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Saving the spandrels? Adaptive genomic variation in conservation and fisheries management[a]

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As highlighted by many of the papers in this issue, research on the genomic basis of adaptive phenotypic variation in natural populations has made spectacular progress in the past few years, largely due to the advances in sequencing technology and analysis. Without question, the resulting genomic data will improve the understanding of regions of the genome under selection and extend knowledge of the genetic basis of adaptive evolution. What is far less clear, but has been the focus of active discussion, is how such information can or should transfer into conservation practice to complement more typical conservation applications of genetic data. Before such applications can be realized, the evolutionary importance of specific targets of selection relative to the genome-wide diversity of the species as a whole must be evaluated. The key issues for the incorporation of adaptive genomic variation in conservation and management are discussed here, using published examples of adaptive genomic variation associated with specific phenotypes in salmonids and other taxa to highlight practical considerations for incorporating such information into conservation programmes. Scenarios are described in which adaptive genomic data could be used in conservation or restoration, constraints on its utility and the importance of validating inferences drawn from new genomic data before applying them in conservation practice. Finally, it is argued that an excessive focus on preserving the adaptive variation that can be measured, while ignoring the vast unknown majority that cannot, is a modern twist on the adaptationist programme that Gould and Lewontin critiqued almost 40 years ago.

Key words: adaptation; evolution; genome; salmonid.

INTRODUCTION

> ‘The outstanding scientific discovery of the twentieth century is not television, or radio, but rather the complexity of the [genome]. Only those who know the most about it can appreciate how little we know about it … every part is good, whether we understand it or not’. Aldo Leopold (1938)

Understanding the connection between fitness-related phenotypes in natural populations and their underlying adaptive genetic basis has been a long-standing goal of evolutionary biology (Naish & Hard, 2008; Bernatchez, 2016). Historically, adaptation was regarded as a special and onerous explanation for phenotypic variation, to

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be invoked only when strong evidence supported it (Williams, 1966). Today, however, numerous studies are finding widespread evidence of an adaptive genetic basis for variation in nature. These data have emerged due to changes in the ability to find individual loci that are under selection using genome-wide DNA data and quantify their phenotypic effects, leading to exciting new research and providing tangible evidence of adaptation (Stapley *et al.*, 2010; Barrett & Hoekstra, 2011). From a conservation perspective, positively identifying genomic variation that has been influenced by selection, particularly that associated with obvious fitness-related traits, offers the potential to focus conservation efforts on the specific genomic elements that will most likely play a role in future adaptation (Allendorf *et al.*, 2010). While such a reductionist approach has been immensely successful in crop and livestock improvement by identifying the genomic basis of heritable traits through quantitative trait loci (QTL) mapping and association studies and then targeting them in breeding programmes, the complexities of selection on natural biological systems make its utility in applied conservation biology unclear (Shafer *et al.*, 2015, 2016; Garner *et al.*, 2016).

This paper has been written almost 10 years after an in-depth review of adaptive genetic variation in Atlantic salmon *Salmo salar* L. 1758 (Garcia de Leaniz *et al.*, 2007). At that time, the authors were forced to conclude that limited progress had been made in identifying molecular adaptations and that data on the adaptive significance of molecular genetic variation were ‘scant and largely circumstantial’ (Garcia de Leaniz *et al.*, 2007). Today, this is no longer the case as the wave of genomic data collection has identified adaptive molecular variants that are far from circumstantial (Hemmer-Hansen *et al.*, 2013; Pearse *et al.*, 2014; Ruegg *et al.*, 2014; Barson *et al.*, 2015; Kardos *et al.*, 2015*a*; Hess *et al.*, 2016; Kirubakaran *et al.*, 2016; Küpper *et al.*, 2016; Lamichhaney *et al.*, 2016). These adaptive variants represent diverse traits and taxa, leaving conservation biologists evaluating real-world applications to ask the questions: Are the identified selective effects large enough to warrant special consideration and protection, and if so, are specific actions needed to protect them that would not be called for based on standard conservation genetic practices?

SAVING THE SPANDRELS

Gould & Lewontin’s (1979) paper on the spandrels of San Marco and the Panglossian paradigm had a profound influence on evolutionary thinking at the time and continues to resonate today; it has received over 6000 citations as of March 2016 (Rose & Lauder, 1996; Nielsen, 2009; Ganieli *et al.*, 2013). In it, they develop the spandrels (triangular architectural features, common in churches, that exist at the intersection between a round dome and a vertical archway) as an analogy for phenotypic traits that may or may not be a result of natural selection. They then criticized scientists for characterizing individual traits as an adaptive features rather than considering the organism as a whole and for failing to consider adequately alternative explanations or carefully evaluating the data. Although Smith (1995) was a prominent critic of Gould & Lewontin (1979), he later admitted that their critique forced the evolutionary biologist to ‘clean up our act and to provide evidence for our stories’, rather than accepting functional adaptation as an explanation for phenotypic variation without rigorous experimental data.

While the haphazard identification of adaptive phenotypes is perhaps the most widely discussed aspect of Gould & Lewontin’s (1979) critique, a second key argument was against the tendency to view traits as separate from one another, capable of experiencing essentially independent positive or negative selection (Gould & Lewontin, 1979). When extended to the identification of adaptive 'molecular spandrels' (Barrett & Hoekstra, 2011), there is a renewed risk in regarding individual genetic loci as separate, atomized, adaptive elements rather than appreciating the interconnected complexity of the genome. This broader evolutionary perspective is critical when considering conservation applications for adaptive genomic variation in efforts to save species that are poorly adapted to current, anthropogenically modified, environments.

THE PROBLEM: ADAPTIVE GENOMIC VARIATION AND CONSERVATION

Without question, the ability to identify adaptive genomic variation (AGV; Table I) under selection in natural populations has made spectacular advances in the past few years, largely due to advances in sequencing technology (Brieuc & Naish, 2011; Hoban *et al.*, 2016; see also special issue of *Molecular Ecology* 22, 2013). What is far less clear and has been the focus of intense debate, is how that new information can or should transfer into conservation practice (McMahon *et al.*, 2014; Shafer *et al.*, 2015, 2016; Garner *et al.*, 2016; see also special issue of *Evolutionary Applications* 7, 2014). Conservation managers have long used ecological and phenotypic variation as proxies for heritable adaptive variation in defining conservation units, which puts the focus on the adaptive environment as a whole (Dizon *et al.*, 1992; Waples, 2006). Now, an increasing number of studies are narrowing down the adaptive genomic basis for specific phenotypes in natural populations to single genomic regions, genes and causative SNPs. Unlike the neutral markers used in population genetics, these loci are expected to have direct effects on fitness-related traits and conservation genomics is emerging as an extension of conservation genetics (Table I) that incorporates the ability to direct conservation efforts to preserve AGV (Primmer, 2009; Allendorf *et al.*, 2010; Ouborg *et al.*, 2010; Funk *et al.*, 2012; Shafer *et al.*, 2015; Benestan *et al.*, 2016). As pointed out by Garner *et al.* (2016), there is no clear distinction between genetic and genomic datasets (Table I), which exist on a continuum of scale, or their applications in conservation. Rather, the appropriate dichotomy is between analyses of DNA data that assume neutrality (*e.g.* population structure or parentage analyses) and those that evaluate selection on adaptive genomic variation. The latter may or may not also be associated with a known specific phenotype. This view is consistent with the conservation genomics approach outlined by Funk *et al.* (2012) and represents a fundamental distinction with important implications for the types of analyses to be applied to the data as well as for the interpretation of results in a conservation context.

The problem that now needs to be addressed is whether to incorporate adaptive genomic variation into conservation programmes and if yes, how to do so in a manner consistent with evolutionary theory so as to protect not just the targeted variation, the parts deemed important, but also the evolutionary processes that led to its existence in the first place (Hendry *et al.*, 2011). This problem is particularly acute because most adaptations are expected to have a highly polygenetic basis (Barrio *et al.*, 2016; Bernatchez, 2016), although some genes will certainly have larger effects than others (Roff, 2007; Hendry *et al.*, 2011; Hendry, 2013). Thus, in only a few cases, such as the salmonid examples described below, can it be expected to have a sufficiently complete understanding of the evolutionary genomics of adaptation for fitness-related traits to predict accurately the consequences of directed conservation efforts to protect them.

TABLE I. Terminology and definitions

Term	Adaptive genomic variation (AGV)
Definition	For purposes of discussion, 'adaptive genomic variants/variation' (AGV) can be defined as any individual single nucleotide polymorphisms (SNP), genes or genomic regions that have been shown to have adaptive significance in natural populations or species. While this definition is broad, it is consistent with the definitions used in recent reviews (Stapley *et al.*, 2010; Tiffin & Ross-Ibarra, 2014) and simply serves to distinguish AGV from the presumably neutral variation used in typical population genetic analyses. It is also important to note that some AGVs may constitute large, linked, genomic regions, such as those maintained by chromosomal inversions, and an increasing number of such complex regions are being identified with major effects on important phenotypes (Wang *et al.*, 2013; Kunte *et al.*, 2014; Pearse *et al.*, 2014; Kirubakaran *et al.*, 2016; Küpper *et al.*, 2016)
Term	Genetics *v.* genomics
Definition	The Oxford English Dictionary defines genomics as 'the scientific study of genomes, using gene mapping, nucleotide sequencing and other techniques; the branch of molecular biology concerned with the structure, function and evolution of genomes'. This definition focuses squarely on study of the genome itself, rather than on population biology using genome-wide data, and supports the view that it is the questions being asked and not the laboratory or bioinformatic approaches that define a field of study. There has been an increasing trend, however, of using the term genomic to distinguish large, high-throughput datasets from more traditional population genetic studies (Primmer, 2009; Allendorf *et al.*, 2010; Ouborg *et al.*, 2010; Stapley *et al.*, 2010; Shafer *et al.*, 2015; Garner *et al.*, 2016). This situation is further complicated by the use of the term next-generation sequencing (NGS), which implies that data produced using these techniques are somehow different from other sequence or assay-based SNP data. While such data do present novel bioanalytical problems (Anderson *et al.*, 2014*a*), there is no qualitative benefit to using more data than necessary for a given application, and in many cases established assay-based techniques using moderate numbers of loci provide sufficient power and continue to offer quantitative advantages in data quality, reliability, flexibility and speed

Here, a synthesis is presented of the important aspects to consider before using information from adaptive genomic variants in management and policy. While many of the topics covered here have been considered in earlier reviews with diverse viewpoints (Primmer, 2009; Allendorf *et al.*, 2010; Ouborg *et al.*, 2010; Funk *et al.*, 2012; Shafer *et al.*, 2015, 2016; Garner *et al.*, 2016), the goal is to consolidate the key considerations for integrating adaptive genomic data into conservation in a single document to inform policy discussions, illustrate the difficulties that must be addressed and highlight the critical role of evolutionary processes in shaping both neutral and adaptive genetic variation. This perspective will be critical in the near future as more examples of adaptive genomic variation are identified in species of conservation concern. Studies on adaptive variation in salmonids are given as examples because their specific habit requirements have resulted in many salmonid populations being severely reduced by anthropogenic effects on rivers (Gustafson *et al.*, 2007). Together with their high economic and cultural value, salmonids represent high profile species garnering conservation, management and research attention. As a result, salmonid species represent the tip of the spear when it comes to confronting many emerging issues at the nexus of science, conservation and management (Waples, 2006). The principles discussed here, however, should broadly apply to almost any species with phenotypically diverse populations distributed across a variable adaptive landscape.

EXAMPLES OF AGV IN SALMONID LIFE HISTORIES

Salmonids have been a focus of intensive efforts to characterize variation associated with life-history traits (Waples *et al.*, 2004; Miller *et al.*, 2012; Dodson *et al.*, 2013; Brieuc *et al.*, 2015; Elmer, 2016; Phillis *et al.*, 2016). From this, several examples have emerged that provide strong evidence for single genes or genomic regions that have a strong influence on specific phenotypic traits with clear conservation and management implications. These examples serve as a focal point from which to review the specific details that must be considered in any practical application of such data to conservation and management plans for anadromous and marine fish species as well as other taxa.

MIGRATION AND RESIDENCY

The ability of some salmonid species to either complete an anadromous migration or remain as freshwater residents has long been known and understood to have a heritable basis (Neave, 1944; Hendry *et al.*, 2004; Quinn & Myers, 2004; Kendall *et al.*, 2014; Phillis *et al.*, 2016). In *Oncorhynchus mykiss* (Walbaum 1792), some individuals are freshwater residents, the well-known rainbow trout, while others mature as steelhead that complete anadromous ocean migrations. This example represents a significant conservation challenge because only anadromous individuals are protected under the U.S. Endangered Species Act (NOAA, 2006), while resident populations are unlisted. This was done to specifically support the anadromous life history, but it significantly complicates the implementation of protection and makes understanding the genetic basis of this trait critical. It is also important to recognize that populations of *O. mykiss* do not contain dichotomous phenotypes of either resident or anadromous individuals, but are typically a mixture, with both forms interbreeding and producing offspring of alternate and variable phenotypes (Hayes *et al.*, 2012; Kendall *et al.*, 2014). In addition, genetic relationships among populations generally follow geography, with both resident and anadromous individuals more closely related within the same river system than among river systems, even when separated by natural or artificial barriers (Olsen *et al.*, 2006; Clemento *et al.*, 2009; Pearse *et al.*, 2009).

Recent efforts using both standard genetic approaches and high-throughput sequencing have greatly improved the understanding of the genetic architecture underlying this trait. First, it is clear that numerous genetic factors (Nichols *et al.*, 2008; Martínez *et al.*, 2011), as well as significant environmental effects (Ohms *et al.*, 2013; Kendall *et al.*, 2014), influence the expression of anadromy. Yet, multiple studies have repeatedly associated a single, large, genomic region of chromosome *Omy5* with expression of residency and anadromy in *O. mykiss* (Nichols *et al.*, 2008; Martínez *et al.*, 2011;

Hecht *et al.*, 2012, 2013; Miller *et al.*, 2012; Pearse *et al.*, 2014). Given that this region appears to represent a 'master control region' (Nichols *et al.*, 2008; Hecht *et al.*, 2012) that has a major effect on a phenotype with significant fitness consequences, how can that information be used in an applied conservation context?

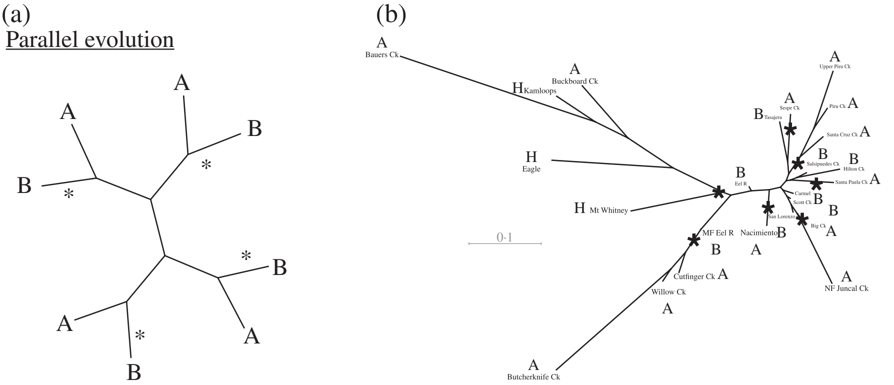
The repeated evolution of the resident phenotype in each catchment clearly follows the 'parallel evolution' model of Waples *et al.* (2004) at the genome-wide level (Pearse *et al.*, 2014). In contrast, from a molecular genetics perspective the *Omy5* region itself follows a single evolutionary event model, providing a common basis for repeated parallel adaptive evolution from this shared standing genetic variation leading to multiple resident populations (Fig. 1). Similar genomic patterns have also been observed in the stationary and migratory phenotypes in Atlantic cod *Gadus morhua* L. 1758 (Hemmer-Hansen *et al.*, 2013; Kirubakaran *et al.*, 2016), which provides encouraging evidence that the conclusions generated here are likely to be widely applicable beyond salmonids and supports the idea that information on the distribution of variation at single, large-effect loci like the *Omy5* region can be used to inform conservation and fishery management efforts about the relative selective environments in different populations (Pearse *et al.*, 2014; Pearse & Garza, 2015; Abadía-Cardoso *et al.*, 2016; Leitwein *et al.*, 2016). Focusing conservation efforts on particular alleles associated with anadromy at *Omy5* loci, however, without considering the genomic background in which they exist, follows the same faulty reasoning used when viewing the spandrels of San Marcos as isolated features, independent of their surrounding architectural context. Decisions based on this information should always evaluate the larger genomic architecture involved, as well as the many practical considerations discussed below.

AGE AT MATURITY

Many species vary in the age at which they change from juvenile stages into reproductively mature adults. A striking example of AGV associated with salmonid life history is the recent characterization of a single genomic region associated with this transition in *S. salar* (Ayllon *et al.*, 2015; Barson *et al.*, 2015). Here a single gene, *vgll3*, was shown to contain specific mutations that strongly predict the age at which *S. salar* become reproductively mature and return to fresh water to spawn (Barson *et al.*, 2015). Strikingly, this same gene has also been associated with several traits linked to puberty in humans, including age at first menarche (Perry *et al.*, 2014), suggesting remarkably conserved function across evolutionary time. Nonetheless, even the relatively large part (39%) of the total phenotypic variation in age at maturity attributable to this single gene leaves the majority to other genetic, epigenetic or ecological factors. In addition, previous studies of the same phenotype did not detect this same gene, at least in part due to using fewer genome-wide single nucleotide polymorphisms (SNPs), or have found significant associations with different genomic regions (Johnston *et al.*, 2014; Gutierrez *et al.*, 2015). Thus, even this strong example of AGV associated with a clear phenotype is underlain by substantial genomic complexity, again supporting a cautious view of the use of this information in conservation and management planning.

TIMING OF SALMONID RUNS

The seasonal timing of migration by adult salmonids into fresh water to spawn is a key life-history trait, with extensive variation across many species and may be linked



Single evolutionary event

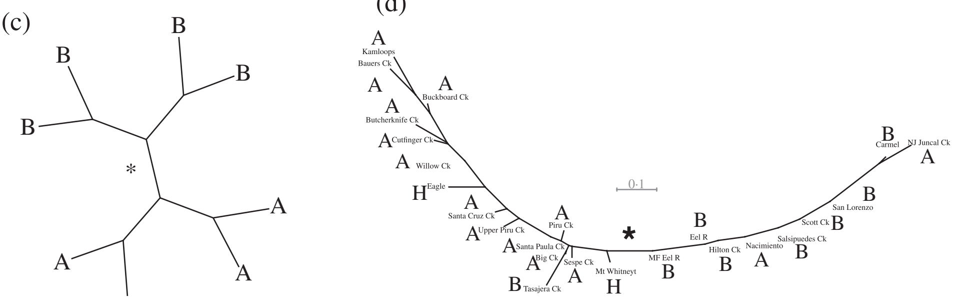


FIG. 1. (a, c) Hypothetical and (b, d) actual relationships between populations with alternate life-history phenotypes based on (a, b) parallel evolution with neutral, genome-wide data and (c, d) a single evolutionary event with adaptive genomic variation (AGV). A and B, alternative life-history forms; H, hatchery *Oncorhynchus mykiss* samples; *, separate evolutionary events leading to the phenotype. Modified from Pearse *et al.* (2014) and Waples *et al.* (2004).

to variation relative to the timing of sexual maturation (*i.e.* premature *v.* mature; Quinn *et al.*, 2016). At neutral loci, such populations have been shown to follow a pattern of parallel evolution, such that populations are related through geographic isolation by distance regardless of ecotype (Arciniega *et al.*, 2016). A recent study identified a single gene, *greb1l*, as being strongly associated with summer and winter-run timing in a population of steelhead, the anadromous form of *O. mykiss* (Hess *et al.*, 2016). Like *vgll3* in *S. salar*, *greb1l* is also a gene that has been associated with reproductive and developmental traits in mice and humans, again supporting the conservation of gene function across vertebrates (Hess *et al.*, 2016). Studies of run timing in salmonid and other taxa, however, have uncovered a complex genomic basis, supporting a highly polygenic view of variation in this trait (Brieuc *et al.*, 2015; Barrio *et al.*, 2016).

From a conservation perspective, premature migrating salmonids are especially vulnerable to anthropogenic interventions even when mature migrating populations exist within the same river system, because they utilize the freshwater habitat for longer as adults and require access to upstream river reaches that are often blocked by dams (Arciniega *et al.*, 2016; Quinn *et al.*, 2016). Thus, these results show the significance of a specific AGV in shaping phenotypic traits with important cultural, commercial and conservation consequences. Despite the detection of a strong genetic basis of migratory timing, however, repeated evolution of this phenotype through adaptive evolutionary change still represents parallel evolution based on standing genetic variation, similar to the evolution of residency from anadromous populations (Fig. 1). Thus, each derived population will have a diverse genetic background at neutral loci, consistent with their geographic ancestries, as well variation in the AGVs themselves.

The three examples described above illustrate the issues associated with incorporation of single-locus AGV into conservation and management of economically and ecologically important fitness-related traits in protected species. Given the unknown but probably extensive additional genetic variation underlying these traits, however, even these cases are limited in their potential for direct conservation actions. For example, studies of both run timing and migratory ecotypic variation in other salmonid species have found evidence of much more polygenic basis for such variation [*Oncorhynchus tshawytscha* (Walbaum 1792); Brieuc *et al.*, 2015; *O. nerka*, Nichols *et al.*, 2016] and future studies will undoubtedly discover more complexity that is currently recognized in all of these systems. In addition, there is a significant amount of variation in salmonid life-history expression, adding complexity to the interpretation of results based on dichotomous characterizations (Hayes *et al.*, 2012; Bond *et al.*, 2015). Most importantly, even when a single gene of major effect is convincingly shown to explain a large proportion of the variance in a given trait or complex phenotype, its effects must be considered in the larger evolutionary context of natural selection acting on whole-organism phenotypes, not single loci that contribute to parts of the phenotype.

PRACTICAL CONSIDERATIONS FOR AGV IN CONSERVATION

> ‘If the biota, in the course of aeons, has built something we like but do not understand, then who but a fool would discard seemingly useless parts? To keep every cog and wheel is the first precaution of intelligent tinkering’.
> Aldo Leopold (1938)

High-throughput sequencing technology has changed the ability to directly detect adaptive genomic variation, but the existence of such variation has long been recognized (Haldane, 1932). Thus, the framework of policies designed to protect biodiversity does not necessarily need to fundamentally change. Nonetheless, several recent papers have envisioned extensions to help bring AGV into applied conservation applications (Funk *et al.*, 2012; Shafer *et al.*, 2016). In some cases, genomic information has allowed the development of increased power in population genetic analyses, for example in the assignment of stock of origin in fisheries applications (Nielsen *et al.*, 2012). In others, demonstrable fitness effects have been attributed to specific alleles at single loci (*e.g.* disease resistance; Savage & Zamudio, 2016). It is important to note, however, that most critical aspects of conservation genetic management (*e.g.* ancestry, population structure, inbreeding and effective population size) do not require larger numbers of loci than are already commonly employed to obtain biologically meaningful accuracy and precision in estimating the key variables (*e.g.* 10–20 microsatellite loci or 96 SNPs; Allendorf *et al.*, 2010; Kardos *et al.*, 2015*b*). In fact, for the vast majority of species of conservation concern, the primary roles of genome-wide data will be direct extensions of the standard practices of conservation genetics (Stockwell *et al.*, 2016) and no distinction needs to be made between genetic and genomic considerations. Given this, several key factors must be considered prior to the incorporation of AGV into monitoring or direct conservation efforts.

COMPLEXITY

First, many identified AGVs will undoubtedly be false positives or otherwise incorrect inferences (Pavlidis *et al.*, 2012). Conversely, even well-designed studies will fail to detect important adaptive variants (Johnston *et al.*, 2014), particularly those that have a relatively small effect on the phenotype, as is common for highly polygenic traits (Bernatchez, 2016). Moreover, studies using different outlier tests may identify significant associations for different AGVs with the same phenotype (Martínez *et al.*, 2011), or a lack of concordant signals in multiple populations expressing similar adaptive phenotypes, consistent with a complex genomic basis (Nichols *et al.*, 2016). All of these issues will be of particular concern as the field is developing its bioinformatics standards (Benestan *et al.*, 2016), leading to uncertainty about the strength of identified adaptive effects until they have been validated and replicated (Brieuc & Naish, 2011; Pavlidis *et al.*, 2012; Moore *et al.*, 2014; Tiffin & Ross-Ibarra, 2014; Stockwell *et al.*, 2016). While the ability to both identify AGVs that show concordant signals of selection on specific phenotypes (Narum & Hess, 2011; Poh *et al.*, 2014; Roesti *et al.*, 2014; Benestan *et al.*, 2016; Springer *et al.*, 2016) and to associate them with environmental variables (Vincent *et al.*, 2013; Leitwein *et al.*, 2016) has greatly improved, rigorous experimentation is not practical for most species of conservation concern. Of course, some putative AGVs will represent truly adaptive loci influencing a specific trait, but even among these, imperfect penetrance, phenotypic plasticity and other factors can all result in specific genotypes not predicting the phenotype (Naish & Hard, 2008).

DYNAMICS OF NEUTRAL AND ADAPTIVE GENOMIC VARIATION

A second important consideration that is often overlooked is that the action of selection on AGVs does not exclude them from also being subject to some evolutionary processes that influence neutral loci. In small populations that may be of particular conservation concern, drift and inbreeding can be expected to affect the distribution of genetic diversity far more strongly than selection and little difference may be apparent between neutral loci and AGVs (Moore *et al.*, 2014). Thus, provisions developed around standard conservation genetic practices designed to maximize the preservation of diversity (Fraser, 2008) will also protect any known or unknown AGV present in the populations.

KNOWN AND UNKNOWN PHENOTYPES

Third, it is important to recognize the distinction between AGVs associated with known phenotypes, such as the salmonid examples described above and those that are not. While the former may provide some basis for conservation, signals of genomic adaptation detected though F_{ST} outlier tests that are not associated with any specific *a priori* hypothesis about the selective landscape cannot be considered as a basis for conservation efforts. This is important because the vast majority of adaptive variation will involve traits for which there is little or no ability to measure selection coefficients, but which nonetheless may have critical effects on organismal fitness. How then can the design of conservation plans around the genomic basis of these traits even begin?

DYNAMICS OF THE GENOME

A fourth consideration is that genomes are not static features that have evolved over time into one perfectly adapted form, but are complex and dynamic collections of diverse genetic elements whose individual adaptive potentials may vary in space and time (Miller & Hedrick, 1991). In addition, individual AGVs exist and interact in the context of their functional pathways, so focusing on single polymorphisms identified as key adaptive variants will not necessarily preserve the full adaptive potential of the phenotype associated with that variation. Recent studies have also highlighted influences on phenotype through epigenetic methylation patterns (Baerwald *et al.*, 2015), transgenerational variation in gene expression (Christie *et al.*, 2016; Schunter *et al.*, 2016) and correlated selection on multiple phenotypes affected by the same gene (Rennison *et al.*, 2015), as well as phenotypic (Hendry, 2016; Phillis *et al.*, 2016) and transgenerational plasticity (Walsh *et al.*, 2016) and fitness trade-offs between phenotypes (Johnston *et al.*, 2013). All of these attributes can affect evolutionary response to the selective environment, creating a complex relationship between individual AGVs and their associated phenotypes.

SETTING LIMITS ON GENOMIC APPLICATIONS

While individual traits and outcomes matter in medicine and to some extent in agriculture, the unit of concern in conservation is the long-term maintenance of population-level biodiversity and adaptive potential of populations and species. This is an important distinction that influences the types of applications for which genomic data may be useful in conservation. Just as medical genetics experts advise the public about the limitations of the knowledge of the genomic basis of human diseases and make specific recommendation on known genes that are not informative for predicting individual risk for a given disease (Johnson, 2015), the evolutionary conservation community must work together to provide evidence-based advice, including recognition of situations in which detailed genomic analyses are not necessary for conservation and management plans to preserve populations or species.

LEVELS OF INTERVENTION

POPULATION

Despite the limitations described above, AGV will probably play a strong role in the active management of threatened populations. In this context, an important distinction should be made between population-level inference, drawn from the distribution of AGV alleles among populations and actions directed at individuals carrying specific alleles. For example, population-level inference based on the frequencies of specific AGV alleles could potentially be used to identify populations in which a particular trait is favoured (Funk *et al.*, 2012) and these populations could then be considered as candidates for transplanting or reintroduction into habitats with similar adaptive environments (Meek *et al.*, 2014; He *et al.*, 2016; Leitwein *et al.*, 2016). Along with other, non-genetic considerations, such information from AGV will complement the standard genetic considerations used in conservation-unit delineation and selection of potential source populations for reintroductions (Anderson *et al.*, 2014*b*; Meek *et al.*, 2014). Active population-level management of AGV could also involve taking direct steps based on specific AGVs by managing gene flow to rescue populations with lost diversity (Whiteley *et al.*, 2015; Hamilton & Miller, 2016) or modifying anthropogenic activities to support a particular selective environment (T. M. Apgar, D. E. Pearse & E. P. Palkovacs, unpubl. data). In all of these situations, however, the AGV data must be evaluated in the context of the broader population genetic and ecological environments involved.

INDIVIDUAL

At the individual level, the use of AGVs could potentially be envisioned in marker-assisted conservation breeding programmes to more accurately select for or retain specific traits of conservation concern. In considering this, other fields in which genomic data are applied at the individual level can be looked into. For example, in the same way that high-profile species such as salmonids have led the way in the application of science to conservation and management of natural populations (Waples, 2006), the field of medical genomics is far ahead in the development and application of genomic techniques. Yet even in humans, rigorous identification of the genetic basis of complex traits remains challenging and the development of personalized medicine and individual-based applications of genomics have been slow to be realized (McCarthy *et al.*, 2008; Manolio *et al.*, 2013). The reason for this is partly the high dimensionality of the genomic basis of complex phenotypic traits, including diseases such as cancer (Bailey *et al.*, 2016). For example, although mutations in two major susceptibility genes, *brca1* and *brca2*, account for a large proportion of the predicted genetic risk for breast and other cancers, estimates of this proportion vary widely (Antoniou *et al.*, 2003). Genomic studies of human disease have also highlighted the need for massive sample sizes in case–control studies and have identified dozens of individual risk factor mutations for breast and ovarian cancers (Easton *et al.*, 2007; Nik-Zainal *et al.*, 2016), as well as multiple independent mutational variants of the same gene (Shi *et al.*, 2016). These results highlight the complex polygenetic basis of phenotypic variation and trait expression at the individual level and the difficulties that will be encountered in characterizing AGV in species of conservation concern.

A similar situation exists in agriculture, where the genetic basis of crop and livestock traits has long been used to improve yields. Genomic marker-assisted selection, in particular, is driving improvements in aquaculture (Yue, 2014), crop (*e.g.* rice; Yang *et al.*, 2014) and livestock breeding programmes (*e.g.* cattle; Charlier *et al.*, 2008). Recent improvements in individual marker-assisted breeding programmes, including genomic selection (Jonas & de Koning, 2013), are expected to double the rate of annual genetic improvement in livestock (Goddard & Hayes, 2009). Nonetheless, even in cases where strong selection is known to have occurred, such as milk yield in cattle, some studies have failed to find significant associations for such complex traits (Kemper *et al.*, 2014). Thus, the complexity of the genomic architecture can be difficult to disentangle for even the most well-characterized phenotypes and may defy attempts to develop useful applied tools for conservation.

Finally, unlike marker-assisted selection in plant and animal breeding, individuals produced in captive conservation breeding and supplementation programmes must contend with both domestication selection, leading to adaptation to the captive environment (Christie *et al.*, 2016) and natural selection in the environment into which they are ultimately released, both of which will affect the fitness of each individual. Thus, any form of individual marker-based selection in a conservation context should be carefully evaluated to avoid the potential undesirable effect of increasing the production of individuals with genotypes and phenotypes that are maladapted for the environmental conditions in which they are expected to live.

CONCLUSIONS

The issues outlined here are neither new (Haldane, 1932; Gould & Lewontin, 1979) nor easily resolved and decisions about the application of new technology to conservation problems will remain challenging. In many ways, the current debate about AGV mirrors discussions from 25 years ago about the relative importance of variation at major histocompatibility complex (MHC) loci associated with disease resistance (Miller & Hedrick, 1991). Both passive monitoring and active genetic management have and will continue to play a critical role in conservation and recovery planning of threatened fish species through conservation unit delineation (Waples, 2006), pedigree reconstruction (Abadía-Cardoso *et al.*, 2013) and captive broodstock management (Fraser, 2008; Conrad *et al.*, 2013; Fisch *et al.*, 2015). In addition, the conservation applications of AGV that do exist clearly show that the appropriate use of such technology has the potential to provide significant conservation benefits (Newhouse *et al.*, 2014; Garner *et al.*, 2016). Even when intensive conservation management is deemed necessary, however, such as in conservation hatcheries, captive breeding programmes and reintroduction efforts, the presumed benefits of incorporating information on adaptive genetic variation into conservation planning must be carefully evaluated relative to the costs and uncertainties. More importantly, the information gained must be evaluated in the context of the larger ecological environment under consideration.

Conservation biology practitioners have a responsibility to apply appropriate new technologies to optimize conservation efforts. While researchers seeking to understand the adaptive genomic basis of phenotypic variation have understandably called for further studies on genomic applications to conservation (Shafer *et al.*, 2015), the best approach may often be the simplest, preserve as much genetic diversity as possible using basic evolutionary and population genetic principles to allow species to express the full range of their evolutionary potential. It can be argued that in the vast majority of the cases, standard conservation genetic management practices along with restoration of physical and biological processes will be both necessary and sufficient to preserve the genomic complexity underlying a specific phenotype, without the need for directed intervention based on targeted AGV. This 'evolutionary enlightened management' (Ashley *et al.*, 2003) or 'prescriptive evolution' (Smith *et al.*, 2014) represents an integration of conservation biology and evolutionary thinking and provides a well-reasoned approach to management of highly affected species.

From a broader conservation biology perspective, focusing an in-ordinate amount of effort on intensively managing a limited subset of specific adaptive alleles would be like saving the spandrels while the building crumbles around them and runs counter to the goal of protecting evolutionary processes that will support future biodiversity. Taken to the extreme, the use of genetic engineering and genome editing technologies has been suggested to introduce adaptive genetic variation into endangered species (Thomas *et al.*, 2013; Johnson *et al.*, 2016). As pointed out by Hedrick *et al.* (2013), such directed genomic tweaking fails to address many basic considerations of conservation genetics and can only be considered a viable approach to conservation of biodiversity in a few limited cases (*e.g.* disease resistance; Newhouse *et al.*, 2014). Instead, within this field, a consensus that maximizes the benefits of applied genetic analysis must be established, while acknowledging that neutral and adaptive genetic considerations will not be the primary determinant of success for many conservation challenges.

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