker set and the 96-SNP monitoring panel developed for Pacific lamprey (*Entosphenus tridentatus*), showing neutral (left) and adaptive (right) SNPs for Columbia River Basin samples. Mantel tests indicate good representation of genomic-scale  $F_{ST}$  values in the monitoring panel. Figure from Hess et al. (2015)

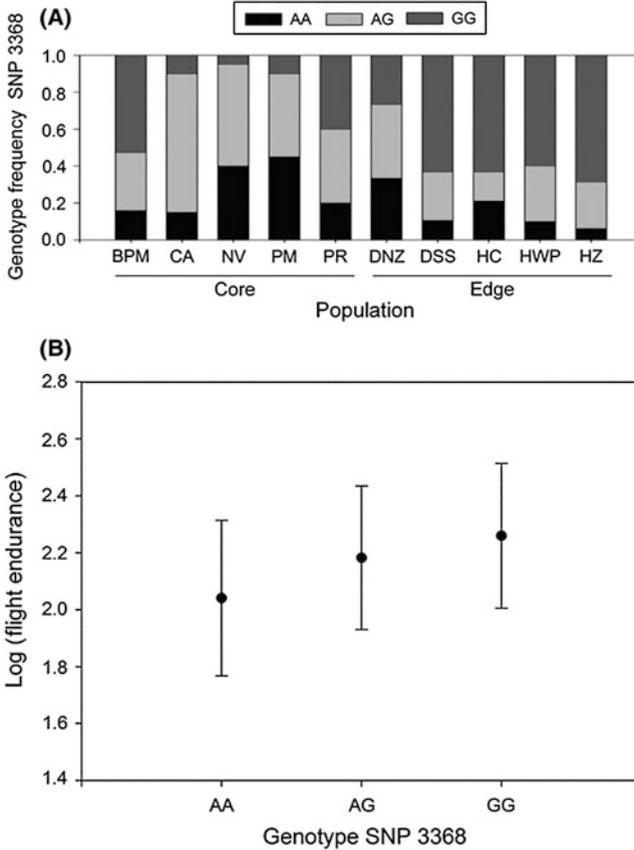
depend on the biology and demography of the species, the study objectives, and the power of the markers and sampled individuals to detect change (Schwartz et al. 2007; Allendorf et al. 2008; Hoban et al. 2014). Simulations, an underutilized tool in conservation management, will continue to play an important role in optimizing sampling design for genomic monitoring (Balkenhol and Landguth 2011; Hoban et al. 2013).

### **3.1.5 What Are the Genomic Implications of Range Expansion Under Climate Change?**

Range shifts are some of the best-documented responses to climate change, with species across many taxa showing (sometimes idiosyncratic) changes in their distribution in response to changing climatic conditions (Hickling et al. 2006; Chen et al. 2011). Range expansions should leave predictable signals of founder effects and allele surfing at neutral loci (Excoffier et al. 2009), accompanied by changes in traits to facilitate adaptation and the rate of spread (Phillips et al. 2010). Linking genomic signals of evolution to these phenotypic changes has been rare, and it is not well understood how rapid trait changes on the expanding front are mediated by allele frequencies within populations. Swaegers et al. (2015) addressed these questions using a carefully planned adaptive landscape genomics study in a range-expanding damselfly (*Coenagrion scitulum*), accompanied by existing phenotypic data. By evaluating five different core-edge sets of populations, these authors demonstrated replicated neutral changes predicted by theory in independently established edge populations: founder effects, reduced gene flow, and higher levels of genetic drift. Using candidate adaptive markers, they identified parallel evolution for increased flight endurance in edge populations across four of the five populations, indicating convergent evolution from a locus that was polymorphic in the shared ancestral population (Fig. 5). Finally, using a multivariate GEA, the authors identified a genomic signal of adaptation to changing thermal regimes. This is one of only a few studies that has demonstrated a genetic basis to phenotypic changes during range expansion in response to climate change.

### **3.1.6 Can We Predict the Spatial Distribution of Adaptive Genetic Variation Under Changing Climates?**

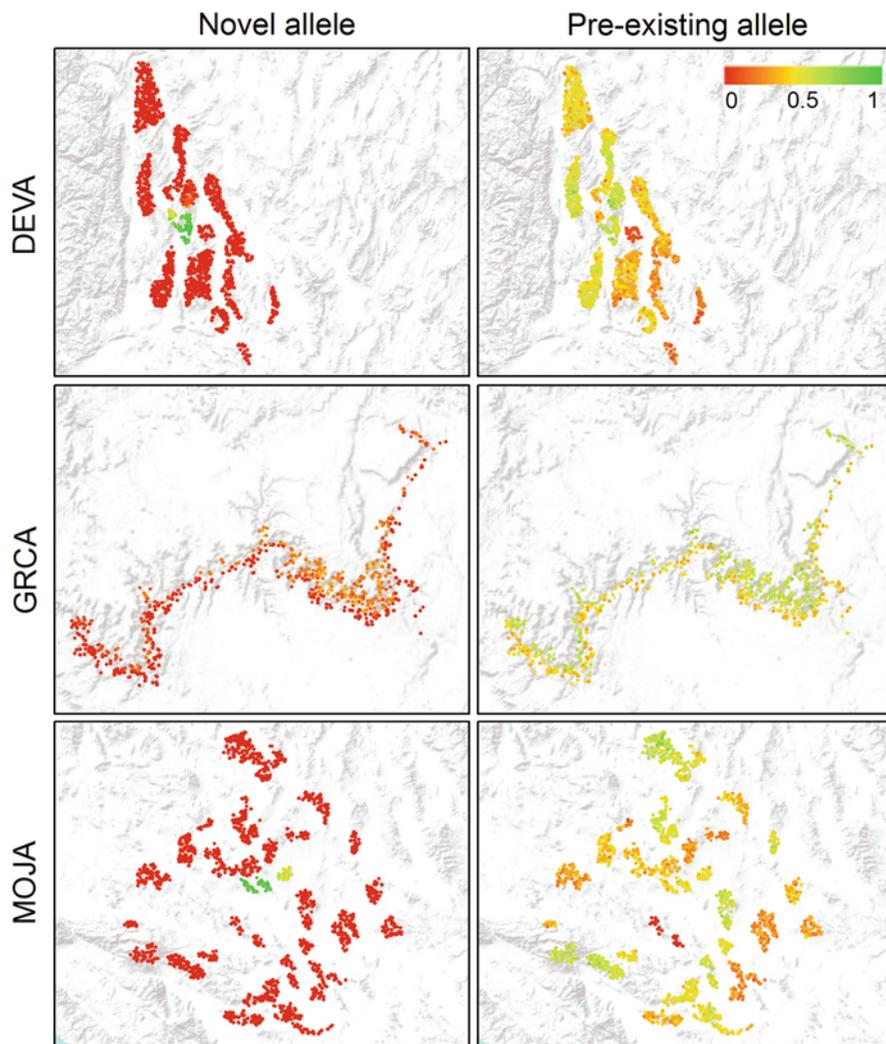
Species distribution models are commonly used in the ecological and conservation literature to predict changes in species distributions in response to climate change (e.g., Early and Sax 2011; Forester et al. 2013; Guisan et al. 2013; Hazen et al. 2013). These models generally use a static species-climate relationship for prediction and do not consider intraspecific variation in climate responses due to plasticity or local adaptation. However, with the increasing availability of genetic data for species of conservation concern, the incorporation of intraspecific variability into these models is now possible (e.g., Ikeda et al. 2017). These genetically informed models have



**Fig. 5** (a) Genotype frequencies of candidate adaptive SNP 3368 in core and edge damselfly (*Coenagrion scitulum*) populations. (b) Flight endurance for the three genotypes of SNP 3368 (log-transformed flight endurance in seconds with 95% confidence intervals). The GG genotype was found at higher frequency in edge (expanding) populations and was associated with the highest mean average flight endurance. Figure from Swaegers et al. (2015)

been used to predict where and when future climates may disrupt patterns of local adaptation (Jay et al. 2012; Fitzpatrick and Keller 2015) and inform assessments of adaptive capacity under future climate change (Razgour et al. 2018; Bay et al. 2018). In a recent study, Creech et al. (2017) used a simulation approach to investigate the spread of adaptive genotypes in desert bighorn sheep, a habitat specialist expected to be threatened by habitat loss and further fragmentation due to climate change. In this novel approach, landscape resistance models were developed for desert bighorn sheep (*Ovis canadensis nelsoni*) in three different regions that varied in habitat quantity and configuration, using data from neutral genetic markers (mostly noninvasively collected). Simulations based on these resistance models were used to investigate how the spread of an adaptive allele varied based on selection strength and whether the adaptive variant was derived from standing genetic variation or a

new mutation. Adaptation from standing genetic variation had a much higher incidence of spread and likelihood of persistence than a novel mutation, especially when landscapes were more highly connected (Fig. 6). These results are in line with



**Fig. 6** Simulated spread of an adaptive allele in populations of desert bighorn sheep (*Ovis canadensis nelsoni*) in different regions of the United States over 100 years. Regions are Death Valley in the northern Mojave Desert (DEVA), the Grand Canyon in northern Arizona (GRCA), and the southern Mojave Desert (MOJA). Colored dots are individual locations with color gradient reflecting the proportion of simulation Monte Carlo replicates in which the adaptive allele is present ( $\geq 1$  copy) in each individual at year 100, assuming strong selection and a medium dispersal threshold. Left and right columns show presence of the adaptive allele after novel mutation and selection on standing genetic variation, respectively. Figure from Creech et al. (2017)

empirical and conceptual work (reviewed in Hendry 2013) and highlight the importance of maintaining standing genetic variation in desert bighorn sheep populations, as well as the potential need for assisted gene flow (see below) targeting multiple locations in isolated populations.

### ***3.2 Underutilized Applications of Adaptive Landscape Genomics in Wildlife Research***

There are a variety of questions and applications informed by adaptive landscape genomics that have not yet been implemented in wildlife research, but which have significant potential to improve our understanding of ecological and evolutionary processes and management applications. Below we highlight the potential of adaptive landscape genomics for questions related to wildlife management.

#### **3.2.1 Using Adaptive Landscape Genomics to Inform Genetic Rescue**

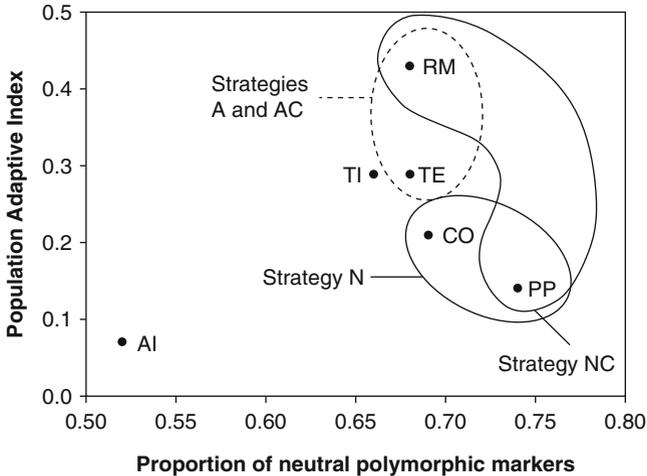
The purpose of genetic rescue is to improve the viability of small, isolated, and declining populations by increasing neutral genetic diversity through the movement of individuals between populations (Whiteley et al. 2015). Genetic rescue can be beneficial for populations that are at risk of or are currently experiencing deleterious effects from inbreeding depression, and has been used successfully in a number of high-profile conservation efforts (e.g., Florida panthers (Johnson et al. 2010); wolves (Vilà et al. 2003; Adams et al. 2011); and bighorn sheep (Miller et al. 2012)). The main concern with genetic rescue is outbreeding depression, a reduction in fitness due to mixing divergently adapted genotypes (Edmands 2007); however, recent reviews have highlighted the potentially large benefits and limited risks when genetic rescue is carefully implemented (Hedrick and Fredrickson 2010; Weeks et al. 2011; Frankham 2015; Whiteley et al. 2015). Adaptive landscape genomics can play an important role in minimizing the risks of outbreeding depression by providing an assessment of the environmental and spatial factors that structure adaptive genetic variation across populations. By identifying source populations that minimize adaptive (and also environmental) divergence from the target population, the risk of adaptive incompatibilities and outbreeding depression can be reduced. While assessment of adaptive genetic differentiation is not a requirement for a successful genetic rescue program, it provides additional insight into the characteristics of target and potential source populations that can be used to maximize the effectiveness of this management intervention (Whiteley et al. 2015; Fitzpatrick and Funk 2018). Since genetics studies in wildlife will increasingly use NGS methods to develop molecular markers, incorporating adaptive variation in plans for genetic rescue should become a more common approach.

### **3.2.2 Using Adaptive Landscape Genomics to Inform Assisted Gene Flow**

In contrast to genetic rescue, assisted gene flow is a proactive management technique that involves the directional movement of “preadapted” individuals between populations (and within a species range) to facilitate adaptation to changing conditions. It has been advocated for long-lived, sessile species such as trees (e.g., Steane et al. 2014) and species that have a limited ability to track climate conditions that they are currently adapted to (Sgro et al. 2011; Aitken and Whitlock 2013). Unlike genetic rescue, the target population for assisted gene flow should have a large effective population size (to maximize the effectiveness of selection and minimize the impact of genetic drift), and the source and target populations should be divergent based on their adaptive genotypes, where the source population has adaptive variation expected to be advantageous under future conditions in the target population. The concerns about assisted gene flow include the disruption of local adaptation; the loss of distinct, locally adapted lineages; and outbreeding depression. Additionally, because NGS methods that sample the genome do not provide a complete assessment of adaptation, it is possible to reduce fitness with introduced individuals due to maladaptation to an unsampled adaptive parameter, in spite of beneficial adaptation to changing climatic conditions. One option for addressing this issue is to maximize available adaptive variation in source individuals by using a “portfolio effect” or “composite provenancing” that covers a broader range of future climate conditions as well as other, potentially unknown but important selective parameters (Schindler et al. 2010; Sgro et al. 2011; Weeks et al. 2011; Aitken and Whitlock 2013). However, for many populations and species that either lack the capacity for long-distance movement or have no available suitable habitats to disperse into, adaptation in place will be the only alternative to maladaptation, extirpation, and extinction. In these cases, consideration of the potentially far-reaching benefits and careful evaluation to minimize the risks of assisted gene flow can provide an important option for the management of vulnerable populations (Weeks et al. 2011; Aitken and Whitlock 2013).

### **3.2.3 Using Adaptive Landscape Genomics to Inform Site Prioritization to Maximize Evolutionary Potential**

Conservation plans are generally focused on protecting the maximum amount of diversity (e.g., the number of different species) in the fewest number of sites and/or at the lowest cost. By selecting sites with complementary sets of species (i.e., sites that are most dissimilar), biodiversity protection can be maximized while minimizing the number of sites in the network (Margules and Pressey 2000). Site prioritization can also be extended to intraspecific diversity to ensure



**Fig. 7** Pairs of populations of the common frog (*Rana temporaria*) chosen for conservation based on different strategies: strategy N, protection of the two populations with the two highest neutral diversities; strategy NC, protection of the two populations with the highest pairwise neutral diversity; strategy A, protection of the two populations with the two highest population adaptive indexes; and strategy AC, protection of the two populations with the highest pairwise population adaptive indexes. NC and AC use the principle of complementarity applied to the neutral and adaptive data, respectively, to maximize the breadth of conserved genetic variation. Figure from Bonin et al. (2007)

sufficient protection of genetic diversity within species conservation plans (Bonin et al. 2007) (Fig. 7). When neutral genetic data are available, the goal is most often to prioritize populations that maximize the within and between group variability of the species (e.g., Ottewell et al. 2016). However, with increasing pressures on species to adapt to rapidly changing environmental conditions, conserving the maximum amount of adaptive genetic diversity is also essential to ensure the evolutionary potential of threatened species (Nicotra et al. 2015). The inclusion of adaptive genetic variation into the site prioritization framework was first advocated a decade ago by Bonin et al. (2007). However, few empirical examples have been published in academic journals, which likely reflects the lack of genomic data for species of conservation concern, though some studies may have been published in the gray literature due to the applied nature of the work (Garner et al. 2016). The decreasing costs of genomics should ensure a revival of this framework for informing conservation plans.

### 3.2.4 Using Museum Collections to Better Understand Changes in Adaptive Variation over Time

Museum collections represent a rich source of historical genetic variation that can be invaluable in understanding the evolutionary consequences of recent environmental

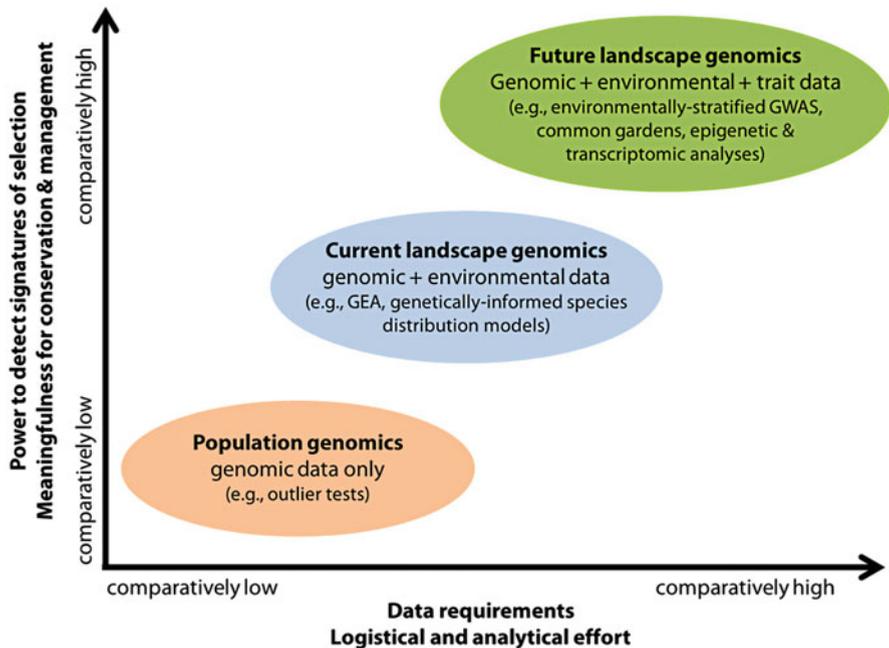
change in wildlife species (Holmes et al. 2016). For example, Miller and Waits (2003) amplified eight neutral microsatellite markers in 110 museum samples of Yellowstone grizzly bear to assess the impact of past anthropogenic isolation and culling on future genetic viability of this population. The transition from these genetic-scale museum studies to genomic-scale data that can be used to investigate selection and adaptation has been hampered by the challenges of working with highly degraded DNA. Fortunately, several recent approaches have been used to develop genomic-scale marker sets, including adaptive markers, from museum samples (Andrews et al. 2018), including targeted sequencing of immune response loci in the Pale-headed Brushfinch (Hartmann et al. 2014), exon capture in alpine chipmunks (Bi et al. 2013), and whole-genome sequencing in honey bees (Mikheyev et al. 2015). These methods currently require more genomic information than can be provided by a reduced representation NGS study, but increasing amounts of genomic data (including reference genomes) for non-model species and falling sequencing costs indicate that historical data may soon be an option for many wildlife species. Techniques are even being developed for formalin-fixed samples (characteristic of, e.g., amphibian, reptile, and fish specimens), though these approaches are currently limited to neutral markers developed for phylogenomic studies (Hykin et al. 2014; Ruane and Austin 2017).

### **3.2.5 Using Adaptive Landscape Genomics to Inform the Management of Hybridization**

Hybridization is a fundamental management problem addressed in conservation genetics (Bohling 2016), and genomic methods are being increasingly used to identify and manage hybridization at high resolution in a diversity of wildlife species (e.g., Fitzpatrick et al. 2009; vonHoldt et al. 2011; Hohenlohe et al. 2013; Kovach et al. 2016; Wayne and Shaffer 2016). However, natural and human-mediated hybridization may also be an effective tool for improving the adaptive capacity of threatened species in response to rapid anthropogenic change, such as climate change (Hoffmann et al. 2015; Hamilton and Miller 2016). To our knowledge there are no examples of managed hybridization in wildlife populations with the specific goal of facilitating adaptive introgression, though experimental (e.g., salt tolerance in yeast, Stelkens et al. 2014) and accidental (e.g., insecticide resistance in mosquitos, Norris et al. 2015) cases demonstrate the power of hybridization to improve adaptive capacity in response to strong selective pressures. As with assisted gene flow, adaptive landscape genomics could play an integral role in determining appropriate source populations for managed adaptive introgression to facilitate evolutionary resilience in the face of rapid environmental change.

## 4 Future Research Avenues in Wildlife Landscape Genomics: Improving and Moving Beyond Genotype-Environment Associations

Adaptive landscape genomics has led to valuable insights in wildlife studies and can be used to address important ecological and evolutionary questions and management issues. Future studies will be able to choose from an even larger number of statistical methods for conducting adaptive landscape genomics, and this choice will hopefully be guided by emerging recommendations regarding their relative suitability for addressing specific research questions (Rellstab et al. 2015; Balkenhol et al. 2017). Here, we have largely focused on one type of analytical approach used in adaptive landscape genomics, the analysis of genotype-environment associations. As discussed above, GEA is a main component of most current landscape genomic studies aiming to find relationships between selection-driven loci and environmental heterogeneity. Nevertheless, we emphasize that using additional analytical approaches and incorporating complementary data in wildlife research can improve our understanding of adaptation (Table 1, Figs. 1 and 8). Some of these are already in use in wildlife studies, such as replication of GEA sampling across gradients (Sect. 2.1), the incorporation of a well-annotated reference genome (Sect. 2.2), and



**Fig. 8** Analytical approaches to understanding local adaptation (ellipses). Their relative data and analytical requirements ( $x$ -axis) and power and utility for conservation and management ( $y$ -axis) range from comparatively low to comparatively high

the use of simulations (Sect. 3.1.6). Simulations in particular are underutilized in landscape genomics research, and recent applications illustrate their value in corroborating empirical findings (e.g., Cooke et al. 2014) and in developing new theories (reviewed in Landguth et al. 2015) (Table 1). Additionally, as sequencing costs fall, whole-genome resequencing is becoming an option for some wildlife species (e.g., Kardos et al. 2015; Toews et al. 2016; Therkildsen and Palumbi 2017), providing increased marker density when compared to reduced representation methods, in addition to identifying other genetic variation such as structural variants (Fuentes-Pardo and Ruzzante 2017) (Table 1). However, the limited accessibility and affordability of this approach over reduced representation methods makes whole-genome resequencing less feasible for conservation and management applications in wildlife (Fuentes-Pardo and Ruzzante 2017).

#### ***4.1 Integrating Phenotypic Data Through Environmentally Stratified GWAS and GEA***

One of the major advantages of the GEA-based approach to adaptive landscape genomics is that no phenotypic data are required. Nevertheless, natural selection acts on the phenotype, not the genotype. Thus, our understanding of the processes that shape patterns of adaptive genetic variation in heterogeneous environments will likely not be complete without considering phenotypic variability. Because of this, particularly interesting complements to GEA are analytical approaches that account for phenotypic variability when assessing landscape influences on genomic variation. There are a few examples of adaptive landscape genomics studies in wildlife that have used a post hoc approach to incorporating phenotypes, by correlating trait data with candidate loci identified through GEA analysis (Swaegers et al. 2015; Funk et al. 2016).

A more promising approach is to combine detections from GEA analysis with those from genome-wide association studies (GWAS) that are conducted for many individuals across environmental gradients. Whereas GEA methods look for relationships between genotypes and environment, GWAS uses statistical approaches to test for relationships between phenotypes and genotypes. For example, Lasky et al. (2015) used GEA associations with climate to predict GWAS-derived phenotypic variation in adaptive traits in the important food crop *Sorghum bicolor*. In another case, Berg and Coop (2014) combined GWAS with quantitative genetics and GEA to detect signals of local adaptation in several human traits. Unless a reference genome is available, the genes detected by GWAS are anonymous, i.e., their exact locations on the genome and their functions are usually unknown. However, one could argue that for the fate of individuals and populations, and for wildlife conservation management, it is not usually crucial to identify the location and function of adaptive genes, but rather to understand their effects on fitness. In either case, linking the phenotype-genotype results of environmentally stratified GWAS

with genotype-environment-derived GEA detections can improve the strength of inference in adaptive landscape genomic studies, since independently detected and overlapping loci are more likely to reflect true adaptive processes.

GWAS studies in wildlife species are currently somewhat limited, and (similar to GWAS in other groups) their success in identifying genetic variation underlying fitness-relevant phenotypes is mixed (e.g., Johnston et al. 2011; Santure et al. 2013; Wenzel et al. 2016). However, in wildlife species where data on fitness-relevant phenotypic traits can be collected, the integration of environmentally stratified GWAS and GEA will provide greatly improved inference for adaptation that can inform ecological, evolutionary, and management questions.

#### ***4.2 The Value of Experimental Manipulations in Informing Assessments of Adaptation***

Experimental manipulations provide the most direct evidence for the genetic basis of a fitness-related trait and/or local adaptation (Savolainen et al. 2013; de Villemereuil et al. 2016). Common gardens are used to rear individuals from different habitats/environmental conditions under common controlled or field conditions. While common gardens are designed to study the genetic basis of traits while controlling for phenotypic plasticity, they can be confounded by genotype-by-environment interactions (Kawecki and Ebert 2004; Merilä and Hendry 2014), though replication across environments can alleviate this problem (de Villemereuil et al. 2016). Reciprocal transplants are a type of common garden where individuals from different environments are reared in both their native and non-native (introduced) environment. Reciprocal transplants measure the contribution of both genetic and environmental variation to fitness and can be used to identify local adaptation. The most robust inference for these methods comes from rearing multiple generations under common conditions to reduce maternal effects (Kawecki and Ebert 2004), and using individuals of known pedigree to facilitate quantitative genetic study (though estimates of relatedness can be made using molecular data).

These stringent conditions will make experimental manipulations inaccessible for most wildlife species due to challenges associated with rearing in controlled conditions, limitations associated with listed species status, and other logistical complications. Experimental studies do exist for wildlife species, including amphibians (e.g., Berven 1982; Bernardo 1994) and salmonids (Fraser et al. 2011; Christie et al. 2016), and it is these studies that provide the highest inferential strength for understanding the functionality of genomic and phenotypic variation in an evolutionary context.

When experimental methods are possible, there are multiple alternatives for integrating these data with GEA results. For example, environmentally stratified common gardens could be used as a follow-up to GEA to compare the fitness (or related trait) of individuals from environmentally divergent habitats who carry

or lack a candidate adaptive allele identified by GEA (Holderegger et al. 2008). Replicating individuals within habitats that carry/do not carry the allele of interest is important to control for divergent genetic backgrounds across populations, so this approach would be most useful for candidate loci that have not diverged to fixation. Another approach is to assess the relationship between candidate SNPs identified with GEA and traits measured in a common garden (De Kort et al. 2014). Recently, Lasky et al. (2018) developed a synthetic approach that integrates data from multiple common gardens stratified across environments with GEA in a genome-wide association model of genotype-by-environment interactions. This novel approach uses imputed fitness values for GEA data to coherently synthesize evidence from common gardens and GEA tests, increased power to detect signatures of local adaptation.

### ***4.3 Epigenetics as a Mechanism for Rapid Adaptive Responses***

Epigenetic modifications (i.e., phenotypic changes that are mediated by the regulation of gene expression, rather than alterations in the DNA sequence) are influenced by genome-environment interactions and can therefore shape patterns of adaptive genomic variation in heterogeneous environments (Verhoeven et al. 2016; Whipple and Holeski 2016). Epigenetic variation may also be a mechanism allowing rapid adaptation to changing environmental conditions (via plasticity), even in the face of small population sizes and low genetic diversity (Massicotte et al. 2011; Bernatchez 2016). However, our understanding of epigenetic processes in natural settings is currently quite limited, and most population and quantitative genetic theory does not include epigenetic effects. Method development in the field is proceeding quickly, with newer approaches based on reduced representation sequencing possible in species without a reference genome (e.g., Trucchi et al. 2016; van Gorp et al. 2016). These advances should make studies of DNA methylation (the most widely studied epigenetic mechanism) more accessible in wildlife species, providing insight into the role of environmentally induced epigenetic modifications in plastic responses to environmental change. For example, a recent study identified a role for epigenetic modifications in plastic responses of three reef-building corals to ocean acidification and thermal stress, demonstrating a previously unknown adaptive response of these species to climate change (Dimond and Roberts 2016). However, experimental designs such as multigenerational common gardens, which are not feasible for most wildlife species, are ultimately needed to establish transgenerational inheritance of epigenetic modifications (Whipple and Holeski 2016). This will constrain our understanding of the role of epigenetics in enhancing the evolutionary potential of wildlife species in a management context.

#### 4.4 *The Importance of Differential Gene Expression Across Landscapes*

Detailed landscape genomic inference can be derived from approaches that analyze the functionality and expression of genes, such as transcriptome analyses (i.e., RNA-seq), across landscapes (Storfer et al. 2015). Because these approaches require experimental work and high-quality gene annotation to establish robust relationships between functional genomic variation and gene expression, they have been most frequently applied to model species. While *de novo* implementations of transcriptomics are available for non-model species (e.g., Haas et al. 2013), the quality of inference from these studies is limited (Alvarez et al. 2015; Todd et al. 2016). The most robust experimental design for transcriptomic studies involves controlled, hypothesis-driven, experimental treatments to identify the processes underlying differential gene expression across relevant tissue types. This imposes limitations for field-based studies of many wildlife species, though progress is being made in investigating alternative, less destructive tissue sampling approaches (Czypionka et al. 2015). While detecting differences in gene expression under field conditions is possible, inference is often confounded due to the sensitivity of gene expression to environmental conditions. Field-based studies therefore require very careful design and execution, (relatively expensive) biological replication, and careful documentation of potentially confounding biological, environmental, and laboratory effects (Todd et al. 2016). Even in these cases, field-based RNA-seq studies are mostly confined to generating hypotheses for future research (Todd et al. 2016). Despite these constraints, there are a few examples of common garden approaches to documenting differential gene expression in wild species in a climate change context (e.g., Barshis et al. 2013; O'Neil et al. 2014; Narum and Campbell 2015; Thomas and Palumbi 2017), which illustrate the potential for transcriptomic studies to inform adaptive capacity in response to climate change (Hoffmann et al. 2015). Additionally, when there are existing transcriptomic resources available, they can be used to help validate and suggest functional relevance of loci detected with GEA (Szulkin et al. 2016).

Finally, a related sequencing method, whole-exome sequencing (WES), uses transcriptomic resources to develop probes targeting exons (protein coding genes) as well as functional but noncoding regions (Warr et al. 2015). WES, not to be confused with exon capture (which targets subsets of the exome, usually based on an annotated genome, e.g., Roffler et al. 2016), is currently restricted to humans and other model species, as well as a few domesticated species and crops. WES is unlikely to be applied in non-model wildlife species in the near future, though exome resources developed for model and domesticated species could be leveraged in studies of closely related species.

## 5 Conclusions

Overall, GEA has already led to several exciting findings in wildlife landscape genomics, and the rapid development of new and improved GEA methods and software for their implementation will likely ensure their continuing role as a workhorse for adaptive landscape genomics. However, we need to be careful not to equate “landscape genomics” with “genotype-environment associations.” The first is a scientific field, while the latter is a mere set of analytical tools. Several authors have already argued that landscape genomics focusing on neutral processes (i.e., “landscape genetics”) is not a distinct scientific field, but rather a collection of new and more powerful methods to test old ideas that mainly stem from other disciplines (e.g., Dyer 2015; Rissler 2016). Even though some of the important “classic” population genetic concepts and theories are certainly still valid for landscape genomics, we agree that the theoretical and conceptual development in both neutral and adaptive landscape genomics lags far behind the methodological progress we have made.

As highlighted by Bernatchez (2016), theories of adaptive capacity and evolutionary potential in nature have generally not been able to keep up with the fast developments for gathering and analyzing large amounts of genomic data. Specifically, most of the theories and models used by geneticists and evolutionary biologists do not account for spatiotemporal impacts of environmental heterogeneity in a realistic manner and also seldom include the complex interrelationships of processes impacting genomic variation (e.g., polygenic and balancing selection, genomic architecture, epigenetics). Because of this, predictions from classical theories and models often do not match the genomic patterns that we see in nature. Hence, it is crucial to compare findings from empirical genomic studies to predictions derived from existing theory and simulation studies. Contrasting expected genomic patterns with those observed in field and experimental settings can shed light on the missing pieces in our understanding of adaptive processes in heterogeneous and changing environments.

This will also be vital for developing new theories and hypotheses that refine our thinking about the links between environmental complexity, genomic variation, and evolutionary processes. Such a theory-focused approach is not only important for the future development of landscape genomics (Balkenhol et al. 2015; Dyer 2015) but is also necessary to better inform conservation managers and policy-makers about the most important challenges to expect under changing environmental conditions. Our predictions of future evolutionary trajectories of populations and species require a much better theoretical and conceptual understanding of how adaptive capacity and evolutionary potential vary across groups with different life histories and ecological niches. As stated before, future studies should evaluate whether and when such detailed information is indeed needed to successfully manage wildlife populations.

Thus, the future of landscape genomics will hopefully move beyond the statistical detection of associations between environmental and genetic data and mature toward a field with a solid theoretical and conceptual foundation. Such progress has to go

hand-in-hand with more holistic research approaches that combine (quasi-) experimental study designs with simulations and empirical analyses that use the full range of available tools for assessing environmental impacts on selection-driven genetic and phenotypic variation and underlying processes. We particularly advocate the integration of GWAS across environmental gradients, because understanding the impacts of environmental heterogeneity on genomic variation that is relevant for phenotypic variation can provide us with information more closely related to fitness and population dynamics. Additionally, GWAS studies, though potentially labor-intensive for the collection of phenotypic trait data, are more feasible in wildlife species compared to other options for improving inference of local adaptation (Table 1). Finally, we need to begin to move beyond the single-species studies that are typical of adaptive landscape genomics to date. Considering multiple species or entire communities in landscape genomics (i.e., community landscape genomics, Hand et al. 2015) is clearly challenging but necessary because neutral and adaptive genomic patterns are not only shaped by the physical characteristics of an area (“landscape” in a strict sense) but also by the interactions among species. Landscape community genomics could be facilitated by eDNA (environmental DNA) approaches that rely on samples of, e.g., water or soil that contain genetic material from wildlife that have been in contact with these environmental samples (Ficetola et al. 2008). While current eDNA approaches do not yet allow population and landscape genomic studies, future technological and analytical developments will likely enable such applications (Bohmann et al. 2014).

Considering all of the abovementioned research approaches in adaptive landscape genomics of wildlife will ultimately help us to not only quantify and predict genetic patterns in changing environments but also to understand the function of these patterns and their relevance for individual fitness, population dynamics, and species persistence.

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